SAMUEL BELZBERG
INTERNATIONAL
DYSTONIA
SYMPOSIUM

SAMUEL BELZBERG

6th INTERNATIONAL

DYSTONIA SYMPOSIUM

1st – 3rd JUNE 2023

CROKE PARK, DUBLIN, IRELAND

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Contents

Dear Colleagues,

Céad Mile Fáilte!

It is with great pleasure – and a traditional Irish 'one hundred thousand welcomes' -- that we welcome you to the 6th Samuel Belzberg International Dystonia Symposium in Dublin.

We are so pleased that you are joining us for this important and long-awaited conference. The original planning began in the spring of 2017 for the symposium that had been set for June 2020. COVID required the rescheduling of the symposium, and finally, three years later, we are so glad to be here in beautiful Dublin with all of you.

Thank you all for recognizing the tremendous benefits of meeting in-person. We encourage you to take advantage of the opportunity to connect with your colleagues from around the world, to meet with the symposium's sponsors, and to view over 100 posters.

Dystonia research has progressed in many ways since the last international symposium held in Barcelona in October 2011. We know you will find this new program enlightening, inspiring and rewarding. It is designed to provide you with an up-to-date overview of the field, highlight new thinking, and pose questions to identify new areas for exploration. We are looking forward to excellent presentations and to your participation in the discussions.

We want to thank the Members of the Scientific Program Committee for their dedicated work that went into developing this excellent program. Thank you, too, to our outstanding faculty for sharing their expertise, and to our sponsors for their support, without which we would not be able to mount this outstanding global event.

We also want to thank our conference organizers, Keynote PCO, for their excellent work in preparing for and managing the many moving parts of this symposium, and the planning, organizing and support of the Dystonia Medical Research Foundation and Dystonia Europe, the co-sponsors of this conference.

Again, one hundred thousand welcomes to you!

H. A Jinnah, MD, PhD
Scientific Program Co-Chair

Antonio Pisani, MD, PhD
Scientific Program Co-Chair

Scientific Program Committee

We are grateful to the Co-Chairs and Scientific Program Committee for their support in bringing this event to life and in helping to reaffirm the very strong international partnership which exists among dystonia scientists, clinicians, and patient organizations.

H.A. Jinnah, MD, PhD - US - Co-Chair
Antonio Pisani, MD, PhD - Italy- Co-Chair

Alberto Albanese, MD - Italy
Kailash Bhatia, FRCP, FAAN - UK
D. Cristopher Bragg, PhD - US
Cynthia Comella, MD - US
Susan Fox, MBBCh, PhD - Canada
Victor Fung, MBBS, PhD, FRACP - Australia
Mark Hallett, MD - US
Joseph Jankovic, MD - US
Ryuji Kaji, MD, PhD - Japan
Christine Klein, MD - Germany
Jean-Pierre Lin, MD, PhD - UK
Joel Perlmutter, MD - US
Maja Relja, MD, PhD - Croatia
Nutan Sharma, MD, PhD - US
Jan Teller, PhD - US
Marina de Koning-Tijssen, MD, PhD - Netherlands
Marie Vidailhet, MD - France

The organizers would also like to thank the dystonia researchers and clinicians who reviewed the many posters on display at the Symposium.

Brian Berman, MD
Aloysius Domingo, MD, PhD
Mark Hallett, MD
H. A. Jinnah, MD, PhD
Davide Martino, MD, PhD
Mark Moehle, PhD
Scott Norris, MD
Samuel Pappas, PhD
Antonio Pisani, MD, PhD
Jan Teller, PhD
Anne Weissbach, MD

Thank you to the following patient advocacy groups for supporting travel awards for young clinicians and investigators:

Beat Dystonia
Benign Essential Blepharospasm Research Foundation
Down with Dystonia
Dysphonia International
Dystonia Medical Research Foundation
Dystonia Medical Research Foundation-Canada
Dystonia Europe
International Parkinson and Movement Disorder Society
Joan Miller Young Investigator Scholarship Award

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DYSTONIA COALITION

Day 1: Thursday, 1 June 2023

HOGAN SUITE – LEVEL 5		
TIME	**TOPIC**	**SPEAKER**
08:00	Welcome message	F. Belzberg
08:10	Meeting goals & plans	H.A. Jinnah, A. Pisani, J. Teller
	I. INTRODUCTION TO DYSTONIA	**Chairs: H.A. Jinnah, M. Tijssen**
	Where are we now?	
08:20	Definition and classification of dystonia: How well is the 2013 Consensus Plan working?	A. Lang
08:45	Dystonia syndromes: Overlapping or distinct?	V. Fung
09:10	What is the relationship between dystonia, tremor, Parkinson disease, and ataxia?	K. Bhatia
09:35	Current treatment for dystonia: What are the successes? What can we do better?	J. Jankovic
10:00	Discussion	
10:10	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Breaking News and Highlights	**Chairs: A. Albanese, M. Relja**
10:30	Motor Cortex Activation During Writing in Focal Upper-Limb Dystonia: An fNIRS Study	R. Proa
10:35	Metabolic patterns in brain 18F-fluorodeoxyglucose PET relate to aetiology in paediatric dystonia	S. Tsagkaris
10:40	Immunological mechanisms in cervical dystonia	L. Scorr
10:45	Plasma proteomics profiling in adult-onset focal dystonia identifies ten proteins altered in focal dystonia as well as cervical and laryngeal dystonia subtypes	J. Timsina
	Point of View: Dystonia and tremor	
10:50	Dystonia plus tremor = a discrete entity known as dystonic tremor	A. Fasano
11:00	Dystonia plus tremor = two separate but frequently overlapping disorders	S. Pandey
11:10	Discussion	
	Hot topics: The science of phenotyping	
11:20	Pseudodystonia: How does it differ from "real" dystonia?	T. Lynch
11:30	Paroxysmal dyskinesias: A subtype of dystonia or a different entity?	S. Galosi
11:40	Discussion	
	Chair's summary & discussion with audience	**A. Albanese, H.A. Jinnah, M. Relja, M. Tijssen**

Day 1: Thursday, 1 June 2023

HOGAN SUITE – LEVEL 5		
TIME	**TOPIC**	**SPEAKER**
11:50	Chair's summary of the morning session	
12:30	**LUNCH BREAK & POSTER SESSION - HOGAN MEZZANINE LEVEL 4**	
	All posters viewable for entire meeting Posters P1.01 – P1.35 to present today from 13:30-14:30	
12:30 - 13:30	Satellite Symposium - Cervical Dystonia and Pain: Breaking Cycle - Canal Suite	Merz Pharmaceuticals
	II.SPECIAL TOPICS IN DYSTONIA	**Chairs: M. Carecchio, F. Morgante**
	Understanding mechanisms through the science of phenotyping	
14:30	Task-specific dystonias: What do they tell us about the etiology of dystonia?	M. Hallett
14:50	Sex differences across the dystonias: How can we begin to delineate mechanisms?	E. Hess
15:10	Autoimmune mechanisms in dystonia: What can they tell us about etiology in dystonia?	B. Balint
15:30	Dystonia in pediatrics: What can we learn from inherited metabolic disorders?	V. Leuzzi
15:50	Discussion	
16:00	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Point of View: Functional (psychogenic) dystonia	**Chairs: A. Espay, N. Sharma**
16:20	Functional dystonia: A manifestation of neurological disease	S. Aybek
16:30	Functional dystonia: A manifestation of psychiatric illness	A. Carson
16:40	Discussion	
	Point of View: Non-motor features of dystonia	
16:50	Non-motor features of dystonia: Shared biological substrates with motor features	K. Peall
17:00	Non-motor features of dystonia: An expected side effect of a chronic disorder	D. Martino
17:10	Discussion	
	Chair's summary & discussion with audience	**M. Carecchio, A. Espay, F. Morgante, N. Sharma**
17:20	Chair's summary of the afternoon session	
17:30	**WELCOME RECEPTON - HOGAN MEZZANINE LEVEL 4**	

Day 2: Friday, 2 June 2023

HOGAN SUITE – LEVEL 5		
TIME	**TOPIC**	**SPEAKER**
	III. ANATOMICAL BASIS FOR DYSTONIA	**Chairs: K. Simonyan, J. Mink**
	What areas of the nervous system are responsible for dystonia?	
08:00	Organization of normal movement: cortex, basal ganglia and cerebellum	J. Rothwell
08:20	Structural imaging of dystonia: Modern lesion network mapping	M. Fox
08:40	Functional imaging of dystonia: Common themes or too much heterogeneity?	J. Stoessl
09:00	Anatomical basis for dystonia: What can we learn from animal studies?	R. Sillitoe
09:20	New imaging methods: How can they be applied in dystonia?	J. Perlmutter
09:40	Discussion	
10:00	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Breaking News and Highlights	**Chairs: J. P. Lin, M. Vidailhet**
10:30	Reduced penetrance, variable clinical expressivity, and genetic overlap in monogenic forms of dystonia and parkinsonism	L. Lange
10:35	Atypical nuclear envelope condensates linked to Dystonia are proteotoxic and reveal nucleoporin-directed chaperone activities	C. Schlieker
10:40	Transcriptomics in postmortem brains and neuronal models uncover targetable signatures for antisense oligonucleotide therapy in X-linked dystonia-parkinsonism	A. Domingo
10:45	Specific cerebellar spike train signatures predict the behavioral presentation of cerebellar pathophysiology	M. van der Heijden
	Point of view: Developmental or degenerative?	
10:50	Dystonia is a developmental disorder	W. Dauer
11:00	Dystonia is a degenerative disorder	R. Kaji
11:10	Discussion	
	Point of view: Integrative models	
11:20	Cervical dystonia is caused by a defect in the neural integrator for head control	A. Shaikh
11:30	Cervical dystonia is caused by a defect in the network for attentional orienting	C. Fearon
11:40	Discussion	

Day 2: Friday, 2 June 2023

HOGAN SUITE – LEVEL 5		
TIME	**TOPIC**	**SPEAKER**
	Chair's summary & discussion with audience	**J. P. Lin, J. Mink, K. Simonyan, M. Vidailhet**
11:50	Chair's summary of the morning session	
12:30	**LUNCH BREAK & POSTER SESSION - HOGAN MEZZANINE LEVEL 4**	
	All posters viewable for entire meeting Posters P2.01 – P2.35 to present today from 13:30-14:30	
12:30 - 13:30	Satellite Symposium - A Closer Look at BOTOX for Treatment of Cervical Dystonia - Canal Suite	AbbVie Inc.
	IV. PHYSIOLOGICAL BASIS FOR DYSTONIA	**Chairs: M. Hallett, D. Standaert**
	Functional changes in neural activity	
14:30	Physiological changes in human dystonia: Where are we now?	R. Chen
14:50	Deep brain stimulation in humans: What can we learn about etiology?	M. Vidailhet
15:10	Physiological basis for dystonia: What can we learn from animal studies?	A. Pisani
15:30	Cerebellar stimulation for dystonia?	A. Lozano
15:50	Discussion	
16:00	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Point of view: Sensorimotor integration	**Chairs: A. Berardelli, E. Roze**
16:20	Abnormal sensory processes are a fundamental defect underlying dystonia	M. Tinazzi
16:30	Abnormal Sensory Processes are a Non-Specific Consequence of the Disorder	A. Conte
16:40	Discussion	
	Point of view: Maladaptive plasticity	
16:50	Abnormal plasticity is the fundamental defect underlying dystonia	A. Quartarone
17:00	Abnormal plasticity is a non-specific consequence of many movement disorders	A. Sadnicka
17:10	Discussion	
	Chair's summary & discussion with audience	**A. Berardelli, M. Hallett, E. Roze, D. Standaert**
17:20	Chair's summary of the afternoon session	

Day 3: Saturday, 3 June 2023

HOGAN SUITE – LEVEL 5

TIME	TOPIC	SPEAKER
	V. MOLECULAR MECHANISMS	**Chairs: N. Calakos, C. Klein**
	Dystonia genes: A growing list	
08:00	Overview of dystonia genetics	M. Zech
08:20	Dystonias with partial penetrance: What are the biological mechanisms?	C. Ip
08:40	Induced pluripotent stem cells: Novel technologies and application to dystonia	C. Bragg
09:00	Shared biological pathways in dystonia: One or many paths to novel therapeutics?	N. Mencacci
09:20	Novel ways to exploit existing resources	J. Teller
09:40	Discussion	
10:00	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Breaking News and Highlights	**Chairs: K. Lohmann, L. Ozelius**
10:30	Pathophysiology of Dyt1 dystonia is mediated by spinal cord dysfunction	A. Pocratsky
10:35	Secondary modifiers in the development of dystonia in genetically predisposed rodents for DYT-TOR1A dystonia – a role for microglia	L. Rauschenberger
10:40	Dopamine-Acetylcholine interplay at the pallidal-amygdala circuit in a DYT1 mouse model of Dystonia	G. Sciamanna
10:45	Cerebellar 5HT-2A receptor mediates stress-induced onset of dystonia	D. Kim
	Point of view: What is a "dystonia gene"?	
10:50	The list of "DYT" genes	C. Marras
11:00	The list of "other" genes	K. Lohmann
11:10	Discussion	
	Point of view: Rare monogenic dystonias vs common idiopathic dystonias	
11:20	Monogenic dystonias: shared mechanisms with common idiopathic dystonias	N. Calakos
11:30	Monogenic dystonias: mechanisms distinct from more common idiopathic dystonias	R. Erro
11:40	Discussion	

Day 3: Saturday, 3 June 2023

HOGAN SUITE – LEVEL 5

TIME	TOPIC	SPEAKER
	Chair's summary & discussion with audience	**N. Calakos, C. Klein, K. Lohmann, L. Ozelius**
11:50	Chair's summary of the morning session	
12:30	**LUNCH BREAK & POSTER SESSION - HOGAN MEZZANINE LEVEL 4**	
	All posters viewable for entire meeting Posters P3.01 – P3.25 to present today from 13:00-14:00	
	VI. EXPERIMENTAL THERAPEUTICS	**Chairs: S. Fox, D. Dressler**
	Novel therapeutics on the horizon	
14:30	Novel experimental oral therapeutics: What are the targets?	H. A. Jinnah
14:50	Botulinum toxin therapy: What are the new trends?	C. Comella
15:10	Surgical therapies: What's next?	E. Moro
15:30	Clinical trials: What are the obstacles to testing new options?	S. Pirio Richardson
15:50	Discussion	
16:00	**COFFEE BREAK - HOGAN MEZZANINE LEVEL 4**	
	Hot topics: Some recent successes	**Chairs: B. Balint, J. Perlmutter**
16:20	Physical and occupational therapy in dystonia:	M. Tijssen
16:40	Inherited dystonias with targeted therapies	A. Meneret
17:00	PKAN: One enzyme defect, multiple targets	B. Pérez Dueñas
	Chair's summary & discussion with audience	**B. Balint, D. Dressler, J. Perlmutter, S. Fox**
17:20	Chair's summary of the afternoon session	
17:30	Closing Remarks	H. A. Jinnah, A. Pisani
18:00	**CONFERENCE CONCLUDES**	

Satellite Symposium

June 1, 2023 - 12:30-13:30

Satellite Session 1

Cervical Dystonia and Pain: Breaking the Cycle

» **Pain in Cervical Dystonia: A Vicious Cycle**
H. A. Jinnah, MD, PhD

» **Pain Reduction in Cervical Dystonia Following Treatment with Botulinum Toxin**
A. Albanese, MD

Sponsored by Merz Pharmaceuticals, Frankfurt am Main, Germany

Satellite Session 1 will be held at Croke Park in the Canal Suite.
Lunch will be provided outside the meeting room.

June 2, 2023 - 12:30-13:30

Satellite Session 2

A Closer Look at BOTOX for the Treatment of Cervical Dystonia

» Mark Klafter, DO

Sponsored by AbbVie Inc., North Chicago, United States of America

Satellite Session 2 will be held at Croke Park in the Canal Suite.
Lunch will be provided outside the meeting room.

Faculty

Alberto Albanese, MD
Humanitas Research Hospital,
Italy

Alberto Albanese graduated from the Catholic University Medical School in Rome, Italy, and received his certification in neurology and psychiatry. In 1984, Alberto Albanese was appointed Assistant Professor in Neurology and Director of the Movement Disorders Clinic at the Gemelli Hospital in Rome, and in 1992, was appointed Associate Professor of Neurology. In 1996, he was appointed Professor of Neurology and co-Chairman of the Department of Neurology, University of Lausanne, Switzerland, where he stayed until 2000. In 2000, Alberto Albanese returned to his native country, where he was appointed Professor of Neurology and Head Neurologist at the National Neurological Hospital "Carlo Besta," Milan. He currently holds the same position.

His research interest became focused mainly on dystonia, Parkinson's disease, and other parkinsonian syndromes. His publications cover an ample spectrum of movement disorders, including choreas and tics. He has been a pioneer in the introduction of botulinum toxins in Italy and has pioneered the use of deep brain stimulation in Parkinson's disease and other movement disorders. In this clinical capacity, Prof. Albanese has raised several generations of Italian neurologists with expertise in movement disorders and has mentored medical graduates who now hold neurological positions of international stance.

Selma Aybek, MD
Inselspital,
Bern, Switzerland

Dr Selma Aybek completed her Medical training and Neurology residency in Lausanne, Switzerland. After she received her specialist title in 2007, she did a 3-year fellowship at the Institute of Psychiatry in London (King's College University) where she trained in Neuroimaging and in Cognitive Neuropsychiatry with Professor Anthony David.

Her main research and clinical interest focuses on Functional Neurological Disorder (Conversion Disorder) a paradigmatic neuropsychiatric disorder. She currently runs a clinic dedicated to patients suffering from Functional Neurological Disorders (FND) at Bern University Hospital in Switzerland and leads a research program aimed at underpinning the neural correlates of this disorder. She has been appointed Associate Professor of Neurology in May 2020 at Bern University, Switzerland. She has been awarded several prizes for her research in the field and is Deputy- Chair of the Committee on Research of the American Neuropsychiatric Association (ANPA) and member of the Board of Directors of the Functional Neurological Disorder Society, where she contributes to the teaching and development of clinical practice recommendations for FND.

She currently runs a 4-year research project funded by the Swiss National Research Foundation to study: 1. the role of Stress in FND, 2. the effect of non-invasive brain stimulation on neuronal network of motor control and 3. the effect of stress reduction techniques on clinical outcome. She recently has been appointed Full Professor of Neurology at Fribourg University in Switzerland where she will continue her teaching and research activities.

Bettina Balint
University of Zurich,
Zurich, Switzerland

Bettina Balint is a professor for clinical research in complex movement disorders at the University of Zurich and head of the movement disorders department of the University Hospital Zurich. She trained in neurology, neuroimmunology and movement disorders in Heidelberg, London and Oxford. Her clinical and academic interest focuses on autoimmune movement disorders, their phenotyping, treatment and identification of new biomarkers.

She serves as chair of the MDS Stiff Person Task Force and German stiff person guidelines, and as scientific advisor of the German Stiff Person patient group. She serves on different editorial boards, reviews for various journals and has numerous publications including journal articles and book chapters, and has lectured at various national and international meetings.

Alfredo Berardelli, MD
Sapienza University of Rome,
Rome, Italy

He received his medical degree Cum Magna Laude in 1976, at the Medical School, University of Rome "La Sapienza" and obtained his neurological training and specialization in Neurology in 1980 at the Department of Neurological Sciences in the same University.

He obtained training at the Brigham and Women's Hospital, Harvard Medical School, Boston, USA, from 1980 to 1981 and subsequently at the Department of Neurology, Institute of Psychiatry, King's College Medical School, University of London, England from 1983 to 1984. He was promoted to Full Professor of Neurology in 2001 at the Department of Human Neuroscience, Sapienza University of Rome.

His main research interest focused on physiology and pathophysiology of the motor system and movement disorders. His work has covered topics such as physiology and pathophysiology of the motor system, Dystonia, Parkinson's disease, Huntington's Disease, Tourette's Syndrome, Tremor, Myoclonus, Paroxysmal dyskinesias, various neurodegenerative disorders, and medical, and experimental therapeutics of movement disorders.

He has conducted numerous basic and clinical researches and published 632 original articles (number of Citations 34305; H-index = 82 Scopus).

Prof. Berardelli has served on the editorial board and has acted as referee on several Journals, including Brain, Clinical Neurophysiology, Experimental Brain Research, Journal of Neurology, Neurosurgery and Psychiatry, Journal of Neurology, Movement Disorders, Muscle and Nerve, Neurology, Neuroscience Letters.

Prof. Berardelli has served as Secretary of the International Motor Disturbances Society (1991-1992) and as Secretary of the Movement Disorders Society (1993-1996), Chairman of the "Educational Committee" of the Movement Disorder Society (1996-1998), Chairman of the European Section of the Movement Disorders Society (2008-2011), General Secretary of the Italian Society of Neurology (2010-2013), President of LIMPE (Parkinson's disease and other extrapyramidal disorders (2011-2013), President of the Academy for Parkinson's disease and other Movement Disorders (2014-2016). He is now President of the Italian Society of NeurologyBrief Bio:

Kailash P. Bhatia, MD, DM, FRCP
University College London,
London, United Kingdom

Professor Bhatia is Professor of Clinical Neurology in the Department of Clinical and Movement Neuroscience at UCL, Queen Square, London. He did his initial medical training in India followed by fellowships in neuro-genetics and movement disorders with the late Profs Anita Harding and David Marsden in London. His main focus is in dystonia and a range of movement disorders, merging clinical, genetic and

electrophysiological methods to describe clinical phenotypes and pathophysiology. Professor Bhatia has over 820 peer reviewed publications and several books. He has been privileged to receive the Honorary membership of the MDS in 2021 and honoured to do the Stanley Fahn Oration in 2022 at the MDS congress in Madrid. He has been nominated the chairman- elect of the MDS-ES and is co-chief editor of the Movement Disorders Clinical Practise (MDCP) journal.

D. Cristopher Bragg, PhD
Massachusetts General Hospital
Boston, United States of America

Cristopher Bragg is an Associate Professor of Neurology at Massachusetts General Hospital and Harvard Medical School. He also serves as Director of the Collaborative Center for X-linked Dystonia-Parkinsonism, an international coalition focused on developing new treatments for XDP, which is a rare form of dystonia endemic to the Philippines. He received his undergraduate degree in psychology at Duke University and his PhD in neurobiology at the University of North Carolina at Chapel Hill, followed by postdoctoral training at Massachusetts General Hospital. Research in the Bragg laboratory is directed toward the identification of pathogenic mechanisms underlying hereditary forms of dystonia primarily through the use of induced pluripotent stem cells (iPSCs) and genome editing.

Nicole Calakos, M.D., Ph.D.
Duke University Medical Center,
Durham, USA

Nicole Calakos, M.D., Ph.D. is the Lincoln Financial Group Distinguished Professor of Neurology and Neurobiology and Chief of the Movement Disorders section in Neurology at Duke University Medical Center. Dr. Calakos received her bachelor's degree from the University of California a-Berkeley, M.D. and Ph.D. degrees from Stanford University, and residency in Neurology at University of California-San Francisco.

Her laboratory studies mechanisms of synaptic plasticity in basal ganglia circuitry. The Calakos lab has advanced understanding of habit formation, compulsive behavior and dystonia and generated new methodologies to study basal ganglia physiology.

Dr. Calakos is a member of the National Academy of Medicine, fellow of the American Association for the Advancement of Sciences, and 2023 recipient of the ASCI/ Korsmeyer research award. Dr. Calakos advocates for basic and translational neuroscience through activities that have included: American Neurological Association, Duke Institute for Brain Sciences, NIH study sections, and scientific advisory boards for Tourette's Syndrome and dystonia foundations.

Miryam Carecchio, MD, PhD
University of Padua,
Padua, Italy

Miryam Carecchio a professor of Neurology at the Department of Neuroscience, Padua University, Italy. She graduated and obtained board certification in Neurology in Italy and did a fellowship in Queen Square, London, under Prof. K. Bhatia. She got a PhD in Milan focusing on pediatric movement disorders and she has developed an expertise in rare genetic movement disorders as well as metabolic ones. Her research interests include rare, genetically undefined movement disorders and disorders of metal and calcium accumulation in the brain, with a special focus on primary familial brain calcification (PFBC). She sits in the Italian Movement Disorder Society executive committee, is a member of the MDS-ES

educational committee and the chair of the Membership Committee of the International Parkinson's disease and Movement Disorder Society; she also sits in the scientific committee of the Italian Association for the study of dystonia (ARD).

Alan Carson MBCHB, MPHIL, MD, FRCPSYCH, FRCP
University of Edinburgh,
Edinburgh, United Kingdom

Prof Carson works as a Consultant Neuropsychiatrist at the Royal Infirmary of Edinburgh where he splits his time between a general neuropsychiatry service and running a hyper-acute rehabilitation service for brain trauma in South East Scotland.

He is also an Honorary Professor in Neuropsychiatry based in Clinical Brain Science at the University of Edinburgh. The Functional Disorders Research group in Edinburgh, which he runs along with Jon Stone has produced influential work on clinical phenotype, classification, epidemiology and treatment. Along with Mark Hallett, Chief of Human Motor Control NINDS, and Jon he published the Handbook of Neurology- Functional Neurological Disorders (Elsevier 2016).

They then launched a new international society the Functional Neurological Disorder Society; he is the current president. He holds a number of advisory posts in neuropsychiatry. He is the associate editor of Journal of Neurology, Neurosurgery and Psychiatry and was a previous President of the British Neuropsychiatry Association. He was awarded the President's Medal of the Royal College of Psychiatrists in 2017.

Robert Chen, MA, MBBChir, MSc, FRCPC
University of Toronto
Toronto, Canada

Robert Chen received an MA and medical degrees from the University of Cambridge, and M.Sc. degree from the University of Toronto.

He undertook Neurology residency at the Western University and fellowship at the NIH. He is currently Professor of Medicine (Neurology) at the University of Toronto, Senior Scientist at the Krembil Brain Institute, Editor-in-Chief of the Canadian Journal of Neurological Sciences and Associate Editor for Movement Disorders.

His research interests are human motor physiology, brain plasticity, understanding the pathophysiology and development of new treatments for movement disorders such as dystonia and Parkinson's disease. He has published over 370 research papers, published a book and edited two books in 2022. He is an expert in the pathophysiology of movement disorders, transcranial magnetic stimulation and transcranial ultrasound stimulation. He has served on the advisory boards of many advocacy groups, including the Dystonia Medical Research Foundation.

Cynthia Comella, MD, FAAN, FASM, FANA
Rush University Medical Center,
Chicago, United States of America

Cynthia L. Comella, MD, is a Professor in the Department of Neurological Sciences at Rush University Medical Center, Chicago, Illinois.

She is an active member of the International Parkinson and Movement Disorders Society, and is the current Past- Chair of the Pan American Section of the MDS, Immediate past Chair of LEAP leadership committee and first Chair of the nominating committee. She is a past Secretary of the MDS and has served in on the Executive Committee,

the Congress Scientific Programming Committee, the Continuing Medical Education committee and chaired the first MDS Education committee.

She is active in the American Academy of Neurology, having served in various committees including the Science Committee, Chair of the Education committee, the Annual Meeting subcommittee, editorial board of Continuum and the Board of Directors of the AAN institute and currently is the director of the Women in Leadership program. She organized and chaired the Dystonia Study Group and serves on the Steering committee of the Dystonia Coalition. Dr. Comella is the author or co-author of more than 175 articles, reviews, research papers, books, and book chapters about various topics including Parkinson's disease, dystonia, sleep-related movement disorders, restless legs syndrome, and botulinum toxin.

She is particularly interested in dystonia treatment and has been very active in the field of botulinum toxins. She was recently elected president of the International Neurotoxins Society.

Antonella Conte, MD, PhD
Sapienza, University of Rome
Rome, Italy

Antonella Conte is an Associate Professor of Neurology at the Department of Human Neurosciences, Sapienza, University of Rome.

She earned her medical degree, Specialty in Neurology and PhD from Sapienza, University of Rome. She is an expert on Parkinson's disease, dystonia, and other movement disorders.

Her research interests include the investigation of the pathophysiological mechanisms of movement disorders, clinical features of dystonia, and non-motor symptoms of dystonia. She is a Board Member of the Italian Neurological Society.

William Dauer, MD
University of Texas,
Southwestern Dallas, United States of America

William (Bill) is Professor of Neurology & Neuroscience and the inaugural Director of the Peter O'Donnell Jr. Brain Institute at the University of Texas Southwestern Medical Center in Dallas, Texas.

His academic career includes a medical degree from Washington University School of Medicine in St. Louis followed by internship and fellowships at Beth Israel Hospital in Boston and Columbia University in New York. For over two decades, the team he leads has performed groundbreaking research focused on the molecular basis of dystonia and the mechanisms of neurodegeneration in Parkinson's disease. Bill is an elected member of the American Society for Clinical Investigation, and his work has been recognized with the Dystonia Medical Research Foundation's Fahn Award, the Michael J. Fox Foundation Bachmann-Strauss Prize for Excellence in Dystonia Research, and the Harold and Golden Lamport Award for excellence in clinical science research from Columbia University.

He has also served on the Medical & Science Advisory Board of the Dystonia Medical Research Foundation.

Marina de Koning-Tijssen, MD, PhD
University Groningen,
Groningen, The Netherlands

Professor Marina AJ Tijssen has clinical and leadership expertise in the area of hyperkinetic movement disorders.

Following her Neurology Residency at the Leiden University, with periods at Johns Hopkins University, USA, and the Institute of Neurology and Neurosurgery, Queens Square, UK, she established an internationally renowned movement disorders group first in Amsterdam and since 2012 at the University Medical Centre Groningen. She is chair of the Movement

Disorder Expertise Centre Groningen, that is officially part of an European Rare Network (ERN).

Her research line 'Hyperkinetic movement disorders' is from basic research to patient care, with a special focus on dystonia and myoclonus. She is president of the Dutch DystoniaNet and secretary-elect of the board of the International Parkinson and Movement Disorder Society.

Dirk Dressler, MD, PhD
Hanover Medical School
Hanover, Germany

Dirk Dressler, MD, PhD, obtained his medical education at Georg-August University, Goettingen, Friedrich-Alexander University, Erlangen and at Harvard Medical School, Boston, MA.

During this time he was scholar of Konrad-Adenauer-Foundation. He is a fully board certified neurologist and psychiatrist. After several years of postgraduate training at the National Hospital for Neurology and the Institute of Neurology, Queen Square, London, UK he took over a position as consultant neurologist and Associate Professor of Neurology at Rostock University, Rostock, Germany. In September 2008 he was appointed Full Professor of Neurology and Head of Movement Disorders Section at the Department of Neurology, Hannover Medical School, Hannover, Germany. Since 2021 he is Co-Director of the Neurotoxin Research Center, Tongji University Medical School, Shanghai, China.

He is one of the pioneers of botulinum toxin therapy in Europe. He published over 800 articles, book chapters and abstracts as well as several books on dystonia, other movement disorders and on botulinum toxin therapy. He is the author with the world-wide largest number of publications on botulinum toxin therapy. He received a honorary professorship of the University of Santiago de Chile, a honorary doctorate of the Medical University of Sofia, Bulgaria and numeous othe prestigious awards for his contributions to the development of botulinum toxin therapy. He holds visiting professorships of Sao Paulo University, Brazil, Monterrey University, Mexico, Sechenov Univerisity, Moscow, Russia and Tongji University, Shanghai, China. He also holds several patents on botulinum toxin therapy. During his career from 1985 until 2020 he attended 786 Meetings and gave 625 lectures in 241 cities in all continents. As of 31.05.22 he had a RG Score of 48.58, a RG h index of 59, 12367 citations and 72008 reads.

Roberto Erro, MD, PhD
University of Salerno
Salerno, Italy

Roberto Erro is senior lecturer in Neurology at the University of Salerno. He graduated and obtained his board certification in Neurology in Italy and did a fellowship in Queen Square, London.

He got a PhD focusing on sensory stimulation in dystonia and is currently coordinating the dystonia program including the botulinum toxin service at the university hospital in Salerno. His research interests include clinical features of tremor, dystonia and Parkinson's disease.

He sits in the Italian Movement Disorder Society executive committee and is member of the MDS Task Force on PD subtypes and of the IAPRD working group on myoclonus. He serves as associate editor for Movement Disorders and is member of the editorial board of Parkinsonism and Related Disorders, Nature Parkinson's Disease, Tremor and other hyperkinetic movement disorders.

Alberto J. Espay, MD, MSc, FAAN, FANA
University of Cincinnati
Cincinnati, United States of America

Alberto Espay is Professor and Endowed Chair of the James J. and Joan A. Gardner Center for Parkinson's disease at the University of Cincinnati.

He has served as Chair of the Movement Disorders Section of the American Academy of Neurology, Associate Editor of the

Movement Disorders journal, and on the Executive Committee of the Parkinson Study Group. He currently serves as President-Elect of the Pan-American Section of the International Parkinson and Movement Disorders Society.

He directs the first biomarker study of aging (CCBPstudy.com) designed to match people with neurodegenerative disorders to available therapies from which they are most biologically suitable to benefit, regardless of their clinical diagnoses.

Alfonso Fasano, MD, PhD, FAAN
University of Toronto,
Toronto, Canada

Dr. Alfonso Fasano holds the Chair in Neuromodulation at the University of Toronto and University Health Network. He is a Professor in the Department of Medicine (Division of Neurology) at the University of Toronto, a staff neurologist and co-director of the Surgical Program for Movement Disorders at Toronto Western Hospital, University Health Network, and a staff neurologist at the Hospital of Sick Children in Toronto.

He is a Clinician Investigator at the Krembil Research Institute and KITE – Toronto Rehabilitation Hospital. He leads the Core E (closed-loop capabilities) of the Center for Advancing Neurotechnological Innovation to Application (CRANIA) and sits in the scientific advisory board of the Dystonia Medical Research Foundation and International Essential Tremor Foundation. He is also an executive board member of the Canadian Neuromodulation Society, and the chair of the Normal Pressure Hydrocephalus study group and of the Tremor study group of the International Parkinson Movement Disorders Society.

Conor Fearon BE MB PhD
Mater Misericordiae University Hospital & St Vincent's University Hospital, Dublin, Ireland.

Conor Fearon is a consultant neurologist at the Mater Misericordiae University Hospital and St Vincent's University Hospital in Dublin. He is a graduate of engineering and medicine from University College Dublin, Ireland. He received his PhD in neural engineering from Trinity College Dublin in 2016 for work focusing on the quantitative assessment of freezing of gait in Parkinson's disease.

He undertook residency training in Ireland and subsequently completed a clinical fellowship in movement disorders as the Edmond J. Safra Fellow in Movement Disorders at Toronto Western Hospital with Prof. Anthony Lang and Prof. Susan Fox. His research focuses on the application of technology for diagnosis and prognosis of movement disorders as well as its use in further our understanding of their pathophysiology He is particularly interested in the quantitative assessment of clinical features of movement disorders including parkinsonism and dystonia.

Michael D. Fox, MD, PhD
Brigham and Women's Hospital,
Boston, United States of America

Michael D. Fox, MD, PhD, is the founding Director of the Center for Brain Circuit Therapeutics at Brigham and Women's Hospital and Associate Professor of Neurology at Harvard Medical School. He is the inaugural Raymond D. Adams Distinguished Chair of Neurology and the Kaye Family Research Director of Psychiatric Brain Stimulation.

Degrees: Electrical Engineering at Ohio State University, an MD and PhD at Washington University in St. Louis, and Neurology Residency and Movement Disorders Fellowship at Mass Gen Brigham. Clinically specializes in the use of invasive and

noninvasive brain stimulation for the treatment of neurological/psychiatric diseases.

Dr. Fox's research focuses on developing new and improved treatments for brain disease by understanding brain circuits and the effects of neuromodulation. His papers have been cited over 39,000 times resulting in awards across the fields of neurology, psychiatry, and brain stimulation. Honors include the inaugural Trailblazer Prize for Clinician Scientists from the NIH.

Susan Fox MB, ChB, MRCP(UK), PHD
University of Toronto,
Toronto, Canada

Dr. Fox is Chair of the Pan-American section of the International Parkinson and Movement Disorder Society (MDS) (2021-23). She was chair of the Evidence based medicine review committee for the MDS 2013 – 2017 and Secretary of the MDS 2017 – 2019. She has served on many committees; grant review and advisory boards for the MDS, NIH, CIHR, and Michael J Fox Foundation for Parkinson research among others. She is a Fellow of the American Neurological Association and the American Academy of Neurology.

Dr. Fox has over 25 years' experience in preclinical models of Parkinson's disease and translational studies of novel pharmacological therapies for Parkinson's disease and other movement disorders such as dystonia. She has published over 200 peer-reviewed papers, reviews and book chapters in the field and is a regular speaker at national and international conferences. She was the Gordon Holmes Invited Lecturer at the annual Association of British Neurologist meeting May 2022.

Victor Fung, MBBS, PhD, FRAep
Westmead Hospital,
Sydney, Australia.

He is President-Elect of the International Parkinson and Movement Disorder Society (MDS), and a past-President of the Movement Disorder Society of Australia and New Zealand (MDSANZ). He was the founding Chairperson of the MDSANZ Clinical Research and Trials Group. He is or has been a member of the Parkinson's Australia, Parkinson's NSW and Dystonia Network Australia Scientific Advisory Boards.

He serves on the Editorial Board of npg Parkinson's Disease, the Journal of Clinical Movement Disorders, previously Movement Disorders (2007-2010 & 2015-2021) and Movement Disorders Clinical Practice (2013-2021), and is a member of Faculty Opinions. He has a clinical and research interest in dystonia and other movement disorders, with Westmead Hospital being a member of the Dystonia Coalition.

Serena Galosi, MD, PhD
Sapienza University
Rome, Italy

Serena Galosi is Assistant Professor in Pediatric Neurology and Childhood and Adolescence Psychiatry at the Department of Human Neuroscience of Sapienza University in Rome. She earned her medical degree and PhD title from the Sapienza University in Rome. During her PhD course she spent a year as Research Fellow at the Movement Disorders Clinic of the University of California San Diego under the supervision of Prof Jennifer Friedman. Her clinical and research activity focuses on pediatric rare movement disorders of neurometabolic and neurogenetic nature, including treatable and neurodegenerative disorders. Her Institution has a longstanding commitment to the study of neurometabolic disorders, and is partner of the European Reference Network for metabolic disorders (MetabERN). She has been an active member of the International

Parkinson and Movement Disorder Society (MDS) since 2016 where she has presented multiple invited lectures on rare pediatric movement disorders.

Mark Hallett, MD
National Institute of Neurological Disorders and Stroke, NIH
Bethesda, United States of America

Mark Hallett is an NIH Distinguished Investigator Emeritus at NINDS. He earned his BA and MD at Harvard, did his neurology training at the Massachusetts General Hospital, and spent a fellowship year at the Institute of Psychiatry in London. He is a clinical neurophysiologist as well as movement disorder expert. His research interest is in the physiology of human movement and the pathophysiology of movement disorders, including dystonia. He is a past president of the Movement Disorder Society, is the current past president of the Functional Neurological Disorder Society, and has served on the advisory boards of many patient advocacy groups, including the Benign Essential Blepharospasm Research Foundation and the Dystonia Medical Research Foundation.

Ellen J. Hess, Ph.D
Emory University,
Atlanta, United States of America

Ellen J. Hess, Ph.D. is a Professor in the Departments of Pharmacology and Chemical Biology and Neurology at Emory University School of Medicine.

Dr. Hess received her B.A. in Psychobiology from Wellesley College and Ph.D. in Neuroscience from University of California at San Diego with postdoctoral training at The Scripps Research Institute. Before joining the faculty at Emory University in 2008, she was a professor at Johns Hopkins University School of Medicine. Dr. Hess' laboratory research focuses on understanding the neurobiological basis of movement disorders including Parkinson's disease and dystonia by understanding the specific abnormal neuronal signals.

Her research is currently focused on understanding why movement disorders appear different in males and females with the ultimate goal of identifying personalized approaches for the treatment of neurological disorders. Dr. Hess has published over 100 scientific papers, chaired numerous scientific review panels and is invited to speak on her work throughout the world.

Chi Wang Ip, MD
University Hospital Würzburg,
Würzburg, Germany

Chi Wang Ip is a professor of neurology and deputy chairman of the Department of Neurology at the University Hospital Würzburg. As a clinician scientist, he is an expert on Parkinson's disease and dystonia and runs a laboratory for translational neurology in parallel. His research is focused on understanding the molecular, cellular and network mechanisms underlying these movement disorders by implementing cell culture and rodent models and utilizing this understanding to develop novel treatment strategies to improve patient outcomes.

Joseph Jankovic, M.D.
Baylor College of Medicine
Houston, United States of America

Joseph Jankovic, M.D. is Professor of Neurology, Distinguished Chair in Movement Disorders, and Founder and Director of the Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas. Past president of the International Parkinson and Movement Disorder Society and of the International Neurotoxin Association, Dr. Jankovic is the recipient of many awards including the American Academy of Neurology Movement Disorders Research Award, Tourette Syndrome Association Lifetime Achievement Award, and Dystonia Medical Research Foundation (DMRF) Distinguished Service Award.

He has conducted many clinical trials, published over 1,500 articles, and has been ranked #1 expert in the world in movement disorders, dyskinesias, and in botulinum toxins (http://expertscape.com/). He has served on the executive scientific advisory board of the Michael J. Fox Foundation for Parkinson's Research and is current or past member of many scientific and medical advisory boards, including the DMRF. Dr. Jankovic has mentored numerous fellows many of whom have become leaders in the field of neurology and movement disorders.

H. A. Jinnah, MD, PhD
Emory University
Atlanta, United States of America

Hyder A. (Buz) Jinnah received his undergraduate degree from Duke University (Durham, North Carolina) and his M.D. and Ph.D. degrees from the University of California (San Diego, CA). He did his Neurology training at Johns Hopkins University (Baltimore, MD), and was on the faculty there for 10 years.

Currently he is Professor of Neurology and Human Genetics at Emory University in Atlanta. He is widely known for his research in movement disorders, and particularly dystonia and neurogenetics. His laboratory focuses on developing a better understanding of these disorders via genetics and biochemistry, cell and animal models, and clinical studies with patients. He has held multiple large NIH grants, and has published more than 300 articles.

Ryuji Kaji, MD, PhD
Tokushima University
Tokushima, Japan

Ryuji Kaji is a Distinguished Professor of Neurological Sciences at Tokushima University and served as First Vice President of World Federation of Neurology (2018-2021).

His career started as an electromyographer at University of Pennsylvania in 1985 after graduating from Kyoto University in Japan. He became interested in botulinum toxin therapy of movement disorders including dystonia. After returning to Kyoto in 1988, he found that dystonic symptoms were abated after blocking muscle afferents with diluted lidocaine, and were reproduced by stimulating muscle afferents with high-frequency vibration (TVR).

His work intrigued many neurologists to investigate the sensory aspects of dystonia. With his colleagues, he found the causative gene causing XDP(DYT3), and its pathology could explain the pathomechanism of dystonia.

Christine Klein, MD, FEAN
University of Luebeck
Luebeck, Germany

Dr. Christine Klein is a Professor of Neurology and Neurogenetics. She completed a fellowship in Molecular Neurogenetics in Boston and a series of summer sabbaticals in movement disorders in Toronto in 2004-2015. She was appointed Lichtenberg Professor at the Department of Neurology of Luebeck University in 2005, where her research has focused on the clinical and molecular genetics of movement disorders and its functional consequences.

In 2009, Dr. Klein was appointed Schilling Professor of Clinical and Molecular Neurogenetics at the University of Luebeck and became Director of the newly founded Institute of Neurogenetics in 2013. Dr. Klein is Deputy Editor of 'Movement Disorders' and 'Science Advances', was President of the German Neurological Society in 2019/2020, and is the current Chair-elect of the European Section of the International Parkinson and Movement Disorder Society (MDS-ES). She was elected a member of the National Academy of Sciences Leopoldina in 2021.

Anthony E. Lang, OC, MD, FRCPC, FAAN, FCAHS, FRSC.
University of Toronto,
Toronto, Canada

Dr. Lang is Professor and previous Director of the Division of Neurology at the University of Toronto where he holds the Jack Clark Chair for Parkinson's Disease Research. He is the Director of the Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre and the Morton and Gloria Shulman Movement Disorders Clinic and holds the Lily Safra Chair in Movement Disorders at the Toronto Western Hospital, University Health Network. He has published over 950 peer-reviewed papers and is one of the most highly cited investigators in the field of Movement Disorders. Among his awards and distinctions he was appointed as an Officer of the Order of Canada in 2010; in 2011 he was elected a Fellow of both the Canadian Academy of Health Sciences and the Royal Society of Canada; in 2014 he was elected by the International Parkinson and Movement Disorder Society (MDS) as an Honorary Member "in recognition of his extraordinary contribution to the field of Movement Disorders"; and in 2017 he was the recipient of the first MDS Pan-American Section Leadership Award. In 2018 he received the Weston Brain Institute International Outstanding Achievement Award for work in accelerating the development of therapeutics for neurodegenerative diseases of aging; in 2020 he received the Dean's Lifetime Achievement Award for global impact from the University of Toronto and in 2022 he received the Jay Van Andel Award for Outstanding Achievement in Parkinson's Disease Research and the Margolese National Brain Disorders Prize.

Vincenzo Leuzzi, MD, PhD
University of Rome La Sapienza,
Rome, Italy

Vincenzo Leuzzi is a full Child Neurology and Psychiatry professor at the Department of Human Neuroscience, University of Rome La Sapienza.

Until November 2022, he was chief of the Unit of Child Neurology and Psychiatry at the same University. Main research interests include pediatric neurometabolic disorders and neurodevelopmental and movement disorders associated with early-onset metabolic diseases. Unit of Child Neurology and Psychiatry and the related lab are Italian reference centres for diagnosing and treating neurotransmitter disorders in children and adults and over 100 rare neurological diseases in children. The unit is a member of European MetabErn.

Prof. Leuzzi participates in the following international boards: International Neurotransmitters Disorders (iNTD), European PKU Guideline Development group, international AADC and TH defect Guideline Development. He is a Member of the Society for the Study of Inborn Errors of Metabolism (SSIEM).

Dr Jean-Pierre Lin, MB ChB, MRCP(UK), PhD, FRCPCH.
Evelina London Children's Hospital,
London, UK

Dr Lin was an Edinburgh University Medical School George Guthrie Research Fellow and trained in pediatric neurology at the Edinburgh Royal Hospital for Sick Children and Great Ormond Street Hospital London with a special interest in movement disorders and the study of motor development.

He joined the Evelina London Children's Hospital, Guy's and St Thomas NHS Foundation Trust in 1996 as a consultant clinical-academic where he created the Complex Motor Disorders Service for Deep Brain Stimulation (DBS) and Intrathecal Baclofen (ITB) pump implantation in children.

He is particularly interested in the interactions between early motor development and movement disorders and promoted early intervention for childhood movement disorders.

