From molecules to networks: How multimodal neuroimaging can help unravel the complexities of dystonia

March 18, 2015

Brian D. Berman
Objectives

• Define dystonia and review its phenomenology

• Review the current classification scheme of dystonia

• Present conceptual model for accommodating similarities and differences among the causes of dystonia

• Present ways molecular and network imaging can be used to investigate pathogenesis and pathophysiology of dystonia
A brief history...

- 1911: Hermann Oppenheim coins the term “dystonia musculorum deformans” for a type of childhood torsion disease.
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- 1975: First International Dystonia Symposium
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- 1975: First International Dystonia Symposium

- 1984: DMRF Consensus Committee on Dystonia defines dystonia as “a syndrome of sustained involuntary muscle contractions, frequently causing twisting or repetitive movements, or abnormal postures.”
Dystonia

- 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.

Albanese et al., Mov Disord 2013
Sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
Typically patterned, twisting, and may be tremulous.
Typically influenced by voluntary action or posture maintenance
Frequent presence of motor overflow and/or mirror dystonia
Frequent presence of alleviating maneuvers (sensory tricks or gestes antagonistes)
Classification

• Axis I: Clinical characteristics
  • Body distribution
  • Age at onset
  • Temporal aspects
  • Associated features

• Axis II: Etiology
  • Neuropathology
  • Inheritance pattern
    • Inherited
    • Acquired
    • Idiopathic

Albanese et al., Mov Disord 2013
Body distribution

- Focal
- Segmental
- Multifocal
- Generalized
- Hemidystonia
Age at onset

- Infancy (birth to 2 yrs)
- Childhood (3–12 yrs)
- Adolescence (13–20 yrs)
- Early adulthood (21–40 yrs)
- Late adulthood (>40 yrs)

O’Riordan et al., Neurology 2004
Temporal aspects

- Disease course
  - Static
  - Progressive
- Variability
  - Persistent
  - Action-specific
  - Diurnal fluctuations
  - Paroxysmal
Associated features

- Isolated (“primary”)
- Combined (“secondary”)
  - Movement disorder
  - Neurologic manifestations
  - Systemic manifestations
- Non-motor
Axis II

- Axis II: Etiology
  - Neuropathology
  - Inheritance pattern
    - Inherited
    - Acquired
    - Idiopathic

McNaught et al., Ann Neurol 2004
<table>
<thead>
<tr>
<th>Designation</th>
<th>Clinical category</th>
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<th>Mode of inheritance</th>
<th>Gene locus</th>
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DYT9 (identical with DYT18) and DYT14 (identical with DYT5) are omitted; DYT22 has not yet been published.
Pathophysiology

• Clinical similarities across different dystonias suggest that there may be commonalities of etiology and pathophysiology.

• Clinical dissimilarities across different dystonias (e.g., different demographics, anatomic sites, prognoses, etc.) suggest that they may not share the same etiology and pathophysiology.
Pathophysiology

- Three main themes:
  - Loss of inhibition
  - Maladaptive neural plasticity
  - Impaired sensorimotor integration
Etiology (Axis II) → Molecular → Cellular → Anatomic → Network → Dystonia (Axis I)
Molecular

- Dopamine
- GABA
- Acetylcholine
- Glutamate

Breakefield et al., Nat Reviews Neurosci 2008
Dopamine

- Neurotransmitter and hormone of the catecholamine and phenethylamine families that plays a number of important roles in the human brain and body.

- In the brain, dopaminergic neurons found in substantia nigra, VTA, hypothalamus, zona incerta.

- Plays an important role in movement, motivation/reward and cognition, and can act as neuromodulator and influence plasticity.
Dopamine
Dopamine

A  Healthy controls (HC)

B  Writer’s Cramp (WC) patients

C  WC patients versus HC

Berman et al., Brain 2013
Dopamine

Berman et al., Brain 2013
Molecular

- Dopamine
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Breakefield et al., Nat Reviews Neurosci 2008
GABA

• Major inhibitory neurotransmitter throughout the CNS.

• Two general classes of GABA receptors:
  
  • $\text{GABA}_A$ — part of a ligand-gated ion channel complex.
  
  • $\text{GABA}_B$ — G protein-coupled receptors that open or close ion channels via intermediaries.

