Neural structures involved in the control of movement

DESCENDING SYSTEMS
Upper Motor Neurons

Motor Cortex
Planning, initiating, and direct voluntary movements

Brainstem Centers
Basic movements and postural control

BASAL GANGLIA
Gating proper initiation of movement

CEREBELLUM
Sensory motor coordination

Local circuit neurons
Lower motor neuron integration

Motor neuron pools
Lower motor neurons

SPINAL CORD AND BRAINSTEM CIRCUITS

Sensory inputs

SKELETAL MUSCLES
Key take-home messages:

- Components of the basal ganglia
- Function of the basal ganglia
- Functional circuitry of the basal ganglia
  e.g., direct and indirect pathways, transmitters
- Circuitry involved in movement disorders discussed
Basal Ganglia

1. Neostriatum
   Caudate nucleus
   Putamen
   Ventral striatum (nucleus accumbens)

2. Paleostriatum
   Globus pallidus external segment (GPe)
   Globus pallidus internal segment (GPi)

3. Substantia Nigra
   Pars compacta (SNc)
   Pars reticulata (SNr)

4. Subthalamic nucleus (STN)
What do the basal ganglia do?

Basal ganglia are involved in generation of *goal-directed voluntary movements*:

- Motor learning
- Motor pattern selection
From *Neuroscience*, Purves et al. eds., 2001
Forebrain
- Motor cortex
- Caudate nucleus
- Putamen
- Globus pallidus, external and internal segments

Midbrain
- Substantia nigra pars compacta
- Substantia nigra pars reticulata

VA/VL complex of thalamus
Subthalamic nuclei

Regions of cortical input to the basal ganglia (blue)
Output to thalamus and cortex

Forebrain

Frontal cortex

Midbrain

Caudate

VA/VL thalamic nuclear complex

Subthalamic nucleus

Putamen

Globus pallidus, external segment

Globus pallidus, internal segment

Substantia nigra pars reticulata

Superior colliculus
Neurons of the basal ganglia
Synaptic input to and output from striatal medium spiny neurons

Smith and Bolam 1990
Medium spiny neuron projections
Convergence

- large dendritic trees of striatal output neurons (medium spiny neurons)
Convergence

- large dendritic trees
- decreasing cell number

Cortex

150,000,000

300:1

500:1

Striatum

30,000

300:1

GPe

100

100:1

GPi/SNr

1
Basal ganglia loops – motor and non-motor

**Motor loop**
- Primary motor, premotor, supplementary motor cortex
- Motor, premotor, somatosensory cortex
- Putamen
- Lateral globus pallidus, internal segment
- Ventral lateral and ventral anterior nuclei

**Prefrontal loop (Associative)**
- Dorsolateral prefrontal cortex
- Anterior caudate
- Globus pallidus, internal segment; substantia nigra pars reticulata
- Mediodorsal and ventral anterior nuclei

**Limbic loop**
- Anterior cingulate, orbital frontal cortex
- Amygdala, hippocampus, orbitofrontal, anterior cingulate, temporal cortex
- Ventral striatum
- Ventral pallidum
- Mediodorsal nucleus

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Input

Output and internal circuitry
Cortex

Striatum

STN

GPe

VA/VL

GPi/SNr

Direct pathway

Excitation (glutamate)

Inhibition (GABA)

* tonically active
~100 Hz

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.
Direct pathway: facilitates movement

- Excitation (glutamate)
- Inhibition (GABA)

* tonically active ~100 Hz

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.
Projections to horizontal and vertical gaze centers

Caudate nucleus

Substantia nigra pars reticulata

Superior colliculus

Eye movement

Patterns of activity when glutamate is applied in striatum
Patterns of activity during motor behavior
Disinhibition

Brain stem/Spinal cord

VA/VL

Indirect pathway:
* inhibits movement

Cortex

Indirect pathway:

Excitation (glutamate)
Inhibition (GABA)

