Dystonia: Phenomenology and Pathogenesis



Dr Susan H Fox
University of Toronto,
Toronto Western Hospital, UHN
Canada

ASPEN 2026

Videos; courtesy Toronto Western Hospital movement disorder clinic video library

Definition of Dystonia:

- *"A movement disorder characterised by sustained or intermittent abnormal movements, postures, or both. Dystonic movements and postures are typically patterned and repetitive and maybe tremulous or **jerky**. They are often initiated or worsened by voluntary action and frequently associated with overflow movements*



Albanese et al 2013
Mov Disord: Special Issue:
Advances in Dystonia, 2013

REVIEW

Definition and Classification of Dystonia

Alberto Albanese, MD,[1,2*] Kailash P. Bhatia, MD, DM, FRCP,[3] Victor S.C. Fung, PhD, FRACP,[4] Mark Hallett, MD,[5] Joseph Jankovic, MD,[6] Christine Klein, MD,[7] Joachim K. Krauss, MD,[8] Anthony E. Lang, MD, FRCPC,[9,10] Jonathan W. Mink, MD, PhD,[11] Sanjay Pandey, DM,[12] Jan K. Teller, MA, PhD,[13] Marina A.J. Tijssen, MD,[14,15] Marie Vidailhet, MD,[16,17,18] and H.A. Jinnah, MD, PhD[19,20]

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30220

2025

Differential diagnosis

- More predictable; patterned (vs *chorea* – random and chaotic and flowing)
- More persistent (vs *tics*)
- Slower speed (vs *myoclonus*)

TABLE 1 *Proposed definitions for terminology relevant to dystonia*

Terminology	Definition
Alleviating maneuver	This term is synonymous with sensory trick and *geste antagoniste*, indicating different types of voluntary maneuvers that temporarily improve dystonic postures.[26]
Dystonia mimics	This term is preferred to pseudodystonia to indicate a variety of motor abnormalities that conform in part to the definition of dystonia. A list of dystonia mimics has been recently proposed.[27] Functional (psychogenic) dystonia is considered a dystonia mimic.
Dystonic muscles, dystonic muscle contractions	Usage of these expressions is discouraged because it may suggest a neuromuscular pathophysiology of dystonia.
Dystonic tremor	There is a close relationship between dystonia and tremor. Some have attempted to characterize tremulous dystonic movements with the term "dystonic tremor," separating this from a distinct postural and action tremor commonly seen in patients with dystonia ("dystonia with tremor"). This has resulted in the term "dystonic tremor" being used inconsistently over time to emphasize different aspects,[28] and thus a recent commentary has discouraged the use of the term due to lack of clarity.[29]
Sustained postures	Dystonic postures are called "sustained" when they are maintained at rest for prolonged periods of time but not fixed in response to passive movement (see below).
Fixed dystonia	Persistent or prolonged postures that cannot be significantly changed by passive movement.[30]
Jerky dystonia	This term is used when dystonic movements resemble myoclonic jerks. It should not be used as a synonym of irregularity of movements or postures. Occasionally electrophysiology may be necessary to distinguish myoclonus from jerky dystonia.
Mirror dystonia	Mirror dystonia is defined as a dystonic posture or movement, usually similar to that produced during action, that can be elicited in a dystonic limb at rest, when contralateral movements or actions are performed with the unaffected limb. When the dystonia is task-specific, the contralateral movement inducing the mirror dystonia is typically the task affected by the dystonia (eg, writing). Mirror dystonia is distinguished from mirror movements.[31]
Overflow dystonia	Dystonic movements and postures can "overflow" into apparently unaffected body segments that are contiguous with the affected body region, causing inappropriate and excessive movements unrelated to the intended voluntary movement.[32]

Tremor and Dystonia

- Tremor in a body part with dystonia

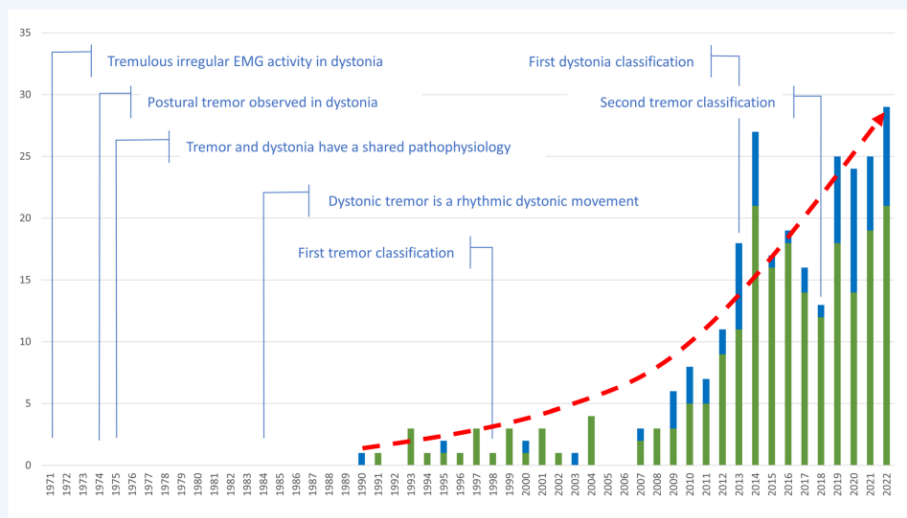


Figure 1. Timeline of landmark publications related to dystonic tremor and results of a PubMed search for publications citing dystonic tremor from first appearance in 1990 until 2022. Each bar indicates the total number of publications per year and specifies whether the term "dystonic tremor" is included in the title (blue) or in any other field (green). *Source*: PubMed.

Lalli and Albanese Mov Disord Clin Pract 2024;

- Tremor that is irregular; with jerky oscillations that have saw tooth appearance with or without overt dystonia.

Shaik and Jinnah Park Relat Disord 2024;

Rest and other types of tremor in adult-onset primary dystonia

Roberto Erro, Ignacio Rubio-Agusti, Tabish A Saifee, et al.

J Neurol Neurosurg Psychiatry 2014 85: 965-968 originally published online November 18, 2013

437 subjects with adult onset dystonia

55% Tremor;
locations = Head> arm>combo

Type = Arm =
Posture>Rest>Action
Rest tremor : 90% unilateral

Commoner in segmental vs focal

Arm tremor common in CD

Table 2 Clinical characteristic of our patients according to localisation of tremor

	Patients with head tremor	Patients with arm tremor	Patients with head and arm tremor	p Value
Number	98	42	98	–
Sex (F:M)	76:22	33:9	78:20	0.19
Age, years, mean (SD)	60.3 (12.5)	63.1 (13.7)	62.7 (11.8)	0.55
Age at onset, years, mean (SD)	43.18 (12.8)	46.3 (11.8)	45.9 (12.1)	0.29
Disease duration, years, mean (SD)	17.2 (12.9)	16.7 (13.2)	15.9 (12.5)	0.65
Distribution of dystonia				
Cervical, n (%)	75 (76.5)	65 (45.7)	79 (80.6)	0.0001
Cranial, n (%)	23 (23.4)	11 (26.2)	22 (22.4)	0.13
Brachial, n (%)	24 (24.4)	26 (61.9)	59 (60.2)	0.0001

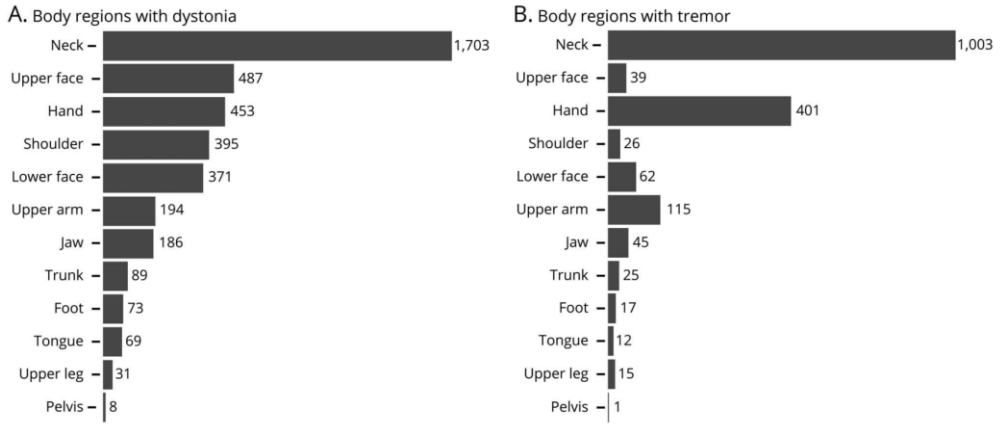
Dystonia and Tremor

A Cross-Sectional Study of the Dystonia Coalition Cohort

Neurology® 2021;96:e563-e574. Shaikh et al

- Neck >> Arm
- Associate with severity
- Associated with duration

Figure 1 Prevalence of Dystonia and Tremor According to Body Regions Among All 2,362 Patients



The totals for individual body regions with dystonia (A) and tremor (B) sum to more than the total number of participants because many participants had more than one body region affected. The numbers in the figures show the actual numbers of participants with each region affected.

- Dystonic tremor defined by co-occurrence with overt dystonia regardless of any irregular or jerky qualities; overall prevalence = **48.4%**.
  - **26.0%** had a strict concordance of tremor with dystonia,
  - 22.4% had concurrent tremor and dystonia with the tremor affecting another body region

Dystonia - phenomenology

- **Alleviating Maneuvers/Sensory tricks (*geste antagoniste*)**
- **Definition**: ‘An episodic and specific tactile manoeuvre that ameliorates dystonia in a manner that is not easily physiologically perceived as necessary to counteract the involuntary movement’.
- Sensory input is not always necessary or sufficient. But has to be self –generated.
- Can work by imagining sensory trick

Alleviating manoeuvres (sensory tricks) in cervical dystonia

Neepa Patel,[1] John Hanfelt,[2] Laura Marsh,[3] Joseph Jankovic,[4] for the members of the Dystonia Coalition

J Neurol Neurosurg Psychiatry 2014;**85**:882–884.

