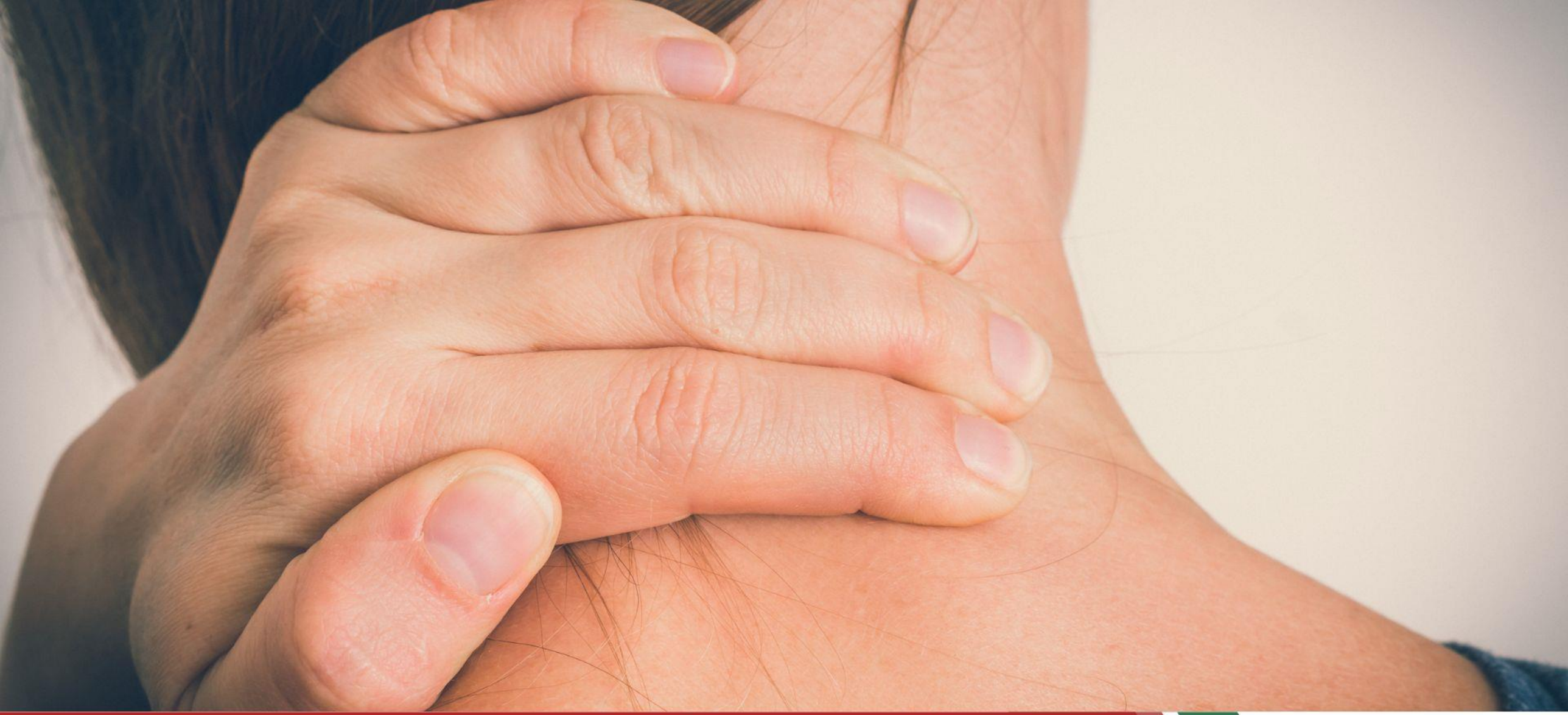


Dystonia: Bridging Theory and Hands-On Expertise

September 5-6, 2025 | Istanbul, Turkey

International Parkinson and Movement Disorder Society European Section

T.C. İSTANBUL ÜNİVERSİTESİ 1453

Mechanisms of dystonia: Neurochemical and circuit abnormalities

Antonio Pisani

University of Pavia, IRCCS Mondino Foundation, Italy

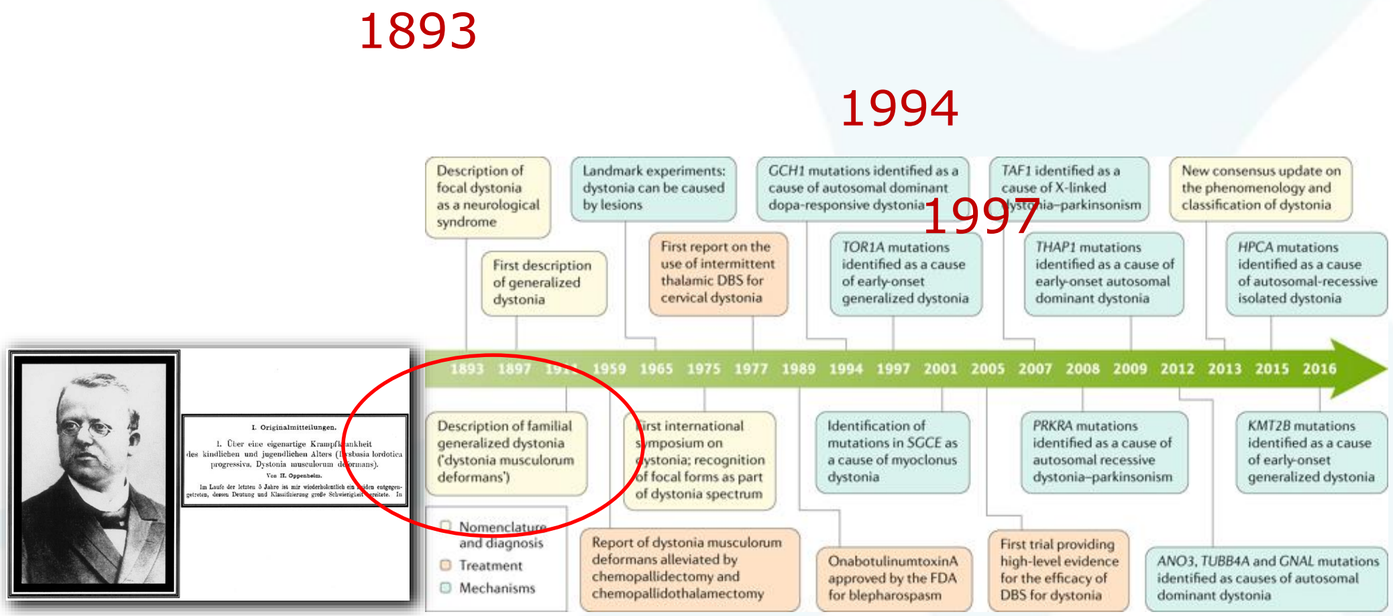
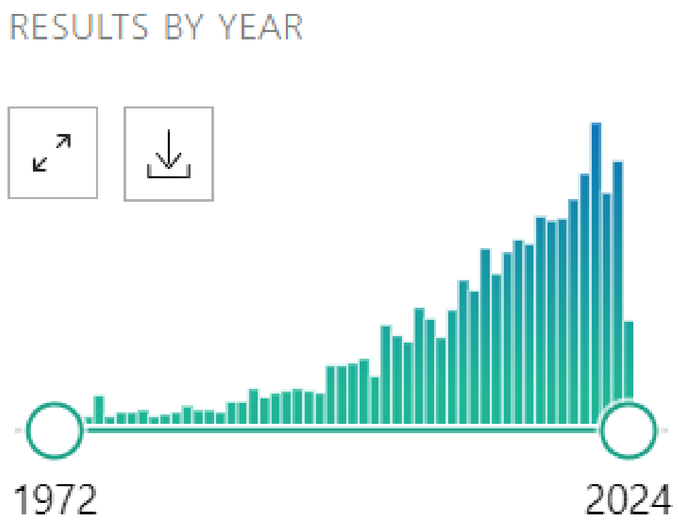


Fig. 1: History of dystonia.

Balint, B., et al. (2018) Dystonia
Nat. Rev. Dis. Primers doi:10.1038/s41572-018-0023-6



Number of publications on dystonia models

2013

REVIEW

CME

Phenomenology and Classification of Dystonia: A Consensus Update

Alberto Albanese, MD,[1,2*] Kailash Bhatia, MD, FRCP,[3] Susan B. Bressman, MD,[4] Mahlon R. DeLong, MD,[5] Stanley Fahn, MD,[6] Victor S.C. Fung, PhD, FRACP,[7] Mark Hallett, MD,[8] Joseph Jankovic, MD,[9] Hyder A. Jinnah, PhD,[10] Christine Klein, MD,[11] Anthony E. Lang, MD,[12] Jonathan W. Mink, MD, PhD,[13] Jan K. Teller, PhD[14]

Journal of Neural Transmission (2021) 128:395–404
https://doi.org/10.1007/s00702-021-02314-2

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Check for updates

Dystonia updates: definition, nomenclature, clinical classification,

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]

2022

Current Neurology and Neuroscience Reports (2021) 21: 8
https://doi.org/10.1007/s11910-021-01095-1

MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Check for updates

Genetic Dystonias: Update on Classification and New Genetic Discoveries

Ignacio Juan Keller Sarmiento[1] · Niccolò Emanuele Mencacci[1]

Accepted: 13 January 2021 / Published online: 9 February 2021

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

Lara M. Lange, MD,[1] Paulina Gonzalez-Latapi, MD, MSc,[2,3] Rajasumi Rajalingam, MD,[2] Marina A.J. Tijssen, MD, PhD,[4] Darius Ebrahimi-Fakhari, MD, PhD,[5,6] Carolin Gabbert, MSc,[1] Christos Ganos, MD,[7] Rhia Ghosh, MD,[8] Kishore R. Kumar, MBBS, PhD, FRACP,[9,10] Anthony E. Lang, MD,[2] Malco Rossi, MD, PhD,[11] Sterre van der Veen, MD,[4] Bart van de Warrenburg, MD, PhD,[12] Tom Warner, MD, PhD,[13] Katja Lohmann, PhD,[1#] Christine Klein, MD,[1#*] Connie Marras, MD, PhD,[2#*] and
on behalf of the Task Force on Genetic Nomenclature in Movement Disorders

Dystonia: fundamental commonalities

1. Pathologically, there is no clear evidence for neural **degeneration** in the few human post-mortem cases of “isolated” dystonia.

2. The lack of a gross pathological correlate also supports the theory that dystonia is a functional disease of **common alterations in neurochemistry, wiring, or physiology.**

3. Experimental models revealed a number of shared biological pathways among dystonia-linked genes

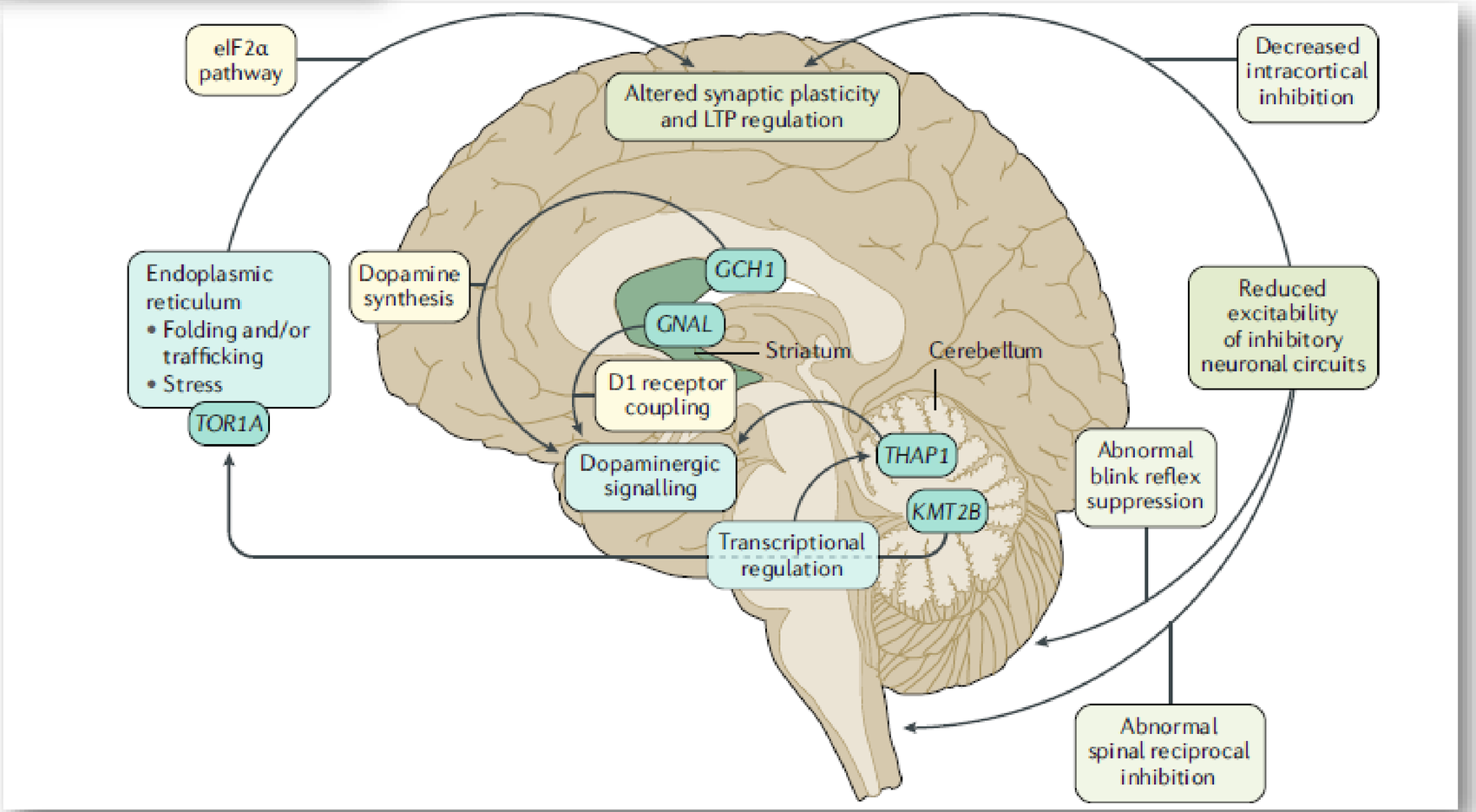
NATURE REVIEWS | DISEASE PRIMERS |

PRIMER

Dystonia

*Bettina Balint[1,2], Niccolò E. Mencacci[3], Enza Maria Valente[4,5], Antonio Pisani[5,6], John Rothwell[1], Joseph Jankovic[7], Marie Vidailhet[8] and Kailash P. Bhatia[1]**

alterations in neurochemistry, wiring, or physiology



While our knowledge on the genetic basis of monogenic dystonias has enormously grown, their clinical borders are becoming increasingly elusive

