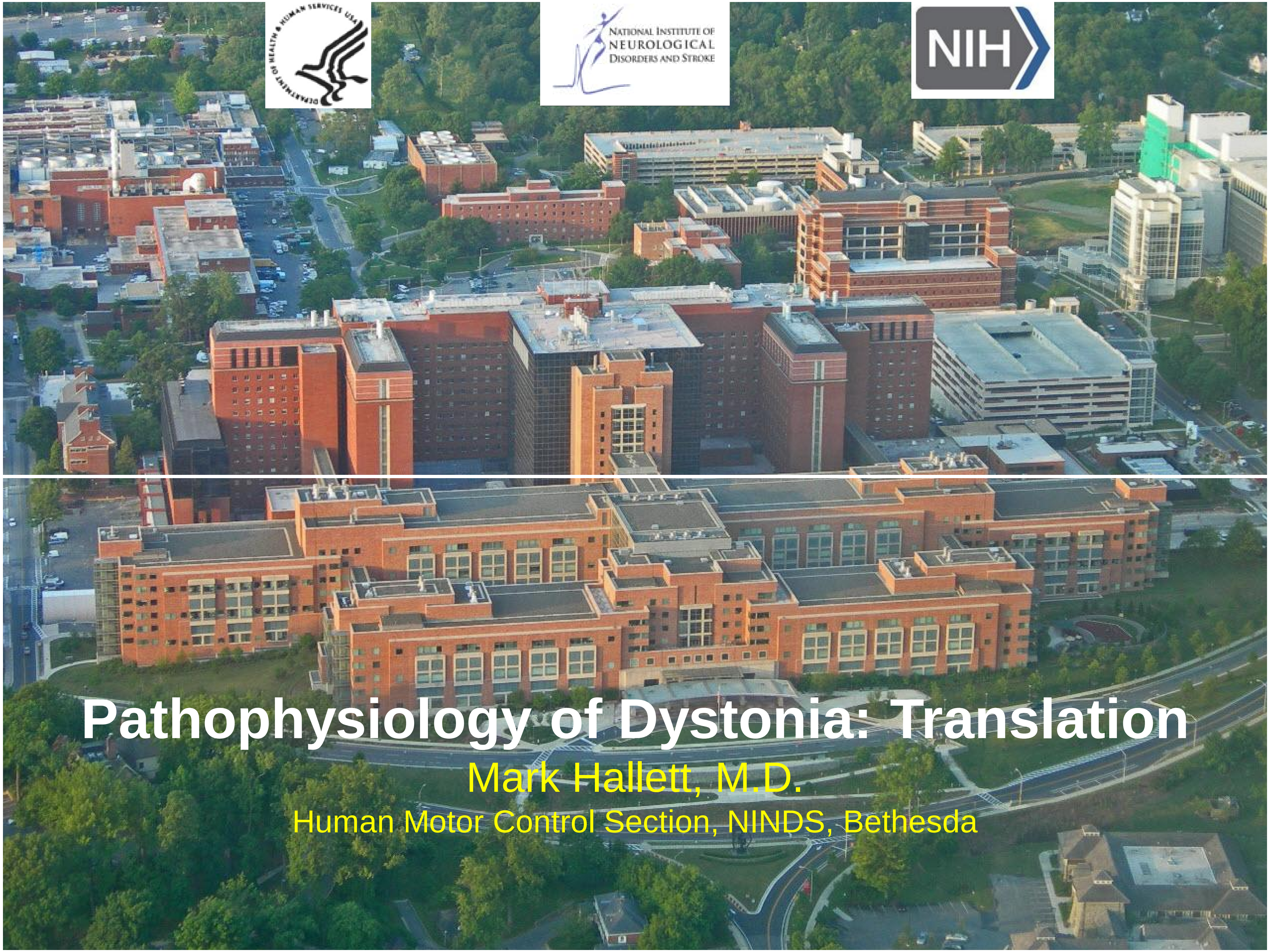
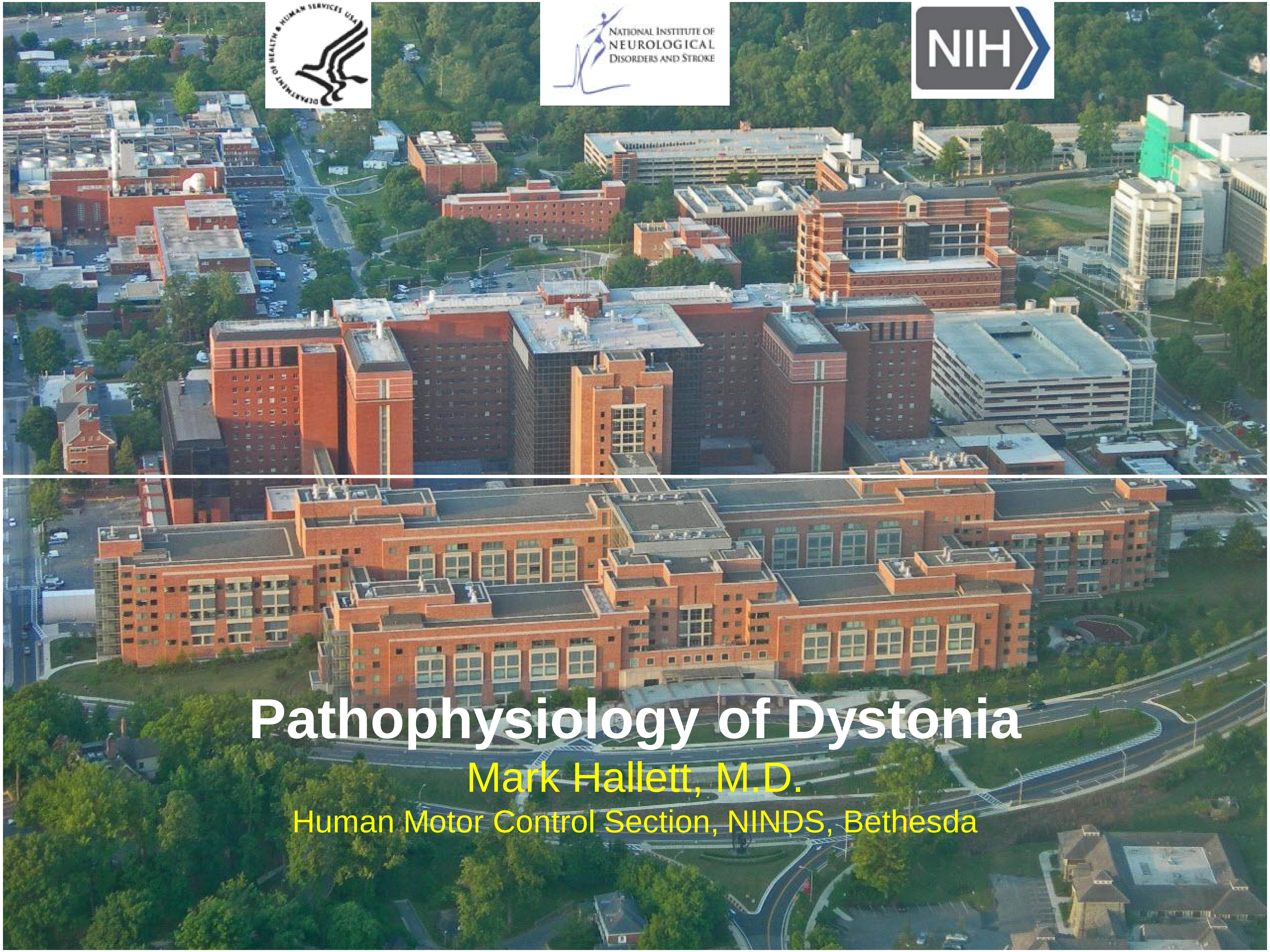


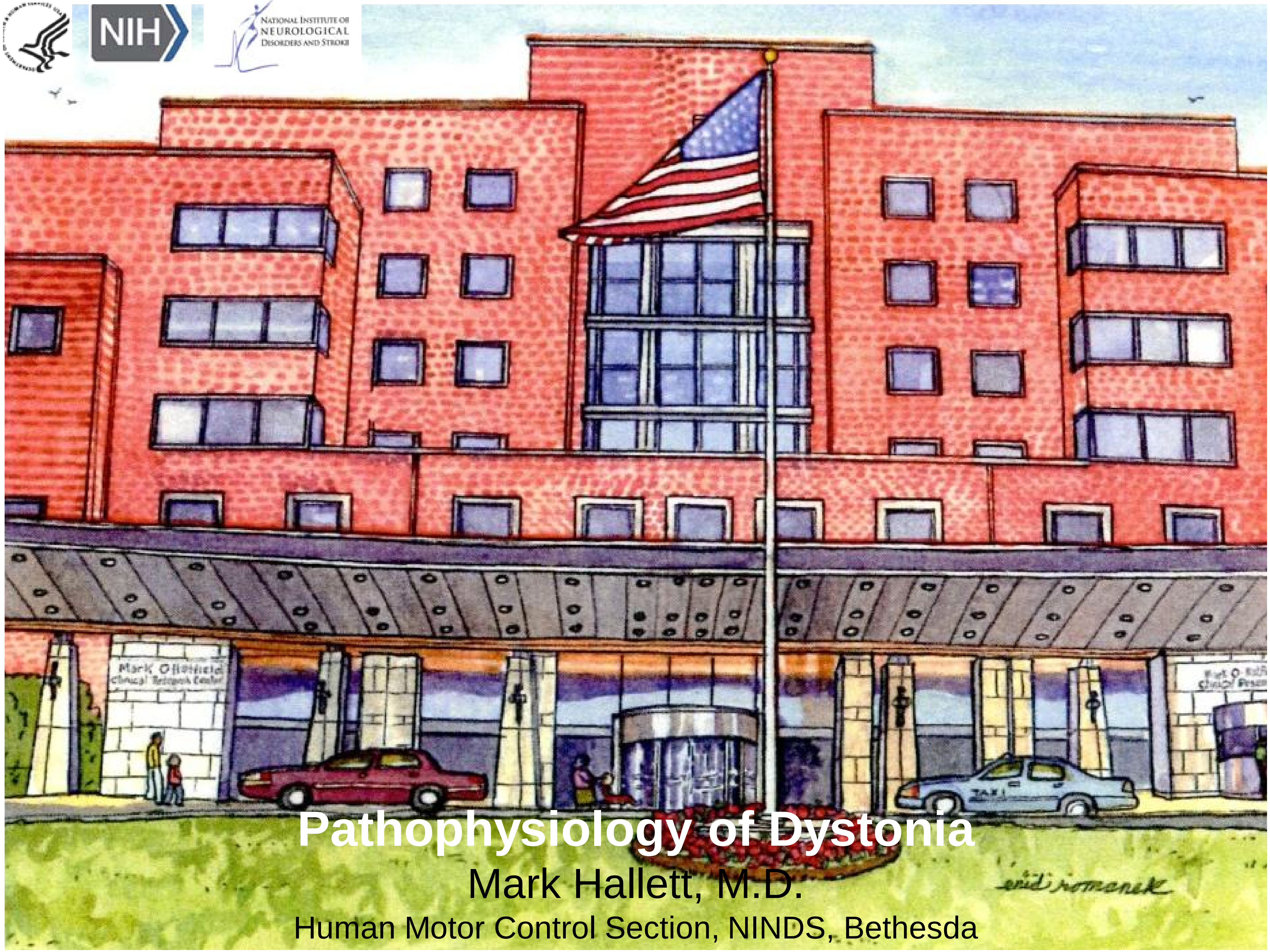
Pathophysiology of Dystonia: Translation

Mark Hallett, M.D.
Human Motor Control Section, NINDS, Bethesda



Pathophysiology of Dystonia

Mark Hallett, M.D.
Human Motor Control Section, NINDS, Bethesda



Pathophysiology of Dystonia

Mark Hallett, M.D.

Human Motor Control Section, NINDS, Bethesda

Disclosures

- No conflict of interest

REVIEW

Phenomenology and Classification of Dystonia: A Consensus Update

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

[1]*Department of Neurology, Catholic University, Milan, Italy*
[2]*Department of Neurology, Carlo Besta National Neurological Institute, Milan, Italy*
[3]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London (UCL), London, United Kingdom*
[4]*Departments of Neurology, Beth Israel Medical Center and Albert Einstein College of Medicine, New York, New York and Bronx, New York, USA*
[5]*Department of Neurology, Emory University, Atlanta, Georgia, USA*
[6]*Department of Neurology, Columbia University, New York, New York, USA*
[7]*Movement Disorders Unit, Department of Neurology, Westmead Hospital and Sydney Medical School, University of Sydney, Sydney, Australia*
[8]*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA*
[9]*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*
[10]*Departments of Neurology, Human Genetics and Pediatrics, Emory University, Atlanta, Georgia, USA*
[11]*Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Lübeck, Lübeck, Germany*
[12]*Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and the University of Toronto, Toronto, Canada*
[13]*Departments of Neurology, Neurobiology, and Anatomy, Brain and Cognitive Sciences, and Pediatrics, University of Rochester, Rochester, New York, USA*
[14]*Dystonia Medical Research Foundation, Chicago, Illinois, USA*

Movement Disorders Online 6 May 2013

New Definition

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Alberto Albanese, Kailash Bhatia, Susan B. Bressman, Mahlon R. DeLong,
Stanley Fahn, Victor S.C. Fung, Mark Hallett, Joseph Jankovic, H.A. Jinnah,
Christine Klein, Anthony E. Lang, Jonathan W. Mink, & Jan K. Teller

An ad hoc committee sponsored by Dystonia Medical Research Foundation,
The Dystonia Coalition, & The European Dystonia COST Action
(COST = Cooperation in Science and Technology)

Generalized Dystonia

Patient of M. Tagliati

Jerky Cervical Dystonia

Fahn, Jankovic & Hallett 2011

Tremulous Cervical Dystonia

Bhidayasiri & Tarsy 2013

Musician's Dystonia with Overflow

Patient from NINDS, NIH

New Classification Scheme

- Two axes
  - Clinical Features
    - age at onset, body distribution, temporal pattern, coexistence of other movement disorders, other neurological manifestations
    - Syndromes are clusters of clinical features
  - Etiology
    - Nervous System Pathology
    - Inherited or Acquired

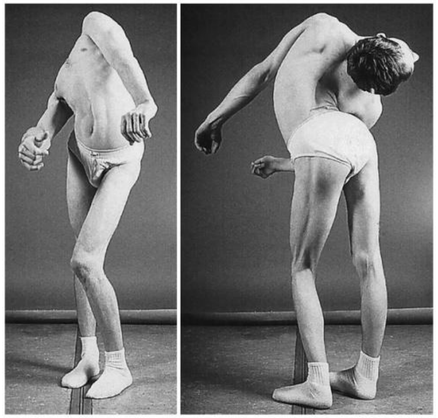
Understanding Dystonia

Genes

Modifiers

Cell biology

Regional anatomical abnormality



Network Dysfunction

Pathophysiology

Axis One

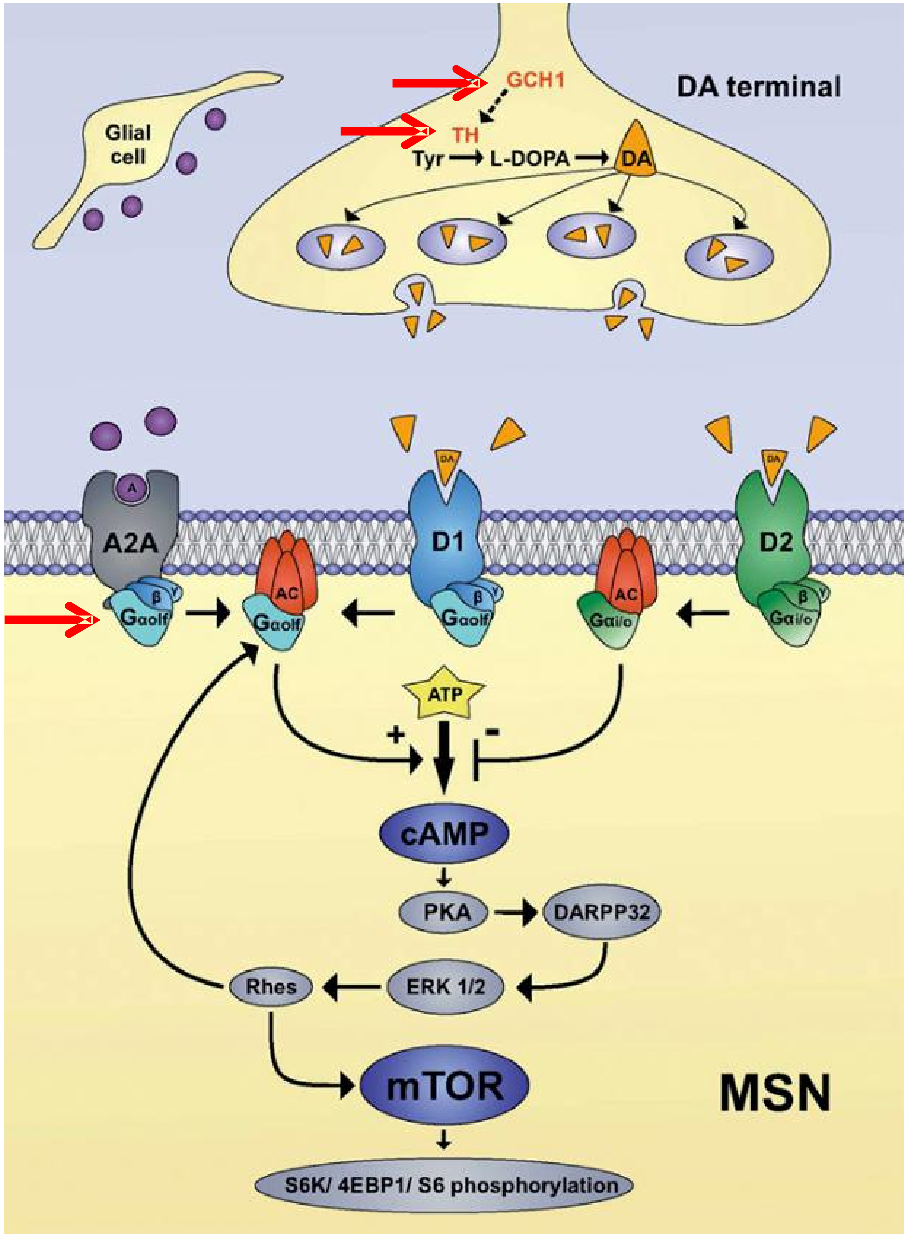
Phenotype

Table 1 | Molecular classification of "DYT" dystonia syndromes.