GPe

Disinhibition

STN

* tonically active
~100 Hz

GPi/SNr

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.
Cortex

| Direct pathway: facilitates movement |
| Indirect pathway: inhibits movement |

- **Striatum**
  - $\text{D}_2$ excitatory
  - $\text{D}_1$ inhibitory

- **SNc**
  - Excitation (glutamate)
  - Inhibition (GABA)

- **GPe**

- **STN**

- **GPi/SNr**
  - * tonically active ~100 Hz

- **VA/VL**

*Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.*
Direct and indirect pathways in mouse brain
Patch-matrix compartmental organization of corticostriatal and striatonigral pathways

Corticostriatal neurons deep in layer V provide -> patches

Superficial layer V neurons -> matrix.

Patch MSNs -> DAergic neurons in SNC

Matrix MSNs -> GABAergic neurons in SNR

Gerfen TINS 1992
Patch-matrix organization of corticostriatal and striatonigral pathways

Gerfen TINS 1992
Ionotopic versus metabotropic
Ionotropic versus metabotropic

**Glutamate**

- Ionotropic

**Dopamine**

- Metabotropic
  - 2nd messenger

R
Direct transmission vs. modulation

Direct transmission
Direct transmission vs. modulation

No direct effect of DA
Direct transmission vs. modulation

Striatal medium spiny neuron

glu

D1-Rs in the direct pathway:
1) increase GluR phosphorylation
2) alters ionic conductances to amplify cortical input

DA

enhanced or diminished response

Modulation
Direct transmission *vs.* modulation

D2-Rs in the indirect pathway:
1) increase GluR phosphorylation
2) alters ionic conductances to *dampen* cortical input
Direct pathway

- Substantia nigra pars compacta
- Caudate/putamen
- Globus pallidus, internal segment
- Frontal cortex
- VA/VL complex of thalamus
Release of DA in substantia nigra, as well as in striatum is required for control of movement by the basal ganglia.
Synaptic DA release in striatum

- Dendritic shafts (35%)
- Spines (59%)
- Cell bodies (6%)
- DA axon from substantia nigra
- GABAergic output

Somatodendritic DA release in SNc

- Cortical input (glutamate)
- Somatodendritic DA release (Jaffe et al. 1998)
- Dendritic release (Geffen et al. 1976; Rice et al. 1994)

Modified from Fallon et al. 1978

Smith and Bolam 1990
DA neuron

Striatonigral axon terminal (direct pathway)

SNr output neurons (GABAergic, tonically active, project to thalamus) are inhibited by the direct, striatonigral pathway, leading to disinhibition of the thalamus and facilitation of movement.
DA neuron

Presynaptic D1 dopamine receptors enhance striatonigral GABA release

Striatonigral axon terminal (direct pathway)

SNc

SNr

Presynaptic D1 dopamine receptors *enhance* striatonigral GABA release
Somatodendritic DA release, therefore, *enhances* the effect of the direct striatonigral pathway to facilitate movement.
Motor behavior is determined by the balance between direct/indirect striatal outputs

Hypokinetic disorders
- insufficient direct pathway output
- excess indirect pathway output

Hyperkinetic disorders
- excess direct pathway output
- insufficient indirect pathway output
Parkinson’s disease

Pathophysiology
Primary: loss of nigrostriatal DA projection

Michael J. Fox  Muhammad Ali  Pope John Paul II  Janet Reno  Katherine Hepburn

Striatum
SNc
Normal Parkinson's disease

Human midbrain

Normal
Parkinson’s disease

- Degenerated neurons in the Substantia nigra pars compacta
- Increased activity in the D1 and D2 receptors
- Diminished activity in the Caudate/putamen
- Increased activity in the Globus pallidus, external segment
- Diminished activity in the Globus pallidus, internal segment
- Increased activity in the Subthalamic nucleus
- Decreased excitation in the Frontal cortex
- More tonic inhibition in the VA/VL complex of thalamus

This diagram illustrates the neural pathways involved in Parkinson’s disease, showing the imbalance between excitatory and inhibitory signals.
Parkinson’s disease