Table 2 Locations and characteristics of alleviating manoeuvres

	Upper face (n=16)	Lower face (n=77)	Chin (n=61)	Posterior neck (n=46)	Shoulder (n=2)
Ipsilateral, LT	13	59	48	29	1
Ipsilateral, FT	1	4	4	3	0
Ipsilateral, URT	2	4	2	5	0
Contralateral, LT	0	6	3	2	0
Contralateral, FT	0	0	0	0	0
Contralateral, URT	0	0	0	0	0
Bilateral, LT	0	4	4	4	0
Bilateral, FT	0	0	0	3	1
Bilateral, URT	0	0	0	0	0

Data collected through systematic review of videotaped neurological examinations. Some patients demonstrated effective tricks in multiple locations.
bilateral, 2 hands touching body; contralateral, hand crossing midline to touch opposite side of the body; FT, forceful touch, a forceful pressure applied to improve dystonic posture; ipsilateral, hand touching same side of body; LT, Light touch, a gentle touch to improve dystonic posture; URT, unrated touch.

Alleviating Manoeuvre to treat dystonia?



Sensory trick effect in craniofacial dystonia as one of the possible impacts of wearing face masks during the COVID-19 pandemic

Frank Erbguth* and Rüdiger Lange Neurol Res Pract 2021

- 100 subjects
  - Subjective evaluations
- Wearing a face mask did not affect self-perceived symptoms in 80% of patients with craniofacial hyperkinesis.
- **11% of patients reported an improvement, which occurred as sensory trick in dystonia patients**
- Plus concealment of a stigmatizing facial expression in patients with HFS.

An Unexpected Benefit From Face Masks During COVID-19. Amorelli G, et al Can J Neurol Sci. 2023

Classification of dystonia

1. **AXIS 1 Clinical characteristics:-**
   - **Age at onset,**
   - **Family History**
   - **Body distribution**
   - **Temporal dimension**
   - **Phenomenology**
   - **Associated features**

2. **AXIS II Aetiology:-**
   - **Genetic**
   - **Acquired**
   - **Neuroanatomical**
   - **Pathogenesis**

Albanese et al Mov Disord 2013/2025

Clinical Characteristics

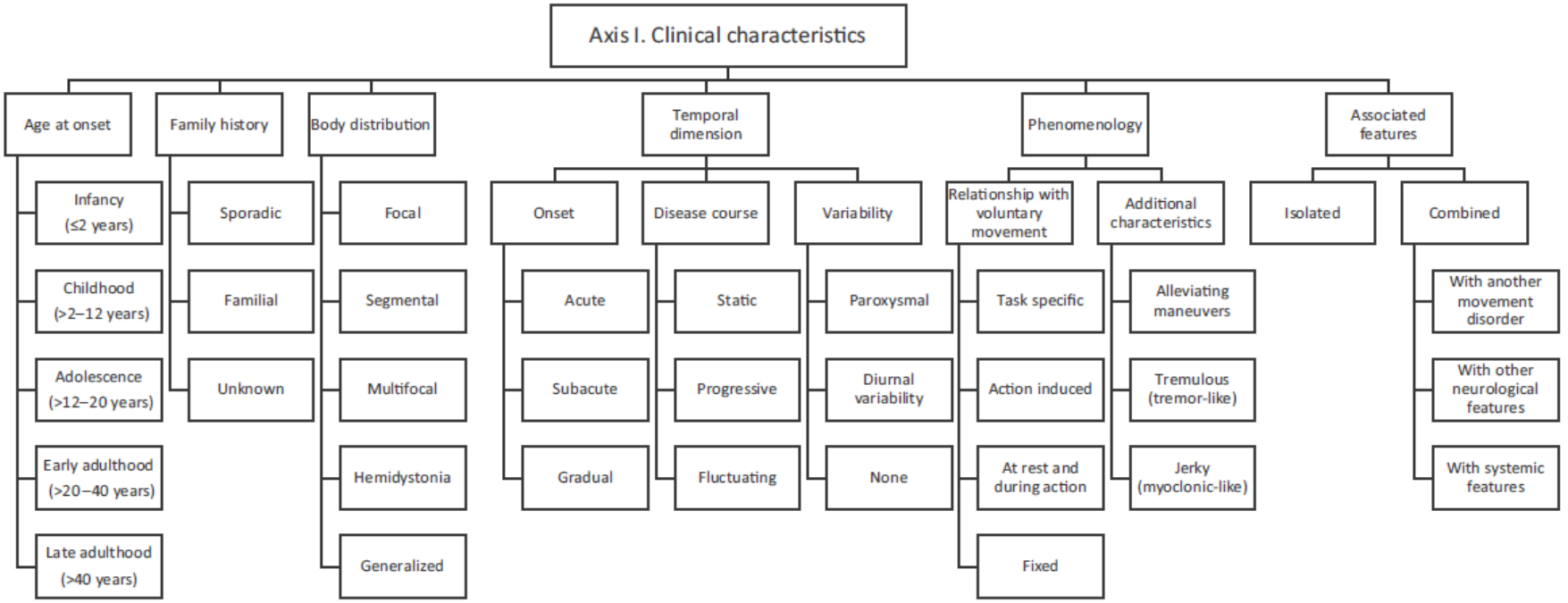


FIG. 1. Organizational structure of Axis I (clinical characteristics).

Temporal pattern

- Persistent. Dystonia that persists to approximately the same extent throughout the day.
- Action-specific. Dystonia that occurs only during a particular activity or task.
- Diurnal fluctuations. Dystonia fluctuates during the day, with recognizable circadian variations in occurrence, severity and phenomenology.
- Paroxysmal. Sudden self-limited episodes of dystonia usually induced by a trigger with return to preexisting neurological state.

Classification by dystonia by body Distribution



Focal

Blepharospasm
Jaw dystonia
Cervical dystonia
Hand dystonia
Toe or foot dystonia





Segmental

Affect contiguous body parts



Generalized

Segmental

- Segmental. Two or more contiguous body regions are affected. Typical examples of segmental forms are: cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bi-brachial dystonia.

Segmental Cranio-cervical dystonia

- **Breug(h)el's Syndrome**

Journal of Neurology, Neurosurgery, and Psychiatry, 1976, **39**, 1204–1209

Blepharospasm-oromandibular dystonia syndrome (Brueghel's syndrome)

A variant of adult-onset torsion dystonia?

C. D. MARSDEN

From the University Department of Neurology, Institute of Psychiatry, and King's College Hospital Medical School, Denmark Hill, London



FIG. 1 '*De Gaper*', *by Pieter Brueghel, The Elder* (*c. 1525–1569*). (*By permission of Musées Royaux des Beaux-Arts, Bruxelles.*)

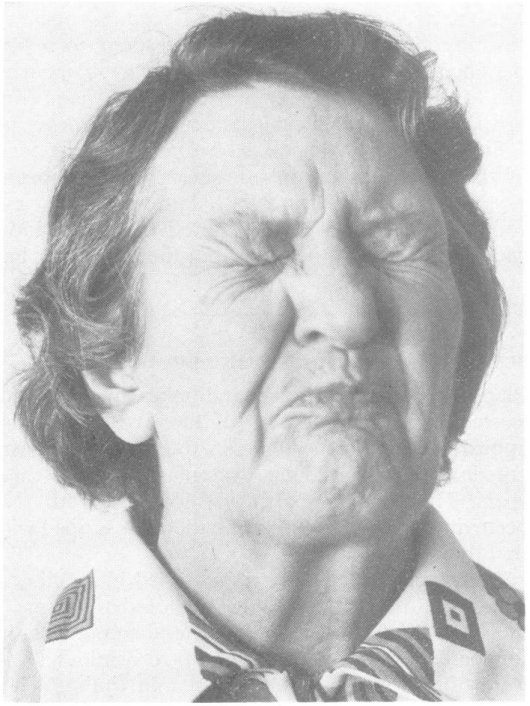


FIG. 2 *Blepharospasm and spasm of jaw closure and mouth-pursing in a 61 year old lady with symptoms for three years.*



FIG. 3 *Spasm of jaw opening and mouth retraction in a 65 year old lady with symptoms for four years.*

Laryngeal Dystonia

- **Abductor spasmodic dysphonia**
  - spasms of the posterior cricoarytenoid muscle
  - **breathy voice quality and voice breaks**.

- **Adductor spasmodic dysphonia** ,
  - sensation of **strangled speech or untimely breaks in speech.**
  - spasms of the laryngeal adductors - thyroarytenoid and lateral cricoarytenoid muscles.

Mixed spasmodic dysphonia contains components of both ADSD and ABSD, and therefore may include spasms of both laryngeal adductor and abductor muscles and can be difficult to treat.

- How to examine for Laryngeal Dystonia.MDCP 2024 https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14131

Non-motor symptoms in Dystonia

- **Pain**
- **Psychiatric disorders**
  - 64% vs. 28%, p = 0.001, Higher than age – matched population
  - Depression (32% vs. 14%)
  - Anxiety disorders (42% vs. 8%)
  - Substance abuse – in male/young with more anxiety and depression.