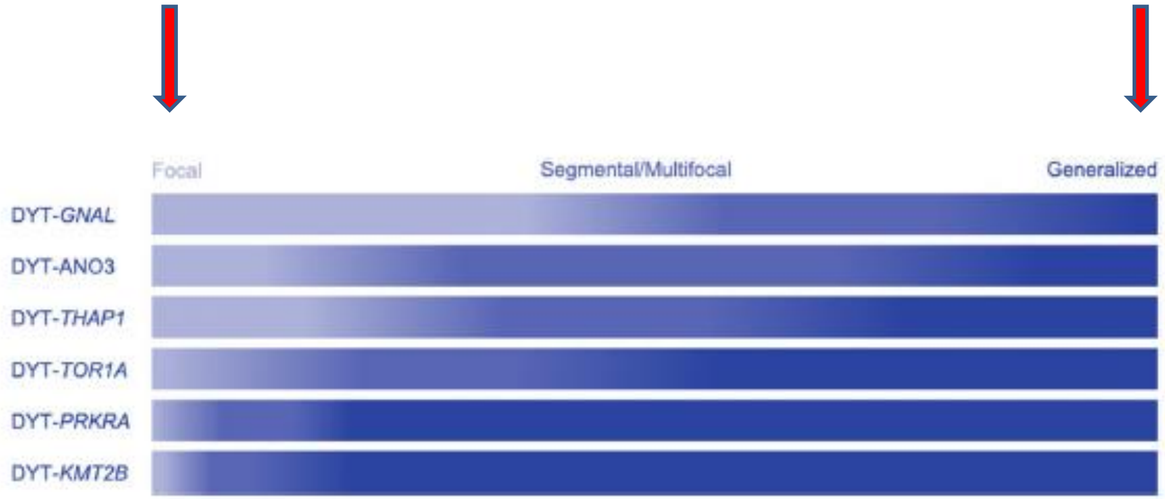
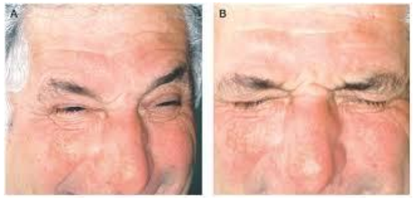
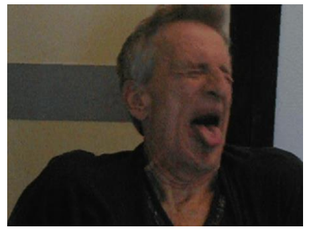


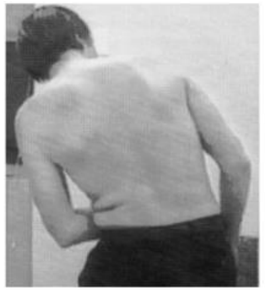
Fig. 5 Body distribution with respect to genetic background. Different shades of blue indicate the different clinical presentations with darker tones relating to more severe presentations. The fractions are in accordance with the numbers reported by Lange et al. (2021)

Klein, Journal of Neural Transmission (2021) 128:395–404

Heterogeneity of phenotypes







2022

The apparent paradox of phenotypic diversity and shared mechanisms across dystonia syndromes

Alessio Di Fonzo[a], *Alberto Albanese*[b], *and Hyder A. Jinnah*[c]

KEY POINTS

- New genetic discoveries reveal common mechanisms underlying the pathogenesis of dystonia.
- Endolysosomal trafficking defect is emerging as a new pathogenetic mechanism in dystonia.
- Dystonia genes interaction with environmental factors account for clinical heterogeneity.

- **Dopamine** – neurochemistry- plasticity
- Gene transcription
- Quality control machinery- trafficking
- Environmental stressors

Rabbits treated with **reserpine** (upper panel) and after DL-Dopa (lower panel) in an experiment by Carlsson, Lindqvist, Magnusson, demonstrating **the relevance of dopamine** in movement

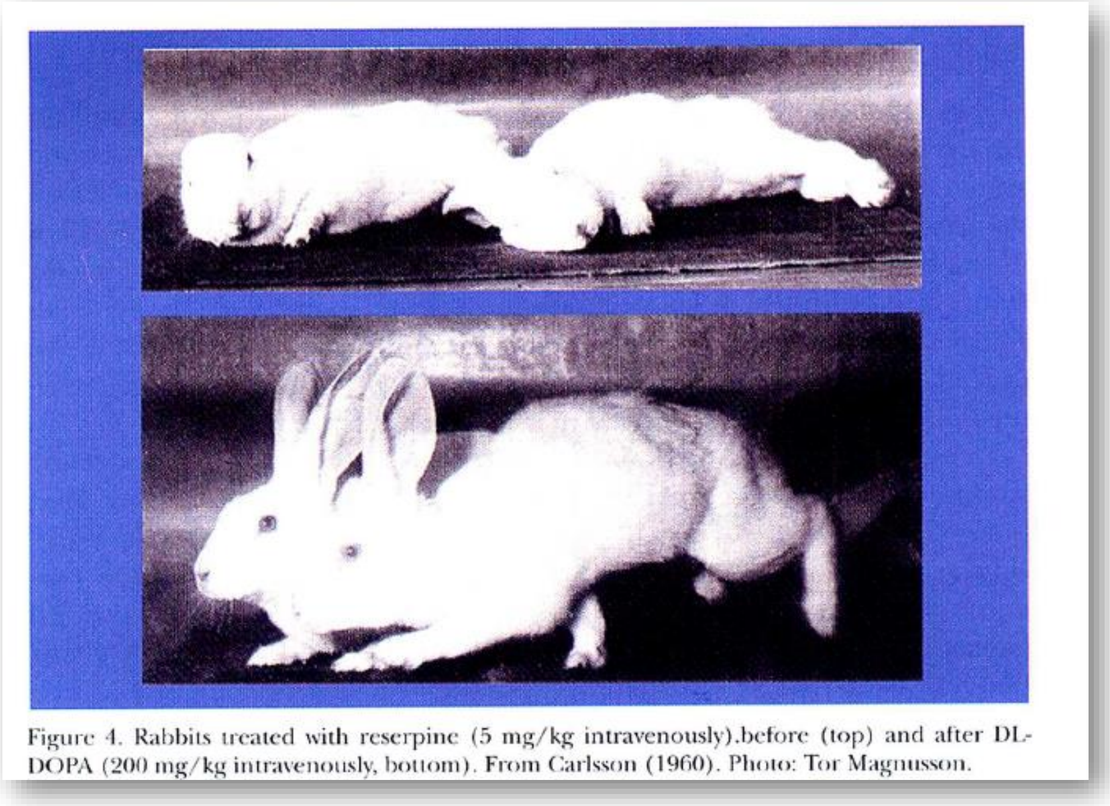


Figure 4. Rabbits treated with reserpine (5 mg/kg intravenously).before (top) and after DL-DOPA (200 mg/kg intravenously, bottom). From Carlsson (1960). Photo: Tor Magnusson.

*From: Lecture of **Arvid Carlsson, Nobel Prize for Medicine and Physiology,** Stockholm 8 december 2000*

Dopamine, striatum and dystonia

- Dopa-responsive dystonia (high phenotypic variability)
- Dystonia in early-onset PD and in low dopaminergic states (off-PD)
- Dystonia caused by dopamine D2 receptor antagonists
- The role of dopamine emerges also in focal forms of dystonia, i.e cervical dystonia (*Walsh et al J Neurol 2009; Simonyan et al., 2013*)

Dopamine and focal dystonia

Brain Advance Access published October 21, 2013
doi:10.1093/brain/awt282 Brain 2013: Page 1
BRAIN
A JOURNAL OF NEUROLOGY

Striatal dopaminergic dysfunction at rest and during task performance in writer's cramp

Brian D. Berman,[1,2] Mark Hallett,[2] Peter Herscovitch[3] and Kristina Simonyan[4]

doi:10.1093/brain/awx263 BRAIN 2017: 140; 3179–3190 | 3179
BRAIN
A JOURNAL OF NEUROLOGY

The direct basal ganglia pathway is hyperfunctional in focal dystonia

Kristina Simonyan,[1,2] Hyun Cho,[3] Azadeh Hamzehei Sichani,[1] Estee Rubien-Thomas[2] and Mark Hallett[3]

J Neurol (2009) 256:1307–1313
DOI 10.1007/s00415-009-5119-1
ORIGINAL COMMUNICATION

Striatal morphology correlates with sensory abnormalities in unaffected relatives of cervical dystonia patients

Richard A. Walsh · Robert Whelan · John O'Dwyer · Sean O'Riordan · Siobhan Hutchinson · Risteard O'Laoide · Kevin Malone · Richard Reilly · Michael Hutchinson

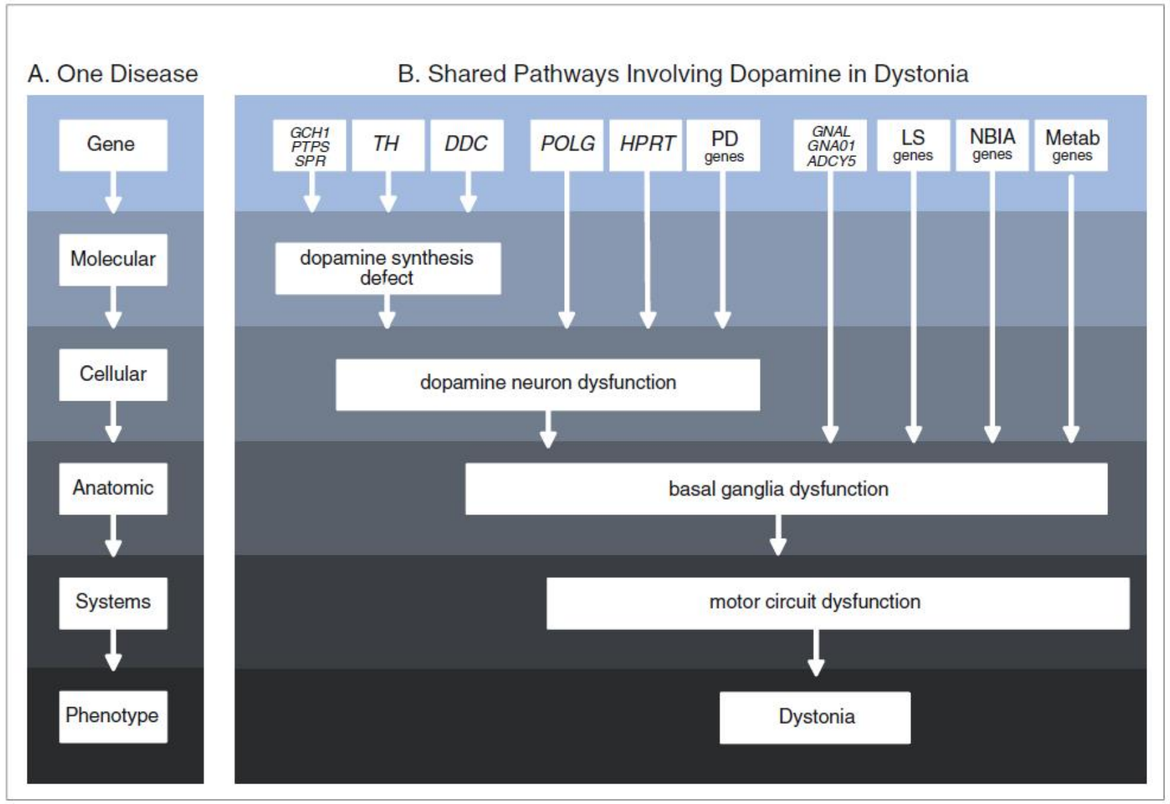
The Journal of Neuroscience, September 11, 2013 • 33(37):14705–14714 • 14705
Neurobiology of Disease

Abnormal Striatal Dopaminergic Neurotransmission during Rest and Task Production in Spasmodic Dysphonia

Kristina Simonyan,[1] Brian D. Berman,[2,3] Peter Herscovitch,[4] and Mark Hallett[2]

Dopamine, striatum and pathways

H.A. Jinnah and Y.V. Sun
Neurobiology of Disease 129 (2019) 159–168



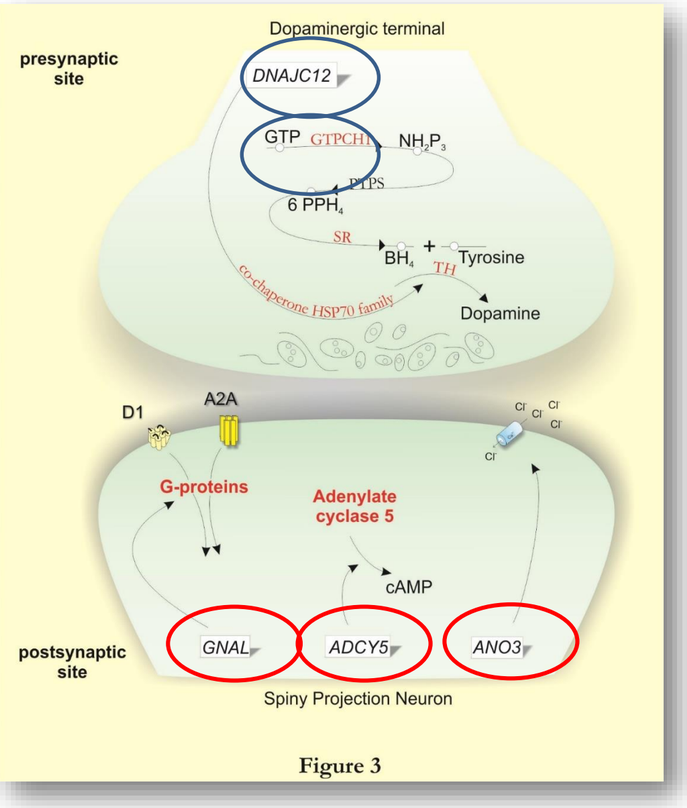


Figure 3

Multiple mutations causing dystonia converge to affect striatal signaling and signal transduction pathways similarly.
Many of them involved in dopamine signaling

Dopamine: shared pathways

- Shared dopamine i) "***expected***" and ii) "***unexpected***" pathways

- pathways includei) Synaptic function, regulation of plasticity, transmitter release and machinery

ii) Changes in the endoplasmic reticulum or nuclear envelope, responsivity to intracellular stress, abnormalities of cell cycling, eIF2α signaling, and others (*Bragg et al., 2011; Gonzalez-Alegre, 2019; LeDoux et al., 2013; Nibbeling et al., 2017; Rittiner et al., 2016; Weisheit et al., 2018, Indelicato et al., 2024*).

