I) Overview – How do Basal Ganglia affect movement
• Basal ganglia enhance cortical motor activity and facilitate movement.
• Basal ganglia are involved in a positive feedback LOOP with cortical motor areas.
• To facilitate movement, basal ganglia use both excitation and inhibition in pathways. Basal ganglia diseases like Parkinson’s and Huntington’s disturb the balance between excitation and inhibition and result in uncontrolled activation of cortical motor areas.

FUNCTIONAL COMPONENTS

<table>
<thead>
<tr>
<th>Function</th>
<th>Component</th>
<th>Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start/initiation</td>
<td>Basal Ganglia</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Move</td>
<td>Cerebral Cortex/Brainstem/SpCord</td>
<td>Weak/Paralyzed</td>
</tr>
<tr>
<td>Plan</td>
<td>Cerebellum</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Adjust</td>
<td>Cerebellum</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Balance/EyeMove</td>
<td>Cerebellum</td>
<td>Falling/nystagmus</td>
</tr>
</tbody>
</table>

SYMPTOMS OF DISEASE
Common to all BG diseases: spontaneous movements such as tremor, tics, restless-type movements of the body, and writhing movements. The movements do not stop except during sleep.

II) Components of the basal ganglia
• The basal ganglia are really NUCLEI!

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Names</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>caudate</td>
<td>striatum</td>
<td>Cereb hemis</td>
</tr>
<tr>
<td>putamen</td>
<td></td>
<td>Cereb hemis</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>pallidum</td>
<td>Cereb hemis</td>
</tr>
<tr>
<td>substantia nigra</td>
<td>nigra</td>
<td>Midbrain</td>
</tr>
</tbody>
</table>

• Globus Pallidus has 2 parts: internal (GPi) and external (GPe)
• Substantia Nigra has 2 parts: pars compacta, pars reticulata

III) Basal ganglia pathways
• A LOOP from cortex to basal ganglia back to cortex
• The pathway begins in cortical motor areas and ends in cortical motor areas.
• Basal ganglia have NO direct connections with spinal cord and have little influence on brainstem nuclei.
• **Efferent pathways from basal ganglia**
  • Axons leave the BG from GP\textsubscript{i} and travel across the internal capsule to VL of thalamus. These axons first form the Lenticular.Fasciculus and then the Thalamic Fasciculus, which terminates in VL.

• Basal Ganglia participate in two functionally different pathways. One pathway facilitates movement; The other pathway involves association/cognitive functions (working memory, executive functions, emotions). Both pathways have a similar organization, utilize parallel circuits, but use slightly different structures.

Non-motor loops influence: eye movements, dorsolateral prefrontal cortex (working memory, planning, attention), and limbic system (emotions). Alterations in these basal ganglia components may explain cognitive and emotional deficits that occur in Parkinson’s and Huntington’s Diseases.
Roles of Subthalamic Nucleus and Substantia Nigra

1. Subthalamic nucleus (STN)
   - STN neurons have excitatory (glutamatergic) synapses on GPi.

2. Substantia nigra - pars compacta (dopaminergic part - SNc)
   - Dopamine released from SNc terminals in the putamen has 2 effects: 1) it excites putamen neurons that have D1 (+) dopamine receptors, 2) it inhibits other putamen neurons that have D2 (–)dopamine receptors.

IV) Physiological Basis of Basal Ganglia Function and Disease

Important Considerations:
- In this circuit, precise control is achieved by balancing 2 competing effects, facilitation of movement (accelerator) and inhibition of movement (brake) through regulation of VL.
- Many components in this circuit are tonically active. Their activity is normally on. Thus, output from the circuit can influence cortical motor areas even when there is no input to Putamen. Damage to almost any component (ie BG disease) does not inactivate the circuit, but instead reduces control of it.
- Dopamine biases the activity of the circuit in favor of facilitating movement. Thus, at rest, VL is almost but not yet active. During initiation of movement, activity from motor cortex to Putamen now results in VL activity.
- Each BG disease results from pathology of a specific BG component and is associated with a unique type of spontaneous movement as well as other movement problems.
• The basal ganglia circuits use **excitation and inhibition** to control movement. The circuits operate in a non-intuitive fashion, making it difficult to understand.

• **VL excites the cortex.** VL is controlled by GPi. Tonic activity causes GPi to inhibit activity of VL, removing VL’s effect on the cortex. The circuit works by turning **VL on or off** at appropriate times, determining whether motor cortex is excited. Immediately before a movement is started, motor cortical areas excite putamen neurons. This causes VL neurons to become active (through the unusual mechanism of disinhibition), which further excites cortical motor areas. This increases activity of upper motoneurons in the cortex, which is necessary for movement.

• VL activity should be **ON** during movement; VL activity should be **OFF** when at rest. *Basal Ganglia lesions cause movement abnormalities because these 2 states become uncontrolled.*

• Neurotransmitters: excitatory – acetylcholine, glutamate, dopamine; Inhibitory – GABA, dopamine

• Let’s look at the complete circuit

• In **Parkinson’s Disease**, the loss of substantia nigra dopamine has several effects:
  1. **Direct pathway**: loss of dopamine causes less activity in the D1R putamen neurons. Thus **GPi is more active** and suppresses VL activity. The result is decreased voluntary movement (bradykinesia/akinesia)
  2. **Indirect pathway**: As motor cortex becomes active, the loss of dopamine results in greater **GPi activity**. Again, this decreases VL activity and causes less excitation of cortical motor areas.
  3. As a result of the loss of dopamine, abnormal **rhythmic** activity develops in basal ganglia neurons, which may explain the resulting tremor. Amplitude of the tremor decreases during voluntary movements, but increases in conditions of stress.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>too little dopamine</td>
<td>↓ accelerator; ↑ brake; ↓ movement</td>
</tr>
<tr>
<td>too much dopamine (meds)</td>
<td>↑ accelerator; ↓ brake; ↑ (spontaneous) movement</td>
</tr>
</tbody>
</table>
• **The acetylcholine story**: ACh and dopamine have antagonistic effects on BG circuitry. With loss of dopamine, ACh release is elevated, which worsens the effects of dopamine loss. Balance in ACh and dopamine levels can be restored by treatment with anticholinergics. (*Hold on to this for Psychiatry*)

• In **Huntington’s Disease**, D2R putamen neurons degenerate. This decreases STN activity, which decreases GPi activity and allows VL activity to increase. This increases cortical motor excitability and is associated with spontaneous movements.