Table 3 NMS (non motor symptoms) burden as computed by the dystonia nonmotor symptoms questionnaire (DNMSQ) DNMSQ total score

	N	%
Low burden (0–4 points)	71	42.5
Medium burden (5–9 points)	59	35.3
High burden (10–14 points)	37	22.2

Table 4 The pattern and type of dystonia and non motor symptoms (NMS) burde

Type of dystonia	Numbers	Mean DNMSQ score ± SD	NMS burden
Cervical	123	6.14 ± 3.79	Medium
Cranial	37	4.54 ± 3.44	Medium
Cranio-cervical	7	9.28 ± 3.09	Medium to high

DNMSQ Dystonia nonmotor symptoms questionnaire

Nonmotor symptoms of craniocervical dystonia: a multicentre international study—using the Dystonia nonmotor symptoms questionnaire

Karolina Poplawska-Domaszewicz[1] · Sonja Boshnjak[2,3] · Carmen Martín de la Morena[2,4] · Carmen Rodriguez-Blazquez[5] · Krzysztof Sroka[1] · Robert Narożny[1] · Mubasher Qamar[2] · Lucia Batzu[2] · Vinay Goyal[8] · Vinod Metta[2,7] · K. Ray Chaudhuri[6,7] · Lisa Klingelhoefer[9,10]

Received: 16 June 2025 / Accepted: 6 November 2025 / Published online: 19 January 2026
© The Author(s) 2026

Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Development of the Comprehensive Cervical Dystonia Rating Scale: Methodology

Cynthia L. Comella, MD,[1,*] Susan H. Fox, MRCP, PhD,[2] Kailash P. Bhatia, FRCP,[3] Joel S. Perlmutter, MD,[4] Hyder A. Jinnah, MD, PhD,[5] Mateusz Zurowski, MD, MSc, FRCPC,[2] William M. McDonald, MD,[5] Laura Marsh, MD,[6] Ami R. Rosen, MS, CGL,[5] Tracy Waliczek,[1] Laura J. Wright, MA,[4] Wendy R. Galpern, MD, PhD,[7] Glenn T. Stebbins, PhD[1]

- **MOTOR**
  - TWSTRS2 (modified motor severity section of the TWSTRS)
- **PSYCHIATRIC**
  - Screening tool for psychiatric symptoms of CD (TWSTRS-Psych)
- **QUALITY OF LIFE**
  - CDIP-58:

DYSTONIA COALITION

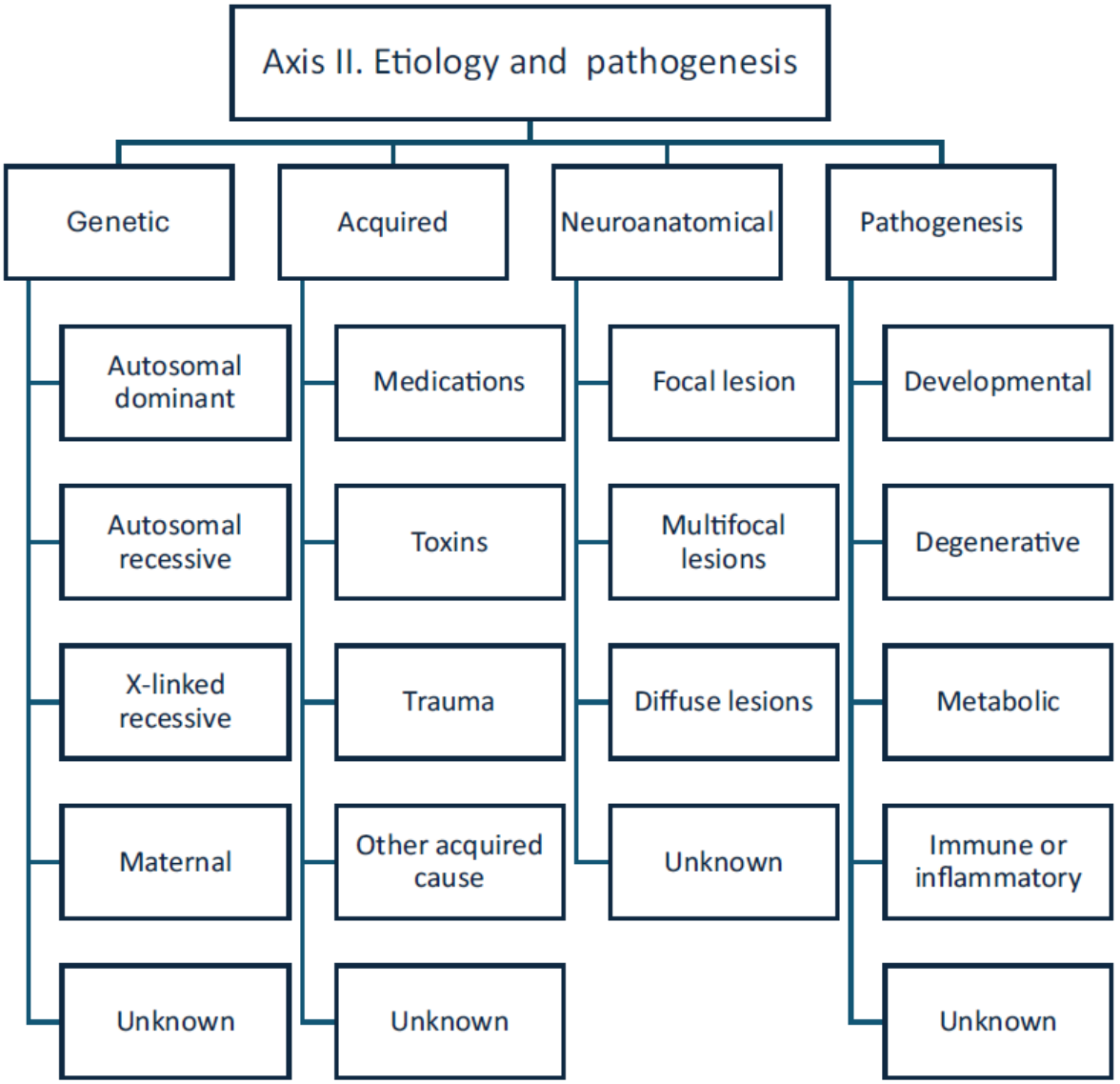
Classification of dystonia

1. **AXIS 1 Clinical characteristics:-**
   - **Age at onset,**
   - **Family History**
   - **Body distribution**
   - **Temporal dimension**
   - **Phenomenology**
   - **Associated features**

2. **AXIS II Aetiology:-**
   - **Genetic**
   - **Acquired**
   - **Neuroanatomical**
   - **Pathogenesis**

Albanese et al Mov Disord 2013/2025

Aetiology and pathogenesis



Genetic dystonia – Classified by Numbers

DYT1	Early-onset generalized torsion dystonia (TD)	AD	9q	GAG deletion in TOR1A
DYT2	Autosomal recessive TD	AR		HPCA (hippocalcin)
DYT3	X-linked dystonia parkinsonism; "Lubag"	XR	Xq	TAF1
DYT4	'Whispering dysphonia'	AD		TUBB4
DYT5a/14	Dopa-responsive dystonia (Segawa's disease)	AD	14q	GTP-cyclo-hydrolase I
DYT5b	Dopa-responsive	AR	11p	Tyrosine hydroxylase
DYT6	Adolescent-onset TD of mixed type	AD	8p	THAP1
DYT7	Adult-onset focal TD	AD	18p	unknown
DYT8	Paroxysmal nonkinesigenic dyskinesia	AD	2q	MR-1
DYT10	Paroxysmal kinesigenic dyskinesia	AD	16p-q	PRRT2
DYT11	Myoclonus-dystonia	AD	7q	*e*-Sarcoglycan
DYT12	Rapid-onset dystonia-parkinsonism	AD	19q	Na/K ATPase alpha 3
DYT13	Multifocal/segmental dystonia	AD	1p	unknown
DYT15	Myoclonus-dystonia	AD	18p	unknown
DYT16	Early-onset generalized dystonia	AR?	2q	PRKRA
DYT17	Recessive primary dystonia	AR	20pq	unknown
DYT9/18	Exertion-induced dyskinesia	AD	1p	SLC2A1 (Glut 1)
DYT19	Episodic kinesigenic dyskinesia 2	AD	16q	unknown
DYT20	Paroxysmal nonkinesigenic dyskinesia 2	AD	2q	unknown
DYT21	Pure torsion dystonia			
DYT23	Adult onset Cervical dystonia	AD	7	CIZ1
DYT24	Adult onset TD Craniocervical	AD		ANO3
DYT25	Adult onset TD Craniocervical	AD		GNAL
DTY26	Myoclonus dystonia	AD		KCTD17

Slide courtesy of Christine Klein

Genetic dystonia –Numbers continued…….

DYT27	Early onset isolated /focal dystonia	AR	COL6A3
DTY28	Early onset generalised dystonia (dysmorphic)	AD	KMT2B
DYT29	MEPAN syndrome (optic atrophy)	AR	MECR
DYT30	Early onset generalised	AD	VPS16
DYT31	Generalised dystonia	AR	AOPEP
DYT32	Adult onset	I case	VPS11
DYT33	Early onset Focal/Generalised	AR	EIF2AK2
DYT34	Myoclonus dystonia	AD	KCNN2
DYT35	Early onset (dopa responsive)	AR	SHQ1

MDSGene: Extending the List of Isolated **Dystonia** Genes by VPS16, EIF2AK2, and AOPEP .Thomsen et al Mov Disord. 2023.

Variants in ATP5F1B are associated with dominantly inherited **dystonia**. Nasca A et al Brain. 2023 early-onset isolated dystonia in two families, both with autosomal dominant mode of inheritance and incomplete penetrance.