Many of the shared pathways are not mutually exclusive. Links between dopamine signaling, mitochondrial function, maintenance of intracellular homeostasis have been established

Movement Disorders, Vol. 37, No. 2, 2022

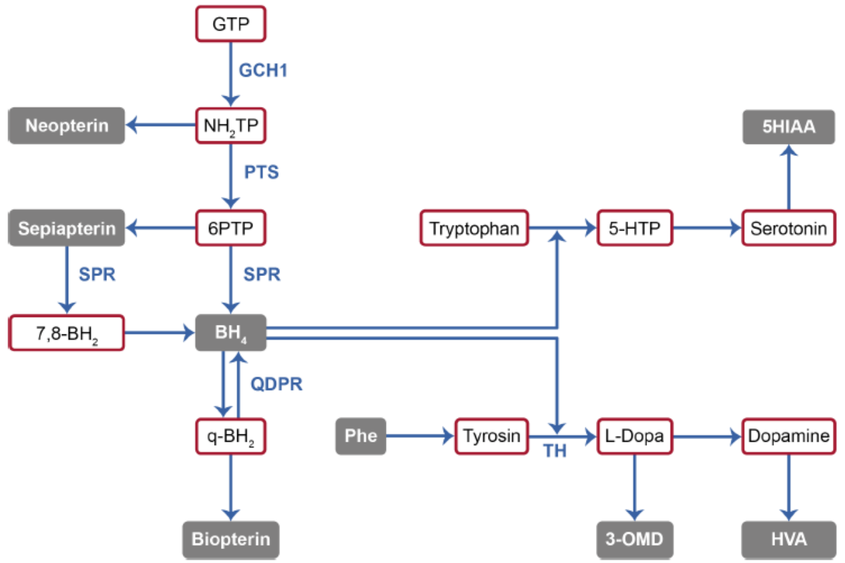
REVIEW

Relationship of Genotype, Phenotype, and Treatment in Dopa-Responsive Dystonia: MDSGene Review

Anne Weissbach, MD,[1,2*] Martje G. Pauly, MD,[1,2,3] Rebecca Herzog, MD,[2,3] Lisa Hahn, MD,[1,2]
Sara Halmans, MSc,[2] Feline Hamami, MSc,[2] Christina Bolte, MSc,[2] Sarah Camargos, MD,[4] Beomseok Jeon, MD,[5]
Manju A. Kurian, PhD,[6] Thomas Opladen, MD,[7] Norbert Brüggemann, MD,[1,3] Hans-Jürgen Huppertz, MD,[8]
Inke R. König, PhD,[9] Christine Klein, MD,[1] and Katja Lohmann, PhD[1]

- Pathogenic variants in the guanosine triphosphate cyclohydrolase-1 (**GCH1**) gene are the most frequent causes of monogenic DRD, with the autosomal dominant form with heterozygous variants being the most common subgroup.
- In addition, recessive/biallelic mutations in GCH1 as well as in four other genes (tyrosine hydroxylase **[TH**], tetrahydrobiopterin synthase [**PTS**], sepiapterin reductase [**SPR**]and quinoid dihydropteridine reductase [**QDPR**] have been frequently associated with monogenic DRD.

2. Supplementary Figures

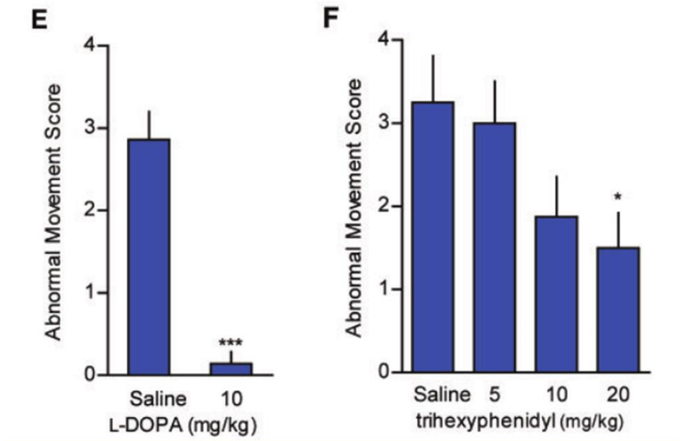


DRD model:
Levodopa and anticholinergics rescue motor abnormalities

doi:10.1093/brain/aww212 BRAIN 2015: 138; 2987–3002 | 2987
BRAIN
A JOURNAL OF NEUROLOGY

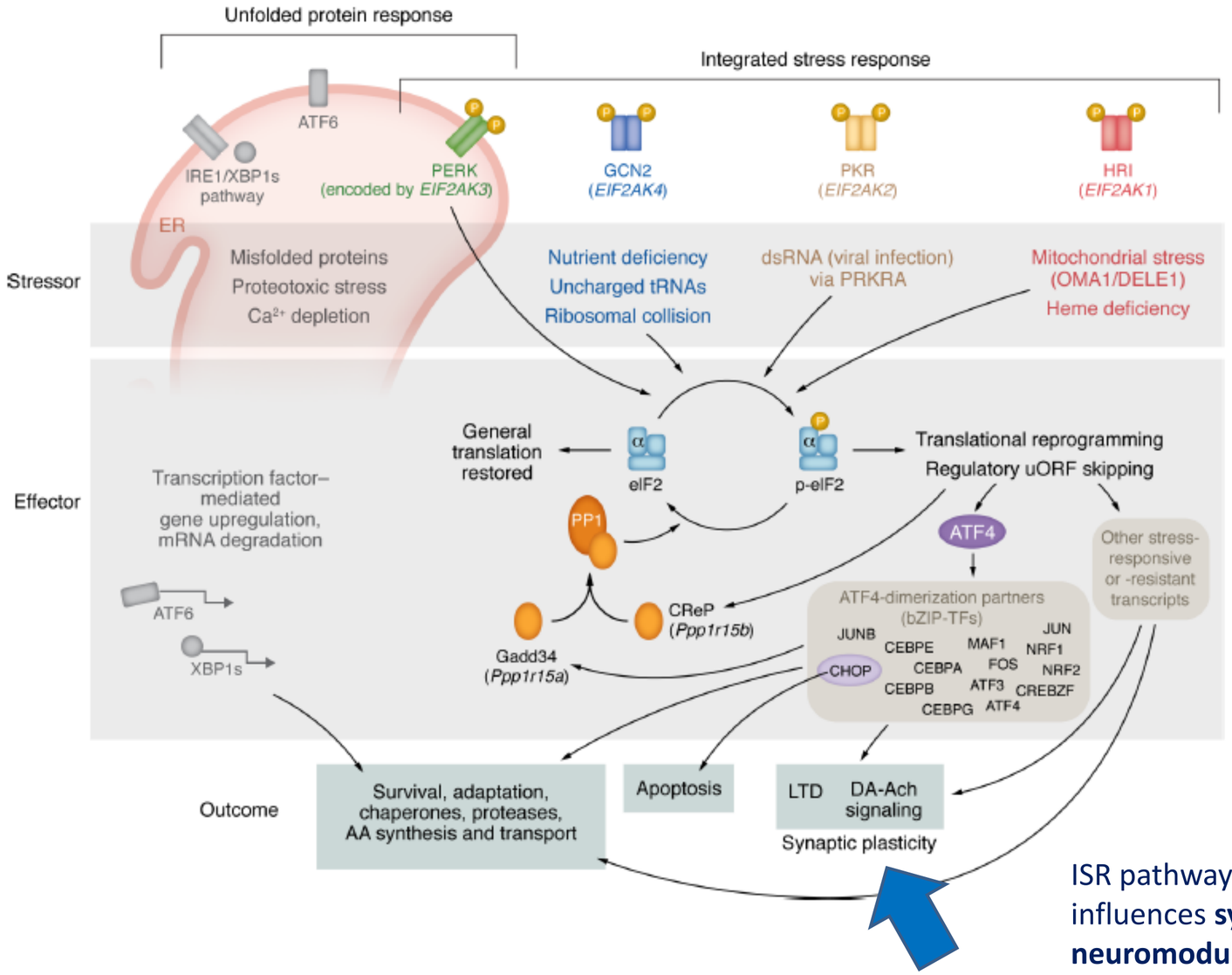
A new knock-in mouse model of L-DOPA-responsive dystonia

Samuel J. Rose,[1] Xin Y. Yu,[1] Ann K. Heinzer,[2] Porter Harrast,[1] Xueliang Fan,[1] Robert S. Raike,[1,*] Valerie B. Thompson,[1,#] Jean-Francois Pare,[3,4] David Weinshenker,[5] Yoland Smith,[3,4,6] Hyder A. Jinnah[5,6,7] and Ellen J. Hess[1,6]



…“***unexpected”*** pathways

- Evidence from human genetic and functional studies that support the consideration of molecular-genetic families in dystonia for two processes, the **endosome-autophagosome-lysosome pathway** (EALP) and the **integrated stress response** (ISR).



The ISR and its intersection, via PERK, with the UPR (upper left) constitute the **2 major proteostasis pathways**.

Phosphorylation of eIF2α induces broad **reprogramming of translation** within the cell, preferentially translating mRNAs and reducing the translation of mRNAs. In addition to **marked reduction in total protein translation, this action reduces cellular stress** through translation and transcription of chaperones, proteases, and amino acid synthesis and transport proteins

ISR pathway activation has roles beyond response to **cellular stresses**, and influences **synaptic plasticity**, such as long-term depression (LTD) and **neuromodulator signaling** involving dopamine (DA) and acetylcholine (Ach)

RESEARCH ARTICLE

NEUROSCIENCE

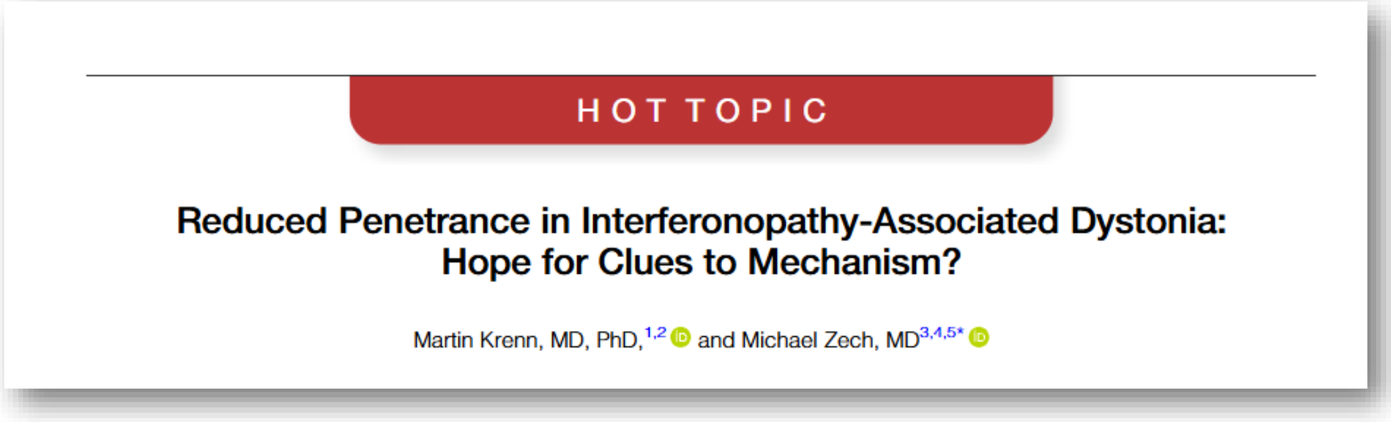
Cholinergic neurons constitutively engage the ISR for dopamine modulation and skill learning in mice

Ashley R. Helseth[1]†, Ricardo Hernandez-Martinez[1]†, Victoria L. Hall[2], Matthew L. Oliver[3], Brandon D. Turner[1], Zachary F. Caffall[1], Joseph E. Rittiner[1], Miranda K. Shipman[1], Connor S. King[1], Viviana Gradinaru[4], Charles Gerfen[5], Mauro Costa-Mattioli[6], Nicole Calakos[1,2,3,7]*

The integrated stress response (ISR) maintains proteostasis by modulating protein synthesis and is important in synaptic plasticity, learning, and memory. We developed a reporter, SPOTlight, for brainwide imaging of ISR state with cellular resolution. Unexpectedly, we found a class of neurons in mouse brain, striatal cholinergic interneurons (CINs), in which the ISR was activated at steady state. Genetic and pharmacological manipulations revealed that ISR signaling was necessary in CINs for normal type 2 dopamine receptor (D2R) modulation. Inhibiting the ISR inverted the sign of D2R modulation of CIN firing and evoked dopamine release and altered skill learning. Thus, a noncanonical, steady-state mode of ISR activation is found in CINs, revealing a neuromodulatory role for the ISR in learning.

The authors developed a reporter to reveal the translational state of the ISR pathway in brain cells.

With this reporter, we made the unexpected discovery that **the ISR was constitutively activated in a subset striatal cholinergic interneurons (CINs**). They then showed that the level of CIN ISR activation **influences dopamine D2R-dependent modulation of CIN firing and striatal dopamine (DA) release, and changed the performance of learned tasks**.



HOT TOPIC

Reduced Penetrance in Interferonopathy-Associated Dystonia: Hope for Clues to Mechanism?

