The Basal Ganglia
Anatomy, Physiology, etc.

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Overview of Basal Ganglia

• Basal Ganglia (BG) made up of several interconnected nuclei at the base of the forebrain.
• Important role in various processes including motor, associative, cognitive, and mnemonic functions, especially action selection and procedural learning
• BG motor circuit is organized anatomically to receive input from virtually all of the cerebral cortex and to send inhibitory output via thalamus
• BG exerts inhibitory influence on motor systems
  – Release of this inhibition allows a motor system to become active
• Dysfunction of BG implicated in movement disorders, most notably Parkinson Disease and Huntington Disease.

Basal Ganglia Anatomy

Divisions of Basal Ganglia

**Dorsal Division:**
- Striatum (caudate and putamen)
- Globus Pallidus
  - external segment (GPe) as the entopeduncular nucleus in rodents
- Subthalamic Nucleus (STN) - nucleus of Luys
- Substantia Nigra
  - Dorsal - pars compacta (SNpc)
  - Ventral - pars reticulata (SNpr)
- Motor and associative functions

**Ventral Division:**
- Dorsal striatum or nucleus accumbens
- Ventral pallidum
- Ventral segmental area
- Associated with limbic functions
  - Control role in reward learning

BG Input and Output

**Primary input structures of the basal ganglia:**
- Striatum (Caudate and Putamen)
- Subthalamic nucleus (STN)
  - Receive excitatory input from cerebral cortex

**Primary output nuclei:**
- Globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNpr)
  - Send **inhibitory output** to thalamus and brainstem targets.
  - Acting through the thalamus, the basal ganglia output influences frontal lobe cortical neurons.
  - Conditions associated with destruction of the output nuclei are associated with unwanted and nonspecific overactivity of thalamocortical and brainstem targets.
  - Conditions associated with excessive activity of the output neurons are associated with underactivity of thalamocortical and brainstem targets.

Striatum

**Striatum: Caudate and Putamen**
- Separated by internal capsule during development
  - Similar in neurons, circuits, neurophysiology, function
  - One structure in rodents

**Inputs:**
- Receives excitatory input from all of cerebral cortex, primarily glutamatergic
  - Organized somatotopically
  - Somatosensory and motor cortex project to putamen
  - Prefrontal cortex projects to caudate
- Dopaminergic input from substantia nigra pars compacta
- Excitatory glutamatergic input from intralaminar and ventrolateral thalamic nuclei
  - Cholinergic input from large aspiny striatal interneurons
- GABA, substance P, and enkephalin input from adjacent medium spiny striatal neurons
- GABA input from striatal inhibitory interneurons

**Function:** transformation, filtering, integration, and focusing of this information

**Output:**
- **Direct** striatal output pathway
  - Neurons contain GABA, dynorphin, and substance P and primarily express D1 dopamine receptors
  - Project to the basal ganglia output nuclei, GPi and SNpr
- **Indirect** striatal output pathway
  - Neurons contain GABA and enkephalin and primarily express D2 dopamine receptors
  - Project to the external segment of the globus pallidus (GPe)
Role of Dopamine in the Striatum

- The differential actions of dopamine released from the terminals of the SNpc neurons on the striatal neurons are responsible for the regulation of the balance between the direct and the indirect pathways.
- Dopamine release in the striatum
  - Increases direct pathway activity via D1 receptors
  - Decreases activity in the indirect pathways via D2 receptors
  - Leads to a net reduction in the activity of Gpi and SNpr (disinhibition of the thalamus and other targets), facilitating movement
- A decrease in striatal dopamine level
  - Decreases direct pathway activity
  - Increases indirect pathway activity
  - Results in an increase in Gpi and SNpr activity and inhibition of movement

Subthalamic Nucleus (STN)

- Only glutamatergic component of the basal ganglia
- Additional pathways through which information flows from the cortex to basal ganglia output nuclei
- STN Inputs:
  - receives an excitatory, glutamatergic input from many areas of frontal lobes with especially large inputs from motor areas of cortex
  - inhibitory GABA input from GPe, the second limb of the "indirect" striatal output pathway
- STN Output:
  - glutamatergic and excitatory to Gpi, GPe, and SNpr. The projection from STN to Gpi and SNpr is the third limb of the "indirect" pathway.

