Deciphering dystonia: an update on research

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Basal Ganglia function in health and disease

Basal Ganglia (BG) functions:

- motor control
- action selection
- decision making
- habit formation
- language

BG dysfunction:

- movement disorders (Parkinson's, dystonia)
- addiction
- OCD, Tourette's, stuttering
- schizophrenia



Next move selection and the striatum (shogi; Wan 2011 Science)

В

Quick generation vs. sensory-motor control



D

Professional vs. amateur





Many factors influencing neural plasticity in striatum



Dopamine effects are pervasive in striatum



This maps to computer learning algorithms



So how do the genetics fit in with this?

"DYT23" craniocervical dystonia and ANO3



predicted to code for Ca++-activated Cl-channel on ER membrane

Mutations in GNAL cause primary torsion dystonia

Tania Fuchs¹, Rachel Saunders-Pullman^{2,3}, Ikuo Masuho⁴, Marta San Luciano⁵, Deborah Raymond², Stewart Factor⁶, Anthony E Lang⁷, Tsao-Wei Liang⁸, Richard M Trosch⁹, Sierra White¹, Edmond Ainehsazan¹, Denis Hervé^{10–12}, Nutan Sharma¹³, Michelle E Ehrlich^{14,15}, Kirill A Martemyanov⁴, Susan B Bressman^{2,3} & Laurie J Ozelius^{1,14}

Nature Genetics, Dec 2012





Dystonia genetics + dopamine signaling



Bragg 2011 Neurobio Dis

Back to the clinic:

the importance of measuring symptoms

Significance

Rating scales critical for:

- Correct/differential diagnosis
 - epidemiological data
 - pathophysiology research (imaging, genetics, pathology)
- Progression in natural history
- Pre-/post-treatment (surgical, BoNT)
- Clinical trials

Measuring symptoms in dystonia

- Multiple options
- No clear standard
- Often NOT used
- "I know it when I see it"
- Most are modifications of Fahn's early scales (Fahn 1989 in Munsat)
- Concerns about interrater reliability (Dystonia Study Group 2004 Adv Neurol)

Cranial dystonias

just 7
emotions?

or is it 2^N
muscle
activation
combinations?



Helping doctors evaluate blepharospasm

Objective, computerized video-based rating of blepharospasm severity

Neurology 2016

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ABSTRACT

Objective: To compare clinical rating scales of blepharospasm severity with involuntary eye closures measured automatically from patient videos with contemporary facial expression software.

Methods: We evaluated video recordings of a standardized clinical examination from 50 patients with blepharospasm in the Dystonia Coalition's Natural History and Biorepository study. Eye closures were measured on a frame-by-frame basis with software known as the Computer Expression Recognition Toolbox (CERT). The proportion of eye closure time was compared with 3 commonly used clinical rating scales: the Burke-Fahn-Marsden Dystonia Rating Scale, Global Dystonia Rating Scale, and Jankovic Rating Scale.

Results: CERT was reliably able to find the face, and its eye closure measure was correlated with all of the clinical severity ratings (Spearman $\rho = 0.56$, 0.52, and 0.56 for the Burke-Fahn-Marsden Dystonia Rating Scale, Global Dystonia Rating Scale, and Jankovic Rating Scale, respectively, all p < 0.0001).

Computer-based video processing



Automating eye closure detection



Automatically rating severity



The two basal ganglia output pathways & laryngeal dystonia



Brain circuits involved in laryngeal dystonia (ver. 1)



Brain circuits involved in laryngeal dystonia (ver. 2)



Brudzynski 2010 ch 8.3 fig 3

Musician's dystonia, and why it matters for other dystonias



Measuring symptoms in musician's dystonia



Measuring symptoms in musician's dystonia



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Treatment effect or measurement effect?

			Su	bjec	tive									Objective		
			Patient		Clinician											
	Study references	Interventions	VAS	DES	Other	F-M	ADDS	TCS	GDS	UDRS	FAM	TRE, etc.	Other	kinematics	MSA	
	Ackermann 2005 MPPA	PT		Х				Χ								
	Altenmuller 2011 ISPS	PT													Х	
	Berque 2010 MPPA	PT					Χ	Χ			Χ		Χ			
	Buttkus 2010b Mov Disord	tDCS			Χ		Х				Χ					
	Buttkus 2010a Mov Disord	PT, tDCS													Х	
	Buttkus 2011 Restor Neurol Neurosci	PT, tDCS													Х	
	Byl 1996 J Orthop Sports Phys Ther	PT											Χ			
	Byl 2000 J Hand Ther	PT											Χ			
	Byl 2003 APMR	PT											Χ			
	Byl 2009 J Hand Ther	PT											Χ			
	Candia 1999 Lancet	PT		Χ										Х		
	Candia 2002 APMR	PT		Χ										Х		
	Candia 2003 PNAS	PT		Χ										Х		
	Cole 1991 MPPA	BTX											Χ			
	Cole 1995 Mov Disord	BTX	Х													
	de Lisle 2006 MPPA	PT		Χ								Х				
	de Lisle 2010 MPPA	PT										Х				
	Hayes 1996 J Clin Neurosci	BTX			Х											
Jabusch 2004 Adv Neurol Peterson et Jalus 2010 4 Maurology		BTX												Х		
		BTX					Х								Х	
	Jabusch 2004a Mov Disord	THC													Х	
	Jabusch 2005 Mov Disord	BTX, PT, Tri			Х											
	Jabusch 2011 ISPS	BTX, PT, Tri													Х	
	Karp 1994 Neurol	BTX			Х								Х			
	Kambar 4007 Man Than	рт											V			

Table 2. Studies involving interventions for MD and associated rating scale use

Summary

- We should be able to develop better treatments if we can improve our understanding of the underlying brain circuit <u>mechanisms</u>.
- If we can improve our understanding of the <u>dynamic pathogenic</u> <u>process</u>, we could develop strategies to reverse, cure, and prevent dystonia.
- The mechanisms and pathogenic process are varied and complex. Progress can be accelerated by <u>integrative</u> approaches. Theory and computational tools are well suited to this.
- Your help is critical to realizing our vision !

Terry Sejnowski CNL, Salk

Thanks

Dystonia Coalition

Christina Zukas, Ling Yan, Matt Hicks, Joel Perlmutter WUSTL

Giovanni Defazio, Antonella Macerollo U Bari

Marni Bartlett and Gwen Littlewort INC, UCSD Benign Essential Blepharospasm Research Foundation

Dystonia Medical Research Foundation

NIH NIMH (5T32-MH020002)