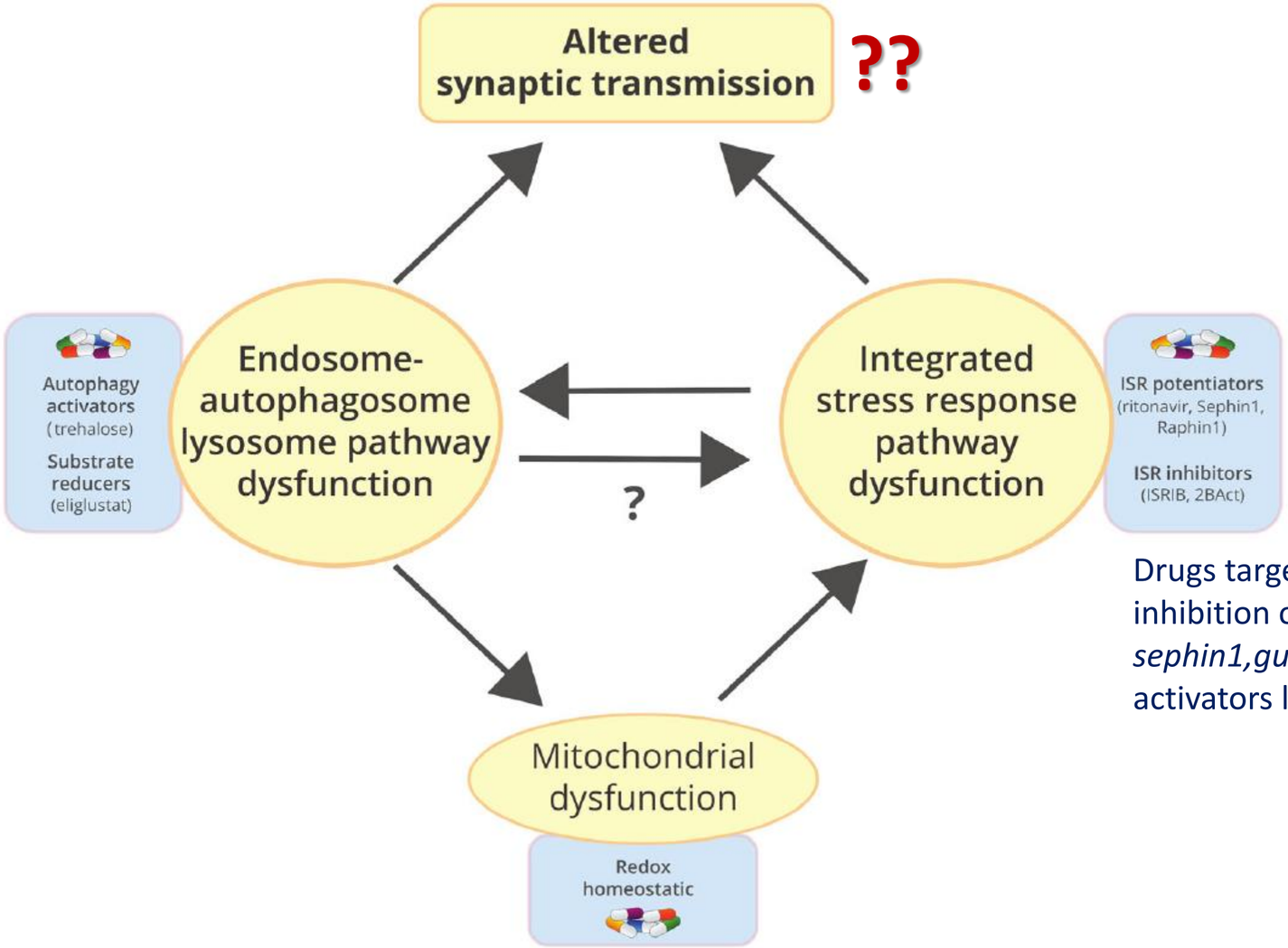
Martin Krenn, MD, PhD,[1,2] and Michael Zech, MD[3,4,5*]

- *"All patients were found to carry heterozygous loss-of-function variants in the previously unassigned disease-gene PTPN1, encoding an essential tyrosine-protein phosphatase (**PTP1B**) that influences immune reactions"*
- *"PTP1B is a key component of **the integrated-stress-response** (**ISR**), a unifying molecular pathway in dystonia in which several effectors have been demonstrated to cause incompletely penetrant dystonic symptoms"*

For EALP, *small molecule* modifiers of autophagy and lysosome may emerge as promising treatments.

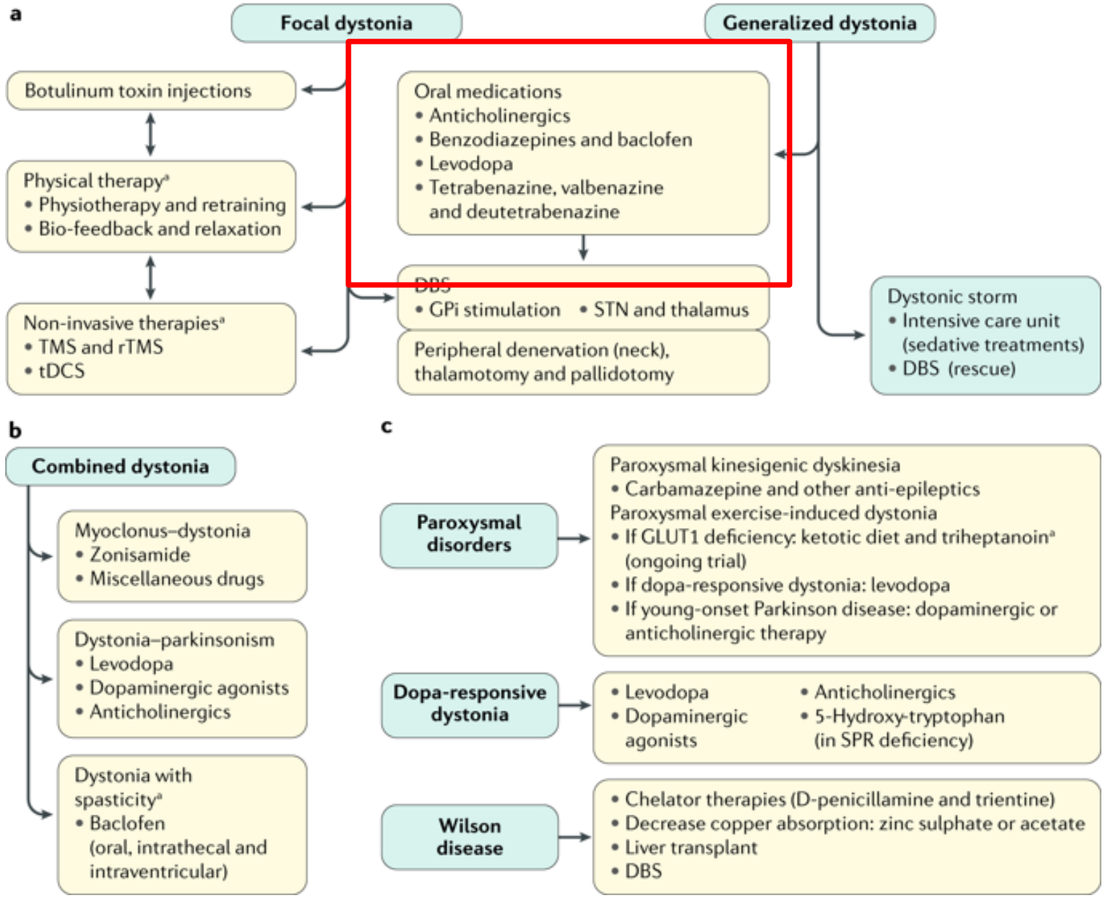
Maintenance or upregulation of EALP activity may foster neuronal health.

Enzymatic activity enhancement in the EALP, specific substrate reduction, and/or autophagic activation may be useful strategies for future clinical trials.



Drugs targeting the ISR include inhibition of its phosphatases (*raphin1, sephin1,guanabenz)* or novel activators like HIV protease inhibitors

Fig. 6: Treatment algorithm for dystonia.



Balint, B. et al. (2018) Dystonia
Nat. Rev. Dis. Primers doi:10.1038/s41572-018-0023-6

Proceedings of the Royal Society of Medicine

Section of Pædiatrics

President—Professor A. G. WATKINS, M.D., F.R.C.P.

Dystonia Musculorum Deformans in Siblings. Treated with Artane (Trihexylphenidyl).—BERYL D. CORNER, M.D.

Family history.—The two children described are the only siblings. Parents healthy; no Russian or Jewish ancestry; family have lived in Bristol for several generations. A paternal uncle has had this disease since the age of 8 years. He is now 44 years and completely bedridden.

[*February* 22, 1952]

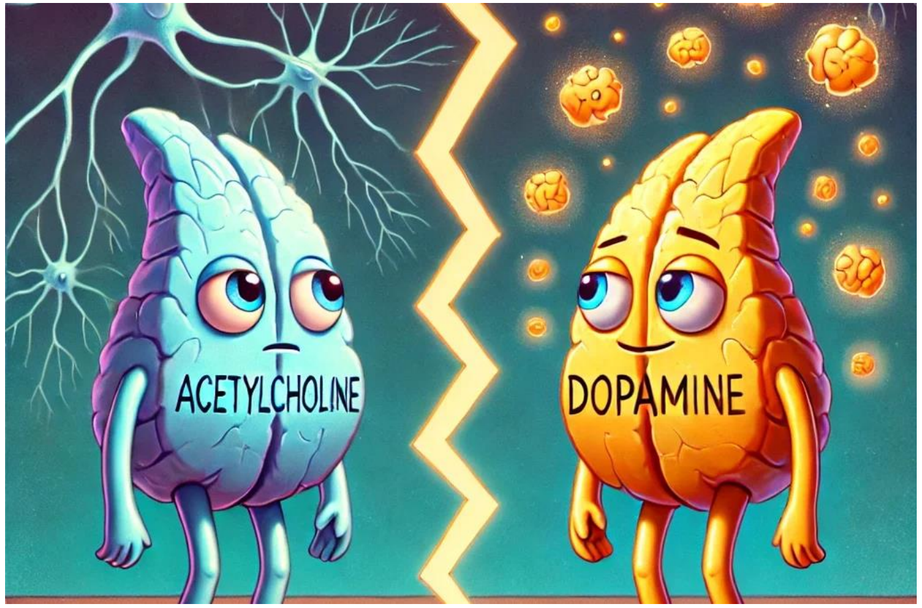
Article abstract—Twenty-three children and 52 adults with torsion dystonia of various etiologies and distribution patterns of the involuntary movements were treated in an open-label study with anticholinergic medication. The dosage was increased gradually until there was either benefit or intolerable adverse effects. Trihexyphenidyl was used initially, but later ethopropazine was given to adult subjects. Significant benefit occurred in 61% of children and in 38% of adults. The average daily dosages were 41 mg trihexyphenidyl for children, 24 mg trihexyphenidyl for adults, and 350 mg ethopropazine for adults. Adverse effects were the major limiting factor to high dosage in adults, but not in children.

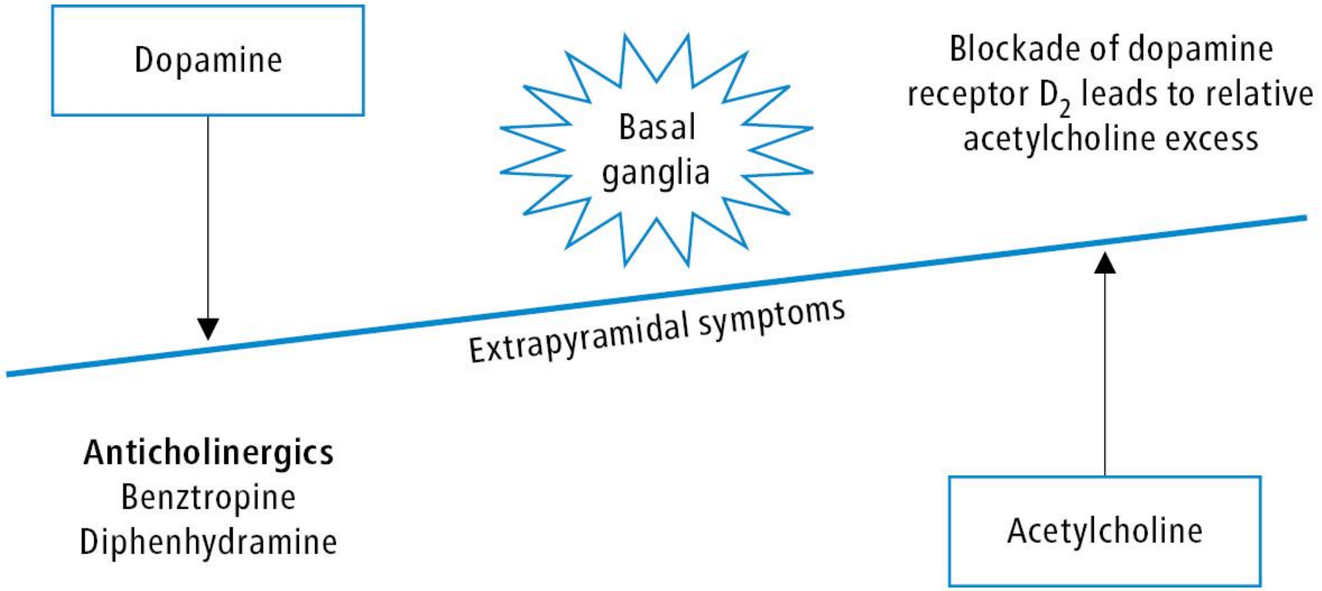
NEUROLOGY (Cleveland) 1983;33:1255-61

High dosage anticholinergic therapy in dystonia

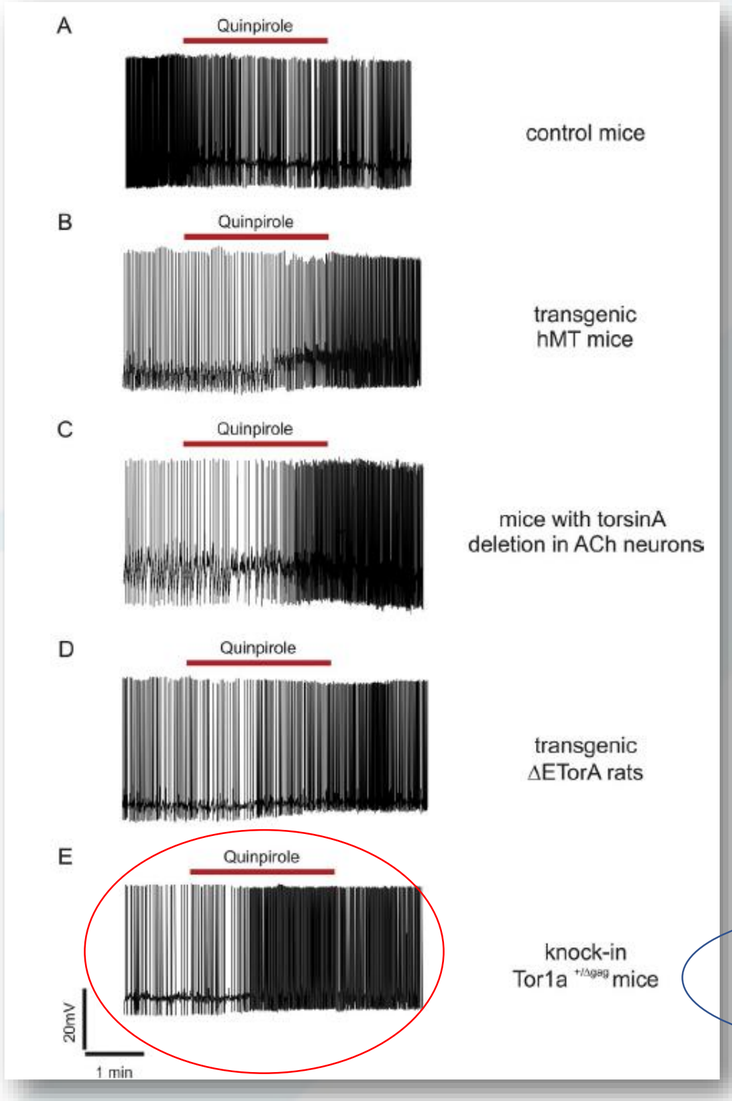
Stanley Fahn, MD

Which is the rationale for the involvement of dopamine and acetylcholine?