Disease (MIM)	Gene	Locus	Phenotype	Inheritance
PURE PRIMARY TORSION DYSTONIA				
DYT1 (128100)	*TOR1A*	9q34	Early-onset generalized limb onset dystonia	AD
DYT2 (224500)	–	–	Early-onset generalized dystonia with prominent cranio-cervical involvement	AR
DYT4 (128101)	*TUBB4a*	19p13.12–13	Whispering dysphonia	AD
DYT6 (602629)	*THAP1*	8p11.21	Generalized cervical and upper-limb-onset dystonia	AD
DYT7 (602124)*	–	18p	Adult-onset cervical dystonia	AD
DYT13 (607671)	–	1p36.32–p36.13	Cervical and upper-limb dystonia	AD
DYT17 (612406)	–	20p11.2–q13.12	Segmental or generalized dystonia with prominent dysphonia	AR
DYT21 (614588)	–	2q14.3–q21.3	Adult-onset generalized or multifocal dystonia, often starting with blepharospasm	AD
DYT23 (614860)	*CIZ1*	9q34	Adult-onset cervical dystonia	AD
DYT24 (615034)	*ANO3*	11p14.2	Cranio-cervical dystonia with laryngeal and upper-limb involvement	AD
DYT25 (615073)	*GNAL*	18p11	Adult-onset cervical dystonia	AD
PRIMARY DYSTONIA-PLUS SYNDROME				
DYT5 (218230)	*GCH1*	14q22.2	Dopa-responsive dystonia	AD
THD (605407)	*TH*	11p15.5	Dopa-responsive dystonia	AR
DYT11 (159900)	*SGCE*	7q21.3	Myoclonus-dystonia	AD
DYT12 (128235)	*ATP1A3*	19q13.2	Rapid-onset dystonia parkinsonism	AD
DYT15 (607488)	–	18p11	Myoclonus-dystonia	AD
DYT16 (612067)	*PRKRA*	2q31.2	Early-onset dystonia parkinsonism	AR
PAROXYSMAL SYNDROME				
DYT8 (118800)	*MR1*	2q35	Paroxysmal non-kinesigenic dyskinesia (PNKD)	AD
DYT9 (601042)/DYT18 (612126)	*SLC2A1*	1p34.2	Paroxysmal dyskinesias with episodic ataxia and spasticity/paroxysmal exercise-induced dystonia (PED)	AD
DYT10 (128200)	*PRRT2*	16p11.2	Paroxysmal kinesigenic dyskinesia (PKD)	AD
DYT19 (611031)	–	16q13–q22.1	Paroxysmal kinesigenic dyskinesia 2 (PKD2)	AD
DYT20 (611147)	–	2q31	Paroxysmal non-kinesigenic dyskinesia 2 (PNKD2)	AD
HEREDODEGENERATIVE DYSTONIA SYNDROME				
DYT3 (314250)	TAF1	Xq13.1	Dystonia parkinsonism	X-R

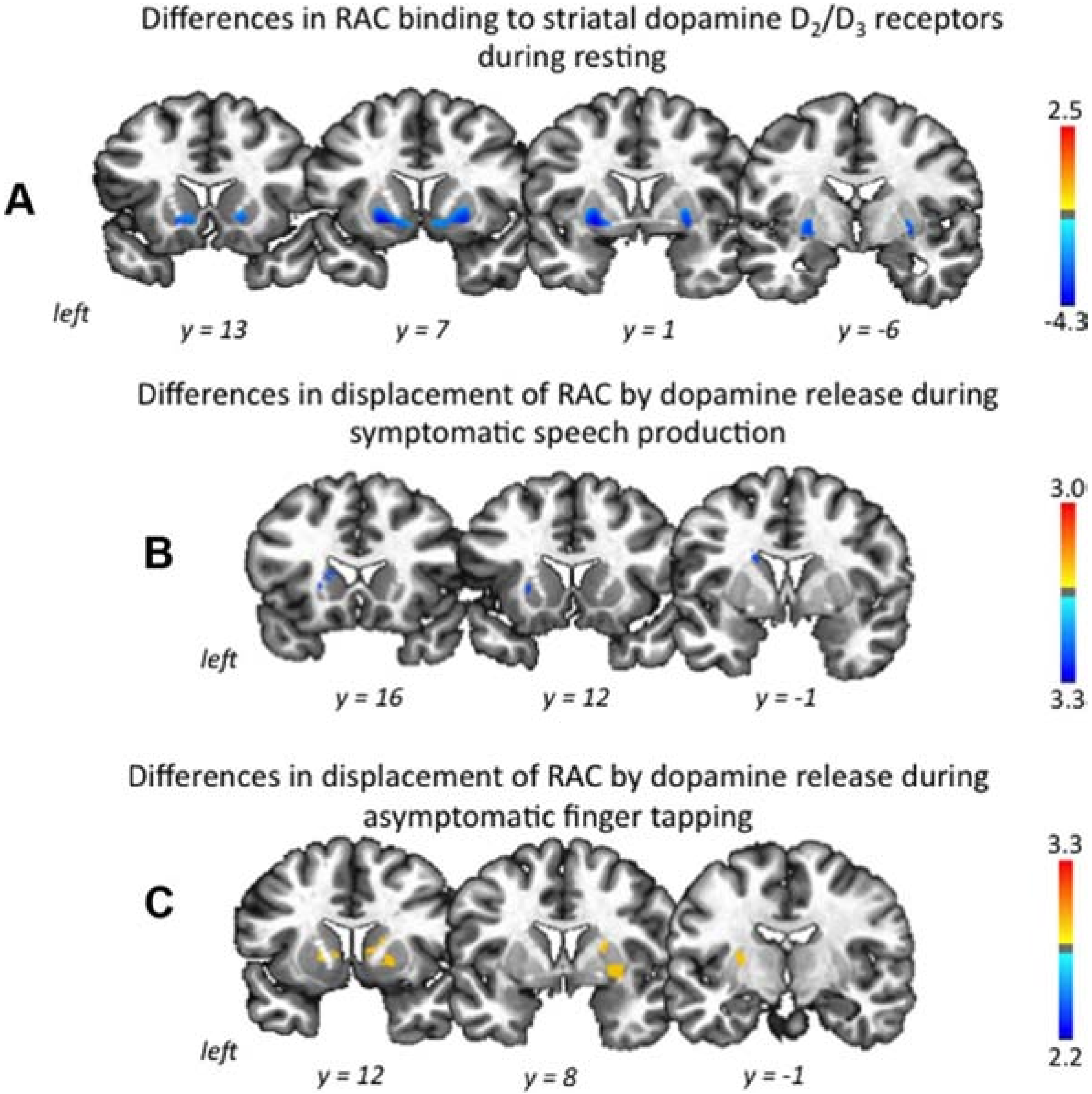
*AD, autosomal dominant; AR autosomal recessive: X-R, X linked recessive. *DYT7 locus on chromosome 18p has been recently questioned (Winter et al., 2012).*

Petrucci & Valente *Frontiers in Neurology* Vol. 4, April 2013



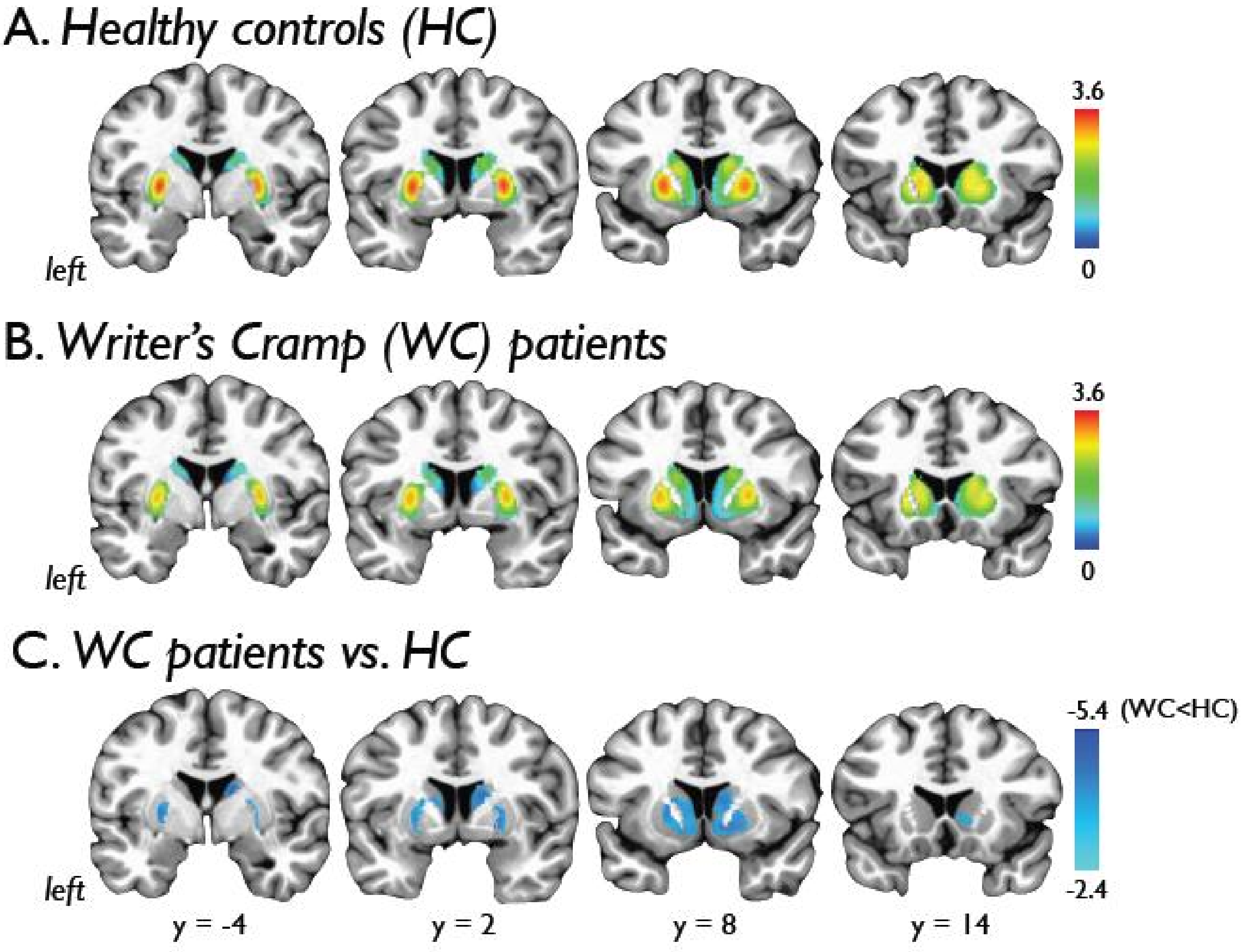
Goodchild et al. TINS in press

Group difference in RAC binding at rest (A) and its change (mean percentage ?BP) during symptomatic speech production (B) and asymptomatic sequential finger tapping (C).



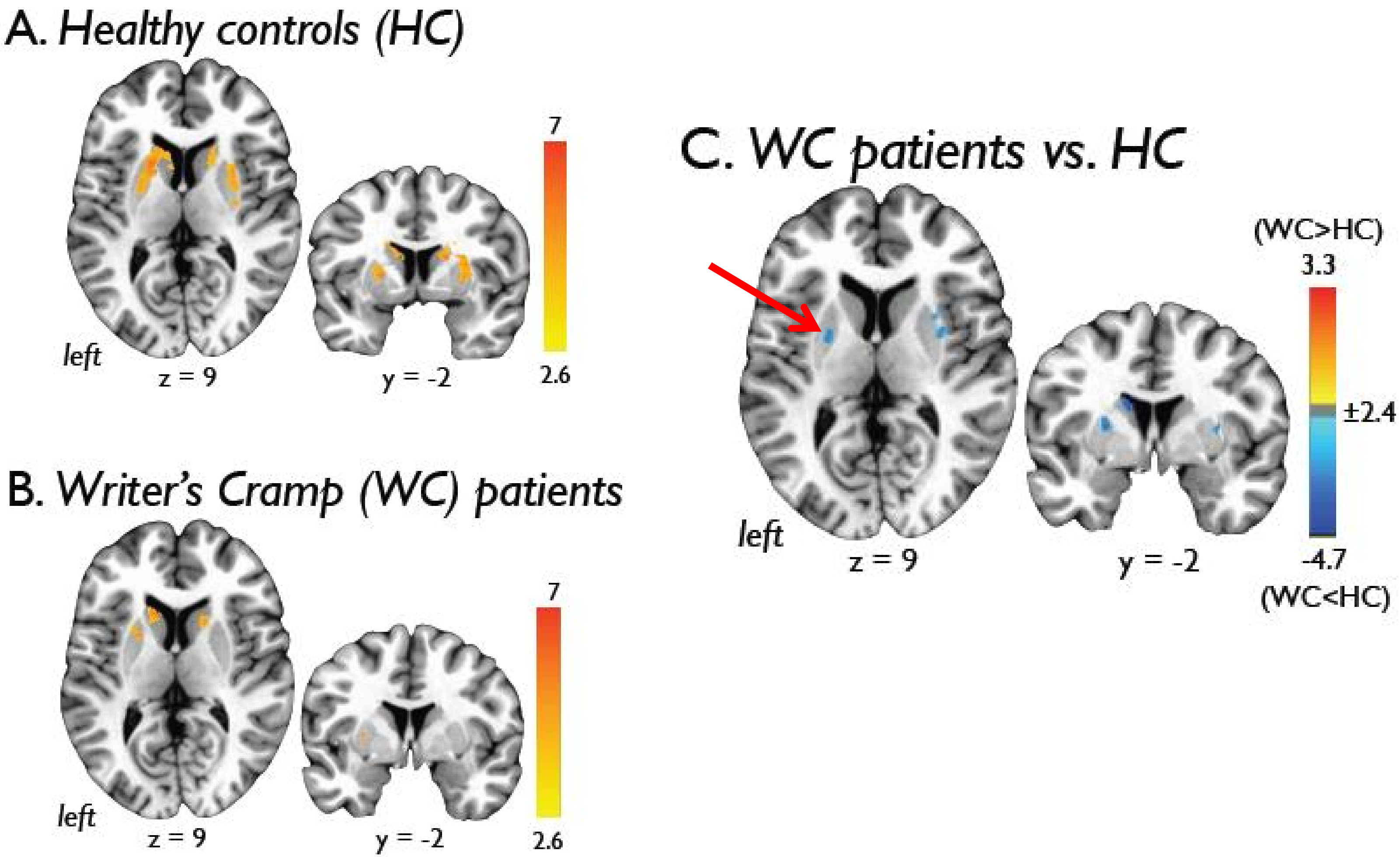
Simonyan, Berman, Herscovitch, Hallett. *J Neurosci* 2013;33:14705-14714

Raclopride binding at rest (D2 receptors)



Berman, Hallett, Herscovitch, Simonyan. *Brain*. In press.

Dopamine release with tapping



Berman, Hallett, Herscovitch, Simonyan. *Brain*. In press.

Translation

- Dopamine can be useful therapy in a number of circumstances

Brain (1985), 108, 463–483

THE ANATOMICAL BASIS OF
YMPTOMATIC HEMIDYSTONIA

N[1], J. A. OBESO[2], J. J. ZARRANZ[3] and A. E. LANG[4] by C. D. MARSDE

TABLE 7. SUMMARY OF DISTRIBUTION OF LESIONS RESPONSIBLE FOR DYSTONIA IN 13 PATIENTS WITH CT SCAN LOCALIZATION AND 7 PATIENTS WITH PATHOLOGY, COMBINED WITH 28 PATIENTS FROM THE PRESENT STUDY

Site of dystonia	*Thalamus*		*Caudate nucleus*		*Lentiform nucleus*		*Internal capsule*		*Cortex*	
	Single	*Combined*	*Single*	*Combined*	*Single*	*Combined*	*Single*	*Combined*	*Single*	*Combined*
Hemidystonia	—	1	1	7	1	8	—	5	—	—
Arm dystonia	1	—	1	3	1	3	—	—	—	—
Hand dystonia	1	1	—	—	1	1	—	—	—	—
Foot dystonia	—	—	—	—	—	—	—	—	—	—
Torticollis	—	—	—	1	—	1	—	—	—	—
Total	2	2	2	11	3	13	0	5	0	0
	4		13		16		5		0	
Data in Table 7 combined with	6	7	5	21	6	24	0	13	0	4
Table 4	13		26		30		13		4	

atients in the literature with thalamus, or in a combination of these structures. Review of 13 other p
th pathologically discrete hemidystonia and lesions defined by CT scan, and of 7 other patients wi
tures. Dystonia may be lesions associated with hemidystonia, also indicated involvement of these struc
he thalamus itself, or due to abnormal input from thalamus to premotor cortex, due to lesions either of th
of the striatum projecting by way of the globus pallidus to the thalamus.

Journal of the Neurological Sciences 331 (2013) 98–101

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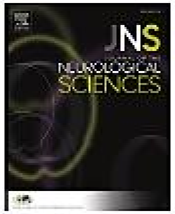


Secondary blepharospasm associated with structural lesions of the brain

M.A. Khooshnoodi, S.A. Factor, H.A. Jinnah *

Department of Neurology, Emory University, Atlanta, USA

A R T I C L E I N F O

A B S T R A C T

Among all 48 cases, lesions were found in multiple regions including the thalamus (n = 12), lower brainstem(n = 11), basal ganglia (n = 9), cerebellum (n = 9), midbrain (n = 7), and cortex (n = 1).

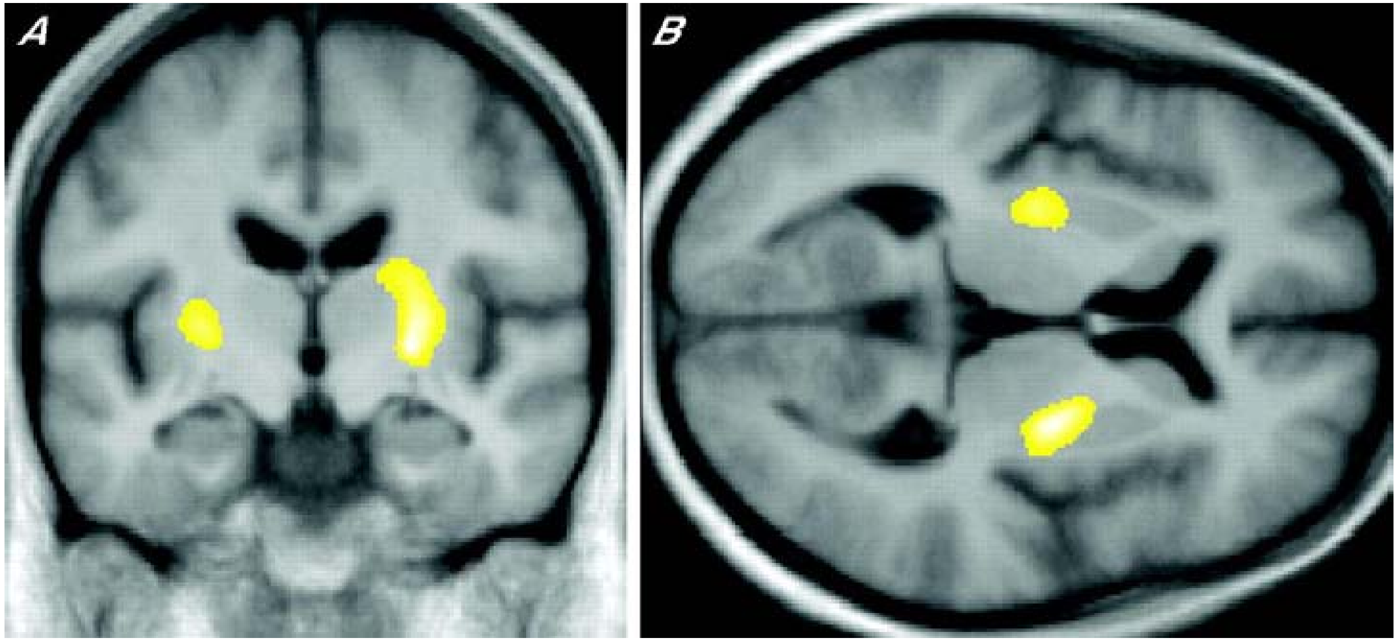
Brainstem
Thalamus

(n = 12), lower brainstem (n = 11), basal ganglia (n = 9), cerebellum (n = 9), midbrain (n = 7), and cortex (n = 1).

Conclusions: These data in combination with functional imaging studies of primary blepharospasm support a model in which a network of different regions plays a role in the pathogenesis of blepharospasm.