Katja Lohmann, PhD
University of Luebeck
Luebeck, Germany

Katja Lohmann is a professor of Molecular Genetics of Rare Diseases at the Institute of Neurogenetics at the University of Luebeck, Luebeck, Germany.

She earned her bachelor's and master´s degree in biology from the Universities of Dresden and Halle (Germany), respectively. She was further trained at the PhD and postdoc level at the University of Luebeck (Germany), the Massachusetts General Hospital (Boston, MA), the Oregon Health and Science University (Portland, OR), and the Radboud University Medical Center Nijmegen (The Netherlands). Her research focuses on elucidating genetic factors for movement disorders such as dystonia, ataxia, and Parkinson´s disease. She is also interested in establishing genotype-phenotype correlations in these disorders. Together with her lab team, she aims to contribute to a better understanding of the molecular mechanism altered by pathogenic variants in disease-linked genes.

She serves in the scientific issues and awards committee for the Movement Disorder Society.

Andres M. Lozano, OC, MD, PhD, FRCSC, FRSC, FCAHS
University of Toronto,
Toronto, Canada

Dr. Lozano is a functional neurosurgeon and past Chairman of Neurosurgery at the University of Toronto. He holds the Alan & Susan Hudson Cornerstone Chair in Neurosurgery at University Health Network.

He is best known for his work in Deep Brain Stimulation and Focused Ultrasound. His world-leading programme has mapped cortical/subcortical circuits in the brain and advanced novel therapies for dystonia, Parkinson's disease, depression, Alzheimer's disease and other disorders.

Dr. Lozano has approximately 800 publications and is the most highly cited neurosurgeon in the world (Clarivate). He is most proud of the MD/PhD students and fellows he has mentored, who have gone on to become international leaders in their field. Dr. Lozano has received a number of honors including the Olivecrona Medal, Salk Award, and Dandy Medal and been elected to the Royal Society of Canada, Order of Spain and an Officer of the Order of Canada.

Timothy Lynch, MRCP, MRCPI
University College Dublin,
Dublin, Ireland

Professor Tim Lynch is Vice Principal for Health Affairs at University College Dublin (UCD), Chief Academic Officer at the Ireland East Hospital Group, Consultant Neurologist at the Mater Misericordiae University Hospital (MMUH), Director of the Dublin Neurological Institute at the Mater (DNI) (www.neurologicalinstitute.ie) and Professor of Neurology at UCD. A Royal College of Surgeons medical graduate and a UCD BSc Pharmacology graduate Prof Lynch trained in clinical medicine and neurology in Dublin and then spent eight years at Columbia Presbyterian Medical Centre/Columbia University New York completing a residency in neurology under the supervision of Prof Lewis P Rowland, a two-year Fellowship in Movement Disorders & Genetics of Neurodegeneration under Prof Stanley Fahn's supervision and was appointed an Assistant Professor of Neurology.

He developed an interest in genetics and studied an Irish-American family with frontotemporal dementia, parkinsonism and amyotrophy. Prof Lynch was part of a collaboration between Columbia University, Mayo Clinic, Washington University, St Louis and Maastricht University that successfully cloned MAPT (tau gene) associated with frontotemporal dementia (Hutton M et al. Nature 1998). Prof Lynch returned to Dublin as a Consultant Neurologist to develop the MMUH Department of Neurology and opened the DNI as a charity to develop excellence in academic clinical neuroscience. Prof Lynch has received grant funding from the NIH, EU, HRB, MJFF and Irish Institute of Clinical Neuroscience and has published over 300 articles in peer-reviewed journals (h index 61).

His research interests include academic health science systems, integrated care, movement disorders, Parkinson's disease, movement control, genetics of neurological disease, and frontotemporal dementia. Past leadership roles includes HSE national clinical lead in neurology, chairperson of the division of medicine, chairperson of the MMUH Medical Executive, and a number of key roles in the International Parkinson's disease & other Movement Disorders society.

Connie Marras, MD, PhD
University of Toronto,
Toronto, Canada

Dr. Marras trained in neurology and movement disorders at the University of Toronto, and subsequently obtained a PhD in epidemiology at the University of Toronto and further trained in epidemiologic research methods at the Parkinson's Institute in California.

She is currently a Professor of Neurology at the University of Toronto and holds the Catherine Manson Chair in Movement Disorders at the Toronto Western Hospital. She also serves as Co-Chair of the MDS Task Forces for Nomenclature of Genetically Determined Movement Disorders, and Parkinson's disease Subtypes and Vice-Chair of the research ethics board of the University Health Network in Toronto.

Areas of research focus include the epidemiology and clinical expression of Parkinson's disease, and evaluating clinical assessment tools in Parkinson's disease.

Davide Martino, MD, PhD
University of Calgary,
Calgary, Canada

Dr. Davide Martino is a Professor and Director of the Movement Disorders Program at the Hotchkiss Brain Institute at the University of Calgary.

His multidisciplinary research program is focused on the identification of endophenotypic and biological markers for the subtyping of complex movement disorders, primarily dystonia, tic and other neurodevelopmental disorders and Parkinson's disease. He is also conducting research to improve multidisciplinary pathways of care for complex movement disorders sitting at the interface between Neurology and Psychiatry, and on novel non-invasive neurostimulation approaches (alternate current stimulation, low intensity focused ultrasound stimulation).

Dr. Martino is the Secretary of the Canadian Movement Disorders Society and Executive Committee member of the Pan-American Section of the International Parkinson's and Movement Disorders Society.

Niccolò E. Mencacci, MD, PhD
Northwestern University,
Chicage, United States of America

Niccolò Mencacci is an Assistant Professor and Movement Disorders neurologist at Northwestern University, Chicago. He received his medical degree and completed his residency in Neurology at the University of Milan, Italy. He then obtained his PhD in neurogenetics at the Department of Molecular Neuroscience at the UCL Institute of Neurology , London UK.

He is now the Director of the Movement Disorders Genetics Clinic at Northwestern, where he focuses on clinical care of movement disorders patients with suspected genetic etiologies, combining in-depth clinical assessment with state of the art clinical and research genetic diagnostics (whole-exome sequencing, whole-genome sequencing). His research focuses on the identification of novel genetic causes of movement disorders, including Parkinson disease, dystonia and chorea. Furthermore, he combines genetics and a range of in vivo and in vitro models of movement disorders to study the molecular pathophysiological mechanisms underlying movement disorders.

Aurélie Méneret, MD, PhD
Pitié-Salpêtrière Hospital
Paris, France

Aurélie Méneret is a neurologist in the movement disorders unit of the Pitié-Salpêtrière Hospital in Paris. She earned her medical degree and PhD in neurosciences from Sorbonne Universités in Paris and was a post-doctoral researcher in Mount Sinai Hospital in New York.

She is an expert on Parkinson's disease, dystonia, and other movement disorders. Her research interests include genetics of dystonia and other rare movement disorders, as well as pathophysiological and pharmacological studies.

Jonathan W. Mink, MD PhD
University of Rochester,
Pittsford, United States of America

Jonathan Mink is a retired professor of Neurology, Neuroscience, and Pediatrics, formerly at the University of Rochester and Washington University in St. Louis. He is board certified in Neurology with Special Qualifications in Child Neurology. He earned his BA in Biology-Psychology and MA in Psychology from Wesleyan University. He earned his MD and PhD from Washington University in St. Louis. He is an expert on movement disorders in children with a focus on dystonia and Tourette syndrome. His research interests include the pathophysiology of movement disorders and experimental therapeutics in rare childhood-onset neurologic disorders.

He is past president of the Child Neurology Society and has served on advisory boards of many professional and patient advocacy groups, including the Dystonia Medical Research Foundation, the Tourette Association of America, the International Child Neurology Association, the Food and Drug Administration (Pediatrics Advisory Board), and National Institute of Neurological Disorders and Stroke (NINDS Advisory Council).

Francesca Morgante, MD, PhD
St. George's University of London,
London, United Kingdom

Francesca Morgante is Professor of Neurology at St. George's University of London, UK, and consultant neurologist at St George's University Hospital where she leads the Advanced Therapies Movement Disorders Team.

Her research mainly focuses on the clinical features and pathophysiological basis of Parkinson's disease, Dystonia and Functional Movement Disorders. One of her main research interests is to understand the neural basis of Cervical Dystonia with the aim to develop tailored neuromodulation strategies.

Prof Morgante has published more than 180 publications in peer-reviewed journals and several book chapters. She is an Associate Editor for Movement Disorders Journal and part of the editorial boards of Movement Disorders Clinical Practice, European Journal of Neurology and Journal of Neurology. She is part of the executive committee of the International Parkinson's disease and Movement Disorder Society, European section.

Elena Moro, M.D., Ph.D.
Grenoble Alpes University,
Grenoble, France

Dr. Elena Moro is a Professor of Neurology at the Grenoble Alpes Univeristy (France). She graduated in Medicine at the University of Trieste (Italy) and completed her residency in Neurology at the Catholic University in Rome (Italy).

She received her PhD in Neurosciences from the Catholic University in Rome. She is currently the Director of the Movement Disorders Center, and the Chair of the Department of Psychiatry, Neurology, Neurological Rehabilitation and Forensic Medicine at the CHU of Grenoble. Her major area of interest is surgical treatment of movement disorders, especially deep brain stimulation. She has been actively involved in the International Movement Disorders Society (MDS).

She is currently the President-Elect of the European Academy of Neurology, and the Treasurer of the International Association of Parkinsonism and Related Disorders (IAPRD).

Laurie Ozelius, PhD
Harvard Medical School
Massachusetts General Hospital
Charlestown, MA USA

Laurie Ozelius is an associate professor of Neurology at Harvard Medical School and associate neuroscientist at Massachusetts General Hospital.

She earned her undergraduate degree in biology from Brown University and her PhD in genetics from Harvard Medical School. She is an expert in genetics of dystonia and her lab has identified genes for several forms of monogenic dystonia. She has served on the scientific advisory boards of multiple patient advocacy groups, including the Dystonia Medical Research Foundation.

Sanjay Pandey, MD, DM
Amrita Hospital, Faridabad,
Delhi, India

Sanjay Pandey is a professor of Neurology and Stroke Medicine at Amrita Hospital, Faridabad, Delhi NCR.

He earned his fellowship in Parkinson's Disease and Movement Disorders from NINDS/NIH, Bethesda, USA under Mark Hallett. He is an expert on Parkinson's disease, dystonia, tremor, and other movement disorders.

His research interests include neurogenetics, clinical features of dystonia, neurophysiological studies of movement disorders, botulinum toxin, and deep brain stimulation. He is an executive committee member of the Asian Oceanian Section of the Movement Disorder Society and Movement Disorder Society of India.

Kathryn Peall, BMBCh, FRCP, PhD
Cardiff University
Cardiff, UK

Kathryn Peall is an MRC Clinician-Scientist and Transition Fellow, Clinical Senior Lecturer and Honorary Consultant Neurologist at Cardiff University and Cardiff and Vale University Health Board.

She attained her medical degree from the University of Oxford, and doctorate from Cardiff University. She has expertise in dystonia, rare genetic causes of dystonia and non-motor symptom phenotypes. Her research interests span population-level linked clinical data, use of wearable devices in phenotypic assessment, and stem cell models of Mendelian inherited forms of dystonia.

She is the director of clinical-academic training in Wales, a member of the Dystonia Medical Research Foundation Scientific Advisory Board, and Medical Advisor to Dystonia UK.

Belen Perez Dueñas, MD
Hospital Vall d'Hebron
Barcelona, Spain

Dr. Perez Duenas is a scientist and pediatric neurologist at Hospital Vall d'Hebrón in Barcelona. At the Pediatric Neurology Department, they are a national-leading group committed to provide the best care to children with complex neurological conditions, and to apply research and innovation to clinical healthcare.

She has been a pediatric neurologist since 2006. From the beginning, she was interested in rare metabolic and genetic conditions causing developmental delay, neurological deterioration and complex motor disorders. She has led several multi-center projects on inborn errors of metabolism, vitamin sensitive encephalopathies, neurodegeneration with brain iron accumulation disorders, mitochondrial disorders and genetic dystonia. In recent years, she has set up a Pediatric Neuromodulation Unit for the treatment of children with movement disorders. She is also a professor at the Department of Pediatrics, Universitat Autònoma de Barcelona, and is the director of several PhD thesis in the field of pediatric neurology.

Joel Perlmutter, MD
Washington University,
St. Louis, United States of America

Dr. Perlmutter received his AB in Biochemistry in 1975 from Princeton, and his MD from the University of Missouri in 1979.

He completed Neurology residency in 1983 at Washington University School of Medicine. He is the Elliot Stein Family Professor of Neurology; Professor of Radiology, Neuroscience, Physical Therapy, and Occupational Therapy; Director of the

American Parkinson Disease Association Advanced Research Center for Parkinson Disease and the Scientific Director of the Dystonia Medical Research Foundation.

His research focuses on biomarker discovery and studies of the pathophysiology of Parkinson disease, dystonia and related conditions. His research spans basic, translational and patient-oriented studies that includes work with nonhuman primates to develop, validate and apply new neuroimaging methods.

These fundamental methods then have been applied to multiple human studies of people with Parkinson disease, dystonia and related disorders. He has had continuous NIH funding for 37 years and published more than 365 peer-reviewed manuscripts.

Sarah Pirio Richardson, MD
University of New Mexico/New Mexico VA Health Care System
Albuquerque, United States

Sarah Pirio Richardson is a Professor of Neurology and Co-Director of the Comprehensive Movement Disorders Center at the University of New Mexico as well as the Chief of the Neurology Service at the New Mexico VA Health care system. She has NIH research support in Parkinson disease and Dystonia and is interested in tools to establish clinical trial readiness in rare disease.

She also has DOD funding in non-invasive neurostimulation in traumatic brain injury. She is on the Executive Committee of the Movement Disorders Society Pan-American Section and serves on the advisory boards of the Dystonia Medical Research Foundation and the Benign Essential Blepharospasm Research Foundation.

Antonio Pisani, MD, PhD
IRCCS Mondino Foundation,
Pavia, Italy

Antonio Pisani is a physician-scientist with a long-standing interest in the basic and clinical aspects of basal ganglia function and dysfunction, and coordinate a research group of both preclinical and clinical fellows.

For the last 20 years, he has been utilizing electrophysiology techniques to investigate the physiology of striatal neurons and the expression of activity-dependent plasticity at corticostriatal synapses. He contributed to the original description of novel forms of striatal synaptic plasticity, named long-term-depression (LTD) and long-term potentiation (LTP). This vital feature of corticostriatal synapses has then been characterized by several other groups.

His lab focused also on striatal interneurons, in particular cholinergic interneurons, a population giving rise to a high acetylcholine content in the basal ganglia. This extensive studies focused on the functional interplay between striatal dopamine and acetylcholine and led to the description of alterations occurring in multiple rodent models of Parkinson's disease and dystonia, reporting the early synaptic plasticity alterations observed in these models. Likewise, he reported the unprecedented evidence for the major role of striatal cholinergic interneurons in dystonia rodent models. These observations were subsequently validated by other research groups and offered the opportunity to test a number of pharmacological rescue approaches. These works were lately complemented by the introduction of optogenetics and molecular biology techniques.

His long-term commitment to research in movement disorders is witnessed by several peer-review publications, as well as by the organization of multiple editions of an international biennial symposium on Parkinson's disease and dystonia in Rome (2007-2019).

Angelo Quartarone, MD
University of Messina
Messina, Italy

Angelo Quartarone is the current Scientific Director of the Institute for Research and Care in Rehabilitative Neurosciences "IRCCS Centro Neurolesi Bonino Pulejo" and a Full Professor of Neurology and Neurophysiology at University of Messina. He earned his Degree in Medicine and Surgery and his Specialization in Neurology from the University of Messina.

His knowledge and research areas are: Clinical Neurophysiology of Movement Disorders, Transcranial Magnetic Stimulation, Study of Neuroplasticity within sensory-motor cortex in healthy humans and in basal ganglia disorders, Pathophysiology of dystonia and Pathophysiology of Parkinson's disease by means of neurophysiology and Neuroimaging., DTI and tractography. He is Deputy Editor of Frontiers System Neurosciences and Editorial Board of Journal of Clinical Movement Disorder.

He was Board Member of Italian Clinical Neurophysiological and of Italian Movement Disorder Society.

Maja Relja, MD, PhD
Zagreb University Medical School,
Zagreb, Croatia

Maja Relja MD, PhD is a full professor of neurology with permanent position at the Medical School University of Zagreb. She was founder and the head of the Referral Center for Movement Disorders and Neurodegeneration Ministry of Health, Republic of Croatia.

Born in Split, Croatia, she graduated in medicine from Zagreb University Medical School where she also received an MSc degree in Biomedical Sciences and Doctorship of Sciences. She was a Research Fellow at NIMH, Washington D.C., USA and Visiting Professor, Department of Neurology, Medical School, Turku University, Finland.

Her main research interests are in movement disorders (Parkinson's disease and dystonia) and in the development of novel clinical application of botulinum toxin. She was co-founder and a vice-president of Dystonia Europe. She is founder and president of Croatian Patients Association for Movement Disorders and a member of Croatian Academy of Medical Sciences.

John Rothwell, PhD
University College London,
London, United Kingdom

John Rothwell is currently Emeritus Professor of Human Neurophysiology at UCL Queen Square Institute of Neurology.

His main interests are in the physiology and pathophysiology of human movement and its disorders, and in basic mechanisms of restoration of function after brain injury, particularly stroke.

Current research projects include using neurophysiological techniques to study the mechanisms of neural plasticity that underpin motor learning, and using this knowledge to devise new therapeutic interventions for rehabilitation after stroke and in patients with Movement Disorders.

Emmanuel Roze, MD, PhD
Hôpital de la Salpêtrière,
Paris, France

Professor of neurology at Sorbonne University in Paris. He is consultant neurologist at the movement disorders clinic of the Salpêtrière hospital with special expertise in children with movement disorders.

He devised a transition program for adolescent and young adults living with chronic neurological illness. He works as a scientific researcher at Paris Brain institute, where his main research interests are neurodevelopmental disorders of the motor system, especially dystonia and mirror movements. He studies clinical aspects, genetic causes, pathogenesis and works on experimental therapeutics in preclinical models and patients with movement disorders.

Finally, he has a keen interest in teaching and developed an innovative simulation-based medical education program to teach neurological features to medical students, and a teaching podcast about care relationships. He co-created a monthly international virtual pediatric videorounds with the support of the movement disorders society.

Anna Sadnicka, MD, PhD
St George's University of London
London, United Kingdom

Anna Sadnicka is a clinical academic working at the interface of movement disorders, motor control and computational neuroscience.

She completed her PhD at University College London (UCL) with Mark Edwards and John Rothwell. Since then she has been a principal investigator at St George's using a range of modalities to unpick the mechanisms of dystonia and other movement disorders. She will soon join the Gatsby Computational Neuroscience Unit at UCL to explore the behavioural mathematics of hyperkinetic movement disorders with Maneesh Sahani funded with a Wellcome early career award.

She is an honorary consultant neurologist at the National Hospital for Neurology and Neurosurgery.

Giuseppe Sciamanna PhD
Unicamillus International Medical University of Rome
Santa Lucia Foundation IRCCS Rome

Prof. Sciamanna is a professor at Unicamillus International Medical University of Rome and is a neurophysiologist with a strong interest and knowledge in basal ganglia physiology in normal and pathological conditions. Graduated in Biology he got his PhD in neuroscience at the University of Rome TorVergata. He greatly improved his expertise by working in several international laboratories as University of Texas at San Antonio, Northwest University of Chicago and Université de Bordeaux, where

Research in animals models of movements disorders, such as dystonia, Parkinson's disease or Huntington's disease represents the most important portion of his scientific background. He has remarkable technical and theoretical skill in electrophysiological recording coupled with fluorometric measurement, in synaptic plasticity of neostriatum and in cellular and molecular mechanisms of striatal and pallidal neurons. He has a growing interest and knowledge in new technology tools as two-photon microscopy and optogenetics approach for in vitro/in vivo experiments. Fanaly, prof Sciamanna is largely involved in use of optogenetics in investigating both in-vitro and in vivo the role of cortico-amygadla circuit in process of fear induction.

Aasef Shaikh, MD, PhD
Case Western Reserve University
Cleveland, United States of America

Aasef Shaikh is a neurologist and neuroscientist from Daroff-Dell'Osso Ocular Motility Laboratory at Cleveland VA Medical Center.

His research focuses on the application of control systems engineering to approach complex disorders of the vestibular system, eye movements, head movements, gait and balance.

The overarching goal is to discover novel network connections and leverage their influence to modulate the motor circuits artificially for the treatment of intractable neurological conditions. Dr. Shaikh was the recipient of the prestigious American Academy of Neurology Alliance Founders Award, The American Neurological Association Grass Foundation Award in Neuroscience, and the AAN Jon Stolz Award in Movement Disorders. He serves as Co-Chief Editor of Dystonia, the leading journal in the field by publishing open access premier research on all basic, clinical and translational aspects of the dystonias.

Nutan Sharma, MD PhD
Harvard University
Boston MA, USA

Nutan Sharma is an associate professor of neurology at Massachusetts General Hospital and Harvard Medical School and is board certified in neurology. She earned her bachelor's degree in human biology from Stanford University and her MD and PhD degrees from the State University of New York at Stony Brook. She is an expert on dystonia. Her research interests include identification and characterization of novel genetic forms of dystonia, identification of pathophysiology in forms of adult-onset focal dystonia and characterization of the natural history of X-linked Dystonia Parkinsonism.

Roy V. Sillitoe, PhD
Baylor College of Medicine
Houston, Texas, USA

Dr. Sillitoe is currently a professor of Pathology and Immunology, Neuroscience, and Pediatrics at Baylor College of Medicine.

He completed his PhD in Neuroscience at the University of Calgary. He received postdoctoral training at the University of Oxford, New York University, and Memorial Sloan-Kettering Cancer Center. The focus of his research is to understand how cerebellar circuits contribute to different diseases.

The canonical cerebellar circuit, with Purkinje cells at the center, play a role in ataxia, tremor, and dystonia. His goal is to determine how the same circuit contributes to different diseases. In addition, he is using the mouse models that his lab generated to test whether cerebellar deep brain stimulation might be an effective therapeutic strategy for treating motor and non-motor diseases.

He is a past member of the medical and scientific advisory board of the DMRF and a founding co-editor in chief of the foundation's flagship journal, Dystonia.

Kristina Simonyan, MD, PhD, DrMed
Harvard Medical School,
Boston, United States of America

Kristina Simonyan is a Professor of Otolaryngology-Head and Neck Surgery at Harvard Medical School, Director of Laryngology Research at Massachusetts Eye and Ear, and Program Director of the NIH P50 Clinical Research Center.

She received her medical degrees (M.D. and Dr. med.) from Yerevan State Medical University in Armenia and Georg-August University in Germany and a Ph.D. degree in Neurobiology from TiHo University of Hannover and German Primate Center in Germany. Following her residency in otolaryngology, she completed a clinical research fellowship in movement disorders, neurolaryngology, and neuroimaging at the NINDS/NIH. Dr. Simonyan studies the neural mechanisms of normal and diseased speech production and other complex voluntary motor behaviors.

Her clinical research program is focused on isolated focal dystonia, a debilitating neurological movement disorder causing involuntary muscle spasms in different body regions. Her methodological approach bridges brain imaging, machine learning, computational neuroscience, genetics, and clinical trials. Her recent studies have mapped the large-scale neural architecture underlying speech production and its impairments in laryngeal dystonia. Her research helped define the current view of isolated focal dystonia as a neural network disorder.

This work led to the identification of a neural biomarker for the objective diagnosis of focal dystonia using a deep learning platform, DystoniaNet. She has also identified a new oral drug, sodium oxybate, for the treatment of alcohol-responsive focal dystonia. Dr. Simonyan's laboratory is currently focused on refining the understanding of the pathophysiological mechanisms of focal dystonia and developing clinically applicable extensions of the DystoniaNet platform for dystonia differential diagnosis, predictive risk in susceptible individuals, and treatment outcomes.

She is also investigating a feasibility of a novel brain-computer interface (BCI) strategy for treating focal dystonia. In addition, she directs the NIH P50 Center on Next-Generation Clinical Phenotyping and Pathophysiology of Laryngeal Dystonia and Voice Tremor, which includes Massachusetts Eye and Ear, Massachusetts General Hospital, the University of California San Francisco, the University of Utah, the University of Iowa, and the University of Massachusetts Chan Medical School. The Center is focused on delineating unique clinical and pathophysiological features of these disorders to establish the fundamental framework for their enhanced clinical management.

Dr. Simonyan's laboratory on Dystonia and Speech Motor Control is supported by the National Institutes of Health (NIDCD, NINDS, NIDCR), Department of Defense, Jazz Pharmaceuticals, Amazon Web Services, Mass General Brigham Innovation, and private foundations.

David Standaert, MD, PhD
University of Alabama-Birmingham
Birmingham, United States of America

Dr. Standaert graduated from Harvard College and received M.D. and Ph.D. degrees from Washington University in St. Louis. Following Neurology residency at the University of Pennsylvania, he was appointed a Howard Hughes Fellow and completed a three-year research and clinical fellowship in Movement Disorders at Massachusetts General Hospital.

He was a member of the faculty at Harvard Medical School from 1995 to 2006 and then relocated to the University of Alabama at Birmingham (UAB). Currently he is the John N. Whitaker Professor and Chair of the UAB Department of Neurology and a senior member of the faculty of the Division of Movement Disorders. He directs the NIH-funded Alabama Morris K. Udall Center of Excellence in Parkinson's Disease Research. He is Chairman of the Scientific Advisory Board of the American Parkinson Disease Association, a Deputy Editor of the journal Movement Disorders, a Fellow of both the American Academy of Neurology and the American Neurological Association, and First Vice President of the Association of University Professors of Neurology.

He has also served on the NINDS Board of Scientific Counselors. His lab has a long-standing interest in the basic mechanisms underlying Parkinson disease and dystonia as well as the complications of therapy.

A. Jon Stoessl
University of British Columbia
Vancouver, Canada

A. Jon Stoessl is Professor & Head of Neurology and previous Director of the Pacific Parkinson's Research Centre, Co-Director, then Director of the Djavad Mowafaghian Centre for Brain Health at UBC.

He previously held a Tier 1 Canada Research Chair in Parkinson's Disease. He is Editor-in-Chief of Movement Disorders, has served on numerous other editorial boards including Lancet Neurology and Annals of Neurology, previously chaired the Scientific Advisory Boards of Parkinson's Canada and the Parkinson's Foundation, is Past-President of the World Parkinson Coalition and is a Member of the Order of Canada. Dr. Stoessl uses positron emission tomography to study Parkinson's.

Jan K. Teller, MA, PhD
Scientific Advisors International
Niemcz, Poland

Jan is a neuroscientist. He earned his undergraduate and master's degrees in physiology and clinical psychology from Adam Mickiewicz University in Poznan, Poland, and his PhD in biological sciences from the same University.

In 2005, after a long and eventful academic career at several universities and medical school in the United States and England, he became Chief Scientific Officer at the Dystonia Medical Research Foundation (DMRF). As an independent scientific consultant since 2019, Jan is now the DMRF's Chief Scientific Advisor contributing his knowledge and expertise to the Foundations' science activities.

He has published influential research papers in the areas of protein biochemistry and neuroscience and is a passionate advocate of evidence-based medicine.

Michele Tinazzi MD, PhD
University of Verona,
Verona, Italy

Michele Tinazzi is a full professor in Neurology, at the Department of Neurosciences, Biomedicine and Movement, University of Verona, Italy.

He is director of Parkinson's disease (PD) and movement disorders Unit, coordinator of the specialty training in Neurology, and president of Società LIMPE-DISMOV (Italian Society of Parkinson's disease and Movement Disorders). He is treasurer of the Functional Neurological Disorders Society (FNDS). He took his specialization in Neurology and PhD in Neuroscience. After that, he further specialized on movement disorders by leading research, as medical fellow at the Functional Neurophysiology Clinic, Lyon, France and as visiting Professor at the Institute of Neurology, London, UK. He also further specialized in functional motor disorders by attending a period at the Neurological Institute of Saint George's University, London, UK, as visiting Professor. His work has focused on clinical and pathophysiological aspects of non-motor symptoms (i.e. pain, fatigue) in PD, of axial postural abnormalities in PD, drug-induced parkinsonism, dystonia, and functional motor disorders. He is author or co-Author of more than 350 publications in international journals, with a H-Index Scopus: 57

Marie Vidailhet, MD
Hôpital de la Salpêtrière,
Paris, France

Pr Marie Vidailhet is Professor of Neurology, in Salpêtrière Hospital, Sorbonne Université, Paris, France. She has a long-standing interest in movement disorders, and her main research is focused on motor control from pathophysiology to experimental therapeutics. Within Salpetriere University hospital, the National Reference center for Dystonia and rare movement disorders is embedded in our clinical team, and we are included into the ERN network. Within the research unit at the ICM (Paris Brain Institute), (co-leader Pr S Lehéricy), she contributed to the field of pathophysiology of dystonia, movement disorders and Parkinson's disease, with a multimodal approach including neurophysiology and neuroimaging. Our main focus is on rare disorders, exploring the motor (dystonia) and behavioural (Gilles de la Tourette) networks.

Over the years, she co-authored Publications (H total H index= 894, H, and since 2016 H= 57). Marie Vidailhet and her team co-authored > 400 papers.

In addition she is actively involved in international Scientific societies (MDS, EAN, WCN), in patient's associations including lectures, conferences and teaching courses, and in training and mentorship of Movement Disorders fellows (France,

Europe and beyond). She was in charge of the International Movement disorders Society meeting in Paris, in 2009, and more recently of the European Academy of Neurology international meeting in 2020 in Paris. She was awarded Honorary Member of the Movement Disorders Society.She is committed to the care of patients (with the responsibility of the outpatient and in patient clinic), and the training of senior Residents or Fellows.

Michael Zech, MD
Technical University of Munich, Munich, Germany

Dr Zech completed his studies in Medicine at the Technical University of Munich, Germany, following internships at the University of Zurich, Switzerland, and Cornell University New York, USA.

He obtained his doctoral degree on studies of cell cycle control and cellular maintenance. Dr Zech completed his residency in Neurology at the Technical University of Munich and received research fellowships to investigate the genetic underpinnings of neurological disorders at Helmholtz Center Munich, Germany. His work focusses on the genetics of movement disorders, especially dystonia.

His habilitation thesis (post-doctoral lecturing qualification; 2020) aimed at revealing the spectrum of monogenic etiologies in large dystonia patient populations and new gene-phenotype associations. He was a guest researcher at the Department of Neurology and Neurological Sciences of Stanford University School of Medicine, USA, and is currently completing a specialization in Human Genetics.

Poster Listings

Hogan Mezzanine – Level 4

CODE	TITLE	AUTHORS
P1.01*	Motor Cortex Activation During Writing in Focal Upper-Limb Dystonia: An fNIRS Study	Renata Prôa, Joana Balardin, Danilo Donizere de Faria, Artur Marques Paulo, João Ricardo Sato, Carlos Arruda Baltazar, Vanderci Borges, Sonia Azevedo Silva, Henrique Ballalai Ferraz, Patricia de Carvalho Aguiar
P1.02*	Metabolic patterns in brain 18F-fluorodeoxyglucose PET relate to aetiology in paediatric dystonia Presenting Author: Stavros Tsagkaris	Stavros Tsagkaris, Eric Yau, Verity McClelland, Apostolos Papandreou, Ata Siddiqui, Daniel Lumsden, Margaret Kaminska, Eric Guedj, Alexander Hammers, Jean-Pierre Lin
P1.03*	Immunological mechanisms in cervical dystonia	Laura Scorr, Gamze Kilic-Berkmen, J. Lucas McKay, Michael Powell, Diane Sutcliffe, Andrew McKeon, H.A. Jinnah
P1.04*	Plasma proteomics profiling in adult-onset focal dystonia identifies ten proteins altered in focal dystonia as well as cervical and laryngeal dystonia subtypes	Jigyasha Timsina
P1.05	Cutaneous silent period in patients with idiopathic craniocervical dystonia	Talyta Cortez Grippe, Natalia Spinola Costa da Cunha, Renata Vargas, Rubens Fernandez, Francisco Cardoso, Robert Chen
P1.06	Genetic landscape of dystonia in Asian Indian patients	Roopa Rajan, Arti Saini, Rahul Mewara, Bhawna Verma, Divya M Radhakrishnan, Ayush Aggarwal, Elavarasi Arunmozhimaran, Anu Gupta, Venugopalan Y Vishnu, Mamta B Singh, Rohit Bhatia, Riyaz Mir, Inder Singh, Faruq Mohammed, Binukumar B K, Vinod Scaria, Achal K Srivastava, M V Padma Srivastava
P1.07	Microstructural asymmetry of the dentato-rubro-thalamo tract in cervical dystonia	Rachel Sondergaard, Conrad Rockel, Fil Cortese, Bruce Pike, Zelma Kiss, Davide Martino
P1.08	Finely-tuned gamma oscillations in patients with isolated dystonia implanted with sensing-enabled pulse generators	Stephanie Cernera, Maria Shcherbakova, Carina Oehrn, Simon Little, Philip Starr
P1.09	Functional MRI-guided personalized TMS decreases basal ganglia activity and improves focal hand dystonia	Noreen Bukhari-Parlakturk, Patrick Mulcahey, Michael Lutz, Rabia Ghazi, Ziping Huang, Moritz Dannhauer, Skylar Groves, Mikaela Lipp, Michael Fei, Tiffany Tran, Eleanor Wood, Lysianne Beynel, Burton Scott, Pichet Termsarasab, Chris Petty, Hussein Al-khalidi, James Voyvodic, Lawrence Appelbaum, Simon Davis, Andrew Michael, Angel Peterchev, Nicole Calakos

CODE	TITLE	AUTHORS
P1.10	When Deep Brain Stimulation in childhood-onset dystonias is not enough. Post-DBS outcomes and the need for rehabilitation to improve everyday activities	Hortensia Gimeno, Daniel Lumsden, Richard Selway, Harutomo Hasegawa, Jean-Pierre Lin
P1.11	Supporting clinical trials with objective outcome measures: the promise of AI and computer vision	David A Peterson, Minnie PT Luu, Jeanne P Vu, Elizabeth Cisneros, Ha Yeon Lee, Linh Le, Xiaoyan A Guo, Ingyun Park, Jerry Zhao, Sarah Pirio Richardson, Rodger Elble, Glenn T Stebbins, Cynthia L Comella, Joel S Perlmutter, HA Jinnah
P1.12	Sex Differences in Dystonia	Gamze Kilic-Berkmen, Laura Scorr, Yuping Donsante, Katja Lohmann, Ellen Hess, Hyder (Buz) Jinnah
P1.13	Pain reduction in adults with cervical dystonia following a single injection of incobotulinumtoxinA: a pooled analysis	Alberto Albanese, Joerg Wissel, Wolfgang Jost, Anna Castagna, Michael Althaus, Georg Comes, Astrid Scheschonka, Matteo Vacchelli, Hyder Jinnah
P1.14	Body region response to pallidal deep brain stimulation in isolated non-acquired dystonia.	Margi Patel, Stewart Factor, Svjetlana Miocinovic
P1.15	An Open-Label Study of Ethanol in Focal Dystonia	Lena C. O'Flynn, Azadeh Hamzehei Sichani, Kristina Simonyan
P1.16	Probing the Inhibitory Motor Circuits in Adductor Laryngeal Dystonia during a Dystonia-Unrelated Finger-Tapping Task	Baothy P Huynh, Mo Chen, Teresa J Kimberley, Yi-Ling Kuo
P1.17	Clinical Analysis of Correlations and Distributions of GDRS and BFM Scales	HA Jinnah, Deniz Boz, Gamze Kilic-Berkmen
P1.18	Dystonia with myoclonus and vertical supranuclear gaze palsy associated with a rare GNB1 variant	Nikolai Gil Reyes, Anthony Lang
P1.19	A 10-year Service Evaluation of a Cervical Dystonia Botulinum Toxin A Clinic: Factors associated with a patient satisfaction.	Maeve Bradley, Margaret Ryan, Fiona Molloy
P1.20	Impaired modulation of sensorimotor cortex mu activity during active and passive movement in children with dystonia and dystonic cerebral palsy	Verity McClelland, Fischer Petra, Eleonora Foddai, Sofia Dall'Orso, Elena Cioffi, Jemima Tsang, Aaron Yurkewich, Etienne Burdet, Peter Brown, Jean-Pierre Lin

CODE	TITLE	AUTHORS
P1.21	Using Ultrasound in the assessment of dystonic Tremor	**Anke Snijders**, Jeroen van Doorn, Rick Helmich, Nens van Alfen
P1.22	Repetitive Transcranial Magnetic Stimulation to the Inferior Parietal Lobule in Task-Specific Focal Hand Dystonia: A Randomized Crossover Blinded Outcome Assessment Study	**Seethalekshmi Bhadran**, Roopa Rajan
P1.23	Generalized dystonia, neurodevelopmental regression, and premature ovarian insufficiency due to an IRF2BPL pathogenic de novo nonsense variant.	**Laura Armengou-Garcia**, Grace Yoon, Katja Lohmann, Marta Ruiz-Lopez, Anthony Lang
P1.24	Form vs Function: Inappropriate Behaviors in Cervical Dystonia Beyond Deficits Predicted by Social Cognition Testing	**Matthew Woodward**, Brian Berman, Jeanne Feuerstein
P1.25	Deep Brain Stimulation for childhood-onset DYT - KMT2B: 2-year functional outcomes	**Sinead Barkey**, Apostolos Papandreou, Lesley Baker, Richard Selway, Harutomo Hasegawa, Manju Kurian, Jean-Pierre Lin, Hortensia Gimeno
P1.26	Development of a Patient-Centered Outcome (PCO) Measure for Dystonia	Arlann Erskine, **Paul Reyes**, Fares Qeadan, Brian Berman, Sarah L. Schneider, Janet Hieshetter, Charlene Hudgins, Kimberly Kuman, Cynthia Comella, David Peterson, Mark Hallett, Gamze Kilic-Berkmen, Laura Wright, Samantha Pentecost, Joel S. Perlmutter, H. A. Jinnah, Sarah Pirio-Richardson
P1.27	Development of a Smartphone Application Able to Capture Patient-Centered Outcome (PCO) Measures for Dystonia	**Paul Reyes**, Arlann Erskine, Brian Berman, Sarah L. Schneider, Janet Hieshetter, Kimberly Kuman, Cynthia Comella, David Peterson, Gamze Kilic-Berkmen, Laura Wright, Fares Qeadan, Samantha Pentecost, Joel S. Perlmutter, Sarah Pirio-Richardson, H. A. Jinnah
P1.28	Thyroid disease in cervical dystonia	Gamze Kilic-Berkmen, Laura Scorr, Ami Rosen, Ellen Wu, Alan Freeman, Michael Silver, John Hanfelt, **Hyder (Buz) Jinnah**
P1.29	Treatment of Task Specific Dystonia in Sports; a Systematic Review	Beorn Nijenhuis, **Erik van Wensen**, Marenka Smit, Tim van Zutphen, Hans Zwerver, Marina de Koning
P1.30	Exploratory Clinical Trial of Dipraglurant for Blepharospasm	Gamze Kilic-Berkmen, Cameron Yeo, Laura Scorr, Woonhong Yeo, Hodam Kim, David Peterson, Rodger Mills, **Hayder (Buz) Jinnah**

CODE	TITLE	AUTHORS
P1.31	The Dystonia Coalition: An International Multicenter Network for Clinical and Translational Studies	Gamze Kilic-Berkmen, Laura Jo Wright, Joel S. Perlmutter, Sarah Pirio-Richardson, David Peterson, Carlos Cruchaga, Hyun Joo Cho, Janet Hieshetter, Kimberly Kuman, **Hyder (Buz) Jinnah**
P1.32	Grandmother's Cramp: Family History as Predictor for Onset and Course of Musician's Dystonia	**Johanna Doll-Lee**, André Lee, Bernhard Haslinger, Eckart Altenmüller
P1.33	Essential tremor and essential tremor plus are essentially similar on electrophysiological tremor analysis	**Roopa Rajan**, Anna Latorre, Anandapadmanabhan Reghu, Aayushi Vishnoi, Deblina Biswas, Alish Dipani, Divya M Radhakrishnan, Nivethida Thirugnanasambandam, Achal K Srivastava, Kailash P Bhatia
P1.34	Dystonia in a PFBC cohort and description of 3 peculiar cases.	**Giulia Bonato**, Miryam Carecchio
P1.35	Suitability of Automated Writing Measures for Clinical Trial Outcome in Writer's Cramp	**Noreen Bukhari-Parlakturk**, Michael Lutz, Hussein Al-Khalidi, Shakthi Unnithan, Joyce Wang, Burton SCott, Pichet Termsarasab, Lawrence Appelbaum, Nicole Calakos
P2.01*	Reduced penetrance, variable clinical expressivity, and genetic overlap in monogenic forms of dystonia and parkinsonism	**Lara M. Lange**, Anastasia Illarionova, Karen Grütz, Eva-Juliane Vollstedt, Björn-Hergen Laabs, Sebastian Löns, Gamze Kilic-Berkmen, Frauke Hinrichs, Heike Pawlack, Laurel Screven, Tobias Bäumer, H. A. Jinnah, Norbert Brüggemann, Zih-Hua Fang, Katja Lohmann, Christine Klein
P2.02*	Atypical nuclear envelope condensates linked to Dystonia are proteotoxic and reveal nucleoporin-directed chaperone activities	Sarah Prophet, Anthony Rampello, Robert Niescier, Anthony Koleske, Sunanda Mallik, **Christian Schlieker**
P2.03*	Transcriptomics in postmortem brains and neuronal models uncover targetable signatures for antisense oligonucleotide therapy in X-linked dystonia-parkinsonism	**Aloysius Domingo**, Christine A. Vaine, Rachita Yadav, Dadi Gao, Shivangi Shah, Ellen B. Penney, Siddharth Reed, Serkan Erdin, Micaela Murcar, Kathryn O'Keefe, John Lemanski, Celine EF De Esch, Moira McMahon, Michaela Jackson, Margo Courtney, Joseph Ochaba, Holly B. Kordasiewicz, C. Frank Bennett, Michael E. Talkowski, D. Cristopher Bragg
P2.04*	Specific cerebellar spike train signatures predict the behavioral presentation of cerebellar pathophysiology	**Meike van der Heijden**, Amanda Brown, Roy Sillitoe

CODE	TITLE	AUTHORS
P2.05	Dystonia Treatment With Injections Supplemented by TMS: the D-TWIST Study	Jessica Frey, John Yu, Janine Lobo Lopes, Lauren Fanty, Manahil Wajid, Adolfo Ramirez-Zamora, Irene A. Malaty, Jackson Cagle, Coralie de Hemptinne, Aparna Wagle Shukla
P2.06	Benefit of multiple incobotulinumtoxinA injections for pain reduction in adults with cervical dystonia: an analysis of pooled data	Alberto Albanese, Joerg Wissel, Wolfgang Jost, Anna Castagna, Georg Comes, Astrid Scheschonka, Matteo Vacchelli, Hyder Jinnah
P2.07	Dystonia- history of a movement disorder	Pawel Tacik
P2.08	A multimodal approach to understanding dystonia: integration of structural, functional and behavioral measures.	Stefan Radu Bostan, Ross King, Conor Fearon, Michael Hutchinson, Richard Reilly
P2.09	Globus Pallidus internus (GPi) Power Spectral Densities Progressively Change With Increasing Dystonia or Parkinsonism Severity	Angela Hewitt, Manuel Gomez-Ramirez, Karlo Lizarraga, Jonathan Mink
P2.10	Clinical Characterization and Treatment Outcomes of VPS16 Dystonia	Mariel Pullman, Deborah Raymond, Walter Molofsky, Naomi Lubarr, Katherine Leaver, Roberto Ortega, Maya Rawal, Steffany Bennett, Evan Bushnik, Azita Khorsandi, Fedor Panov, Jean Paul Vonsattel, Laurie Ozelius, Rachel Saunders-Pullman, Susan Bressman
P2.11	Validation of a Clinical Rating Scale for Embouchure Dystonia	André Lee, Tobias Mantel, Bernhard Haslinger, Eckart Altenmüller
P2.12	Proprioceptive stimuli trigger abnormal micro-scale neuronal connectivity in children with dystonia	Dimitris Sakellariou, Sofia Dall'Orso, Etienne Burdet, Jean-Pierre Lin, Mark Richardson, Verity McClelland
P2.13	In vivo assessment of striatal compartments in patients with idiopathic upper limb dystonia	Artur José Marques Paulo, Jeffrey Waugh, Joselisa Péres Queiros de Paiva, Danilo Donizete de Faria, João Ricardo Sato, Vanderci Borges, Sonia Azevedo Silva, Henrique Ballalai Ferraz, Patricia de Carvalho Aguiar
P2.14	Preliminary functional changes in superior temporal gyrus in task-specific focal dystonia based on individualized parcellations	Yuchao Wang, Dan Hu, Reuben Newton Addison, Baothy Huynh, Hesheng Liu, Teresa Jacobson Kimberley

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P2.15	**Injections of incobotulinumtoxinA at intervals less than 10 weeks are effective and safe for cervical dystonia patients with inadequate benefit from standard injection intervals**	**Cynthia Comella**, Robert A. Hauser, Stuart Isaacson, Daniel Truong, Odinachi Oguh, Jennifer Hui, Eric S. Molho, Matthew Brodsky, Erin Furr-Stimming, Georg Comes, Michael Hast, David Charles
P2.16	**Analysis of functional connectivity using machine learning and deep learning in EEG data from patients with focal dystonia.**	Caroline Lourenço Alves, Artur Jose Marques Paulo, Danilo Donizete de Faria, Joao Ricardo Sato, Vanderci Borges, Sonia Azevedo Silva, Henrique Ballalai Ferraz, Francisco Aparecido Rodrigues, Christiane Thielemann, **Patricia de Carvalho Aguiar**
P2.17	**Deep Brain Stimulation Evoked Potentials (DBSEPs) in children with dystonia**	**Verity McClelland**, Antonio Valentin, Eleonora Foddai, Tim Dennison, Jean-Pierre Lin
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* Poster Codes with an asterisk denote platform presentations.

Poster Abstracts

P1.01

Motor Cortex Activation During Writing in Focal Upper-Limb Dystonia: An fNIRS Study

Renata Prôa[1,2], Joana Balardin[1], Danilo Donizere de Faria[3,4], Artur Marques Paulo[1], João Ricardo Sato[5], Carlos Arruda Baltazar[1], Vanderci Borges[3], Sonia Azevedo Silva[4,3], Henrique Ballalai Ferraz[3], Patricia de Carvalho Aguiar[1,3]

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Abstract

Introduction: Functional analysis of movement in dystonia is a complex task. Techniques such as functional magnetic resonance imaging usually impose physical constraints, limiting the experimental paradigms. Functional near-infrared spectroscopy (fNIRS) offers a new noninvasive possibility for investigating cortical areas and the neural correlates of complex motor behaviors in unconstrained settings.

