Conflict of Interest

• I have no relevant COIs for any of the therapies that I will be discussing in this course

• Many of the recommendations that I will present will be off-label
Full Conflict of Interest

Irrelevant disclosures: Dr. Hallett may accrue revenue on US Patent: Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent: Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. Dr. Hallett is a (unpaid) member of the Medical Advisory Boards of Brainsway and CALA Health. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by Medtronic, Inc., for studies of deep brain stimulation, Allergan for studies of methods to inject botulinum toxins, and CALA Health for studies of tremor.

First principles

• Movement arises from contraction of muscle
• Muscles are under the control of the alpha-motoneurons
Involuntary movements arising from neuromuscular conditions

- Muscle
  - Rippling Muscle Disease
- Alpha motor neuron axon
  - Hemifacial spasm
  - Peripheral myoclonus
  - Fasciculation
  - Neuromyotonia
  - Schwartz-Jampel syndrome
- Anterior horn cell
  - Fasciculation
  - Spinal Alpha Rigidity
Segmental influences on the alpha motoneuron
INHIBITORY NEUROTRANSMISSION
Presynaptic inhibition typically GABA
Postsynaptic inhibition typically glycine
…but there are exceptions and overlaps

Movement disorders arising from segmental dysfunction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>Tetanus toxin blocks the release of GABA and glycine at spinal synapses</td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>Mainly a disorder of GABA and presynaptic inhibition in the spinal cord</td>
</tr>
<tr>
<td>Hereditary hyperekplexia</td>
<td>A disorder of glycine receptors with deficient inhibition at multiple synapses including that from the Ia inhibitory interneuron</td>
</tr>
</tbody>
</table>
Suprasegmental influences on the alpha motoneuron

PENFIELD and RASMUSSEN, 1950
Internal Capsule

Descending Tracts

Molavi, Neuroscience Tutorial, Washington University
Reticular Formation

Injury to corticospinal tract

- “Upper motor neuron syndrome”
- Negative features
  - Weakness (in a “pyramidal” distribution)
  - Fatigue
  - Loss of coordination
  - Decrease of some cutaneous reflexes
Spasticity

- **Clinical features**
  - Increased resistance to stretch is velocity sensitive
  - Spastic catch
  - Clasped-knife phenomenon
  - Increased tendon jerks, clonus, increased flexor reflexes, spontaneous flexor spasms, and abnormal postures (spastic dystonia)

Spasticity: Pathophysiology

- “pyramidal tract”: Wrong!
- “upper motor neuron”: Vague!
- Lesions of the pyramidal tract (CST) or M1 do not cause spasticity
- Etiology still unclear, but likely involves a cortico-reticulo-spinal tract
  - Premotor cortex damage can be etiologic
  - Dysfunction of dorsal reticulospinal tract likely to be relevant
Subcortical influences on the primary motor cortex
Subcortical Influences

Motor Cortex

Via thalamus

Basal Ganglia

Via thalamus

Cerebellum

Motor Command

Baseline Influences

Motor Cortex

Via thalamus

Cerebellum

Motor Command

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
The SNc facilitates the Direct Pathway and Inhibits the Indirect Pathway

Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry

Abecia V, Krantal J, Benjamin S, Fazzolari 1,2,3, Philip K L, Parker 1,2,3, Kenneth Kay 1,2,3, Myer T, Thiele 1, Karl Deisseroth 1,4,5

Vol 466 29 July 2010 doi:10.1038/nature09159

Percentage of time: freezing, ambulation, fine movement

Normalized fine movement velocity: D1, D2
Basal ganglia disorders

- Hypokinetic, too little movement
  - Parkinson disease
- Hyperkinetic, too much movement
  - Dystonia
  - Chorea, dyskinesias

Fundamental disturbances of bradykinesia in Parkinson Disease

- Insufficient energy for movement
  - Both for movement initiation and execution
  - Greater difficulty with more complex movement
  - Sequence effect
  - Fatigue
- Insufficient scaling
- Particular difficulty with internal versus external triggering
- Loss of automaticity
Changes of function in PD

Basal ganglia pathways
(This is the “rate model” for pathophysiology)

Fundamental problem in PD

- Reduction in facilitation of movement in both the direct and indirect pathways
- Bradykinesia is the main result
- Bradykinesia correlates well with the dopamine deficiency and is the most responsive to dopamine replacement
Dystonia Pathophysiology

- Defective inhibition
- Specifically, defective “center-surround” inhibition
Changes of function in Dystonia

Basal ganglia pathways

Fundamental Problem of Dystonia

- Imbalance of excitation and inhibition with reduction of inhibition
- One main type of deficient inhibition is surround inhibition
The Basal Ganglia