NOTCH2NLC GGC Repeat Expansion Presenting as Adult-Onset Cervical **Dystonia**. Williams et al. Mov Disord Clin Pract. 2023

Genetics and Pathogenesis of Dystonia.Thomsen M, Lange LM, Zech M, Lohmann K.Annu Rev Pathol. 2024 Jan 24;19:99-131.

Genetic Dystonia – classified by phenotype

Updated with 21 new Dystonia genes and classified according to clinical features :-

1. **Isolated** Dystonia
2. **Combined:** Dystonia plus Parkinsonism/ataxia/myoclonus
3. **Complex** : eg Dystonia with Deafness/ With Developmental delay

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force – An Update

Lange, Marras et al Mov Disord 2022

Pathophysiology of Dystonia

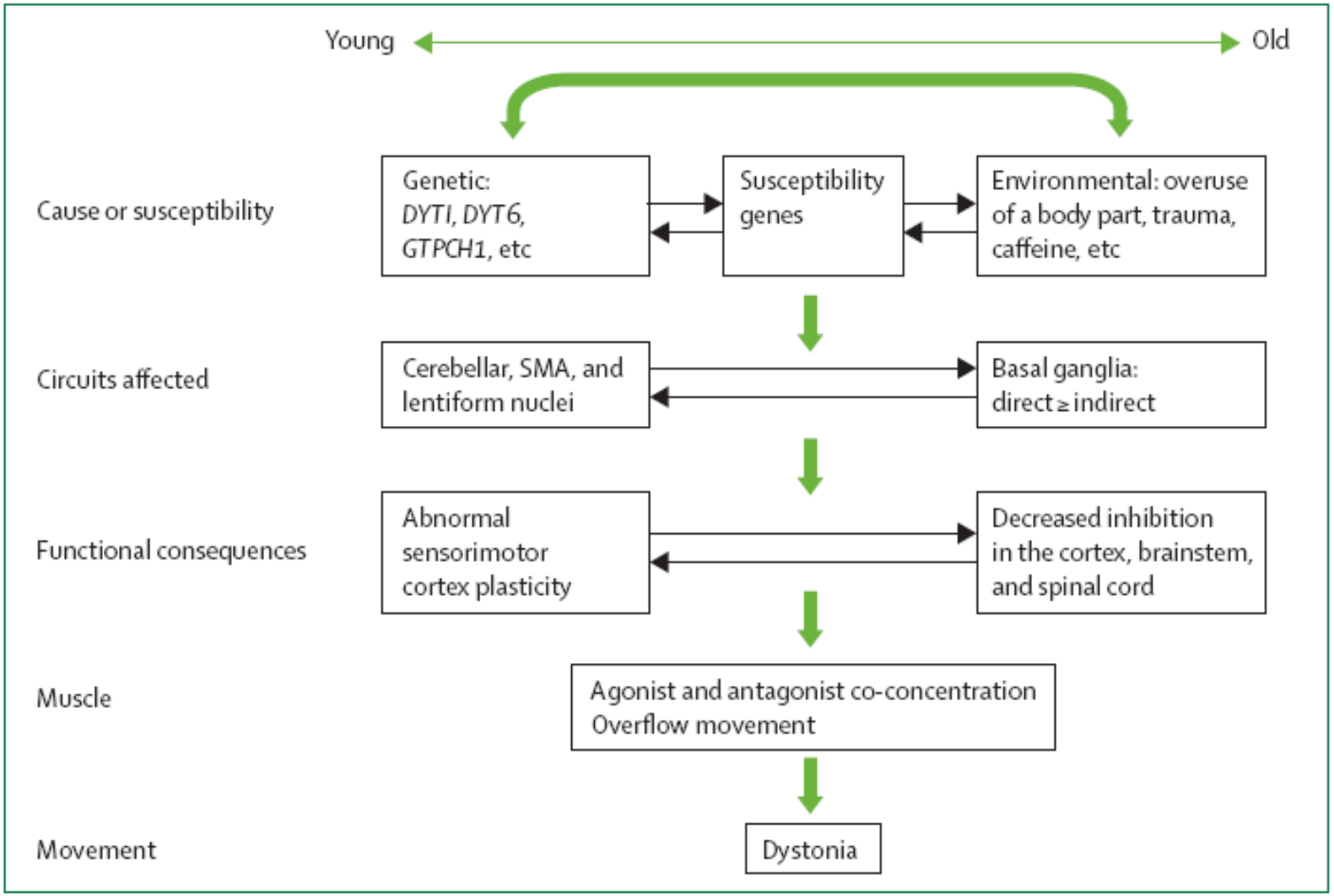


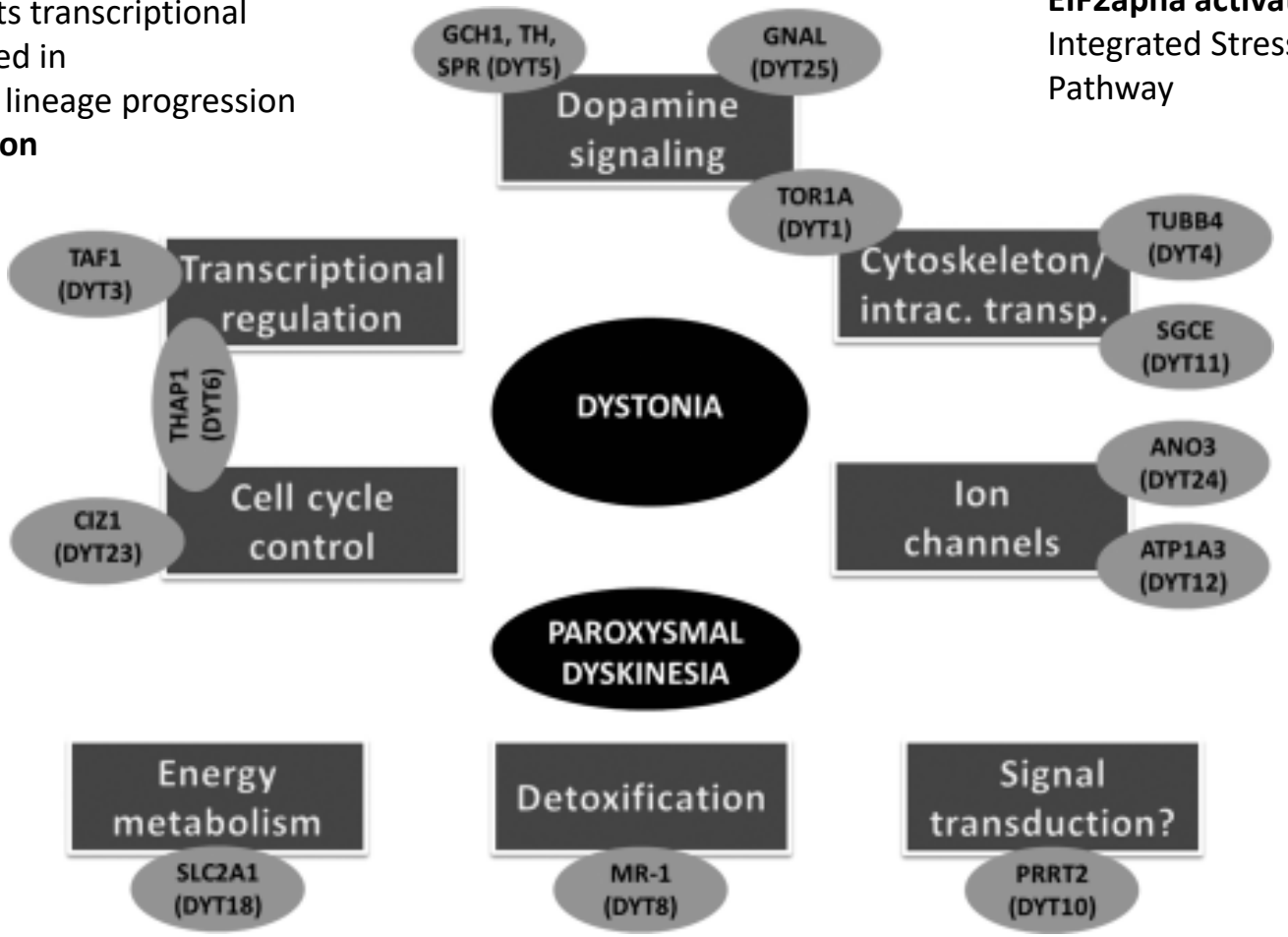
Figure: **Pathogenetic mechanisms in primary dystonia**
GTPCH1=GTP cyclohydrolase 1. SMA=supplementary motor area.