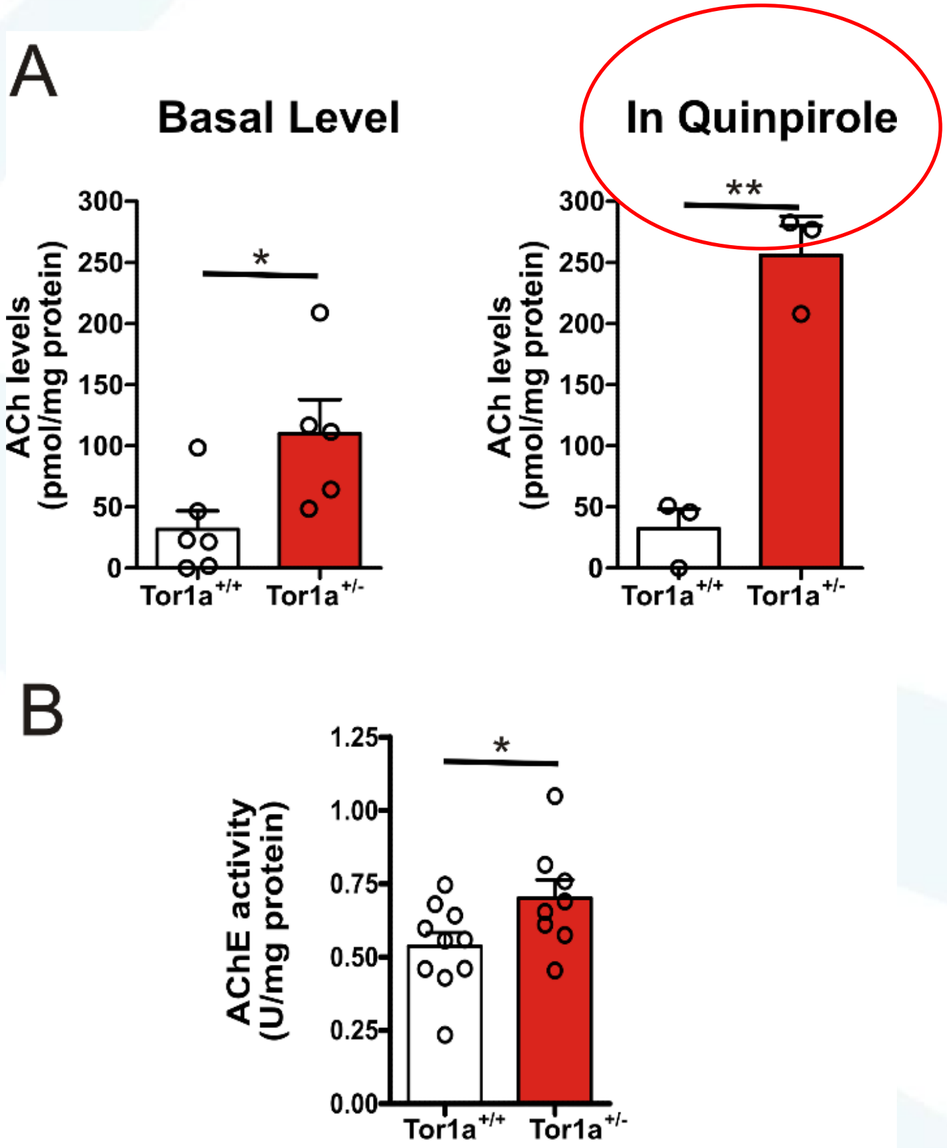

ACETYLCHOLINE
DOPAMINE


Dopamine
Basal ganglia
Blockade of dopamine receptor D_2 leads to relative acetylcholine excess
Extrapyramidal symptoms
Anticholinergics
Benztropine
Diphenhydramine
Acetylcholine

D2 receptor dysfunction in different models of dystonia



Paradoxical excitation



Dystonia: Bridging Theory and Hands-On Expertise

September 5-6, 2025 | Istanbul, Turkey

International Parkinson and Movement Disorder Society European Section

Published online: December 14, 2018

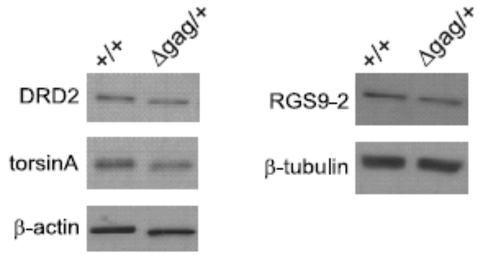
Research Article

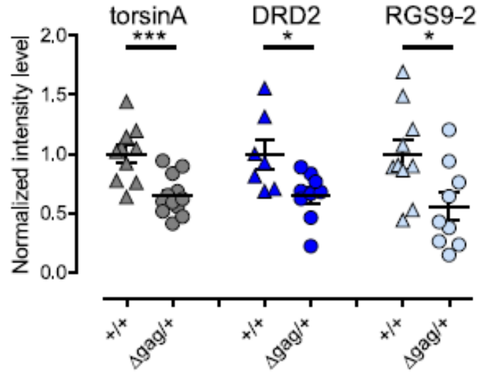
SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

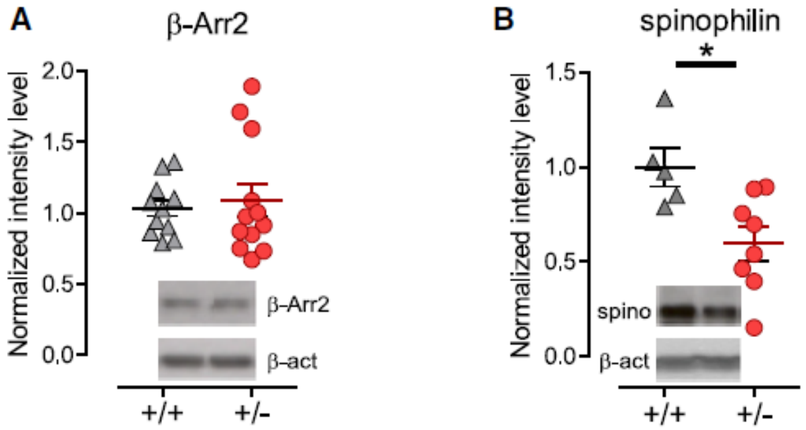
EMBO Molecular Medicine

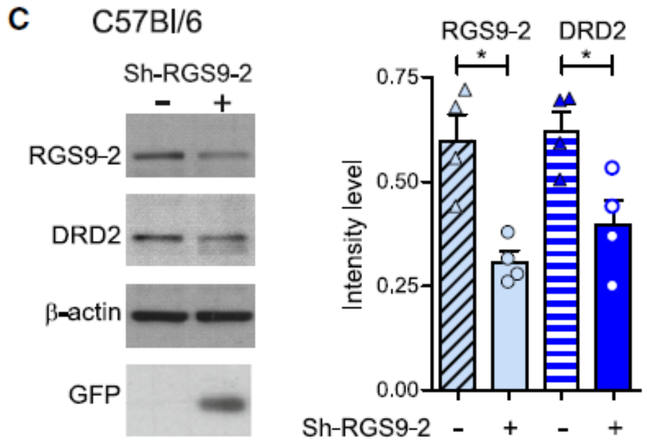
RGS9-2 rescues dopamine D2 receptor levels and signaling in *DYT1* dystonia mouse models

Paola Bonsi[1,*], Giulia Ponterio[1,2], Valentina Vanni[1,2], Annalisa Tassone[1,2], Giuseppe Sciamanna[1,2], Sara Migliarini[3], Giuseppina Martella[1,2], Maria Meringolo[1,2], Benjamin Dehay[4,5], Evelyne Doudnikoff[4,5], Venetia Zachariou[6], Rose E Goodchild[7], Nicola B Mercuri[1,2], Marcello D'Amelio[8,9], Massimo Pasqualetti[3,10], Erwan Bezard[4,5] & Antonio Pisani[1,2,**]









Shared pathways - dopamine and acetylcholine

The Journal of Neuroscience, September 4, 2019 • 39(36):7195–7205 • 7195

Neurobiology of Disease

Diverse Mechanisms Lead to Common Dysfunction of Striatal Cholinergic Interneurons in Distinct Genetic Mouse Models of Dystonia

Karen L. Eskow Jaunarajs,[1]* Mariangela Scarduzio,[1]* Michelle E. Ehrlich,[3] Lori L. McMahon,[1,2] and David G. Standaert[1]

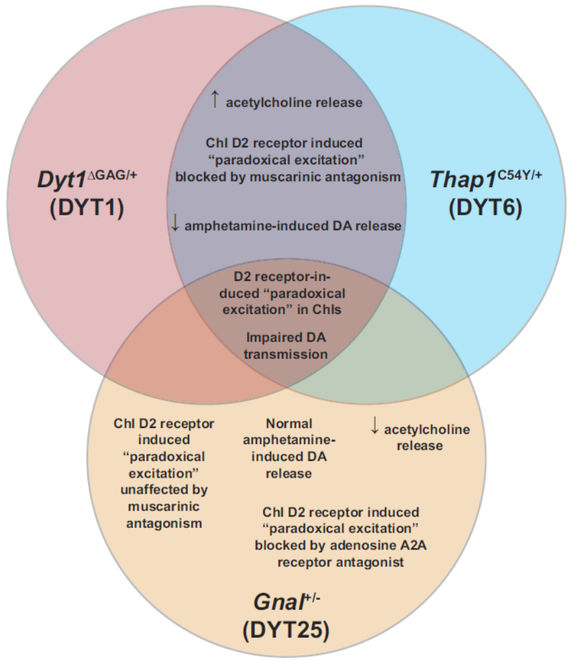
[1]Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, [2]Department of Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, Birmingham, Alabama 35294, and [3]Department of Neurology and Pediatrics, Icahn School of Medicine at Mount Sinai, New York City, New York 10029

https://doi.org/10.1093/brain/awac001 BRAIN 2022: 145; 3968–3984 | 3968

BRAIN
ORIGINAL ARTICLE

DYT6 mutated THAP1 is a cell type dependent regulator of the SP1 family

Fubo Cheng,[1,2] Wenxu Zheng,[3] Peter Antony Barbuti,[4,5] Paola Bonsi,[6] Chang Liu,[7] Nicolas Casadei,[1,8] Giulia Ponterio,[6] Maria Meringolo,[6] Jakob Admard,[1,8] Claire Marie Dording,[4] Libo Yu-Taeger,[1,9] Huu Phuc Nguyen,[9] Kathrin Grundmann-Hauser,[1] Thomas Ott,[1] Henry Houlden,[10] Antonio Pisani,[11,12] Rejko Krüger[4,13,14] and Olaf Riess[1,8]



Shared dopaminergic dysfunction- GNAL KO

Neurobiology of Disease 191 (2024) 106403

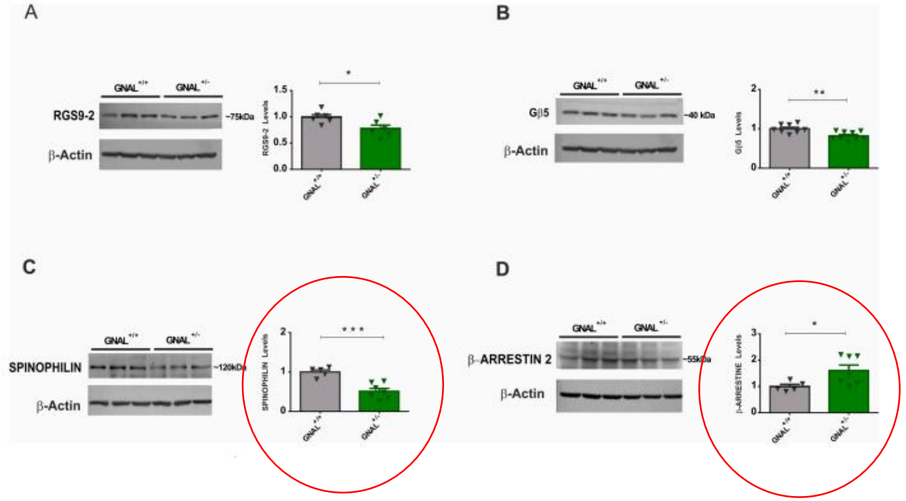
Contents lists available at ScienceDirect

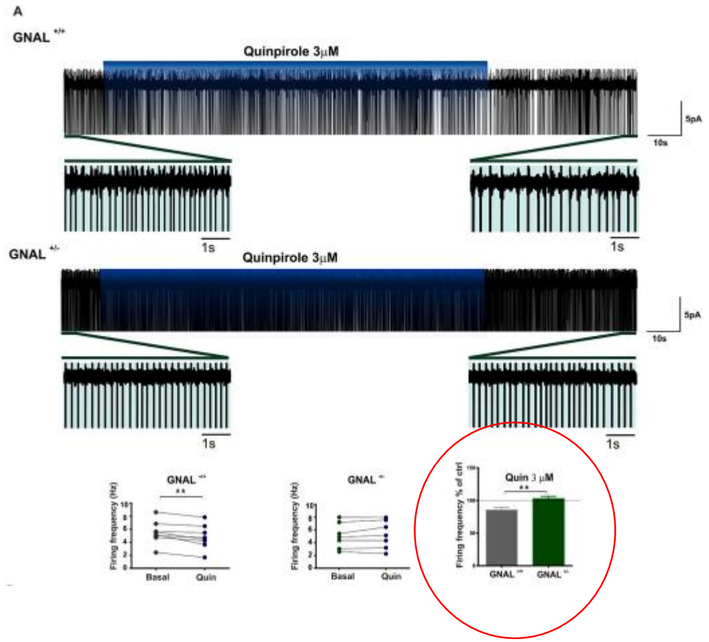
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Loss-of-function of GNAL dystonia gene impairs striatal dopamine receptors-mediated adenylyl cyclase/ cyclic AMP signaling pathway

Ilham El Atiallah [a,1], Giulia Ponterio [a,1], Maria Meringolo [a,b], Giuseppina Martella [a], Giuseppe Sciamanna [a,b], Annalisa Tassone [a], Martina Montanari [a], Maria Mancini [c,d], Antonio N. Castagno [c,d], Libo Yu-Taeger [e], Hoa Huu Phuc Nguyen [e], Paola Bonsi [a], Antonio Pisani [c,d,*]





Neurobiology of Disease 179 (2023) 106056

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Neurobiology of Disease

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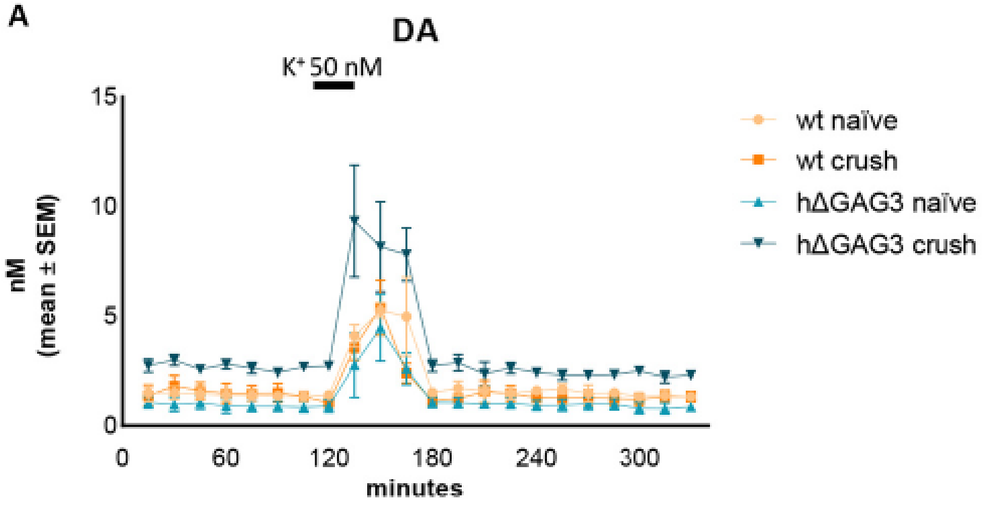
Peripheral nerve injury elicits microstructural and neurochemical changes in the striatum and substantia nigra of a DYT-TOR1A mouse model with dystonia-like movements