Materials and Methods: We compared the cortical brain activation of patients with idiopathic focal upper-limb dystonia and controls during the writing task under natural conditions using fNIRS. The paradigm consisted of four epochs of alternate writing/resting blocks of 30 seconds each. The total number of written letters, as well as legibility, assessed by two blinded investigators, were analyzed. The primary motor cortex (M1), the primary somatosensory cortex (S1), and the supplementary motor area were chosen as regions of interest (ROIs) to assess differences in changes in both oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) between groups.

Results: All patients presented dystonic posture during the writing task. Regarding the number of written letters, controls had a statistically significant better performance ($p = 0.003$). We observed no association between group and legibility. Group average activation maps revealed an expected pattern of contralateral recruitment of motor and somatosensory cortices in the control group and a more bilateral activation pattern in the dystonia group (figure 1). Between-group comparisons focused on specific ROIs revealed an increased activation of the contralateral M1 and S1 cortices and also of the ipsilateral M1 cortex in patients.

Discussion: Overactivity of contralateral M1 and S1 in dystonia suggests a reduced specificity of the task-related cortical areas, in agreement with the pathological mechanism of cortical inhibition failure known to happen in dystonia. Ipsilateral cortical activation has been observed in healthy subjects during complex tasks which demand high accuracy. In this study, where the task was not highly demanding, patients' ipsilateral activation was significantly higher than controls. This could indicate a primary disorder of the motor cortex or an endophenotypic pattern. To our knowledge, this is the first study using fNIRS to assess cortical activity in dystonia during the writing task under natural settings, outlining

the potential of this highly portable and low-cost technique for monitoring sensory and motor retraining in dystonia rehabilitation.

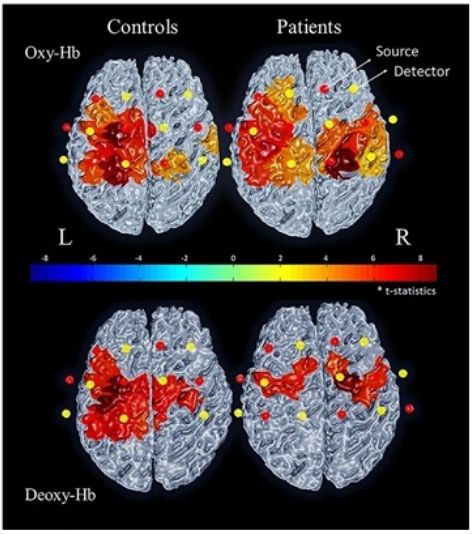

Figure 1. Oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) activation maps for the contrast Writing > Resting. Activation maps from the channel-wise analysis showing the mean activation of controls (left) and patients (right) for oxy-Hb (above) and deoxy-Hb (below). Patients' map shows a more bilateral activation pattern. Red and yellow dots represent sources and detectors, respectively. Results for each channel were Bonferroni corrected for multiple comparisons (P value < .002).

P1.02

Metabolic patterns in brain 18F-fluorodeoxyglucose PET relate to aetiology in paediatric dystonia

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Abstract

Introduction: There is a lack of imaging markers revealing the functional characteristics of different brain regions in paediatric dystonia. In this observational study, we assessed the utility of [18F]2-fluoro-2-deoxy-D-glucose (FDG)-PET in understanding dystonia pathophysiology by revealing specific resting awake brain glucose metabolism patterns in different childhood dystonia subgroups.

Materials and Methods: PET scans from 267 children with dystonia being evaluated for possible deep brain stimulation surgery between September 2007 and February 2018 at Evelina London Children's Hospital (ELCH), UK, were examined. Scans without gross anatomical abnormality (e.g. large cysts, significant ventriculomegaly; n = 240) were analysed with Statistical Parametric Mapping (SPM12). Glucose metabolism patterns were examined in the 144/240 (60%) cases with the 10 commonest childhood-onset dystonias, focusing on nine anatomical regions. A group of 39 adult controls was used for comparisons. The genetic dystonias were associated with the following genes: TOR1A, THAP1, SGCE, KMT2B, HPRT1 (Lesch Nyhan disease), PANK2 and GCDH (Glutaric Aciduria type 1). The acquired cerebral palsy (CP) cases were divided into those related to prematurity (CP-Preterm), neonatal jaundice/kernicterus (CP-Kernicterus) and hypoxic-ischaemic encephalopathy (CP-Term).

Results: Each dystonia subgroup had distinct patterns of altered FDG-PET uptake. Focal glucose hypometabolism of the pallidi, putamina or both, was the commonest finding, except in PANK2, where basal ganglia metabolism appeared normal. HPRT1 uniquely showed glucose hypometabolism across all nine cerebral regions. Temporal lobe glucose hypometabolism was found in KMT2B, HPRT1 and CP-Kernicterus. Frontal lobe hypometabolism was found in SGCE, HPRT1 and PANK2. Thalamic and brainstem hypometabolism were seen only in HPRT1, CP-Preterm and CP-term dystonia cases. The combination of frontal and parietal lobe hypermetabolism was uniquely found in CP-term cases. PANK2 cases showed a distinct combination of parietal hypermetabolism with cerebellar hypometabolism but intact putaminal-pallidal glucose metabolism. HPRT1, PANK2, CP-kernicterus and CP-preterm cases had cerebellar and insula glucose hypometabolism as well as parietal glucose hypermetabolism.

Discussion: The study findings offer insights into the pathophysiology of dystonia and support the network theory for dystonia pathogenesis. 'Signature' patterns for each dystonia subgroup could be a useful biomarker to guide differential diagnosis and inform personalized management strategies.

P1.03

Immunological mechanisms in cervical dystonia

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Abstract

Introduction: Although there are many possible causes for cervical dystonia (CD), a specific cause cannot be identified in most cases. Several prior studies have suggested a relationship between CD and autoimmune thyroid disease, pointing to potential immunological methods. Our goal was to delineate potential abnormal immunological mechanisms in CD.

Materials and Methods: A potential relationship between CD and immune mechanisms was explored via several independent methods, in subjects with and without co-incidental autoimmune thyroid disease to enrich for a possible population where immune mechanisms might be more relevant. First, a broad screening test compared neuronal antibodies in normal controls (n=30) and CD (N=58). Second, unbiased blood-based shotgun proteomics provided a broad screen for potential biologic differences between normal controls (N=10) and CD (N=20). Third, a multiplex immunoassay compared 37 markers associated with immunological processes in normal controls (N=20) and CD cases (N=20). Fourth, peripheral blood mononuclear cell immunophenotyping was performed to quantify relative immune cell frequencies in normal controls (N=20) and CD subjects (N=20).

Results: Screens for anti-neuronal antibodies did not reveal any obvious abnormalities in CD. Plasma proteomic methods pointed towards abnormalities of immune mechanisms, and the multiplex assay pointed more specifically towards T cells. Immunophenotyping studies revealed a third of cases had an increased relative abundance of B cells and monocytes compared to controls. Additionally, a third of cases had an altered proportion of CD8+ cytotoxic T cells to CD4+ helper T cells.

Discussion: Altogether, the association of CD with autoimmune thyroid disease and blood-based immune measures point to abnormalities in cell-mediated immunity that may play a pathogenic role for a subgroup of subjects with CD.

P1.04

Plasma proteomics profiling in adult-onset focal dystonia identifies ten proteins altered in focal dystonia as well as cervical and laryngeal dystonia subtypes

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Abstract

Introduction: Dystonia is one of the most common movement disorders with a wide spectrum of clinical presentation and subtypes. In light of the heterogenous nature of dystonia, it is expected that several pathological pathways and processes will be implicated on disease presentation and progression. High-throughput unbiased proteomic analyses can provide insights into these cellular mechanisms and help identify potential diagnostic and therapeutic targets.

Methods: We examined a dystonia cohort of 143 cases, comprising of three distinct subtypes: 45 cervical dystonia (CD), 49 laryngeal dystonia (LD) and 49 blepharospasm (BL). To examine protein alterations by dystonia, 49 controls were also included. We measured 6,169 unique plasma proteins using 6,985 aptamers with high-throughput SOMAscan (v4) from these samples. We performed differential abundance analysis using linear regression including age and plate as covariates, for each dystonia subtype as well as the entire dystonia cases. Pathway analysis were performed using clusterProfiler (v4.6.2) and DOSE (v3.24.2) packages implemented through R statistical software.

Results: We identified 15 proteins significantly altered in the entire dystonia sample after multiple test correction (FDR < 0.05). In the subtype specific analysis, we identified 84 proteins altered in CD and 345 proteins altered in LD. No proteins passed the significance threshold in BL. Ten proteins including interferon beta (IFN-b) and 14-3-3 protein gamma were consistently associated with overall dystonia status and both subtypes. In particular, IFN-b was the most significantly associated (P = 2.16e-13 in overall dystonia; P = 2.92e-10 in CD; P = 1.54e-10 in LD). Pathway analysis of 404 significant proteins highlighted altered immune system mechanisms (GO:0002683; P = 5.08e-07; enrichment score (ES) = 2.98) along with leukocyte activation (GO:0002695; P = 2.86e-06; ES = 3.99), migration (GO:0050900; P= 6.11e-07; ES = 3.11) and proliferation (GO:0070661; P = 9.08e-06; ES = 2.99). Hematuria (C0018965; P = 3.26e-11; ES = 5.57) and Neuropathy (C0442874; P = 6.67e-10, ES = 3.64) were most significantly associated disease ontologies.

Discussion: Our study identified proteins dysregulated in dystonia and highlighted pathways associated with the condition. IFN-b, the most significantly altered protein, has been linked to nuclear gene products of oxidative phosphorylation (OXPHOS) pathway, which in turn has been implicated in movement disorder dystonia. Follow-up study with a larger sample size will be required to confirm the findings from this study. More detailed characterization of proteomic signatures of dystonia subtypes to understand its heterogeneous nature will be needed.

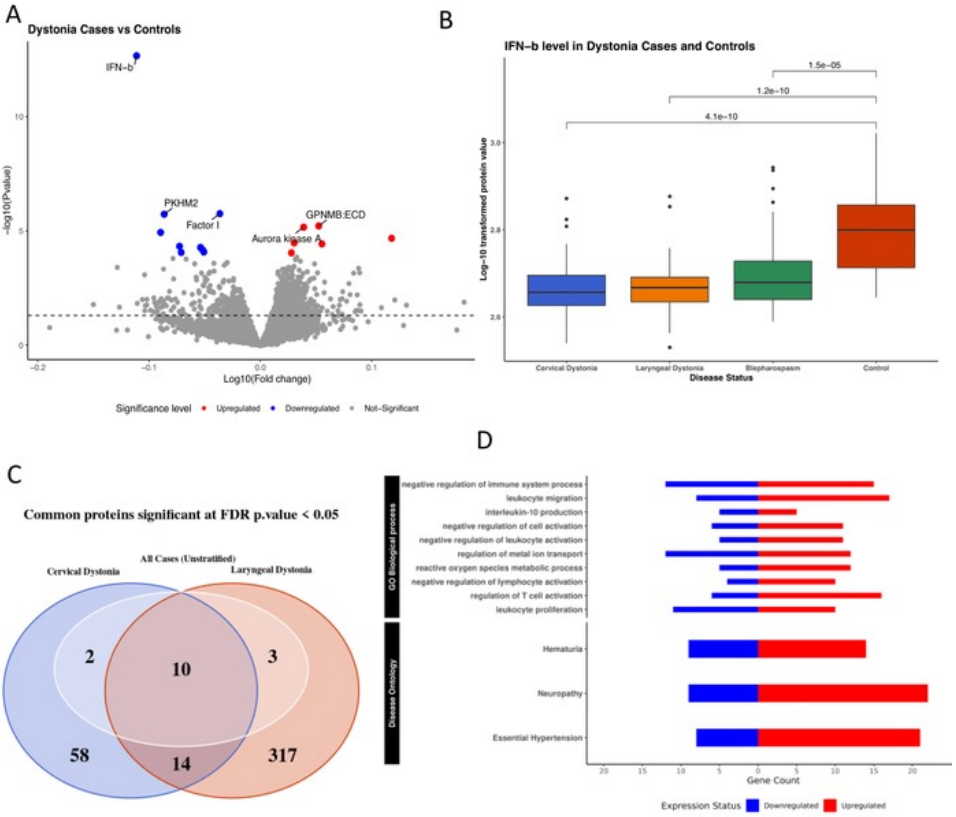

Figure 1: Multi-panel plot depicting findings from proteomic analysis in a Dystonia cohort. (A) Volcano plot showing top differentially abundant protein targets in cases compared to controls. Significance determined based on FDR < 0.05. Black dotted line represents nominal p-value cutoff of 0.05. (B) Boxplot showing protein expression label in Dystonia cases subtypes and controls. Significance determined based on two-sample T-test without adjustment for covariates. (C) Venn Diagram showing overlap between significantly differentially expressed (FDR < 0.05) hits among subtype stratified and combined analysis. Blepharospasm cases did not have any significantly differentially expressed at FDR < 0.05 threshold. (D) Plot showing significant pathways enriched using hits from differential expression analysis. Pathways are arranged in ascending order of p-value for each ontology type. Blue bar represents number of genes enriched for the pathway and were down regulated in Dystonia cases compared controls in our analysis. Red Bars represent upregulated genes

P1.05

Cutaneous silent period in patients with idiopathic craniocervical dystonia

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Abstract

Introduction: The cutaneous silent period (CSP) refers to the reduction in voluntary muscle contraction recorded by EMG due to sensory stimuli applied at distal locations in the limbs. It is a robust cutaneomuscular reflex and evaluates sensorimotor integration involved in the regulation of spinal cord excitability. The main parameters of CSP include onset latency, duration, and end latency. Previous studies reported conflicting results regarding the differences between patients with dystonia and controls. We aimed to evaluate the CSP of patients with craniocervical dystonia compared to healthy controls.

Methods: 17 patients with idiopathic craniocervical dystonia (age, 53.7 10.3 years; mean standard deviation; 9 women and 8 man) and 10 age-matched normal subjects (age, 48.9 8.5 years; 5 women and 5 men). Eleven patients had only cervical dystonia, three patients had blepharospasm, one patient had cervical and limb dystonia, one patient had facial dystonia, and one patient had facial and laryngeal dystonia. All patients were treated with botulinum toxin and at least 3 months had elapsed since the last injections. All subjects underwent nerve conduction studies. We evaluated the CSP with electrical stimulus in digit 5 (D5) and recording from the abductor digiti minimi (ADM) muscles bilaterally.

Results:31 arms were evaluated in the dystonia group. The median, the 2nd and 98th percentile for CSP duration was 22.7 (11.3 – 48.1) ms, for onset latency was 84 (68.6 – 115) ms, and for end latency was 107 (88.6 – 140) ms. Twenty-one arms were evaluated in the control group. The median for CSP duration was 28.9 (18 – 51) ms, onset latency was 86.2 (69.4 – 108) ms, and median end latency was 120 (93.4 – 143) ms. The CSP duration (Mann Whitney test p=0.022) and the end latency (p=0.036) were significantly shorter in the idiopathic craniocervical dystonia group compared to the control group. The linear regression for CSP duration (R=0.45; p=0.014) and end latency (R=0.38; p=0.04) showed that only the ulnar F wave latency was a significant predictor.

Discussion: The patients with idiopathic craniocervical dystonia had a reduced CSP duration compared to controls. This may indicate reduction of inhibitory function during sensory motor integration involving the spinal cord in the craniocervical dystonic patients. The F wave values correlate with the reduced duration and end latency in CSP of the dystonic patients and reinforces the role of the spinal cord in this alteration. Further studies are needed to confirm these findings.

P1.06

Genetic landscape of dystonia in Asian Indian patients

Roopa Rajan[1], Arti Saini[1], Rahul Mewara[1], Bhawna Verma[1], Divya M Radhakrishnan[1], Ayush Aggarwal[1], Elavarasi Arunmozhimaran[1], Anu Gupta[1], Venugopalan Y Vishnu[1], Mamta B Singh[1], Rohit Bhatia[1], Riyaz Mir[1], Inder Singh[1], Faruq Mohammed[2], Binukumar B K[2], Vinod Scaria[2], Achal K Srivastava[1], M V Padma Srivastava[1]

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Abstract

Introduction: The Asian Indian population is underrepresented in genetic studies of dystonia and the pathogenic variations associated with dystonia in this population remain largely unknown. We aimed to identify potentially pathogenic genomic variations associated with dystonia phenotypes in Asian Indian patients.

Methods: The Indian Movement Disorder Registry and Biobank is a multi-centric clinical registry and DNA biorepository for Indian patients with suspected genetic movement disorders. As part of this registry, our center enrolled 570 probands and affected/unaffected family members with dystonia from Sep 2018- Sep 2021. Standardized videotaped clinical examination, family history and relevant investigations were captured and stored on a REDCap platform. We performed whole exome sequencing (WES) of DNA specimens obtained from 254 probands with isolated, combined or complex dystonia in this cohort. DNA libraries were sequenced to depths of 80-100X on an Illumina platform. We followed the GATK best practices framework for variant calling and prioritized variants according to prespecified criteria. Finally, variants were classified according to ACMG guidelines.

Results: The mean age of the WES cohort was 35.1316.2 years and age at onset was 27.2317.4 years. Dystonia was early onset in 43.3% and generalized in 23.2%. Family history was positive for dystonia or another movement disorder in 35.8%. 68.5% had isolated dystonia, 11.8% were combined and 18.9% were complex phenotypes. WES identified pathogenic/ likely pathogenic variants in 49 patients (19.2%) including 9 novel variants in known dystonia genes. Mutations in *THAP1* were most common followed by *SCGE, VPS16, PANK2, GLB1, FTL, TOR1A, TUBB4A, ATP13A2, ANO3, TH, FBN1, RTN2, COQ8A* and other genes (Figure 1). Variants of uncertain significance were identified in additional 106 participants-most commonly in the *COL6A3* gene.

Discussion: WES identified potentially pathogenic variations in 19.2% patients in this cohort. Several genes known to be associated with dystonia were replicated in this cohort of Indian dystonia, with novel variants in some. This is the largest cohort of genetically defined dystonia from the Asian Indian population. Ethnicity specific genetic information from underrepresented populations may help to further identify novel genes/variants and address the missing heritability in rare disorders.

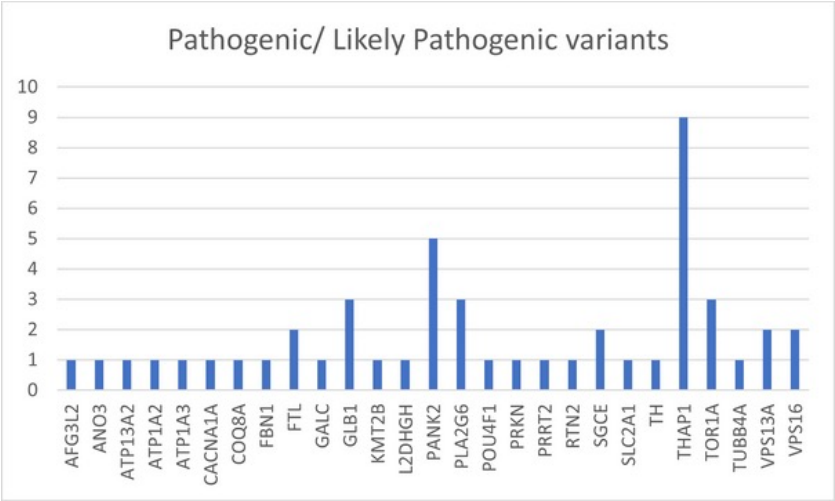

Figure 1: Pathogenic/ likely pathogenic variants in known dystonia genes identified in this cohort.

P1.07

Microstructural asymmetry of the dentato-rubro-thalamo tract in cervical dystonia

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Abstract

Introduction: The dentato-rubro-thalamic tracts (DRTT) are underexplored in cervical dystonia (CD), despite the relevance of the cerebellum in both CD and cerebellum-mediated inhibition of movement. A proposed model of idiopathic cervical dystonia (CD) suggests that feedback asymmetry arising within the motor network drives dysfunction in a graded manner. Substantiation of this so-called faulty head neural integrator (HNi) model of CD presently converges at the globus pallidus internus (GPi) as physiological and structural evidence originating elsewhere in the motor network is currently lacking. Advancements in neuroimaging have made it possible to explore microstructural aspects of the DRTT with tractography. In fact, we have previously reported bilateral microstructural abnormalities of the DRTT. We were interested to see if there was evidence of microstructural asymmetry along these tracts in CD, and if they scaled with CD severity.

Materials and Methods: Diffusion and T1 weighted magnetic resonance imaging scans were acquired in n=35 healthy controls and n=32 subjects with CD at least 12 weeks after botulinum toxin injections in the CD patients. Diffusion images were pre-processed using FSL *topup* and *eddy* programs to register the images and correct for susceptibility, eddy current and motion distortion. A template of the DRTT was created and probabilistic tractography was completed; diffusion tractography imaging (dti) metrics were calculated for all subjects (fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD)). Asymmetry index (AI) for these measures (i.e., (left-right metric)/(left+right metric)) was calculated.

A GLM comparing asymmetry index of MD, AD, RD and FA between healthy controls and CD subjects and controlling for age, sex and handedness revealed a significant effect of group (Wilks' Lambda =0.840, F=2.811, p=0.03). Asymmetry index of mean diffusivity was significantly impacted by group with CD subjects having reduced AI of MD relative to controls (F=3.115, p=0.021, estimated means CD: -0.012, HC: 0.005). There were no significant correlations between CD severity and AI measures, however a sub-analysis of 'left' affected CD subjects (n=13) revealed a negative correlation between torticollis severity and AI of MD (PCC:-0.552, p=0.031).

Results: It appears that asymmetry index of MD is significantly different between HC and CD patients. Interestingly a relationship between asymmetry, sidedness of torticollis and severity emerged in a sub-analysis, requiring a larger sample size to confirm but providing potential for support of the faulty HNi model derived from outside of the basal ganglia.

P1.08

Finely-tuned gamma oscillations in patients with isolated dystonia implanted with sensing-enabled pulse generators

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Abstract

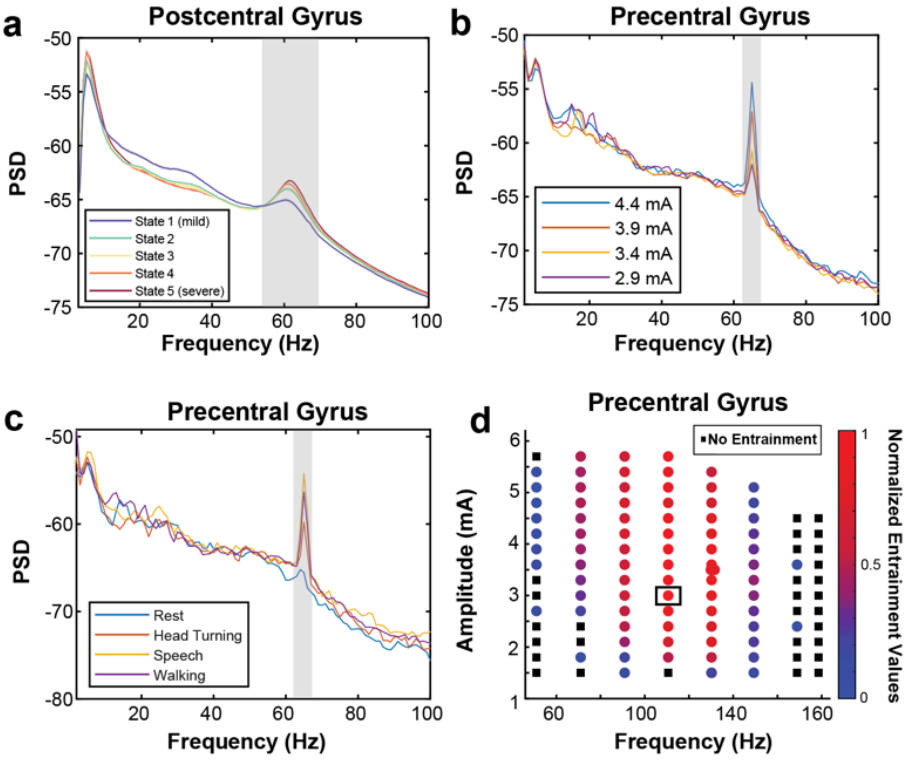
Introduction: Finely-tuned gamma (FTG) has been implicated as a "prokinetic" neural oscillation in dystonia[1] and Parkinson's disease[2]. Intraoperative recordings in isolated dystonia show that native cortical FTG emerged during dystonic posturing[1]. The entrainment of FTG to the harmonics of stimulation frequency by deep brain stimulation (DBS) is hypothesized to be a mechanism of therapeutic effect[2]. However, the functional relevance of both native (pre-stimulation) and DBS-entrained FTG in naturalistic settings has never been studied.

Methods: We recorded local field potentials from basal ganglia and cortical leads (covering precentral and postcentral gyri) in two patients with isolated dystonia at-home, using a sensing-enabled DBS device (Summit® RC+S, Medtronic). We assessed head tremor with a head-worn accelerometer. Patients reported activities through a patient-facing graphical user interface[3]. We divided time series into 20-second epochs and estimated power spectral density using Welch's method. We determined the degree of native and entrained gamma using the fooof algorithm[4]. The severity of head acceleration was measured as the 20th, 40th, 60th, and 80th percentiles derived from the envelope across an individual's at-home recording. Additionally, we collected in-clinic data to assess changes in entrained FTG as a function of stimulation amplitude and frequency while patients performed standardized tasks and rated symptom severity.

We recorded >500 hours of at-home neural data. We observed spatially specific native and entrained FTG. In one patient, native FTG was of highest amplitude on postcentral gyrus and increased with more severe head movements (Fig. a). Across patients, entrained FTG was more prominent on precentral gyrus, modulated with stimulation amplitude (Fig. b), and activities (Fig. c). Further, gamma entrainment amplitude depended on stimulation frequency and amplitude in a non-linear manner. In one patient, the highest entrained FTG amplitude on precentral gyrus was at 3 mA, 110.6 Hz and decreased with relatively higher stimulation amplitudes (Fig. d). Entrained FTG on precentral gyrus was negatively correlated with subjective symptom severity when controlling for stimulation amplitude (partial Pearson correlation, $R = -0.436$, $p = 0.023$).

Discussion: Chronic sensorimotor recordings in patients with isolated dystonia reveal that native and entrained FTG are spatially specific and are related to symptom severity. Further, there are amplitude-frequency combination sweet spots for entraining FTG. These signals may potentially be used to optimize programming or in adaptive DBS protocols.

References: 1. Miocinovic et al., 2018. 2. Muthuraman et al., 2020. 3. Gilron et al., 2021. 4. Donoghue et al., 2020.



P1.09

Functional MRI-guided personalized TMS decreases basal ganglia activity and improves focal hand dystonia

Noreen Bukhari-Parlakturk[1], Patrick Mulcahey[2], Michael Lutz[2], Rabia Ghazi[2], Ziping Huang[1], Moritz Dannhauer[3], Skylar Groves[1], Mikaela Lipp[1], Michael Fei[4], Tiffany Tran[5], Eleanor Wood[6], Lysianne Beynel[3], Burton Scott[1], Pichet Termsarasab[7], Chris Petty[4], Hussein Al-khalidi[4], James Voyvodic[1], Lawrence Appelbaum[8], Simon Davis[2], Andrew Michael[4], Angel Peterchev[4], Nicole Calakos[2]

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Abstract

Introduction: Dystonia is an involuntary movement disorder involving the superficial cortex and deep brain region of basal ganglia, interconnected through the corticostriatal circuit. Prior studies in focal hand dystonia (FHD) showed transient clinical benefit after multiple sessions of repetitive transcranial magnetic stimulation (rTMS) was delivered to the premotor cortex (PMC) or primary somatosensory cortex (PSC). The effect of cortically delivered rTMS on the basal ganglia in FHD remains unclear. The primary objective of this study was to determine if rTMS delivered to the cortical regions of PMC and PSC will modify basal ganglia activity. Since basal ganglia region is abnormal in dystonia, we hypothesized that cortically delivered rTMS that modifies corticostriatal connectivity will allow for greater clinical efficacy in dystonia.

Methods: Study was a double-blind, sham-controlled, cross-over design. Twelve adult participants with isolated right-hand focal dystonia received a 20-minute session of 10 Hz rTMS (total 1000 pulses) to PMC, PSC, and sham TMS to PMC. The order of TMS sessions was randomized, with at least one week between sessions. TMS delivery was personalized to each participant's brain using fMRI and electric field simulations. To ensure a consistent brain state, TMS was targeted, delivered and its brain effect was evaluated as participants performed a writing task. To measure TMS-induced behavioral effect, participants performed writing in a kinematic software before and after TMS session. Peak acceleration, a measure of writing dysfluency, was then calculated. To measure TMS-induced brain effect, fMRI was collected after each TMS condition, and data was analyzed using region-of-interest analysis in FSL software. Corticostriatal (PMC-putamen) and intracortical (PSC-PMC) functional connectivity was calculated using Pearson's correlation, and transformed to a Fisher z-score. Behavior and fMRI data were analyzed using mixed model for repeated measures and corrected for multiple comparisons.

Results: PSC-TMS, compared to sham-TMS showed an estimated 2.73 $\pm$0.47 counts ($p < 0.0001$) reduction in writing dysfluency and 0.12 $\pm$0.03 ($p=0.001$) z-scaled unit reduction in putamen BOLD activity. Corticostriatal connectivity and writing dysfluency after PSC-TMS were not significantly correlated ($R=0.26$ $p=0.41$). However, intracortical (PSC-PMC) con-

nectivity inversely correlated with writing dysfluency after PSC-TMS (R=-0.68, p=0.015).

Discussion: fMRI-guided personalized TMS to PSC decreases basal ganglia activity and increases intracortical connectivity compared to sham. These TMS-induced brain changes after PSC-TMS were associated with greater behavioral improvement than sham-TMS. Findings from this study may identify key brain regions for use as predictive biomarkers for clinical response to TMS for focal hand dystonia.

P1.10

When Deep Brain Stimulation in childhood-onset dystonias is not enough. Post-DBS outcomes and the need for rehabilitation to improve everyday activities

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Abstract

Introduction: Childhood-onset dystonias are a heterogeneous group of disorders. Whilst patient-reported outcomes have been described, objective outcome measures of self-care and daily life activities post-DBS are lacking.

The assessment of motor and process skills (AMPS), a standardised observational evaluation, measures a person's observed quality of activities of daily living performance.

We hypothesised that:

(i) individuals with childhood-onset dystonia would display motor and process skills difficulties,

(ii) motor skills would change post-DBS but not process skills.

Materials and Methods: Blind-rated open-label case series. AMPS was administered by an AMPS-accredited occupational therapist at baseline, 1- and 2-years post-DBS. Burke-Fahn-Marsden Dystonia Rating scale (BFMDRS) was also used. Ordinal scores were transformed into motor (AMPS-m) and process (AMPS-p) skills logits, using a Rasch measurement model (age, task challenge, skill difficulty and rater severity considered). At baseline, gross motor function and manual classification systems (GMFCS/MACS) were used.

Independent Samples Kruskal-Walls Test was used (significance level <0.05) to explore distribution of logits across aetiology, and GMFCS/MACS groups. Baseline and follow-up differences were examined using the Wilcoxon Signed Rank Test.

Median and interquartile box whisker plots (Figure-1) show differences between aetiology groups and GMFCS/MACS levels, for AMPS-m and AMPS-p.

Motor logits <2 and process logits <1 indicate the person is below the threshold of what would be expected for their age (Figure-1).

Results: All patients with idiopathic (n=11) or inherited monogenetic dystonias (n=33) and post-DBS data were included.

The distribution of baseline AMPS-m was significantly different across GMFCS (p=0.012) and MACS (p<0.001) levels. For AMPS-p only MACS levels showed a significant difference (p=0.010) but not for GMFCS levels (p=0.495).

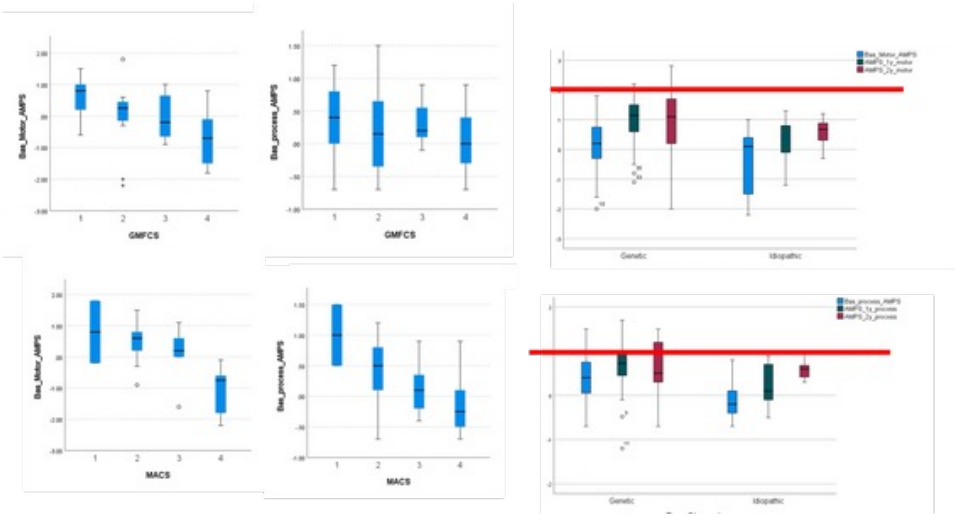
The distribution of AMPS-m was the same across both aetiology groups (p=0.267) but significantly different for AMPS-p skills (p=0.005). There were no differences across BFMDRS (p=0.726)

A significant change in all measures (AMPS-m-, AMPS-p, and BFMDRS) was seen at all timepoints (p<0.001).

When thresholds were applied, most individuals remained below normative data (<2 for AMPS-m and <1 for AMPS-p).

Discussion: Both motor and process skills are affected in childhood-onset dystonias and below normative data post-DBS. Whilst there is a focus on motor symptoms in these disorders, additional non-motor difficulties (i.e., process skills) play an important role in our understanding of DBS effect.

Despite statistical improvement in dystonia severity, and motor and process skills, augmentation of DBS outcomes might be needed via complementary interventions such as occupational therapy to support further skill acquisition.



P1.11

Supporting clinical trials with objective outcome measures: the promise of AI and computer vision

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Abstract

Introduction: Clinical research in dystonia depends upon quantifying the disorder's motor severity. This is typically done with rating scales, but those scales are inherently subjective. As a result, rating scales are susceptible to inter- and intra-rater variability, have limited sensitivity to changes in severity, and increase samples sizes needed to power clinical trials. These limitations of rating scales can be circumvented with objective measures. Advances in technology offer many options for quantifying dystonia motor severity objectively.

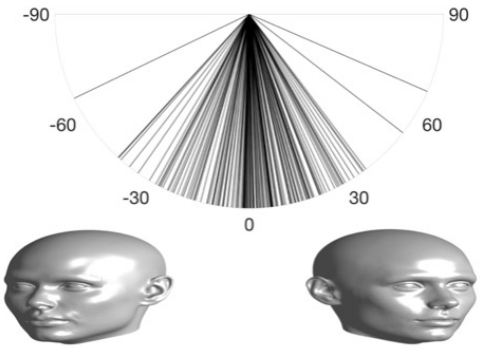
Methods: We have been investigating the potential of computer vision and AI to quantify motor severity from conventional video recordings. The video recordings and associated clinical data have been collected through the Dystonia Coalition, an international multicenter consortium based in the U.S. and supported by the NIH and the Dystonia Medical Research Foundation. We have been evaluating cohorts of approximately 200 isolated dystonia patients from each of the three most common forms of dystonia: blepharospasm, cervical dystonia (CD), and laryngeal dystonia.

Results: In each case, the severity measures derived from computer vision-based analyses of the video recordings exhibit convergent validity with severity ratings from experienced clinicians. In this presentation, we will explain the approach and architecture of our software system (the Computational Motor Objective Rater, CMOR) and summarize our published and unpublished results. In the case of CD, for example, CMOR captures both tonic (e.g. postural) and phasic (e.g. tremor) features (see Figure depicting torticollis/angle of rotation, from Zhang et al. 2022 ACTN, Fig 3.). CMOR can also determine the effect of the sensory trick in ameliorating CD motor symptoms.

Discussion: Our results support CMOR's potential utility as an outcome measure in future clinical trials. And because it is based on software and conventional video recordings, it can ultimately be fielded on mobile devices to support more frequent and convenient assessments beyond the clinic without additional equipment or expertise. Collectively these features will support future clinical trials and therefore improved treatment options for

patients of these most common forms of dystonia.

References: Zhang Z, Cisneros E, Lee H, Vu JP, Chen Q, Benadof CN, Whitehill J, Rouzbehani R, Sy DT, Huang JS, Sejnowski TJ, Jankovic J, Factor S, Goetz CG, Barbano RL, Perlmutter JS, Jinnah HA, Berman BD, Pirio Richardson S, Stebbins GT, Comella CL, Peterson DA. Hold that pose: capturing cervical dystonia's head deviation severity from video. Ann Clin Transl Neurol., 9(5): 684-694, 2022. doi:10.1002/acn3.51549, PMC9082391



P1.12

Sex Differences in Dystonia

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Abstract

Introduction: Most prior epidemiological studies have noted significant sex differences for the adult-onset focal dystonias and some early-onset inherited dystonias. The goal of this study was to evaluate sex differences in two large public databases. One was the Dystonia Coalition database, a large international multicenter collaborative network with mostly adult-onset focal dystonias. The other was the MDSgene database, which contains a systematic collection of previously reported cases with mostly early-onset monogenic cases.

Methods: Cross sectional data from 3222 individuals with predominantly adult-onset focal dystonia were obtained from the Dystonia Coalition. Data from 1396 individuals with predominantly early-onset monogenic dystonia were obtained from MDSgene. Data for these two sources were analyzed separately because of their different content and format. Data were analyzed according to sex, along with a number of other variables.

Results: Among 3222 individuals in the DC database, 71% were females and 29% were males, for an overall female to male ratio of 2.4. Females outnumbered males for almost all types of dystonia, with some variations according to body region affected. Sex did not have a significant impact on co-existing tremor, *geste antagoniste*, depression or anxiety. However, there was a significant impact of sex on use of thyroid medications. Among 1396 cases from MDSgene database, females outnumbered males for some genes (GNAL, GCH1, and ANO3) but not others (THAP1, TH, and TOR1A). In both databases, sex differences appeared to emerge between 10-20 years of age, coinciding with puberty.

Conclusions: Our results are in line with prior epidemiological and clinical studies that have indicated females outnumber males for both adult-onset idiopathic and some early onset monogenic dystonias. Our results extend these prior observations by revealing that the predominance of females is dependent on gene and age, potentially implying a hormonal influence. Understanding the reasons of sex differences in dystonia is important because they may provide insights into the pathogenesis of dystonia or its treatments.

P1.13

Pain reduction in adults with cervical dystonia following a single injection of incobotulinumtoxinA: a pooled analysis

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Abstract

Introduction: Pain is a common and disabling symptom of cervical dystonia (CD). This pooled analysis evaluated the effects of a single injection of incobotulinumtoxinA (incoBoNT-A) on pain in adults with CD-related pain.

Methods: Pain severity data were pooled from four phase 3 and 4 studies of incoBoNT-A for the treatment of CD in adults. CD-related pain was assessed at baseline and 4 weeks after a single injection of incoBoNT-A using the TWSTRS-pain severity subscale or a pain VAS. Both were analysed using a score range 0-10 and pain was categorised as mild (>0-<3.5), moderate (3.5-<6.5) or severe (6.5-10). Response was defined as ≥30% or ≥50% reduction from baseline pain severity score. Percentage of patients with complete pain relief (pain score=0) at 4 weeks after incoBoNT-A injection was determined. Sensitivity analyses evaluated pain responses in the subgroup of patients not taking concomitant pain medication. Change in pain severity from baseline to Week 4 was assessed using a one-sample t-test.

Results: Of the 678 patients with pain at baseline, 36.4% had mild pain, 42.9% moderate pain and 20.7% severe pain; mean pain severity score was 4.26 (SD 2.32). At Week 4 after incoBoNT-A injection, there was a significant reduction from baseline in mean pain severity score (-1.25 (SD 2.04; p<0.0001), a shift to a lower level of pain severity, response rates reflected clinically important improvements (48.1% had ≥30% pain reduction and 34.4% had ≥50% pain reduction), and 10.3% were pain free. Of the 678 patients, 64.2% were not taking concomitant pain medication and had a baseline mean pain severity score of 3.83 (SD 2.41). Pain improvements in this subgroup were consistent with those in the total population.

Conclusion: These results show significant pain reduction in patients with and without concomitant pain medication following a single injection of incoBoNT-A in patients with CD.

P1.14

Body region response to pallidal deep brain stimulation in isolated non-acquired dystonia.

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Abstract

Objective: To evaluate response of dystonia in distinct body regions to pallidal deep brain stimulation (DBS) using the Global Dystonia Rating Scale (GDRS) scores in isolated non-acquired dystonia patients.

Background: It has been demonstrated that pallidal DBS reduces dystonia, but it remains unclear whether a differential response across the body parts exists. Limited evidence suggests that blepharospasm, cervical dystonia, dystonia affecting speech and swallowing do not respond as well as limb dystonia, but contrary findings have also been reported 1,2 . For any given patient, an affected body region might be causing more or less disability. Establishing which regions are most impacted by DBS would guide clinicians in choosing the correct patient for this treatment.

Methodology: This was a retrospective examination of subjects who underwent pallidal DBS at a university hospital between 2008 and 2020 for isolated non-acquired dystonia. GDRS scores were obtained through blinded, randomized assessment of standardized video exams, rated by two movement trained neurologists, separately and then averaged. If a patient had an individual body part score difference >=2 and/or total score difference of >=3, a third rater independently reviewed the video. The primary outcome measure was the change in GDRS score in each body region from baseline to follow-up.

Results: Twenty subjects were identified, ten were female, average age of dystonia onset was 35 3 20 (range 5-70) years with disease duration of 15 3 11 (range 2-34) years at the time of surgery. Among these, 8 (40%) had generalized dystonia (3 DYT-1 and 1 DYT-6), 9 (45%) segmental dystonia, 2 (10%) hemidystonia and 1 (5%) had focal dystonia. Average follow-up postoperative interval was 14 3 7 months (range 6-30). Table 1 summarizes the GDRS score change across different body parts, as well as the total score. It shows a significant response in neck, shoulder and proximal arm, distal leg and foot including knee as well as trunk in a differential pattern.

Conclusions: Pallidal DBS is an effective treatment for isolated non-acquired dystonia. There is likely a differential response to DBS among the various body regions.

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Table 1. GDRS subscores before and after DBS surgery (median (interquartile range^))

	Baseline GDRS	*Follow-up GDRS*	*p-value**	*# patients with dystonia (score >=1)*	*Point change if dystonia present*
Eyes	0.00 (0.00)	0.00 (0.00)	0.313	4 → 1	2.9±4.3
Lower face	0.00 (0.75)	0.00 (0.83)	0.578	5 → 5	1.1±2.5
Jaw and tongue	0.00 (2.25)	0.00 (2.25)	0.754	6 → 7	-0.2±3.2
Larynx	0.00 (0.00)	0.00 (0.50)	0.688	3 → 5	-0.5±2.0
Neck	6.17 (5.50)	2.50 (3.75)	**<0.001**	17 → 14	3.5±2.5
Shoulder and proximal arm	2.00 (5.67)	0.00 (1.50)	**<0.001**	14 → 8	3.3±3.7
Distal arm and hand including elbow	2.00 (6.50)	1.75 (5.67)	0.531	12 → 11	0.3±4.8
Pelvis and proximal leg	0.00 (1.25)	0.00 (0.00)	0.125	5 → 2	7.0±7.8
Distal leg and foot including knee	0.00 (2.00)	0.00 (0.67)	**0.031**	6 → 5	3.3±2.5
Trunk	0.00 (2.58)	0.00 (0.00)	**0.016**	6 → 1	5.0±2.4
TOTAL	16.91 (8.66)	10.00 (9.75)	**<0.001**	20 → 18	10.5±9.3

^ difference between the 75th and the 25th percentiles

* Paired, two-sided Wilcoxon signed rank test since data not normally distributed

P1.15

An Open-Label Study of Ethanol in Focal Dystonia

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Abstract

Introduction: In addition to prominent motor symptoms, interesting clinical observations in patients with isolated dystonia revealed that over 50% of patients self-report an improvement in symptoms after the intake of one to two alcoholic beverages. However, no studies to date followed up to objectively investigate the effects of ethanol on dystonic symptoms.

Materials and Methods: A total of 106 patients with isolated focal laryngeal dystonia (75 females/31 males, average age 58.4 3 11.6 years) participated in a standardized ethanol-challenge test to determine the therapeutic effects of ethanol on dystonic symptoms. Patients were recruited based on their self-assessment of symptom improvement after ethanol intake, including 79 self-reported responders, 22 self-reported non-responders, and 5 patients unsure of their response. Patients were administered two non-diluted shots of ethanol 30 minutes apart, each containing 0.8 g/L of 40-proof vodka, calculated based on the patient's total body water. Assessments of dystonic symptoms, breath alcohol content (BrAC), cognitive ability (MoCA), suicidality (CCSR-S), sleepiness, vital signs, symptoms self-evaluation, and side effects were performed before and 15, 30, 45, 60, and 120 minutes after ethanol intake. Voice and speech recordings were anonymized and blindly quantified for dystonia-characteristic voice breaks, voice harshness/strain, breathiness, and dystonic tremor. Changes in symptoms were assessed at each timepoint as (baseline-ethanol intake)/baseline)x100%. Patients were considered ethanol-responsive if their symptoms changed by ≥ 10% from baseline.

Results: All patients tolerated the ethanol challenge test well, without major adverse effects. Vital signs, cognitive status, suicidal ideations, and sleepiness scales remained normal 45 min and 2 hours after ethanol intake. Among all 106 patients, 52 patients (49.1%) had an average 45.6 3 25.8% reduction of LD symptoms 45 min after ethanol intake ($p \leq 0.0001$). These included 43 self-reported responders (82.7%) and 7 self-reported non-responders (13.5%). The remaining 54 patients (50.9%) had no significant changes in their symptoms following ethanol intake ($p \geq 0.05$), including 36 self-reported responders (66.7%) and 15 self-reported non-responders (27.8%).

