Circuit Disorders of the Basal Ganglia: Parkinson’s Disease

Pathophysiology and Surgical Treatments

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The Basal Ganglia

The basal ganglia include the structures indicated in red. They are components of large segregated cortical-subcortical neural networks.

- **STN**: Subthalamic Nucleus
- **GPe**: Globus Pallidus, pars externa
- **GPi**: Globus Pallidus, pars interna
- **SNC**: Substantia Nigra, pars compacta
Basal Ganglia Circuits

• For decades the basal ganglia were viewed as playing a role in movement by selecting from competing commands from diverse cortical areas sent to the input regions of the basal ganglia, which provided a pathway for funneling this command to the motor cortex, thus leading to movement.

• The prevailing schema was summarized by Kemp and Powell in the 1970s.
Basal Ganglia and Cerebellar Systems:
Kemp and Powell-Circa 1970
“Funneling of Cortical Commands to the Motor Cortex”
Segregated Circuit Hypothesis

Physiologic studies carried out by DeLong and colleagues led to a major revision of the basal ganglia circuitry, whereby the sub-nuclei of the basal ganglia are viewed as components of a distributed family of segregated cortical-subcortical networks with separate domains involving four major functions:

- Motor (bodily movements and posture)
- Oculomotor (eye movement)
- Prefrontal (executive/cognitive)
- Limbic (emotional/reward)
Basal Ganglia-Thalamo-Cortical Circuits

*Cortical Domains and Principal Networks*

Alexander, DeLong & Strick, Ann Review of Neuroscience, ‘85
Segregated Circuit Hypothesis

- The revised anatomic/physiologic framework provided the basis for an understanding of the role of these structures in multiple broadly segregated functional domains as well as the presence of disturbances of movement as well as of cognition, mood and behavior in clinical disorders involving the basal ganglia, such as Parkinson’s disease.

- Parkinson’s is now recognized as one of a number of “Circuit Disorders”
Circuit Disorders of the Basal Ganglia

• Multiple neurologic and psychiatric disorders may be viewed as resulting from abnormalities of neuronal activity within specific anatomically and functionally defined neuronal networks.
  – Many of these disorders involve the family of cortical-basal ganglia thalamocortical circuits

• The signs and symptoms of these disorders appear to result from signature abnormal neuronal activity within individual networks, which can be modulated by various clinical approaches, including drugs as well as surgical ablation or deep brain stimulation (DBS)
Basal Ganglia Circuit Disorders

• **Movement Disorders (Motor circuit)**
  – Parkinson’s Disease (PD)
  – Dystonia
  – Hemiballismus
  – Huntington’s chorea (HD)

• **Neuropsychiatric Disorders (Limbic circuit)**
  – Tourette’s Syndrome (TS)
  – Obsessive Compulsive Disorder (OCD)
  – Depression
Basal Ganglia-Thalamocortical Circuits

**Associated Clinical Disorders**

- **Motor**
  - Cortex
    - SMA, PMC, CMA, M1
    - Putamen
    - SNr/GPi (motor territory)
    - VLo, VLm, VApc
  - Striatum
    - Putamen
  - Pallidum Subst. nigra
    - SNr/GPi (motor territory)
  - Thalamus
    - VLo, VLm, VApc
  - PD, HD, TS DYSTONIA

- **Oculomotor**
  - Cortex
    - FEF, SEF
    - Caudate
    - SNr/GPi (oculom. territory)
    - MDpl, VLcr, VApc
  - Striatum
    - Caudate
  - Pallidum Subst. nigra
    - SNr/GPi (assoc. territory)
  - Thalamus
    - VLo, VLm, VApc
  - PD, HD

- **Prefrontal**
  - Cortex
    - DLPFC, LOFC
    - Caudate
    - SNr/GPi (assoc. territory)
    - MDpl, VLcr, MDpl
  - Striatum
    - Caudate
  - Pallidum Subst. nigra
    - SNr/GPi (limbic territory)
  - Thalamus
    - VApc, VAmc, VLm, MD
  - PD, HD

- **Limbic**
  - Cortex
    - MOFC, ACA
    - Caudate (ventr.)
    - SNr/GPi (limbic territory)
  - Striatum
    - MOFC, ACA
  - Pallidum Subst. nigra
    - SNr/GPi (limbic territory)
  - Thalamus
    - VApc, VAmc
    - VAmc, VLm, MD
  - TS, OCD, DEPRESSION

Wichmann and Delong, Neuron (2006)
Parkinson’s Disease

- **Cardinal motor features** (Parkinsonism)
  - Akinesia/Bradykinesia
    - (paucity and slowness of movement)
  - Tremor at rest
  - Muscular rigidity

- **Non-motor features**
  - Depression/ anxiety
  - Autonomic dysfunction
  - Sleep disorders
  - Cognitive impairment
  - Anosmia (loss of sense of smell)
Parkinson’s Disease

Historical Aspects

• Parkinson’s disease, a progressive neurologic disorder, characterized by tremor, rigidity and slowness of movement (parkinsonism) was shown in the 1960’s to result from loss of the neurotransmitter dopamine (DA) within the basal ganglia.

