Two major descending pathways
Pyramidal vs. extrapyramidal

Pyramidal system
- Pathway for voluntary movement
- Most fibers originate in motor cortex (BA 4&6)
- Most fibers cross to contralateral side at the medulla

Extrapyramidal system
- Pathways for postural control/certain reflex movement
- Originates in brainstem
- Fibers do not cross
- Cortex can influence this system via inputs to brain stem

Motor cortex

Brain stem centers

Lower motor neurons (brain stem and spinal cord)

Striated muscles
In order to generate voluntary movement many components are necessary:

1) A representation of the actual position of the body segments (current program)..... somatosensory systems

2) A representation of the desired position of the body segments in time (model program)..... pre motor cortex

3) Execution system..... motor cortex

4) Error correction system: A spatial and temporal motor plan for achieving 2) starting from 1)..... cerebellum

5) Sensory guidance system..... posterior parietal cortex

6) Reinforcement system: Initiating, stopping, monitoring and maintaining the appropriate movement..... basal ganglia
Cortical Motor System

Pre-motor cortex

*Movement planning/sequencing*
- Many projections to M1
- But also many projections directly into pyramidal tract
- Damage => more complex motor coordination deficits; anosognosia (loss of awareness)
- Stimulation => more complex mov’t
- Two distinct somatotopically organized subregions
  - SMA (dorso-medial)
    - May be more involved in internally generated movement (anti-mirror neurons)
  - Lateral pre-motor
    - May be more involved in externally guided movement (mirror neurons)
These various motor areas execute different tasks relative to motor learning:

Supplementary motor area initiates learning
Premotor area starts a learnt motor program
Primary motor cortex coordinates the details of the movement
Cortical Motor System

Primary motor cortex

*Execution of movement*

- Somatotopically organized
- Massive descending projections to spinal cord
- Damage => pronounced weakness in affected body parts
- Stimulation => simple mov’t in small muscle groups
Somatotopy in M1
Cortical Motor System

Posterior parietal cortex (PPC)

*Sensory guidance of movement*

- Many projections to pre-motor cortex
- But also many projections directly into pyramidal tract
- Damage can cause deficits in visually guided reaching (Balint’s syndrome) and/or apraxia
- Likely part of the dorsal visual stream

Areas 5, 7 – visuo-motor integration
Subcortical Motor System: Basal Ganglia

Cortex [input]  
[output]  
(STN)  
(Input)

Caudate nucleus  
Putamen  
Globus pallidus (internal/external)  
Subthalamic nucleus  
Substantia nigra

Cerebrum  
Cerebellum  
Spinal cord  
Deep cerebellar nuclei
Subcortical Motor System: Basal Ganglia
FIG. 9.1. Schematic representation of a transverse section through a human brain hemisphere showing the sizes and locations of several important components of the basal ganglia.
BG is a basic release circuit that works through disinhibition to open/close thalamic gates specific to movement.

VA – BG input;
VL – cerebellum input
Basal Ganglia Functions

• Rule-based and habit (reinforcement) learning system
  – Initiating, stopping, monitoring and maintaining the appropriate movement

• Braking function: inhibit undesired movement and permits desired ones

• More cognitive role
  – Motor planning, sequencing, learning, maintenance
  – Predictive control
  – Working memory
  – Attention
  – Switches in behavioral set
Motor Cortex-Basal Ganglia-Cerebellum Circuit

- M1, PM, SMA
- Cortex
- Striatum
  - Indirect pathway: GPe, STN
  - Direct pathway: GPe, STN, GPi/SNr
- Thalamus
- Somatosensory systems
- Cerebellum

 excitative pathways
 inhibitory pathways
Abnormal functioning in the basal ganglia has been implicated in both hypokinetic (too little movement) and hyperkinetic (too much movement) disorders.