Lisa Rauschenberger [a], Esther-Marie Krenig [a], Alea Stengl [a], Susanne Knorr [a], Tristan H. Harder [a], Felix Steeg [a], Maximilian U. Friedrich [a], Kathrin Grundmann-Hauser [b,c], Jens Volkmann [a], Chi Wang Ip [a,*]



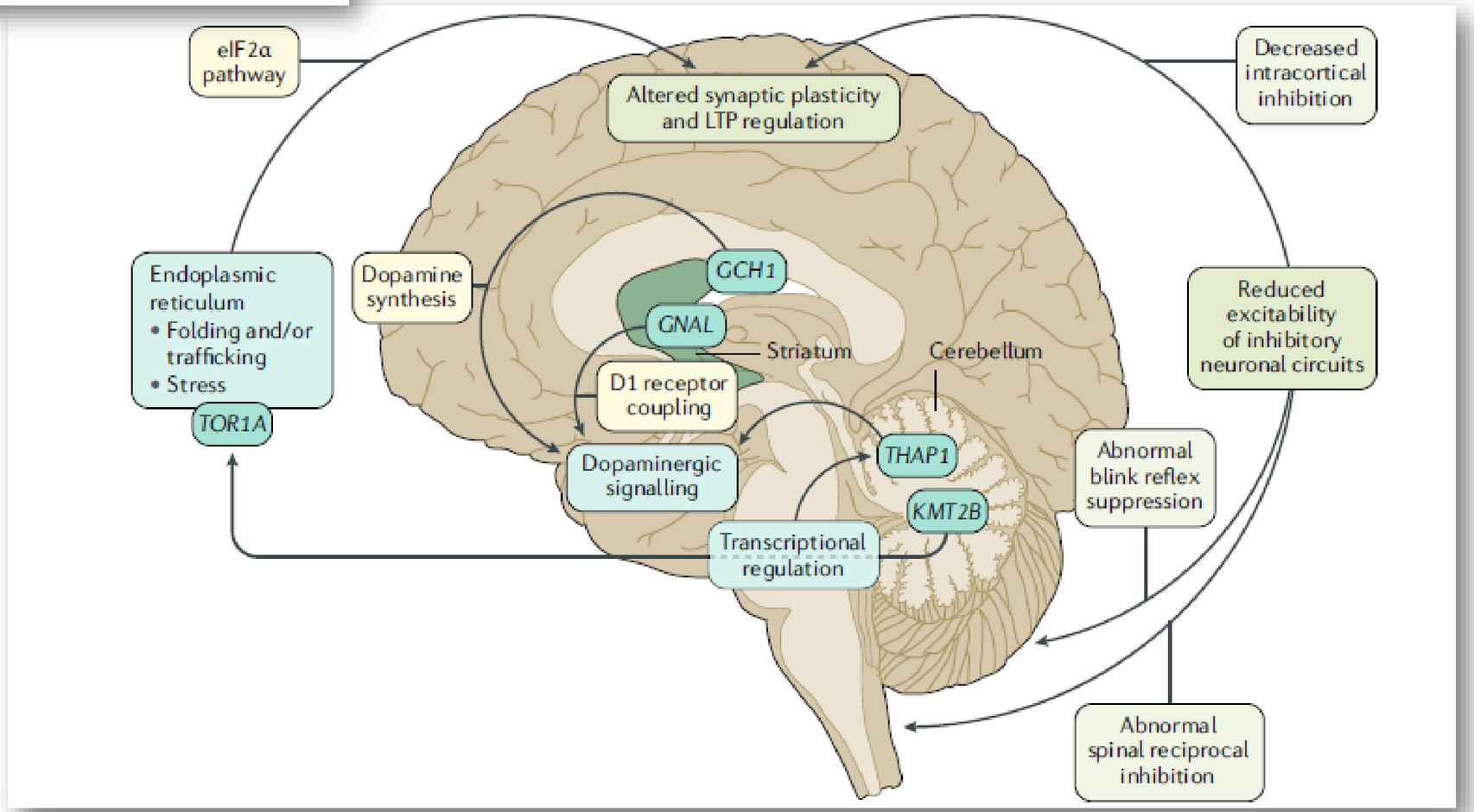
NATURE REVIEWS | DISEASE PRIMERS |

PRIMER

Dystonia

*Bettina Balint[1,2], Niccolò E. Mencacci[3], Enza Maria Valente[4,5], Antonio Pisani[5,6], John Rothwell[1], Joseph Jankovic[7], Marie Vidailhet[8] and Kailash P. Bhatia[1]**

common alterations in neurochemistry, wiring, or **physiology**



Is plasticity an issue to human dystonia?

◆ Human Brain Mapping 36:793–803 (2015) ◆

Changes in Corticostriatal Connectivity During Reinforcement Learning in Humans

Guillermo Horga,[1] Tiago V. Maia,[1,2] Rachel Marsh,[1] Xuejun Hao,[1] Dongrong Xu,[1] Yunsuo Duan,[1] Gregory Z. Tau,[1] Barbara Graniello,[1] Zhishun Wang,[1] Alayar Kangarlu,[1] Diana Martinez,[1] Mark G. Packard,[3] and Bradley S. Peterson[4]*

Abstract: Many computational models assume that reinforcement learning relies on changes in synaptic efficacy between cortical regions representing stimuli and striatal regions involved in response selection, but this assumption has thus far lacked empirical support in humans. We recorded hemodynamic signals with fMRI while participants navigated a virtual maze to find hidden rewards. We fitted a reinforcement-learning algorithm to participants' choice behavior and evaluated the neural activity and the changes in functional connectivity related to trial-by-trial learning variables. Activity in the posterior putamen during choice periods increased progressively during learning. Furthermore, the functional connections between the sensorimotor cortex and the posterior putamen strengthened progressively as participants learned the task. These changes in corticostriatal connectivity differentiated participants who learned the task from those who did not. These findings provide a direct link between changes in corticostriatal connectivity and learning, thereby supporting a central assumption common to several computational models of reinforcement learning. *Hum Brain Mapp 00:000–000, 2014.*

Plasticity impairment in generalized and focal dystonia

Ann Neurol 2003;54:102–109

Impaired Sequence Learning in Carriers of the DYT1 Dystonia Mutation

Maria-Felice Ghilardi, MD,[1,2] Maren Carbon, MD,[3] Giulia Silvestri, MD,[1] Vijay Dhawan, PhD,[3,4] Michele Tagliati, MD,[4] Susan Bressman, MD,[5] Claude Ghez, MD,[1] and David Eidelberg, MD[3,4]

Movement Disorders
Vol. 21, No. 12, 2006, pp. 2181–2186

Abnormalities in Motor Cortical Plasticity Differentiate Manifesting and Nonmanifesting DYT1 Carriers

Mark J. Edwards, MBBS,[1] Ying-Zu Huang, PhD,[1,2] Pablo Mir, PhD,[1,3] John C. Rothwell, PhD,[1] and Kailash P. Bhatia, MD[1]*

DOI: 10.1093/brain/awg209 Advanced Access publication June 23, 2003 *Brain* (2003), **126**, 2074–2080

Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the *DYT1* gene mutation

Mark J. Edwards,[1] Ying-Zu Huang,[1] Nicholas W. Wood,[2] John C. Rothwell[1] and Kailash P. Bhatia[1]

749–755 | 749
BRAIN
A JOURNAL OF NEUROLOGY

Disordered plasticity in the primary somatosensory cortex in focal hand dystonia

Yohei Tamura,[1,2] Yoshino Ueki,[1] Pete
Ryusuke Kakigi[4] and Mark Hallett[1]

Opinion TRENDS in Neurosciences Vol.29 No.4 April 2006
Full text provided by www.sciencedirect.com
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Task-specific hand dystonia: can too much plasticity be bad for you?

Angelo Quartarone[1], Hartwig R. Siebner[2] and J.C. Rothwell[3]

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[2]Department of Neurology, Christian-Albrechts-University, 24105 Kiel, Germany
[3]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College of London, London WC1N 3BG, UK

Review Adv Exp Med Biol. 2016;957:197-208. doi: 10.1007/978-3-319-47313-0_11.

Brain Plasticity and the Concept of Metaplasticity in Skilled Musicians

Eckart Altenmüller [1], Shinichi Furuya [2 3]

Neurophysiology, synaptic plasticity, endophenotypes

1. The main pathophysiological mechanisms recognized for human dystonia include an **imbalance between inhibition and excitation, abnormalities in sensorimotor integration, and maladaptive plasticity**. Maladaptive plasticity may play a particularly important role in task-specific dystonia like musician's dystonia, where repetitive practice triggers the development of abnormal movements.
2. Several studies have consistently shown that, in patients with isolated dystonia, sensory and motor cortex exhibit an exaggerated responsiveness to rTMS conditioning protocols, expression of **enhanced plasticity** (Quartarone et al., 2003, Quartarone et al., 2008, Weise et al., 2006, Edwards et al., 2006, Tamura et al., 2009).
3. The loss of spatial specificity is a robust finding and is related to the abnormalities of neuronal inhibition identified both in the motor and somatosensory system in dystonic patients (Hallett, 2011), and may well be explained by a **failure of neuronal (surround) inhibition**.
4. Impaired synaptic plasticity has been described in carriers, and even in unaffected body parts (Quartarone et al., 2008), suggesting that altered synaptic processes can represent a susceptibility factor, or an **endophenotypic trait** of dystonia, **regardless of clinical penetrance** (Edwards et al., 2006).

Nora Krohn

Musician's Focal Dystonia Recovery

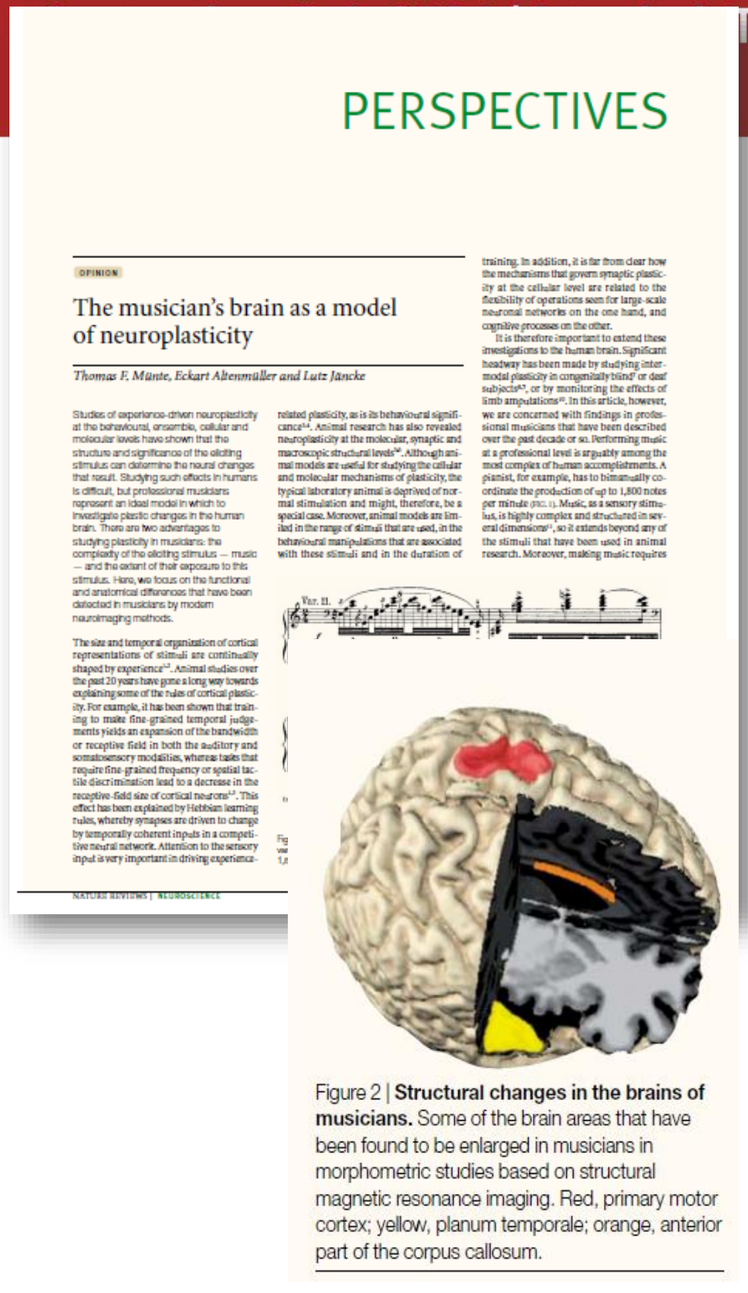
If you're struggling with Musician's Focal Dystonia, the first thing I want you to know is that recovery IS possible. My story in a nutshell, which probably bears some similarities to yours:

In 2018 I began experiencing strange symptoms in my left hand, which seemed to appear practically overnight: a feeling of sluggishness, lack of control, and eventually involuntary curling in my ring and pinky fingers. Even though I intuited pretty quickly that I was dealing with MFD (not necessarily the case for everyone!), I faced the same dispiriting assessment often seen in medical literature and all over the internet: this affliction would be lifelong, progressive, and only treatable through Botox. Luckily, I also came across accounts of musicians who'd healed themselves—fully—through neuromuscular retraining. So I set about achieving the same results. Three years later, I finally resumed my playing career. So, how did I recover from MFD? The quick layperson's version is that, by learning a new system of playing that was comfortable, sensible, and reliable, I gradually induced neuroplastic changes to my brain.

The path to recovery is not necessarily a straight one, nor is it easy, but with the help of a multidisciplinary strategy that promotes truly efficient technique and an accompanying retuning of the nervous system, I believe it is 100% possible.

If you'd like to know more, please feel free to contact me!