Discussions: We demonstrate a robust measured response of LD symptoms to ethanol ingestion, suggesting that ethanol responsiveness is a phenotypical characteristic of the disorder. However, an objective, standardized ethanol challenge test is necessary for the assessment of the accurate therapeutic responsiveness of dystonic symptoms. Although ethanol cannot be recommended as a therapeutic option, oral medications with a mechanism of action similar to that of ethanol may likely be potent drugs for the treatment of patients with ethanol-responsive dystonia.

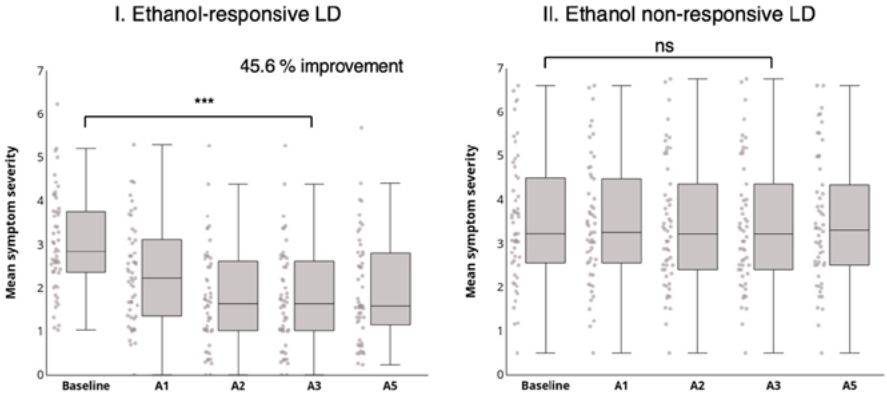

Figure 1: Effects of ethanol on dystonic symptoms. *** = $p \leq 0.0001$; ns = not significant.

P1.16

Probing the Inhibitory Motor Circuits in Adductor Laryngeal Dystonia during a Dystonia-Unrelated Finger-Tapping Task

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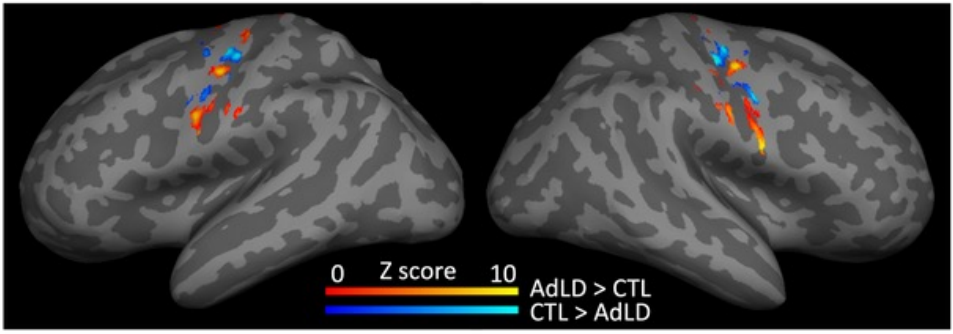
Abstract

Adductor laryngeal dystonia (AdLD) is a task-specific focal dystonia that impairs verbal communication due to excessive contraction of the intrinsic thyroarytenoid and lateral cricoarytenoid muscles in the larynx. For individuals with AdLD, this results in a strained, harsh, or tremulous voice characterized by irregular voice breaks or aphonia when attempting speech, impacting speech intelligibility and effective communication. The pathophysiology of AdLD is currently not known. However, growing evidence suggests that focal dystonia is associated with abnormalities in cortical inhibition within the primary motor cortex (M1), as measured using transcranial magnetic stimulation (TMS). Previous work using task-based functional magnetic resonance imaging (fMRI) has indicated abnormal activation in the sensorimotor networks during phonation and speech. While neuroimaging and TMS provide specific insights into the pathophysiology of dystonia, it is unclear if inhibition measured by TMS relates to the hemodynamic response measured by fMRI. This study investigated the relationship between M1 cortical responses obtained by TMS and fMRI, two complementary techniques, in a dystonia-unrelated (finger-tapping) task in AdLD and controls. We hypothesized that, due to widespread abnormalities of inhibitory motor networks, participants with AdLD would demonstrate greater neural activation in the M1 and increased intracortical inhibition during the dystonia-unrelated task as compared to controls. Sixteen adults with AdLD (63.934.8 years) and 16 adult controls (51.537.9 years) completed fMRI and TMS assessments over two study visits. Individual T1 anatomical scans were used for neuronavigation with TMS. Intracortical inhibition was assessed by examining the TMS-evoked cortical silent period (cSP) in the left hemisphere with responses measured from the right first dorsal interosseous during voluntary contraction. Neural activation was measured using blood-oxygen-level-dependent (BOLD) responses to a finger-tapping task. Results indicated that cSP duration was significantly shorter in AdLD (88.41 3 22.55 ms) than in controls (111.16 3 31.30 ms) ($p = 0.03$, $d = -0.83$, 95% CI [-42.45, -3.05]), indicating reduced intracortical inhibition (corresponding to the dystonia-unrelated hand muscle) in those with AdLD. AdLD also demonstrated more dispersed BOLD activation responses that were not localized to the M1 hand region. We found greater positive correlations between BOLD responses and cSP duration task in AdLD, as compared to controls. This complements our previous work, which found positive correlations between BOLD responses during phonation and inhibition in the laryngeal motor cortex in AdLD. Abnormalities in neural networks related to dystonia are not limited to the representation of the dystonic musculature alone but may indicate more global

inhibitory dysfunction.



P1.17

Clinical Analysis of Correlations and Distributions of GDRS and BFM Scales

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Abstract

Introduction: The two most commonly used general scales for documenting the severity and distribution of dystonia include the Global Dystonia Rating Scale (GDRS) and the Burke-Fahn-Marsden Scale (BFM). The goal of this study was to explore the performance of these scales in a large group of individuals with different types of isolated dystonias.

Materials and Methods: A total of 3240 subjects with different types of isolated dystonia were included. Most were adults with focal or segmental dystonia, but children and generalized dystonia patients were not excluded. A total of 3067 subjects had both GDRS and BFM scores. Results were compared using GraphPad software. Additionally, 209 subjects with cervical dystonia that had Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores and another 210 with blepharospasm that had Blepharospasm Severity Scale (BSRS) scores were analyzed for correlations.

Results: Both total and regional GDRS scores were not found to be normally distributed due to the overabundance of 1 scores. Regional and total BFM scores were not normally distributed, but severity scores taken alone were normally distributed. Scores for both scales correlated with age at onset, and age at assessment ($p < 0.001$). There was a strong positive correlation between the total GDRS and total BFM scores ($r = 0.8201$), as well as individual region sub-scores. Correlation matrix analyses revealed that lower limbs tend to feature positive correlations ($r > 0.5$). Strong correlations were found between regional and total scores between tests for localized dystonia patients and these correlations matched with the TWSTRS ($r = 0.5867$) and BSRS ($r = 0.6438$) scores for cervical dystonia and blepharospasm patients, respectively.

Discussion: These results confirm a good correlation between the GDRS and BFM total scores, although region-specific sub-scores sometimes show poor correlations because they do not exactly measure the same things. These correlations between GDRS and BFM are better when the provoking factor of the BFM is not included. Neither scale showed a normal distribution, suggesting the usual approach with parametric statistics may not be appropriate.

P1.18

Dystonia with myoclonus and vertical supranuclear gaze palsy associated with a rare GNB1 variant

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Abstract

Introduction: GNB1 encephalopathy (OMIM: 616973), caused by pathogenic variants in the GNB1 gene, is a rare neurodevelopmental syndrome characterized by global developmental delay (GDD) variably co-occurring with movement disorders. For the latter, dystonia, although the most frequent, remains uncommon, and other phenomenologies including myoclonus, tics, chorea, and ataxia, and oculomotor abnormalities are rare.

Materials and Methods: We report a case of GNB1 encephalopathy arising from a de novo mutation in a gene region with few reported pathogenic variants (i.e., exon 11) presenting with a unique phenotype consisting of dystonia with myoclonus and vertical supranuclear gaze palsy.

Case Report: A 27-year-old female from a non-consanguineous union presented with hypotonia, global developmental delay, intellectual disability, short stature, and low body weight postnatally. Subsequently, she developed dysarthria, a wide-based gait, and dystonia. She did not tolerate trials of levodopa and pergolide. Amantadine improved her dystonic symptoms, but she then developed spontaneous and action-induced myoclonus, which lessened after a gradual tapering. She improved with increasing doses of trihexyphenidyl; however, she developed intermittent choreoathetoid movements. Neurologic and formal neuro-ophthalmologic examination disclosed a vertical supranuclear gaze palsy. Her axial dystonia, posture, and gait significantly improved with botulinum toxin (BoNTA) injections to the paraspinal muscles. Examination disclosed microcephaly, high-grade myopia, hypermobility of the fingers, scoliosis, and nonspecific dysmorphic facial features. She also had reduced muscle bulk and hypoactive deep tendon reflexes throughout.

Blood, cerebrospinal fluid, metabolic screening, brain magnetic resonance imaging with spectroscopy, and electroencephalography were unrevealing. Electrophysiologic testing demonstrated short-duration muscle bursts suggestive of myoclonus superimposed on more continuous activity consistent with dystonia. Initial genetic investigations were nondiagnostic, but an ppdated trio whole exome sequencing (WES) six years after the initial WES identified a de novo heterozygous missense variant in the GNB1 gene (c.1009A>C (p.Lys337Gln); exon 11; GenBank: NM_002074.5) classified as likely pathogenic.

Discussion: To our knowledge, myoclonus combined with dystonia has only been described in one previous case. Although amantadine could have accentuated her myoclonus, its persistence long after drug discontinuation strongly favors the GNB1 variant as the cause. Our report is also the first to fully document a vertical supranuclear gaze palsy in GNB1 encephalopathy. Taken together, this case illustrates the evolving clinical phenotypes of GNB1 encephalopathy. In instances where the constellation of clinical findings is suggestive of a genetic syndrome yet diagnosis remains obscure, next-generation sequencing (NGS) tests such as WES can be helpful.

P1.19

A 10-year Service Evaluation of a Cervical Dystonia Botulinum Toxin A Clinic: Factors associated with a patient satisfaction.

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Abstract

Introduction: Cervical Dystonia (CD) is a chronic condition with significant impact on quality of life (1). Botulinum Toxin A (BoNT A) is the mainstay of symptomatic treatment typically injected into affected muscles every 3-4 months. The efficacy and safety of BoNT-A has been well established for CD but in clinical practice the individual injection schemes vary substantially (2). We aimed to review the factors associated with patient satisfaction of routine care with BoNT-A injections for CD in a "real world" clinical setting.

Methods: Patients with primary Cervical Dystonia attending a specialist botulinum toxin clinic were evaluated over a 10-year period (2008-2018). At each clinic visit, patients were asked to complete a questionnaire with a visual analogue score between 0 and 100 to rate their response from the previous injection. Outcomes were then recorded as static measurements of the time to reach 50% improvement and 75% improvement. The association between patient factors and outcome were assessed using Fisher exact test and standard t test.

Results: Data was recorded for 135 patients attending for 1665 injections over a 10-year period. Overall, 84% of patients achieved 50% improvement (n=114) and 73% (n=99) achieved 75% improvement. The median time to 75% improvement was 9 months (range 1-77months). The median time to 50% improvement (if achieved) was 3 months (range: 1-74months).

There was no statistically significant association between gender, presence or absence of head tremor, toxin preparation or head posture with either the likelihood of achieving 50% improvement or the time to achieve 50% improvement.

A sensory trick was reported in 82% (n=111). The patients who did not have a sensory trick were significantly more likely to have reported a proceeding trauma (62% vs 18%, p=0.05). There was a significant association between the absence of a sensory trick and not achieving 50% clinical improvement.

Discussion:

In this study, BoNT-A was again shown to overall be safe and effective for CD. In the absence of a sensory trick, patients were more likely to report a preceding trauma and less likely to respond to BoNT-A therapy. Other factors did not show a clear association.

1.Camfield L, Ben-Shlomo Y, Warner TT, Group TES of D in E (ESDE) C. Impact of cervical dystonia on quality of life. Mov Disord. 2002;17:838–41.

P1.20

Impaired modulation of sensorimotor cortex mu activity during active and passive movement in children with dystonia and dystonic cerebral palsy

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Abstract

Introduction: Sensorimotor processing is abnormal in adult genetic/idiopathic dystonia, but has rarely been explored in acquired or childhood dystonia. This study investigates cortical sensorimotor processing by measuring event-related desynchronization (ERD) and synchronisation (ERS) in response to passive and active movement tasks in children/young people with dystonia/dystonic cerebral palsy (CP).

Materials and Methods: The study received ethical approval. Informed consent was obtained from each participant or, if <16 years, the parent/guardian. 30 young people with dystonia (20 genetic/idiopathic; 10 dystonic CP) and 22 controls age 5-21years, participated in a passive movement task in which a robotic wrist interface delivered passive wrist extension movements, producing a brief stretch stimulus of the wrist flexors (10 degrees from neutral). Each hand was tested separately except for 5 patients, in whom only the dominant hand was tested. 23 participants (9 dystonia, 14 controls) also performed an equivalent active wrist extension task. Scalp EEG was recorded with a BrainVision amplifier using the 10-20 international system. Impedances were maintained below 10kOhm. EEG was amplified, filtered (DC-500Hz) and sampled at 2500Hz. Wrist position was monitored and movement onset synchronised with EEG recordings. Data were segmented into 4.5 second epochs (1 second pre- and 3.5 seconds post-stimulus). Epochs with inadequate wrist movement profile or contaminated by excessive movement or eye blink artefacts were rejected. Up to 160 data epochs were collected per subject. Time-frequency analyses were performed using continuous Morlet wavelet transforms (1Hz bins from 5-40Hz, 8 wavelet cycles). Relative changes in post-stimulus power with respect to baseline, were calculated for the alpha/mu (8-12Hz) band.

Results: For the passive task, controls showed a prominent early alpha/mu ERD (0.5-1s post-stimulus) and later alpha/mu ERS (1.5–2.5s post-stimulus) over contralateral sensorimotor cortex. The dystonia group showed significantly smaller alpha/mu ERD compared with controls for the dominant (ANCOVA $F(2,47)=4.45$ $p=0.017$) and non-dominant hand (ANCOVA $F(2,42)=9.397$ $p<0.001$). Alpha ERS was also significantly smaller in dystonia than in controls for the dominant hand (ANCOVA $F(2,47)=7.786$ $p=0.001$). Findings were comparable for genetic/idiopathic dystonia and dystonic CP. For the active task, a similar pattern of reduced mu modulation was observed in dystonia compared with controls.

Discussion: The impaired alpha/mu modulation indicates an abnormality of sensorimotor processing of proprioceptive information during both active and passive movement, which is common to many genetic/idiopathic dystonias and dystonic CP.

P1.21

Using Ultrasound in the assessment of dystonic Tremor

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Abstract

Introduction: Traditionally polymyography is used to select muscles for treatment with botulinum toxin in more complex cases of dystonic tremor. Surface polymyography, mostly used assessment of arm tremor, has the advantage of a high temporal resolution and allows to investigate multiple muscles at the same time under different test conditions. Surface polymyography is however not able to differentiate activity of anatomically overlapping muscles. In cervical dystonia, intramuscular (needle) polymyography is used to assess the overlapping muscles. Still, needle polymyography of multiple muscles in a tremulous arm or neck can be quite a challenge for the examiner and painful for patients. Here ultrasound may offer a solution.

We present a case of dystonic tremor to show the add-on value of ultrasound in the assessment of arm tremor.

A 78-year-old man presented with a 11-year history of tremulous movements of the arms, with insufficient effect of propranolol, topiramate and primidone treatment. Based on the jerky bilateral postural tremor (right > left) without resetting, with a dystonic posturing of the head and subtle dystonia of the right arm, he was diagnosed with dystonic tremor. To assess which muscles to select for botulinum toxin treatment, polymyography was performed, followed by ultrasound in B-mode (two dimensional) and M-mode (observing the difference over time). Both surface polymyography and M-mode ultrasound showed a 5 Hz tremor of mainly the right arm, increasing with certain postures. In polymyography, most activity was seen in m. biceps brachii, m. brachioradialis, m. supinator, m. flexor carpi radialis, and m. extensor digitorum communis. With visual inspection of B-mode ultrasound video, tremulous activity could be more specifically localized to the m. pronator teres, and not the m. flexor carpi radialis (Figure 1). In addition, tremor in m. biceps brachii, m. triceps, and m. extensor digitorum communis was confirmed. Botulinum toxin injections in his biceps brachii, extensor digitorum communis and pronator teres gave the patient a satisfactory reduction of the tremor.

This case shows ultrasound has a high spatial resolution, which is more accurate than polymyography when overlapping muscles are involved in tremor. Thus, B-mode ultrasound may help to select muscles for treatment with botulinum toxin. In addition, M-mode ultrasound can be used to quantify tremor frequency.

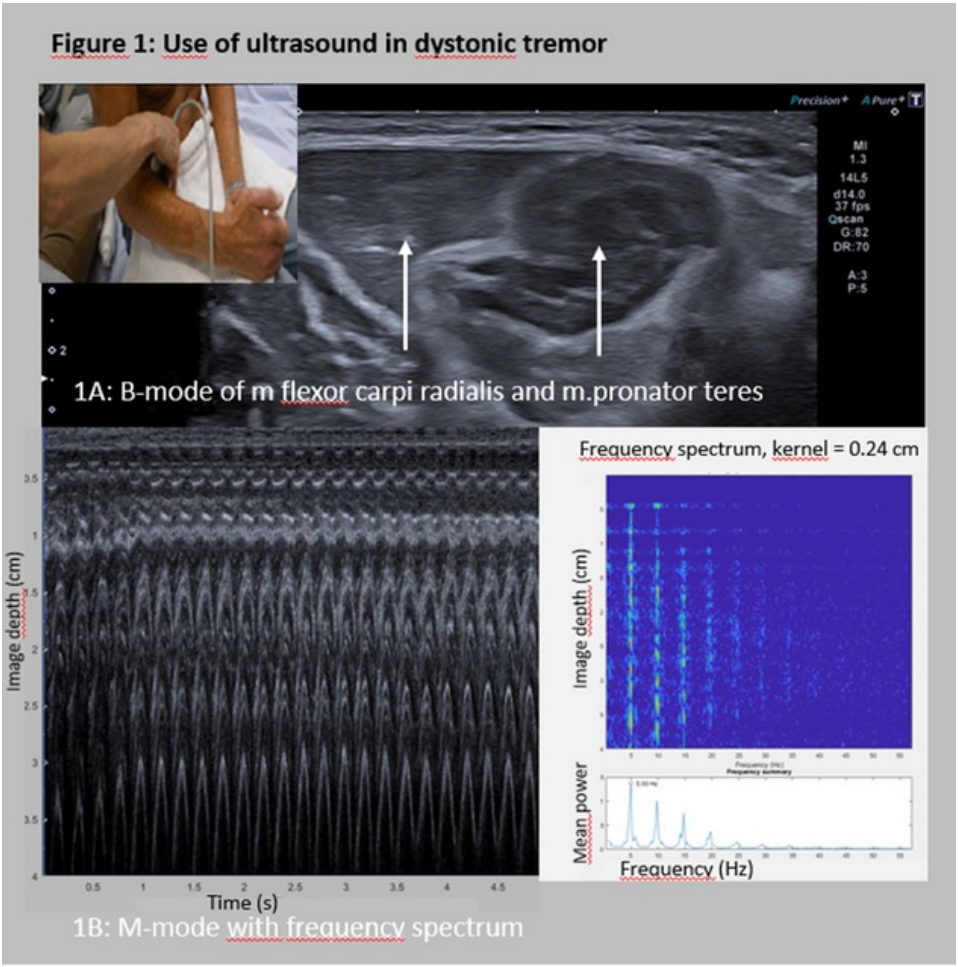

Figure 1: use of ultrasound in dystonic tremor: 1A: B-mode still of video, showing anatomical 'yin yang' configuration of right pronator teres and flexor carpi; in the video the pronator teres is very active. 2B: M-mode with frequency spectrum.

P1.22

Repetitive Transcranial Magnetic Stimulation to the Inferior Parietal Lobule in Task-Specific Focal Hand Dystonia: A Randomized Crossover Blinded Outcome Assessment Study

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Abstract

Background: Dystonia is a network disorder due to impaired homeostatic plasticity and abnormal sensorimotor connectivity. The posterior parietal cortex, specifically the inferior parietal lobule has extensive projections to the premotor cortex which is found to be aberrant in focal hand dystonia (FHD). Modulation of motor areas via stimulation of the parietal cortex may have downstream effects on the premotor cortex, which in turn connects to the M1 hand area.

Objective: To determine the effect of an inhibitory rTMS protocol delivered to the left inferior parietal lobule in dystonia severity in right-handed patients with focal hand dystonia as assessed by the Writer's cramp rating scale (WCRS).

Materials and Methods: We conducted a randomized, sham control, double-blind, crossover study. All participants received single sessions of low frequency (1Hz) inhibitory rTMS [Intervention] and Sham stimulation [Control] over the left inferior parietal lobule (IPL) in random order, as per the group allotted. Each stimulation session lasted for 20 minutes and 300 pulses in 4 blocks were delivered at 90% RMT to the anatomically localized left IPL. At baseline and the end of each session of rTMS and sham stimulation, WCRS, kinematic analysis using electrogoniometer and torsiometer, and subjective improvement by Likert scale were assessed.

Results: We recruited 16 right-handed patients with task-specific focal hand dystonia [mean age: 25.1 (range 19-54) years, gender (Men-13), mean duration of symptoms: 8.3 (range 1-25 years)]. The mean WCRS score at baseline was 5.8 3 3.4 in group A (received 1Hz rTMS initially) and 13.4 3 5.2 in group B (received sham stimulation initially). An inhibitory rTMS protocol applied to the left inferior parietal lobule resulted in significant improvement in dystonia severity measured by the WCRS total score (WCRS difference REAL minus SHAM mean (SD): -1(1.3), 95% CI -2, -1, p= 0.002) and Writing Movement Score (WMS difference REAL minus SHAM mean (SD): -1(1.4), C.I. -2 to 0, p=0.005) and thus significant treatment effect within individual subjects, irrespective of the sequence in which they received the intervention.

Conclusion: In patients with task-specific focal hand dystonia, an inhibitory TMS protocol delivered to the inferior parietal lobule may modulate the abnormally hyperexcitable premotor-parietal-putaminal circuitry and reduce FHD severity.

P1.23

Generalized dystonia, neurodevelopmental regression, and premature ovarian insufficiency due to an *IRF2BPL* pathogenic de novo nonsense variant.

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Abstract

Introduction: Interferon regulatory factor 2 binding protein-like (IRF2BPL) de novo variants have been linked to a Neurodevelopmental Disorder with Regression, Abnormal Movements, Loss of Speech, and Seizures (NEDAMSS). Dystonia may be a prominent manifestation.

Methods: We evaluated a 19-year-old female with progressive gait, speech and behavioral disturbances, and cognitive decline. Her delivery was normal after an uneventful pregnancy. There was a family history of breast and colon cancers but no neurological disease. She achieved normal motor developmental milestones until the age of 7 years. She then developed progressive gait dysfunction, learning disability, generalized dystonia, spasticity, dysarthria, and oculomotor abnormalities. By age 19 she was wheelchair-bound and communicated with an electronic device. On examination, she was almost mute, had preserved simple-command comprehension but processing delay, disconjugate gaze, saccadic pursuit and absence of optokinetic nystagmus, spasticity with bilateral pyramidal tract signs, and generalized dystonia. Trials of levodopa and baclofen were unsuccessful. Botulinum toxin has been effective for generalized dystonia and spasticity for 5 years. Short-lasting episodes of upward eye deviation and dystonic posturing of the extremities without EEG correlate have been treated with lamotrigine.

Results: 3T brain magnetic resonance (MR) demonstrated posterior atrophy in the parietal and occipital lobes with T2-weighted hyperintensities around the posterior horns of the lateral ventricles. Initial brain MR spectroscopy showed decreased N-acetyl-aspartate not evident on a later study. Further investigations were negative for lysosomal and metal storage diseases, organic acidurias, and autoimmune disorders. CSF 5-hydroxyindoleacetic acid was borderline low and homovanillic acid was decreased. Repeated EEGs were within normal limits. Somatosensory evoked potentials showed absent cortical responses bilaterally, with delayed cortical response in visual evoked potentials. Initial diagnostic exome sequencing was negative but later re-analysis and novel sequencing revealed a de novo, nonsense pathogenic variant in the *IRF2BPL* gene (NM_024496.3:c.499C>T, p.Gln167*). Amenorrhea and decreased bone density resulted in a diagnosis of premature ovarian insufficiency due to hypergonadotropic hypogonadism.

Discussions: NEDAMSS due to *IRF2BPL* mutations should be considered in these patients

with prominent dystonia. IRF2BPL transcripts are expressed in multiple tissues with functions related to neuronal development, cell homeostasis, and regulation of gonadotropin-releasing hormone (GnRH). The latter might have predicted a central mechanism underlying ovarian failure; however, our patient had hypergonadotropic hypogonadism. To our knowledge, this is the first case reported to have premature ovarian insufficiency and supports the evaluation of gonadal function in all patients with this disorder both for patient management and to advance our understanding of disease mechanisms.

P1.24

Form vs Function: Inappropriate Behaviors in Cervical Dystonia Beyond Deficits Predicted by Social Cognition Testing

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Abstract

Objective: Describe the discordance of social cognition testing and observed socially inappropriate behaviors in adult-onset focal cervical dystonia (CD).

Background: Impairment in social cognition has been identified in CD. Though impairment on formal social cognition testing is assumed to be reflected in real world behavior, the validity of this relationship is seldom studied. We present a case series of study participants with CD who participated in a social cognition study and were observed to exhibit socially inappropriate behavior during the study visit.

Methods: We reviewed data from our cross-sectional study evaluating social cognition in CD using the Social Norms Questionnaire (SNQ22).i Socially inappropriate behavior exhibited during study visits was documented and categorized.ii If a participant repeated multiple acts in the same category the category was recorded only once for that participant.

Results: 32 CD participants were included in this descriptive analysis. 31% (n=10) of the participants exhibited at least one socially inappropriate behavior during their study visit. Out of 20 behaviors recorded, 45% were categorized as tactlessness (poor manners), 10% as inappropriate emotional responses, 25% as social awkwardness, 5% as improper verbal acts, 5% as disagreeableness, 5% as improper physical acts, and 5% as inappropriate physical contact (see Table 1).

Discussion: We observed a variety of inappropriate social behaviors during a study of social cognition in CD that were not reflected in their SNQ22 testing results. For example, two participants directly answered questions incongruent with observed behaviors (one hugged the researcher but answered that it was not socially acceptable to hug a stranger, and another asked the researcher their age but answered it was not socially acceptable to ask a coworker their age). Our findings suggest self-report scales such as the SNQ22 may fail to detect some social cognition deficits in CD which may be better identified with alternative observation-based assessments.

P1.25

Deep Brain Stimulation for childhood-onset DYT - KMT2B: 2-year functional outcomes

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Abstract

Introduction: DYT- KMT2B dystonia is clinically and genetically heterogeneous, with a broad spectrum of motor phenotypes and functional profiles. To date, only common dystonia rating scales have measured Deep Brain Stimulation (DBS) outcomes. We report DBS-related outcomes in childhood dystonia using standardised tools capturing a wider functional profile & goal acquisition relating to Activity and Participation domains of the International Classification of Function (ICF).

Materials and Methods: Standardised assessments (see Table-1) were completed at baseline, 1- & 2-years post-DBS in eleven children with DYT-KMT2B (mean and median age at implantation 11 and 9.2years, respectively).

Differences in means and 95% confidence intervals between pre, 1- and 2-years post-DBS were explored using paired t-test. Mutation types were also examined.

Results: Mean BFMDRS-m score was 75 at baseline (range 46.5 – 101.5). A statistically significant improvement was seen at 1 year ($p=0.05$) but not at 2 years post DBS.

The Canadian Occupational Performance Measures (COPM) defined baseline priority functional areas, which were similar across all patients: self-care, mobility and participation were most frequently encountered. Improvements were seen for goal-related performance (P) & satisfaction (S) at 1-year (COPM P&S $p=0.001$) and 2-years (COPM P&S $p<0.001$) post-DBS.

Assessment of Motor & Process Skills (AMPS) motor scores also improved 2 years post-DBS ($p=0.004$). On the Melbourne Assessment of Unilateral Upper limb Function (MA2), fluency significantly improved for the dominant (D) hand indicating reduced phasic movements at 2 years post-DBS ($p=0.003$).

A statistically significant change in six-minute walk test (6MWT) was not seen, but 3 young people who were unable to complete this at baseline were able to do so post-DBS. Gross Motor Function Measure (GMFM) scores were stable, or improved, for those who had not

reached ceiling effects at baseline.

At two years post-DBS, patients reported no significant change to bulbar symptoms, despite some improvements in speech quality, sialorrhoea and dysphagia in some cases.

Cognitive testing suggested generally impaired non-verbal intellectual ability (mean=65.5, 61–94) The majority of patients were in the impaired range for intellectual ability, 2 had borderline learning impairment (70-79) and 1 had average intellect.

No significant genotype phenotype correlations were immediately identifiable.

Discussion: Despite wide heterogeneity, DBS-surgery improved function in childhood KMT2B dystonia. We show improvements in patient-selected daily-life goals at 1-year. Further improvements in other motor function domains take longer, emerging at 2-years. Long term and multi-centre follow-up is important to help elucidate the impact of DBS-surgery in this increasingly recognised genetic condition.

Table 1: Assessments at 1- and 2-years post DBS with P value and 95% CI

Dystonia Assessments	1 year Post DBS *p value, (95% CI)*	2 years post DBS *p value, (95% CI)*
BFMDRS-M	p=0.50 (-11.27 to -0.01)	p=0.247 (-6.52 to 1.88)
Goal acquisition		
COPM-P	**p=.001** (1.47 to 4.03)	**P<.001** (2.15 to 3.97)
COPM-S	**p=.001** (1.76 – 4.96)	**P<.001** (2.87 to 4.85)
Motor assessments		
GMFM	p = 0.71 (-1.09 to 22.46)	p=0.119 (-3.66 to 27.51)
MA2: ROM	D: p=0.286 (-6.12 to 19.52) ND: p=0.370 (-9.65 to 23.45)	D: p=0.13 (-5.81 to 36.10) ND: p=0.067 (-1.92 to 42.78)
MA2: Accuracy	D: p=0.181 (-8.06 to – 36.86) ND: p=0.060 (-1.05 to 40.25)	D: p=0.135 (-8.74 to 50.50) ND: p=0.148 (-12.09 to 63.24)
MA2: Dexterity	D: p=0.515 (-10.28 to 19.08) ND: p=0.566 (-11.90 to 20.41)	D: p=0.201 (-11.39 to 43.67) ND: p=0.440 (-19.29 to 39.01)
MA2: Fluency	**D: p=0.014** (4.52 to 30.28) ND: p=0.159 (-5.66 to 29.66)	**D: p=0.033** (15.47 48.25) ND: p=0.092 (-4.51 to 45.36)
6MWT	p=0.551 (-52.9 to 93.45)	p=0.393 (-46.88 to 109.54)
TUG	p=0.349 (-13.14 to 32.52)	p=0.367 (-7.45 to 17.32)
Functional Assessments		
AMPS: Motor	p=.351 (-1.31 to 1.05)	**p=0.004** (0.77 to 2.03)
AMPS: Process	p=0.49 (-0.22 to 0.38)	p=0.22 (-0.18 to 0.58)

P1.26

Development of a Patient-Centered Outcome (PCO) Measure for Dystonia

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Abstract

Background: The purpose of the Patient-Centered Outcome (PCO) Project is to establish clinical trial readiness for novel treatments of dystonia. Botulinum neurotoxin (BoNT) is a first-line therapy for focal dystonia including cervical dystonia (CD), blepharospasm (BSP), and laryngeal dystonia (LD). Although BoNT provides significant improvement, approximately one-third of patients discontinue use suggesting that BoNT therapy may not meet patient expectations.

Methods: We set out to develop a PCO that accurately captures the patient experience during therapy. After a modified Delphi process to identify candidate PCO items and based on FDA guidance, we surveyed a large number of patients with dystonia to explore the following: 1) PCO item relevance to the patient's disease; 2) PCO item importance to improve or change with therapy; and 3) minimal change in the PCO item that would be meaningful to the patient.

Results: We surveyed approximately 500 CD patients, 300 BSP patients, and 600 LD patients. All PCO items surveyed were rated as highly relevant to the patient experience and would be important to treat. A minimal meaningful change in the PCO items overall was reported by the majority of patients as 25% (CD), 20% (BSP), and 27% (LD).

Conclusion: We used robust patient engagement and verification to identify PCO items for CD, BSP, and LD with relevance to their disease and importance to reflect response to therapy. In addition, we have prospective data on what the minimal meaningful change will be in each PCO item that we can compare with the live data we are collecting from the 300 patients participating in this project.

P1.27

Development of a Smartphone Application Able to Capture Patient-Centered Outcome (PCO) Measures for Dystonia

Paul Reyes[1], Arlann Erskine[1], Brian Berman[2], Sarah L. Schneider[3], Janet Hieshetter[4], Kimberly Kuman[5], Cynthia Comella[6], David Peterson[7], Gamze Kilic-Berkmen[8], Laura Wright[9], Fares Qeadan[10], Samantha Pentecost[1], Joel S. Perlmutter[9], Sarah Pirio-Richardson[1], H. A. Jinnah[8]

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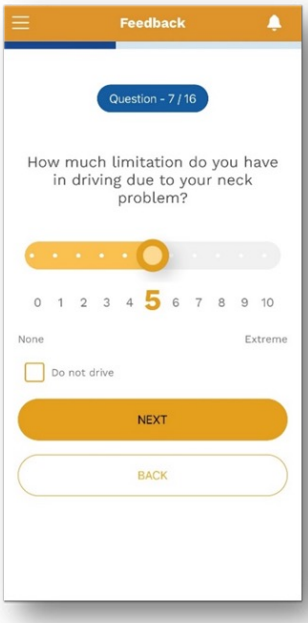
Abstract

Introduction: Botulinum neurotoxin (BoNT) is a first line therapy for many types of dystonia and results in significant improvement, yet approximately one-third of patients discontinue use of BoNT suggesting that BoNT therapy may not fully address patient expectations. Symptom Snap was developed to capture Patient-Centered Outcome (PCO) measures across motor, disability, and psychosocial domains, enabling clinicians and researchers to characterize the therapeutic response to BoNT therapy over time on a frequent basis.

Methods: In collaboration with TekSynap, we developed a smartphone application able to capture PCO measures tailored for three major dystonia subtypes: cervical dystonia (CD), blepharospasm (BSP), and laryngeal dystonia (LD). The app is accessible to users on both Android and iOS operating systems. We also developed a web-based admin panel able to track all data entered in the app. The admin panel is accessible to study personnel only. The admin panel is also used for generating login credentials.



Results: Symptom Snap features a user-friendly interface with easy-to-read text, making data entry a very straightforward process. Within the app, each major dystonia subtype has its own set of questions (16 questions for CD, 18 questions for BSP, and 15 questions for LD). All questions are formatted in a numerical rating scale, and some have an additional answer box to choose when appropriate (the figure shows a screenshot taken from the CD category). Throughout each questionnaire and before submission, users have the option to revise their answers to previous questions. After submission, users are unable to enter questionnaire data until one week has passed. There are additional tools integrated into the app including a "Contact Us" menu option and a notification switch. The "Contact Us" menu option serves as a platform where users can submit troubleshooting inquiries. The notification switch, when turned on, allows the app to send push notifications when a weekly questionnaire is due for submission.

Conclusion: Symptom Snap will be tested as a primary outcome measure and, in the future, may be used as a journal for users with dystonia to document the impact that their symptoms have over various lifestyle domains. Not only will their data help to improve the care they receive, but also allow researchers to assess which domain(s) BoNT therapy does not fully address, helping provide direction in the development of novel treatments for dystonia.

P1.28

Thyroid disease in cervical dystonia

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Abstract

Introduction: Cervical dystonia (CD) is the most common of the adult-onset focal dystonias. There are many possible causes for CD, but a cause cannot be identified in most cases. Recent studies have focused mainly on genetic causes, and a subgroup of cases are known to be caused by specific gene defects. Other studies have suggested a subgroup that may result from autoimmune mechanisms. Because autoimmune disorders frequently co-exist, the current study evaluated if autoimmune disorders are more common in CD than neurological controls.

Methods: We evaluated the frequency of 32 common autoimmune disorders using a systematic survey to compare 300 subjects with CD with 391 neurological controls.

Results: The frequency of thyroid disease was significantly higher in CD (20%) compared with controls (6%). Regression analyses that accounted for age and sex revealed an odds ratio of 4.5 (95% CI 2.5–8.1, $p < 0.001$). All other autoimmune disorders occurred with similar frequencies in CD and controls.

Conclusions: Our study suggests a link between CD and thyroid disease, a finding noted in numerous prior anecdotal reports. Further studies are needed to determine if this link means that there is a subgroup of CD that results from autoimmune mechanisms. Identifying this subgroup would have obvious therapeutic implications.

Reference: Kilic-Berkmen et al., Parkinsonism and Related Disorders 107 (2023) 105274

P1.29

Treatment of Task Specific Dystonia in Sports; a Systematic Review

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Abstract

Introduction: Task specific dystonia is a movement disorder only affecting a highly practiced skill, and is found in a broad set of expert movements including in sports. Despite affecting many sports, there is no comprehensive review of treatment options, which is in contrast to better studied forms of task specific dystonia in musicians and writers.

Materials and Methods: Studies involving an intervention to treat task specific dystonia in sports were systematically reviewed, with special attention for the quality of outcome measures. Guidelines for the Preferred Reporting Items for Systematic Reviews and MetaAnalysis were followed.

Results: In April 2022 Pubmed, Embase, Web of Science, and Psychinfo were searched. Of the 7000 articles identified, 31 were included that described non-invasive psychological and invasive and/or pharmacological interventions. The quality of studies was low with a lack of formal standardized outcome measures resulting in low quality evidence for the effectiveness of treatment options. A descriptive synthesis showed emotional regulation was effective, but was exclusively tried in golfers. We found almost no formal evidence for using botulinum toxin or pharmacology.

Discussion: Future studies with larger cohorts and quantitative outcome measures are needed to improve understanding of treatments for task specific dystonia in athletes.

P1.30

Exploratory Clinical Trial of Dipraglurant for Blepharospasm

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Abstract

Introduction: Injections of botulinum toxin are the main treatment for blepharospasm. However, it is not entirely satisfactory for all patients. Adjunctive oral therapies are limited and include benzodiazepines, anticholinergics, and some others. Additional oral therapies would be welcome. Dipraglurant is an inhibitor of the metabotropic glutamate receptor type 5, one of the brain's major excitatory neurotransmitters. Dipraglurant therefore reduces neuronal excitability, a fundamental physiological abnormality in dystonia. Dipraglurant also appeared to be useful in preclinical studies of dystonia. The goal of this study was to delineate safety and efficacy of dipraglurant oral tablets for blepharospasm via this exploratory, randomized, double-blind, single-center clinical trial.

Methods: Participants were randomized in a 1:1:1 ratio to receive dipraglurant 50 mg, 100 mg, or matching placebo. Safety and tolerability were evaluated at several time points following administration. Efficacy was evaluated by using several clinical rating scales including the Jankovic Rating Scale, Defazio Rating Scale, Global Dystonia Rating Scale, Clinical Global Impression of Change, Patient Global Impression of Change, and Blepharospasm Disability Index. Efficacy was also assessed using a wearable device that measured blinks and spasms, and digital analysis of blinks and spasms from video.

Results: Fifteen patients were enrolled (8 females, 7 males), 5 in each treatment group. A total of 13 adverse events were reported. All were mild and resolved without intervention. Only dizziness appeared to be related to drug treatment, occurring in 80% of those receiving active drug. Pairwise comparisons of measures from baseline to 1 or 2 hrs following dosing showed no significant effect of the drug for any of the clinician-rated or patient-rated scales or objective measures. Direct visualization of the data did not suggest any consistent improvement or worsening either. All measures showed significant variability, even within cases.

Conclusions: This study suggests that dipraglurant at applied doses is safe and well-tolerated, but without measurable benefit. The results are valuable for guiding future clinical trials by enabling studies of measurement variability and power analyses for several outcome measures.

P1.31

The Dystonia Coalition: An International Multicenter Network for Clinical and Translational Studies

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Abstract

Introduction: The Dystonia Coalition (DC) is a collaboration of medical researchers and patient advocacy groups (PAG) working together. It was started in 2009 to facilitate collaborations needed to advance the pace of clinical and translational research in dystonias to find better treatments and a cure.

Methods: We reviewed the projects and products of the DC since it began in 2009.

Results: Since it began, the DC has encouraged collaboration by engaging 58 sites across North America, Europe, Asia, and Australia. It has conducted several major international projects, facilitated 82 Pilot Projects with either direct funding or provision of data or resources, and provided 19 Career Development Awards. The major international projects have included the development of a large database with more than 3500 cases, a biorepository for these cases that contains DNA and plasma, the development or revision of rating tools for the most common adult-onset focal dystonias, and digital tools for more precisely monitoring symptoms of dystonia.

Conclusions: The DC has facilitated collaborations that led to international consensus on the definition and classification of dystonia, development of several diagnostic and severity tools for focal dystonias, establishment of the largest database and biobank of patients with dystonia in the world, and more than 200 peer-reviewed publications. The DC will continue to facilitate such collaborations in the future.

P1.32

Grandmother's Cramp: Family History as Predictor for Onset and Course of Musician's Dystonia

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Abstract

Background and purpose: Musician's dystonia (MD) is a task specific movement disorder that leads to involuntary cramping of the affected limb and severely impairs the executions of highly trained movements at the instrument and may end a professional musician's career. The pathophysiology is not fully understood; however, several risk factors are known – among them workload, psychological factors and genetic predisposition. Interestingly, it has been shown that a positive family history not only of dystonia itself, but also of other movement disorders such as such as tremor and Parkinson's disease is a major risk factor for the onset of MD. As it is known in other Movement Disorders that a genetic predisposition may lead to earlier onset of symptoms and worse course of disease, our aim was to assess the influence of genetic predisposition on the onset and course of MD, hypothesizing that in MD as well, genetic predisposition might lead to an earlier onset of disease with worse outcome.

Methods: We present a follow up study of 364 patients with MD treated at a specialized outpatient clinic, in which we assessed the onset-age and the course of dystonia, the workload/practice time and family history. Based on the collected data, we formed two groups: those with a negative family history for neurological diseases (FH-), and those with a positive family history for movement disorders (FH+).

Statistics: Because of nonparametrically distributed data, we used the Wilcoxon test. To test for differences in distributions we applied the chi-square test. The significance level was set at $\alpha = 0.05$.

Results: Cumulative practice time until the onset of dystonia in the FH+ group was significantly lower (median difference: over 5000 hours). Also, the age of onset in the FH+ group was significantly earlier than in the FH- group (median difference: 3 years).

Furthermore, the course of disease in the FH+ group was significantly worse than in the FH- group with improvement/equality/deterioration of symptoms being 60% / 12% / 28% vs. 47% / 4% / 49% in the FH+ respectively.

Discussion: Our study showed that MD patients with positive family history for movement disorders need a smaller amount of workload to elicit MD, have an earlier onset of symptoms and more often report a deterioration of dystonia over time, confirming our hypotheses. This could have implications for the medical advice that should be given to patients dependent on their family history.

P1.33

Essential tremor and essential tremor plus are essentially similar on electrophysiological tremor analysis

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Abstract

Introduction: There is an on-going debate about the merits of classifying the heterogeneous group of essential tremor patients into essential tremor (ET) and essential tremor plus (ETP). It is not known whether this subclassification captures the phenotypic heterogeneity in ET or whether ETP represents a distinct etiological category from ET. We aimed to study whether tremor electrophysiological and spiral characteristics vary in patients classified clinically as ET or ETP.

Materials and Methods: Three movement disorder specialists reviewed standardized video recordings from a tremor database and classified patients into ET, ETP or dystonic tremor (DT). Tremor severity was assessed using the Fahn-Tolosa-Marin tremor rating scale (FTM-TRS). Tremor was recorded in 8 positions using combined tri-axial accelerometry-surface electromyography and the following variables derived after power spectral density transform- peak frequency (PF), total power (TP), peak power (PP), full width half maximum (FWHM), tremor stability index (TSI) and EMG-coherence between flexors and extensors. Participants drew free hand Archimedes spirals which were analysed to derive mean deviation (MD), tremor variability (TV), inter- and intra-loop widths. Electrophysiological and spiral characteristics were compared among ET, ETP and DT.

Results: We screened 80 and included 72 participants in the study. Mean (SD) was 47.7 (16.1) years, 59 (81.9%) were male and the mean disease duration was 9.5(6.7) years. Mean total FTM-TRS score was 31.1(14.1). Patients with ET were younger (p=0.014) and had less severe tremor (p=0.020) compared to the ETP and DT groups. Peak frequency was greater in ETP [7.3(0.3) Hz] compared to DT [6.1(0.4) Hz; p=0.024]. PP was greater in ETP and DT at posture 1 (ET vs ETP, p=0.009; ET vs DT, p=0.024) and posture 2 (ET vs ETP, p=0.041; ET vs DT, p=0.009). TP, FWHM, TSI, EMG coherence and spiral parameters were similar among the groups (Figure 1).

Discussion: Electrophysiological evaluation revealed a predominant postural tremor of frequency 6-7 Hz in both ET and ETP. ETP was associated with more severe tremor and trend towards longer disease duration. Notwithstanding the presence of additional clinical features, electrophysiological and spiral tremor characteristics were essentially similar between the groups ET and ETP.

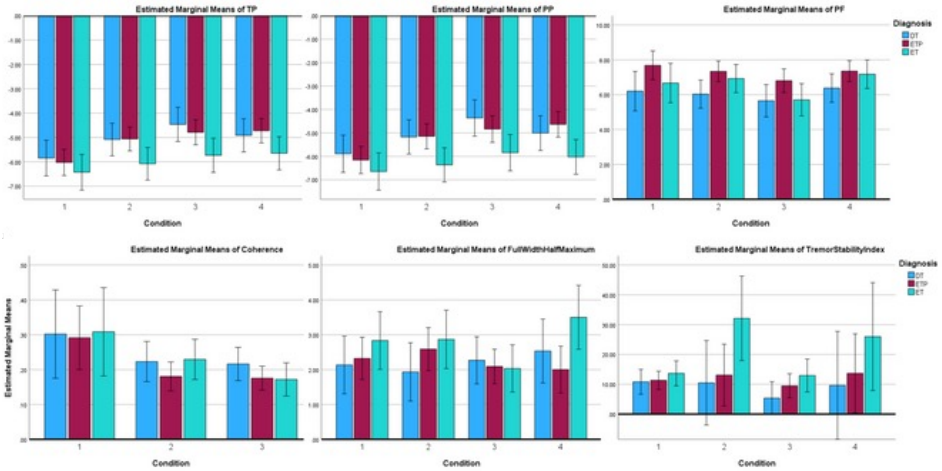

Figure 1. Estimated marginal means of TP, PP, PF, FWHM, TSI and EMG Coherence in ET, ETP and DT. Condition 1- Rest, 2- Posture 1, 3- Posture 2, 4- Load. Error bars represent 32SE.

