Basal Ganglia: Parkinson disease

David G. Standaert, M.D., Ph.D.
Key Points

- Basal ganglia circuits are loops that regulate behavior.
- The striatum (caudate and putamen) is the input of the basal ganglia. It integrates glutamate and dopamine input, and uses GABA for output.
- Parkinson disease caused degeneration of neurons, leading to loss of the dopamine input.
- The cause of most cases of Parkinson disease is unknown.
- Most treatments for Parkinson disease are based on replacing dopaminergic stimulation.
Basal Ganglia are Circuits that regulate motor behavior
Multiple Basal Ganglia circuits for multiple functions

Alexander et al., 1986
The Motor Circuit

- **Input:** the striatum (caudate and putamen)
- **Output:** The GPi and SNpr
- **Intrinsic nuclei:**
  - GPe
  - STN
  - SNpc
Human basal ganglia

Caudate
Putamen
GPe
GPi
STN
SNc
SNr

Input
Output
Intrinsic
The Striatum

- **Sources of afferent input:**
  - The cerebral cortex (glutamatergic)
  - The SNpc (dopaminergic)

- **Cellular composition**
  - 90% Projection neurons: medium sized GABA neurons with spiny dendrites
  - 10% Interneurons:
    » cholinergic
    » NOS, somatostatin
    » GABA, calcium binding proteins
Striatal Neurons

- Spiny neurons
  - GABA
  - D1, D2 receptors
- Giant aspiny neurons
  - cholinergic
- Small and medium aspiny
  - NOS/somatostatin
  - GABA, Ca++ binding proteins

Wilson, 1990
Afferents to Medium Spiny Neurons

- Glutamatergic corticostriatal inputs to the heads of spines
- Dopaminergic inputs to the shafts of spines and dendrites
- Cholinergic and GABA inputs to the dendrites and soma

Smith and Bolam, 1990
Striatal efferents

◆ To the GPi/SNpr
  – GABAergic
  – D1 Receptors
  – Substance P

◆ To the GPe
  – GABAergic
  – D2 Receptors
  – Enkephalin
Parkinson Disease

- Described by James Parkinson, 1817
- Affects 3% of the population over the age of 65 years
- About 500,000 patients in the US

AN ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.
“Cardinal Features” of Parkinson Disease

- Tremor
- Rigidity
- Bradykinesia
- Postural Instability
What causes PD?

**Genetics**
- Most cases are not genetic in origin
- Rare families with inherited PD
- Genetic cause more likely in early onset cases

**Risk Factors**
- Male Gender
- Environment

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### Table of Genes Involved in PD

<table>
<thead>
<tr>
<th>Locus</th>
<th>Protein or Location</th>
<th>Function</th>
<th>Inheritance</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park 1</td>
<td>alpha-synuclein mutation, duplication</td>
<td>Unknown – vesicle transport</td>
<td>AD</td>
<td>Italian, Greek, German</td>
</tr>
<tr>
<td>Park 8</td>
<td>leucine-rich repeat kinase (LRRK2)</td>
<td>Vesicle dynamics, cell signaling</td>
<td>AD, reduced penetrance</td>
<td>multiple</td>
</tr>
<tr>
<td>Park 2</td>
<td>Parkin</td>
<td>Ubiquitin E3 ligase</td>
<td>mainly AR</td>
<td>Global</td>
</tr>
<tr>
<td>Park 6</td>
<td>PINK1</td>
<td>Mitochondrial protein kinase</td>
<td>AR</td>
<td>Italian</td>
</tr>
<tr>
<td>Park 7</td>
<td>DJ-1</td>
<td>Unknown – antioxidant</td>
<td>AR</td>
<td>Dutch</td>
</tr>
<tr>
<td>Park 5</td>
<td>UCHL1</td>
<td>Ubiquitin hydrolase</td>
<td>Possibly AD</td>
<td>German kindred</td>
</tr>
</tbody>
</table>

- Well water and rural living
- Pesticides, toxins
- Smoking
- Caffeine
Pathology of Parkinson’s Disease

- Depigmentation of the substantia nigra pars compacta
- Formation of Lewy Bodies

Feany Lab
Striatum: Inputs, outputs, and interneurons

Glutamate

D1
Activated by dopamine

Ach

D2
Inhibited by dopamine

GABA

Dopamine
PARKINSON’S DISEASE

CEREBRAL CORTEX

STRIATUM

DA

D1

D2

SP

ENK

ACh

SS

GABA

SNpc

GABA

GABA

TO SPINAL CORD, BRAINSTEM

GABA

GABA

GABA

STN

GPe

Gpi/SNpr

GLU

GLU

GLU

GLU

GABA

GABA

GABA

VA/VL THALAMUS
Levodopa Therapy for Parkinson Disease

- Most effective treatment is levodopa (also called L-DOPA, L-dihydroxyphenylalanine)
- Works by replacing biosynthetic precursor:
  - TH
  - AADC
  - tyrosine ➔ L-DOPA ➔ DA

- Most important limitation of treatment is the development of “complications of levodopa therapy” - wearing off and dyskinesias
Motor complications - a patient’s view
## Ocular Complications of PD

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Parkinson’s disease, n = 30</th>
<th>Controls, n = 31</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complaints of surface irritation, including photophobia, tearing, crusting on lashes, eyes stuck in morning, dry eye, burning eye, gritty or sandy sensation, red eye, eye pain</td>
<td>19 (63.3)</td>
<td>9 (29.0)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Dipleia</td>
<td>3 (10.0)</td>
<td>1 (3.2)</td>
<td>0.354</td>
</tr>
<tr>
<td>Difficulty reading</td>
<td>8 (26.7)</td>
<td>3 (9.7)</td>
<td>0.106</td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>4 (13.3)</td>
<td>0 (0)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Apraxia of eyelid opening</td>
<td>2 (6.7)</td>
<td>0 (0)</td>
<td>0.238</td>
</tr>
<tr>
<td>Blink rate, BPM</td>
<td>17.1 ± 12.7 (1-45)</td>
<td>24.8 ± 7 (12-41)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>23 (76.7)</td>
<td>22 (71.0)</td>
<td>0.339</td>
</tr>
<tr>
<td>Dry eye</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schirmer</td>
<td>14 (46.7)</td>
<td>10 (32.3)</td>
<td>0.249</td>
</tr>
<tr>
<td>TFBUT</td>
<td>18 (53.3)</td>
<td>7 (22.6)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Rose Bengal</td>
<td>1 (3.3)</td>
<td>5 (16.1)</td>
<td>0.185</td>
</tr>
<tr>
<td>Convergence insufficiency</td>
<td>7 (23.3)</td>
<td>6 (19.4)</td>
<td>0.704</td>
</tr>
<tr>
<td>Decreased near point of convergence</td>
<td>9 (30.0)</td>
<td>7 (22.6)</td>
<td>0.644</td>
</tr>
<tr>
<td>Decreased convergence amplitudes</td>
<td>24 (80.0)</td>
<td>8 (25.8)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Biousse et al., 2004, Neurology 62:177-180*
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