Dystonia: Bridging Theory and Hands-On Expertise



PERSPECTIVES

OPINION

The musician's brain as a model of neuroplasticity

Thomas F. Münte, Eckart Altenmüller and Lutz Jäncke

Studies of experience-driven neuroplasticity at the behavioural, ensemble, cellular and molecular levels have shown that the structure and significance of the eliciting stimulus can determine the neural changes that result. Studying such effects in humans is difficult, but professional musicians represent an ideal model in which to investigate plastic changes in the human brain. There are two advantages to studying plasticity in musicians: the complexity of the eliciting stimulus — music — and the extent of their exposure to this stimulus. Here, we focus on the functional and anatomical differences that have been detected in musicians by modern neuroimaging methods.

The size and temporal organization of cortical representations of stimuli are continually shaped by experience[1,2]. Animal studies over the past 20 years have gone a long way towards explaining some of the rules of cortical plasticity. For example, it has been shown that training to make fine-grained temporal judgements yields an expansion of the bandwidth or receptive field in both the auditory and somatosensory modalities, whereas tasks that require fine-grained frequency or spatial tactile discrimination lead to a decrease in the receptive-field size of cortical neurons[1,2]. This effect has been explained by Hebbian learning rules, whereby synapses are driven to change by temporally coherent inputs in a competitive neural network. Attention to the sensory input is very important in driving experience-related plasticity, as is its behavioural significance[3,4]. Animal research has also revealed neuroplasticity at the molecular, synaptic and macroscopic structural levels[5,6]. Although animal models are useful for studying the cellular and molecular mechanisms of plasticity, the typical laboratory animal is deprived of normal stimulation and might, therefore, be a special case. Moreover, animal models are limited in the range of stimuli that are used, in the behavioural manipulations that are associated with these stimuli and in the duration of training. In addition, it is far from clear how the mechanisms that govern synaptic plasticity at the cellular level are related to the flexibility of operations seen for large-scale neuronal networks on the one hand, and cognitive processes on the other.

It is therefore important to extend these investigations to the human brain. Significant headway has been made by studying intermodal plasticity in congenitally blind[7] or deaf subjects[8,9], or by monitoring the effects of limb amputations[10]. In this article, however, we are concerned with findings in professional musicians that have been described over the past decade or so. Performing music at a professional level is arguably among the most complex of human accomplishments. A pianist, for example, has to bimanually coordinate the production of up to 1,800 notes per minute (FIG. 1). Music, as a sensory stimulus, is highly complex and structured in several dimensions[11], so it extends beyond any of the stimuli that have been used in animal research. Moreover, making music requires

Vol. II.

Figure 2 | **Structural changes in the brains of musicians.** Some of the brain areas that have been found to be enlarged in musicians in morphometric studies based on structural magnetic resonance imaging. Red, primary motor cortex; yellow, planum temporale; orange, anterior part of the corpus callosum.

Brain Plasticity: Findings in Musicians

In general terms, brain plasticity means that our brain can be molded and formed. It is brain plasticity what allows us to learn throughout our lifetime. Mechanisms include not only strengthening or weakening of synaptic connections, but also structural changes such as growth of neurons, dendrites, myelin sheets, and neuroglia and reduced physiological loss (apoptosis) of neurons. Brain plasticity is best observed in complex tasks with high behavioral relevance for the individual such that they cause strong emotional and motivational activation. Plastic changes are more pronounced in situations where the task or activity is intense and the earlier in life it has been developed. Obviously, the continued activities of accomplished

There is a dark side to the increasing specialization and prolonged training of modern musicians, namely loss of control and degradation of skilled movements, a disorder referred to as musicians' cramp or focal dystonia. The first historical record, from 1830, appeared in the diaries of the ambitious pianist and composer Robert Schumann. As was probably the case for Schumann, prolonged practice, late onset with instrumental training prolonged practice and pain syndromes due to overuse can precipitate dystonia, which is developed by about 1 % of professional musicians and frequently ends their career. Neuroimaging studies point to dysfunctional (or maladaptive) neuroplasticity as its cause [for a review see (Altenmüller et al. 2015)].

Musician's dystonia

Jon Sussman

Figure 1 An oboist with spontaneous flexion of the left fourth and fifth digits. She could extend the fingers sufficiently rapidly to maintain rhythm on playing up scales but not down scales.

Figure 2 A percussionist showing intermittent left wrist flexion and shoulder abduction while mimicking playing.

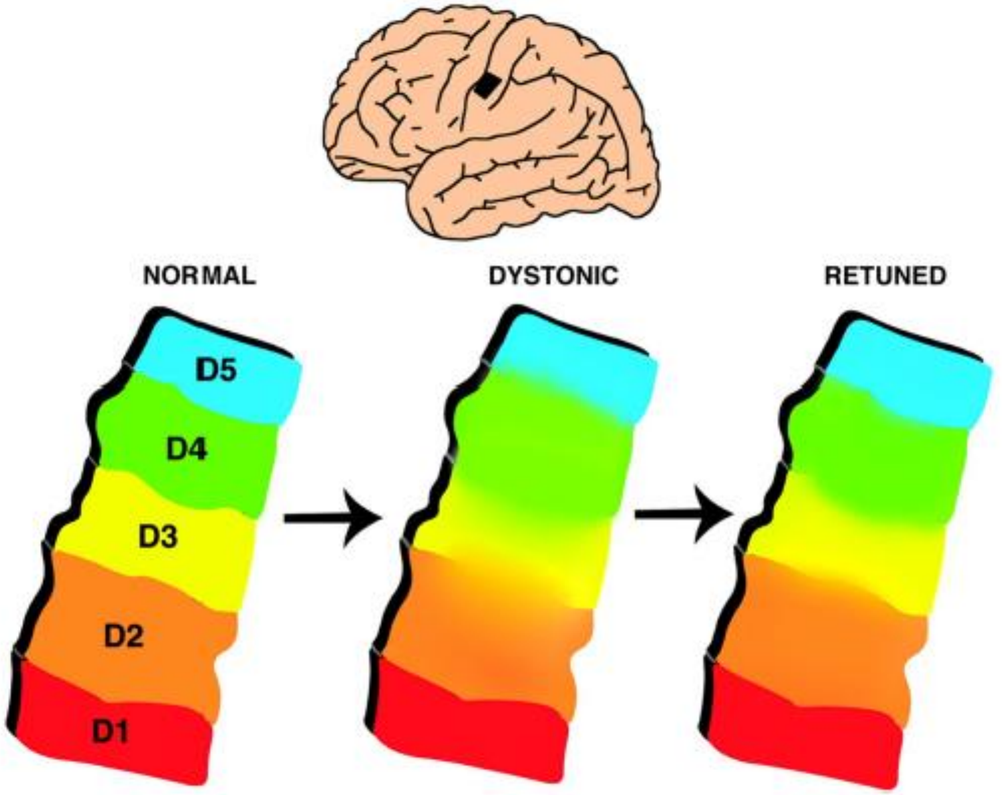
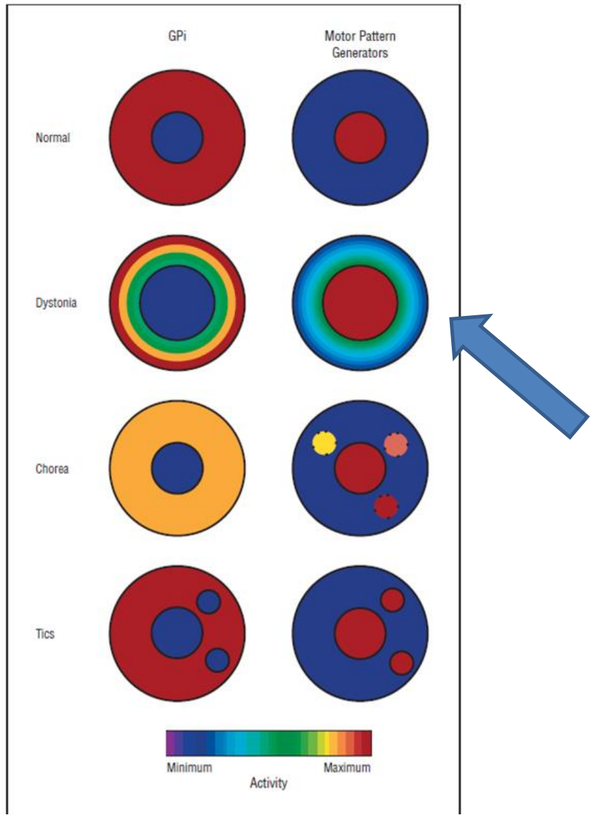


Figure 6 Cartoon depicting hypothetical alteration in the topography of the hand's representation in somatosensory cortex after developing dystonia and following 'sensory motor retuning' using constraint therapy. Taken with permission from Nudo.[13]

Endophenotype in dystonia: *early loss of surround inhibition*



NEUROLOGICAL REVIEW

SECTION EDITOR: DAVID E. PLEASURE, MD

The Basal Ganglia and Involuntary Movements

Impaired Inhibition of Competing Motor Patterns

Jonathan W. Mink, MD, PhD

Arch Neurol. 2003;60:1365-1368

Delineating the endophenotype in DYT1 dystonia models: *early loss of inhibition*

- Loss of corticostriatal LTD
- Enhanced LTP
- Loss of synaptic depotentiation

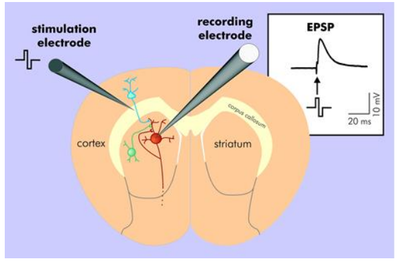
Functional and structural corticostriatal synaptic plasticity impairment

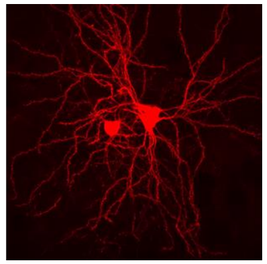
Plasticity in experimental models:

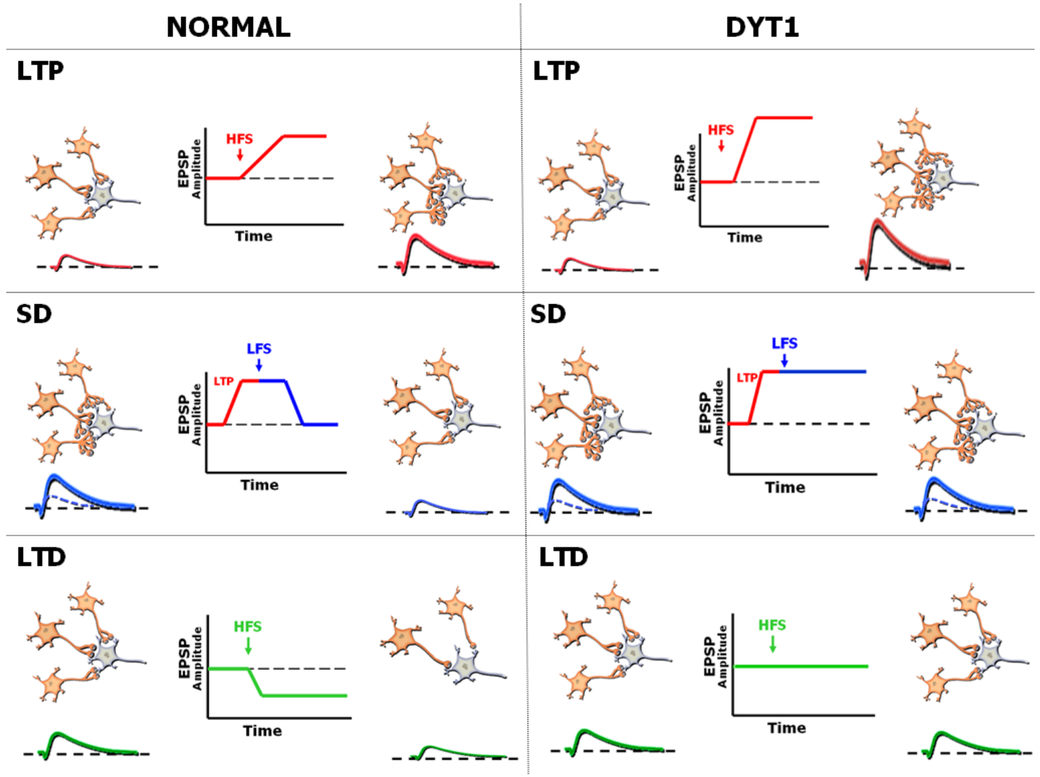
Enhanced LTP

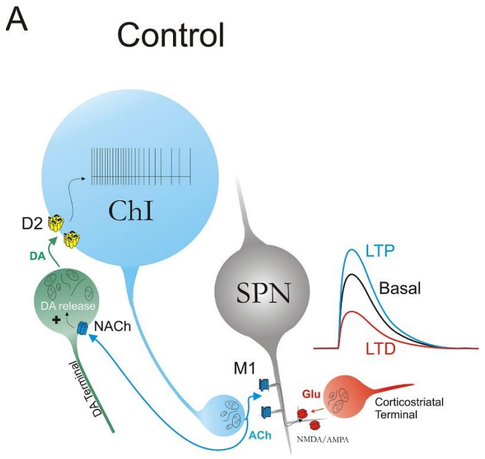
Loss of synaptic depotentiation

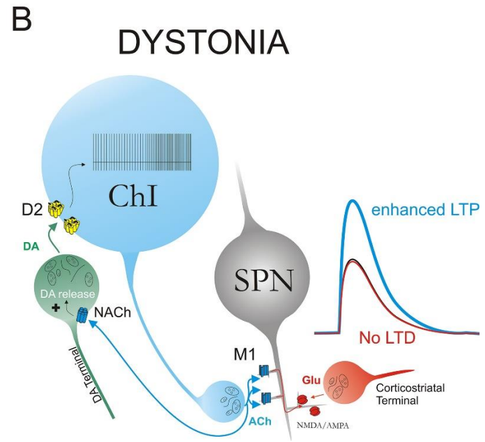
Loss of LTD











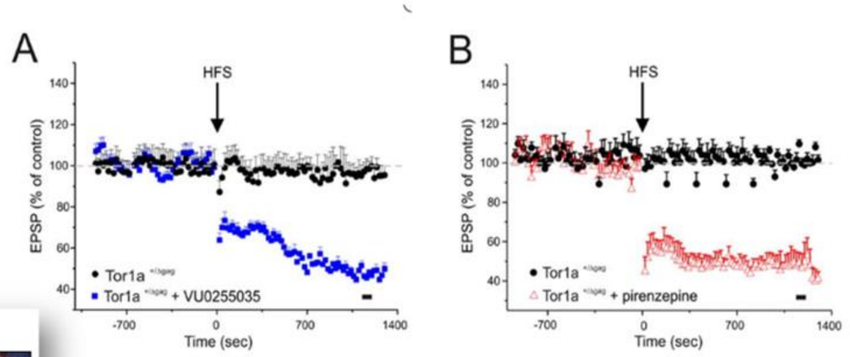
Anticholinergics restore synaptic plasticity in dystonia models