P1.34

Dystonia in a PFBC cohort and description of 3 peculiar cases.

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Abstract

Introduction: Primary familial brain calcification (PFBC) is a rare neurodegenerative disorder of adulthood characterized by calcium deposition in basal ganglia. Parkinsonism is the main manifestation. Dystonia is reported in up to 20% of cases in large series, with limited characterization. Seven causative genes are known so far, with an autosomal dominant (SLC20A2, XPR1, PDGFB, PDGFRB) or recessive (MYORG, JAM2, CMPK2) inheritance. Mutations can be found in almost 50% of cases.

Materials and Methods: We examined a cohort of 65 PFBC patients followed at our institution, with special focus on dystonic manifestations.

Results: Dystonic features were observed in 15/65 patients (23%), mainly dystonic tremor or posturing of the upper limbs, in 3 cases involvement of face/neck; 10 had concomitant parkinsonism and pyramidal signs, 3 had cerebellar signs. Psychiatric or cognitive symptoms were reported in half of the patients. Mean age at onset was 47 years, 60% of the subjects were females. Genetic analysis was negative in 6 patients (40%), whereas pathogenic mutations were found in 7 subjects (46.6%; 3 SLC20A2, 1 PDGFB, 1 PDGFRB and 2 MYORG); 2 tests are still ongoing.

Dystonia was the most prominent feature in 3 patients.

The first is a 40-year-old female with a 2-year history of severe dystonia of the larynx, oromandibular district and blepharospasm (Meige syndrome), which hasn't been previously reported in correlation with PFBC; she also had brisk reflexes, mild upper limb tremor and anxiety; her CT scan showed pontine involvement. Genetic test is still ongoing.

The second patient is a 70-year-old woman presenting at age 54 with cervical and laryngeal dystonia with associated tremor of upper limbs, mild slowness and brisk reflexes; brain CT showed cerebellar involvement; genetic testing detected a pathogenic mutation in PDGFB gene (p.Arg100Cys).

The third patient is a 48-year-old female with paroxysmal dystonic spasms in the right hand triggered by physical exercise and emotional stress lasting up to one minute, occurring several times a day from age 42, with good response to carbamazepine. She carried a mutation in SLC20A2 gene (p.Leu127Argfs44*).

Discussion: dystonia was previously reported in 20% of PFBC symptomatic patients, often without details on anatomical distribution and disease course. We found dystonic manifestations in 23% of our cohort, being the prominent clinical feature in 4.6% of cases. Dystonia occurred in association with additional neurological and psychiatric manifestations in most cases and had a progressive course in all but one case, that presented paroxysmal attacks.

P1.35

Suitability of Automated Writing Measures for Clinical Trial Outcome in Writer's Cramp

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Abstract

Introduction: Writer's cramp (WC) dystonia is a rare disease that causes abnormal postures during the writing task. Successful research studies for WC and other forms of dystonia are contingent on identifying sensitive and specific measures that relate to the clinical syndrome and achieve a realistic sample size to power research studies for a rare disease. Although prior studies have used writing kinematics, their diagnostic performance remains unclear. This study aimed to evaluate the diagnostic performance of automated measures that distinguish subjects with WC from healthy volunteers.

Methods: A total of 21 subjects with WC and 22 healthy volunteers performed a sentence-copying assessment on a digital tablet using kinematic and hand recognition softwares. The sensitivity and specificity of automated measures were calculated using a logistic regression model. Power analysis was performed for two clinical research designs using these measures. The test and retest reliability of select automated measures was compared across repeat sentence-copying assessments. Lastly, a correlational analysis with subject- and clinician-rated outcomes was performed to understand the clinical meaning of automated measures.

Results: Of the 23 measures analyzed, the measures of word legibility and peak accelerations distinguished WC from healthy volunteers with high sensitivity and specificity. The measures of word legibility and peak accelerations also demonstrated smaller sample sizes suitable for rare disease studies. The kinematic measure of peak accelerations showed high reliability across repeat visits, while both word legibility and peak accelerations measures showed significant correlations with the subject- and clinician-rated outcomes.

Discussion: Novel automated measures that capture key aspects of the disease and are suitable for use in clinical research studies of WC dystonia were identified.

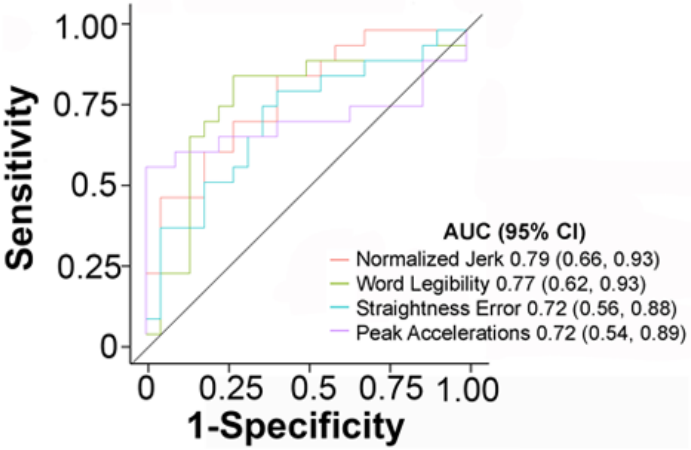

Figure 1: Four automated writing measures show high sensitivity and specificity to predict WC status. For each automated measure, a logistic regression test was run to model WC status and the diagnostic performance of each measure plotted (ROC curve). ROC curves above the diagonal gray line show high sensitivity and specificity to predict WC status. An aggregate measure of diagnostic performance (AUC) is also provided with 95% confidence intervals in the parenthesis.

P2.01

Reduced penetrance, variable clinical expressivity, and genetic overlap in monogenic forms of dystonia and parkinsonism

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Abstract

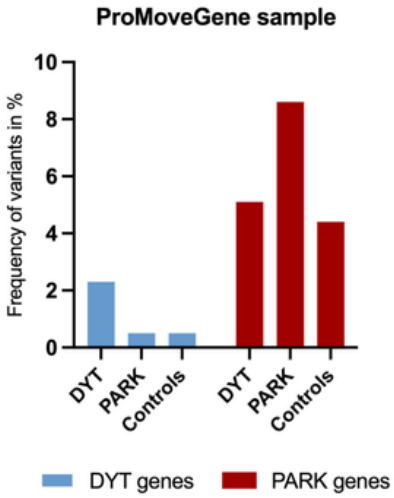
Introduction: Reduced penetrance, defined as the presence of pathogenic genetic variants without developing the corresponding phenotype, and variable clinical expressivity, referring to the variable degree of phenotypic expression of the same pathogenic variant in different individuals, are mechanisms known in several genetic disorders, including dominantly inherited forms of dystonia. Further, there can be clinical and genetic overlap across movement disorders, e.g., pathogenic variants in dystonia genes can be observed in individuals with parkinsonism (without dystonia) and vice versa. The underlying mechanisms of these phenomena are poorly understood.

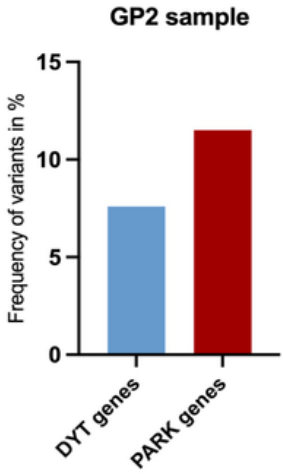
Materials and Methods: The ProMoveGene sample (https://protect-move.de/) with >12,000 participants, including individuals with Parkinson's disease (PD), dystonia, and healthy controls, was genotyped using the Global Screening Array (GSA, Illumina) containing a custom content covering ~1000 PD or dystonia related variants. Further, a cohort of 962 individuals with early-onset or familial parkinsonism was investigated using short-read genome sequencing as part of the GP2 project (https://gp2.org). All patients were screened for rare variants (minor allele frequency <0.005) in genes known to cause monogenic forms of dystonia and PD. Only (likely) pathogenic variants and variants of unknown significance (VUS) were taken into account. The genes of interest were TOR1A, THAP1, GNAL, ANO3, KMT2B, PRKRA, GCH1, and SGCE (DYT genes), and GBA1 (excluding coding GBA1 risk variants), LRRK2, SNCA, VPS35, PINK1, PRKN, and PARK7 (PARK genes).

Results: The ProMoveGene sample includes 2,596 individuals with PD/parkinsonism, 4,371 with dystonia, and 5,752 healthy controls. Variants in dystonia genes were most frequent in individuals with dystonia (2.3%), but also a small percentage of patients with PD and healthy controls carried variants in DYT genes (0.5% each). While variants in PD genes were most frequent in PD patients (8.6%), a considerable number of variants were also detected in dystonia patients (5.1%) and controls (4.4%), respectively (Figure 1A).

Of the 962 patients with early-onset and/or familial parkinsonism from the GP2 sample, 7.6% carried variants in dystonia genes and 11.5% in PD genes (Figure 1B); controls have not been analyzed yet.

Figure 1. Preliminary genetic results of both investigated samples





A. Detected variants in the ProMoveGene sample. This chart reflects the percentage of patients with dystonia (DYT) or parkinsonism (PARK), and healthy controls with detected variants in dystonia (DYT; blue bars) or parkinsonism (PARK, red bars) genes via hotspot screening through GSA genotyping.

B. Detected variants in the GP2 sample. This chart shows the percentage of individuals with detected variants in dystonia (DYT, blue) and parkinsonism (PARK, red) genes in the investigated GP2 sample, including patients with early-onset and/or familial PD, via whole-genome

Discussion and outlook: Variants in dystonia genes can be found not only in patients with dystonia but also in healthy controls and patients with PD/parkinsonism, suggesting that modifying factors play a role in developing the disease and its phenotypic expression.

As a next step, we aim to enlarge the sample size by analyzing the entire GP2 sample and comprehensive genotyping by genome sequencing vs. hot spot screening.

P2.02

Atypical nuclear envelope condensates linked to Dystonia are proteotoxic and reveal nucleoporin-directed chaperone activities

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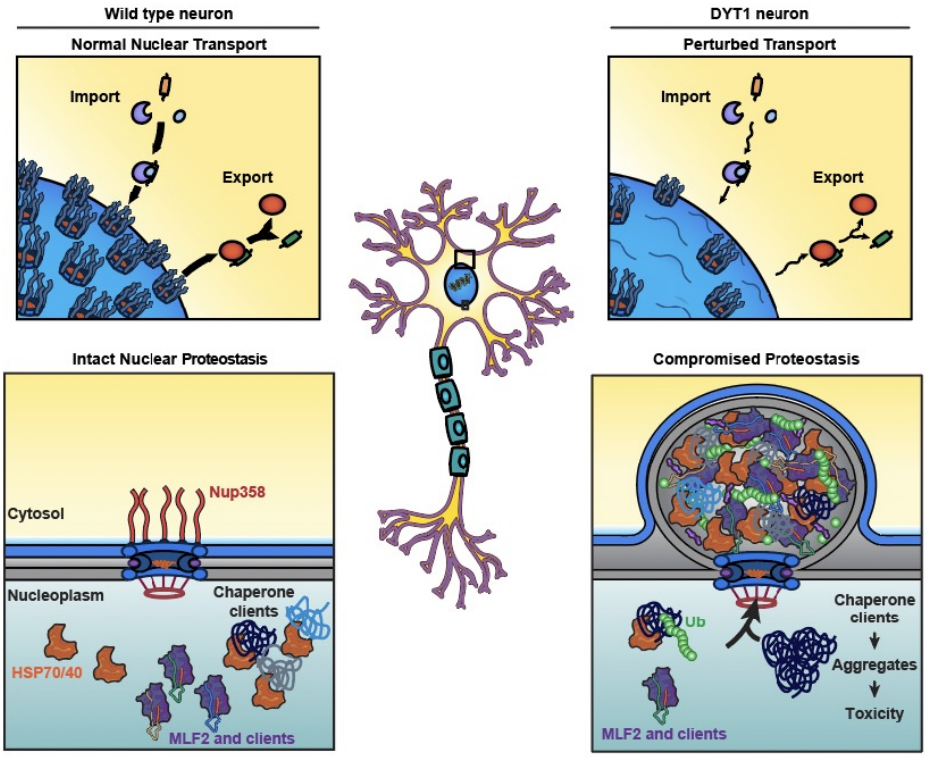
Abstract

DYT1 dystonia is a debilitating neurological movement disorder arising from mutation in the AAA+ ATPase TorsinA. The hallmark of Torsin dysfunction across disease models is nuclear envelope (NE) blebbing resulting from defects in nuclear pore complex biogenesis. However, whether blebs actively contribute to disease manifestation is unknown, as we lack molecular markers that can be harnessed for functional investigations and probing possible implications for disease etiology. We developed a series of novel proteomic tools and model substrates, allowing us for the first time to define the proteome of NE blebs. We further report that FG-nucleoporins (FG-Nups) in the bleb lumen form aberrant condensates and contribute to DYT1 dystonia by provoking two proteotoxic insults. First, short-lived ubiquitylated proteins that are normally rapidly degraded partition into the bleb lumen and become stabilized. Additionally, our proteome analysis reveals that blebs selectively sequester a specific HSP40/HSP70 chaperone network in dependence of the bleb component MLF2, a poorly understood yet highly abundant component of these NE lesions. Using in vitro reconstitution, we show that MLF2 suppresses the ectopic accumulation of FG-Nups and modulates the selective properties and size of condensates in vitro. Importantly, MLF2 also potently suppresses amyloid formation of asparagine-rich FG-NUPs, and regulates the subcellular localization of DNAJB6, a key player for neuronal protein homeostasis. These data lead us to propose a “two-hit” hypothesis for disease etiology of DYT1 dystonia. We posit that the combined cellular defects stemming from perturbed nuclear transport and a severe misbalance of neuronal protein homeostasis (proteostasis) are major contributing factors. Since NE blebs in animal models form transiently around the time of symptom onset, it is tempting to speculate that this proteostatic imbalance poses a transient threat for neurons that could be manipulated pharmacologically to reduce the risk of dystonia onset. Ongoing efforts in this direction exploiting MLF2 as biomarker for high-throughput screening will be discussed.


Wild type neuron
Normal Nuclear Transport
Import
Export
DYT1 neuron
Perturbed Transport
Import
Export
Intact Nuclear Proteostasis
Cytosol
Nup358
Nucleoplasm
Chaperone clients
HSP70/40
MLF2 and clients
Compromised Proteostasis
Ub
Chaperone clients
Aggregates
Toxicity
MLF2 and clients

P2.03

Transcriptomics in postmortem brains and neuronal models uncover targetable signatures for antisense oligonucleotide therapy in X-linked dystonia-parkinsonism

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Abstract

X-linked dystonia-parkinsonism (XDP) is an adult-onset, genetic neurodegenerative disorder indigenous to the Philippines with features of both dystonia and parkinsonism. On neuroimaging and neuropathology, there is a striking and progressive loss of neuronal populations in the striatum. Therapy is currently symptomatic, largely inadequate, and patients suffer from poor quality of life throughout their illness. Our assembly of the XDP genome and transcriptome in patient-derived neural stem cells (NSCs) revealed aberrant splicing (AS) and intron retention (IR) occurring proximal to a disease-specific SVA insertion within intron 32 of the *TAF1* gene, that was accompanied by a modest but significant (18%) reduction of *TAF1* gene expression. Excision of this XDP-specific SVA via CRISPR-engineering rescued the disrupted splicing and expression signatures in our cell models. To determine whether these transcriptomic hallmarks are consistent in disease-relevant tissue, we accessed a collection of postmortem brains from 21 XDP-affected individuals, and detected AS, IR, and reduction of *TAF1* expression across the multiple brain regions profiled (n=up to 15 regions), with the strongest signatures observed in structures associated with XDP and dystonia in general, such as in the striatum and cerebellum. Motivated by the convergence of these findings, we designed a platform for testing genetic therapy for this disease using NSCs and in partnership with Ionis Therapeutics. We screened 37 antisense oligonucleotides (ASO), each targeting a segment of the causative locus in *TAF1* intron 32. Functional genomic analyses via RNA-Sequencing of ~1500 ASO-treated libraries revealed that a subset of ASOs could repress AS, and ameliorate IR and the aberrant signatures in *TAF1*. Up to 43% of the transcriptome-wide XDP expression signatures observed in NSCs were rescued, including expression changes in genes that belong to neurodegenerative processes and neuronal signaling pathways. This study highlights the potential of exploiting systematic genomics discovery anchored in transcriptomics in neuronal cell models and postmortem brain tissue in the design of precision therapy for dystonic diseases.

P2.04

Specific cerebellar spike train signatures predict the behavioral presentation of cerebellar pathophysiology

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Abstract

Introduction: Dystonia can arise from dysfunctional cerebellar circuits. Yet, cerebellar dysfunction is also known to produce other movement disorders that can be comorbid with dystonia, namely ataxia and tremor. How altering the same cerebellar circuit can cause distinct movement defects remains unknown. We set out to examine whether signals generated in the cerebellum can be used to distinguish unique predictive signatures that induce abnormal movements.

Material and Methods: We performed in vivo awake head-fixed recordings of cerebellar output neurons, known as the nuclei neurons, in healthy control mice and mouse models of dystonia, ataxia, and tremor. We comprehensively defined the spike train activity of each neuron using over twenty measurements. We trained an unsupervised classifier model on the spike train measurements to distinguish neural signatures between dystonia, ataxia, tremor, and control mice. We tested whether different mouse models, but with similar phenotypes, displayed similar neural activity. We then used optogenetics to mimic the neural activity signatures associated with each disease phenotype.

Results: The classifier network found differences in spiking activity between dystonic, ataxic, and tremoring mice. More than half the neurons in mice with abnormal phenotypes had a spiking signature corresponding to the phenotypic presentation (dystonia, ataxia, tremor), irrespective of the mouse model used. Optogenetic stimulation of Purkinje cell terminals in the interposed cerebellar nucleus mimicked distinct neural activity signatures suggested by the classifier: a constant pattern (ataxia), a regularly oscillating pattern (tremor), or an irregularly bursting pattern (dystonia). Optogenetic stimulation caused abnormal motor phenotypes in freely moving mice.

Discussion and Conclusions: We show that alterations in cerebellar nuclei spiking activity predict the presentation of cerebellar movement disorders. We find that cerebellar models have distinct spiking signatures that are shared across mouse models with different etiologies and are sufficient to induce motor impairments in otherwise healthy mice.

P2.05

Dystonia Treatment With Injections Supplemented by TMS: the D-TWIST Study

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Abstract

Introduction: Patients commonly report that the benefit from botulinum toxin (BoNT) injections does not last the entire 12 weeks. Repetitive transcranial magnetic stimulation (rTMS) may prolong the benefits of BoNT for patients with cervical dystonia. Low-frequency rTMS targeted at the dorsal premotor cortex (dPMC) has been shown to improve arm and hand dystonia, but has not yet been studied in cervical dystonia.

Materials and Methods: This was a double-blind, sham-controlled, crossover study for adult patients with cervical dystonia who report BoNT benefit lasting ≤ 9 weeks. At 9 weeks following BoNT, patients were randomized to active or sham neurostimulation: 1-Hz rTMS over the dPMC for 30 minutes (1800 pulses) at 90% resting motor threshold. Patients underwent 4 sessions per day for 4 consecutive days. Primary outcome was blinded video ratings of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Secondary outcomes included mood symptoms measured by Beck Depression Inventory (BDI), cognitive symptoms measured by the trail making test (TMT), and safety and tolerability measured via patient-reported outcomes. Two-way ANOVA was used for statistical analysis. Outcome measures were collected at three time points: baseline, immediately after rTMS, and 2 weeks after rTMS.

Results: Demographically, the patient population (N=5) was as follows: average age was 68.7 years (range 52-79) and 4/5 were female. Average years since onset of cervical dystonia was 9.2 years (range 5-20 years). In addition, 1/5 had blepharospasm, 4/5 had isolated cervical dystonia, and 2/5 had sensory tricks. There was no statistically significant difference in TWSTRS scores in active or sham groups (p=0.5861), or following TMS (p=0.258). There was a significant difference in BDI scores between groups (p =0.0495) although Bonferroni correction was unrevealing. There were no statistical differences between the average TMT times for Figure A (p=0.2299) or Figure B (p=0.9222). All patients tolerated the stimulation sessions well, with 3/5 reporting transient headache/neck discomfort, which is typical for standard TMS sessions. In terms of blinding, 3/5 reported “no idea” which coil was the sham, and 1/5 correctly identified the sham coil suggesting effective blinding.

Discussion: This novel, accelerated rTMS protocol is safe and well-tolerated for cervical dystonia. There were trends toward improvement following TMS, although future larger studies are needed to confirm these results. Synergism between rTMS and BoNT can potentially be used for dystonia patients experiencing suboptimal benefits with BoNT, and further work is needed to explore the non-motor and physiological implications of this intervention.

P2.06

Benefit of multiple incobotulinumtoxinA injections for pain reduction in adults with cervical dystonia: an analysis of pooled data

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Abstract

Introduction: The long-term effects of repeated incobotulinumtoxinA (incoBoNT-A) injections on cervical dystonia (CD)-related pain were assessed in a pooled analysis of studies in adults with CD.

Methods: Pooled data from four phase 3 and 4 studies in adults with CD-related pain at baseline (N=678) were analysed over five incoBoNT-A injection cycles. Pain was assessed at each injection visit (IV) and control visit (CV) 4 weeks post-injection using the TWSTRS-pain severity subscale or a pain VAS. Both pain scales were analysed using a score range 0-10 and pain was categorised as mild (>0-<3.5), moderate (3.5-<6.5) or severe (6.5-10). Response was defined as ≥30% or ≥50% reduction in baseline pain score, reflecting at least moderate or substantial clinically important improvements, respectively. Complete pain relief (pain score=0) was evaluated at each IV and CV. Pain scores in the subgroup of patients not taking concomitant pain medication (N=379) were also examined.

Results: Baseline pain was moderate or severe for 64% of patients. Pain reduction was observed over multiple treatment cycles; response rates and % with complete pain relief tended to increase over the 5 injection cycles (Table). A cumulative effect was demonstrated in the proportion of patients whose pain had not returned to baseline levels by the next IV. Pain responses were generally slightly higher in the subgroup not taking concomitant pain medication (Table).

	Patients (%) with pain response at Control Visit (CV) 4 weeks after incoBoNT-A injection				
	CV1	CV2	CV3	CV4	CV5
All patients	N=669	N=263	N=235	N=215	N=179
≥30% pain reduction from baseline	48.1%	49.8%	54.0%	57.2%	53.1%
≥50% pain reduction from baseline	34.4%	34.2%	40.4%	39.1%	40.2%
Complete pain relief	10.3%	11.8%	13.2%	12.6%	16.8%
No pain medication	N=379	N=116	N=107	N=101	N=86
≥30% pain reduction from baseline	54.4%	49.1%	57.9%	57.4%	55.8%
≥50% pain reduction from baseline	41.4%	32.8%	46.7%	37.6%	45.4%
Complete pain relief	13.2%	14.7%	16.8%	14.9%	22.1%

Table. Pain severity results at each control visit for all patients with a pain assessment at that visit and in the subgroup not taking concomitant pain medication

Discussions: DPatients with CD-related pain experienced clinically important and sustained reductions in pain during repeated incoBoNT-A injections with or without concomitant pain medication, confirming the benefits of long-term incoBoNT-A treatment.

P2.07

Dystonia- history of a movement disorder

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Abstract

Introduction: 1911 is considered to be a crucial year in the history of dystonia due to a number of memorable publications. The German psychiatrist Theodor Ziehen coined in 1911 the term “tonic torsion neurosis” in relation to dystonia indicating its psychogenic origin. In 1911 two Polish neurologists Edward Flatau and Władysław Sterling spoke of it as a “progressive torsion spasm” drawing attention to its genetic nature and stressing that it was not a muscular disorder. Finally, in the same year the German neurologist Hermann Oppenheim introduced the term “dystonia musculorum deformans” and postulated its organic aetiology. However, dystonia seems to have been known to the artists and physicians a long time before its first description in 1911.

Methods: Paintings and sculptures of famous artists such as Sandro Botticelli, Amedeo Modigliani, Constantin Brâncusi, Egon Schiele, Josep Ribera y Cucó, Stanisław Wyspia ski, Pieter Bruegel the Elder, Pieter Brueghel the Younger, Matthias Grünewald, Franz Xaver Messerschmidt, Peter Anton von Verschaffelt, Francisco de Zurbarán were analysed for medical signs that could indicate the presence of dystonia in their models. In addition, excerpts from the 1983 film “Spring Symphony” by Peter Schamoni, handwriting samples and biographical data of Robert Schumann, Albert Schweitzer and Demosthenes with regard to dystonia were studied.

Results: It seems plausible that Robert Schumann, Albert Schweitzer and Demosthenes suffered from different types of dystonia. Dystonic movement disorders due to ergotism can be suspected in works of Matthias Grünewald. Also works of the remaining artists are highly suggestive of different dystonic conditions.

Discussion: Dystonia had been known to the artists and physicians a long time before it was first described in 1911.

P2.08

A multimodal approach to understanding dystonia: integration of structural, functional and behavioral measures.

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Abstract

Introduction: Dystonia is one of the most common movement disorders, with a prevalence of 17.8 per 100,000 in Ireland alone. Despite this, the pathophysiology of the disease is poorly understood, leading to limited objective measures for diagnosis. Unlike other movement disorders, dystonia appears to be heterogenous in nature, likely affecting the brain at a network level. The complex nature of dystonia demands a more global approach in testing methodology.

Methods: The current understanding of the heritability of dystonia shows a pattern of incomplete penetrance. While certain family members may not exhibit the motor phenotype, they may still be affected in other neuroprocessing pathways. This has been shown through measures of increased Temporal Discrimination Thresholds (TDT) in patients with dystonia and in some non-motor affected relatives. This demonstrates an unexplored clinical population in patient relatives. Using a multimodal model encompassing both patients and relatives we aim to tackle both issues.

Emerging work has demonstrated significant differences in microstructural areas between healthy controls and patients with dystonia. These areas are quite varied and provide targeted regions of interest for seed-based connectivity analysis of resting state and functional MRI data. Network level differences may correlate with behavioral level abnormalities in patients and relatives.

Data was collected across 64 subjects including cervical dystonia patients (16) from the St. Vincent's University Hospital in Dublin, first-degree relatives (16 abnormal, 16 normal), as well as healthy age and gender-matched controls (16). Data includes behavioural measures of TDT, structural MRI, resting state fMRI and temporal discrimination-focused fMRI.

Results: Using a multivariate approach, we incorporated information across structural, functional, and behavioural differences between patients, relatives, and healthy individuals. Replicating previous results, significant differences in TDT values were demonstrated in an initial subset ($p<0.05$). The Default Mode Network, commonly used in functional analysis and previously correlated with abnormalities in dystonia was used in seed-based connectivity analysis [Figure 1]. This showed significant between group differences in mean connectivity values ($p<0.05$). Connectivity in this region was not significantly correlated with TDT values (r 0.08, $p>0.05$). We plan to reveal further network-level variability between

patients, relatives, and healthy controls which may account for behavioural differences seen at each group level.

Discussions: Advances in neuroimaging modalities have allowed for such approaches. With MRI and fMRI, we can now create disease models at a structural, functional, and resting state neural network level. By integrating each in a multimodal approach, we can gain a more concrete understanding of dystonia.

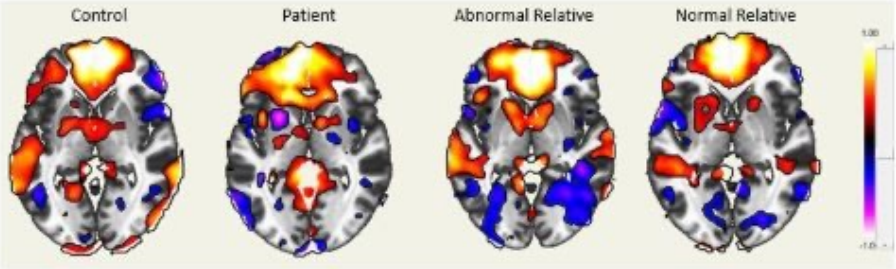

Figure 1. *Slice display of the Seed-based Connectivity Map using the Default Mode Network. Image based on correlational r value.*

P2.09

Globus Pallidus internus (GPi) Power Spectral Densities Progressively Change With Increasing Dystonia or Parkinsonism Severity

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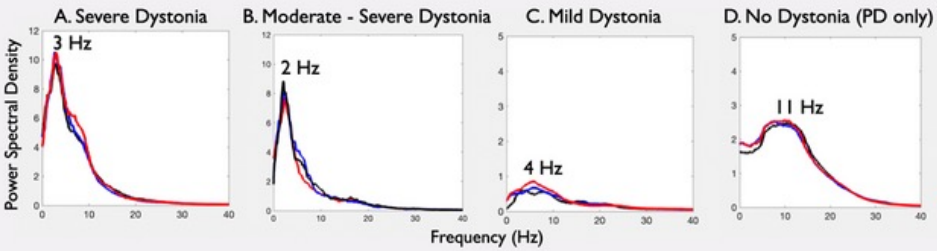
Abstract

Introduction: Abnormal globus pallidus internus (GPi) neural activity likely contributes to both Parkinsonism and dystonia symptoms, but investigations in humans have been limited to recordings collected from patients shortly after deep brain stimulation (DBS) electrode surgical implantation. Findings suggest that GPi local field potential (LFP) activity differs between dystonia and Parkinsonian symptoms. However, the clinical significance is unknown because post-surgical changes (e.g. inflammation, microlesion effect) could affect neural firing and dystonia symptoms typically take weeks to respond to DBS therapy. The new Percept PC neurostimulator allows us to evaluate how GPi LFP activity correlates with Parkinsonism and dystonia symptoms over longer time periods.

Materials and Methods: Dystonia symptom severity was quantified using the Unified Dystonia Rating Scale (UDRS) and neurologic exam videos. We recorded 1 minute samples of LFP activity while subjects performed 3 trials each of finger taps with their right hand, left hand, or rest. Recordings were collected at multiple time points (3-5 recording sessions for each subject) ranging from 3 weeks to 3 months post DBS surgery. Peak power spectral densities were determined for each subject and task, and the area under the curve was calculated for different frequency bins. Ratios compared delta, theta, alpha, and beta activity with the severity of dystonia or Parkinsonism symptoms.

Results: Recordings were collected from 4 subjects (3 M, 1F) with different combinations of dystonia and Parkinsonism. Individuals with moderate to severe dystonia symptoms all had peaks in the delta-theta range (2-4 Hz). Both delta (3 Hz) and alpha (9 Hz) peaks were identified when moderate dystonia and Parkinsonism were both present. Conversely, a patient with Parkinsonism and no dystonia had relatively low delta-theta power and a prominent alpha-beta peak. Peak frequencies for all subjects were consistent regardless of the movement task. Individual ratios of delta to theta power tended to increase with worsening dystonia severity, while alpha and beta ratios decreased.

Discussion: GPi LFP frequencies may be a biomarker of dystonia symptom severity. Preliminary analyses suggest GPi LFP activity in the delta-theta range correlates with dystonia symptom severity, while higher frequency alpha peaks correlate with Parkinsonism. Importantly, the ability to record LFP activity over weeks to months now allows us to study these signals over a time frame that is more clinically relevant. Future analyses will evaluate how signals change over time in response to DBS therapy.



% Area Under Curve	A	B	C	D
Delta- theta (1-7 Hz)	0.66	0.69	0.39	0.32
Alpha-beta (8-29 Hz)	0.33	0.29	0.55	0.65
Gamma (≥ 30 Hz)	0.01	0.02	0.07	0.02

P2.10

Clinical Characterization and Treatment Outcomes of VPS16 Dystonia

Mariel Pullman[1], Deborah Raymond[1], Walter Molofsky[1], Naomi Lubarr[1], Katherine Leaver[1], Roberto Ortega[1], Maya Rawal[1], Steffany Bennett[2], Evan Bushnik[2], Azita Khorsandi[3], Fedor Panov[4], Jean Paul Vonsattel[5], Laurie Ozelius[6], Rachel Saunders-Pullman[1], Susan Bressman[1]

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Abstract

Objective: To expand the clinical, radiologic and pathologic understanding of VPS16 related dystonia.

Background: Variants in VPS16 have been associated with isolated dystonia in 35 cases from Chinese and European cohorts, including report of brainstem signal change on MRI.

Design/Methods: We describe clinical features in 10 additional individuals with isolated dystonia and VPS16 variants, pathology in one, and perform pooled analysis with published cases.

Results: 80% were men, mean age onset was 14.1 years (range 5-30), and mean age at exam was 35.89 years (range 11-73). Four began with arm, 3 with leg, and 3 with neck dystonia. Only one remained focal (arm); others became generalized (7), multifocal (1) or segmental (1). Brachial involvement was present in 90%, with 80% crural, 70% cranial/bulbar, and 50% cervical involvement. Four cases were related, and five others had family history. Neuropathologic evaluation in one case (post bilateral GPi DBS) demonstrated asymmetric severe gliosis and marked neuronal loss of the left subthalamic nucleus with optically empty vacuoles and much less right-sided involvement.

Four individuals underwent bilateral GPi DBS (1 in adolescence, 3 in adulthood); two with significant improvement in all symptoms except speech, which was maintained for 8+ years; one with surgery at age 64 had approximately 50% response in limb and truncal dystonia but persistent dysarthria; a fourth with surgery in adulthood did not report significant benefit. A fifth had bilateral thalamotomy, and speech deficits were reported post-surgery.

Of the 10 participants, seven were known to have levodopa trials, two with significant early benefit, however this was not fully sustained, and three without improvement. In addition the following medications were utilized without dramatic improvement: trihexyphenidyl (7 participants), baclofen (4), benzodiazepines (5), carbamazepine (2), benztropine, haloperidol, thioridazine, reserpine, tetrabenazine (1 each).

Conclusions: Expansion of known cases of VPS16 dystonia further support that it is a childhood- or adolescent-onset disorder, typically with limb or cervical onset that often spreads to the arm and leg. While deep brain stimulation and oral medications may improve symptoms, additional therapies are needed as these lead to incomplete response. Additional histopathologic and metabolomic evaluation is underway; additional cases and pathologic samples will ultimately help elucidate the contribution of lysosomal and endolysosomal pathophysiology to VPS16 dystonia.

P2.11

Validation of a Clinical Rating Scale for Embouchure Dystonia

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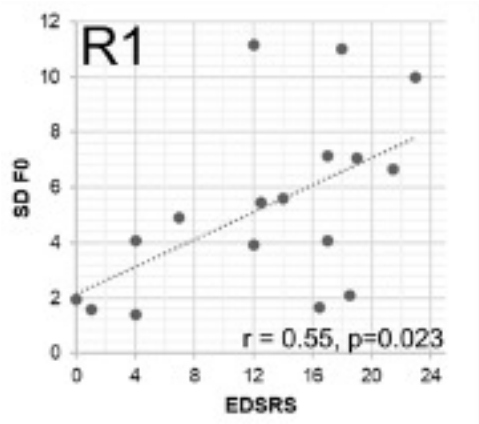
Abstract

Introduction: Embouchure dystonia (ED) is a task-specific movement disorder that leads to loss of fine-motor control of the embouchure in wind instrumentalists, thus ending musicians' careers. While in musician's hand dystonia, identification of involved muscles is generally possible by observation of the dystonic task, this is more challenging in ED due to the variety of muscles that may be involved, including embouchure, laryngeal muscles or the tongue. This poses a major disadvantage for the clinical and scientific assessment and in contrast to musicians' hand dystonia, no validated clinical rating scale for ED exists. We therefore aimed at validating an ED severity rating-scale (EDSRS) allowing for a standardized estimation of symptom severity.

Methods: The EDSRS is composed of six items consisting of three standardized musical tasks (sustained notes, scales, fourths) played at three different pitch-registers typical for the respective instrument and assessed from a right and a left lateral view to account for potential symptom asymmetries (i.e. three tasks two sides=six items). For validation we audio-visually recorded the six items in 17 musicians with ED. The anonymized and randomized recordings were assessed by two experts in ED on a 5-point Likert scale (0-4) with regard to playing ability and quality, resulting in an EDSRS range between 0-24 points. We assessed internal consistency, inter- and intra-rater reliability by presenting both raters the videos again after >30 months, reliability, and construct validity with the fluctuation of the fundamental frequency of the acoustic signal as an objective measure (F0) (obtained in an audio-analysis of the sustained notes).

Results: The EDSRS showed high internal consistency (Cronbach's α=0.975−0.983, corrected item-total correlations r=0.90-0.96), inter-rater reliability (intraclass correlation coefficient [ICC] for agreement/consistency=0.90/0.96), intra-rater reliability over time (ICC per rater=0.93/0.87), good precision (standard error of measurement=2.19/2.65), and correlated significantly with F0 variability (r=0.55-0.60, p=0.011-0.023) (Figure 1).

Discussions: We found the EDSRS to be a valid and reliable clinical assessment tool of ED severity when applied by expert raters. It showed a high internal consistency as well as inter-rater and intra-rater reproducibility, fulfilling three of four criteria for scores used to assess MD as proposed by Spector and Brandfonbrener: it is 1) reliable and valid, 2) specifically designed for MD since it assesses symptom severity at the instrument with dystonia-inducing tasks dystonia, and 3) practical in clinical setting. We consider it to be suited in everyday clinical routine and in clinical studies at clinics specialized in musicians' medicine.


R1
SD F0
EDSRS
r = 0.55, p=0.023
0
2
4
6
8
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12
0
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16
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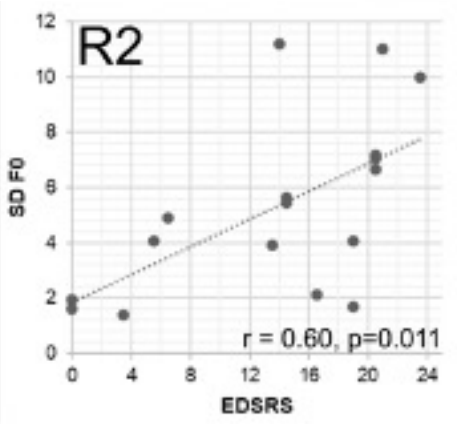
24


R2
SD F0
EDSRS
r = 0.60, p=0.011
0
2
4
6
8
10
12
0
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16
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24

P2.12

Proprioceptive stimuli trigger abnormal micro-scale neuronal connectivity in children with dystonia

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Abstract

Introduction: Dystonia is a network disorder resulting from dysfunction of, or abnormal connectivity between, sites within the cortico-basal ganglia-cerebellar network. Despite the dynamic nature of the disorder, stimulus-related changes in neuronal connectivity have not previously been explored. This study investigates modulation of functional neuronal connectivity by a proprioceptive stimulus in young people with dystonia.

Materials and Methods: Sixteen young people with dystonia and eight controls participated (age 6-20years, mean 12.5). The study received ethical approval and informed consent was obtained from each participant or, if <16 years, the parent/guardian. A robotic wrist interface delivered passive wrist extension movements of the right upper limb, producing a brief controlled stretch of the wrist flexors (10 degrees from neutral position, rise-time 240ms). Scalp EEG was recorded with a BrainVision amplifier using the 10-20 international system, with impedances below 10kOhm. EEG was amplified, filtered (DC-500Hz) and sampled at 2500Hz. Wrist position was monitored and movement onset was synchronised with EEG recordings. Data were segmented into 4.5 second epochs (1 second pre- and 3.5 seconds post-stimulus). Manual artefact rejection was performed to remove epochs with inadequate wrist movement profile and those contaminated by excessive movement or eye blink artefacts. Up to 160 epochs were averaged to produce a Stretch Evoked Potential (Stretch EP) in each individual.

Event-related network dynamics were estimated using the imaginary component of Wavelet Transform Coherency (WTC), excluding volume conduction. Bootstrapping was applied to test for significance against random coupling between brain areas. Global microscale connectivity (GMC) was calculated to estimate the overall engagement of areas into short-lived networks related to the Stretch EP. Global connectedness (GC) was calculated to estimate the spatial extent of the StretchEP networks.

Results: Clear Stretch EPs were evoked over contralateral sensorimotor cortex, with similar amplitudes between groups. Individual dynamic connectivity maps revealed a striking difference between dystonia and controls, with particularly strong event-related connectivity in the theta (4-8Hz) band in dystonia, across multiple brain regions. At group level, theta band connectivity (GMC) was significantly higher in dystonia than controls ($p=0.045$). GC was also stronger in dystonia than controls (non-significant trend).

Discussion/Conclusion: Young people with dystonia show an exaggerated dynamic network response to proprioceptive stimuli, displaying excessive, widespread theta-band synchronisation and over-recruitment across the sensorimotor network.

P2.13

In vivo assessment of striatal compartments in patients with idiopathic upper limb dystonia

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Abstract

Introduction: The striatum is an essential hub in the motor system associated with dystonia and other movement disorders. The function of the striosomes and matrix in motor control is not clear. Anatomopathological findings of dopa-responsive dystonia (DRD) in the early dystonic stage of X-linked dystonia-parkinsonism, as well as in a DRD transgenic mouse model, indicate that striosomes are affected in dystonia. A recently developed method using diffusion tensor imaging (DTI) enables us to distinguish compartments of the striatum, namely matrixes-like and striosomes-like voxels, in vivo. Evaluating the striatum in terms of matrixes and striosomes may allow the understanding of the neurobiology of dystonia and ultimately lead to more targeted treatments. This study aims to assess the volume of striatal matrix and striosome compartments in patients with idiopathic upper limb dystonia using DTI.

Material and Methods: We analyzed 3T MRI images from 26 patients with idiopathic upper limb dystonia aged 43.88 3 11.32 years (SD; range 19–60) with a mean disease duration of 12.55 3 10.25 years (SD; range 1–25) and healthy controls aged 39.42 3 11.42 years (SD; range 19–58).The striatum was parcellated by targeting cortical regions that favored striosomes (pregenual anterior cingulate, posterior orbitofrontal, anterior insular cortex, and basolateral amygdala) and matrix-favoring areas (gyrus rectus, supplementary motor area, and primary sensory and motor cortex). The bilateral striatum was assessed for changes in volume using fractional anisotropy.

Results: Patients with dystonia showed a trend of decreased volume of left Striosome-like voxels ($p = 0.063$) with a moderate effect size (cohen's $d = 0.510$) as shown in Figure 1A. The disease duration showed a weak negative correlation with left Matrix-like voxels volume but was not significant (Pearson $r = -0.34$, $p = 0.076$, Figure 1B). No difference was observed in right matrix and striosome compartments

Discussion: By parcellating the striatum into striosome and matrix-like voxels, we showed that patients with idiopathic dystonia have a trend of diminished volume in striosome-like voxels, in agreement with anatomopathological findings of some genetic types of dystonia. Even in non-degenerative dystonias, volume differences may reflect an imbalance between

striosome and matrix signaling, ultimately favoring the direct pathway. Our findings might be limited by the sample size, and studies with larger samples and different types of dystonia may improve our knowledge on this subject.

Acknowledgments: funding FAPESP and CNPq

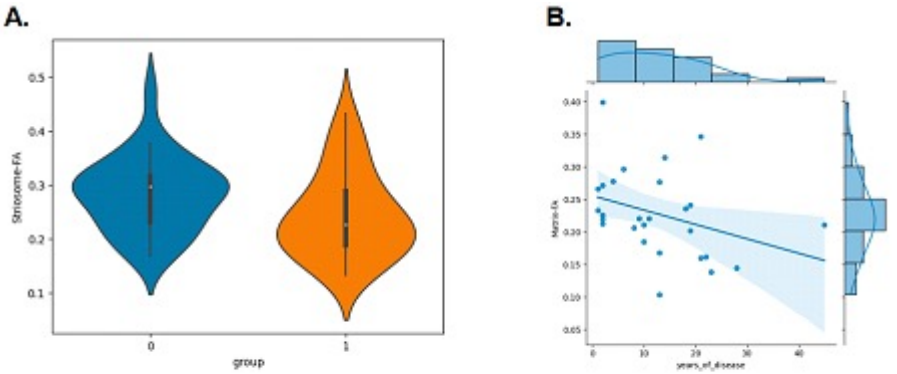

Figure 1: **A.** Striosome-like voxels volume between controls (0) and patients (1), (p = 0.063). **B.** Relationship between disease duration and Matrix-like voxels volume shows a trend for a negative correlation but was not statistically significant (r = -0.34, p = 0.076).

P2.14

Preliminary functional changes in superior temporal gyrus in task-specific focal dystonia based on individualized parcellations

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Abstract

Task-specific focal dystonia (TSFD) is characterized by excessive muscle contractions in a body part during the performance of certain complex and highly trained tasks, such as speaking or writing. While there is emerging evidence for altered cortical network functioning underlying such task specificity, the pathophysiology of TSFD remains unclear. In this ongoing study, we investigate cortical network differences between subjects with TSFD and healthy controls (HC). Notably, we use individualized brain parcellations which adjust network boundaries to minimize within-network heterogeneity, thus offering greater accuracy than population-level atlases alone and enabling comparisons in both network topography and connectivity.

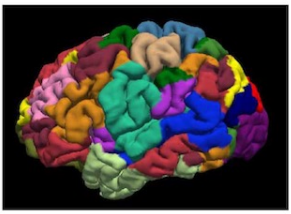
Here we report preliminary analysis on resting-state fMRI from subjects with TSFD (*N*=18 with laryngeal dystonia, LD; *N*=6 with focal hand dystonia, FHD) and HC (*N*=20). Based on an iterative multi-scale individualized functional parcellation algorithm, individual brains were parcellated into native space with a) 18 networks for first-level topographical comparison and b) 92 networks for detailed analysis (Figure a-b. FHD example). Jaccard coefficients were computed to quantify inter-subject network spatial similarities using the *fsaverage6* surface. Functional connectivity was computed as Pearson's *r* correlations between mean BOLD signals of each network.

18-network parcellations revealed atypical inclusion of middle superior temporal gyrus (STG) in sensorimotor network (Figure a, in mint-green) in subjects with TSFD, but not HC. This region of interest in STG was consistent with network 35 in 92-network parcellations (Figure b), to which we restricted our preliminary analysis. Network 35 showed significantly higher spatial similarity in both hemispheres in LD than in HC (Figure c. Jaccard coefficient comparison). The inclusion of STG (network 35) in the sensorimotor network was potentially driven by strong functional connectivity with network 11 (corresponding with sensorimotor representation of lip/tongue) in LD and network 8 (corresponding to hand region) in both LD and FHD.