Symptoms

Motoric

• Tremor (~4-5 Hz, resting)
• Bradykinesia
• Rigidity
• Loss of postural reflexes

Depression

Dementia
Parkinson’s disease
Tremor (~4-5 Hz, resting)

Parkinson’s disease
Bradykinesia
Parkinson’s disease
Loss of postural reflexes

...even with mild tremor and bradykinesia
Parkinson’s disease

Rigidity
Parkinson’s disease

Treatment

L-DOPA

The primary treatment for Parkinson’s is administration of the dopamine precursor, L-DOPA. This is initially effective, but after 5-10 years, 50% of patients develop DOPA-induced dyskinesia.
Parkinson’s disease

Treatment

Deep brain stimulation

The activity of the subthalamic nucleus (STN) is increased in Parkinson’s. This parkinsonian patient has bilateral STN stimulating electrodes:

*high frequency stimulation inactivates the STN.*
# Hyperkinetic disorders: choreatic syndromes

<table>
<thead>
<tr>
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<th>Causes:</th>
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<td>6.</td>
<td>Tourette’s syndrome</td>
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</table>
Choreatic symptoms

Involuntary (unwanted) movements

• Chorea (dance-like)

• Athetosis (changeable or writhing movements)

• Dystonia (torsion spasm)
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette’s syndrome
Huntington’s disease

Pathophysiology

• Atrophy of striatum
• Loss of striatal GABAergic neurons
• Neuropathological sequence
  
  1st:  loss of striatal GABA/enkephalin/D2-R neurons (indirect pathway)

  2nd:  loss of striatal GABA/dynorphin/D1-R neurons (direct pathway) & cortical atrophy
Huntington’s disease pathology
Huntington’s disease

Symptoms

Early motor signs

- chorea (brief, involuntary movements)
- dystonia (abnormal postures)
Huntington’s disease

Cognitive abnormalities
- Executive function (complex tasks)
- Recent and remote memory (poor retrieval)

Psychiatric changes
- Depression
- Psychosis

Later decline
- Immobility
- Weight loss
- Death within 10-25 years (often from pneumonia)
Huntington’s disease

- Substantia nigra pars compacta
  - D1
  - D2
  - Degenerated

- Caudate/putamen
  - Globus pallidus, external segment
  - Increased
  - Subthalamus
    - Diminished

- Cerebral cortex
  - Frontal cortex
  - Increased excitation

- VA/VL complex of thalamus
  - Less tonic inhibition

ARTICLE

NEUROSCIENCE, Third Edition, Figure 17.10 (Part 2) © 2004 Sinauer Associates, Inc.
Etiology of Huntington’s disease

Huntingtin mutation

- Mutation near 5’ end contains >>CAG repeats
- Produces protein with excess glutamines near NH$_2$ terminus

Why cell death?

- Not yet certain
- Excitotoxicity? Glutamate acting via NMDA receptors can kill medium spiny neurons; glutamate antagonists block
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette’s syndrome

Cervical dystonia (torticollis)

After botulinum toxin
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Axial (thoracic and/or lumbar) dystonia

Tourette’s syndrome
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette’s syndrome
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

*DOPA-induced dyskinesia

Hemiballismus

Tourette’s syndrome

*50% of PD patients on L-DOPA will develop DOPA dyskinesia
Hyperkinetic disorders: choreatic syndromes

Huntington’s disease
Dystonia
Tardive dyskinesia
DOPA-induced dyskinesia
Hemiballismus
Tourette’s syndrome
Hyperkinetic disorders: chorreal tic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus – unilateral
STN stroke

Tourette’s syndrome

After treatment with the D2-R blocker sulpiride
Hyperkinetic disorders improved by D2 blockers

Substantia nigra pars compacta

Caudate/putamen

Frontal cortex

Increased excitation

VA/VL complex of thalamus

Subthalamic nucleus

Globus pallidus, external segment

Globus pallidus, internal segment

Increased

Diminished

Less tonic inhibition

D1

D2

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Hyperkinetic disorders: choreatic syndromes

Huntington’s disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette’s syndrome