Voxel Based Morphometry, VBM

**Grey-matter increase bilaterally in the putamen in Blepharospasm.
Results are projected on (A) coronal and (B) axial slices of the study-specific averaged T1-image in a standard stereotactic space derived from all the 32 study participants.**



Etgen, T et al. J Neurol Neurosurg Psychiatry 2006;77:1017-1020

JNNP ONLINE

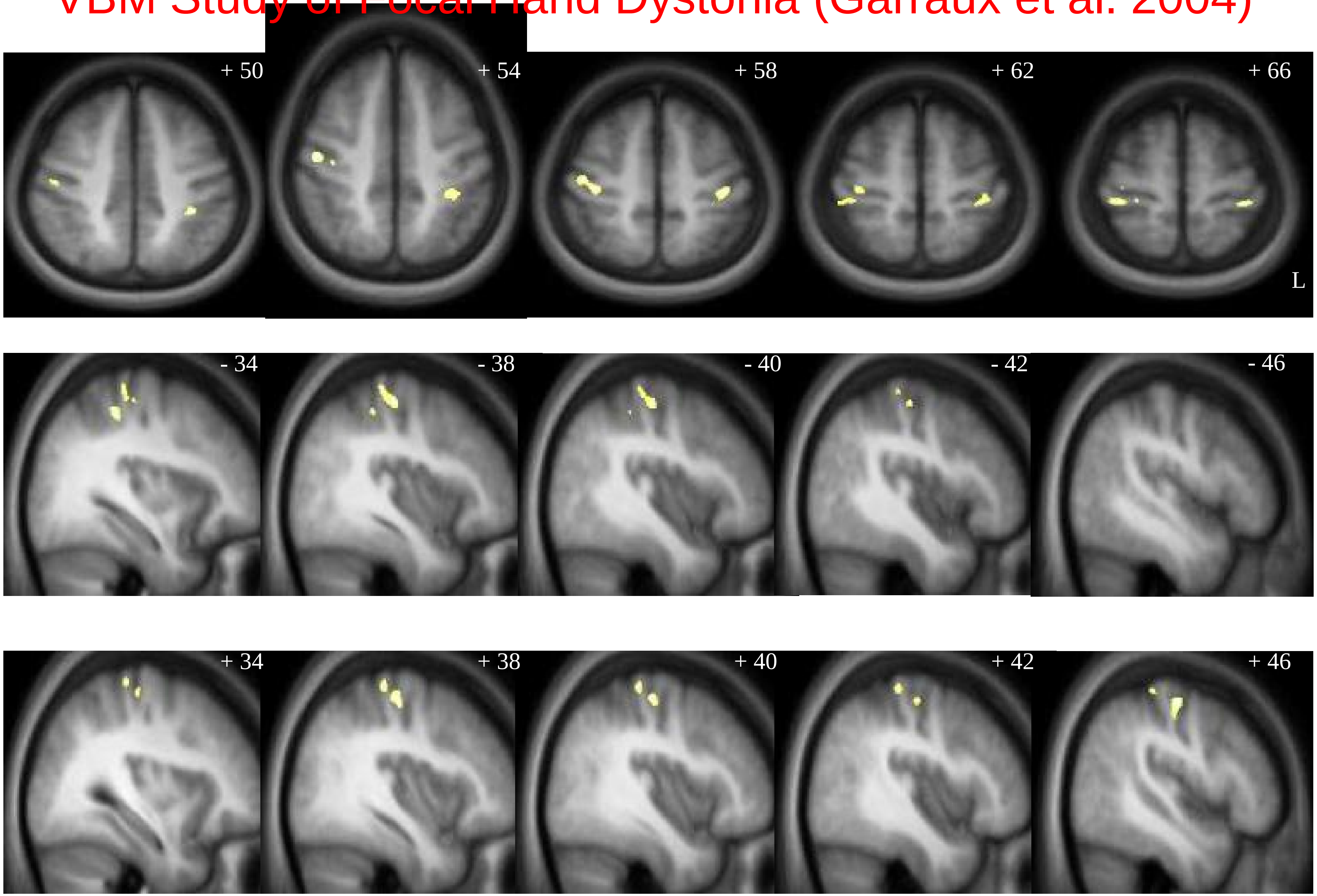
FIG. 3. Blepharospasm patients show gray matter density increase compared with healthy controls.

FIG. 4. Blepharospasm patients show gray matter density decrease compared with healthy controls.

BEB subjects had increased gray matter in the caudate head and cerebellum bilaterally as well as decrease in the putamen and thalamus bilaterally.

Obermann et al. 2007

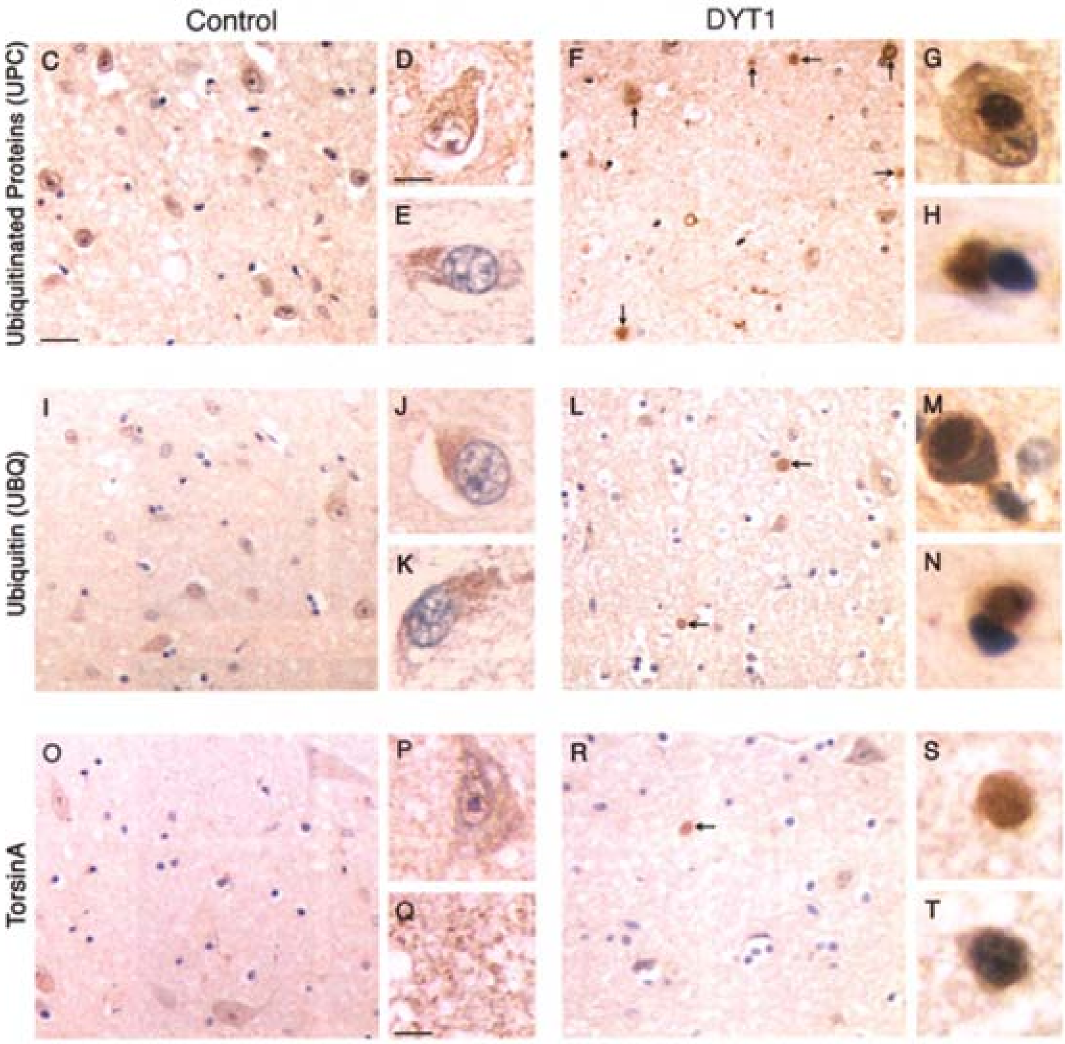
VBM Study of Focal Hand Dystonia (Garraux et al. 2004)



Increased gray matter in sensory cortex bilaterally

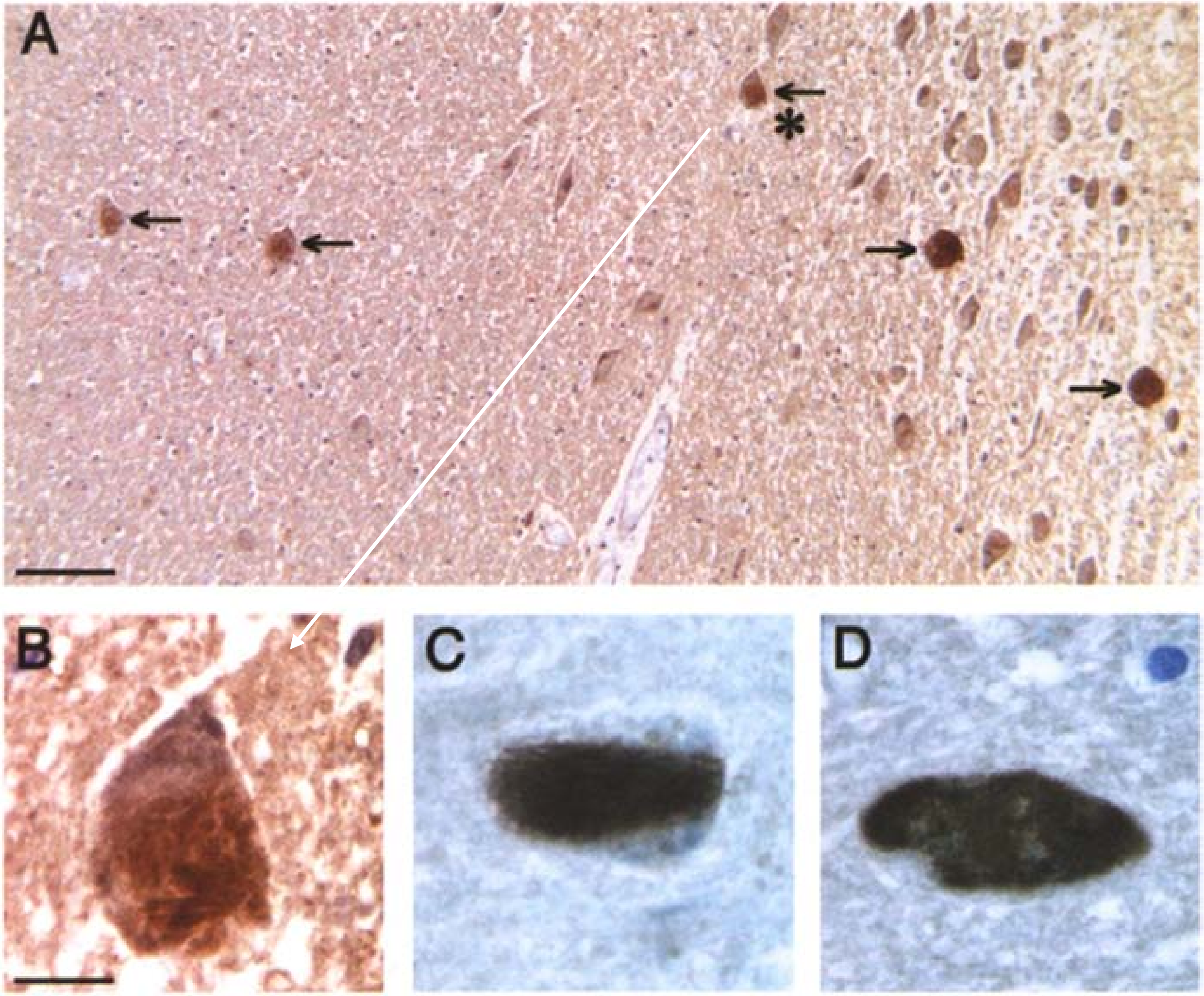
Pathology in DYT1 dystonia:

Perinuclear inclusions in midbrain reticular formation and periaqueductal gray (including the PPN)



McNaught et al. 2004

Pathology in DYT1 dystonia:
Tau/Ubiquitin staining in SNpc and LC



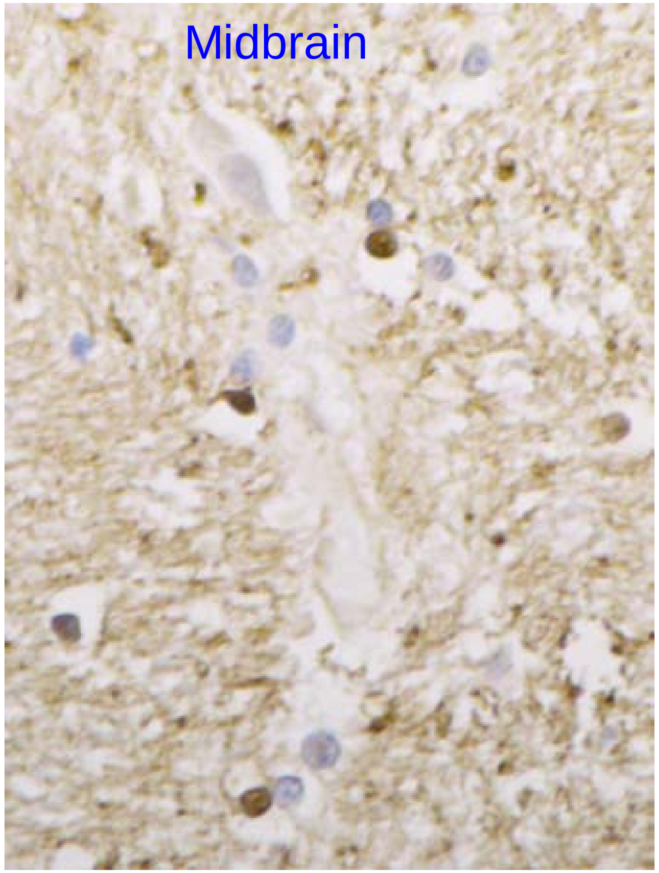
A-C is LC
D is SNpc

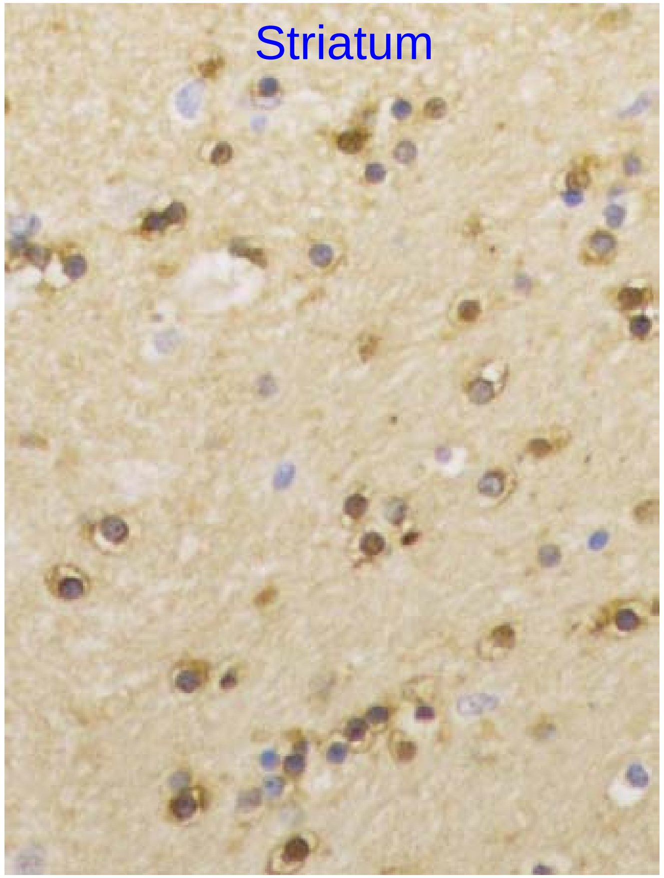
A-B is ubiquitin staining

C-D is tau staining

McNaught et al. 2004

Pathology in DYT1 dystonia: NIH work in progress



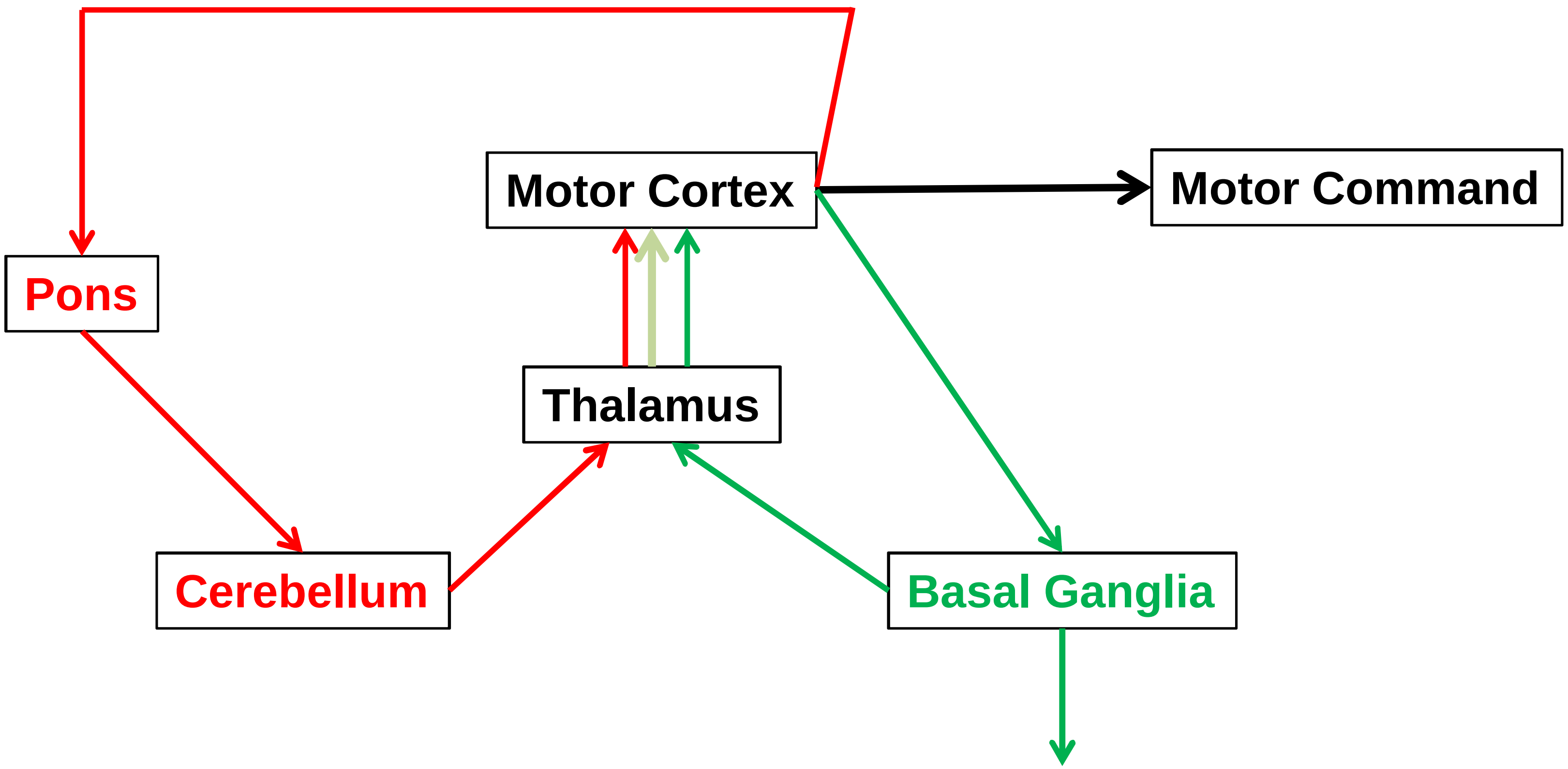


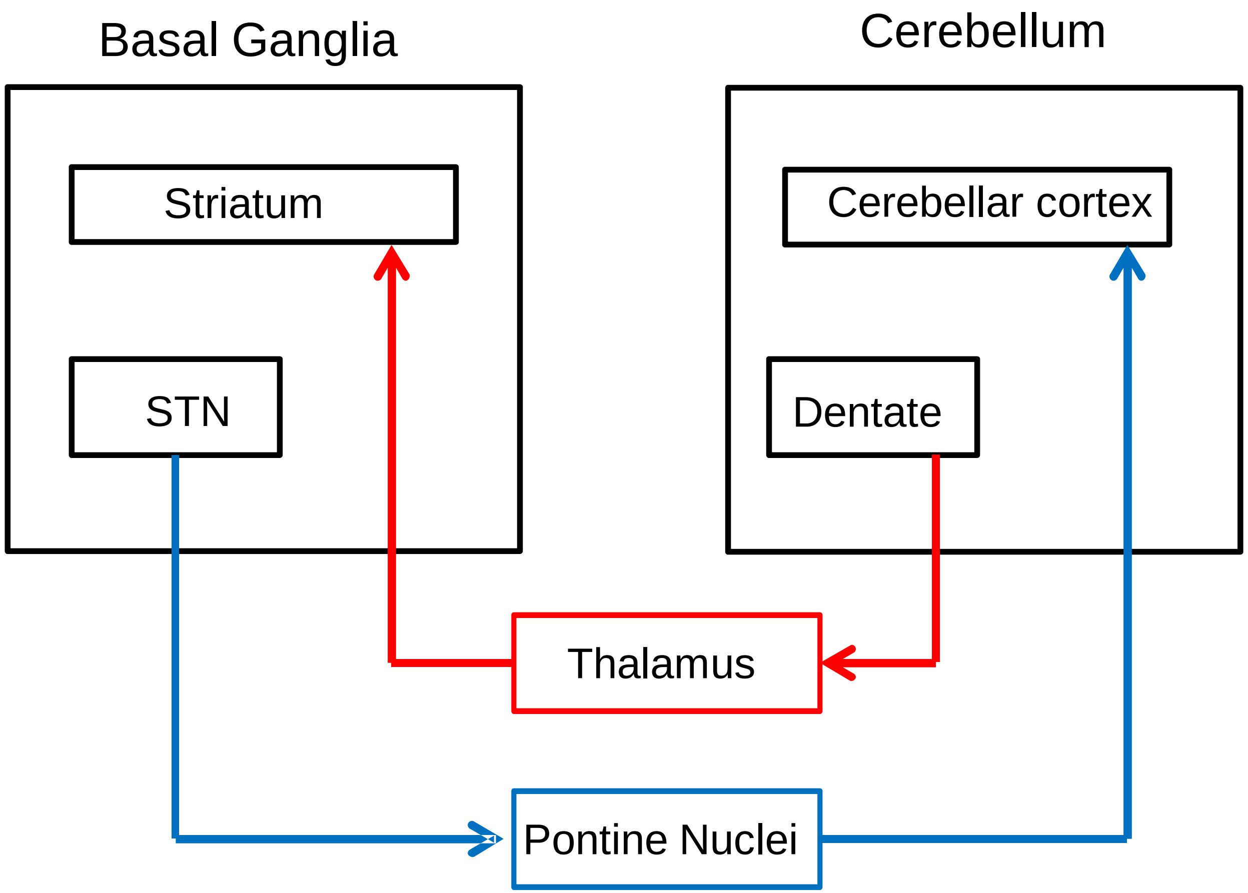
Ubiquitin protein conjugate staining of midbrain (3 of 5 cases) AND striatum (5 of 7 cases)