We demonstrate that individualized parcellation is a valuable tool in understanding cortical changes in dystonia. Our preliminary results suggest the involvement of STG in the pathophysiology of TSFD during rest without symptom engagement, similar to task-related changes in STG that have been previously reported. Increased connectivity between the middle STG and traditional sensorimotor regions may reflect increased demand for sensory

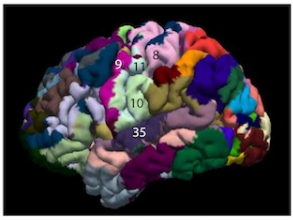
processing. Future work will include multimodal analysis with behavioral, task-based fMRI, and TMS data to explore the common and distinct changes in cortical dynamics of TSFD.

a)



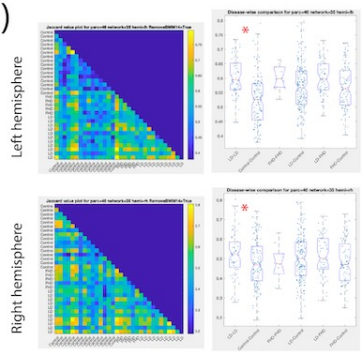
18-network parcellation

b)



92-network parcellation

c)



Network 35(Mid STG)

P2.15

Injections of incobotulinumtoxinA at intervals less than 10 weeks are effective and safe for cervical dystonia patients with inadequate benefit from standard injection intervals

Cynthia Comella[1], Robert A. Hauser[2], Stuart Isaacson[3], Daniel Truong[4], Odinachi Oguh[5], Jennifer Hui[6], Eric S. Molho[7], Matthew Brodsky[8], Erin Furr-Stimming[9], Georg Comes[10], Michael Hast[11], David Charles[12]

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Abstract

In clinical practice, some cervical dystonia (CD) patients receiving long-term botulinum toxin (BoNT) therapy report early waning of treatment benefit (even after favorable peak response) before a typical 3-month reinjection interval. This study addresses the safety and efficacy of incobotulinumtoxinA injection intervals <10 weeks to meet the needs of such patients. We compare efficacy and safety of two injection schedules of incobotulinumtoxinA for treating CD.

CD Flex (NCT01486264) was a phase IV, open-label, randomized, noninferiority study comparing 2 incobotulinumtoxinA injection schedules (short-flex: 832 weeks; long-flex: 1432 weeks) in CD subjects. BoNT-responsive subjects (≥2 prior successful injections) reporting acceptable clinical benefit lasting <10 weeks were recruited. Efficacy and safety were evaluated after 8 injection cycles. The primary endpoint was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale (blinded rater) 4 weeks after injection 8. Secondary endpoints included TWSTRS total and other subscale scores. Immunogenicity was assessed in a subset of patients at baseline/post-injection 8. Safety was monitored throughout the study.

282 CD subjects were randomized (short-flex, N=142; long-flex, N=140), and 207 completed the study. Mean dosing was similar in the short-flex (272U) and long-flex (268U); mean intervals were 54 days (short-flex) and 86 days (long-flex). Significant improvements in TWSTRS-severity from study baseline to 4 weeks after cycle 8 were observed in both the short-flex (4.1 pts; P<0.0001) and long-flex (2.4 pts; P=0.002), and short-flex was noninferior to long-flex (LS mean difference=1.4 pts; P=0.0693). Responder rates (≥20% improvement in TWSTRS-severity) after injection 8 did not differ significantly between groups.

Adverse events (AEs) were comparable between groups. There was no secondary loss of treatment effect due to neutralizing antibodies after 8 cycles among those tested.

Injection cycles <10 weeks for incobotulinumtoxinA are effective (and noninferior to longer intervals) for treating CD patients with early waning of clinical benefit. Shorter intervals did not increase AEs or lead to loss of treatment effect due to neutralizing antibodies.

Funding: This research was supported by Merz Therapeutics GmbH.

P2.16

Analysis of functional connectivity using machine learning and deep learning in EEG data from patients with focal dystonia.

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[1]Universidade de Sao Paulo, Sao Carlos do Pinhal, Brazil. [2]Aschaffenburg University of Applied Sciences, Aschaffenburg, Germany. [3]Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil. [4]Universidade Federal de Sao Paulo, Sao Paulo, SP, Brazil. [5]Universidade Federal do ABC, Santo Andre, SP, Brazil. [6]Hospital do Servidor Publico Estadual de Sao Paulo, Sao Paulo, SP, Brazil

Abstract

Introduction: Recent evidence suggests a brain network disorder as the main explanation for the sensorimotor program dysregulation in dystonia. Current diagnostic approaches rely mainly on clinical features and some cases may pose diagnostic challenges with a lack of accuracy. Machine learning techniques can aid in interpreting EEG data by utilizing deep learning networks, particularly convolutional neural networks (CNN) in order to identify a dystonia signature.

Materials and Methods: With multivariate EEG acquired from patients with idiopathic right upper limb focal dystonia (n =20) and healthy controls (n=21) during resting-state, writing, and finger-tapping tasks, this study proposes a machine learning method for distinguishing both groups. As a data augmentation technique, time series are split into windows of 10 seconds, which are correlated to construct a connectivity matrix through eight distinct pairwise statistical metrics to feed our machine-learning approach to determining the optimum metric for distinguishing brain connectivity patterns between groups. In our previous work, we showed that the construction of the connectivity matrix, compared to the old technique using raw EEG data, is more accurate, emphasizing the importance of network topology in characterizing brain data. Further, we used the Shapley (SHAP) value method to interpret the results (Figure 1).

Results: All the classifications resulted in excellent performances with AUC and an accuracy of 99%. The best metric was transfer of entropy. The primary connections related to dystonia were, in order of importance: C4-CP5, F3-FC5, C4-TP9. Regarding CNN, the best EEG task was resting, followed by finger-tapping.

Discussion: Overall, our methodology is capable of capturing the brain alterations caused by dystonia with a performance superior to that found in the literature, despite the small sample size. We discovered the best pairwise statistical measure, transfer entropy, and the best EEG tasks, resting and finger-tapping, for the first time in the literature. Furthermore, our technique outperformed existing research because we employed connectivity matrices, better representing EEG brain changes with less computation cost than raw

time series. Moreover, with the SHAP value method, we found the best three regions least connected in dystonia. Using a low-cost technique such as the EEG, this method provides high accuracy in diagnosing focal right upper limb dystonia and can be further explored with other types of dystonia. It can also help to expand the knowledge regarding dystonia's pathophysiology with a potential to be applied to design brain-machine interfaces to treat this condition.

Acknowledgments: FAPESP grant 2021/14108-4.

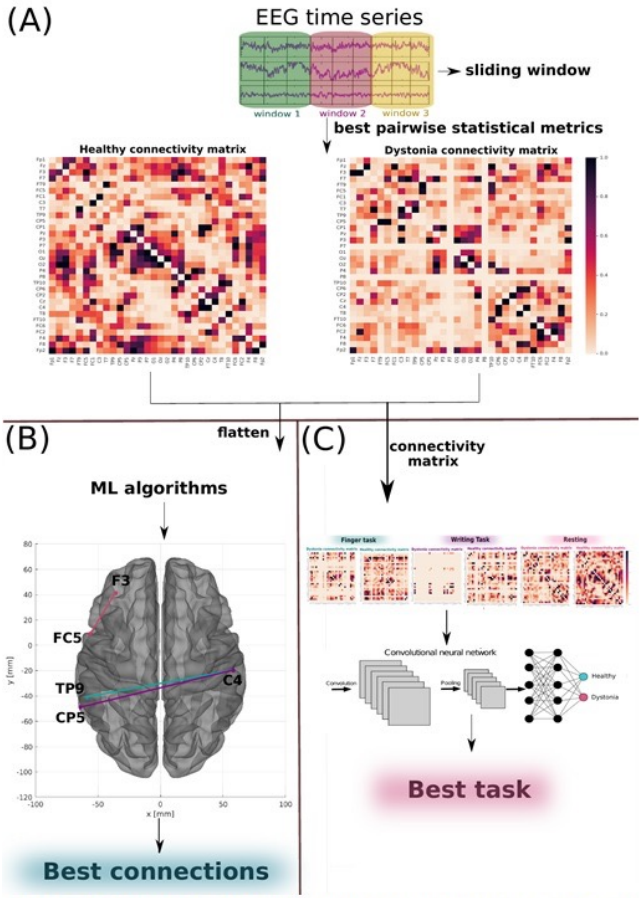

Figure 1. Methodology applied for the diagnosis of dystonia using EEG data and machine learning (ML). In (A), the EEG time series are split into windows (sliding window technique), then eight different pairwise statistical measures are employed to correlate EEG time series, which are examined by the ML algorithm to determine the best measure for capturing dystonia brain network changes. In (B), the best measure's connectivity matrices are fed into the ML to determine the best connections impacted by this disease. Finally, in (C), the connectivity matrices feed the CNN method for evaluating the EEG task more critical for capturing brain alterations due to dystonia.

P2.17

Deep Brain Stimulation Evoked Potentials (DBSEPs) in children with dystonia

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Abstract

Introduction: Pallidal Deep Brain Stimulation (DBS) is an established therapy for dystonia in adults and children. Stimulation parameters, including selection of active electrode contacts, are currently determined empirically. Recording the cortical response to the pallidal stimulus, using a technique called Deep Brain Stimulation Evoked Potentials (DBSEPs)[1,2] could provide a more objective measure of optimal contact selection. This study reports on the feasibility of conducting this investigation in children with genetic/idiopathic or acquired dystonia in a UK national referral centre for paediatric neuromodulation.

Materials and Methods: Fifteen young people (age 7-19years, mean 13.71) with dystonia participated, all with bilateral pallidal DBS implanted at least 6 months previously. Dystonia was genetic/idiopathic in eight and acquired in seven. Scalp EEG was recorded with an ASA (ANT-Neuro) system, using 10-20 international electrode placement and sampling at 5kHz. Impedances were reduced below 10kOhm. Contacts from the left and right stimulating electrode were tested separately, using 6Hz bipolar stimulation, with the other side turned off. Pairs of electrode contacts were tested sequentially using combinations of cathodal stimulation with an adjacent anode. Voltage was 2V, with pulse-width maintained at the patient's therapeutic level. Each combination was recorded for 3 minutes, giving >1000 stimuli per contact pair. Therapeutic settings were restored on study completion.

Offline, the DBS stimulus artefact was used to segment EEG data into epochs (10ms pre-stimulus, 150ms post-stimulus). Raw data were inspected manually and portions of data contaminated by movement/muscle artefact excluded. Remaining epochs (900-1100 per patient after removing artefacts) were averaged to obtain the DBSEP for each contact pair. Onset and peak latencies and peak amplitudes were recorded.

Results: Clear DBSEPs were obtained in 12/15 patients from one or both stimulation sides. Peak latency was 20ms. The largest amplitude response was recorded over the ipsilateral central/centro-parietal region in each patient. Both the peak latency and topography were in keeping with adult literature [1]. In 3/15 patients no convincing DBSEP was obtained from stimulation of either side.

Discussion/Conclusion: This study confirms the feasibility and tolerability of this technique in children with DBS for dystonia. The findings are consistent with adult studies [1], confirming reproducibility of the method. Future work will investigate the potential clinical application of DBSEPs to inform an objective and individualised approach to DBS contact and parameter selection.

References:|
1. Tisch et al. 2008. Movement Disorders. 23:265-73.

2. Bhanpuri et al 2014. Brain Stimulation 7:718-26.

P2.18

Theta-alpha activity in pallidal recordings: a signature of dystonia or a tremor-related artifact?

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Abstract

Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) is an effective treatment for drug-refractory dystonia. New implantable DBS devices can record local field potentials (LFPs) from the chronically implanted electrodes, holding promise for the development of adaptive DBS protocols (aDBS) to improve therapeutic efficacy and battery life. Low-frequency (theta-alpha band: 3-12Hz) oscillatory patterns of pallidal LFPs have been suggested as a possible physiomarker for aDBS in dystonic patients, being correlated with symptom severity. However, the possible presence of motion artifacts in LFP recordings suggests caution in the use of this neural biomarker. Specifically, movement artifacts due to dystonic head-tremor are characterized by low-frequency content and may interfere with the monitoring of neural oscillations in the theta-alpha band. We investigated pallidal LFPs recorded with the Percept PC device (Medtronic, PLC) from the chronically implanted electrodes in eight subjects with dystonia (four patients had cervical dystonia, three myoclonus dystonia, and one segmental dystonia primarily affecting the head and the upper limbs). Five patients showed dystonic head-tremor. All data were recorded in stimulation-off condition at least six months after the DBS implant while patients were at rest, comfortably sitting in a chair. Head-tremor was monitored with a head-mounted triaxial inertial measurement unit (IMU) and surface electromyographic probes placed bilaterally on the sternocleidomastoid and trapezius muscles. We applied a multiple regression approach to LFP signals to assess and remove head tremor activity as measured with the IMU. We assessed the effect of our regression analysis on i) LFP power spectral density (PSD) and ii) pallido-muscular coherence (COH) in the theta-alpha band. Regression of IMU content resulted in a significant LFP-PSD reduction in the theta-alpha band in patients with head tremor (4.66 3 2.12 au (mean 3standard deviation power difference); p-value < 0.05, matched pairs Wilcoxon Signed Rank test), suggesting the tremor-related contamination of GPi-LFPs. Pallido-muscular COH in the theta-alpha band also significantly decreased (p-value < 0.05, matched pairs Wilcoxon Signed Rank test) after IMU regression selectively in patients with head-tremor, thus supporting the idea of its artifactual origin. Our results indicate the presence of head tremor-related artifacts in pallidal LFPs recorded with the Percept PC device in dystonic patients. The proposed approach can capture such artifact contamination and could be a suitable tool for its removal, thus facilitating the neurophysiological interpretation of pallidal LFPs and the identification of robust biomarkers for the development of aDBS protocols for dystonic patients.

P2.19

Neurophysiological measurement of social cognition in cervical dystonia

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Abstract

Cervical dystonia is a rare hyperkinetic movement disorder characterised by sustained or intermittent muscle contractions that can present as twisting, repetitive or patterned movements and abnormal postures. It has a number of motor (dystonia) and non-motor (cognitive, psychiatric and sensory) features. Recent evidence has suggested that abnormalities in social cognition are part of the non-motor syndrome of cervical dystonia.

Methods: 12 patients with cervical dystonia and 12 healthy controls were recruited to undergo 128 lead EEG recording while passively viewing a standardised facial expression images database. The following ERPs were analysed during this task: P300, EPN, N170 and LPP.

Results: We noted several differences in ERPs between patients and controls. The P300 components showed the most robust changes, followed by the LPP. The N170 and EPN only showed differences in specific hemispheres.

Conclusion: Processing of facial emotions is abnormal in patients with cervical dystonia. These subtle covert deficits indicate abnormalities in a network involving the superior colliculus and amygdala. This study provides evidence of cognitive dysfunction in cervical dystonia and lends credence to a network disorder theory of idiopathic focal dystonias.

P2.20

Real-World Use of Clinical Scales to assess Botulinum Toxin Efficacy in Cervical Dystonia Treatment.

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Abstract

Botulinum toxin type A (BoNT/A) is the first-line treatment in symptomatic management of cervical dystonia (CD) and repeated injections are required for life-long symptom control. Treatment can be complex and documenting the effect is an important tool to optimize patient outcomes. A previously conducted survey showed the heterogeneity of efficacy scales used in routine clinical practice. This follow-up survey further characterizes real-world use of different scales.

38 centers in Canada, Poland, and Spain completed an online survey including questions about number of CD patients, frequency of injection sessions, type and frequency of efficacy scales, type of quality of life (QoL) scales, and safety.

The centers reported a total of 5968 CD patients currently treated with BoNT/A. Average number of injection sessions per year was 3.8 (3.6, 3.7, and 4.0 in Poland, Spain, and Canada, respectively). 29 of 38 centers documented patient-reported waning or duration of effect, and the type of guidance technique used; 71 % documented patient BoNT/A treatment in other indications (including Aesthetics) and 84 % documented suspected cause of treatment issues such as lack of effect. 27 centers used at least one type of efficacy scale while 11 centers did not routinely assess efficacy using a scale. Most frequently used was a 7-point Global Impression of Change Scale (GICS, patient or physician), reported by 21 centers who used the GICS in 81 % of their patients. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used in 14 centers and application rate varied between countries (15 % and 69 % in Spain and Poland, respectively). Only one center in Canada reported use of the TWSTRS. Various other scales were reported including the Tsui scale, Visual Analogue and Likert scales. Only 21 % used a questionnaire to assess QoL (SF-36, EQ-5D, CDC24).

This survey confirms the previously reported heterogeneity of efficacy scales and further gives evidence of the variability within centers how efficacy scales are applied. While the importance of quantifying quality of life is increasingly recognized, use of standardized patient reported outcomes remains the exception.

P2.21

Device led social cognition measurement in Cervical Dystonia (proof of concept)

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Abstract

Introduction: Patients with cervical dystonia (CD) suffer from of motor and non-motor symptoms. The non-motor symptoms include sensory, psychiatric and cognitive features. The often-neglected non-motor symptoms have a major impact on quality of life (QoL). We showed that our patients with CD have deficits in social cognition. One aspect of this is difficulty in recognising facial expression. This can affect interpersonal relationships; patients' understanding of the emotions of others and provides insights into disease mechanism.

Neuropsychologists use clinical interviews and a range of standardized questionnaires to diagnose social cognition. No "gold standard" exists for diagnosing social cognition.

There is no device for measuring social cognition. Several physiological signals (heart rate, galvanic skin response, blood pressure) show abnormal responses in patients with social cognition deficits. A device can be worn by patients to track responses in certain conditions e.g. during conversations with others. Such a device can be implemented to provide feedback where needed e.g. in interpreting facial expressions, a trained algorithm with a camera can detect facial expressions and provide "answers" to patients.

Objective: Design a device that integrates physiological signals and a camera to aid in diagnosing social cognition deficits and provide feedback to participants. We will test volunteers with cervical dystonia and social cognition abnormalities and healthy volunteers.

Methods: Our device integrates a heart rate sensor, galvanic skin response sensor, a blood oxygen sensor and a camera on a portable single board computer. Data will transfer via Wi-Fi to a workstation. We tested the device on healthy and cervical dystonia volunteers under a range of face emotion recognition tasks from a standardized database. A convoluted neural network is used to detect facial expressions and integrate the physiological signals. The camera can face externally to detect the facial expressions displayed or gauge the facial expressions of the wearer.

Results: Our device reliably measures physiological signals. The camera reliably detects facial expressions using our machine learning algorithm and provides appropriate feedback. The physiological sensors are accurately time locked to the facial expressions. The device also provides appropriate feedback to wearers.

Conclusion: This proof-of-concept study provides evidence for a larger trial. We aim to recruit more patients with CD and healthy volunteers. The non-motor symptoms are often ignored in neurology services even though they contribute significantly to QoL. Device led measurements could act as diagnostic aids and reduce the burden of diagnosing social cognitive deficits.

P2.22

Dystonia Without Abnormal Movements or Postures?

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Abstract

Background. Cervical dystonia is defined by excessive contraction of muscles that produce abnormal postures and movements of the head, neck, and sometimes the shoulders. Many affected individuals also develop associated pain and muscle hypertrophy, but abnormal movements are considered the defining feature.

Materials and Methods: We describe five cases who were suspected to have cervical dystonia, but without abnormal movements of the head, neck or shoulders.

Results: All five cases presented with neck pain and sensation of tightness in the neck, without abnormal movements. In three cases neck pain was preceded by focal dystonia, such as blepharospasm, laryngeal dystonia or combination of both. Four of the cases had focal neck muscle hypertrophy, and/or decreased range of head/neck motion, and/or EMG findings of overactivity of selected neck muscles. One patient reported head jerks only later in the day, which were not visible on exam. One of the cases developed abnormal movements within a year.

Discussion: Six cases are described illustrating that cervical dystonia may occur without abnormal movements or postures. In these cases, the only clinical features may be pain, decreased range of motion, local muscle hypertrophy, or abnormal EMG activity. These features may occur years before abnormal movements emerge, they may occur coincidentally with dystonia outside of the neck, or they may occur without any obvious abnormal movements. The cases presented here raise the question whether neck pain without abnormal movements may reflect cervical dystonia. And if cervical dystonia may occur without abnormal movements, it is important to recognize, because symptoms are readily alleviated with botulinum toxin.

P2.23

Pooled safety analysis of incobotulinumtoxinA in the treatment of neurological disorders in adults

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Abstract

The safety and efficacy of incobotulinumtoxinA in adults with neurological disorders have been investigated in multiple prospective clinical trials. We examine the pooled incidence of treatment-emergent adverse events (TEAEs) and immunogenicity by indication in sponsored incobotulinumtoxinA clinical trials in adults.

TEAEs were identified in the integrated clinical database of Merz-sponsored placebo-controlled studies in adults with cervical dystonia (CD), blepharospasm, upper limb (UL) and lower limb (LL) spasticity, sialorrhea or essential tremor of the UL. Overall incidences of TEAEs and the categories of serious TEAEs (SAEs), TEAEs leading to discontinuation, fatal TEAEs, TEAEs of special interest (AESIs; indicating possible toxin spread) and treatment-related (TR) events were determined for incobotulinumtoxinA and placebo after a single injection cycle and for incobotulinumtoxinA after multiple cycles. Neutralizing antibody (NAb) testing was performed in most studies.

After a single cycle, incidences of overall TEAEs were similar between incobotulinumtoxinA and placebo in all indications, although between-indication differences were observed. Most TEAEs were mild to moderate; only one subject experienced a TR-SAE. Few TEAEs led to discontinuation of incobotulinumtoxinA; no fatal TEAEs occurred with incobotulinumtoxinA. Repeated cycles generally did not increase the incidence of any TEAE category. The most frequent TEAEs and TR-TEAEs were indication-dependent. The most common TR-AESIs across all indications were muscular weakness and dry mouth. Few subjects developed NAb and most had been positive at baseline.

This pooled analysis supports and extends the favorable safety/tolerability profile of incobotulinumtoxinA for the treatment of adult neurological disorders established by individual clinical studies.

P2.24

Treatment of cervical dystonia using shorter incobotulinumtoxinA injection intervals improves patient-reported outcomes in those with inadequate benefits from standard intervals

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Abstract

There is individual variation in the reported waning of botulinum toxin (BoNT) treatment benefit in patients with cervical dystonia (CD), even among patients who experience a favorable peak response. Thus, some patients prefer injection intervals shorter than the standard 12 weeks. This study assesses whether individualized treatment intervals can lead to improved patient experience without compromising safety. We assess the impact of 2 different injection schedules of incobotulinumtoxinA on patient-reported assessments in CD.

An open-label, randomized, phase IV study (CD Flex; NCT01486264) was designed to compare 2 incobotulinumtoxinA injection intervals (short-flex: 832 weeks [N=142]; long-flex: 1432 weeks [N=140]) in BoNT-responsive subjects with CD who report typical waning of clinical benefit at <10 weeks. Subjects received 8 injections over a period of up to 2 years. Patient-reported outcomes (4 weeks post-injection 8) included satisfaction (10-point scale), patient-reported global response (9-point Likert scale), and the CD impact profile (CDIP-58). Additional endpoints included a physician-assessed global response and a clinical global impression of severity.

Subject satisfaction was significantly improved vs study baseline over 8 cycles in the short-flex group (mean change=1.2 points, P=0.0007), but not in the long-flex group. A significant improvement was also observed in the short-flex group in the physician-assessed global impression of severity 4 weeks after injection 8. Most domains of the CDIP-58 analysis (pain/discomfort, sleep, annoyance) demonstrated numerical trends favoring the short-flex group. At 4 weeks post-injection 8, a similar distribution of scores was observed for both groups on the subject- and physician-rated global response assessments with no

relevant difference between groups. No differences in safety profile were noted.

Subjects with shorter incobotulinumtoxinA injection intervals reported improved satisfaction after 8 injections. Trends favoring short-flex were observed in both the CDIP-58 analysis and physician-rated clinical global impression of severity. Evidence suggests that individualizing injection intervals to treat CD may improve patient-reported outcomes without compromising safety.

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P2.25

fMRI analysis of social cognition in cervical dystonia

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Abstract

Introduction: Cervical dystonia (CD) is a rare hyperkinetic disorder characterised by abnormal, repetitive, twisting movements affecting the cervical neck muscles. It is the most common phenotype of the adult onset idiopathic focal dystonias. CD has a range of motor and non-motor symptoms. Recently, we demonstrated that patients with CD have abnormalities in social cognition. This has the potential to greatly impact on quality of life in this disorder and raises interesting pathophysiological questions. The superior colliculus, amygdala and pulvinar network mediates aspects of social cognition and may demonstrate changes in patients with CD.

Objective: Study functional changes within a network that mediates recognition of facial expressions in patients with cervical dystonia by MRI.

Methods: A functional MRI task was designed using happy and disgust facial expressions. Participants were scanned while viewing changing facial expressions using an oddball paradigm. Patients also had TWSTRS2-severity and mood measurements.

Results: 8 patients with cervical dystonia and 8 healthy volunteers participated in the study. Results suggest changes within functional and resting state networks in patients with cervical dystonia and control subjects.

Discussion: The network involving the superior colliculus, amygdala and pulvinar nuclei showed functional changes in patients with CD. This network could mediate the motor and non-motor symptoms, including facial expression recognition, in CD. Targeting non-motor symptoms could improve quality of life in this disorder. Larger functional MRI studies into this network could help develop mechanistic models in a condition that has to date, remained elusive.

P2.26

Immunogenicity of botulinum toxin formulations: potential therapeutic implications

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Abstract

Botulinum neurotoxins (BoNT) are proteins produced by bacteria of the Clostridium family. Upon oral ingestion, BoNT causes the neuroparalytic syndrome botulism. There are seven serotypes of BoNT (A-G); BoNT-A and BoNT-B are the serotypes utilized for therapeutic applications. BoNT injections are used to manage chronic medical conditions across multiple indications. As with other biologic drugs, immunogenicity after long-term treatment with BoNT formulations may occur, and repeated use may elicit antibody production leading to reduced efficacy. Thus, approaching BoNT treatment of chronic conditions with therapeutic formulations that minimize immunogenicity while balancing patient responsiveness to therapy is ideal. Reduction in immunogenicity and anti-biologic antibody production has been achieved through engineering smaller protein constructs and reducing unnecessary formulation components. A similar approach has influenced the evolution of BoNT formulations. We describe the basic science of immunogenicity as a potential clinical barrier to the efficacy of biologic therapies and the evolution of BoNT formulations.

Three BoNT-A products and one BoNT-B product have been approved by the Food and Drug Administration for therapeutic use: onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB. Additionally, daxibotulinumtoxinA and prabotulinumtoxinA are BoNT-A products that have been approved for aesthetic indications but not therapeutic use.

Available nonclinical and clinical evidence of immunogenicity and clinical nonresponsiveness associated with different BoNT formulations are summarized and the potential lower risk of immunogenicity with a second-generation BoNT formulation, incobotulinumtoxinA, is discussed.

We provide an immunological perspective for considering immunogenicity as a factor in choosing a BoNT formulation.

Funding: This research was supported by Merz Therapeutics GmbH.

P2.27

The role of physical therapy in the management of dystonia.

Darcy Cooper

Duke Health System, Durham, USA

Abstract

When to Consider PT: Focal dystonia. Dystonia contributes to pain, impaired functional mobility, or impaired gait. Underlying musculoskeletal issues: strength, range of motion, posture, flexibility, coordination. Poor biomechanics have been adopted. To enhance effects of botulinum toxin injections

PT Evaluation: PTs will assess multiple systems including musculoskeletal (pain, ROM, strength, joint mobility, neural dynamics), sensory (laterality, sensory tricks, localization, proprioception), autonomic (vitals, breath assessment), motor control (biomechanics, coordination, speed), and psychosocial (stress, anxiety, coping strategies).

Goals: Pain reduction. Improve physical fitness and wellbeing. Address underlying musculoskeletal factors. Promote more optimal movement. Take an active role in managing the condition.

Common Treatment Strategies: Stop the abnormal movement (use of sensory tricks, change in position or environment or speed, break task into components). Quiet the nervous system. Promote positive health behaviors. Improve biomechanics. Improve sensory discrimination skills (including graded motor imagery). Retrain more optimal movement. Use of the OPTIMAL Theory of Motor Learning.

Research: PT + botulinum toxin injections may reduce future botulinum dose and increase duration of dose. This may be mediated through modulation of sensorimotor plasticity.

References are listed.

P2.28

Individual-specific brain functional connectivity mapping of therapeutic response in task-specific focal dystonia

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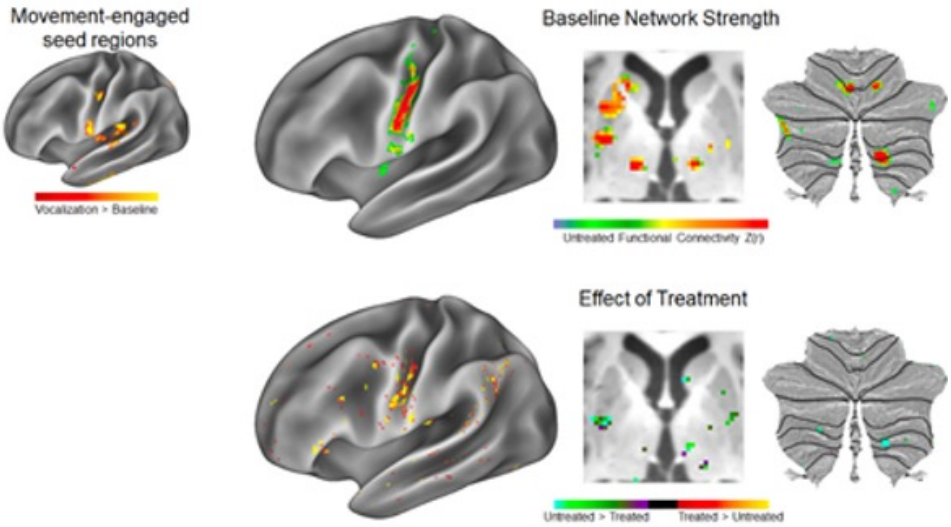
Abstract

Introduction: Isolated task-specific dystonia occurs during specific activities, but not at rest. This allows for neuroimaging study with reduced potential state-related confounds, particularly when considering studies of treatment response. Current therapeutic gold standards for task-specific dystonia rely on recurring botulinum toxin injections. Therapeutic advancement requires improved understanding of neural mechanisms related to adaptive treatment response. Resting-state fMRI measures brain network functional connectivity (FC), where botulinum toxin therapy may alter FC in patients with non-task-specific dystonia, but intra-scan movement potentially confounds interpretation. Furthermore, group averaging in prior studies combine regions with and without dysfunction across patients and may fail to detect effects localized to individual-specific brain regions. The objective of this study is to determine therapeutic effects of botulinum toxin on functional connectivity in individuals with task-specific dystonia.

Materials and Methods: We conducted a treatment response application of precision functional mapping (PFM) in patients with task-specific dystonia (writer's cramp & laryngeal dystonia). PFM involves repeated collection of fMRI data in the same patient to characterize individual-specific brain network organization without averaging across patients. We collected 125 minutes rs-fMRI/40 minutes task fMRI in each patient, both before and after successful therapeutic botulinum toxin. Tasks included impairment-specific motor tasks (vocalization; hand movement). Within each individual, we compared task activation and resting-state FC before and after successful therapeutic botulinum toxin.

Results: PFM allowed us to 1) determine the task activated somatomotor functional network in individuals, and 2) detect highly localized changes in individual's task engagement and brain network connectivity that related to successful therapeutic intervention. In pre-treatment conditions, the impairment-specific motor task engaged localized regions of M1 that were more strongly engaged after treatment. These task-related regions exhibited strong FC to somatomotor, striatal, and cerebellar regions. After successful botulinum toxin treatment, FC increased within cortex but decreased in subcortical structures.

Discussion: PFM in task-specific focal dystonia offers advantages to understand individualized network alterations in response to successful botulinum toxin treament, and thus sheds light on pathophysiologic mechanisms. Altered treatment related FC in somatotopically specific regions might represent potential target engagement sites or future therapeutic trials.


Movement-engaged seed regions
Vocalization > Baseline
Baseline Network Strength
Untreated Functional Connectivity Z(r)
Effect of Treatment
Untreated > Treated
Treated > Untreated

P2.29

Is sinusoidal head tremor and jerky movements characterized by similar basal ganglia neurophysiology in dystonia?

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Abstract

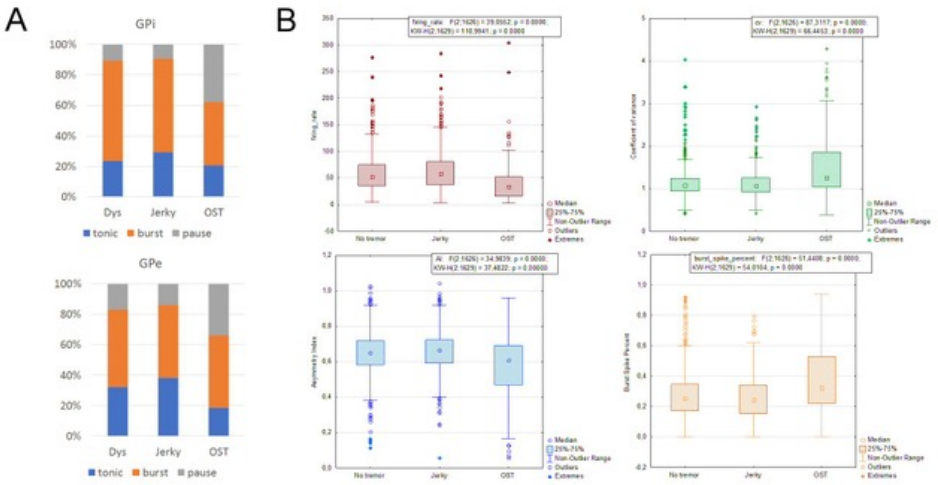
The relationship between two common movement disorders, dystonia and tremor, is controversial. Recent study showed biological differences in the basal ganglia network behavior in pure cervical dystonia or cervical dystonia combined with irregular head oscillations compared with cervical dystonia with sinusoidal oscillations. We tested the hypothesis that sinusoidal tremor has a different nature than jerky movements.

We analized single unit activity of 1629 pallidal (GPi and GPe) cells, registered by microelectrode during DBS surgeries in 27 dystonic patients. We divided neurons into 3 groups – burst, pause, and tonic by means of an unsupervised clusterization. Then we calculated the firing rate, spike regularity, oscillation scores, burst and pause indexes, and other parameters of pallidal cells. We also performed spectral analysis of local field potentials (LFP) recorded by means of externalized LEADs on the second day after DBS surgeries in 5 dystonia patients. We compared parameters of pallidal activity between 3 groups: pure dystonia (Dys) without tremor, dystonia with oscillatory tremor (OST) and dystonia with jerky movements (Jerky).

We found robust differences in both firing rate and firing pattern of pallidal cells between OST and Jerky groups as well as between OST and Dys group and no differences between Dys and Jerky group. We found significant increase of pause cells percentage in both GPi (11% in Dys, 9% in Jerky and 38% in OST) and GPe (16% in Dys, 14% in Jerky and 35% in OST) nuclei (fig 1 A). Burst and pause cells in OST group were also characterized by lower firing rate, higher irregularity and more bursty pattern compared to the other two groups (fig 1, B). The differences were observed in GPi in cervical dystonia and in GPe in generalized dystonia. Spectral analysis of LFP showed significantly higher theta and alpha oscillations in the OST group and higher low beta activity in the Dys group. We found significant increase of theta activity in Jerky group, increase of alpha activity in Jerky and OST group and no changes in Dyt group during voluntary head movement.

Our results prove hypothesis that pure dystonia and dystonia with jerky movement have similar neurophysiological mechanisms while oscillatory tremor could be an additional symptom, having a different origin. On the other hand, our data showed that theta-alpha activity, which has been considered as a biomarker for dystonia, appears to be a biomarker for dystonic tremor.

The study was funded by the Russian Science Foundation (23-15-00487).



P2.30

An aberrant embouchure dystonia network predicts objective and functional measures of severity

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Abstract

Introduction: FED impairs orofacial motor control in wind instrument musicians and causes professional disability. Little is known about its pathophysiology, but striatal abnormalities and altered sensorimotor cortical plasticity have been identified in many forms of dystonia. Across focal dystonia subtypes, striatal changes may be restricted to somatotopically distinct subregions, but many of these studies had participants perform dystonia-eliciting tasks during imaging and thus were confounded by secondary responses to abnormal movement. Imaging in the resting-state minimizes this confound of interpretation. We sought to investigate functional brain networks underlying focal embouchure dystonia (FED) using resting-state functional connectivity (FC) magnetic resonance imaging and to correlate abnormal connectivity with functional impairment and quantitative measures of FED severity. We hypothesized that participants with FED would have altered functional connectivity (FC) in a striatal subregion implicated in laryngeal dystonia (LD) and lateral sensorimotor cortex.

Materials & Methods: Fourteen brass musicians with and eleven without FED underwent 30 minutes of resting-state BOLD scans. We defined seeds in putamen subregions implicated in LD and writer's cramp (WC), pallidum, lateral sensorimotor cortex, and posterior cingulate cortex (PCC) and computed the correlations between seed average time courses and BOLD activity in every voxel across the brain. Group-level differences in seed-voxel BOLD correlations (i.e. FC) were assessed on a cluster-wise basis.

Results: FED is characterized by an abnormal anticorrelated functional network comprising the putamen LD subregion, right superior temporal sulcus and surrounding cortex, and PCC. Presence of this network had 100% sensitivity (95% CI: 74-100%) and 91% specificity (95% CI: 59-100%) for the diagnosis of FED in our sample of musicians. Intra-network FC correlated with functional impairment and an objective, quantitative measure of FED severity. FC patterns of the putamen WC subregion, pallidum, and lateral sensorimotor cortex seeds were unaffected.

Discussion: We identified an abnormal striatal-temporal-PCC network in musicians with FED that is sensitive and specific for musicians with FED and correlates with functional and objective impairment metrics, suggesting clinical relevance. Altered FC for the LD but not WC striatal subregion adds cross-modal support for differential somatotopically-distinct striatal subregion abnormalities in focal dystonia.

P2.31

Lost of Pallidal Multifractal Complexity is regained during DBS in Patients with Dystonia

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Abstract

The internal segment of globus pallidus (GPi) is the most common target for surgical treatment of dystonia. Currently, low-frequency 3-12 Hz oscillations in the globus pallidus are considered the only potential biomarker of pathological activity in dystonia (Neumann et al., 2017). However, it remains unclear what rearrangements of the pattern temporal organization are behind the emergence of these rhythms. It is assumed that the emergence of simpler dynamics can be seen as a degradation of multifractal complexity.

Previously, we have shown that dystonic BFMDRS symptom severity significantly correlated with the width and the shape of the multifractal spectrum (Semenova et al., 2021). An increase in severity scores was accompanied by a decrease of multifractal spectrum width and rise of its asymmetry.

In this study, we examined how these characteristics change during DBS. The data were recorded during planned neurosurgical operations at the National Medical Research Center for Neurosurgery N.N. Burdenko for implantation of stimulating electrodes (DBS). Four patients underwent externalization of LEAD electrodes for postoperative 16-channel recording of local potentials (LFP) of the globus pallidus. We calculated the width and asymmetry of LFPs multifractal spectra estimated based on wavelet leaders at rest and during stimulation.

In all patients we observed substantial increase of multifractal spectrum width and restoration of its symmetry during DBS. We localized pallidal areas associated with the largest change in the width of the multifractal spectrum in response to DBS. Using LEAD-DBS software we modeled VTAs corresponding to the most efficacious DBS and looked at how these areas overlap. For all patients, the thesholded peak intensities of increase in the multifractal spectrum width was within the optimal VTA or significantly overlapped with it. We also found that the wider the spectrum became during the DBS, the better the clinical effect was observed in follow-up study.

In sum, our data indicate the promise of using multifractal characteristics of pallidal neuronal activity as biomarkers of pathological activity in dystonia, as well as for evaluating and predicting the clinical effect of DBS.

This study was supported by Russian Science Foundation (23-25-00406).

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P2.32

Practice Behaviors as Trigger Factor for the Onset of Musicians' Dystonia

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Abstract

Introduction: Musician's Dystonia (MD) is a task specific movement disorder. It results in involuntary cramping of muscles involved in playing an instrument. It is usually painless, and it generally occurs when playing the instrument. Although several risk factors have been identified, the pathophysiology of MD is not completely understood.

The present study investigated the extent to which musical practice can be considered a trigger factor for MD. Therefore, it aimed at assessing differences in practice behaviors between Healthy Control (HC) pianists and pianists affected by MD in the years preceding the onset of the disease.

Materials and Methods: The study retrospectively investigated practice behaviors between the age of 5 and 30 years in HC pianists (N = 32) and pianists affected by MD (N = 46). All participants were professional pianists above the age of 30 years. Only pianists who developed MD after 31 years of age were allowed to take part in the study.

Participants were asked to fill out a questionnaire and to recall the average length of their daily practice sessions over four timeframes (see Table 1). This data was used to compute cumulative practice quantity, the cumulative amount of practice hours reached at 10, 15, 20 and 30 years of age.

Participants also provided information about their musical background, previous playing-related injuries as well as family health history.

Results: A Bayesian mixed effect regression model was run to investigate the increment in cumulative practice quantity overtime. The results indicated a meaningful age*group interaction, $\beta = 8.85$ [1.62, 16.17], suggesting that pianists in the MD group practiced at a higher rate over the first 30 years of life than HC pianists. Subsequent analyses showed that despite comparable practice behaviors in childhood and adolescence, MD pianists practiced significantly more than HC pianists in the third decade of life, $t(76) = 2.01$, $p < .05$ (see Table 1). Finally, logistic regression analysis indicated a meaningful increase in MD's occurrence in association with the average amount of daily practice achieved between 21 and 30 years of age, $\beta = 1.182$ [0.093, 2.270], Odds Ratio = 3.260 [1.098, 9.681].

Discussion: This study identified differences in practice behaviors between healthy pianists and pianists affected by MD before the onset of the disease. MD pianists tended to practice less until 15 years of age, when they practiced considerably more than HC pianists. Clinical and educational implications are discussed.

Table 1. Descriptive statistics for the MD and HC groups.

	MD Group (N = 32)	HC group (N = 46)
Age	54.96 (9.031)	41.13 (11.36)***
Gender		
Females	10	24
Males	22	22
Age at which participants started playing piano	7.3 (2.206)	6.5 (2.927)
Cumulative amount of practice at age 30	28081(9254)	25885 (9783)
Average amount of daily practice (hours) between:		
5 and 10 years of age	0.8 (0.5)	1.0 (0.8)
11 and 15 years of age	1.8 (1.0)	2.0 (1.2)
16 and 20 years of age	3.6 (1.7)	3.4 (1.7)
21 and 30 years of age	4.7 (1.5)	4.0 (1.6)*
Median onset age of Musicians' Dystonia	40.0 (8.0)	

Notes: N = 78; *between groups t-test significant at $p < 0.05$, ***between groups t-test significant at $p < 0.001$

P2.33

Music, Stress, and Childhood Trauma – Differences in Stress-Reactivity between Musician's Dystonia Patients and Healthy Musicians

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Abstract

Musician's dystonia (MD) is a task-specific focal dystonia characterized by muscle cramps and impaired voluntary motor-control whilst playing a musical instrument. Even though several risk factors have been established, the exact pathophysiology remains unknown. In the last years, the network hypothesis predominated, stating that MD is caused by dysfunctional neural networks in sensory-motor, basal ganglia, cerebellar and limbic loops. Since many psychological components associated with MD are related to increased stress, this study aims to examine limbic loops and stress-reactivity of MD patients on a neuronal and neurobiological level. Additionally, adverse childhood experiences (ACEs) are investigated as possible influencing factors.

We hypothesize that MD patients show increased stress-reactivity and lower resilience compared to healthy controls. More specifically, we expect altered activation in stress-related networks, including the limbic system, the hippocampus, and the prefrontal cortex. We suggest that there is an association between stress-reactivity, dystonia, and ACEs.

This ongoing study compares eighty-two musician's dystonia patients and matched healthy musicians using functional magnetic resonance imaging (fMRI) and psychological questionnaires. The Montreal Imaging Stress Task is administered to induce stress in the fMRI setting, using arithmetic tasks and social-evaluate pressure in three different conditions (rest, control, experimental). Salivary cortisol levels are measured throughout the task. The parameter estimates from the stress > control contrast are fitted into a regression model with dystonia, adverse childhood experiences, and sex as covariates.

Preliminary results of 62 participants show increased activation in the visual association area of MD patients during the stress condition. However, since MD patients moved significantly more throughout the scan than healthy controls, additional motion corrections are currently performed and might impact the results. Preliminary analysis of the questionnaire data has shown that MD patients report significantly more sexual abuse than healthy controls. They further score significantly lower on the sub-scales "regulation of emotion and cognition" and "adaptability/flexibility" of the Connor-Davidson Resilience Scale.

So far, altered activation of the limbic system could not be observed in this sample. However, increased activation of visual areas has also been reported in several studies linking stress and emotion and should be investigated further. Confirmation of differences in

stress-reactivity would support the theory that musician's dystonia is not only the result of motor circuit dysfunctions, but also a manifestation of dysfunctional stress-coping-mechanisms. These findings would supply important contributions to improved and individually tailored treatment and prevention methods.

P2.34

Altered Inhibitory and Excitatory Signaling Within the Sensorimotor Network is Associated with Motor and Neuropsychiatric Symptoms in Blepharospasm.

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Abstract

Objective: Determine if concentration levels of inhibitory and excitatory molecules within the sensorimotor cortex, basal ganglia and cerebellum underlie motor and non-motor symptoms in blepharospasm (BSP).

Background: A variety of investigative lines suggest an imbalance between inhibition and excitation in neuronal circuits could be an important contributor to the pathophysiology of movement disorders including dystonia. Magnetic resonance spectroscopy (MRS) with modern spectral editing methods provide estimates of levels of gamma-aminobutyric acid (GABA) and glutamate, the most abundant inhibitory and excitatory neurotransmitters in the brain respectively Previous GABA MRS studies had mixed results but suggest GABA levels may be abnormal within sensorimotor networks in focal hand and cervical dystonia. Neuropsychiatric symptoms of depression and anxiety have been associated with decreases in GABA, but such relationships have not previously been reported in those with BSP.