**V) Clinical Symptoms of Basal ganglia Dysfunction**

• Occurs from disruption of any of the basal ganglia components. Symptoms generally involve:

1. **Involuntary movements (dyskinesias)** (abate during sleep)
   • Hemiballismus- flailing movements of one or both limbs
   • Chorea- involuntary, jerky movements of the face, body, or extremities (resembling fidgetiness)
   • Dystonia- prolonged contractions of axial or extremity musculature affecting posture
   • Athetosis- slow, twisting movements of distal extremities (hands,fingers,feet)
   • Resting tremor- involuntary tremor (not associated with voluntary movement)

2. **Decreased overall movement**
   • Hypokinesia- decreased movement
   • Bradykinesia- slowing of movement

3. **Changes in posture and muscle tone**
   • Rigidity – involves increased muscle tone in both extensors and flexors causing resistance to passive movement in all directions (unlike spasticity). Thus, it is referred to as “lead pipe” rigidity. Resistance to passive movement also may have a jerky, "catch and give" quality due to an underlying tremor, which then is referred to a cogwheel rigidity.

4. **Changes in Mood** – interaction of basal ganglia and cortical association areas.

<table>
<thead>
<tr>
<th><strong>Disease</strong></th>
<th><strong>Lesion Site</strong></th>
<th><strong>Symptoms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiballismus</td>
<td>STN</td>
<td>Wild, flailing movements of arms/legs</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>SNc</td>
<td>Resting tremor, bradykinesia, rigidity, abnormal gait and posture, autonomic dysfunction</td>
</tr>
<tr>
<td>Huntington’s</td>
<td>Caudate/Putamen</td>
<td>Chorea, dementia</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>Dopamine receptors</td>
<td>Chorea/athetosis especially in face</td>
</tr>
<tr>
<td>Tourette’s</td>
<td>unknown</td>
<td>Motor and verbal tics</td>
</tr>
</tbody>
</table>

1. **Hemiballismus**
   • Lesion of STN results in increased VL activity movement
   • Movements are contralateral to side of lesion

2. **Parkinson's Disease**
   • the most common neurodegenerative movement disorder and the #2 neurodegenerative disease; in US/western Europe 1-2 per 1000 people
   • Cause: loss of neurons in Substantia Nigra pars compacta
   • symptoms also include postural instability, autonomic dysfunction (drooling, sweating, orthostatic hypotension, urinary disturbance) and psychiatric problems (depression, dementia).
• Therapies:
  • administration of dopaminergic drugs, eg L-DOPA;
  • lesion of GPi (pallidotomy) to reduce its inhibition of VL, but this is risky due to the nearby internal capsule that might also be affected;
  • Deep Brain Stimulation: stimulator implanted into STN or GP, which decreases tremor (presumably by inhibition) and then bradykinesia is treated with meds. This has become a popular strategy for treatment because: it does not damage brain tissue, it is reversible, it can be adjusted as the disease progresses, it can be performed bilaterally if necessary.
  • implanting dopamine secreting cells into striatum has been tried unsuccessfully, but a new clinical trial is underway.

3. Huntington's Disease
  • hereditary defect on chromosome 4 inherited as an autosomal dominant
  • symptoms include choreiform movements and dementia (later onset)
  • symptoms usually don’t appear until adulthood (30-50)
  • causes degeneration of D2R neurons in putamen (movement deficit); caudate neurons also degenerate (cognitive deficit).
  • This initially affects the indirect circuit, resulting in lowered STN activity and consequently lower GPi activity and higher VL activity that explains the choreic movements.

4. Tardive Dyskinesia
  • Caused by long term treatment with antipsychotic drugs (block D2 receptors).
  • Symptoms eventually irreversible if causative drug is not altered.
  • Long term D2 receptor blockers probably cause D2R upregulation and supersensitivity. This affects the indirect circuit by lowering the inhibitory output of the putamen (too much dopamine inhibition to putamen), which has an outcome similar to Huntington’s Disease.

5. Wilson’s Disease
  • Caused by a defect in copper metabolism that results in increased serum copper levels
  • Results in widespread changes throughout body and nervous system, where it can affect the caudate, putamen, cerebral cortex, and cerebellum. Thus, neurological symptoms can include resting tremor, chorea, rigidity, hypokinesia among other changes.

6. Carbon Monoxide Intoxication
  • The basal ganglia are sensitive to CO exposure, which destroys neurons in putamen and globus pallidus.

Objectives:
  • Describe the function of the Basal Ganglia in movement
  • Define the BG components and their locations
  • Describe the motor and association loops of BG
  • Describe the direct motor circuit of the BG and how it functions
  • Understand how the indirect motor circuit influences BG function
  • Describe the effects of the substantia nigra on BG circuits
  • Describe the symptoms of BG disease and understand the vocabulary of movement disorders
  • Describe the types of BG diseases, their causes, and their potential treatments