Also some TorsinA staining in both regions…

Ray-Chaudhury, Rahimpour, Tinaz, Edwards, Hallett

Subcortical Influences




Basal Ganglia
Cerebellum
Striatum
Cerebellar cortex
STN
Dentate
Thalamus
Pontine Nuclei

Role of the Cerebellum in Dystonia

- Animal models
  - Calderon et al. *Nat Neurosci* 2011: model of DYT12
  - Raike et al. *Neurobiol Dis* 2012: limited Purkinje cell lesions produced focal dystonias
- TMS studies
  - Brighina et al. *Exp Brain Res* 2009: reduced cerebellar-motor cortex inhibition
- Cerebellar control of cortical plasticity
  - Hubsch et al. *Brain* 2013: reduced cerebellar influence on paired-associative stimulation in motor cortex
- Eye blink conditioning
  - Teo et al. *JNNP* 2009: reduced conditioning

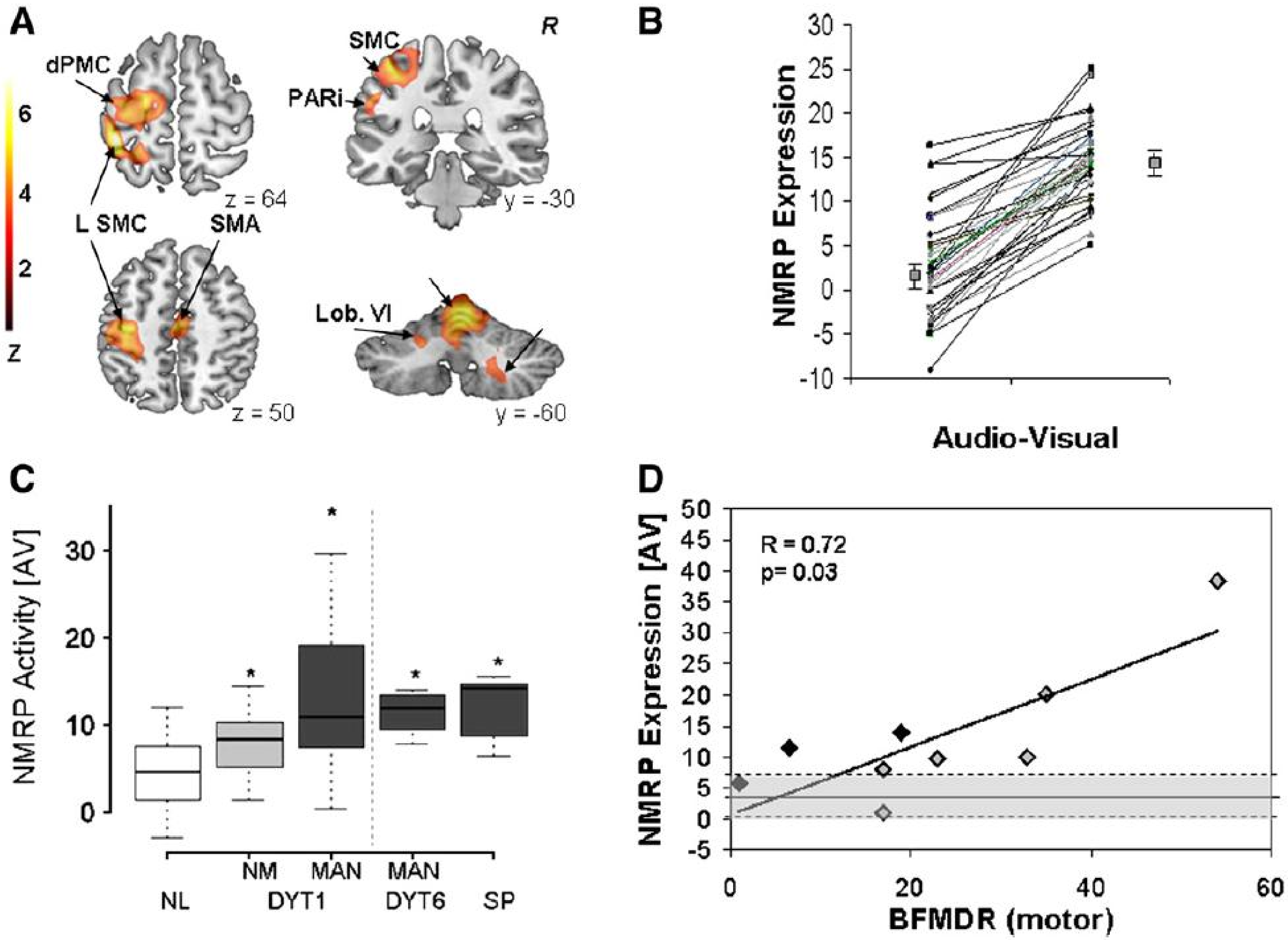
Role of the Cerebellum in Dystonia

- Imaging
  - Structural abnormalities
    - Delmaire et al. *Neurology* 2007: decreased gray matter
  - Activation abnormalities
    - Niethammer et al. *Neurobiol Dis* 2011: PET: increase in normal motor-related activation pattern (NMRP)
    - Several studies: fMRI: various (mild) abnormalities
  - Connectivity abnormalities
    - Argyelan et al. *J Neurosci* 2009
    - Gallea et al. In preparation

Statistical parametric maps demonstrating structural decrease in gray matter between patients with focal hand dystonia and control subjects

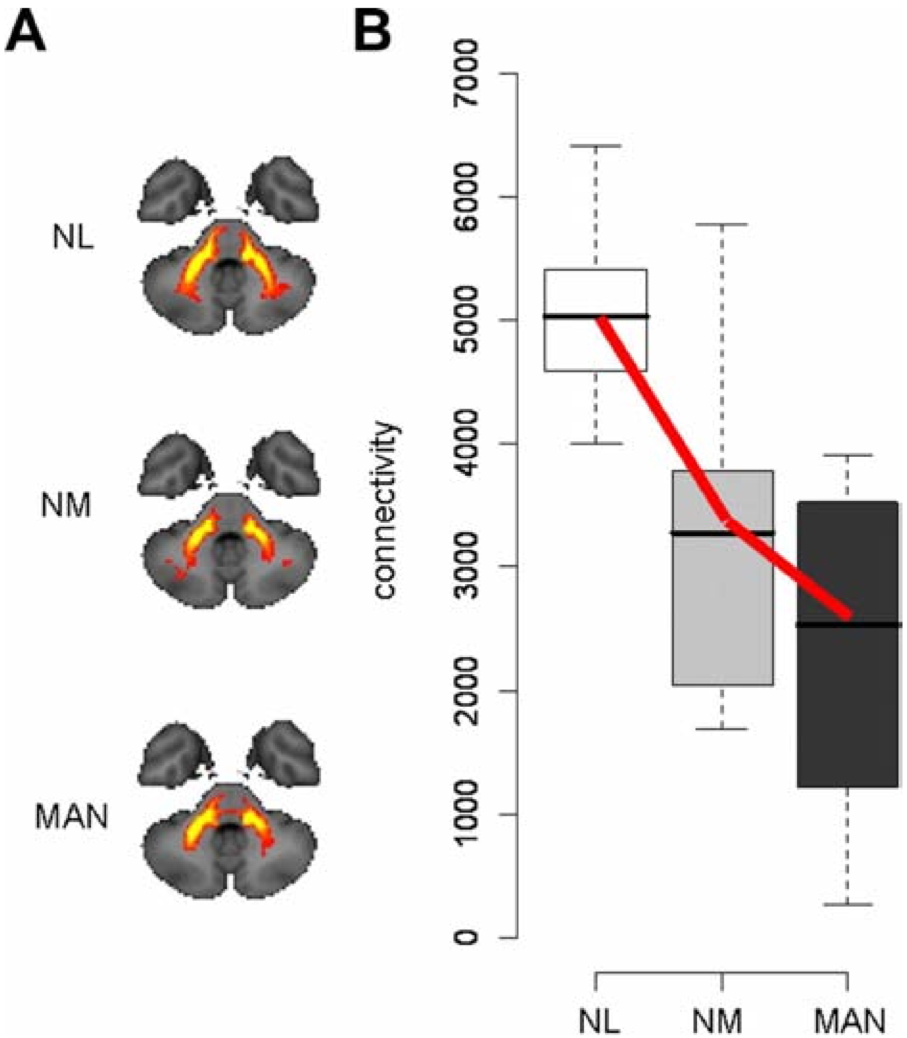
Delmaire C et al. Neurology 2007;69:376-380

“Normal motor-related activation pattern” (NMRP) in DYT1



Martin Niethammer , Maren Carbon , Miklos Argyelan , David Eidelberg
Hereditary dystonia as a neurodevelopmental circuit disorder: Evidence from neuroimaging
Neurobiology of Disease Volume 42, Issue 2 2011 202 - 209
http://dx.doi.org/10.1016/j.nbd.2010.10.010

Reduced dentatothalamic DTI in DYT1 gene carriers



Argyelan M et al. J. Neurosci. 2009;29:9740-9747

The Journal of Neuroscience

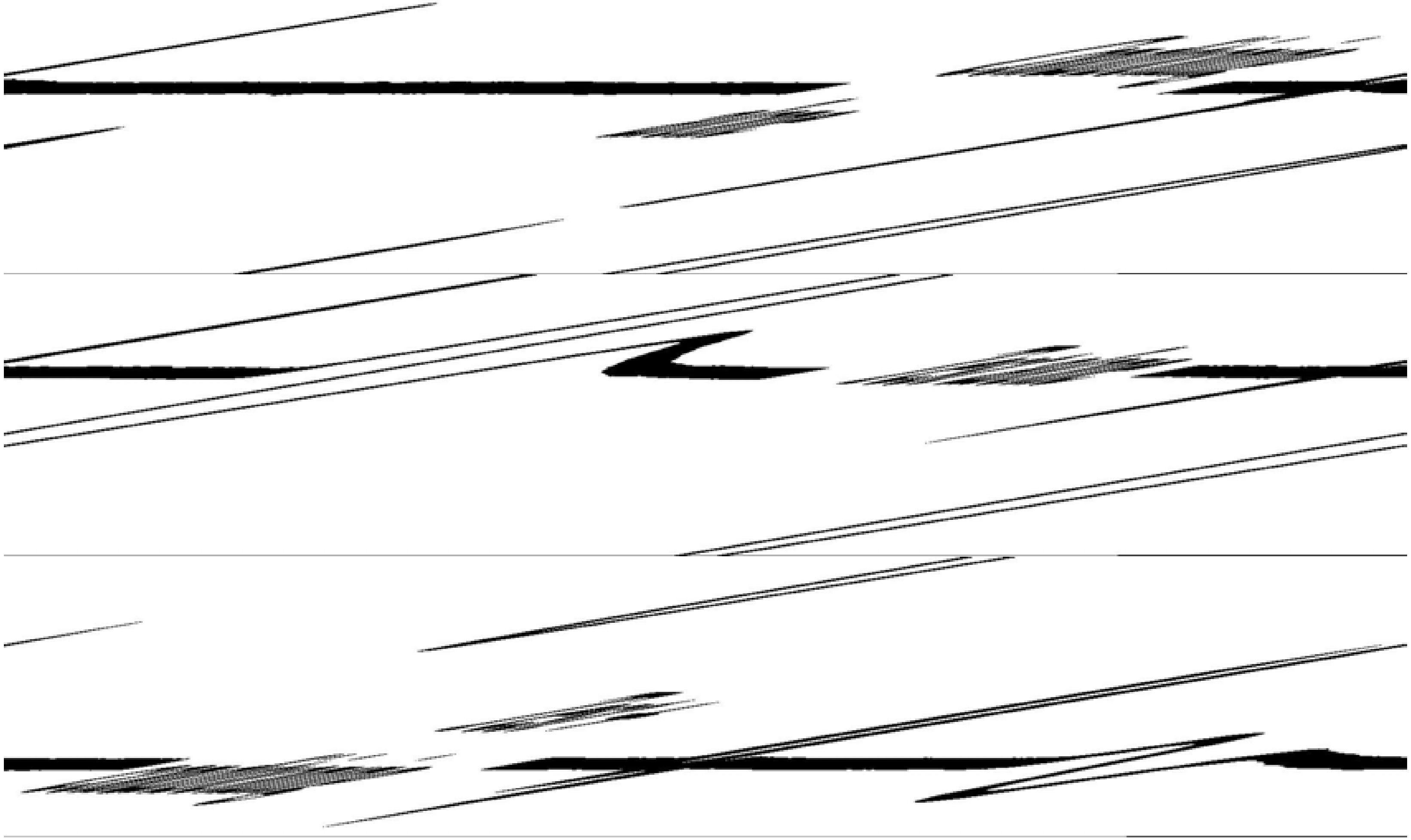
Pathophysiology

- Loss of inhibition
  - Demonstrated in many inhibitory networks at spinal, brainstem and cortical levels
  - Surround inhibition is specifically affected
- Sensory abnormalities
  - Subtle but definite effects in both spatial and temporal discrimination
- Abnormal plasticity
  - "Enhanced" but loss of homeostatic feature

Technique of Paired-Pulse Stimulation

To assess short intracortical inhibition, SICI

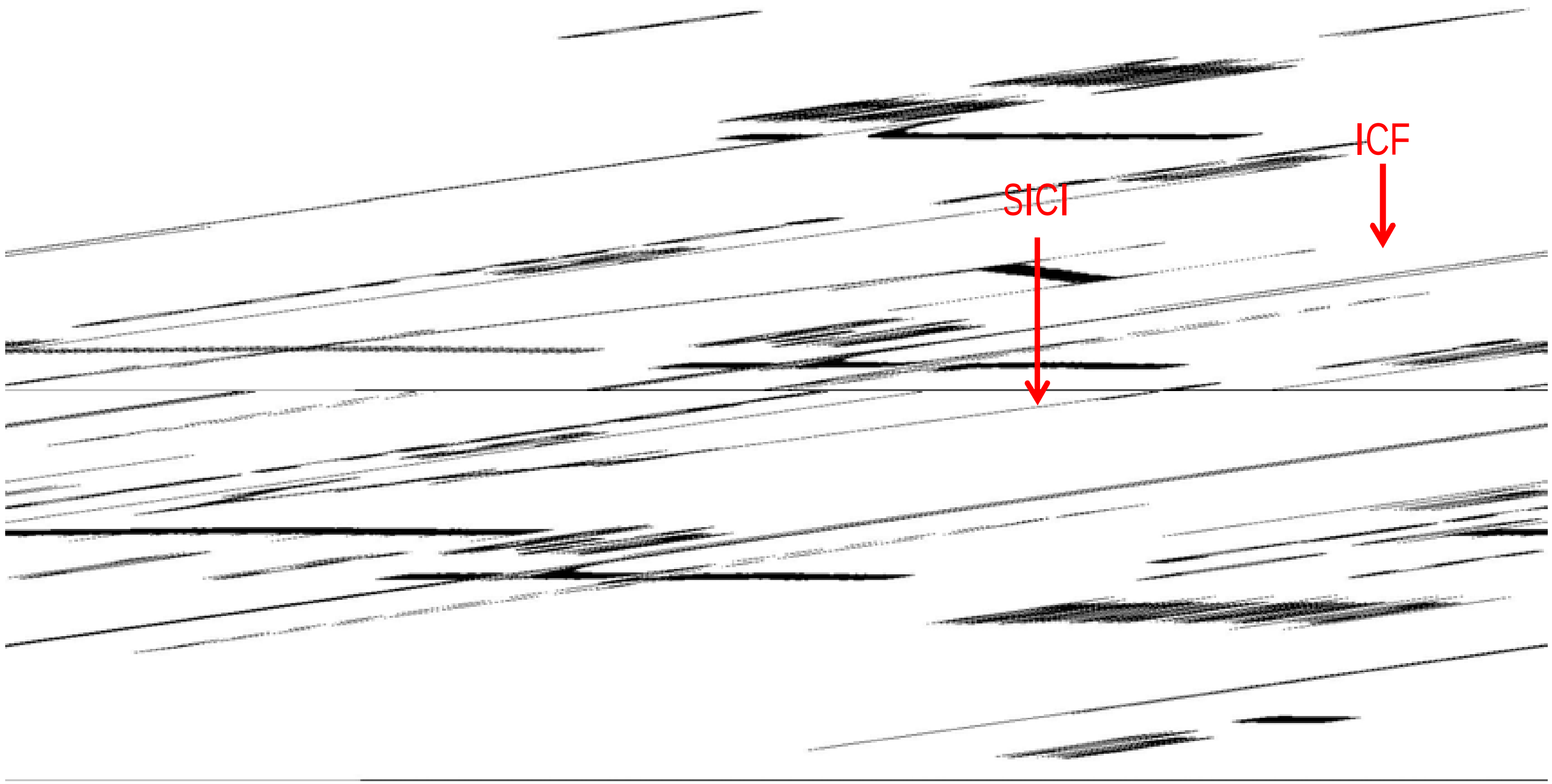
(and intracortical facilitation, ICF)