Design/Methods: Nine BSP patients (7F; 66.45 3 9.5 yrs) underwent MRS on a 3T MRI using the MEGA-PRESS pulse sequence and voxels placed in the left sensorimotor cortex, left basal ganglia (lentiform nucleus), and right cerebellum. Concentrations of GABA (GABA+/Water) and glutamate + glutamine (Glx/Water) levels were derived using Gannet open-source software (v3.3.0). BSP severity and disability was assessed using the Blepharospasm Severity Rating Scale, Burke-Fahn-Marsden Rating Scale (BFM-eyes), and Blepharospasm Disability Index (BDI). Neuropsychiatric symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory II (BDI). Pearson's coefficient was used to test for correlations between neurometabolite levels and clinical scale scores. Significance was defined as a $p<0.05$.

Results: BSP severity as measured by BFM-eyes ($r=-0.738$, $p=0.050$) negatively correlated with GABA levels in the cerebellum while BSP disability (BDI) positively correlated with Glx levels in the sensorimotor cortex ($r=0.791$, $p=0.016$) and basal ganglia ($r=0.809$, $p=0.012$). Glx levels in the basal ganglia positively correlated with severity of anxiety (HADS-A; $r=0.821$, $p=0.010$) and depression (BDI-II; $r=0.843$, $p=0.006$).

Conclusions: Loss of inhibition in the cerebellum was associated with increased motor severity in BSP, while increased excitation within the basal ganglia was associated with increased severity of anxiety and depressive symptoms as well as self-rated degree of disability from BSP. Together these findings suggest that altered inhibitory and excitatory neuronal activity within the sensorimotor network contributes to the pathophysiology of dystonia and may underlie motor and non-motor symptoms in BSP.

P2.35

Striatal Cholinergic Transmission in a Mouse Model of Paroxysmal Dystonia-Dyskinesia.

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Abstract

Introduction. Previous research from our lab identified paradoxical excitatory responses to dopamine D2 receptor (D2R) activation as a shared endophenotype of striatal cholinergic interneurons (ChIs) in various genetic mouse models of dystonia. However, none of these models display a dystonic motor phenotype, leaving a gap in our understanding of the role of striatal ChI activity in the development of dystonic and dyskinetic movements. To address this question, we investigated a transgenic mouse model of paroxysmal non-kinesiogenic dyskinesia/dystonia (PNKD), which displays reproducible motor symptoms akin to human hyperkinetic conditions in response to stress or specific drugs like caffeine.

Methods: To study the correlation between cholinergic transmission and dystonic and dyskinetic movements, we used a combination of *ex vivo* slice physiology and *in vivo* monitoring of striatal acetylcholine (ACh) by microdialysis and fiber photometry during behavioral quantification.

Results: Direct activation of D2Rs with quinpirole *ex vivo* induced paradoxical excitation of ChI firing in PNKD striatal slices, similar to that observed previously in DYT1, DYT6, and DYT25 models. In the PNKD animals and their littermate controls (WT), systemic injection of quinpirole *in vivo* had a strong inhibitory effect on movement which was associated with reduced striatal ACh release measured by microdialysis and fiber photometry.

Both PNKD and WT animals showed increased locomotion in response to caffeine, which also induced a complex mixed dystonia-dyskinesia phenotype only in the PNKD animals. Fiber photometry recordings showed that caffeine-induced hyperlocomotion correlated with sustained ACh activity in WT. In contrast, in PNKD mice, ACh transients were elevated at baseline while the onset of caffeine-induced abnormal movements correlated with reduced ACh transmission.

Interestingly, in *ex vivo* slices caffeine inhibited ChI firing in both PNKD and WT animals, but its presence reversed the effect of quinpirole on ChI activity: quinpirole became excitatory for WT-ChIs and inhibitory for PNKD-ChIs, mimicking the ACh profile seen *in vivo* after caffeine injections.

Discussion: These findings show that in the inducible PNKD model, caffeine triggers dystonic symptoms while reducing baseline striatal cholinergic activity and reversing the D2R excitation of ChIs. In WT animals, caffeine stimulates spontaneous locomotion through a similar mechanism involving a dynamic switch of the D2R control of ChI activity. Together, these observations suggest that the D2R "paradoxical excitation" endophenotype described in non-phenotypic dystonia models, and in this model in the asymptomatic phase, could represent a compensatory or protective mechanism that prevents manifestation of movement abnormalities and allows for phenotypic dystonia when lost.

P3.01

Pathophysiology of Dyt1 dystonia is mediated by spinal cord dysfunction

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Abstract

Introduction: Dystonia is a circuit disorder wherein dysfunction arising within and between supraspinal centres leads to downstream abnormal muscle contractions and disorganised movements. Given that spinal circuits directly organise and produce movements, we sought to determine whether spinal circuit dysfunction contributes to dystonia pathophysiology, focusing on a prevalent form of primary dystonia: DYT1-*TOR1A*.

Methods: To confine our manipulation of *Tor1a* to the spinal neuraxis, we developed a new model wherein exons 3-5 are flanked by flippase-sensitive recognition sites (Tor1a-frt). Through multigenerational breeding of Tor1a-frt with the caudalising Cdx2::FlpO mouse (recombinase activity in the spinal cord and dorsal root ganglia), we produced a biallelic "double" conditional knockout of *Tor1a* in the caudal neuraxis whilst sparing the brain ("spinal Tor1a d-cko"). After confirming the site-specificity of the d-cko (qPCR, Western blot, ultrastructure), we used a suite of techniques to investigate the dystonic-like phenotype and its underlying pathophysiology, including: postnatal video recordings, electromyography (EMG) recordings, extracellular recordings from isolated spinal cords, and intracellular patch-clamp recordings from motoneurons.

Results: Video recordings revealed that spinal *Tor1a* d-cko mice develop a striking early-onset dystonic-like phenotype that mimics DYT1-*TOR1A*. Motor issues emerged early in the hindlimbs and then - over postnatal maturation - generalised caudo-rostrally to affect the trunk and forelimbs. EMG recordings revealed that spinal *Tor1a* d-cko mice bear the pathophysiological biosignatures of dystonia: involuntary muscle contractions at rest, disorganised activity during volitional movements, and co-contractions. These pathophysiological biosignatures are produced by dysfunctional spinal circuits as revealed by extracellular ventral root recordings from hindlimb motor pools in isolated spinal cords. To unravel circuit-specific dysfunction, we investigated the monosynaptic reflex. Extracellular ventral root recordings from hindlimb motor pools following dorsal root stimulation revealed that the caudal-most reflexes were affected first and then - throughout postnatal maturation - the more rostral reflexes became impaired. Focusing individual motoneurons, intracellular patch-clamp recordings revealed that motoneurons are smaller and slower in their intrinsic firing properties. Following dorsal root stimulation, motoneurons showed altered excitatory post-synaptic currents that bore the same pathophysiological signatures detected in the motoneuron pools: reduced amplitude, increased latency, and multiple asynchronous peaks. That is, spinal *Tor1a* d-cko mice show altered sensory-motor integration, another key biosignature of dystonia.

Discussion: In summary, the spinal knockout of Tor1a reproduces the pathophysiology of DYT1-*TOR1A*, uncovering a key role for spinal circuit dysfunction in early-onset generalised dystonia. Ongoing work in heterozygous cko mice is also revealing pathophysiological changes that are consistent with DYT1-*TOR1A* dystonia.

P3.02

Secondary modifiers in the development of dystonia in genetically predisposed rodents for DYT-TOR1A dystonia – a role for microglia

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Abstract

DYT-TOR1A dystonia is an autosomal-dominant, neurodevelopmental disorder characterized by the onset of generalized dystonic symptoms during childhood. A remarkably reduced penetrance of 30% has led to the hypothesis that extragenetic factors in form of environmental stressors trigger dystonia development. Potential additional modifiers could be microglia, which are critical contributors to synaptic plasticity and the shaping of neural circuits during the neurodevelopmental phase.

To study the effect of an environmental stressor and the role of microglia in DYT-TOR1A dystonia, DYT1 knock-in (KI) mice, which are asymptomatic in their naïve state, were utilized. As an environmental stressor, a right sciatic nerve crush was performed at 3 months of age. Microglia were partially depleted via the colony-stimulating factor 1 receptor inhibitor PLX3397 starting either immediately after birth (P0) or at an age of 3 months. Dystonia-like movements of the right hindlimb were identified in a tail suspension test via a deep-learning algorithm; a pole test, an open field test and rotarod performance test were used for further behavioral characterization. Dopaminergic cells in the substantia nigra were analyzed for microstructural changes.

DYT1 KI nerve-crushed mice developed persistent dystonia-like movements over an observational period of 12 weeks, while wildtype littermates recovered almost completely from the nerve injury. However, DYT1 KI nerve-crushed mice depleted with PLX3397 from P0 onwards presented with even significantly more dystonia-like movements than the non-depleted DYT1 KI nerve-crushed mice. No change in the severity of the phenotype was found in DYT1 KI nerve-crushed mice PLX3397-depleted at an age of 3 months. The latency to descend in the pole test was significantly higher in DYT1 KI nerve-crushed mice depleted with PLX3397 at P0 compared to all other groups. No behavioral changes were found in the open field test and the rotarod performance test. Dopaminergic cells in the substantia nigra were significantly reduced in the DYT1 KI mice independent of treatment compared to wildtype mice. The cells were significantly hypertrophic in both DYT1 KI nerve-crushed mice with and without microglia depletion compared to their wildtype counterparts and DYT1 KI naïve mice.

In conclusion, extragenetic factors such as a sciatic nerve crush induce a dystonia-like phenotype in DYT1 KI mice, a microstructural analysis points towards changes of dopaminergic cells. Microglia dysfunction simulated by a partial depletion during the neurodevelopmental phase significantly aggravates the phenotype in these genetically predisposed mice, putting a spotlight on microglia playing a potential modifying role in the symptomatogene-

sis of DYT-TOR1A dystonia.

P3.03

Dopamine-Acetylcholine interplay at the pallidal-amygdala circuit in a DYT1 mouse model of Dystonia.

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Abstract

Introduction. DYT1 dystonia is an early-onset, hyperkinetic movement disorder caused by a deletion in the gene TOR1A, which encodes the protein torsinA. Abnormal firing activity of external globus pallidus (GPe,) has been reported both in dystonic patients and animal models, supporting an altered corticostriatal-GPe transmission. Because of its mutual projections to all Basal Ganglia nuclei, GPe is centrally placed in the motor selection process. Phasic changes in the firing activity of GPe neurons are associated with initiation of active movements, as well as with amplitude and direction of movement. Thus, alteration of neuronal activity of GPe neurons may unbalance whole BG activity and motor control. Interestingly, GPe has been reported to have a newly identified connection with structures involved in fear-and anxiety-related behaviors such as amygdala and in particular the CeA region (Giovanniello, J. et al; J. Soc. Neurosci. 2020). Non-motor symptoms, such as depression and anxiety, are commonly observed in some form of dystonia in addition to the characteristic motor symptoms (Kuyper, D. J. et al; Mov. Disord. 2011). Experimental research in both patients and rodents suggested a massive link between torsinA and dopaminergic signaling. Dopamine has a strong impact on the GPe by also modulating a class of pallidal cholinergic interneurons (ChAT+). Deficits in dopaminergic signaling have been documented in GPe of both DYT1 dystonia rodent models and patients as well, pointing at this subcortical area as a crucial region that, when altered, could brings about motor and cognitive dysfunctions by also affecting the amygdala.

Material and Methods. Ex-vivo electrophysiological patch-clamp recording at PV+ and ChAT+ pallidal neurons and neurons of amygdala at CeA region from wild-type and dystonic knock-in mice (Tor1a+/ΔGAG). Biochemical investigation by western blotting analysis of dopaminergic signaling of tissue from GPe and Amygdala from both mice group

Results. We found an unbalanced autonomous firing rate of ChAT+ neurons, with a reduced efficacy of dopamine DRD2-mediated response in Tor1a+/ΔGAG. Levels of dopamine transporter (DAT) in GPe tissue from Tor1a+/ΔGAG result significantly reduced. Finally, neurons of CeA from Tor1a+/ΔGAG show a clear increase in excitatory spontaneous synaptic currents (EPSCs).

Discussion. Our data show that dopaminergic signaling affect the GPe excitability through also cholinergic functional interplay. We found for the first time alterations of excitability of amygdala neurons, an anxiety-related area to date not considered in dystonia pathophysiology. By the pallidal-amygdala connection, GPe could have pivotal role underlying both motor and cognitive dysfunctions of dystonia.

P3.04

Cerebellar 5HT-2A receptor mediates stress-induced onset of dystonia

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Abstract

Stress is a major contributing factor to dystonia, a debilitating motor disorder that causes abnormal muscle contractions and posture. While the relationship between the serotonin (5HT) system and stress is well-known, its role in dystonia has remained unclear. Our research has revealed that 5HT neurons in the dorsal raphe nuclei (DRN) are connected to the fastigial deep cerebellar nuclei (fDCN) and that activation of these 5HT-fDCN neurons causes dystonia in normal mice. Additionally, we found that inhibiting 5HT-fDCN reduces dystonia in a genetic model of stress-induced dystonia, and that blocking 5HT-2A receptors can prevent the onset of dystonia. These findings provide new insights into the role of the serotonin system in dystonia and suggest possible treatment options for reducing symptoms in human patients.

P3.05

Investigating abnormal neurodevelopment during a critical window of vulnerability in an invertebrate model of dystonia

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Abstract

An emerging body of evidence suggests that altered neurodevelopment during critical windows of vulnerability is key to the pathogenesis of inherited dystonia [1]. Recent studies in a mouse model of DYT1 dystonia identified a specific developmental window in which forebrain loss of TOR1A disrupted motor control [2]. However, it is unclear whether similar pathogenic processes are involved in other forms of dystonia. Invertebrate models, such as the fruitfly *Drosophila melanogaster*, are a powerful tool to answer this question.

Here we investigate this question using a *Drosophila* model of paroxysmal non-kinesigenic dyskinesia (PNKD3), caused by a gain-of-function mutation in the *KCNMA1*/hSlo1 BK potassium channel [3]. In a recent paper we demonstrated that this model, with an equivalent mutation in the highly conserved gene *slowpoke* ($slo^{E366G/+}$), displays profound motor defects [4]. Here, we demonstrate that expression of SLO^{E366G} channels during a short critical window during neurodevelopment is necessary and sufficient to cause permanent motor defects in adult flies, while adult expression has no deleterious effect. Neurodevelopmental processes occurring during this critical window are altered: the highly stereotyped spontaneously-generated neuronal activity occurring at this time [5] is suppressed, and brain-wide expression of a key pre-synaptic protein is permanently reduced. Excitingly, preliminary data suggests that raising neuronal activity during the critical window partially rescues the motor phenotype.

These data present compelling evidence from an invertebrate model that PNKD3 is a neurodevelopmental disorder. This insight has clear therapeutic implications and makes an important contribution to the emerging understanding of critical windows in dystonia pathogenesis.

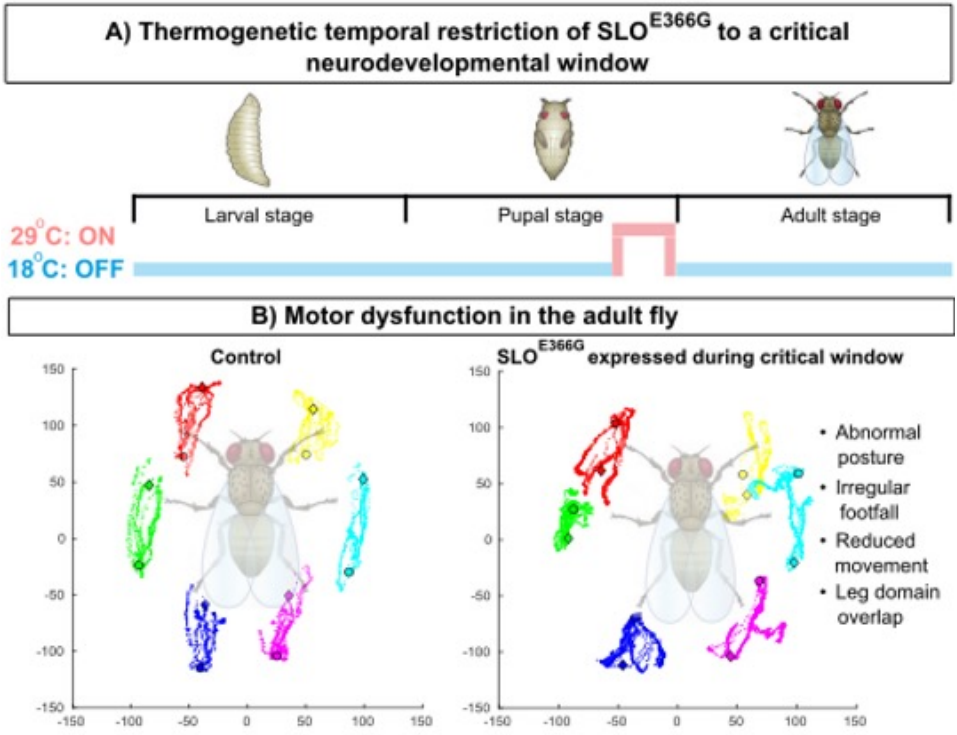

Fig 1: A) Temporal restriction of SLO^{E366G} expression to a critical neurodevelopmental window B) Simplified output of machine-learning based analysis of videos of fly locomotion indicating positions of each footclaw during ~3 strides. SLO^{E366G} expression only during the critical window causes postural and gait abnormalities in the adult fly.

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P3.06

Single-nuclear RNA-seq reveals loss of glutamatergic neuron in DYT6 dystonia

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Abstract

Mutations in THAP1 gene are responsible for DYT6 dystonia. Until now, the pathogenesis of DYT6 dystonia is not well characterized. In our previously study, we generated a THAP1 heterozygous knock-out rat model for DYT6 dystonia, and the bulk RNA-seq analysis revealed the involvement of pathways related to chemical synaptic transmission and nervous system development in DYT6 dystonia. However, the gene expression changes at the single-neuron level are not clear so far. Identifying gene expression changes at single-neuron level may help us to further understand the pathogenesis of DYT6 dystonia and also help us to find out new therapeutic target for this neurological disease.

In this study, we performed single-nuclear RNA-seq (snRNA-seq) to characterize gene expression change at single-neuron level of our DYT6 rat model. The rat striatal tissues were dissected from 9-month-old wild-type and THAP1 heterozygous knock-out rats. After homogenized the striatal tissues and sorted by fluorescence activated cell sorting (FACS) using anti-NeuN antibody, the single nuclei of neuron were isolated and used for single-nuclear RNA-seq and bioinformatic analyses.

The snRNA-seq analyses identified 14 different cell clusters in wild-type rat striatum, while two of them showed significant differences on both cell number and gene expression level when comparing THAP1 heterozygous knock-out rat striatum with wild-type control rat striatum. Cell number of one cluster, which highly expresses Adamts19 and Bcar3, is strikingly increased after heterozygous deletion of THAP1, while the cell number of another cluster, which specifically expresses markers for glutamatergic neuron, like Slc17a7 and Bdnf, is significantly decreased in the THAP1 heterozygous knock-out rat striatum compared to the control rat striatum.

These observations indicate that reduction of glutamatergic neurons might be associated to the pathogenesis of DYT6 dystonia. Our results may help us to understand the pathogenesis of DYT6 dystonia and also provide clues to find out new treatment for this disease.

P3.07

Central motor circuit changes in a new symptomatic rodent model for DYT-TOR1A dystonia

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Abstract

A three-nucleotide deletion in the TOR1A gene is associated with the occurrence of DYT-TOR1A dystonia. However, the presence of mutated torsinA does not necessarily result in overt dystonic symptoms. The presence of extragenetic factors such as environmental stressors could explain the incomplete penetrance of this hyperkinetic movement disorder. We have worked towards developing a translationally relevant rodent model of DYT-TOR1A dystonia by subjecting genetically predisposed, but asymptomatic rats to repetitive forelimb overuse. Furthermore, we have been exploring neurobiological and motor network changes that underlie the manifestation of dystonic movements and postures.

Rats overexpressing the mutated human TOR1A gene (ΔETorA) as well as their wildtype littermates were trained to perform a single-limb lever press task. Once trained, the rats performed 2000 repetitive lever presses/day with the right forelimb for 3 days/week for 5 weeks. The kinematic data were analyzed using a deep learning algorithm. At the end of 5 weeks of overuse, 18F-FDG PET/CT scans were performed in order to investigate central metabolic changes. The morphology of medium spiny neurons within the striatum was analyzed using a Sholl analysis.

Repetitive forelimb overuse in wildtype rats did not alter their success rate, whereas it gradually worsened over the experimental period in ΔETorA rats. ΔETorA rats exhibited progressively higher maxima of the trajectory with abnormal paw placement when pressing the lever. While the wildtype group displayed increasingly stereotypical trajectories of movement towards the lever, the ΔETorA rats instead exhibited a higher variability of the trajectory as measured by the standard deviation of the maximum of trajectory as the overuse progressed. Voxel-wise whole brain comparison of the 18F-FDG PET/CT scans revealed hypermetabolism in a cluster ΔETorA overuse rats compared to their naïve counterpart. A hypothesis-driven analysis of the identified clusters comparing the four groups revealed significant interactions of overuse and genotype indicative of “dystonia clusters”. On a microstructural level, the spine density of striatal medium spiny neurons revealed a significant interaction of radius, overuse and genotype with a decrease in spines in wildtype overuse

animals compared to their naïve counterparts. This effect was less pronounced in ETorA overuse animals with even a suggested increase in spine density at certain radii.

Our results demonstrate that when genetically predisposed DYT-TOR1A rats encounter environmental stressors such as an unphysiological overuse, motor abnormalities as well as central motor circuit changes occur. These rodents represent a novel, translationally relevant model of symptomatogenesis in DYT-TOR1A dystonia.

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P3.08

Disrupting eIF2α signaling evokes dystonia-like movements

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Abstract

Introduction: Despite progress in dystonia gene discovery and understanding brain circuit abnormalities leading to dystonia, the molecular and cellular mechanisms between genes and circuits has remained enigmatic. Mouse and human DYT1 brain tissue studies have identified links between dystonia and perturbations of the cellular stress-response protein, eIF2α. However, whether eIF2α creates changes leading to dystonia is unknown.

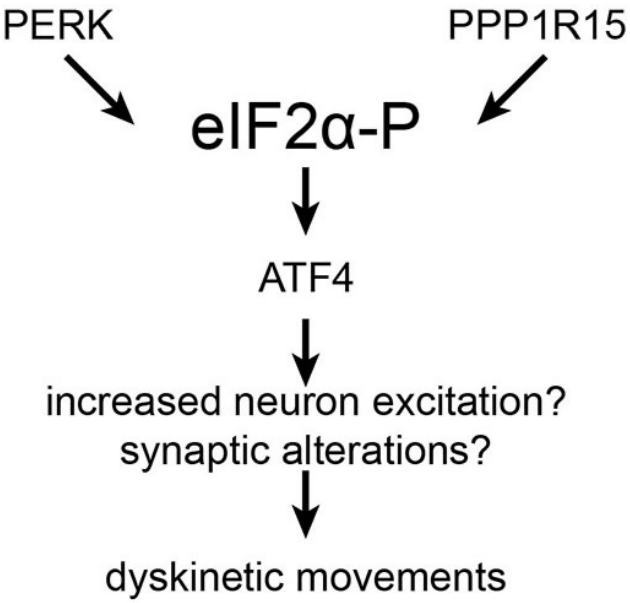
Materials and Methods: With cytotoxic stressors, eIF2α is phosphorylated (eIF2α-P) to decrease global protein translation and upregulate stress response gene expression. Phosphorylation of eIF2α promotes long-term depression while de-phosphorylation favors long-term potentiation for regulating synaptic connectivity and circuit formation. Here, we directly test whether increases/decreases of eIF2α-P can affect motor function in a Drosophila model. We find altering eIF2α signaling produces abnormal posturing and disordered movements in flies, recapitulating the dystonia-like dyskinetic movements previously observed in the DYT1 fly model. We analyze cell type specificity, altered neuronal excitability, and synaptic connectivity in flies with increased/decreased eIF2α-P.

We used loss-of-function alleles of eIF2α kinase (PEK) to increase and phosphatase (PPP1R15A) to decrease eIF2α-P. We used Gal4 drivers for cell-type specific overexpression of the eIF2α-P kinase, phosphatase, and htorΔE (DYT1). Alterations to eIF2α-P were confirmed via western blot. Motor function assays performed in 14-day old adult flies. Axon terminal size assayed using anti-HRP to visualize neuron membrane and phalloidin for muscle.

Results: Genetically increasing or decreasing eIF2α-P in whole animals or neurons impairs locomotion as measured by distance traveled. Overexpression of the stress response gene, ATF4, also impaired locomotion. We found suppressing eIF2α-P in glutamatergic, dopaminergic, and D1-type neurons decreased distance traveled. Suppressing eIF2α-P or overexpressing human DYT1 allele htorΔE in cholinergic neurons elicited dyskinetic dystonia-like movements with mechanosensory stimulation. Decreased or increased of eIF2α-P in D2-receptor neurons disrupted the motor control of landings, elicited dyskinetic movements, and bidirectional alterations in distance traveled. Finally, elevated eIF2α-P correlated with increased axon terminal size, revealing alterations at the synapse.

Discussion: Our findings support a crucial role of eIF2α-P regulation in motor control, with key roles for dopaminergic signaling, particularly D2 receptors, and cholinergic neurons. We observed dyskinetic movements in mutant animals with either increased or decreased eIF2a-P, providing proof of principle data that perturbations in the eIF2a axis directly im-

pact motor function. We also saw enhanced synaptic connectivity as a potential structural basis linking disrupted eIF2α-P and increased ATF4 with changes in motor control. Overall, we show molecular alterations in eIF2α-P can create neuron/circuit changes and result in dystonia-like movements.



P3.09

Central pattern generator dysfunction is a common phenomenon across diverse *Drosophila* models of inherited dystonia

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Abstract

Dystonia is a highly debilitating movement disorder with limited therapeutic options. Mutations in a broad range of genes with distinct functions have been linked to inherited dystonia. However, whether there are common pathophysiological processes shared across diverse forms of dystonia remains unclear, as are the key neural circuits responsible for dystonic movements. The genetically tractable model *Drosophila* provides a unique platform to address these questions.

Abnormal co-contraction of antagonistic muscles is a central feature of dystonia, and reduced reciprocal inhibition within spinal central pattern generator (CPG) circuits has also been reported in dystonia patients[1,2]. Therefore, we assessed whether CPG activity was disrupted in a range of *Drosophila* dystonia models. GCaMP-based optical imaging was used to record CPG activity in the *ex vivo* ventral nerve cord (analogous to the spinal cord) of larval *Drosophila* harbouring mutations in an array of dystonia-related genes: TOR1A/*Torsin*; KCNMA1/*slo*; TBC1D24/*skywalker* and LAMB1/*LanB1*.

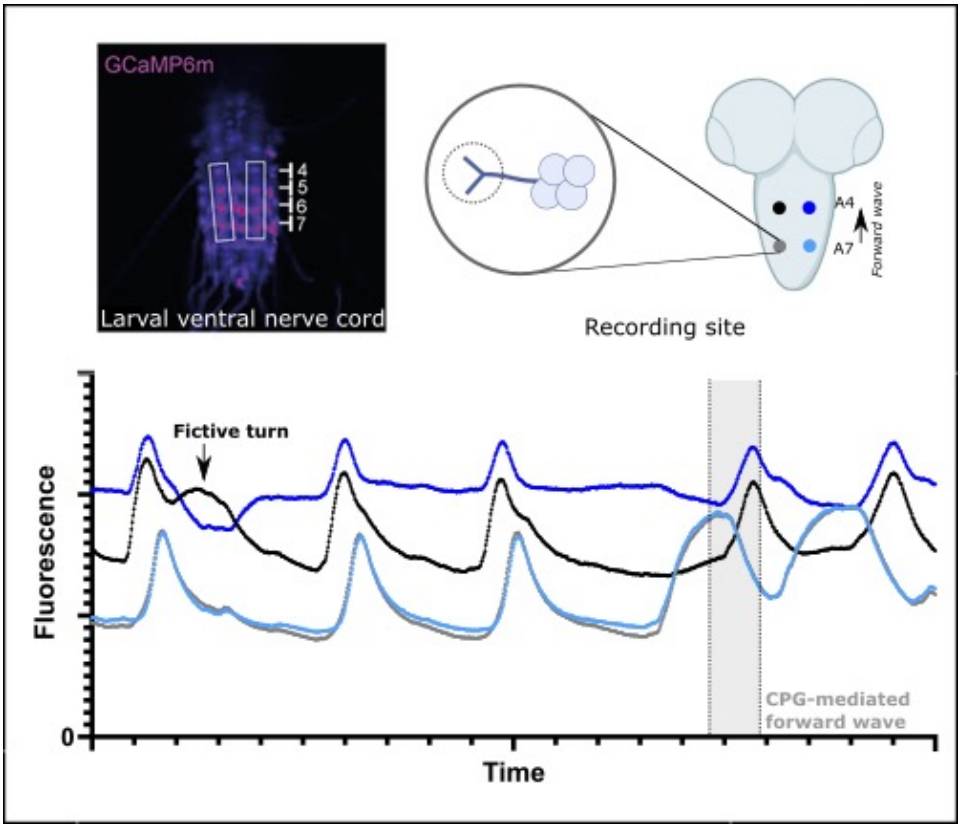

Figure: CPG-driven peristaltic behaviour recorded from *Drosophila* ventral nerve cord motor neurons

All dystonia-linked genes that were assessed exhibited dysfunctional CPG activity compared to control. The KCNMA1/*slo* gain-of-function mutant[3] exhibited extremely disrupted CPG activity with no forward waves and almost no fictive turn activity. The TBC1D24/*skywalker Drosophila* model of exercise-induced dystonia[4] again exhibited a decrease in forward wave propagation with no observable fictive turns. The LAMB1/*LanB1* overexpression model, associated with dystonia-linked movement disorders in mouse models[5], caused a reduction of forward wave propagation time and frequency as well as a reduction in the number of fictive turns. Finally, a *Torsin* knockout *Drosophila* model of TOR1A (DYT1) dystonia[6] also exhibited a decrease in the forward wave propagation time but instead with no alteration in the number of fictive turns.

Drosophila models of dystonia provide an effective platform to assess disrupted CPG activity. Our work suggests that CPG dysfunction is a common process disrupted by distinct dystonia-linked mutations. Through ongoing experiments, we aim to define the cellular

basis of this phenomenon.

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P3.10

Patterned activation of cerebellar neurons differentially drives dystonic twisting and tremor in mice.

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Abstract

Introduction: Identifying the neural mechanisms that give rise to the diverse manifestations of dystonia remains a major goal in dystonia research. Progress has been hindered by the complicated heterogeneity of the disease and the involvement of many brain regions. Dystonic symptoms can appear as twisting postures, tremorous activity, or a combination thereof and in addition, in susceptible individuals these motor problems can occur spontaneously or be induced by specific tasks. Although enlightening, evidence suggesting that dystonia is a motor network disorder has nevertheless further complicated efforts to pinpoint how different brain regions contribute to distinct dystonic behaviors. Recent findings support a cerebellar contribution to dystonia, showing that aberrant cerebellar activity is necessary and sufficient for some forms of dystonia. However, such studies typically alter multiple types of cerebellar neurons and don't distinguish if specific circuits promote distinct dystonic symptoms. It is also unclear which connected brain regions are impacted by abnormal cerebellar activity during dystonic behavior. Here, we test whether a newly identified long-range cerebellar pathway defines the presentation of dystonic symptoms.

Materials and Methods: To address these problems, I devised an optogenetics approach to selectively manipulate inhibitory cerebellar nuclei neurons (iCN), which were only recently shown to project out of the cerebellum. We tested how iCN activity shapes behavior when only this pathway is altered (*Ptf1a^{Cre};Rosa$^{lsl\text{-}ChR2}$* mice that are controls with normal behavior before optogenetic stimulation) and when all cerebellar outputs are defective (*Ptf1a^{Cre};Vglut-2$^{fx/fx}$;Rosa$^{lsl\text{-}ChR2}$* that already have dystonia because both the iCN and the excitatory cerebellar nuclei neurons are affected). I measured diverse dystonic behavioral outcomes using quantitative tools including electromyography, tremor recordings, and a dystonia rating scale.

Results: I found that 10Hz sinusoidal photoactivation of the iCN in dystonic *Ptf1a^{Cre};Vglut2$^{fx/fx}$;Rosa$^{lsl\text{-}ChR2}$* mice induced severe and consistent dystonic postures and tremor, which usually occur spontaneously but intermittently in this model. Interestingly, the 10Hz sinusoidal stimulation only generated tremor in the healthy *Ptf1a^{Cre};Rosa$^{lsl\text{-}ChR2}$* mice. Changing the stimulation pattern to 50Hz square pulses initiated dystonic postures on-demand in the *Ptf1a^{Cre};Vglut2$^{fx/fx}$;Rosa$^{lsl\text{-}ChR2}$* mice with no responses in *Ptf1a^{Cre};Rosa$^{lsl\text{-}ChR2}$* mice. Photostimulating the iCN terminals in the subthalamic nucleus, zona incerta, and thalamic reticular nucleus, known cerebellar targets that are involved in dystonia, did not acutely induce any dystonic behaviors in *Ptf1a^{Cre};Vglut2$^{fx/fx}$;Rosa$^{lsl\text{-}ChR2}$* mice.

Discussion: These data suggest that specific patterns of iCN activity can drive dystonic behaviors, although they may mediate these behaviors through non-canonical circuits that could be therapeutically promising.

P3.11

The DYT1 transcriptome in human cells unravels pathogenic pathways.

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Abstract

Dystonia is a movement disorder characterised by involuntary muscle contractions and abnormal posture with twisting of one or more parts of the body. The commonest genetic form of dystonia is caused by mutations in *TOR1A* gene (DYT1) often with an early-onset severe outcome but reduced penetrance. In many cases, the cause of dystonia is not known and very few studies in humans have been performed. The aim of this project is to study post-mortem brain tissues, iPSC and iPSC-derived neurons from controls and DYT1 pathogenic carriers of the trinucleotide deletion (GAG c.907–909) to find transcriptomic signatures that underlie abnormal cellular pathways.

Fibroblasts from 5 controls and 5 symptomatic DYT1 patients were reprogramed using episomal plasmid transduction and used to derive medium spiny and cortical neurons. Brain tissues from 3 DYT1 patients and 3 controls were also included. RNA was extracted from mature neurons (80 DIV and 100 DIV) and brain tissues (frontal cortex and basal ganglia), and sent to Novogene Co for transcriptome profiling and differential gene expression analysis.

We have identified genes with consistent differential expression patterns between patients and controls in neuronal cell lines and brain tissues (96 upregulated and 73 downregulated) in DYT1 samples vs. controls.

Further analysis is ongoing to identify transcripts that show the greatest change and have biological relevance for dystonia. This will be followed with functional analysis to identify cell specific pathways involved in dystonia to develop therapeutic targets and biomarkers for future clinical trials.

We would like to thank all patients, families and donors for their contribution. We would also like to thank Rosetrees Trust Foundation, UCLH BRC for the funding and Novogene Co for the analysis and logistic support.

P3.12

Characterizing striatal microcircuitry in a mouse model of early-onset DYT1 dystonia

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Abstract

Dystonia is neurodevelopmental disease characterized by involuntary twisting movements. A TOR1A mutation that impairs torsinA function causes early-onset DYT1 dystonia. A profound challenge to treating DYT1 dystonia is our limited understanding of the dysfunctional circuit(s) driving abnormal movements. Neuroimaging findings using functional MRI (fMRI) demonstrate altered activity of the corticostriatal circuit in DYT1 dystonia, but the substrates underlying blood flow changes (BOLD signal activation) remain unclear. To define these substrates, we engineered a DYT1-based mouse model that mimics the natural history of dystonia by conditionally deleting TOR1A from forebrain GABAergic and cholinergic neurons ("Dlx-CKO"). In this model, robust motor abnormalities emerge during juvenile development in Dlx-CKO mice and persist into adulthood. Accompanying these abnormal movements are morphological and electrophysiological alterations in striatal cholinergic interneurons. Both re-expressing TOR1A selectively in striatal cholinergic interneurons and administering anticholinergic drugs used clinically suppress abnormal movements in Dlx-CKO mice, providing strong support for a key role of cholinergic interneurons in dystonia-like behavior as well as model face and therapeutic validity. Subsequent imaging of striatal cholinergic interneurons throughout development, followed by detailed morphological and synaptic analyses, reveal deficits in dendritic outgrowth and afferent recruitment, just prior to the onset of abnormal behavior. We hypothesize that early structural and synaptic alterations in cholinergic interneurons predispose the striatal microcircuit to lifelong dysfunction. Future studies aim to characterize the functional significance of aberrant cholinergic interneuron development on motor circuit performance and the manifestation of dystonia-like behaviors. Understanding DYT1 circuit development and functioning over time will ultimately inform more targeted therapeutic interventions.

P3.13

Adult loss of Gnal in the striatum or cerebellum causes dystonia phenotypes in mice

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Abstract

Loss of function mutations in *GNAL*, which encodes for a unique alpha subunit of heterotrimeric G protein, $G\alpha_{olf}$, are causative for an adult onset form of dystonia. $G\alpha_{olf}$ has a unique expression profile where it replaces $G\alpha_{s}$ in the striatum and is expressed in Purkinje Cells of the cerebellum. Both of these nuclei are consistently linked to dystonia pathophysiology, and suggests that $G\alpha_{olf}$ may critically regulate these cells and the circuits they are involved in to mechanistically cause dystonia symptoms. However, current models of *GNAL* linked dystonia do not have overt dystonic phenotypes, which makes tying cellular and circuit dysfunction to distinct dystonia phenotypes challenging. Using a new model of *GNAL* where we floxed exons 3 and 4 of *Gnal*, we used viral delivery of cre or well established cre lines to selectively remove *Gnal* embryonically or in adulthood in specific cell populations. Interestingly, we found that viral mediated adult knockout, but not embryonic, knockout, of *Gnal* causes dystonic like motor phenotypes in mice when removed from the cerebellum or striatum of *Gnal* flx/flx mice. These behavioral phenotypes correlate to altered intrinsic properties of striatal spiny projection neurons as determined through patch-clamp electrophysiology. These findings suggest that loss of $G\alpha_{olf}$ expression causes dysregulated striatal or cerebellar function which leads to subsequent basal ganglia circuit dysfunction to cause dystonia. Adult mediated knockout of Gnal may serve as a unique model to mechanistically determine the underlying circuit dysfunction that causes dystonia, and as a novel testing platform for new therapeutic strategies for adult onset dystonia.

P3.14

Striatal synaptic endophenotype in the Tor1a+/ gag mouse model of DYT1 dystonia

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Abstract

Introduction: Impairment of synaptic activity is a hallmark of movement disorders such as dystonia. In particular, DYT1 dystonia is characterized by reduced penetrance and several endophenotypes converging on synaptic dysfunction have been shown in different experimental models. Intriguingly, torsinA (TA), the protein causative of DYT1 dystonia, has been found to interact with alpha-synuclein (α-Syn). Both proteins act as molecular chaperones and control synaptic machinery. Despite such evidence, the role of α-Syn in dystonia has never been investigated. We explored whether α-Syn and N-ethylmaleimide sensitive fusion attachment protein receptor proteins (SNAREs), that are known to be modulated by α-Syn, may be involved in DYT1 dystonia synaptic dysfunction.

Materials and Methods: We used electrophysiological and biochemical techniques to study synaptic alterations in the dorsal striatum of the Tor1a$^{+/\Delta gag}$ mouse model of DYT1 dystonia.

Results: In the Tor1a$^{+/\Delta gag}$ DYT1 mutant mice, we found a significant reduction of α-Syn levels in whole striata, mainly involving glutamatergic corticostriatal terminals. Strikingly, the striatal levels of the vesicular SNARE VAMP-2, a direct α-Syn interactor, and of the transmembrane SNARE synaptosome-associated protein 23 (SNAP-23), that promotes glutamate synaptic vesicles release, were markedly decreased in mutant mice. Moreover, we detected an impairment of miniature glutamatergic postsynaptic currents (mEPSCs) recorded from striatal spiny neurons, in parallel with a robust alteration in release probability. Finally, we also observed a significant reduction of TA striatal expression in α-Syn null mice.

Discussion: Our data demonstrate an unprecedented relationship between TA and α-Syn, and reveal that α-Syn and SNAREs alterations characterize the synaptic dysfunction underlying DYT1 dystonia.

P3.15

Spike-triggered adaptive closed-loop cerebellar Deep Brain Stimulation (DBS) for dystonia

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Abstract

Despite a wide range of manifestations and causes, current hypotheses suggest that dystonia arises from a faulty network that includes the cerebral cortex, basal ganglia, and cerebellum. Cerebellar nuclei (CN) neurons, the main output of the cerebellum, may be particularly susceptible to dystonia-related insults. Here, I leverage this CN sensitivity to develop a "signature signal" therapeutic approach for restoring movement in dystonia. We previously generated Ptf1aCre/+;Vglut2fl/fl mutant mice with selective loss of glutamatergic neurotransmission at climbing fiber to Purkinje cell synapses. These mice have severe early-onset dystonia. In this model, abnormal Purkinje cell "burst" activity drives similar erratic firing downstream in the connected CN neurons. Regardless of the initial insult and mechanism of action, one common consequence among several models of dystonia is the abnormal irregular firing of the CN. We also showed that pharmacological inhibition and DBS of the CN in Ptf1aCre/+;Vglut2fl/fl mice reduced many, but not all, dystonia symptoms. Current DBS targets (thalamus, subthalamic nucleus, internal segment of the globus pallidus) are adopted from Parkinson's disease and were not optimized for dystonia, often ignoring dynamic cerebellar outflow to the motor network. A major problem is that the current chronic stimulation strategies fail to account for the progression of aberrant neuronal dynamics in the cerebellum and the greater motor network in real-time. To address this, I am testing the hypothesis that the unique pathophysiological cerebellar neural signals can serve as robust biomarkers for triggering an adaptable closed-loop DBS response to restore movement in a mouse model of dystonia (Ptf1aCre/+;Vglut2fl/f). A closed-loop approach with more robust triggers and clearer feedback signals will aid in identifying specific neurophysiological parameters that underlie different features of dystonia, such as twisting postures, co-/over-contractions, and initiation and progression of tremor; the goal is to provide accurate dialing of DBS for a specific disease symptom. This work ultimately models unique neurophysiological signatures of a dysfunctional CN outflow that could drive different aspects of dystonia and addresses a universal problem with chronic DBS, which is the failure to adapt in real-time to changing neuronal dynamics. Therefore, a major advance that my approach offers is an online and progressive "dosing" of DBS that monitors the current state of disease initiation, progression, and severity with millisecond precision. This work will address a major gap in treatment options for dystonia by defining disease-specific neural targets for designing a customizable therapy that is self-controlled with great precision.

P3.16

Specific role of dopaminergic neurons in DYT1 dystonia striatal dysfunction

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Abstract

Introduction: DYT1 early-onset torsion dystonia (DYT-TOR1A) is caused by a 3 base-pair in-frame deletion (ΔGAG) in the TOR1A gene. The mechanism by which the mutation causes dystonia is unclear, but a great deal of evidence points to alterations in both dopaminergic and cholinergic neurotransmission, whereby dopamine (DA) release is reduced and the acetylcholine tone is increased. Nevertheless, the specific cell types and striatal microcircuits involved in the pathophysiology of dystonia are still unknown. Recent work showed that the expression of Tor1a(ΔGAG) mutant gene in DA neurons reduces striatal DA release.

Materials and Methods: Here we performed an electrophysiological and biochemical investigation to analyze the specific contribution of dopaminergic neurons to the striatal microcircuit alterations in DYT1 dystonia.

Results: We show that the selective expression of the Tor1a(ΔGAG) mutant gene in DA neurons reproduces the striatal dysfunctions previously reported in the DYT1 knock-in mouse model, expressing ubiquitously the mutation. In particular, we observed both a paradoxical excitation of striatal cholinergic interneurons in response to the activation of dopamine D2 receptors, and an impairment of corticostriatal long-term synaptic depression (LTD).

Discussion: Our results demonstrate a central role of dopaminergic dysfunction in the expression of the DYT1 synaptic endophenotype, shedding light on the neurobiological mechanisms involved in dystonia pathophysiology.

P3.17

Striatal receptors signaling dysfunction in a DYT25 dystonia model

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Abstract

Introduction: DYT25 (DYT-GNAL) is an autosomal-dominant form of focal dystonia typically characterized by craniocervical distribution and adult-onset, caused by loss-of-function mutations of the GNAL gene, encoding Gαolf, a Gs-protein isoform. Gαolf is highly expressed in the striatum, where it couples to adenosine A2A (A2AR) receptors in indirect pathway projection neurons (SPNs) and dopamine D1 (D1R) receptors in direct pathway SPNs, to activate adenylyl cyclase type 5 (AC5) and production of cAMP, a ubiquitous second messenger critical for many fundamental neuronal mechanisms, including synaptic plasticity and neuronal excitability. In addition, Gαolf is co-expressed with Gs in striatal cholinergic interneurons (ChIs), where it contributes to both D1R and A2AR signaling. Complete loss of Gαolf results in hyperkinetic movements in mice, indicating its involvement in motor function. However, how GNAL loss of function contributes to striatal synaptic dysfunction is still unclear.

Materials and Methods: By means of a combined electrophysiological and molecular approach, we investigated striatal adenosine and dopamine post-receptor signaling in a GNAL+/- rat model, where we previously reported the loss of dopamine D2R-dependent corticostriatal long-term synaptic depression, and its rescue by A2AR antagonism.

Results: We found that total striatal A2AR levels were increased, whereas D2R expression along with the basal levels of AC5 were decreased, in GNAL+/- rats. In GNAL+/- ChIs, we found a significantly attenuated excitatory effect produced by both D1R agonists and AC5 activation. While in wild-type animals A2AR antagonists potentiate the inhibitory action of D2R agonists on ChIs spontaneous firing activity, this effect was not observed in GNAL+/- ChIs, indicating an abnormal A2AR-D2R interaction. Accordingly, we also found altered striatal levels of the D2R interacting proteins RGS9-2, spinophilin, Gβ5, and β-arrestin2.

Discussion: Altogether, our findings demonstrate a profound alteration in the expression and signal transduction of striatal adenosine and dopamine receptors in a DYT25 dystonia model.

P3.18

DYT1 DYSTONIA: NEUROPHYSIOLOGICAL ASPECTS

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Abstract

Introduction: The aim of this study was a comparative analysis of the neuronal activity of globus pallidus in patients with DYT1 dystonia and idiopathic dystonia.

The DYT1 mutation leads to dysfunction of the torsin A protein, resulting in increased activation of striatum neurons that suppress the globus pallidus. We wonder how DYT1 mutation can affect the electrophysiological properties of neuronal activity in both segments of globus pallidus (GPe and GPi).