Phukan, Warner et al Lancet Neurol 2011

Genetics of Dystonia and Clues to Pathophysiology

THAP1 significantly reduced DNA binding of **YY1**, its transcriptional partner is involved in oligodendrocyte lineage progression = **hypomyelination**

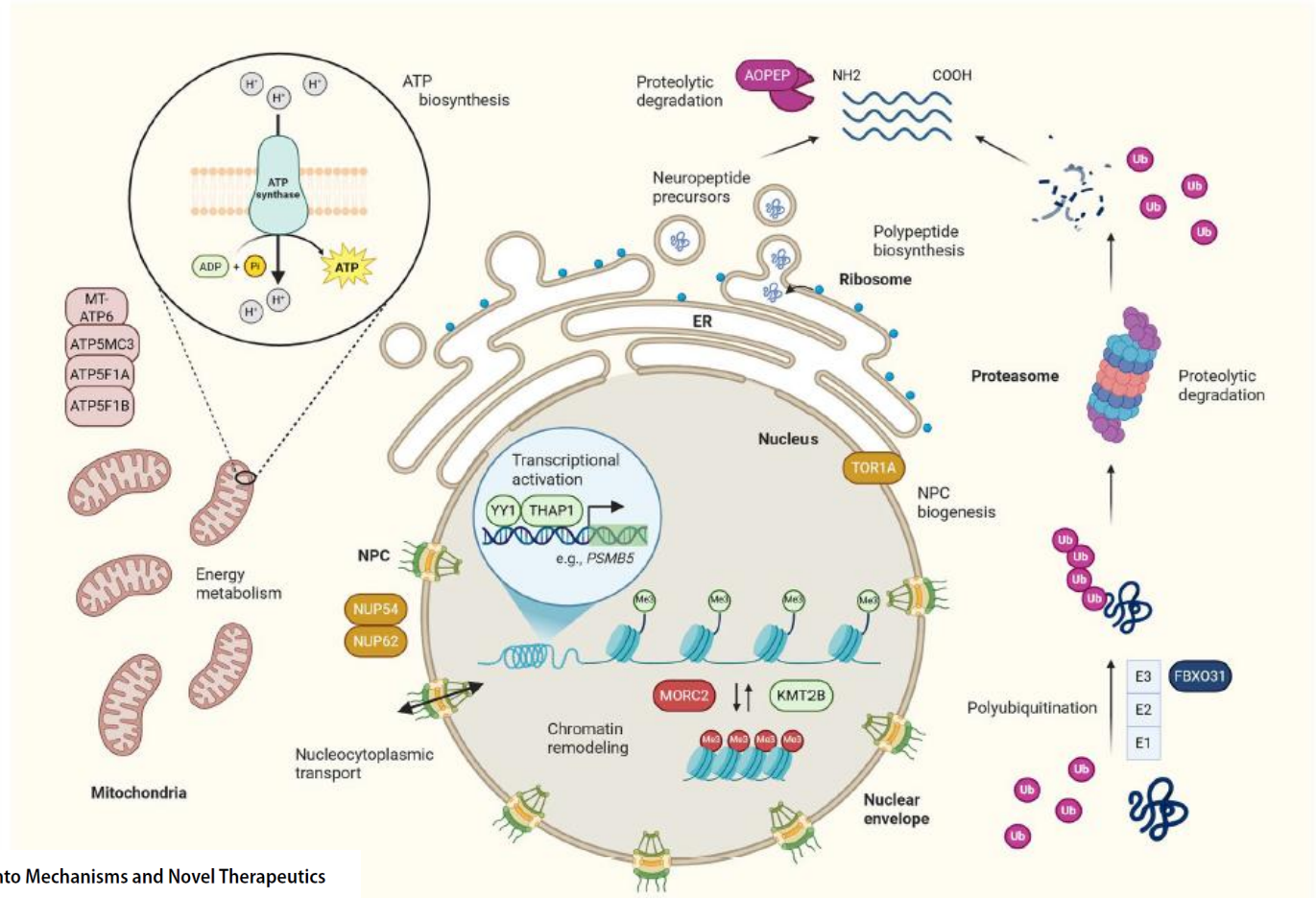
EIF2apha activation and Integrated Stressor Response Pathway



MSH3 and **PMS2** genes may be additional modifiers that delay age of onset.

Lohmann and Klein Mov Disord 2013
Laabs et al Nat Comm 2021
Thomsen et al Ann Rev Pathol 2024

Emerging molecular pathways underlying dystonia



Dystonia: Insights into Mechanisms and Novel Therapeutics

Ivana Dzinovic[1,2] · Michael Zech[1,2,3,4]

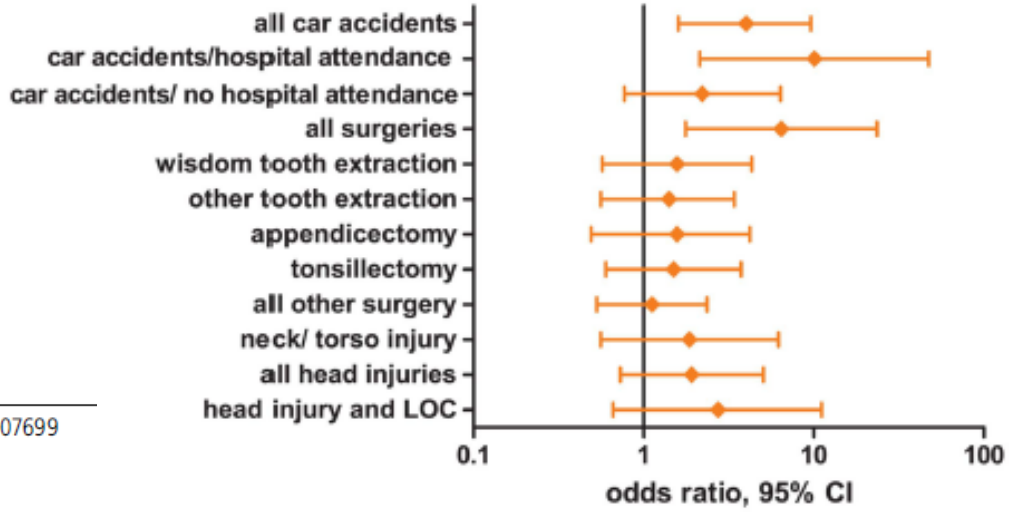
Environmental risk factors?

- Reduced penetrance (30-40%) of some DYT genes suggests a 'second-hit' theory
- Environmental factors –
  - Task-specific dystonia ('overuse')
  - Head injury? trauma? Smoking? Mood disorders?

An evaluation of the role of environmental factors in the disease penetrance of cervical dystonia

Anna Molloy,[1,2] Okka Kimmich,[1,2] Laura Williams,[1,2] John S Butler,[9] Niall Byrne,[1,2] Fiona Molloy,[3] Helena Moore,[4] Daniel G Healy,[5] Tim Lynch,[6] Mark J Edwards,[7] Cathal Walsh,[8] Richard B Reilly,[9] Sean O'Riordan,[1,2] Michael Hutchinson[1,2]

Molloy A, *et al. J Neurol Neurosurg Psychiatry* 2014;**0**:1–5. doi:10.1136/jnnp-2014-307699



No change in Prevalence over 40 years

- No change in prevalence of focal dystonias..from 1980s – 2020s
- What does that tell us about causes?
  - (Scrolling on your Phone isn't a risk factor..)

TABLE 3 *Dystonia prevalence per 100,000, sub analysis by time period of study publication*

Dystonia subtype	1985–2010	2010–2022	Heterogeneity and *P* value
Cervical dystonia	4.98, 95% CI = 3.58, 6.94 $I^2 = 34.5$ $Q = 12.2$	9.95, 95% CI = 3.51, 28.17 $I^2 = 4$, $Q = 6.3$	$Q = 1.5$, $P = 0.22$
Blepharospasm	4.24, 95% CI = 2.92, 6.18 $I^2 = 8.5$, $Q = 9.8$	2.82, 95% CI = 1.12, 7.12 $I^2 = 0$, $Q = 2.4$	$Q = 0.6$, $P = 0.42$
Laryngeal dystonia	1.54, 95% CI = 0.65, 3.61 $I^2 = 0$, $Q = 3.6$	0.40, 95% CI = 0.09, 1.83 $I^2 = 26$, $Q = 5.4$	$Q = 2.3$, $P = 0.13$
Upper limb dystonia	2.23, 95% CI = 1.31, 3.80 $I^2 = 0.9$, $Q = 6.1$	1.27, 95% CI = 0.36, 4.52 $I^2 = 0$, $Q = 5.0$	$Q = 0.6$, $P = 0.42$
Oromandibular dystonia	0.51, 95% CI = 0.17, 1.53 $I^2 = 0$, $Q = 4.2$	0.57, 95% CI = 0.15, 2.15 $I^2 = 0$, $Q = 4.8$	$Q = 0.01$, $P = 0.90$
All dystonia subtypes combined	16.42, 95% CI = 12.10, 22.31 $I^2 = 46.6$, $Q = 7.5$	30.85, 95% CI = 5.06, 187.74 $I^2 = 0$, $Q = 3.1$	$Q = 0.6$, $P = 0.46$

Medina et al The Prevalence of Idiopathic or Inherited Isolated Dystonia: A Systematic Review and Meta-Analysis. Mov Disord Clin Pract 2022

Hormonal factors?

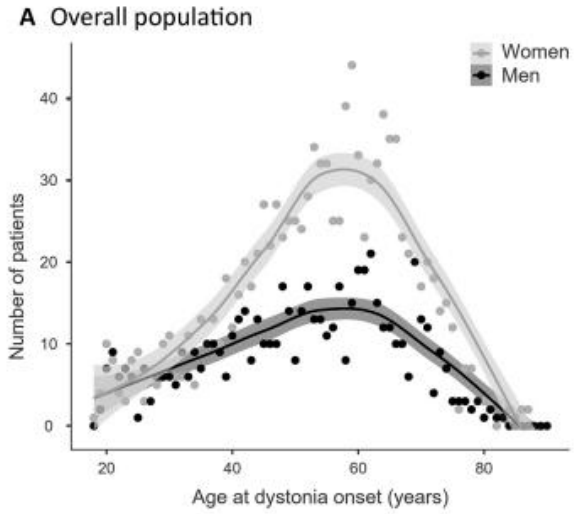
Women predominant

- blepharospasm
- oromandibular
- laryngeal

Men predominant

- task-specific upper limb dystonia

Kilic-Berkman et al
MDCP 2024
N = 3222 Dystonia Coalition
(adult onset focal dystonia) 71% F



1700 Italian registry; Velucci et al JNNP 2024

Is Dystonia an immune mediated disorder?