• In the developing brain, is primarily excitatory and regulates the proliferation of neural progenitor cells, the migration, differentiation and elongation of neurites, the formation of synapses, and the growth of embryonic and neural stem cells.
GABA

GABA<sub>A</sub> receptor

Jacob et al., Nature Reviews Neuroscience, 2008
Garibotto et al., Mov Disord 2011

GABA

N=9

T values

N=5

DYT1 carriers < controls

Sporadic dystonia patients < controls

z=42

z=39

z=36

z=33

z=30

z=27

z=24

z=21

z=18

z=15

z=12

z=9
GABA

$^{11}$C-flumazenil PET

6 CD patients vs. 6 HC
Magnetic Resonance Spectroscopy
GABA MRS
$^{11}$C-flumazenil PET

GABA MRS
Cellular

• Three main themes:
  • Abnormal control of synaptic function
  • Endoplasmic reticulum and nuclear envelope dysfunction
  • Cell-cycle and transcriptional dysregulation
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**Table Note:** DYT9 (identical with DYT18) and DYT14 (identical with DYT5) are omitted; DYT22 has not yet been published.
Anatomical

- Cerebral cortex
- Cerebral white matter
- Corpus callosum
- Anterior horn of lateral ventricle
- Head of caudate nucleus
- Putamen
- Globus pallidus
- Thalamus
- Tail of caudate nucleus
- Third ventricle
- Posterior horn of lateral ventricle
## Voxel Based Morphometry

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<th>Type of dystonia</th>
<th>Cases/controls</th>
<th>Regions affected</th>
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p < 0.001 and k > 50 voxels

N=27
Figure 1: Results of RNAcc shape analysis. A, B) visual representation of effects of group and subtype, respectively; statistically significantly differing vertices are depicted in orange. C) Graph demonstrating significant correlation between degree of shape difference and MDS-UPDRS TD/PIGD ratio.
Etiology (Axis II) -> Cellular -> Anatomic -> Network -> Dystonia (Axis I)

- Molecular
- PET
- MRS
- PET
- MRI
- VBM
Network
Basal ganglia

- Comprise multiple subcortical nuclei that are strongly interconnected with the cerebral cortex, thalamus, and brainstem, as well as several other brain areas.

- Associated with variety of functions including control of voluntary motor movements, procedural learning, routine behaviors, eye movements, cognition and emotion.

- Considerable body of evidence, including animal models and human lesion and imaging studies, support that dysfunction of the basal ganglia and its connections underlie dystonia.
Resting state fMRI

Dorsal rostral putamen (DRP)

Dorsal caudal putamen (DCP)

Ventral putamen (VP)
Resting state fMRI

Dorsal caudate nucleus (DC)

Ventral caudate nucleus (VC)

Nucleus accumbens (NA)
• Increased connectivity between putamen and motor cortices (SMA, precentral) and some DLPFC and parietal cortices

• Increased connectivity between striatum and cerebellum

• Decreased connectivity between the striatum and brainstem, hippocampus, insula, and frontal, parietal and occipital cortices
Putamen  
SMA  

Resting state fMRI  

Dorsal  
Ventral  

$^{11}$C-flumazenil PET  

GABA?
• Can modulate motor cortex excitability in relation to the incoming sensory input (Luft et al., 2005).

• Is interconnected with premotor (Dum and Strick, 2003) and supplementary motor areas (Rouiller et al., 1994) and involved in movement planning.

• Increasing evidence suggests that it is involved in the pathophysiology of dystonia.
10 CD patients vs. 10 HC

- Decreased connectivity within cerebellum and to brainstem, sensorimotor cortices (SMA, postcentral) and frontal and parietal cortices

- Increased connectivity within cerebellum and to caudate, pons, motor cortices (SMA, precentral, paracentral), and temporal cortices
Resting state fMRI

(Striatum)

$^{11}$C-flumazenil PET

GABA?

Plasticity?

Resting state fMRI

(Cerebellum)
Resting state fMRI (Striatum)

Resting state fMRI (Cerebellum)
Etiology (Axis II) → Molecular → Cellular → Anatomic → Network → Dystonia (Axis I)

- PET
- MRS
- PET
- MRI
- VBM
- fMRI
- DTI
Clinical implications

• Identification and characterization of molecular disturbances to correct:
  
  • Dipraglurant—novel small molecule inhibitor of the metabotropic glutamate receptor 5 (mGluR5)—found to normalize the effects of the TOR1A/DYT1 dystonia mutation in the brains of mice
  
  • AZD1446—selective α4β2 nicotinic acetylcholine receptor agonist—might help correct abnormal neuronal signaling and restore the balance of neurotransmitters that could provide relief for dystonia patients
Clinical implications

• Guidance for **network** modulating therapies (TMS, DBS, etc.)

• TMS of the cerebellum can affect the contralateral cerebral motor cortex (Oliveri et al., 2005) and regulate the functional connectivity between Purkinje cells and deep cerebellar nuclei by modifying the excitability of inter-connected motor areas through changing motor-evoked potential amplitude and short and long intracortical inhibition (Koch et al., 2009a).

• Development of imaging biomarkers to identify at risk individuals (endophenotypes, tardive syndromes, trauma, etc.), improve diagnosis, monitor treatment response, track disease progression, etc.
Acknowledgements

• Team: Erika Shelton, Chris Kennel, Rebecca Pollard, Diane Kelly, Alex McCarthy, Cody Sellers, Eric Nyberg, Justin Honce, Lidia Nagae, Jessica Hedeman, Taylor Finseth, Jason Smucny

• Mentors: Mark Hallett, Buz Jinnah, Maureen Leehey, Jody Tanabe, Jason Tregellas