Materials and Methods: The data were obtained during stereotactic implantation of electrodes for deep brain stimulation (DBS). During the operations we performed microelectrode recording of the single unit activity in the GPe and the GPi in 5 patients with DYT1 and in 6 patients without DYT1. We performed offline analysis of neuronal activity parameters and visualized neurons localization in Lead-DBS. All neurons were divided into 3 neuron activity types (burst, pause and tonic) depending on neuron activity pattern by using unsupervised clusterization method.

Results: In total, the activity of 662 neurons were analyzed. We found a significantly reduced firing rate, burst index and burst rate in both segments of the globus pallidus in DYT1 patients. Also, we found significantly increased interburst interval, preburst interval and pause index. Clusterization showed that in the GPe the differences between DYT1 and non-DYT1 neuron activity parameters were significant only in burst neurons, while in the GPi the same differences were observed in both burst and pause neurons. The visualization showed diversity localization of pause neurons in the GPe.

Discussion: Obtained results indicate that DYT1 neurons tend to be more 'pausy' and less 'bursty'. Also, the similarity of changes in neural activity in GPe and GPi points on a common pathological focus for these structures, which may be located in the striatum. Difference in the location of pause neurons in the GPe may be due to strong striatal influence which alters the activity pattern of the neurons.

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P3.19

Cerebellar network in a model of paroxysmal dystonia

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Abstract

Introduction: Dystonia is a neurological syndrome that alters muscle control for voluntary movement and sustained posture. Although the basal ganglia play a role in dystonia, an abnormal cerebellar function is also involved. Deep brain stimulation (DBS) is a standard treatment option for drug-refractory dystonia, and the most promising targets are the Globus Pallidus internus (GPi) or the subthalamic nucleus. The mechanisms of DBS, however, are as yet unclear. In this context, we were interested in the impact of DBS on cerebellar activity and, specifically, the role of glutamatergic transmission in DBS-induced changes.

Materials and Method: We explored this question in a genetic animal model of primary paroxysmal dystonia (dtsz mutant hamster) and appropriate controls, bilaterally implanted with bipolar DBS electrodes in the entopeduncular nucleus (homolog to the GPi in humans).

The dtsz hamster is known for alteration in the ganglia–thalamocortical circuit, cortico-striatal circuit, and limbic structures. These further support us in investigating the cerebellum network, especially the synapse plasticity and the expression of NR2A subunits of NMDA since we already know that the NR2A/NR2B ratio is increased in the striatum of dystonic hamsters.

To gauge cerebellar activity, parasagittal slices were recorded with a high-density microelectrode array (200 Qm thick) (HD-MEA; 3Brain AG). To analyze the involvement of the glutamatergic system, cerebellar slices were treated with 50 QM of PEAQX, an antagonist selective GluN2A, and their activity compared to baseline recordings in Krebs solution (10 minutes, 2 mL/min, at room temperature).

Results: Our previous results indicate that blocking the NMDA receptor with PEAQX might modulate the Purkinje cell spike firing concerning amplitude and frequency differentially between the DBS and sham-DBS groups.

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P3.20

Luteolin disrupts the interaction between PKR and PACT to prevent pathological and maladaptive ISR in DYT-PRKRA.

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Abstract

Introduction: DYT-PRKRA is caused by mutations in the PRKRA gene [1], which encodes for PACT, the protein activator of interferon-induced, double-stranded RNA (dsRNA)-activated protein kinase PKR [2]. PACT causes PKR's catalytic activation by a direct binding in response to stress signals and activated PKR phosphorylates the translation initiation factor eIF2α. Phosphorylation of eIF2α is the central regulatory event that is part of the integrated stress response (ISR), an evolutionarily conserved signaling network essential for adapting to environmental stresses [3]. A dysregulation of either the level or the duration of eIF2α phosphorylation causes the normally pro-survival ISR to become pro-apoptotic.

Materials and Method: Our research previously established that eight reported DYT-PRKRA mutations lead to enhanced PACT-PKR interactions causing hyperactivation of PKR, dysregulation of ISR and an increased sensitivity to apoptosis [4, 5]. In the present study, we wanted to determine if disrupting the heightened PACT-PKR interaction in DYT-PRKRA patient cells can bring homeostasis and protect from increased apoptosis. We previously identified luteolin, a plant flavonoid, as an inhibitor of the PACT-PKR interaction using high-throughput screening of chemical libraries [6]. We determined the ability of luteolin to protect cells using biochemical and molecular techniques to study the ISR and apoptosis in DYT-PRKRA.

Results: Our results indicate that luteolin is markedly effective in disrupting the pathological PACT-PKR interactions to protect DYT-PRKRA cells against apoptosis, thus suggesting a therapeutic option for using luteolin for DYT-PRKRA and possibly other diseases resulting from enhanced PACT-PKR interactions.

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P3.21

Application of exome sequencing to solve the genetic etiology in a large dystonia sample

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Abstract

Introduction: Dystonia is a rare movement disorder with relevant clinical and genetic heterogeneity. The genetic etiology in most patients remains elusive, even though the disorder has a high heritability (>25%). Using a large patient sample, this study aims to further elucidate the genetic causes underlying dystonia.

Materials and Method: About 2,000 dystonia patients were mainly selected from two large dystonia registries (DysTract [https://www.isms.uni-luebeck.de/en/research/dystract/] and the Dystonia Coalition [https://dystonia-foundation.org/research/dystonia-coalition/]) based on inconclusive prior hot spot screening for about 300 known pathogenic variants in dystonia genes or GenePanel analysis. Whole-exome sequencing was performed at a median coverage of 102 reads. Established preprocessing tools, along with deepvariant and GLnexus, were used to create the cohort vcf file. As a first step, we searched for rare variants (MAF<0.001) in genes previously implicated in dystonia (n=412). Variants were Sanger confirmed and tested for segregation when possible.

Results: The majority of selected patients presented with isolated dystonia (~90%; thereof ~55% focal, 30% segmental, and 15% generalized dystonia); the remainder had combined dystonia (with parkinsonism or myoclonus, ~5%) or dystonia as part of a complex neurological syndrome (~5%). The median age at onset (AAO) was 33 years (interquartile range (IQR): 22-44); 40.5% of patients were male; family history was positive in 24.2% of index patients.

We identified 132 patients (6.6%) with pathogenic or likely pathogenic variants (according to the VarSome ACMG classifier; version 11.6.4) in 31 genes. The median AAO in this group was 13 years (IQR: 7-27.5); 51% presented with generalized, 18% with segmental, and 22% with focal dystonia. Additionally, we found 162 patients (8.1%) with variants of uncertain significance in 28 genes.

Genes with >10 mutation carriers included *GCH1, SGCE, THAP1,* and *VPS16*, while the GAG deletion in *TOR1A* was excluded by prescreening. (Likely) pathogenic variants were also found in *ADCY5, ANO3, ATP1A3, CACNA1A, CHD6, CHD8, EIF2AK2, GNAL, GNAO1, GNB1, HS1BP3, IRF2BPL, KCNN2, KLC1, KMT2B, PDE10A, PNKD, PRKCG, PRRT2, RELN,*

RHOBTB2, SETX, STUB1, TCF20, TUBB4A, and *ZMYND11*. At least four variants occurred de novo, supporting pathogenicity.

Discussion: This study demonstrates the value of exome sequencing in establishing diagnoses in dystonia, a disease for which variants in more than 400 genes have been linked to diverse clinical expressions. Despite prescreening and selecting presumably mutation-negative patients, we found (likely) pathogenic variants in 6.6% of patients in well-established and newly identified dystonia candidate genes. Additional analyses of our exome datasets will likely further expand the growing list of dystonia genes.

P3.22

Use of Induced Pluripotent Stem Cells for Delineating the Consequence of Impaired Purine Recycling in Developing Dopamine Neurons

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Abstract

Introduction: Purines are essential for many cellular processes including DNA synthesis and ATP. Cells maintain purine pools using two main pathways: de novo purine synthesis and purine recycling. Lack of purine recycling is associated with abnormal brain function in Lesch-Nyhan disease (LND), which is associated with behavioral changes, cognitive impairment, and dystonia. These problems are thought to reflect abnormal development or function of brain dopamine neurons. LND is caused by mutations in the HPRT1 gene, which encodes a purine recycling enzyme, HGprt. One of the main problems in studying LND pathogenesis has been lack of a good model to study human brain development. Therefore, we aimed to establish a bank of human-derived induced pluripotent stem cells (iPSC) from patients as well as gene edited lines to study purine metabolism during differentiation of midbrain dopamine neurons.

Materials and Methods: Fibroblasts from patients with 4 LND and 4 matched controls were reprogrammed into iPSCs. iPSCs were validated for pluripotency. A floor-plate midbrain neuronal induction method was used to develop dopamine neurons. The numbers of dopamine neurons as well as dopamine markers were assessed. The levels of purine enzymes and purine levels were measured at 4 time points during differentiation. After studying patient-derived lines, the same studies were repeated using 3 gene-edited lines with stop codon mutations in the HPRT1 gene as well.

Results: Twelve iPSC clones from four patient fibroblasts as well as 12 matched controls were developed. Four biologically distinct clones of patient-derived lines alongside 4 control lines were differentiated into dopamine neurons. Neurons expressed high levels of tyrosine hydroxylase and dopamine in both LND and control lines. Levels of TH correlated with levels of dopamine, but there were no differences between the LND and control lines, in part due to large variability between lines. Purine contents were also similar in LND and control lines, except for high levels of hypoxanthine in the LND lines. These results imply compensation by the de novo purine synthesis pathway. Similar results were found using 3 gene edited lines with c.508C>T stop codon knock-in, which causes complete deficiency of the enzyme.

Discussion: iPSCs have different capacity for differentiating into dopamine neurons. Neurons without ability to recycle purines appear to differentiate normally, but they show evidence for changes in purine metabolism that imply compensation by purine synthesis.

P3.23

Depotentiation in human dystonia: A hypothesis

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Abstract

Introduction: The possibility of increased plasticity in dystonia has been suspected for some time given that repetitive activity over long periods seems to be a trigger for its development in many cases of focal dystonia. Moreover, it may take several months to achieve maximum clinical benefit of deep brain stimulation (DBS) in patients with dystonia. The slowly progressive nature of changes suggests that a process of progressive plasticity accompanies the long-term effects of globus pallidus DBS. [1] Several studies showed dystonia patients have impairment in specific cognitive domains reflecting abnormalities in the plasticity. [2]

Human studies: An increase of plasticity was found within the blink reflex circuits in patients with blepharospasm.[3] In another study, patients with cervical dystonia were found to have behavioral reversal learning deficits. In writer's cramp studies, both LTP-like and LTD-like facilitatory and inhibitory effects on TMS-evoked motor evoked potentials are enhanced.[4]

Animal models: In different rodent models of DYT1 dystonia, striatal medium spiny neurons exhibit a loss of LTD and enhanced LTP. Low-frequency stimulation can induce depotentiation in normal mice. However, low frequency stimulation fails to induce depotentiation in mutant Torsin A mice. Both LTD and depotentiation were rescued in mutant mice either by lowering endogenous acetylcholine levels or by antagonizing muscarinic M1 receptors. [5]

The role of depotentiation abnormality in dystonia

Results: It can be postulated that in dystonic patients during skilled motor practice, there is an increased tendency to form associations between sensory inputs and motor outputs. This may lead to the consolidation of abnormal motor engrams containing excessive facilitatory motor commands, which could underlie the overflow phenomena typical of dystonia. This could also explain why the abnormal plasticity of dystonia appears difficult to reverse. depotentiation should be able to be tested in dystonia patients.

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P3.24

Applied anatomy retraining protocol for embouchure dystonia in musicians

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Abstract

Introduction: Embouchure dystonia (ED) is a task-specific form of musicians' dystonia, a motor control disorder characterised by features such as tremor or overactivity of one or more oro-facial muscles, leading to an inability of the musician to play. This condition is regarded as difficult to treat, with no evidence informed treatment guidelines available to retrain this condition.

Methods: Formative evaluation was used to design an off-instrument embouchure re-training program, utilising a literature review, applied anatomy, fMRI footage analysis and clinical expertise. The first stage involved a comprehensive screening and diagnosis of embouchure dystonia by a specialist neurologist. Nine musicians diagnosed with ED, 6 males and 3 females, 8 brass musicians and one flautist, volunteered to participate in the process evaluation stage of this project.
Participants were guided through the ED protocol by a physiotherapist on average twice weekly for the first 6 months and 4-weekly the second 6 months until re-evaluated by the neurologist at 12 months. Due to the Covid 19 pandemic, nearly all training was conducted online via Zoom.

Results: Results included the neurologist evaluation of changes observed between initial diagnosis and review at 12 months, and results from a purpose-designed survey using a mix of quantitative and qualitative methods. An 11-point Likert scale was utilised to rank initial self-reported playing capacity, self-reported playing capacity at 12 months and perceived usefulness of the off-instrument retraining protocol. Patients were asked whether they were able to return to professional playing. Of the 9 ED patients, all reported improvements ranging from 27 to 64% over the 12-month period with 7/9 returning to professional playing. Thematic analysis of the narrative feedback identified several themes including: perceived multifactorial causes of dystonia; high value of off-instrument retraining (ratings from 8-10/10); need for moderation of this new strength when returning to play; barriers with ongoing psychological issues; that exercises were in general useful for performance. Several reported incorporating exercises to augment their own teaching, and most reported continuing the exercises and observing ongoing improvements after the 12 month trial was completed.

Discussion: All participants perceived exercises to be beneficial and showed improved muscle function and control and feelings of regaining control over their embouchure. Findings were encouraging given the usual very poor prognosis of this condition and the challenges of conducting the retraining protocol online.
Further large-scale research is planned, ideally incorporating multimodal retraining, such as including psychological interventions and potentially medication support.

P3.25

A Phenotypic Drug Discovery Pipeline to Identify First in Class Medications for Dystonia

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Abstract

Introduction: Dystonias comprise a group of movement disorders that arise in diverse clinical settings and impair normal daily movement and function. Most forms of dystonia lack highly effective oral medications and disease modifying therapies. More invasive procedures such as botulinum toxin injections and deep brain stimulation (DBS) surgery are currently the most effective treatments. Therefore, we aim to develop highly efficacious orally bioavailable first in class medications to treat dystonia. Here we present our workflow and progress toward achieving drug-like compound milestones. We

Materials and Methods: We recently demonstrated preclinical Proof-of-Concept for a Phenotypic Drug Discovery (PPD) screening pipeline using a high-content, high-throughput cell-based screening (HC/HTS) assay based on a DYT1 dystonia-associated cellular phenotype of TorsinA mislocalization. In this pipeline, small molecule hits progress from the HC/HTS assay through validation in orthogonal cell assays, ex vivo drug applications with brain slice electrophysiology of cholinergic neurons, then to in vivo treatment followed by diffusion tensor magnetic resonance imaging (DTI MRI).

Results: This approach identified ritonavir as a novel therapeutic class for dystonia and with potential for disease modifying effects (Caffall et al. *Sci. Transl. Med.* 2021). We have now used the DYT1 TorsinA mislocalization HC/HTS assay to screen > 40,000 novel compounds and identified chemotypes normalizing the TorsinA mislocalization cellular phenotype with high potency (low QM EC_{50}) and efficacy (>90%). After more than 20 rounds of iterative medicinal chemistry optimizations (10-50 analogs/round), lead compounds have been identified with EC_{50} values 80-260nM representing ~50-fold improvement of potency over initial hit compounds and ritonavir (EC_{50} ~2QM). The improved chemotypes maintain activity of the parent compound in orthogonal cell assays and striatal brain slice electrophysiology. However, we also determined that liabilities in metabolism (ADME) and CNS pharmacokinetic properties required further optimization to allow for in vivo applications. Subsequent medicinal chemistry rounds have improved metabolic stability (MLM $T_{1/2}$) and CNS access (P-gp efflux Papp AtoB/Papp BtoA Efflux ratio, ER). The most recent analogs show CNS availability following a single 30 mg/kg intraperitoneal dose (>100nM brain concentrations for up to 2hr; EC_{50} 4-15nM cellular phenotype). Maximum tolerated dosing (MTD) further indicates that chronic intraperitoneal dosing at 30mg/kg is well tolerated. This work establishes a pipeline to support the discovery, development, and advancement of novel dystonia drugs.

P3.26

Contributions of the direct and indirect basal ganglia pathways to dystonia

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Abstract

Introduction: Evidence from clinical studies implicates basal ganglia dysfunction as a component of the pathophysiology of dystonia. The basal ganglia orchestrate movement by balancing excitatory and inhibitory activity to thalamocortical neurons. Dopamine neurotransmission mediates this balance by acting on striatal medium spiny neurons (SPNs) that comprise the direct and indirect pathways of the basal ganglia. In the classical view of basal ganglia function, medium spiny neurons that comprise the direct pathway (dSPNs) facilitate movement, and medium spiny neurons of the indirect pathway (iSPNs) inhibit movement. In dystonia, this balance is thought to be disrupted, yet our knowledge of direct and indirect pathway contributions to the expression of dystonia is limited. Thus, goal of this study was to determine the role of SPN activity on the expression of dystonia in an animal model.

Materials and Methods: Here, dSPNs and iSPNs were stimulated or silenced using Cre-dependent viral expression of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in a knock-in mouse model of DOPA-responsive dystonia (DRD). DRD mice contain a point-mutation in the tyrosine hydroxylase gene, and exhibit dystonia as a result of striatal dysfunction. Specifically, the stimulating DREADD hM3D(Gq) was bilaterally infused into the striatum of DRD mice and expressed in dSPNs or iSPNs, and the inhibitory DREADD hM4D(Gi) was administered in the same manner in a separate cohort. Next, mice were treated with clozapine-n-oxide (CNO) to stimulate DREADDs expressed in dSPNs or iSPNs, or vehicle, and the expression of dystonia was assessed.

Results: Importantly, peripheral administration of CNO in the absence of hM3D(Gq) in dSPNs was not found to affect dystonia in DRD mice. Dystonia was significantly ameliorated in response to dSPN stimulation, and no changes dystonia were observed after dSPN silencing. Neither stimulation or silencing of iSPNs impacted dystonia in DRD mice. Additionally, DRD mice showed altered locomotor responses to SPN manipulation when compared to normal littermates, indicating that the functional regulation of locomotor activity in DRD mice is altered. These results provide further evidence that striatal dysfunction underlies dystonia and demonstrates that dSPNs mediate of the expression of dystonia.

P3.27

Exploring the effects of torsinA dysfunction in an iPSC-derived cortical neuronal model of DYT1-TOR1A dystonia

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Abstract

Introduction: DYT1-TOR1A dystonia is a neurodevelopmental disorder of motor function. It is caused by autosomal dominant mutation of the TOR1A gene. The exact function of the TorsinA protein within neurons and how its dysfunction leads to dystonia is unknown. Previous cellular and murine models of DYT1-TOR1A dystonia describe changes in nuclear envelope structure, with accumulation of ubiquitin and nuclear pore complex proteins within nuclear envelope buds, and redistribution of TorsinA from the endoplasmic reticulum to the nuclear envelope. Furthermore, alterations in synaptic plasticity as evidenced by altered electrophysiological responses to high and low frequency stimulation of corticostriatal synapses, with corresponding changes in striatal synaptic levels of a number of neurotransmitter receptors and transporters, have been reported.

Materials and Methods: We developed induced pluripotent stem cell (iPSC) lines derived from the fibroblasts of patients with DYT1 dystonia and differentiated them into glutamatergic cortical neurons according to established protocols. We are studying these neurons at several developmental timepoints to clarify the developmental expression profile of TorsinA and TorsinB in our model and identify the optimal neurodevelopmental timepoint for disease modelling. A wide panel of preliminary immunocytochemical staining has been performed, assessing for changes in nuclear envelope structure and neuronal outgrowth in patient neurons compared to controls.

Three DYT1 patient-derived iPSC lines and three controls were differentiated into cortical neurons and underwent fixation and immunostaining at day 60. The following immunocytochemical assays were performed:

1. TubulinβIII antibody to assess neuritic outgrowth and anti-lamininB nuclear envelope marker to examine nuclear envelope structure.

2. Anti-MAP2 antibody to assess for changes in dendritic arborization plus anti-synaptophysin antibody as a marker of synaptic development.

3. Anti-Ubiquitin (linkage-specific K48) antibody with anti-nuclear pore complex (mAb414) antibody as further assessment nuclear envelope architecture, and for the presence of nuclear envelope ubiquitin inclusions and nuclear pore complex clustering

Results: Both the cases and controls demonstrated positive nuclear ubiquitin-K48 staining, without differences in nuclear pore complex morphology. Furthermore, there were no changes in nuclear envelope structure as evidenced by lamininB staining. This differs from studies in iPSC-derived ventral motor neurons, suggesting that the DYT1-TOR1A mutation has differential effects among different neuronal populations. Preliminary immunostaining at Day60 was suggestive of more complex neuritic architecture and greater dendritic synaptophysin staining in patient-derived neurons compared to controls which may indicate enhanced neuronal maturation at this early timepoint. We currently are undertaking semi-quantitative using western blot measurements and further immunocytochemistry at later developmental timepoints to investigate these trends.

P3.28

In vivo evidence of an imbalance between the direct and indirect basal ganglia pathways of freely moving DYT-TOR1A mice

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Abstract

Introduction: Dystonia is a movement disorder characterized by involuntary muscle contractions. Theoretical models of dystonia suggest that these abnormal movements could emerge due to an imbalance in pathways of the basal ganglia, a group of nuclei within the brain that regulate motor control. The striatum is at the core of these pathways since it receives cortical and subcortical inputs that will ultimately guide motor behavior. These models propose that a higher activity in the direct pathway (responsible for action selection, involving D1 medium spiny neurons (MSNs)) and a lower activity in the indirect pathway (responsible for inhibiting competing actions, involving D2 MSNs) is at the core of dystonia. In patients with dystonia, this abnormal activity pattern would give rise to an impaired action selection and result in the over-activation of antagonistic pairs of muscles. Yet, there is a lack of in vivo studies dissecting the activity of D1 or D2 MSNs in dystonia.

Material and methods: DYT-TOR1AΔGAG knock-in and wild-type (WT) mice expressing Cre recombinase under the control of the dopamine D1 or A2A receptors (for D2 populations). Using *in vivo* calcium imaging, MSNs activity was recorded in freely moving animals, during an open field test, while behavior was assessed by high-resolution video and head-mounted accelerometers. Assessments were performed weekly, before and up to nine weeks after a standardized sciatic nerve crush lesion (SNCL) – a procedure known to induce dystonic-like movement in genetically-predisposed animals. Dystonia-like movements were also assessed using a tail suspension test (TST).

Results: No significant differences were found between DYT1-TOR1A and WT mice in the overall time spent locomoting or the speed ranges attained in each group. In the TST, although not all DYT1-TOR1A mice developed persistent dystonia-like movements of the hindlimb submitted to the SNCL, the group had on average dystonia scores higher than controls. Analyses of neuronal activity did not reveal generalized changes in the activity of D1-or D2 -MSNs during self-paced movement. However, when we compared the activity of neurons that were specifically modulated by movement initiation after the SNCL, the activity of D1 MSNs significantly increased, while the activity of D2 MSNs showed a decreasing trend, as dystonic-like movements developed in DYT-TOR1A but not in WT mice.

Discussion: Our observations shed light into the pathophysiology of DYT-TOR1A dystonia by revealing an imbalance between the D1 and D2 pathways at movement onset, compatible with the focused selection and inhibition model of the basal ganglia.

P3.29

Translational studies of murine extracellular vesicles to support disease biomarker discovery in people with dystonia

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Abstract

Introduction: Biomarkers for dystonia are being developed to fill unmet needs in the current approach to diagnosis, prognosis, clinical trial candidate selection and pharmacodynamic response to therapeutics. Extracellular vesicles are an attractive potential biomarker source because they are secreted from cells and may provide a readout of cell state. EVs can be isolated from plasma and cerebrospinal fluid. In addition, at least a portion of peripherally circulating EVs are thought to derive from the CNS. We hypothesized that the composition of secreted extracellular vesicles (EVs) would be altered in DYT1 dystonia because defects in a major pathway that regulates protein synthesis (ISR, integrated stress response/eIF2alpha) have been associated with DYT1 and a number of other dystonias. We recently reported proteomic differences associated with EVs from DYT1 knockin mouse embryonic fibroblast (MEF) cultures (King et al., Dystonia 2023). Here we test whether microRNAs also show genotype effects, as miRNAs have distinct advantages to develop into laboratory assays for clinical use.

Methods: EVs were isolated from a 24h media collection from murine embryonic fibroblast cultures established from 3 delGAG Tor1a knockin mice and 3 wildtype littermate controls. RNA was purified and used to establish a library for microRNA sequencing using Small RNAseq. Candidate biomarker miRNAs were validated using RT-qPCR TaqMan assays.

Results: We detected a total of 694 miRNAs in MEF EV preparations. Genotype effects showed Z scores ranging from -5.2 to 14. RT-qPCR performed on 9 biomarker candidates showed significant correlation (Pearson r = 0.7393; P value = 0.023) with miRNA-Seq results. We further present bioinformatic considerations to prioritize candidates and propose design of human subject discovery experiments.

Discussion: EVs secreted from cell cultures derived from DYT1 knockin mice show trends that microRNA abundances may be disrupted. These data, along with EV protein disruptions, provide proof-of-concept to support studies of EVs in human subjects. Because many murine candidate biomarkers have high homology with human proteins and miRNAs, knowledge of murine candidates will be used to prioritize human dystonia biomarker candidates identified in the discovery phase.

P3.30

Effects of deep brain stimulation (DBS) in the entopeduncular nucleus (EPN) in dystonic *dtsz* hamsters

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Abstract

Introduction: DBS of the globus pallidus internus (GPi; EPN in rodents) has become important for the treatment of generalized dystonia. There is evidence that striatal dysfunctions cause a disturbed thalamocortical inhibition in the GPi/EPN. However, the pathophysiology and mechanisms of DBS, are largely unknown, which hampers the detection of biomarkers for optimization of DBS.

Materials and Methods: In our project of the CRC "Electrically active implants" we aim to elucidate mechanisms of DBS in animal models of dystonia. We recently found that EPN-DBS improves dystonia in the *dt^{sz}* hamster and reduces spontaneous excitatory cortico-striatal activity, indicating fast effects in synaptic plasticity. In the present study, we examined the effects of DBS on c-Fos, an immunohistochemical marker of neuronal activity, and brevican, a perineuronal net protein involved in the regulation of synaptic plasticity.

For immunohistochemistry, we used brains of stimulated *dt^{sz}* hamsters and control animals, as well as sham-stimulated and naïve animals and performed cell counting and fluorescence intensity measurements within the basal ganglia (BG) network.

Results: After DBS vs. sham, c-Fos$^+$ around the electrode was increased. Unexpectedly, c-Fos$^+$ cells were decreased in deep cerebellar nuclei (DCN) after DBS, but no changes became evident within the whole EPN, habenula, ventromedial thalamus, cortex and striatum. Cell counting of c-Fos activated GAD67$^+$ as well as activated PV$^+$ cells showed no differences between the groups in motor cortex and striatum. Brevican comparison of *dt^{sz}* and control hamsters revealed interesting differences within the BG-thalamo-cortical circuit, but no changes after DBS became evident.

Discussion: With regard to recent electrophysiological data, we expected c-Fos changes especially in cortical GABAergic neurons after DBS in *dt*^{sz} hamsters. The lack of changes within the BG network could be related to the short duration of stimulation or the time interval between stimulation and c-Fos staining. The changes in brevican in naïve animals could point to a developmental disruption of PN which may contribute to the presumed disinhibition of PV^{+} neurons and abnormal plasticity within the BG circuit. However, it remains unclear whether the findings represent a cause of dystonia or the consequences of other changes. Ongoing long-term EPN stimulations, now feasible by a new fully implantable stimulator (STELLA), probably lead to more pronounced effects within the network and will be useful to verify the DCN effects.

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P3.31

Omics investigation on the brain of a DYT-TOR1A mouse model exposed to a 2nd hit.

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Abstract

Introduction: Dystonia is a rare movement disorder characterized by involuntary muscle contractions, such as twisting or cramps. DYT-TOR1A is the most common inherited form of dystonia caused by a GAG deletion in the TOR1A gene and has a disease penetrance of only 30%. Although the gene responsible for the disease is known, the pathophysiology remains unclear. The low penetrance indicates a gene-environment interaction, trigged by a genetic and/or environmental factor. Previous studies have shown that a peripheral nerve crush, acting as the environmental trigger, induces a dystonia like phenotype in genetically predisposed rodents. In this study, we performed a sciatic nerve crush in a DYT-TOR1A KI mouse model, carrying the human TORA1 mutation, to study the role of the DYT-TOR1A mutation and the gene-environment interaction by multi-omics in three different brain regions.

Materials and Methods: Dystonia like movements (DLM), after sciatic nerve crush injury of the right hindlimb were assessed by a deep learning network during the tail suspension test (TST). Pathophysiological pathways were investigated using Omics technologies in the ipsilateral cerebellum, and contralateral striatum and cortex.

Results: The nerve-injured DYT-TOR1A KI animals had more DLM per minute than DYT-TOR1A KI naive mice during the 12 weeks experiments. The highest score was reached three weeks after nerve crush injury and started to decrease four to five weeks after nerve crush injury. Omics analysis revealed translational changes in the ipsilateral cerebellum, but not in the contralateral cortex and striatum of nerve-injured wildtype animals. Interestingly, the nerve crush injury induces changes in DYT-TOR1A KI mice, with translational regulation in the contralateral striatum and cortex, but not in the ipsilateral cerebellum.

Discussion: The nerve-injured DYT-TOR1A KI mice showed a more severe clinical phenotype, compared to the DYT-TOR1A KI naive mice. The Omics investigation suggests that translation regulation in the cerebellum, acts as a rescue mechanism in nerve-injured wildtype mice. However, cortical, and striatal translational regulation might be the underlying cause for the dystonic phenotype in DYT-TOR1A KI nerve injured mice.

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P3.32

Effects of a peripheral nerve injury on the dystonic phenotype and striatal synaptic function of a DYT1 mouse model

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Abstract

Introduction: Gene-environment interactions may be relevant in the pathogenesis of hereditary forms of dystonia with reduced penetrance, such as DYT1 (DYT-TOR1A), DYT6 (DYT-THAP1), DYT25 (DYT-GNAL). Based on the hypothesis of a “second hit”, proposing that the manifestation of dystonia

Results: from the interplay of an intrinsic predisposition and an environmental trigger, a dystonia-like phenotype has been disclosed in genetic rodent models by exposing them to a sensorimotor stressor, the compression of the sciatic nerve.

Materials and Methods: Here, we utilized electrophysiological recordings from striatal slices of Tor1a$^{+/\Delta gag}$ mice at different times after the compression of the sciatic nerve, to determine the synaptic correlates of the dystonia-like phenotype. We performed the compression of the sciatic nerve, for either 15 or 30 seconds, on Tor1a$^{+/\Delta gag}$ mice aged 30 days. The tail suspension test (TST) was performed 24 hrs before and after surgery, and then weekly for further 8 weeks. The video recordings of the TST sessions were analyzed with an automated system.

Results: The analysis of the motor score in the TST for the evaluation of the dystonic phenotype on mice subjected to compression of the sciatic nerve for 15 seconds at the age of 30 postnatal days showed a difference between the genotypes in the recovery of normal postures during the Tail Suspension Test. In fact, we observed a higher frequency and duration of nerve lesion-induced dystonic movements in Tor1a$^{+/\ gag}$ mice compared to their wildtype littermates. This difference was particularly evident 4 weeks after the injury. To investigate the relationship between sensorimotor integration and the manifestation of a dystonic-like motor phenotype, an electrophysiological analysis of thalamo-cortical synaptic integation in the striatum is ongoing on the animals subjected to compression of the sciatic nerve.

Discussion: Our previous data showed that thalamostriatal fibers stimulation, that mimics the signal induced by salient sensory stimuli, evokes a shorter pause and an altered discharge of action potentials in striatal cholinergic interneurons in DYT1 mice compared to wildtype controls. Preliminary data suggest that compression of the sciatic nerve exacerbates the impairment of thalamo-cortical synaptic integation.

P3.33

Modeling DYT1 Dystonia with Human Induced Pluripotent Stem Cells

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Abstract

Introduction: DYT1 Dystonia (DYT1) is a central nervous system disease that is autosomal dominant yet with only a 30% penetrance. The disease is early onset and manifests as abnormal, involuntary twisting movements. A GAG 3-base pair deletion in TOR1A gene is responsible for the condition. Many studies have used over expression cell models to study the disorder. These studies have concluded that mutant torsinA is mislocalized to the nuclear membrane where it forms perinuclear inclusions. Although numerous cellular consequences of the mutant protein have been suggested, the dystonia-causing abnormalities remain unclear.

Materials and Methods: IPSc lines were made from reprogrammed fibroblasts consisting of 3 DYT1 and 3 controls, each with 2 clones. The iPSc lines were subsequently differentiated to neuroprogenitor cells (NPC) and then to cortical neurons. The resulting neurons were evaluated morphologically, along with transcriptomics, proteomics, and lipidomics.

Results: Six iPSc clones from 3 DYT1 patients and 6 clones from 3 control donors were induced from their respective fibroblast lines to iPS cells. All were differentiated to NPCs and on to cortical neurons. Cortical neuron populations were confirmed by neuronal stains, with no obvious differences between DYT1 and control lines. Transmission electron microscopy showed no perinuclear inclusions in iPSc, NPC, or cortical neurons. Gene expression profiling using RNAseq showed multiple differentially expressed genes involved in nuclear division and neurogenesis. Lipidomic analyses showed only minor glycerolipid/glycerophospholipid dysregulation in DYT1 neurons. Proteomic profiling using gas-chromatography with mass spectrometry showed no substantial changes in torsinA or torsinB or its known interactors. There were no substantial changes in eIF2A pathways. However, there was dysregulation of several proteins involved in energy production, nucleoporins, and ribonucleoprotein pathways.

Discussion: Studies of DYT1 iPSC cortical neurons did not reveal obvious changes in some pathways previously reported to be affected, but showed numerous other abnormalities that need further scrutiny.

P3.34

In vivo optogenetic Inhibition of striatal Parvalbumin-reactive Interneurons induced Genotype-specific Changes in neuronal Activity without dystonic Signs in DYT1 knock-in Mice

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Abstract

Introduction: The pathophysiology of early-onset torsion dystonia (TOR1A/DYT1) remains unclear. Like 70% of human mutation carriers, rodent models such as DYT1 knock-in (KI) mice do not show overt dystonia, but have subtle sensorimotor deficits and pattern of abnormal synaptic plasticity. Aberrant neuronal plasticity in the striatum, e.g., increased long-term potentiation and decreased long-term depression, as well as impaired GABAergic inhibition in various types of human dystonia support the hypothesis of a loss of inhibition in the striatum. Evidence from animal models suggest a dysfunction of striatal parvalbumin-reactive interneurons (PV+), which provide strong feedforward inhibition of striatal projection neurons.

Materials and Methods: To investigate the importance of a loss of inhibition in the striatum triggered by dysfunction of striatal PV+, we used the DYT1 KI mouse model, a genetic mouse model without a dystonic phenotype. We used in vivo optogenetic inhibition of PV+ to detect changes in motor behavior and neuronal activity of striatal projection neurons and interneurons. Optogenetic fibers were bilaterally implanted into the dorsal striatum of male DYT1 KI mice and wild-type (wt) littermates expressing halorhodopsin (eNpHR3.0) in PV+. Excitation with yellow light pulses activated the chloride ion pump eNpHR3.0, resulting in hyperpolarization of PV+.

Results: Optogenetic inhibition with yellow light pulses at different pulse durations and interval lengths for up to 60 min did not induce abnormal movements, such as dystonic signs, and did not affect locomotor behavior. Immunohistochemical examinations revealed genotype-dependent differences. In contrast to stimulated wt mice, stimulated DYT1 KI showed reduced overall striatal neuronal activity, i.e., fewer c-Fos reactive neurons distributed throughout the striatum. Likewise, stimulated DYT1 KI mice showed decreased activity of eNpHR3.0-positive neurons than stimulated wt, indicating lasting inhibition of PV+, as well as increased activation of cholinergic interneurons after optogenetic inhibition of PV+.

Discussion: In conclusion, in vivo optogenetic inhibition of striatal PV+ was not sufficient to elicit dystonic symptoms and did not affect locomotor behavior in wt and DYT1 KI mice. Nevertheless, genotype differences in neuronal activity between stimulated mice suggest an abnormal response to optogenetic inhibition of PV+ and striatal dysfunction in the DYT1 KI mice. Further studies combining optogenetic manipulations of PV+ and neurotransmitter measurements may provide explanatory approaches to changes in neuronal activity and give insights into neurotransmitter imbalances underlying dystonia.

P3.35

Investigating the dysregulation of ISR pathway by antipsychotics as a possible cause of drug-induced dystonia (DID)

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Abstract

Introduction: A maladaptive integrated stress response (ISR) involving dysregulation of the eukaryotic translation initiation factor a (eIF2a) mediated signaling is observed in DYT-PRKRA patient cells (1,2). Additionally, recent research has indicated that dysregulated eIF2a signaling is one of the convergent mechanisms in etiologically diverse dystonias (3). Dystonia is observed as a side effect during antipsychotic therapy and people often discontinue their medications due to side effects (4). In this study, we investigated if ISR pathway is also dysregulated in response to antipsychotic drugs and could contribute to drug-induced dystonia (DID).

Materials and Methods: Using human lymphoblasts, we investigated the ability of antipsychotic drugs to modulate ISR. This was done by using western blot analysis to study induction of the transcription factor ATF4 after endoplasmic reticulum (ER) stress with or without prior treatment with the antipsychotic drugs.

Results: Our results indicate that the antipsychotic drugs alter the ISR by either changing the intensity or the duration of the response. Based on our previous research with DYT-PRKRA, we also tested the ability of a natural plant flavonoid, luteolin, to restore normal ISR in the presence of antipsychotics. Our results indicate that luteolin can alleviate the ISR dysregulation caused by antipsychotic drugs, thereby suggesting its possible application in avoiding DID. Precise regulation of eIF2a signaling in neurons is critical and skewing of ISR pathway in either direction can have significant negative consequences (5). We plan on testing the effect of antipsychotic drugs on neurite outgrowth and maintenance using cultured neurons.

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P3.36

Investigating the molecular and cellular basis of epsilon-sarcoglycan-related myoclonus-dystonia in an iPSC-derived neuronal model

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Abstract

Introduction: *SGCE*-related myoclonus-dystonia (M-D) underlies the epigenetic process of imprinting. This leads to the phenomenon of reduced penetrance upon maternal transmission of a pathogenic variant. We previously demonstrated that induced pluripotent stem cell (iPSC)-derived cortical neurons of carriers of pathogenic *SGCE* variants can serve as an adequate disease model for *SGCE*-related M-D[1], enabling the investigation of functional properties, such as the cellular localization of epsilon-sarcoglycan (encoded by *SGCE*). Interestingly, epsilon-sarcoglycan has been linked to the dystrophin-associated glycoprotein complex (DGC) which is located at the plasma membrane and varies in its composition.

Materials and Methods: iPSC lines of two M-D patients with pathogenic variants in *SGCE* (c.298T>G, p.Trp100Gly and c.304C>T, p.Arg102Ter) and two control iPSC lines were differentiated into mature cortical neurons. Localization of the brain-specific epsilon-sarcoglycan was investigated by cell-surface biotinylation and Western blotting in controls and the missense variant line with and without proteasomal inhibition (MG132). The nonsense variant was excluded since no protein was detectable in previous analyses. RNA samples of all four iPSC-derived cortical neuron lines were subjected to transcriptome analysis. Candidate transcripts were validated by quantitative real-time PCR (qPCR).

Results: Upon biotin treatment, brain-specific epsilon-sarcoglycan was detected in the membrane fraction of the controls. The protein with the missense variant was detected in whole-cell lysates, but not located at the cell surface. Incubation with MG132 increased levels of whole-cell epsilon-sarcoglycan but the location at the plasma membrane could not be restored. Transcriptome analysis revealed that of the DGC components *SGCA*, *SGCB*, *SGCG*, *SGCD*, and *SGCZ*, only *SGCD* and *SGCZ* (encoding delta- and zeta-sarcoglycan) were upregulated in neurons with *SGCE* variants with foldchanges and p-values of 20.96; 7.64*10-6 and 14.67; 5.05*10-4, respectively. Validation by qPCR indicated only small expression changes of these two genes. Six further differentially expressed candidate genes are under investigation.

Discussion: The endogenous M-D model studied here indicates that the brain-specific isoform of epsilon-sarcoglycan is indeed localized at the cell surface in control neurons but not in patient-derived cells. Proteasomal inhibition increases the amount of epsilon-sarcoglycan but has no effect on the cellular localization of the missense variant. mRNA expression analyses revealed that *SGCD* and *SGCZ* are upregulated in both lines with pathogenic *SGCE* variants, indicating a possible compensation in the composition of the DGC. Further analyses are warranted to expand our preliminary findings and understand the changes on the protein complex level.

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Zheng, Wenxu	P3.06
Zwerver, Hans	P1.29
Özyurt, M. Görkem	P3.01

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Date of preparation: May 2023

General Information

COFFEE AND LUNCH BREAKS

All coffee breaks and lunches will be served in the Exhibition Hall on Level 4 Hogan Mezzanine Suite.

Thursday, 1st June

Lunch will also be available outside the Canal Suite, Level 5 for those attending the Merz sponsored lunchtime session.

Friday, 2nd June

Lunch will also be available outside the Canal Suite, Level 5 for those attending the AbbVie sponsored lunchtime session.

CURRENCY AND BANKING

The Euro is the official currency of Ireland. Bank opening hours are generally 10:00 – 16:00, Monday to Friday. International credit cards – Mastercard and Visa are widely accepted.

ELECTRICITY

Ireland has a 230v system. Flat three-pin plugs (Type G) are used.

EXHIBITION

The Exhibition Hall is based on Level 4 Hogan Mezzanine Suite from Thursday, 1st June to Saturday, 3rd June.

MOBILE PHONES

As a courtesy to fellow participants, mobile phones should be turned to silent or switched off during sessions.

NAME BADGES

Each participant will receive a badge upon registration. For security purposes, this badge must be worn at all times while in the conference venue.

POSTER PRESENTATIONS

Posters are displayed for the duration of the conference in the foyer of the Hogan Mezzanine – Level 4. Posters presenters are requested to be next to their posters at the following times for presentations and discussion with delegates.

THURSDAY, 1ST JUNE		
Level 4 Foyer	13:30 – 14:30	P1.01 – P1.35
FRIDAY, 2ND JUNE		
Level 4 Foyer	13:30 – 14:30	P2.01 – P2.35
SATURDAY, 3RD JUNE		
Level 4 Foyer	13:00 – 14:00	P3.01 – P3.36

REGISTRATION & INFORMATION DESK

WEDNESDAY, 31ST MAY	
Level 5 Hogan Suite Foyer	15:00 – 18:30
THURSDAY, 1ST JUNE	
Level 5 Hogan Suite Foyer	07:15 – 18:30
FRIDAY, 2ND JUNE	
Level 5 Hogan Suite Foyer	07:30 – 17:30
SATURDAY, 3RD JUNE	
Level 5 Hogan Suite Foyer	07:30 – 16:30

SMOKING POLICY

Please note that no smoking is allowed in any area of Croke Park, including the stands. This applies also to e-cigarettes. The smoking area is on the ground level outside the Jones' Road entrance. Smoking is prohibited in all buildings in Ireland.

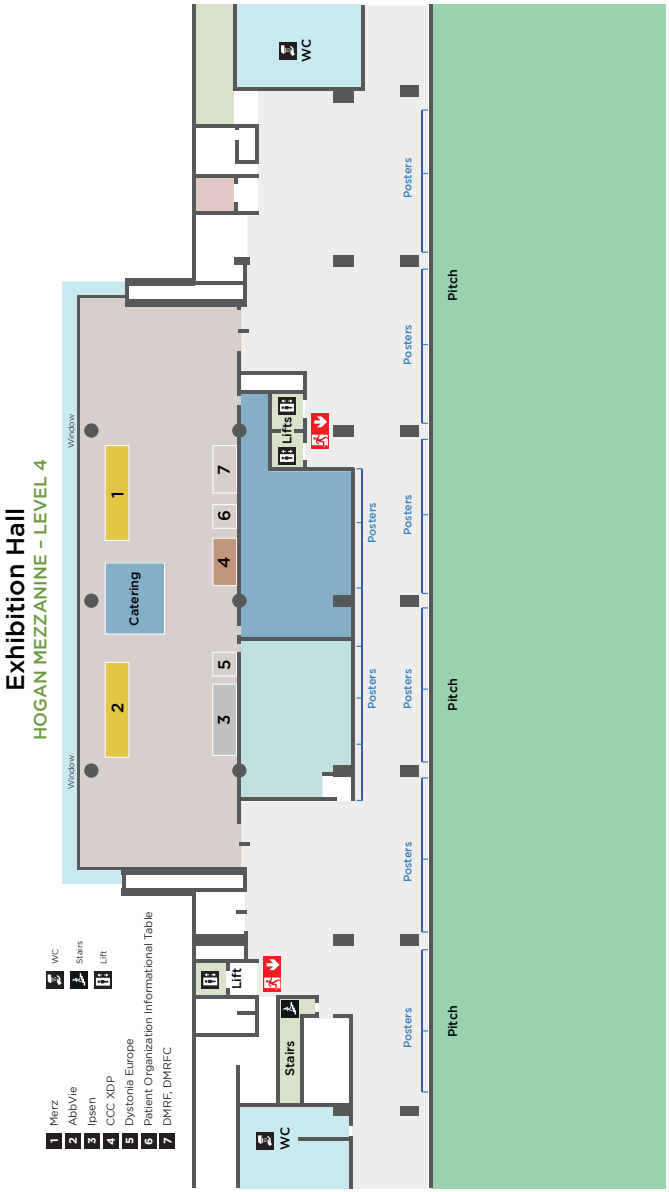
SPEAKERS LOUNGE

The speaker's lounge is located in the Canal Café on Level 5. This lounge is a quiet space for speakers to prepare for their presentations. Presentations should be supplied to the technician in the Hogan Suite, on Level 5, 24-hours before speakers are due to present.

WI-FI CONNECTION

There is Wi-Fi available throughout the Croke Park Conference Centre. Connect to Croke Park WIFI using the password DMRF2023.

Exhibition Floorplan



Everything you need from the ground up

Level 6

87 MEETING ROOMS

Level 5

- (A) CANAL SUITE
- (B) HOGAN SUITE
- (C) HOGAN FOYER
- (R) RECEPTION DESK
- (F) FACULTY LOUNGE

Level 4

- (D) HOGAN MEZZANINE
- (E) HOGAN MEZZANINE FOYER
  Poster Presentations

Ground Floor

HOGAN ENTRANCE
THE CROKE PARK HOTEL

Lower Ground

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- DISABLED TOILETS
- CORPORATE LIFTS

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