2 ms ISI

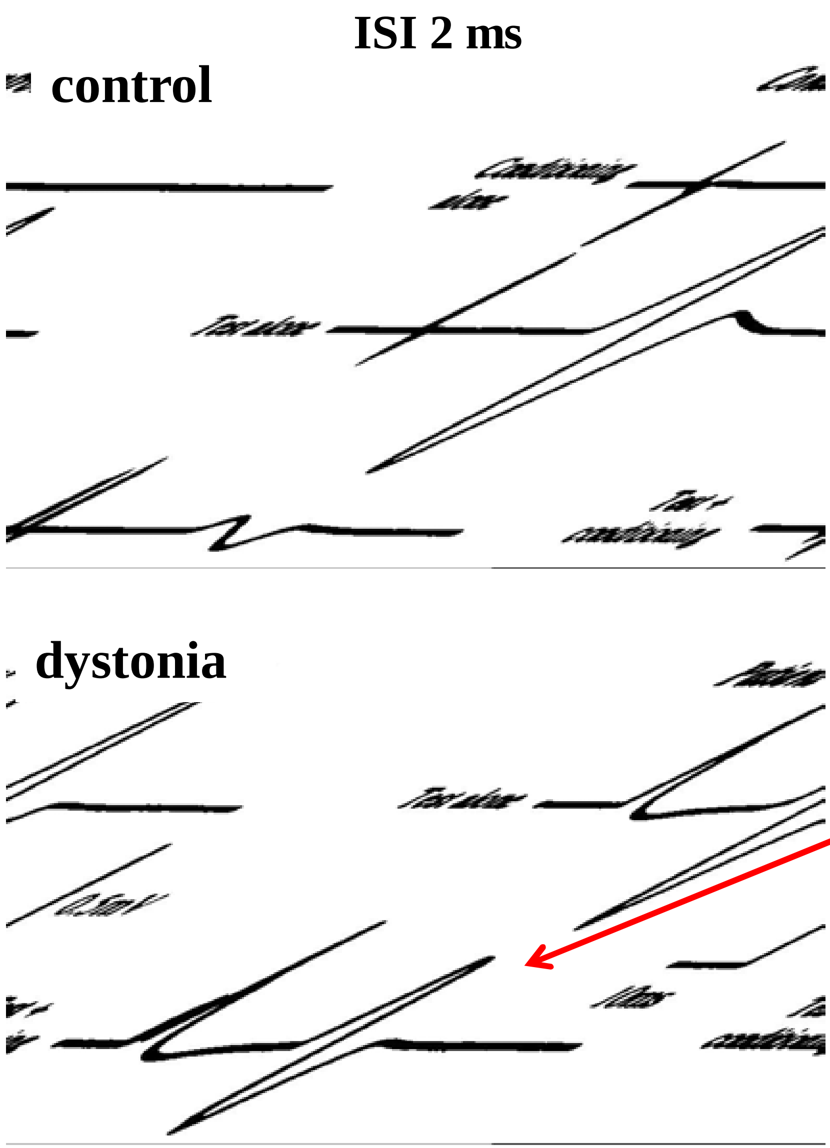
Kujirai et al. 1993

Technique of Paired-Pulse Stimulation



Kujirai et al. 1993

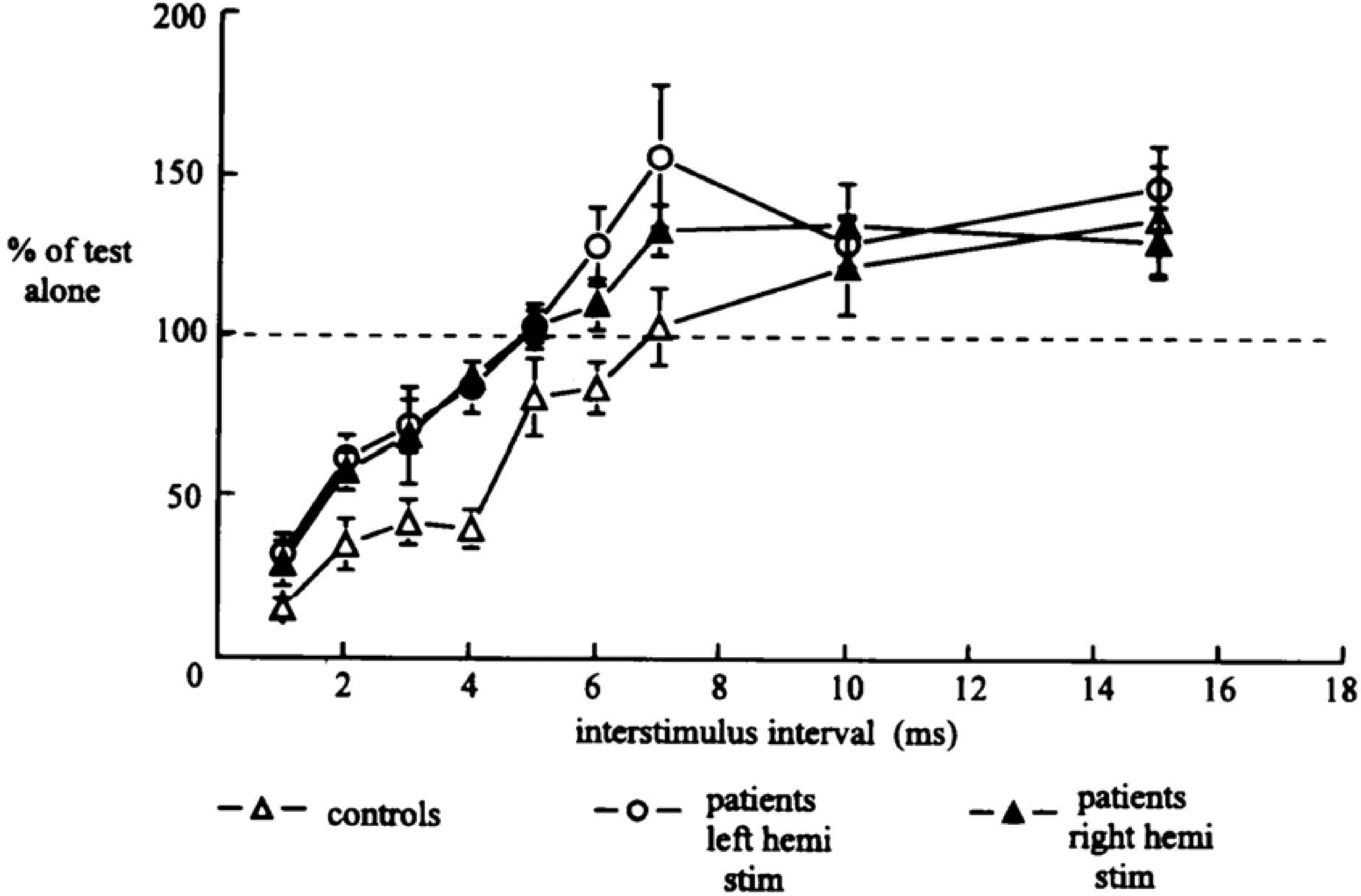
Intracortical Inhibition In Dystonia



Less inhibition

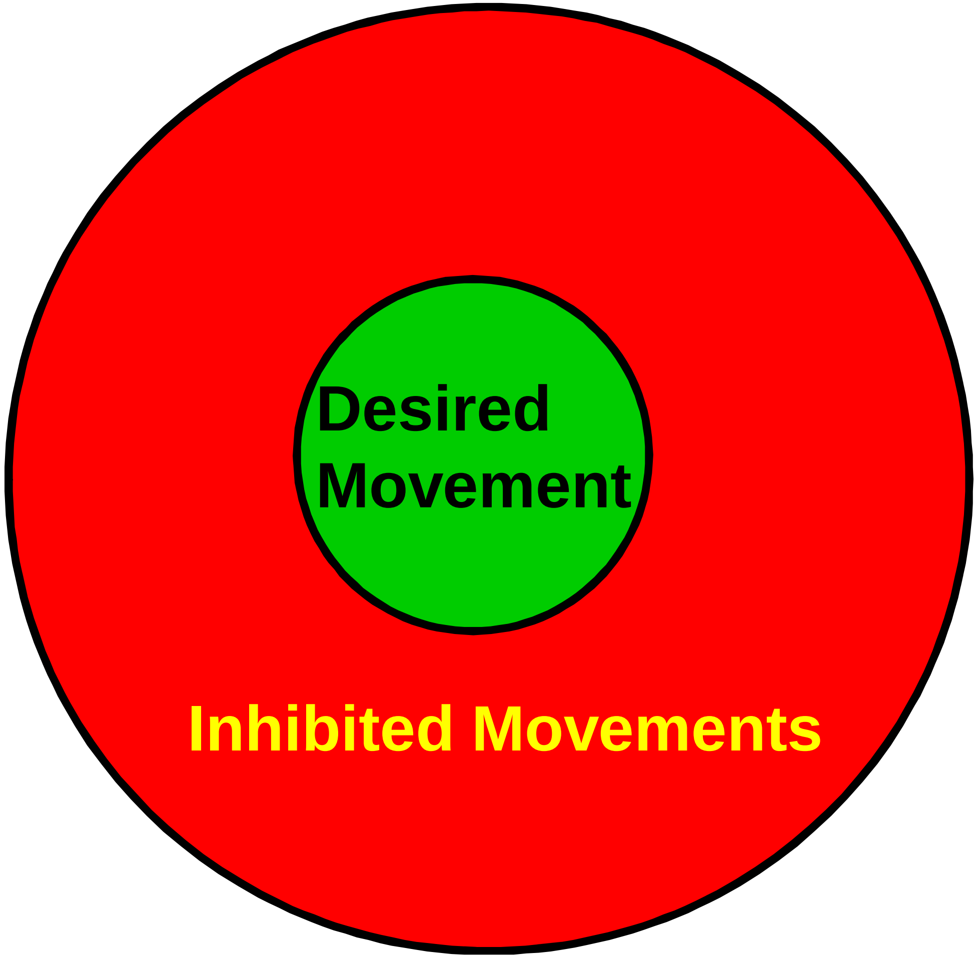
Ridding et al. 1995

ICI and ICF in Dystonia

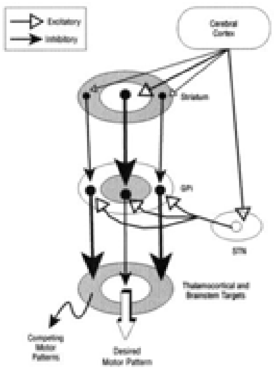


Ridding et al. 1995

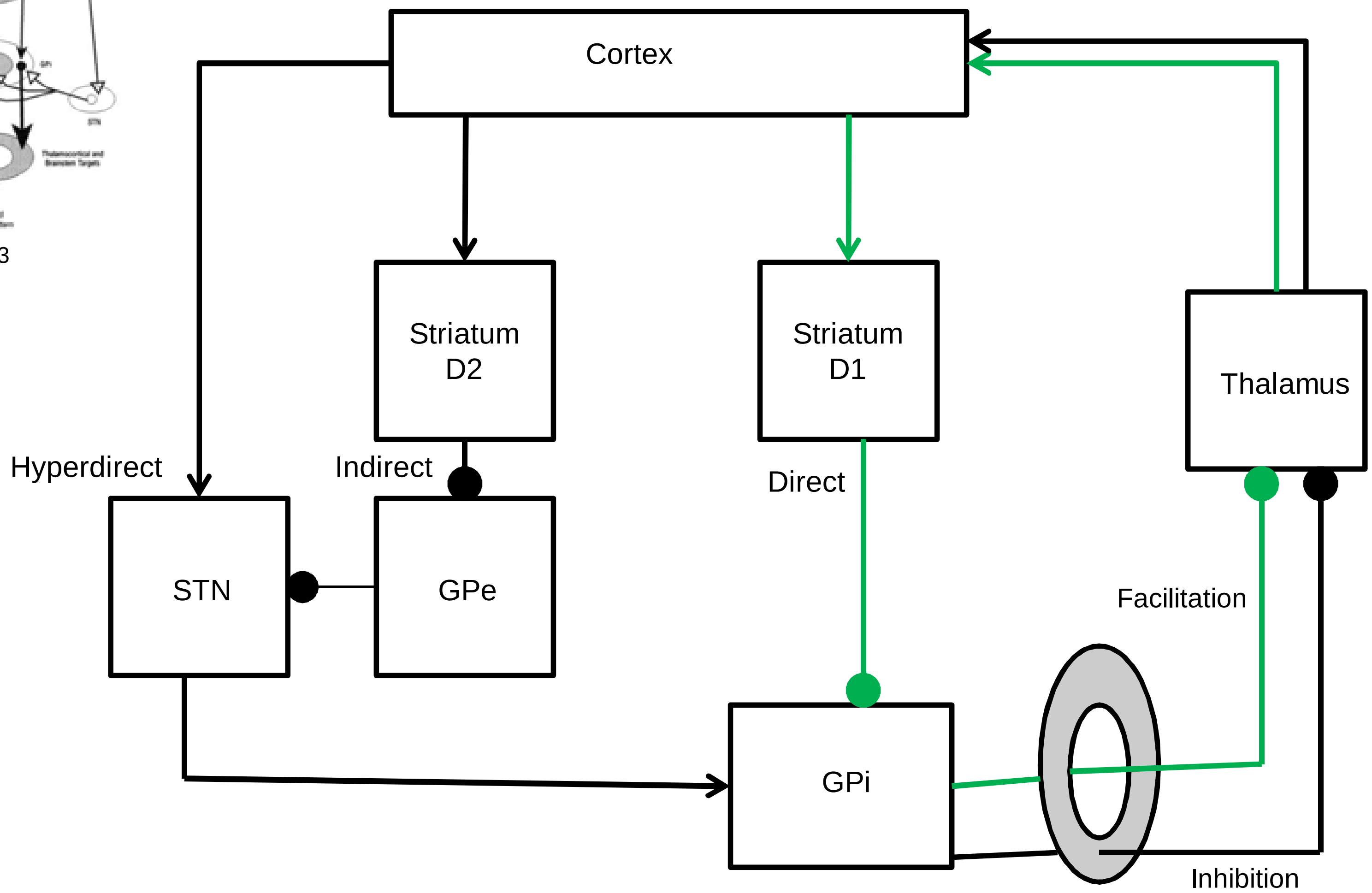
Physiology of making selective movement



Surround Inhibition



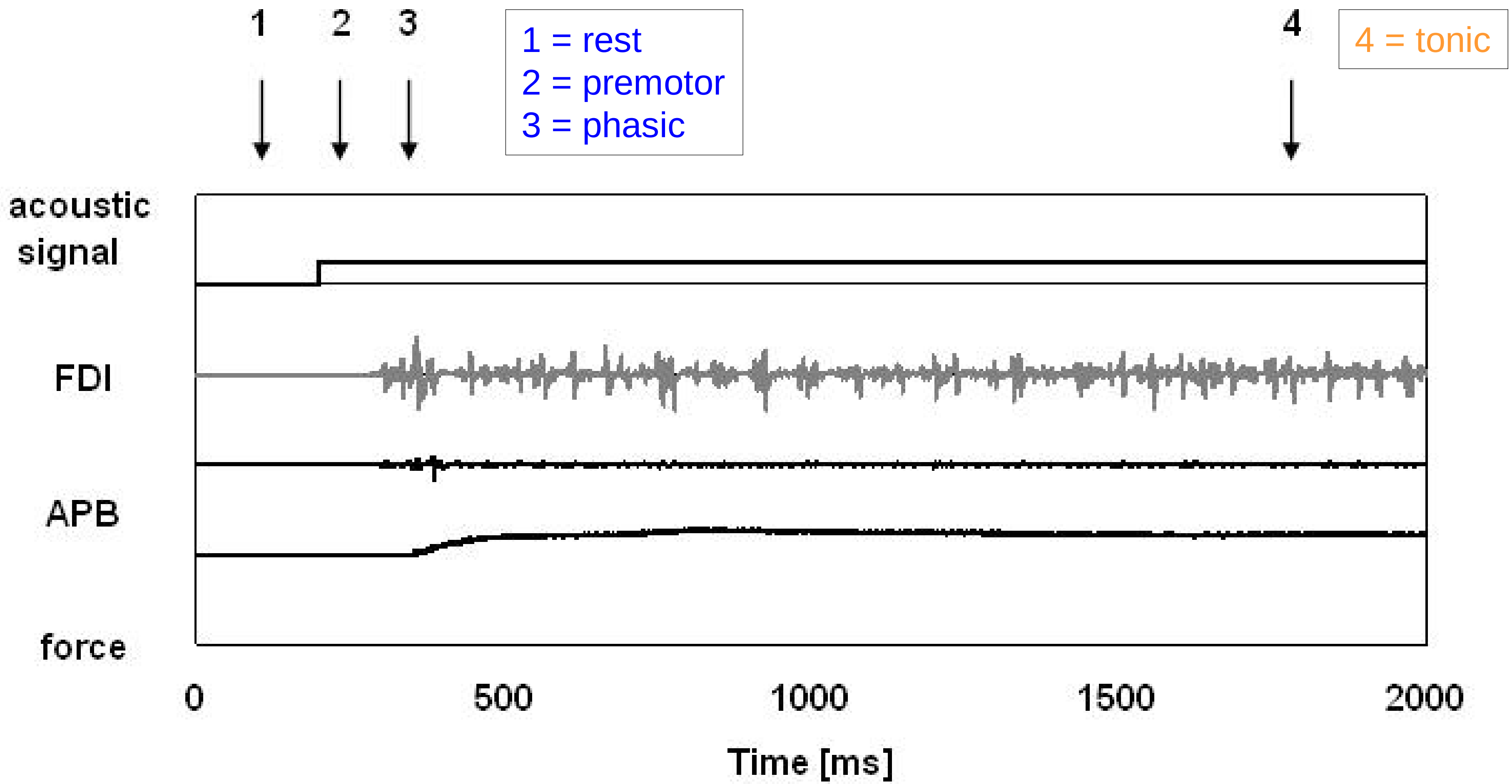
Mink 2003



Facilitation occurs with reduction of GPi output
Inhibition occurs with increase in GPi output

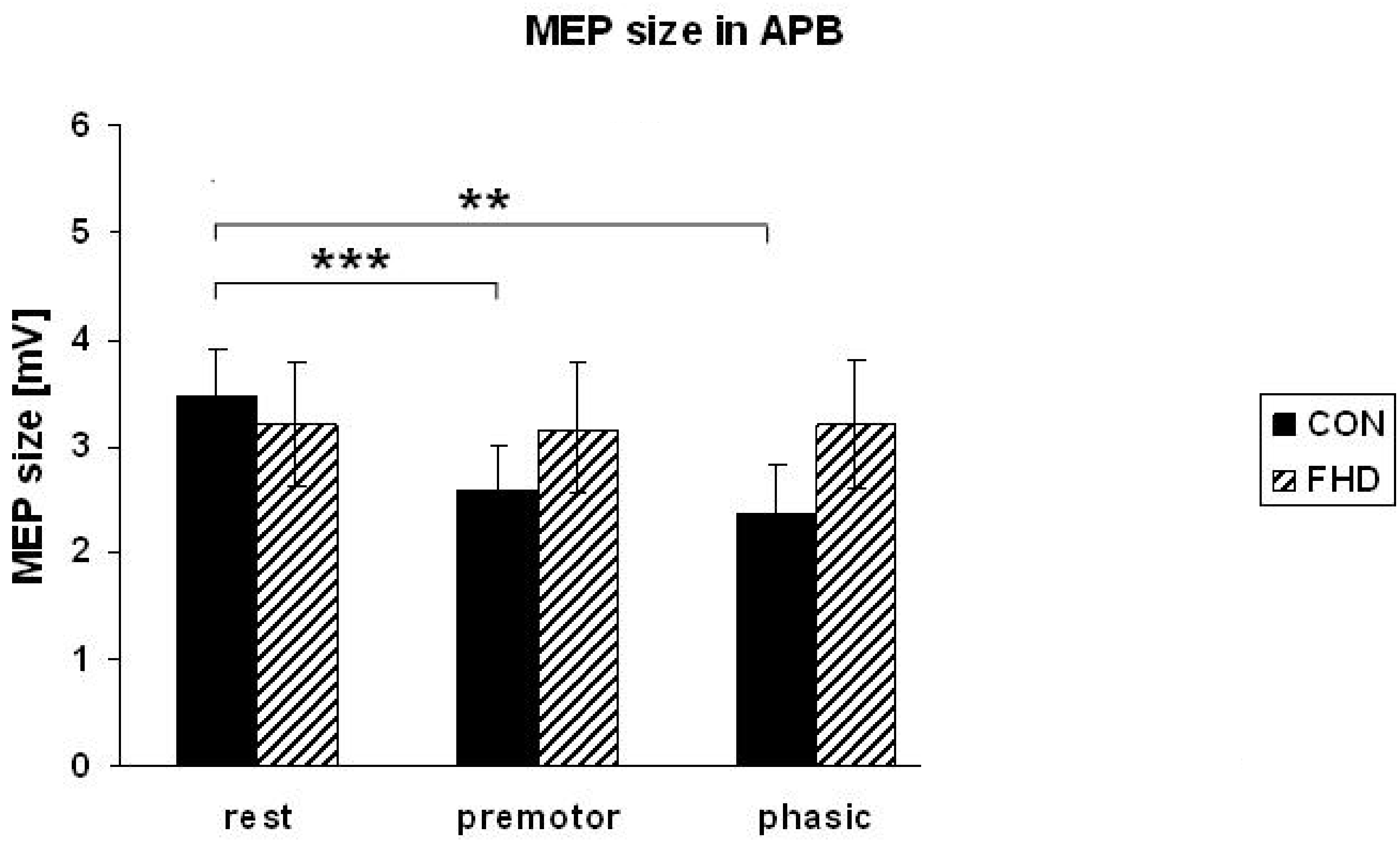
A center-surround organization of GPi output can sharpen the motor command