• A fundamental action is to aid in the process of muscle selection and inhibition, including scaling of magnitude, particularly when movement is initiated internally
• Disorders will lead to reduced movement or overflow and involuntary movement
Cerebellar Loop

Modified from Molavi, Neuroscience Tutorial, Washington University

Ref: Brodal et al. 1950 J Neurophysiol 13:431

AND http://humanphysiology.academy/Neurosciences
Physiology of ataxia

- Dysmetria
- Dyssynergia (decomposition of movement)
- Dysrhythmia
- Dysdiadochokinesia
- Tremor
- Impaired motor learning
  - particularly adaptation learning

The cerebellum

- Important role in the timing of movement
- Error corrections and adjustments to movement
- Adaptation learning
Subcortical Influences

Motor Cortex

Via thalamus

Basal Ganglia

Cerebellum

WHAT TO DO
WHAT NOT TO DO

TIMING OF WHAT
IS TO BE DONE

Motor Command

Basal ganglia and cerebellum interconnect

Basal Ganglia

Striatum

STN

Cerebellum

Cerebellar cortex

Dentate

STN Dentate

Thalamus

Pontine Nuclei
Cortical influences on the primary motor cortex

Parieto-frontal areas and their connections

Rizzolatti et al. 1998
Praxis

- Ability to perform skilled and/or learned movements
Apraxia

- Apraxia
  - Inability to perform praxis movements
  - The problem cannot be ascribed to a language comprehension disorder or elemental sensorimotor deficit, including ataxia and bradykinesia

Volition

(Free will)
Movement disorders with confusion about voluntariness

- **Tics:** often said to be voluntary, but patients cannot make them
- **Chorea:** early in the illness patients do not recognize their involuntary movements as being involuntary
- **Alien hand phenomenon:** unwanted movements arise without sense of their being willed, with associated difficulty in self-initiated movement
- **Functional (psychogenic) movements:** look voluntary but said to be involuntary
- **Schizophrenia:** look normal and are goal directed, but the patient may think that they are being externally controlled.

Free Will Model
(Common view = “folk psychology”)

Consciousness --> Motor system --> Movement
Free Will Model
(Perception Model)

Motor system --> Movement

Consciousness

Physiology of Free Will

Mark Hallett, MD

Free will is a perception that people have that they choose to make their movements. This perception includes a sense of willing the movement and self-agency that they are responsible for the movement. If there is a "free will force" that plays a role in movement selection, it should precede movement. There is no evidence for a driving force, and the perception of willing is not fully processed until after the movement. The perceptions of free will likely arise from an interaction between frontal and parietal areas. Free will might be considered to exist if a person's brain is functioning normally without coercion.

ANN NEUROL 2016;80:5-12
Voluntary Movement

• How does movement originate?
• For each neuron, there is a complex summation of EPSPs and IPSPs, and the cell fires when the threshold is surpassed. Groups of neurons will have influence more than single neurons.
• Motor cortex will issue a command when its inputs are sufficient. Inputs come from wide regions of brain including sensory areas, frontal lobe and limbic system.

Convergence of premotor influences

• The mesial motor areas, including supplementary motor areas and cingulate motor areas receive widespread inputs, and are also more activated with internally initiated movement compared with externally triggered movement

Sowards et al. 2003
Parietal and cingulate inputs to motor areas
External and Internal Drivers of Movement

Some Brain Networks

TPJ-based network: impaired self-agency perception through feedforward processing deficits
Salience network: altered homeostatic balance, interoception, multimodal integration and emotional/self-awareness
Limbic network: impaired emotion regulation, fear extinction, value-based viscerosomatic processing
Dorsal attention network: altered goal-directed attentional mechanisms
Ventral attention network: altered stimulus-driven attentional mechanisms
Cognitive control and motor planning networks: motor planning deficits

Drane, Fari, Hallett, Khalsa, Perez, Roberts (2020)
How is “free will” perceived?

• There are studies of “agency”, the sense of personal control
  – See Hallett 2016 Ann Neurol
• Free will is a “quale” of consciousness
• We don’t understand consciousness....

Summary of our tour

• Muscle
• Alpha motor neuron
  – Segmental influences
  – Suprasegmental influences
• Primary motor cortex
  – Subcortical influences
    • Basal ganglia and cerebellum
  – Cortical influences
    • Parietal and premotor
    • Mesial motor areas
    • Limbic and frontal areas
• Consciousness (awareness of action)
Conclusions about the motor system

• While movement is produced by muscle, the control signals come from the entire central nervous system as influenced by external stimuli, internal drives and emotions.
• Voluntary movement can be distorted in many ways depending on site of disorder.
• Involuntary movements are produced in different areas of the brain, but not “interpreted” as voluntary (likely because the TPJ network is not properly engaged).