- Association of CD with multiple different blood-based immune measures ? abnormalities in cell-mediated immunity that may play a pathogenic role for a subgroup of individuals with CD.

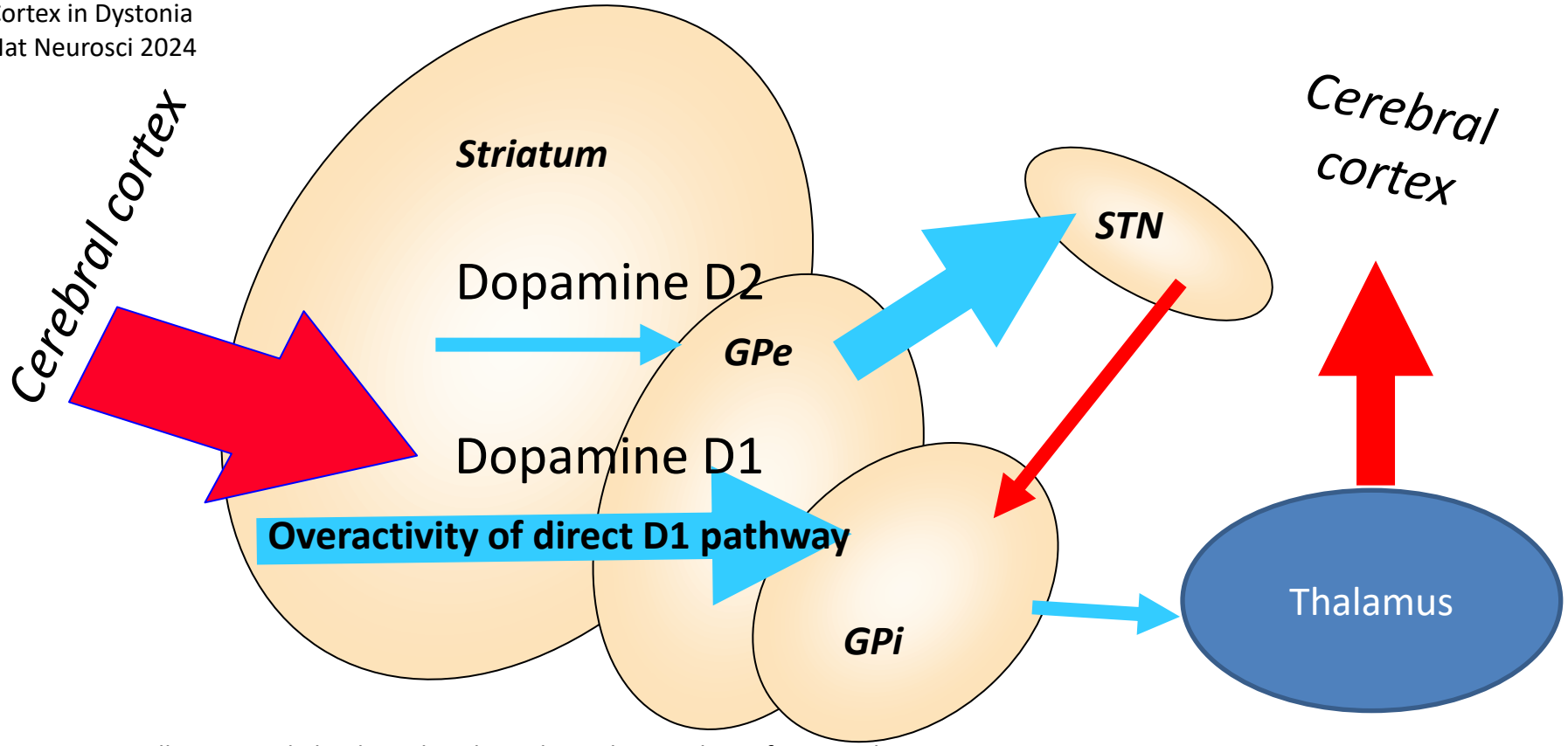
Exploration of potential immune mechanisms in cervical dystonia☆

Laura M. Scorr[a], Gamze Kilic-Berkmen[a], Diane J. Sutcliffe[a], Ashok R. Dinasarapu[b], J. Lucas McKay[a,c], Pritha Bagchi[d], Michael D. Powell[e], Jeremy M. Boss[e], Nezih Cereb[f], Marian Little[g], Loren Gragert[g], John Hanfelt[h], Andrew McKeon[i], William Tyor[a,j], H. A. Jinnah[a,b,*]

Park Rel Disord 2024

Classic Corticobasal thalamo-cortical Motor Circuitry of 'Hyperkinetic' Movements

Hollunder et al Primary Motor Cortex in Dystonia
Nat Neurosci 2024



Simonyan, K, Hallet M. et al The direct basal ganglia pathway is hyperfunctional in focal dystonia. Brain 2017:140, 3179–3190.
Lofredi et al Nature Communications 2024; 15:8475

overactive

underactive

GABA

Glutamate

Updates on basal ganglia circuitry in Dystonia?

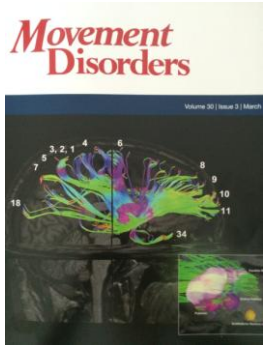
RESEARCH ARTICLE

Basal Ganglia Network by Constrained Spherical Deconvolution: A Possible Cortico-Pallidal Pathway?

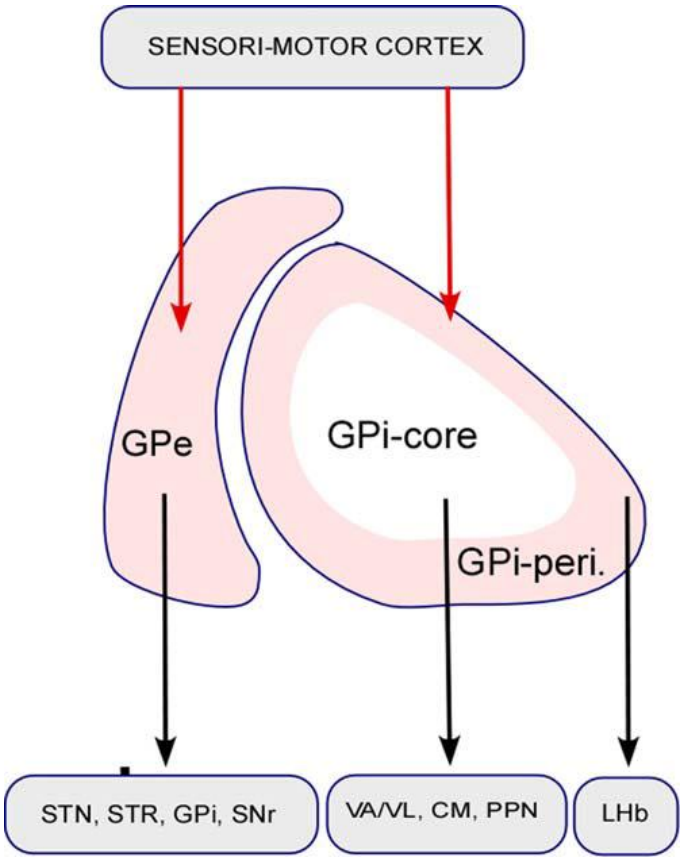
Demetrio Milardi, MD,[1,2] Michele Gaeta, MD,[1] Silvia Marino, MD,[2] Alessandro Arrigo, MD,[1] Gianluigi Vaccarino, MD,[1] Enricomaria Mormina, MD,[1] Giuseppina Rizzo, MD,[1] Carmelo Milazzo, BPhys,[1] Giovanni Finocchio, BPhys,[4] Annalisa Baglieri, MSc,[2] Giuseppe Anastasi, MD,[1] and Angelo Quartarone, MD[3]*

[1]*Department of Biomedical Sciences and Morphological and Functional Images, University of Messina, Italy*
[2]*IRCCS Centro Neurolesi Bonino Pulejo, Messina, Italy*
[3]*Department of Neurosciences, University of Messina, Italy*
[4]*Department of Electronic Engineering, Chemistry e Industrial Engineering, University of Messina, Italy*

Second 'hyperdirect glutamatergic pathway between prefrontal and sensorimotor cortex and globus pallidus in humans