Method for Studying Surround Inhibition



Beck et al. *J Neurosci* 2008;28:10363

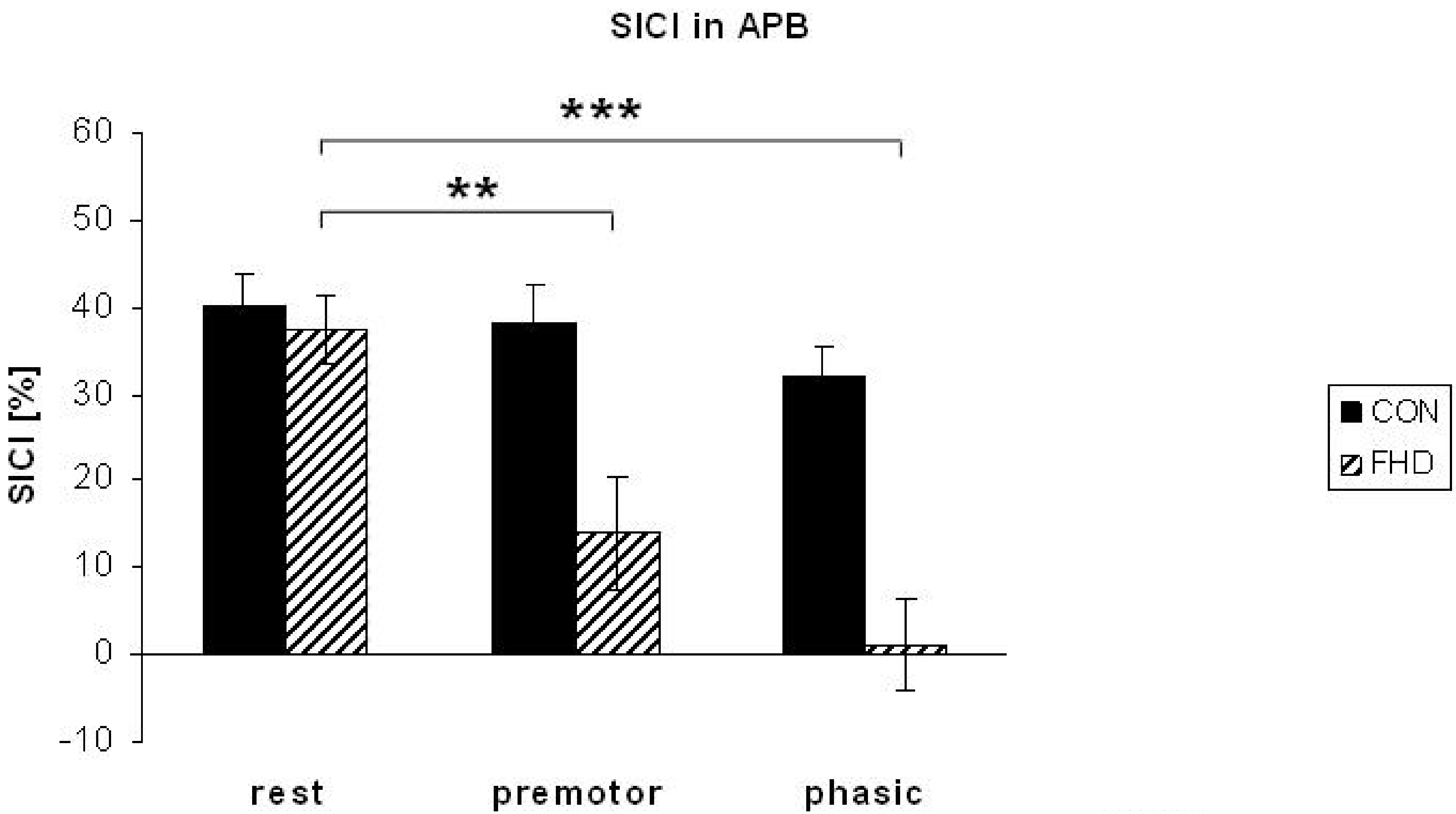
Surround Inhibition is absent in Focal Hand Dystonia



Beck et al. *J Neurosci* 2008;28:10363

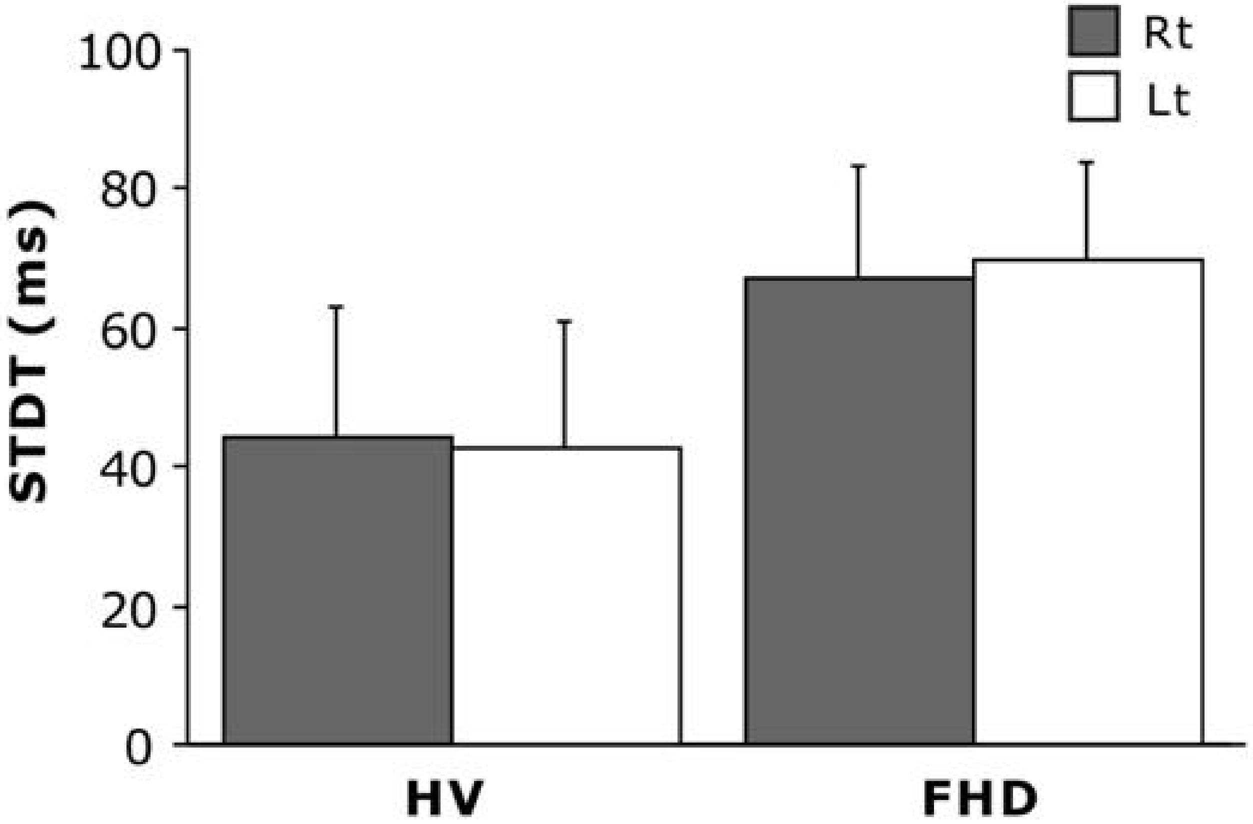
Conclude: Overflow seems due to loss of inhibition

SICI in normals is not a mechanism for SI, but it is abnormal in focal hand dystonia



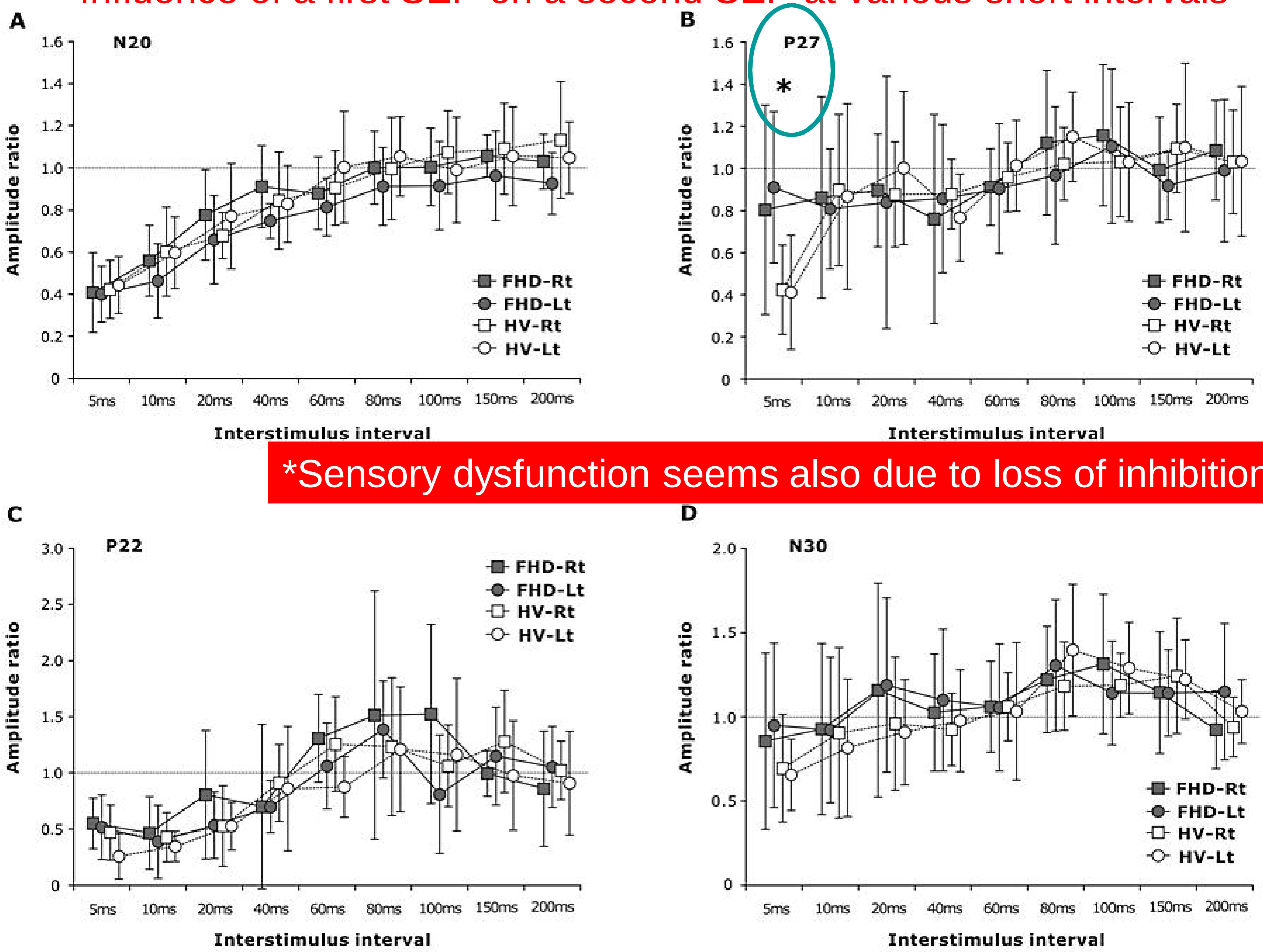
Beck et al. *J Neurosci* 2008;28:10363

Temporal Discrimination



Tamura et al. *Mov Disord* 2008;23:558

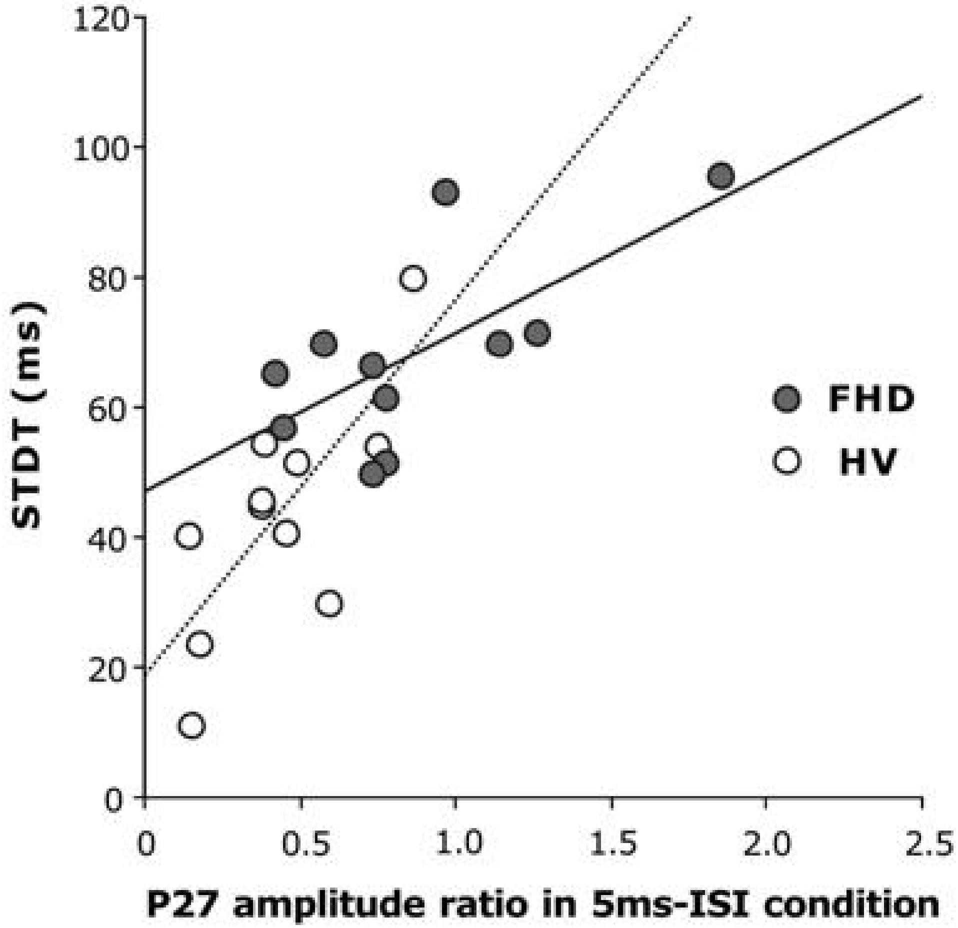
Influence of a first SEP on a second SEP at various short intervals



Sensory dysfunction seems also due to loss of inhibition

Tamura et al. *Mov Disord* 2008;23:558

Temporal Discrimination Correlates with Loss of Sensory Inhibition

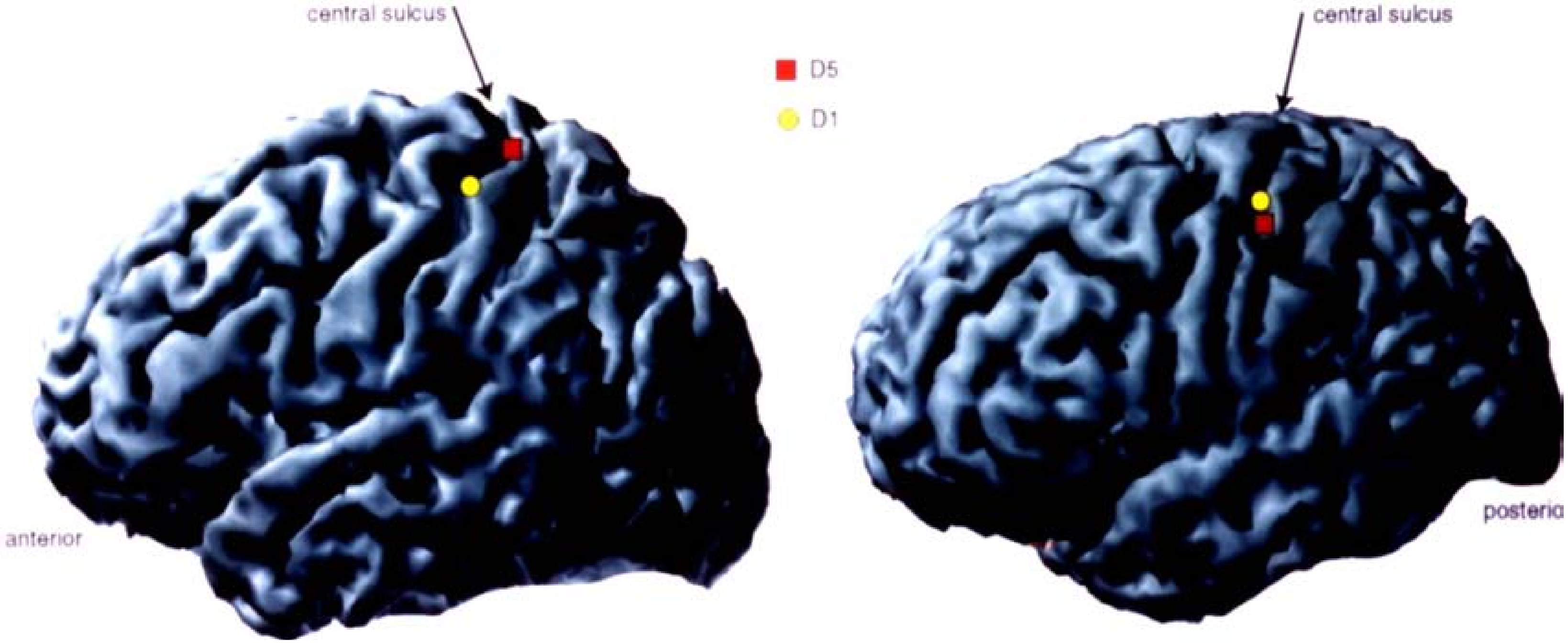


Tamura et al. *Mov Disord* 2008;23:558

SEP mapping of fingers

Normal

Dystonia



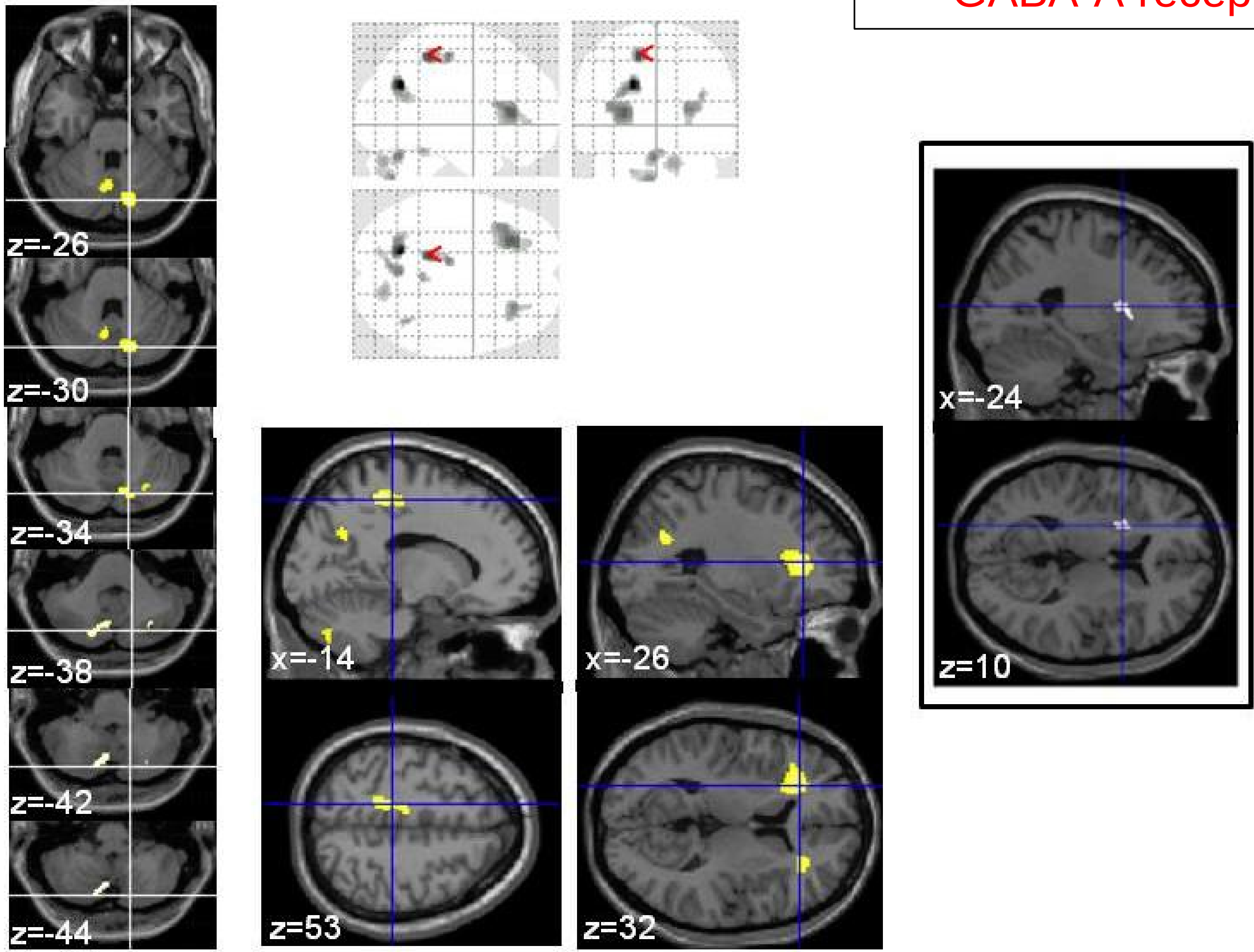
Bara et al. *Ann Neurol* 1998;44:828

Loss of GABA

- GABA MRS
  - Levy & Hallett 2002
  - Herath et al. 2010
- Flumazenil PET
  - Garibotto et al. 2011
  - Gallea et al. in preparation
    - M1, Putamen, Cerebellum