For example:  
Hyperkinetic: Huntington’s disease, Tourette’s Syndrome, Ballism
Hypokinetic: Parkinson’s disease (loss of SN cells)

Although these diseases are typically thought of as movement disorders, they contain both physical (motor) and emotional (non-motor) aspects. BG are also thought to be involved in non-motor disorders such as schizophrenia and OCD.
MEDIUM SPINY NEURON

- 95% of neurons in BG
- Bistable Vm (-85 and -60 mV)
- Context-dependent firing
- Phasically active
- Divided into those with D1/D2 receptors
- Use GABA+neuropeptides

DA binding to D1 depolarizes
binding to D2 inhibits

D1 cells form direct pathway
D2 cells form indirect pathway
• Striatum: caudate - putamen
• 80-95% medium spiny neurons
  • GABAergic; ~ 0.1 - 1 Hz rate
• Receives vast majority of BG input
  • cortical
  • excitatory (glutamatergic)
• 2 types of medium spiny cells
  • Those expressing D1 receptors
    • **Excited** by DA
    • contain dynorphin/Subst P
    • send to GPi & SNpr (direct)
  • Those expressing D2 receptors
    • **Inhibited** by DA
    • contain enkephalin
    • send to Gpe (indirect)
Basal Ganglia Circuit

- M1, PM, SMA
- Cortex
- Striatum
- SNc
- GPe
- STN
- Thalamus
- GPi/SNr

- Direct pathway
- Indirect pathway
- Hyperdirect pathway

- Excitatory
- Inhibitory
Basal Ganglia Circuit

M1, PM
SMA

Cortex

Striatum

Indirect pathway

SNc

Direct pathway

GPe

Thalamus

STN

GPi/SNr

Hyperdirect pathway

excitatory
inhibitory

Reinforcement learning

reward

input

output
**Parallel processing hypothesis**
- multiple segregated loops
- no integration

**Information funneling hypothesis**
- absolute convergence
  - cortical neurons > striatal neurons
  - areas of cortex far apart project to adjacent areas of striatum
  - striatal cells synapse across a broad area of GP and SN

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**Loops**
- **Skel to motor**
- **Oculomotor**
- **Dorsolateral PrefrontalCtx (46)**
- **Lateral OrbitofrontalCtx (12)**
- **Anterior Cingulate/ Medial OrbitofrontalCtx (13, 24)**
- **Inferior TemporalCtx (TE)**
- ACh: striosomes
  - gets limbic input
  - sends to SNpc
- GABA: matrisomes
  - gets most cortical input
  - sends to GPi and SNpr
Limbic areas

Sensorimotor association areas

striasomes

matrisomes
• GPi (Globus Pallidus internal)
  • Major BG output for limb movement
  • DIRECT pathway from striatum
    • (striatopallidal pathway)
  • Also receives STN input
    • excitatory
    • contacts many neurons
    • 10-15ms faster than striatum
  • GABA output to thalamus & brain stem
• SNpr (Substantia Nigra pars reticulata)
  • Major BG output for eye movement
  • Also gets striatum & STN input
  • SNpr projects to SC to control eye movements
• **GPe (Globus Pallidus external)**
  • Much like internal segment:
    • Gets striatum & STN input
    • Sends output to STN
    • Striatum → GPe → STN → GPi → Thalamus
  • INDIRECT striatopallidal pathway
• SNpc (Substantia Nigra pars compacta)
  • Most studied structure in the basal ganglia
  • Large DAergic cells
    • Receives inhibitory input from striasomes in striatum
  • Sends DAergic output to same/adjacent striatal areas
    • DA action (inhibitory/excitatory) depends on striatal receptors.
      • D1 receptors excite
      • D2 receptors inhibit
Basal Ganglia Circuit

- Striatum receives input from cortical areas
  - inputs are roughly topographical (multiple parallel circuits)
- GPi/SNr are the major output nuclei
  - Output is inhibitory
  - Gpi/SNr neurons have high baseline firing rates (baseline = inhibition)
  - Gpi/SNr input from the striatum is focal and inhibitory, whereas input from the STN is diffuse and excitatory
- Direct vs. indirect striatal pathways have opposing effects (inhib. vs. excit.)
- Output of thalamus is primary to motor areas
Malfunctioning of basal ganglia induces dramatic abnormalities in voluntary movement.