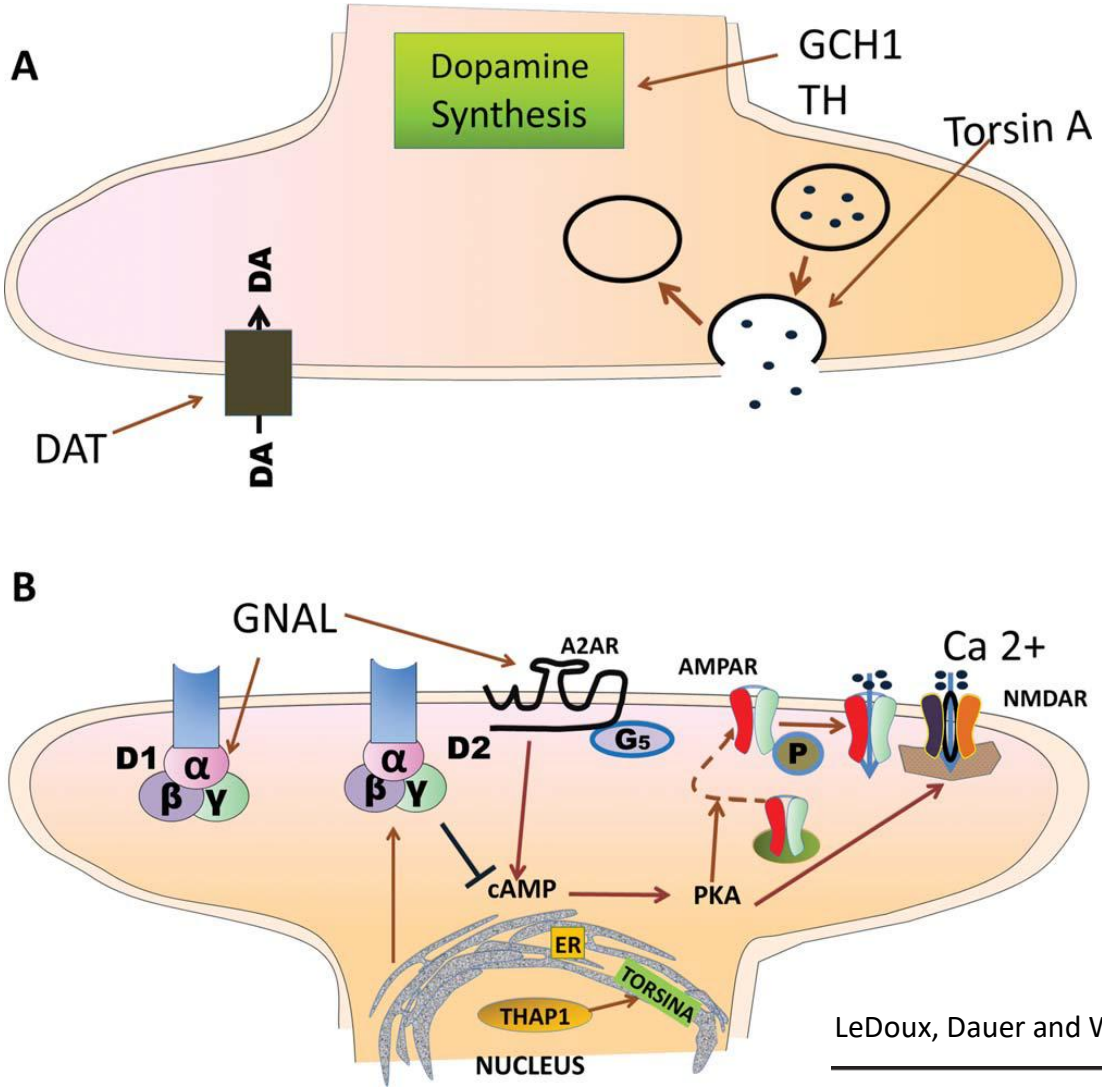


Hollunder et al Nat Neurosci 2024



Smith and Wichmann, 2015;

Genetic dystonias – links to dopamine neurotransmission in basal ganglia



DYT5/14 DRD GCH1, TH deficiency
DYT1 ; decreased striatal DA release

DYT 25 GNAL +/-mice.
Adenosine A2AR/dopamine D2 signaling altered resulting in loss of dopamine D2R function
Atiallah..Pisani et al Neurobiol Dis 2024

LeDoux, Dauer and Warner

Movement Disorders, Vol. 28, No. 7, 2013

Dopamine in dystonia

Role of dopamine in isolated dystonia is still unclear

- Low D2 /impaired turnover/transport??
- Spatial re-organisation of putaminal dopamine D2 receptors in cranial and hand dystonia (Black et al 2014)

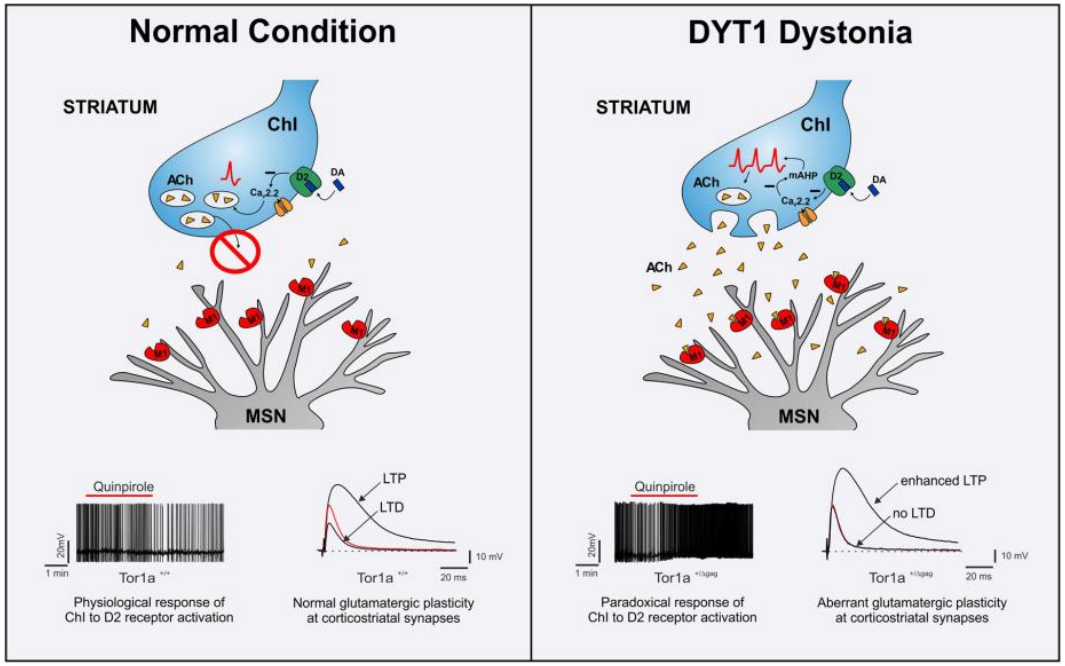
Acetylcholine in Dystonia

- Anticholinergics (muscarinic) drugs remain most effective oral agents for dystonia.

- Mechanism of action?

Cholinergic dysfunction in dystonia

- **“Hyper cholinergic” state in dystonia?**



- Over activation of M1 receptors on MSNs increases excitation of MSN and causes loss of LTD = ***perseveration of unwanted sensorimotor learning*** may occur, one of the hallmark pathophysiological findings in dystonia

Maltese et al. Mov Disord 2014; Eskow Jaunarajs et al. *Prog Neurobiol*. 2015; Ribot et al Brain 2025; Lagerweij et al Neurobiol Dis 2026

The Basal Ganglia in Dystonia

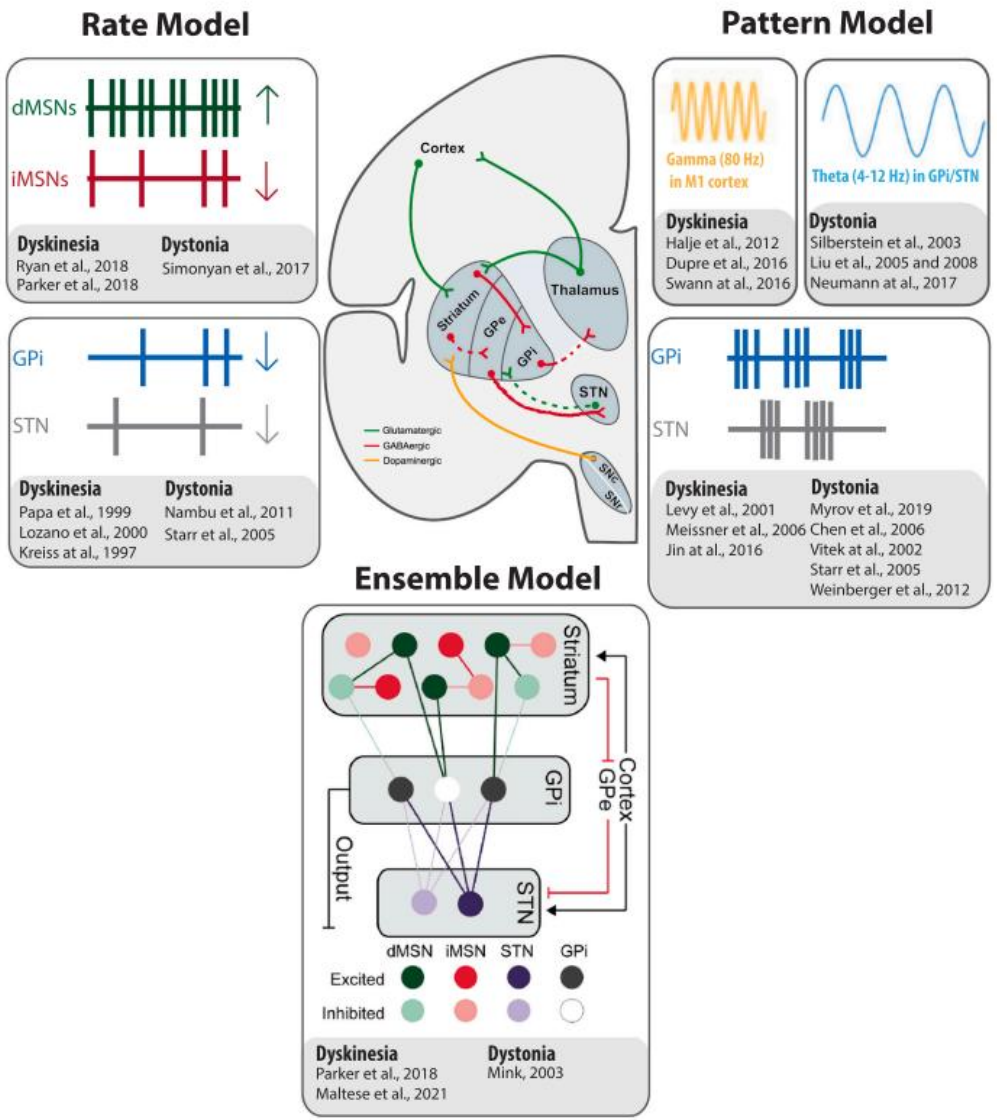
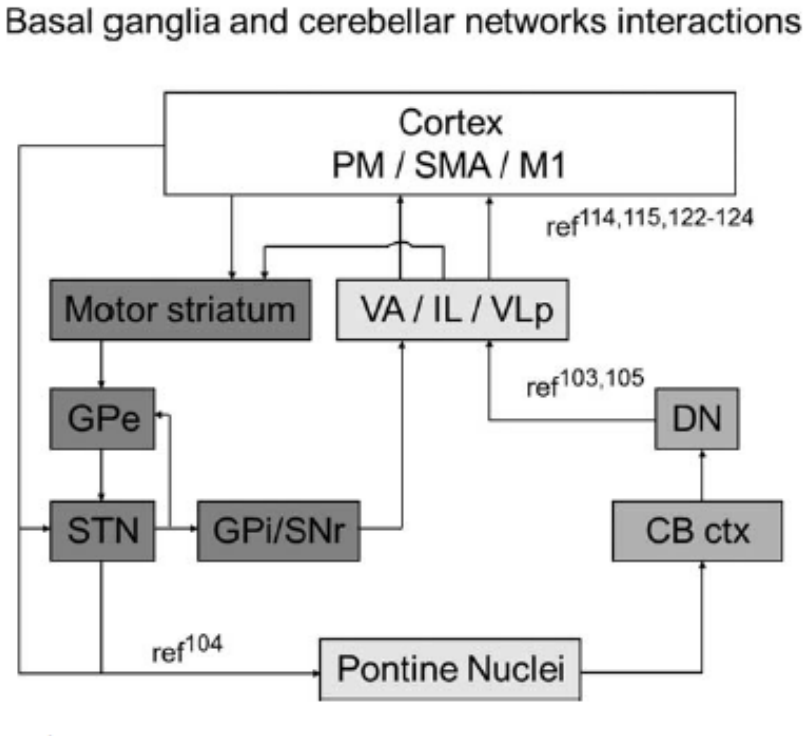