RESEARCH ARTICLE

Anticholinergic Drugs Rescue Synaptic Plasticity in DYT1 Dystonia: Role of M_1 Muscarinic Receptors

Marta Maltese, PhD,[1,2] Giuseppina Martella, PhD,[1,2] Graziella Madeo, MD,[1,2] Irene Fagiolo, MD,[1,2] Annalisa Tassone, PhD,[1,2] Giulia Ponterio, PhD,[1,2] Giuseppe Sciamanna, PhD,[1,2] Pierre Burbaud, MD, PhD,[3] P. Jeffrey Conn, PhD,[4] Paola Bonsi, PhD,[2] and Antonio Pisani, MD, PhD[1,2*]

[1]Department of Systems Medicine, University of Rome "Tor Vergata", Italy
[2]IRCCS Fondazione Santa Lucia, Rome, Italy
[3]Institut des Maladies Neurodégénératives, Université Victor Segalen, Bordeaux, France
[4]Vanderbilt Center for Neuroscience Drug Discovery, Department of Pharmacology, Vanderbilt University, Nashville, Tennessee, USA



Behavioural Brain Research 226 (2012) 465–472
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Behavioural Brain Research
journal homepage: www.elsevier.com/locate/bbr

Research report

An anticholinergic reverses motor control and corticostriatal LTD deficits in *Dyt1* ΔGAG knock-in mice

Mai T. Dang[a], Fumiaki Yokoi[b], Chad C. Cheetham[c], Jun Lu[c], Viet Vo[d], David M. Lovinger[e], Yuqing Li[b,*]

Neurobiology of Disease 93 (2016) 137–145
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Mouse model of rare *TOR1A* variant found in sporadic focal dystonia impairs domains affected in DYT1 dystonia patients and animal models

Srishti L. Bhagat[a,b,1], Sunny Qiu[a,1], Zachary F. Caffall[a], Yehong Wan[a], Yuanji Pan[a], Ramona M. Rc
William C. Wetsel[c,d], Alexandra Badea[e], Ute Hochgeschwender[a], Nicole Calakos[a,b,c,*]

Neurobiology of Disease 125 (2019) 115–122
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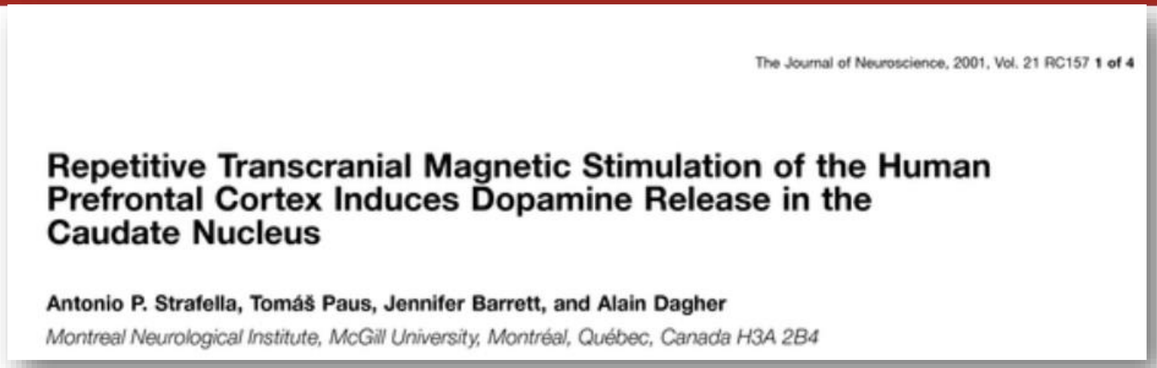
journal homepage: www.elsevier.com/locate/ynbdi

Trihexyphenidyl rescues the deficit in dopamine neurotransmission in a mouse model of DYT1 dystonia

Anthony M. Downs[a], Xueliang Fan[a], Christine Donsante[a], H.A. Jinnah[b,c,d], Ellen J. Hess[a,b,*]

How to rewire abnormal circuits in dystonia by targeting neurotransmitter systems?

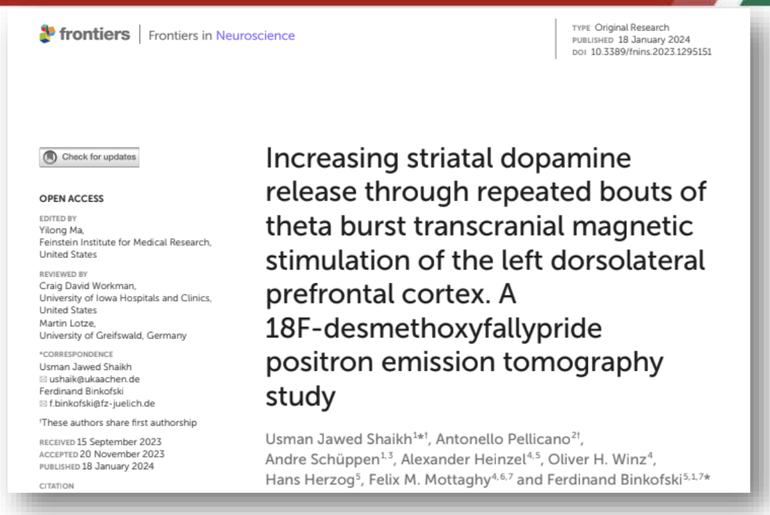


The Journal of Neuroscience, 2001, Vol. 21 RC157 1 of 4

Repetitive Transcranial Magnetic Stimulation of the Human Prefrontal Cortex Induces Dopamine Release in the Caudate Nucleus

Antonio P. Strafella, Tomáš Paus, Jennifer Barrett, and Alain Dagher

Montreal Neurological Institute, McGill University, Montréal, Québec, Canada H3A 2B4



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CITATION

Increasing striatal dopamine release through repeated bouts of theta burst transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. A 18F-desmethoxyfallypride positron emission tomography study

Usman Jawed Shaikh[1*†], Antonello Pellicano[2†], Andre Schüppen[1,3], Alexander Heinzel[4,5], Oliver H. Winz[4], Hans Herzog[5], Felix M. Mottaghy[4,6,7] and Ferdinand Binkofski[5,1,7*]

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PLoS one

rTMS of the Left Dorsolateral Prefrontal Cortex Modulates Dopamine Release in the Ipsilateral Anterior Cingulate Cortex and Orbitofrontal Cortex

Sang Soo Cho[1,2], Antonio P. Strafella[1,2]*

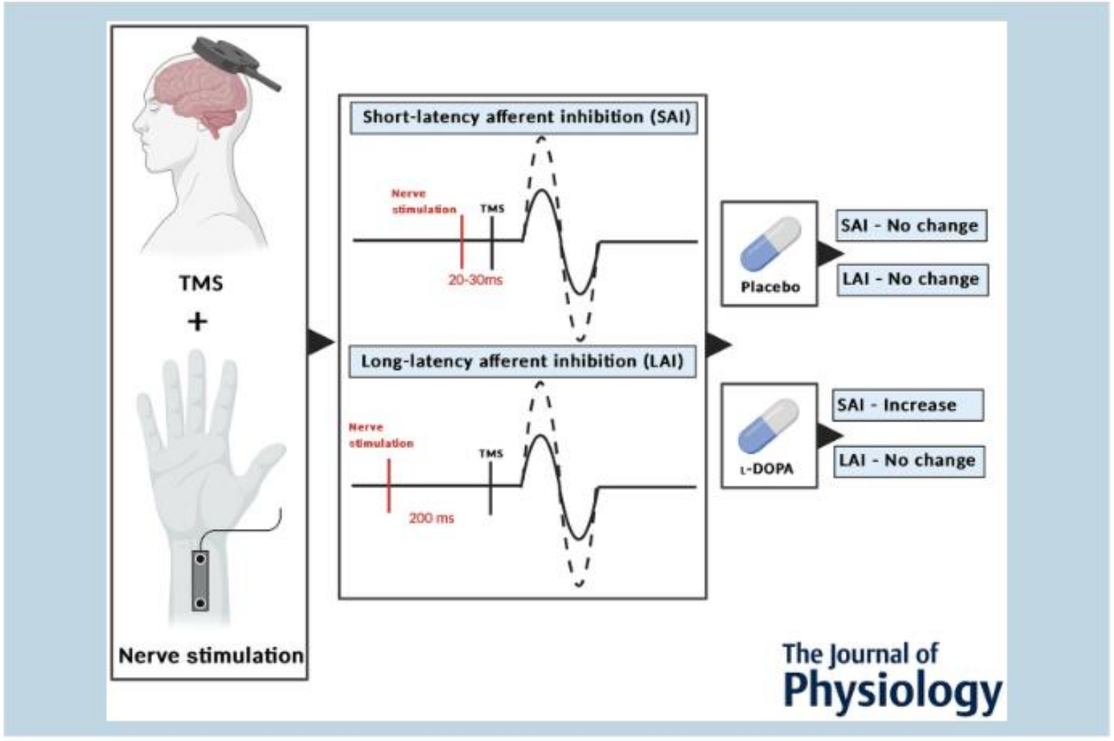
1 Toronto Western Research Institute and Hospital, UHN, University of Toronto, Toronto, Canada of Toronto, Toronto, Canada

August 2009 | Volume 4 | Issue 8 | e6725

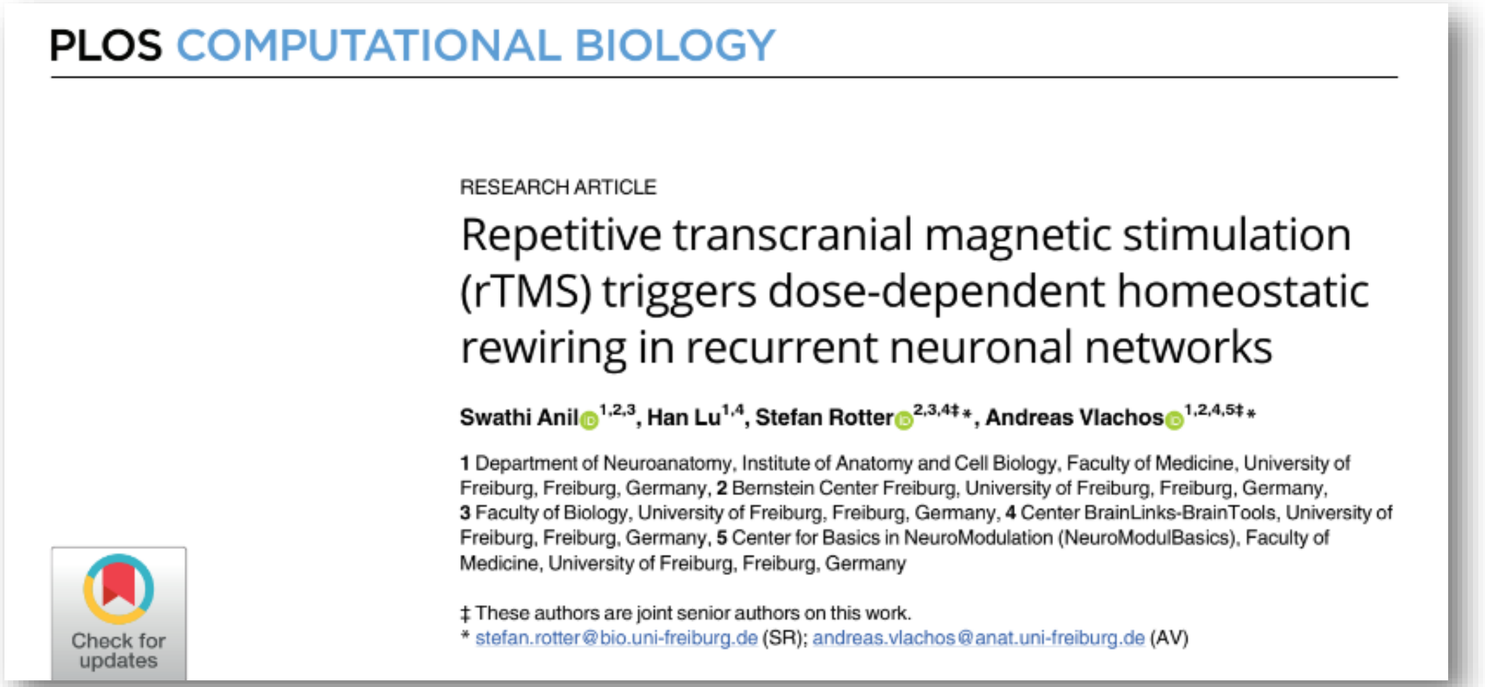
J Physiol 602.10 (2024) pp 2253–2264

Investigating the effects of dopamine on short- and long-latency afferent inhibition

Stevie D. Foglia[1], Faith C. Adams[2], Karishma R. Ramdeo[2], Chloe C. Drapeau[2], Claudia V. Turco[3], Mark Tarnopolsky[4], Jinhui Ma[5] and Aimee J. Nelson[1,2]



SAI is increased **in the presence of l-DOPA** while LAI is not significantly altered.



PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Repetitive transcranial magnetic stimulation (rTMS) triggers dose-dependent homeostatic rewiring in recurrent neuronal networks

Swathi Anil[1,2,3], **Han Lu**[1,4], **Stefan Rotter**[2,3,4‡*], **Andreas Vlachos**[1,2,4,5‡*]

1 Department of Neuroanatomy, Institute of Anatomy and Cell Biology, Faculty of Medicine, University of Freiburg, Freiburg, Germany, **2** Bernstein Center Freiburg, University of Freiburg, Freiburg, Germany, **3** Faculty of Biology, University of Freiburg, Freiburg, Germany, **4** Center BrainLinks-BrainTools, University of Freiburg, Freiburg, Germany, **5** Center for Basics in NeuroModulation (NeuroModulBasics), Faculty of Medicine, University of Freiburg, Freiburg, Germany

‡ These authors are joint senior authors on this work.
* stefan.rotter@bio.uni-freiburg.de (SR); andreas.vlachos@anat.uni-freiburg.de (AV)

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The authors propose a new mechanism “activity-dependent homeostatic structural remodeling“, which is sensitive to specific parameters of the stimulation protocol, i.e. frequency, intensity, and duration of stimulation.

Particularly, the feedback-inhibition initiated by network stimulation influenced the net stimulation outcome and hindered the rTMS-induced structural reorganization, highlighting the role of inhibitory networks.

Conclusions

The past decade has witnessed an important advance in genetics of dystonia, and in turn, in the generation of animal models.

Extensive characterization of models of dystonia provided evidence for specific alterations, such as altered neurochemical and synaptic plasticity alterations.

Shared pathways are now being recognized, and characterized. These advances might pave the way to a novel, biological classification of dystonia, which might help designing common therapeutic strategies.

Dystonia: Bridging Theory and Hands-On Expertise

September 5-6, 2025 | Istanbul, Turkey

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