Flumazenil binds to the GABA-A receptor

FMZ-BP
Patients<Controls



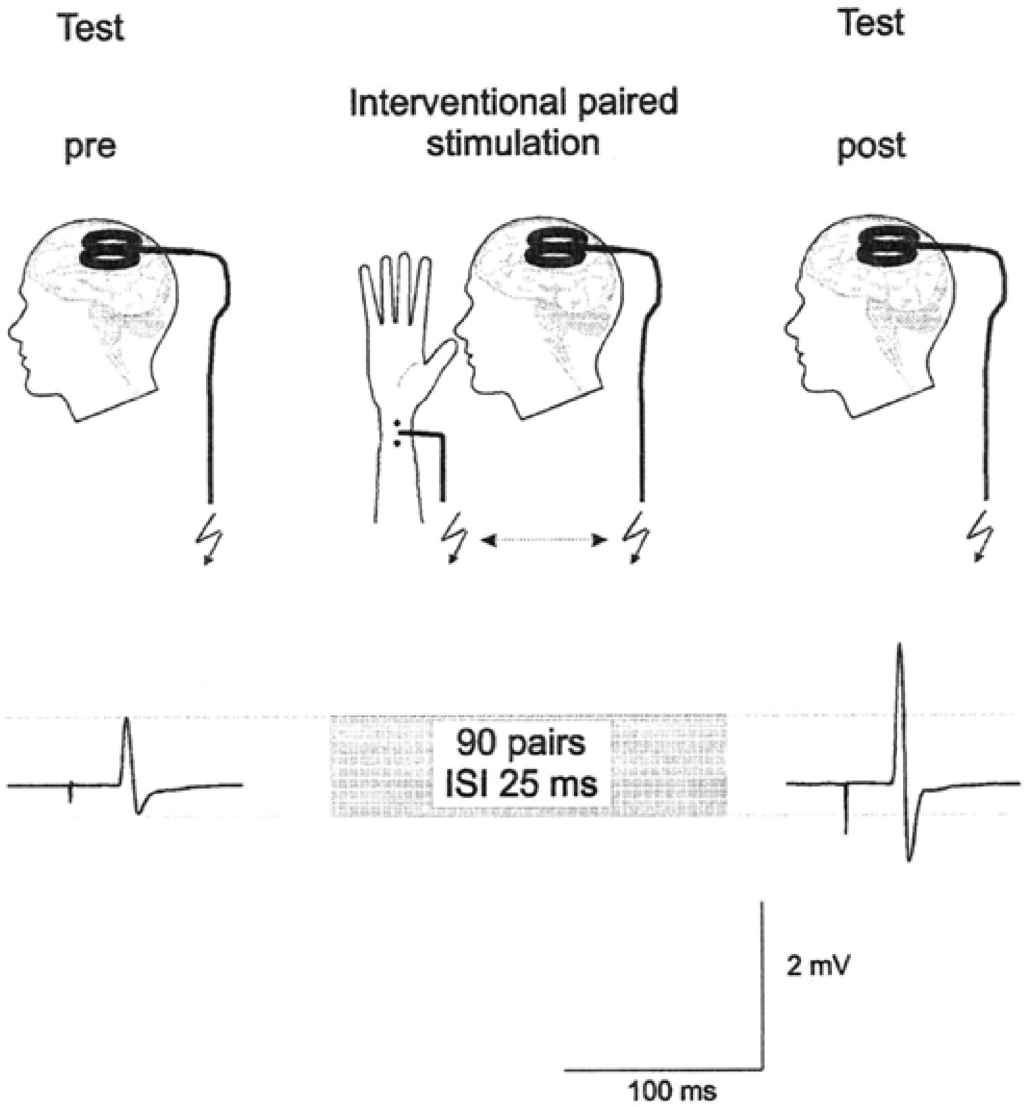
Lower Flumazenil Binding in FHD in right cerebellum, left sensorimotor cortex, bilateral anterior insula, left dorsal posterior putamen (Gallea et al in preparation).

Translation

- Increasing inhibition with GABAergic agents can be useful therapy in a number of circumstances
- Increasing cortical inhibition with TMS techniques has also shown transient benefit

Increase of Plasticity

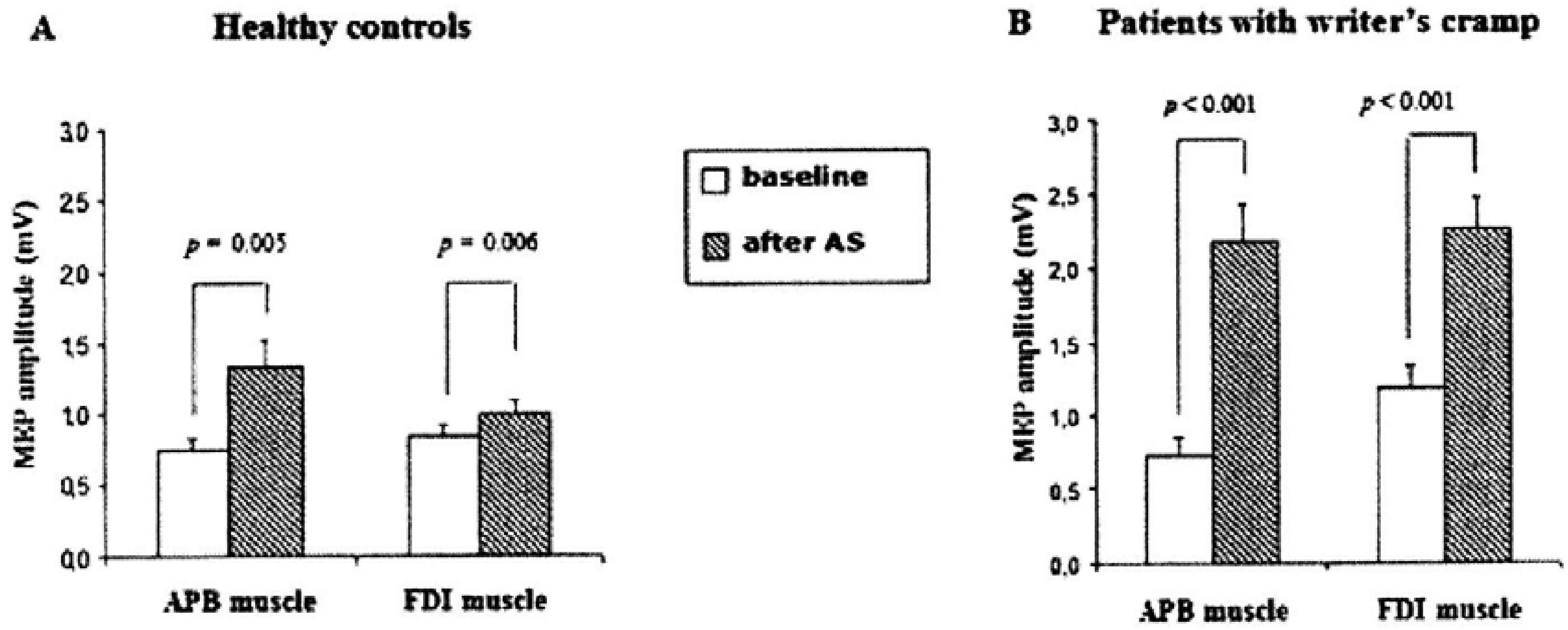
Technique of Paired Associative Stimulation



LTP-like plasticity

Stefan et al. 2000 (Classen Laboratory)

Increase in PAS in Dystonia



Quartarone et al 2003

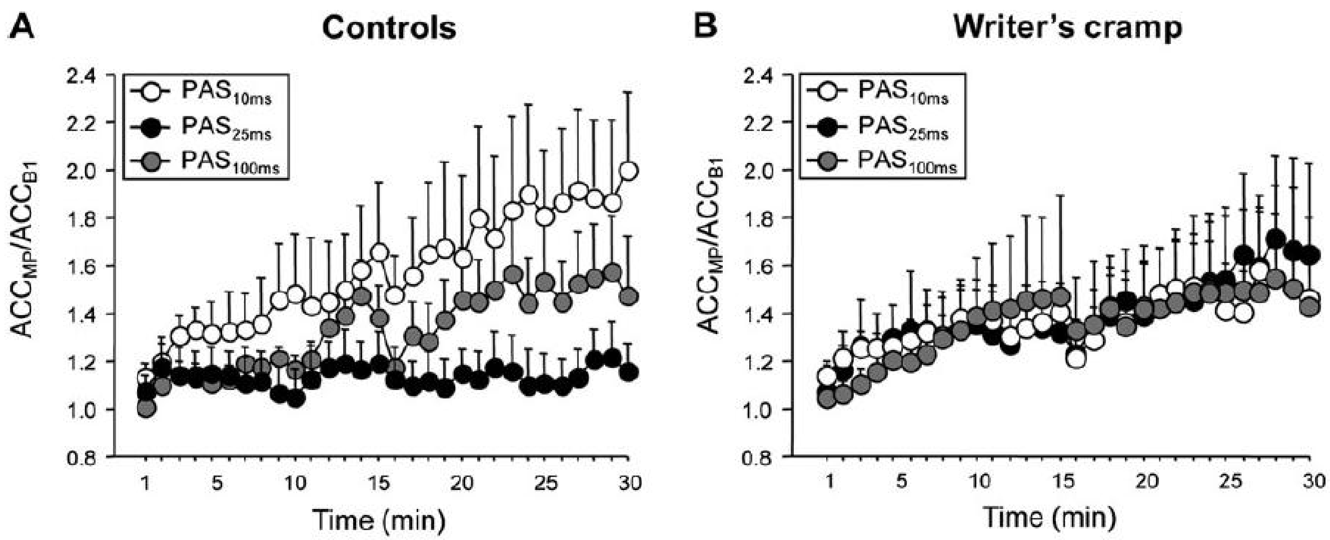
Homeostatic property of motor cortex learning

- Demonstrated by interaction of learning and paired-associative stimulation (PAS)

Cerebral Cortex May 2011;21:1203-1212
doi:10.1093/cercor/bhq204
Advance Access publication October 25, 2010

Deficient Homeostatic Regulation of Practice-Dependent Plasticity in Writer's Cramp

Jun-Suk Kang[1], Carmen Terranova[2], Rüdiger Hilker[1], Angelo Quartarone[2] and Ulf Ziemann[1]



Translation

- For hand dystonia, at least, it seems that aberrant plasticity triggers the disorder
- There is some evidence that certain types of motor and sensory training can improve the dystonia (at least transiently)

How is it possible to have a task specific deficit in one hand?

- Basically the hand is fine since it can perform other tasks without difficulty.
- Basically the motor program is fine since it can be carried out by other limbs.
- The difficulty must be in the linkage of task and effector for the particular task.

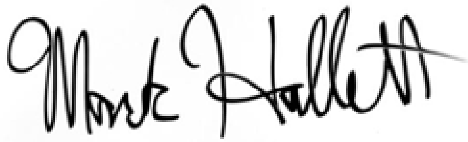
Signatures with Different Effectors

Right hand

Left hand

Right arm
(large size on board)

Left arm
(large size on board)



Mouth (moving head)

Right foot

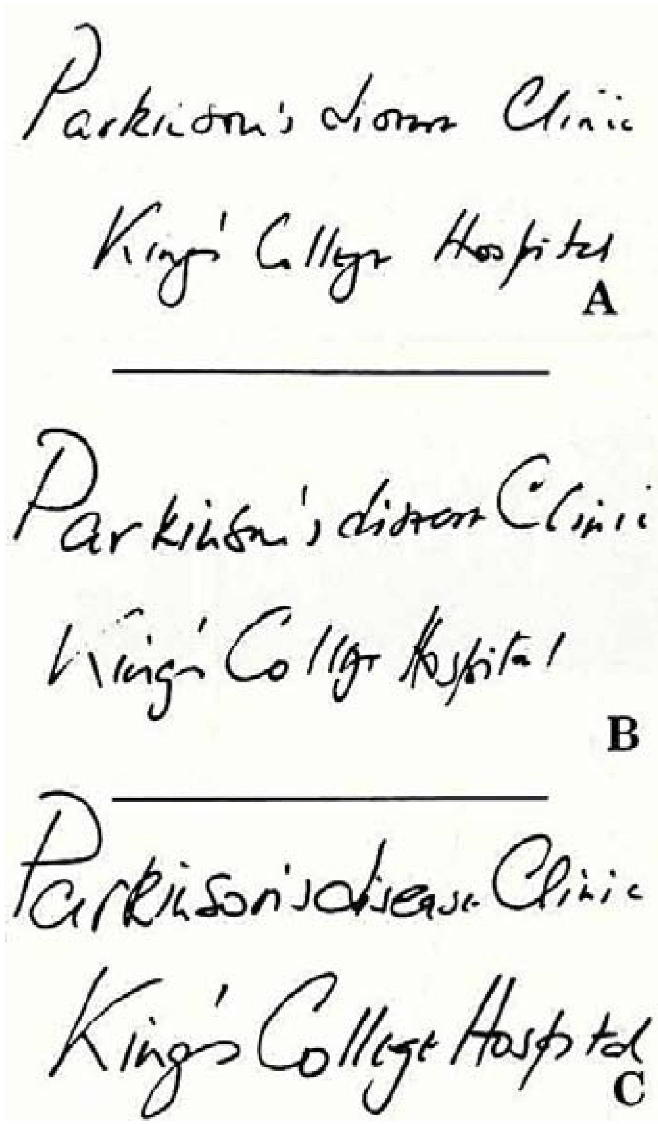
Writing with Different Effectors

C. David Marsden writing with right arm, using:

A. Fingers

B. Forearm

C. Shoulder

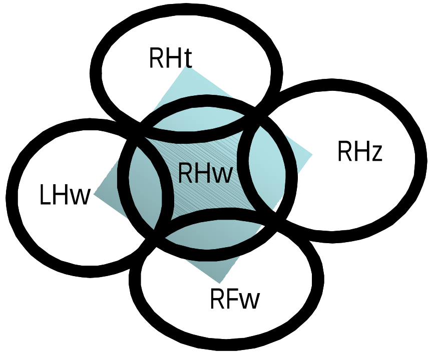


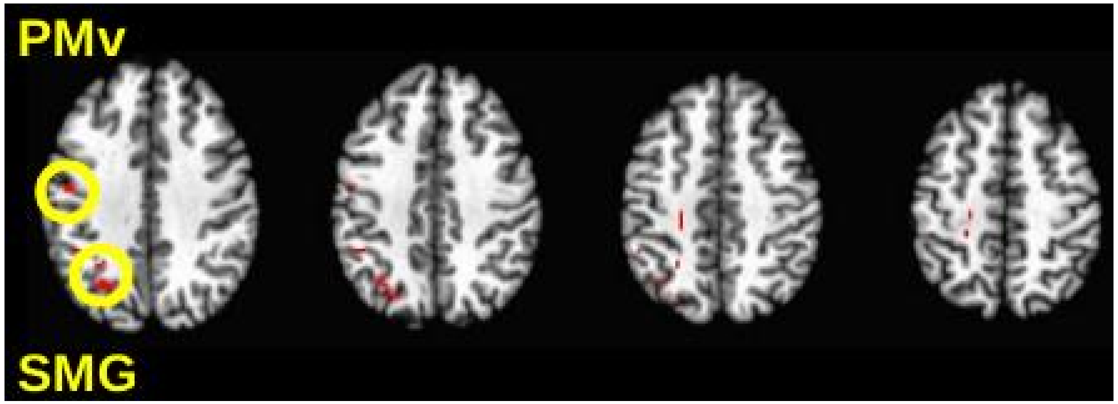
Marsden CD. The mysterious motor function of the basal ganglia. *Neurology* 1982

fMRI Experiment

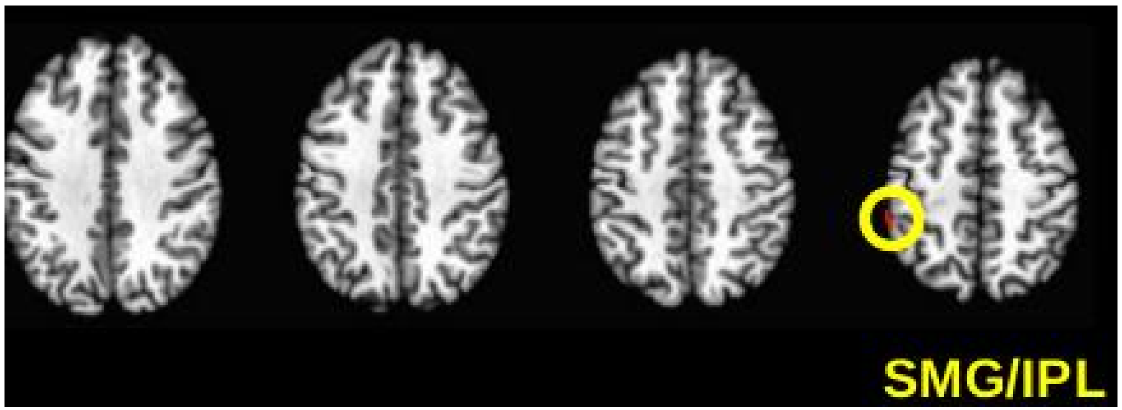
- Purpose: to identify activation relating to effector, activation due to task, and then to look at the combination
- Block design with 9 conditions:
  - 3 effectors: right hand, left hand, right foot
  - 3 tasks: writing, zigzagging, tapping
  - Each effector did each task
- Normal subjects and right handed patients with (right hand) writer's cramp

Exclusive for Right Hand Writing





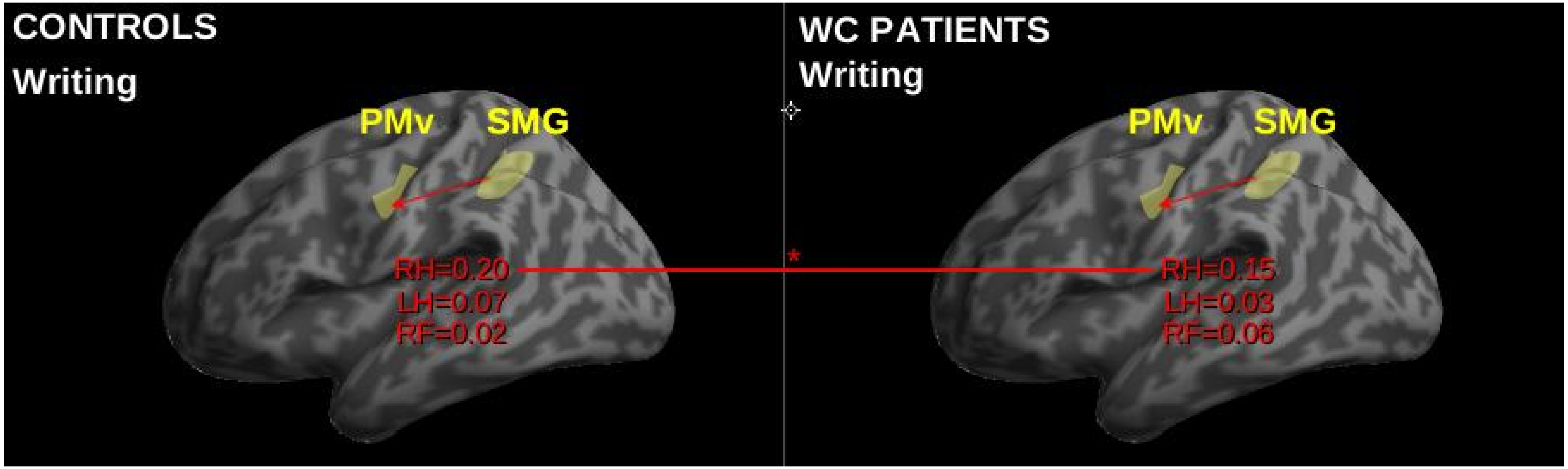
Control Subjects



Patients with WC

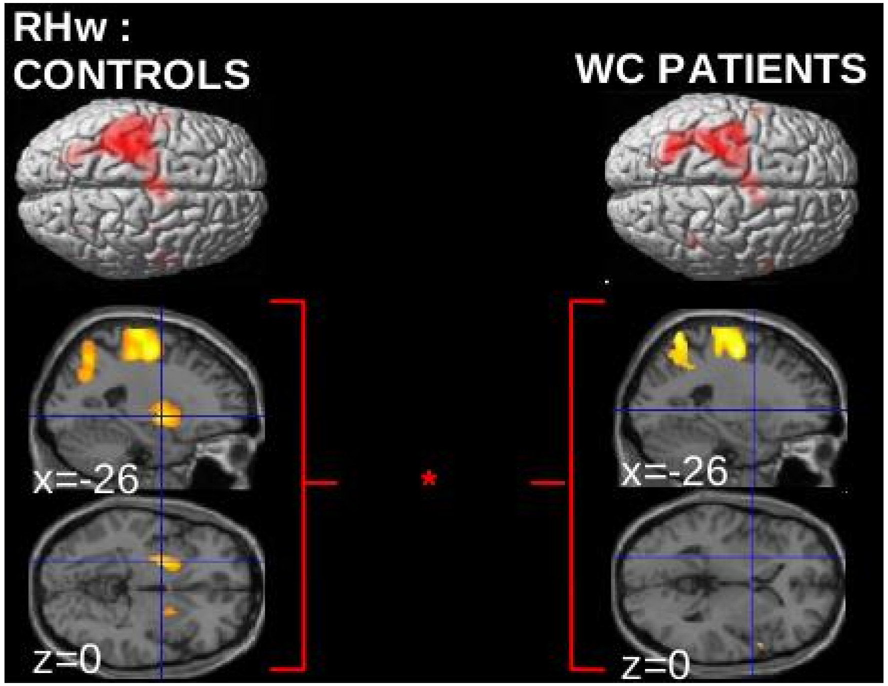
Gallea, Horovitz et al. PLoS 2013 & unpublished data