Basal ganglia coordinates movement indirectly, by receiving information from motor cortex and re-sending back to the motor cortex processed information through the thalamus.
Basal Ganglia Circuit

M1, PM
SMA
Cortex

Striatum

Indirect pathway
Direct pathway

Indirect
Hyperdirect
pathway

D2(-)  D1 (+)
Indirect  Direct

(bias is to maintain thalamic channels opened and info flowing to cortex)
Parkinson’s Disease

- **Etiology**
  - Adult onset, thought to be genetic without 100% penetrance.
  - One hypothesis is that it results from a genetic susceptibility to an environmental factor.
- Loss of DA input to striatum from SNpc
- Loss must involve over 90% of cells before symptoms appear.
Parkinson’s Disease: Clinical Symptoms

• Motor
  – Tremor
  – Cogwheel rigidity
  – Shuffling steps
  – Akinesia
  – Bradykinesia
  – Dystonia

• Non-motor
  – Cognitive slowing
  – Difficulty with tasks requiring high level processing
  – Depression

*Akinesia:* Difficulty beginning or maintaining a body motion
*Bradykinesia:* Slowness of movement; paucity or incompleteness of movement
*Dystonia:* Sustained involuntary muscle contractions and spasms
Parkinson’s Disease (Hypokineti

• Decreased output of SNC dopaminergic projections
  • Decrease excitation in direct pathway
  • Increase inhibition in indirect pathway
• Net effect: more inhibition of thalamus and therefore less excitatory input to motor cortex

M1, PM SMA | Cortex

Striatum

Indirect pathway

SNc

Direct pathway

GPe

STN

Thalamus

D2(-) D1 (+)

Indirect Direct

exci
tor
ty

inhibitory
Parkinson’s Disease: Treatment

• **L-DOPA** (taken up by DA terminals in the striatum); converted to DA and then released.
  – Not effective for long-term treatment
  – Patients develop a tolerance to it
  – Has many side effects (honeymoon period 3-5 years)

• **Transplantation of fetal tissue**

• **Pallidotomy** (cells in the posteroverentral GPi are surgically ablated either unilaterally or bilaterally)

• **Deep Brain Stimulation (DBS):** a surgical treatment involving the implantation of a brain pacemaker, which sends electrical impulses to brain.
DBS

DBS leads are placed in the brain according to the type of symptoms to be addressed. For essential tremor and Parkinsonian tremors, the lead is placed in the thalamus. For symptoms associated with Parkinson's disease (rigidity, bradykinesia/akinesia and tremor), the lead may be placed in either the globus pallidus or subthalamic nucleus.
Huntington’s Disease (Hyperkinetic Movement)

- Cell loss in the striatum that seems to affect the indirect pathway disproportionately
- Net effect: less inhibition of the thalamus and therefore excessive excitation of motor cortex

Diagram:
- M1, PM SMA → Cortex
- Cortex → Striatum
- Striatum → GPe → STN → Thalamus
- Striatum → SNc → GPi/SNr
- GPi/SNr → Thalamus
- Cortex

Pathways:
- Indirect pathway
- Direct pathway

Colors:
- Green: excitatory
- Red: inhibitory
Subcortical Motor System: Basal Ganglia

So what is the basal ganglia circuit doing?

• The “Brake” hypothesis
  B.G. essentially acts like a brake to prevent unwanted movement.
  • Excitation of STN via motor input leads to diffuse increase in inhibition.
  • Excitation of the striatum in one motor circuit decreasing this inhibition focally thus “releasing the brake” for the selected movement.