Fig. 1. Summary of network models of basal ganglia function and relevant literature in dyskinesia and dystonia. In the center an illustration of the anatomy of the basal ganglia circuitry simplies basal ganglia connectivity, highlighting the role of striatal direct and indirect pathways on motor output in hyperkinetic conditions (modied from Madeo and Pisani, 2017). According to the classical rate model (top left), hyperactivity of dMSNs and/or hypoactivity of iMSNs lead to reduced GPi and STN outputs, disinhibition of the thalamus and cortex, and involuntary movements. The pattern models (top right) adds the notion that, not only increased or decreased activity, but changes in activity pattern and neural oscillation may underlie network dysfunction. The ensemble model (bottom) builds upon the center-surround model of the basal ganglia rst proposed by Mink, which highlights the complementary function of dMSNs and iMSNs in movement initiation and action selection (modied from McGregor and Nelson, 2019). Simultaneous activation of striatal dMSNs and iMSNs focally inhibits GPi and GPe, releasing downstream inhibition and permitting action selection.

Structural and functional abnormalities of cerebellar function linked to dystonia



Lehericy et al Mov Disord 2013

Cerebellum rapidly modulates the activity of the striatum via a di-synaptic pathway from dentate gyrus to centrolateral thalamic nucleus

(using optogenetics in RDP mouse model) Chen et al Nat Neurosci 2014

Cerebellar pathways may be implicated in tremor in dystonia

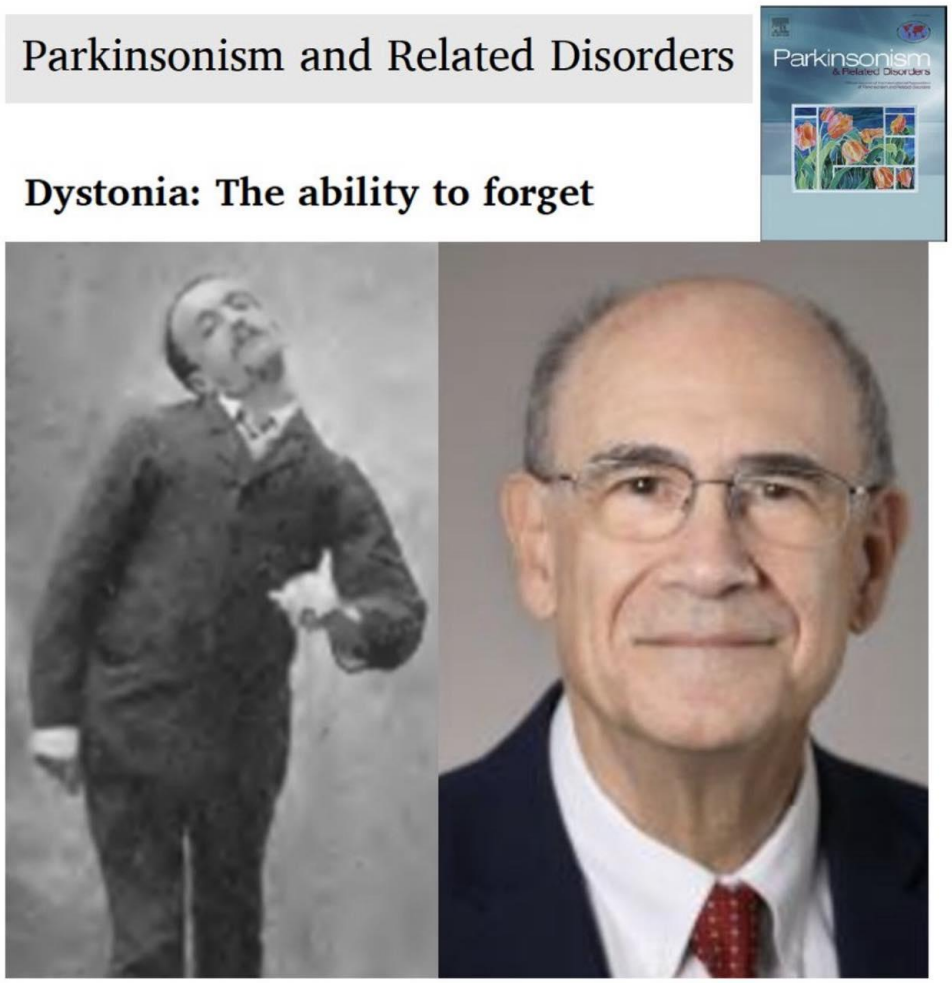
- Reviewed in Morigaki et al 2021

Sensorimotor integration and plasticity

1. Abnormal sensorimotor integration,
2. Loss of inhibitory control on several levels of the central nervous system
3. Changes in synaptic plasticity.

Chen et al Clin Neurophys 2022
Conte et al Nat Rev Neurol. 2019
Shukla and Vaillancourt Curr Neurol Neurosci rep 2014
Wang et al Mov Disord 2025

Neuroplasticity and Dystonia



"Forgetting pathways' may be impaired, and thus the memories are locked in"

Hallet M.Park Rel Disord August 2025

Picture courtesy of @Michael Okun

Dystonia can be mediated via Spinal Pathways Doesn't need a Brain??

- Mouse model of DYT1-TOR1A
  - confined Tor1a deletion to spinal cord and dorsal root ganglion (DRG) neurons ie not in the brain
- Phenotype= generalized dystonia
- Loss of Torsin A in spine
- Reduce mono-synaptic reflex

Pocrascky et al Sci Transl Med 2023

Dystonia Funding Opportunities

Dystonia Coalition



Dystonia Medical Research Foundation



Reading

- Definition and Classification of Dystonia Albanese et al Mov Disord 2025
- Dystonia. Balint B, et al Nat Rev Dis Primers. 2018;4:25
- Dystonia. Sadnika et al BMJ 2022;377
- Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force – An Update. Lange et al Mov Disord 2022
- Clinical features, pathophysiology, treatment, and controversies of tremor in dystonia. Panyakaew et al J Neurol Sci 2022
- Challenges in Describing Tremor and Dystonia. Shaikh et al Neurology 2025
- Striatal Synaptic Dysfunction in Dystonia and Levodopa-Induced Dyskinesia. Scarduzio et al Neuro Biol Dis 2022
- The Dystonias. Stephen CD. Continuum (Minneap Minn). 2022 Oct
- Emerging and converging molecular mechanisms in dystonia. Gonzalez-Latapi P et al J Neural Transm 2021
- Striato-pallidal oscillatory connectivity correlates with symptom severity in dystonia patients. Lofredi et al Nat Comms 2024
- Diagnosis and pathogenesis of dystonia: clinical heterogeneity, shared mechanisms, and neurodevelopmental origins Roze et al Lancet Neurol 2026
- Neurobiology of Dystonia: Review of Genetics, Animal Models, and Neuroimaging. Rissardo JP et al Brain Sci 2025
- More than a Movement Disorder: Non-Motor Features and Future Directions in Dystonia Research Rampes S, Batla A, Brain Sci 2025
- The Second Hit Hypothesis in Animal and Human Dystonia: The Role of Peripheral Nerve Trauma and Spinal Cord Injury. Harder-Rauschenberger, and Wang Ip. Mov Disord 2025