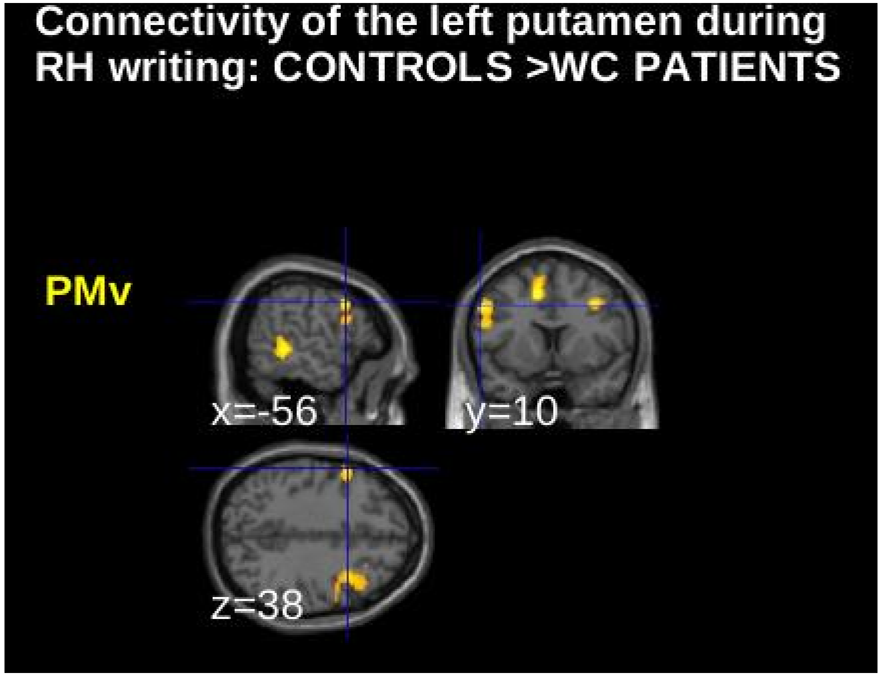
There is also a specific deficit in the connectivity of the parietal-premotor pathway in FHD



Gallea, Horovitz et al. In preparation

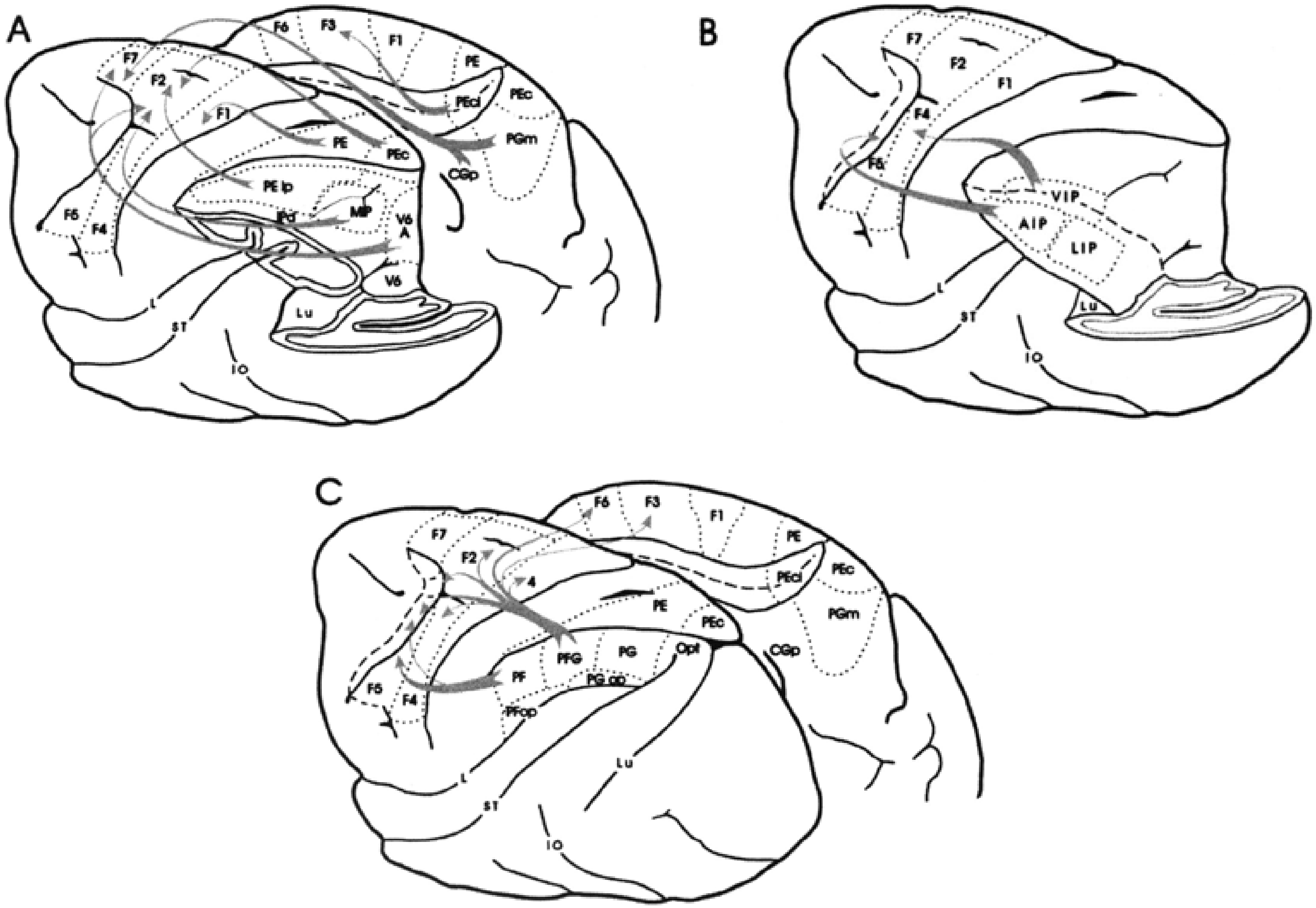
The left putamen is not significantly active with RHw in patients, and less connected to the PMv





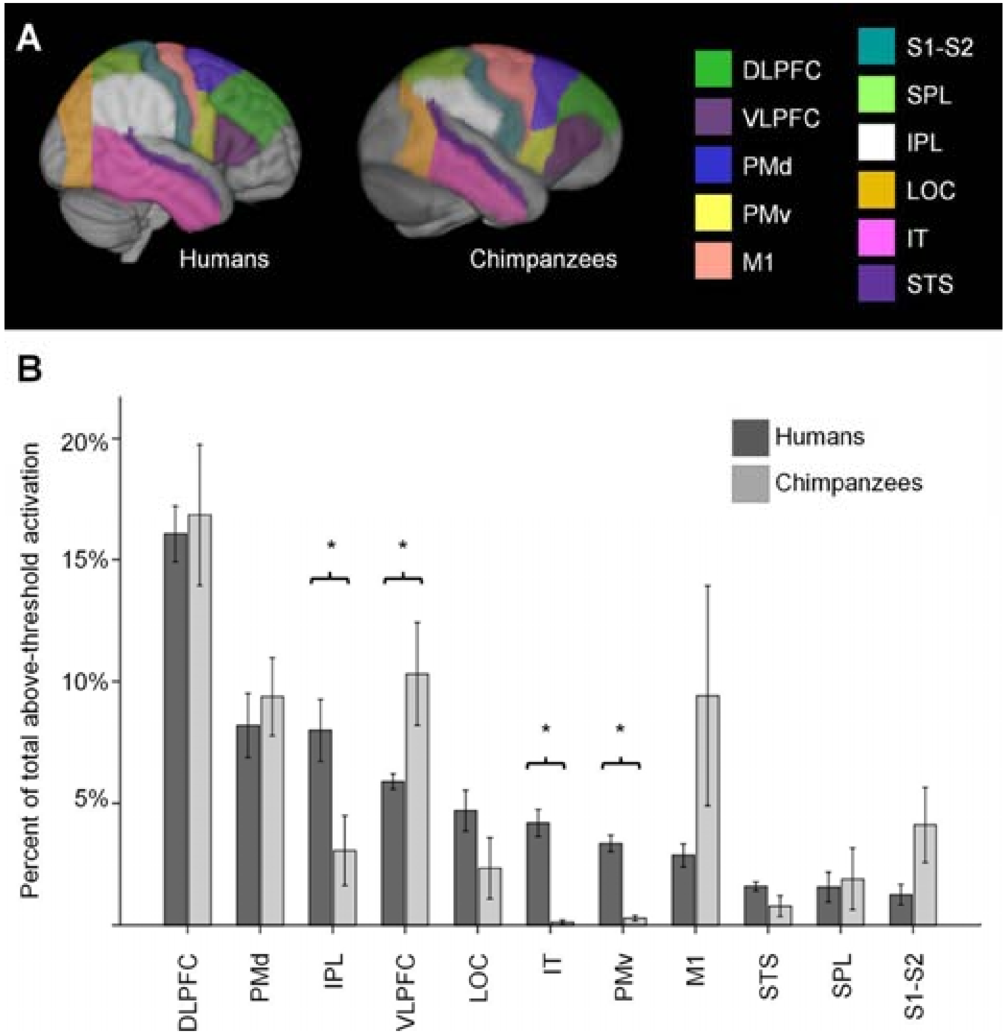
Gallea, Horovitz et al. In preparation

Parietal-Premotor Connections



Rizzolatti et al. 1998

Quantitative comparison of chimpanzee and human activation during transitive grasping observation



Hecht E E et al. J. Neurosci. 2013;33:14117-14134

Translation

- Dystonia, in the end, is produced by a network abnormality, and the efficacy of DBS in dystonia is likely due to alterations in network function

REVIEW

CME

Nonmotor Manifestations of Dystonia: A Systematic Review

Daniel J. Kuyper, MD,[1] Veronica Parra,[2] Shanae Aerts,[2] Michael S. Okun, MD,[3] and Benzi M. Kluger, MD, MS[2*]

Movement Disorders, Vol. 26, No. 7, 2011 Page 1206

doi:10.1093/brain/awr224 Brain 2012: 135; 1668–1681 | 1668

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

The non-motor syndrome of primary dystonia: clinical and pathophysiological implications

Maria Stamelou,[1] Mark J. Edwards,[1] Mark Hallett[2] and Kailash P. Bhatia[1]

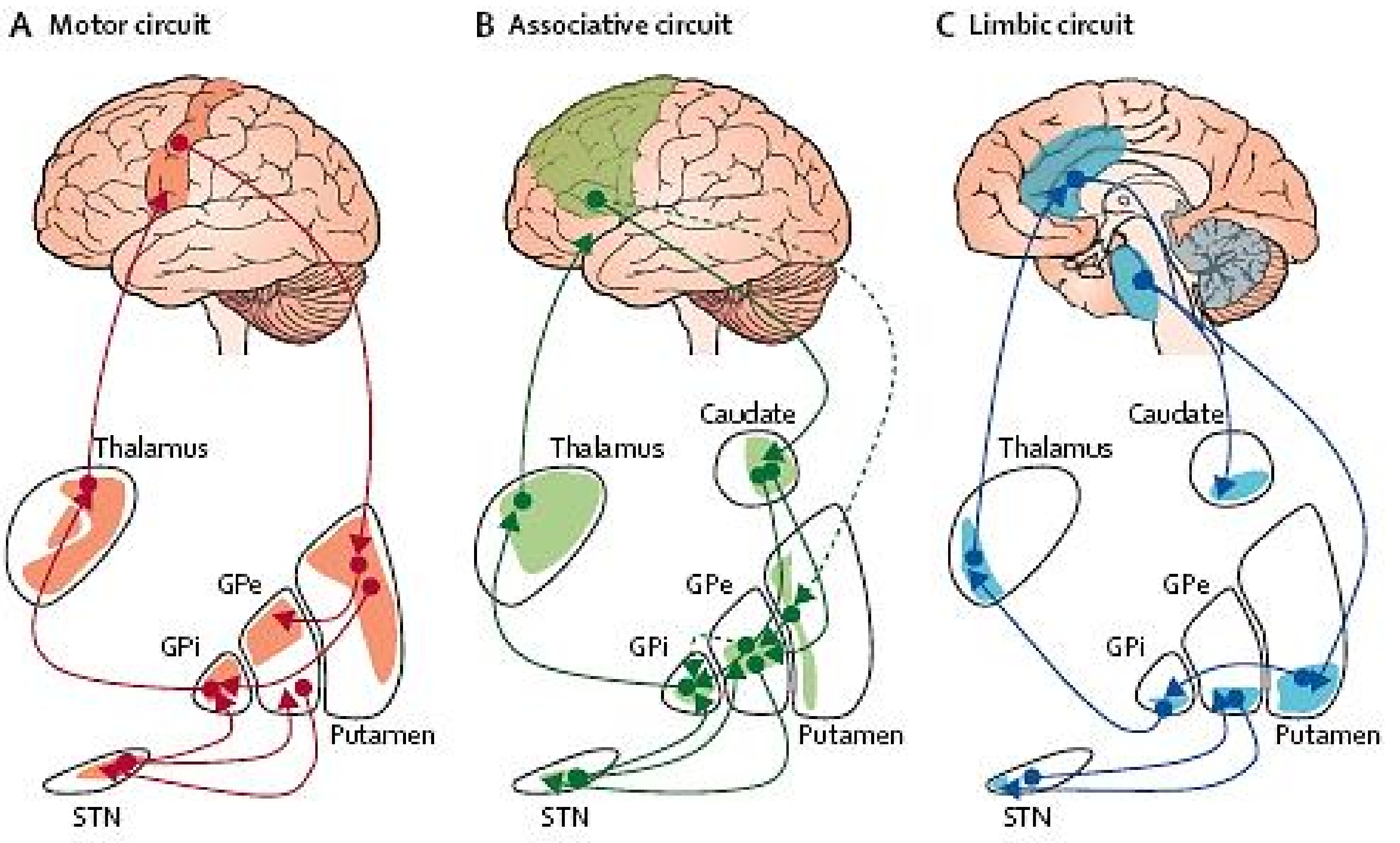
Non-motor Manifestations

- Sensory abnormalities
  - Mild sensory deficits
  - Pain
- Depression
  - No strong evidence for anxiety
- Sleep impairment
  - Possibly related to depression
- (No cognitive or attention deficit)
- Reduced quality of life

Depression

- Not related to severity of motor disorder
- Some component is likely to be secondary
  - Improvement of mood occurs with successful motor treatment
- Can start prior to motor disorder

Separate basal ganglia loops may give rise to motor and non-motor symptoms



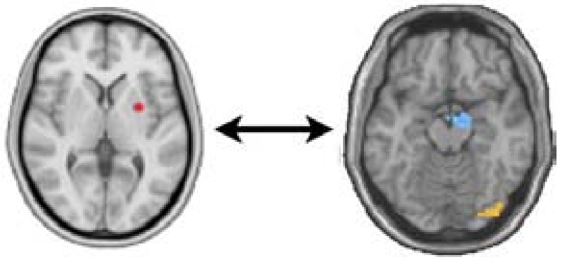
Rodriguez-Oroz et al., Lancet Neurology 2009;8:1128

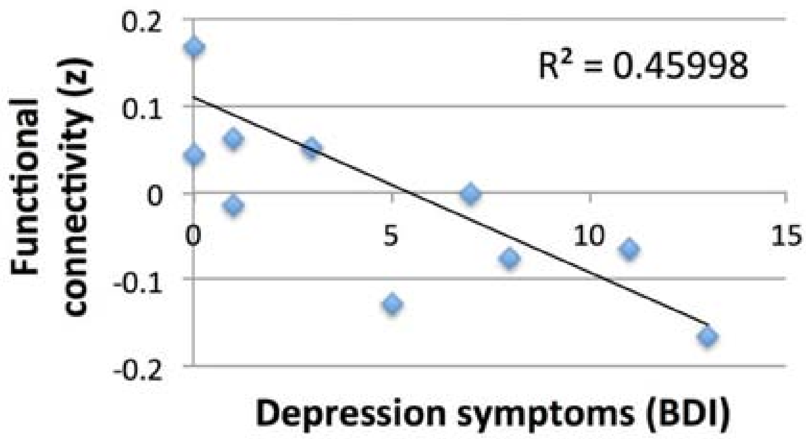
Resting-state fcMRI

11 Primary Focal Dystonia vs. 10 normal controls

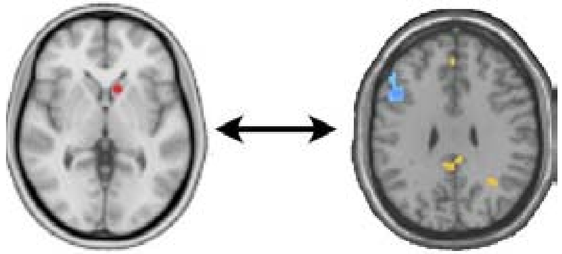
(8F; 63±6) (5F;62±6)

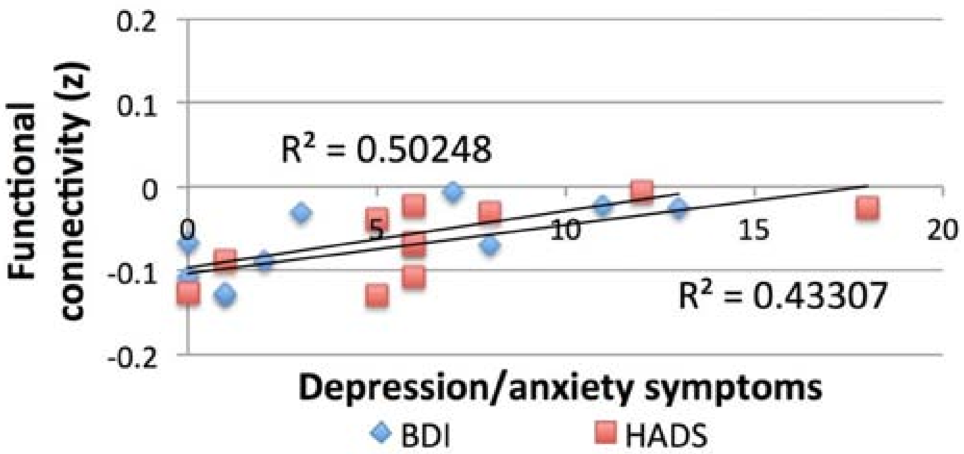
Increased FC between dorsal *putamen* and *lingual gyrus* (p=0.0002)





Decreased FC between *ventral caudate* and *inferior frontal gyrus* (p<0.00001)





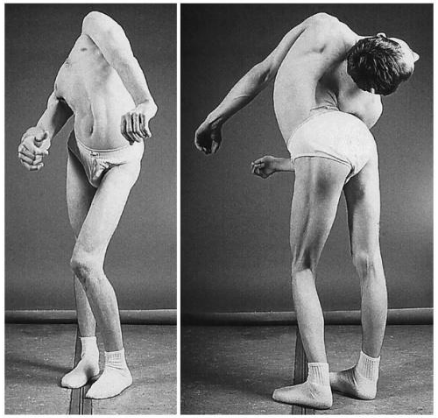
Understanding Dystonia

Genes

Modifiers

Dopamine dysregulation
GABA deficiency

Basal Ganglia
Cerebellum
Cortex



Cortical and
Subcortical
Network
Dysfunction

Defective Inhibition
and Plasticity

Excessive Movement
AND the Non-motor
Manifestations too

Save the date!

30th International Congress of Clinical Neurophysiology of the International Federation of Clinical Neurophysiology (IFCN)

21–24 March 2014, Berlin/Germany

58th Annual Meeting of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN)
20–23 March 2014, Berlin/Germany

ICCN 2014 BERLIN

Conveners
Prof. Otto W. Witte, Jena/Germany
Prof. Reinhard Dengler, Hannover/Germany

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