• Parkinsonism was subsequently found to respond dramatically to oral administration of levodopa, its precursor of DA.

• Unfortunately levodopa replacement is often associated with a number of significant side effects after five or more years of treatment and there remains a great need for more effective treatments for both the movement and other aspects of the disease.
PARKINSONISM
A Dopamine Deficiency Disorder

PET scan showing striatal fluorodopa uptake of a normal brain (left) versus PD brain (right). Note loss of uptake in the putamen.

Gross pathology of the midbrain showing a normal brain (left) versus a PD brain (note loss of darkly pigmented Dopamine-containing neurons).
Basal Ganglia-Thalamocortical Circuit

What are the Changes in neuronal discharge in the motor circuit in PD?

Intrinsic Connections from striatum to GPi

Indirect pathway
Direct pathway

Major Inputs to Basal Ganglia:
- Cortex
- Thalamus
- SNc (Dopamine)
- PPN

Major Outputs of Basal Ganglia:
- GPi/SNr
- Inhibitory (GABAergic)
Basal Ganglia Neuronal Discharge Patterns

Microelectrode Recording
Parkinson’s Disease

Pathophysiology

• Physiologic studies using single cell microelectrode recording carried out in the 1980s and 90s in a primate model of Parkinson’s disease, revealed clear disturbances in neuronal activity in the sub-nuclei of the basal ganglia, including increased discharge rate, as well as abnormal pattern of discharge including increased bursting abnormal oscillations.

• The observed changes in neuronal activity in the subnuclei of the basal ganglia was consistent with the prevailing circuit model of PD, which postulated abnormally increased (inhibitory) output from the basal ganglia (GPi) resulting from excessive excitatory drive from the STN.
Circuit Model of Parkinsonism

Loss of DA leads to excessive and abnormal neuronal activity in the motor circuit portions of the STN and GPi

Normal Parkinsonism

Brain stem/Spinal cord

CM VA/ VL

STN

GPe

GPi/SNr

SNC

Brain stem/Spinal cord

PPN
Primate (MPTP) Parkinsonism

Changes in Discharge Patterns in Basal Ganglia Nuclei
(representative microelectrode recordings)

**Normal**

<table>
<thead>
<tr>
<th>GPe</th>
<th>STN</th>
<th>GPi</th>
<th>SNr</th>
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<tr>
<td><img src="image" alt="Normal GPe" /></td>
<td><img src="image" alt="Normal STN" /></td>
<td><img src="image" alt="Normal GPi" /></td>
<td><img src="image" alt="Normal SNr" /></td>
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**PD**

<table>
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<th>Discharge rate</th>
<th>Pattern</th>
<th>Synchronization</th>
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<td>increased</td>
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Rate Changes in Primate Models of PD
Oscillatory STN Activity in the Primate MPTP Model of PD

Bergman et al., J Neurophysiology, 1994
Testing the Hypothesis

Inactivation of the STN in the Primate Model of Parkinsonism

• In order to test the circuit model of PD, the STN was lesioned in the primate model of PD
• Direct neurotoxin lesioning of the STN immediately abolished the cardinal features of parkinsonism (bradykinesia, tremor and rigidity) in the contralateral limbs and led to increased overall motility.
• These and subsequent studies of lesioning of the GPi demonstrated the key role of abnormal discharge in the sensorimotor portions of the STN and the GPi in the pathophysiology of PD.
Reversal of Parkinsonism in the Primate Model of PD by STN Lesioning

Bergman, Wichmann and DeLong., Science 1990
The Renaissance in Function Surgery

- The striking abolition of parkinsonism with STN lesioning, combined with the earlier advances in our understanding of the network abnormalities underlying parkinsonism, provided a clear rational for surgical lesioning of the motor circuit, including pallidotomy (lesioning of Gpi).

- These discoveries contributed greatly to the renaissance in functional surgery for PD and related disorders in the 1990’s, including pallidotomy and subthalamotomy.

- High-frequency Deep Brain Stimulation (DBS) of the STN, which was introduced subsequently as a less invasive, reversible and adjustable surgical approach, is currently the treatment of choice for advanced PD, with over 100,000 surgeries performed worldwide.

- Although many questions remain unanswered about the mechanism of action of these surgical approaches, in general, whereas lesioning acts directly to block abnormal network activity, DBS appears to act by overriding and replacing abnormal activity in the network.