Globus Pallidus Internal Segment (Gpi) and Substantia Nigra pars reticulata (SNpr)

- Gpi and SNpr are single functional unit
- Separated during development by internal capsule
- Inputs to Gpi and SNpr
  - excitatory glutamate input from STN
  - inhibitory GABA input from striatum
  - inhibitory GABA input from GPe
- Output of Gpi and SNpr
  - GABAergic and inhibitory
  - Principal outputs project to parts of the ventral anterior, ventral lateral, and mediodorsal thalamic nuclei
  - The thalamic targets of Gpi and SNpr project, in turn, to frontal lobes, with the strongest output going to motor areas
  - Ventral thalami also projects to striatum, forming a potential feedback circuit
  - Basal ganglia motor output has a somatotopic organization such that the body below the neck is largely represented in Gpi, and the head and eyes are largely represented in SNpr
GPI

- GPI is the principal basal ganglia output for control of limb movement.
- Neurons in GPI fire tonically at 60 spikes/sec to 80 spikes/sec at rest.
- The discharge of many GPI neurons is related to direction of limb movement.
- GPI activity is not correlated with other physical parameters of movement including joint position, force production, movement amplitude, or movement velocity.
- Some GPI neurons have activity related to movement preparation.
- Timing of movement-related GPI activity is late compared to the activation of agonist muscles.
  - The average onset of GPI activity is after the onset of electromyography, but before the onset of movement.
  - Late timing of GPI movement-related activity suggests that the output of the basal ganglia is unlikely to initiate movement.

Globus Pallidus external segment (GPe)

- GPe is an intrinsic nucleus of the basal ganglia. Receives input from and sends output to other basal ganglia nuclei.
- Inputs:
  - Inhibitory GABAergic projections from the striatum and an excitatory glutamatergic one from SNpr.
  - As with GPe, the STN input to GPe is divergent, and the related input is focused.
  - Unlike GPe, the striatal projection to GPe contains enkephalin and not substance P or dynorphin.
  - Physiologic effects of these peptide neurotransmitters are not well understood, it is clear that the primary effect of the related input is inhibitory.
- Outputs:
  - GABAergic and inhibitory
  - Majority of the output projects back to STN
  - Bifurcation of the GABAergic inhibitory output from GPe directly to GPI and to SNpr.
  - GABAergic projection back to striatum.
  - GPI neurons are in a close proximity to neurons in striatum and SNpr and brain reward circuitry to neurons in SNpr and SNpc.
- Specific function is not well understood.
  - Appears to regulate and focus activity patterns in striatum, STN, GPI, and SNpc.
- GPe is mostly made up of projection neurons that contain glutamate decarboxylase.

Substantia Nigra pars compacta (SNpc)

- Made up of large dopamine-containing cells
  - It is these neurons that degenerate in Parkinson disease
- Input:
  - Most from striatal GABAergic neurons
  - Some from frontal lobe
- Output:
  - SNpc dopamine neurons project to all of caudate and putamen in a topographic manner.
  - Also a dopamine input (?) to GPI, SNpr, and STN
- Function:
  - Activity does not appear related directly to movement
  - Neuronal activity is in relation to sensory stimuli with behavioral significance
  - Involved in learning and task reward
Direct vs Indirect Pathways

**Direct Pathway**
- Cortex (stimulates) → Striatum (inhibits) → "SNr-GPi" complex (less inhibition of thalamus) → Thalamus (stimulates) → Cortex (stimulates) → Muscles, etc. → Hypokinetic state
  - Cortical cells project excitatory inputs to the striatum.
  - Striatum projects inhibitory neurons onto the cells of the SNr-GPi complex.
  - Dopamine activation of D1 receptors increases GABAergic inhibitory activity.
  - SNr-GPi complex projects directly onto the thalamus through the inhibitory ansa lenticularis pathway.
  - Striatal inhibition of the SNr-GPi complex coupled with SNr-GPi inhibition of the thalamus therefore results in a net reduction of inhibition of the thalamus via the striatum.

**Indirect Pathway**
- Cortex (stimulates) → Striatum (inhibits) → GPe (less inhibition of STN) → STN (stimulates) → "SNr-GPi" complex (inhibits) → Thalamus (is stimulating less) → Cortex (is stimulating less) → Muscles, etc. → Hypokinetic state
  - Striatal cells project inhibitory axons onto the cells of the globus pallidus externa (GPe).
  - Dopamine activation of D2 receptors decreases GABAergic inhibitory activity.
  - GPe tonically inhibits the subthalamic nucleus (STN).
  - Inhibition (by the striatum) of the inhibitory projections of the GPe results in the net reduction of inhibition of the STN.
  - STN projects excitatory inputs to the SNr-GPi complex which inhibits the thalamus. The end result is inhibition of the thalamus and, therefore, decreased stimulation of the motor cortex by the thalamus and reduced muscle activity. The direct and indirect pathways are therefore antagonistic in their functions.

STN vs Striatal Pathways

• Cortex → STN → GPI & SNpr
  - Cortical input only from frontal lobes
  - Pathway is excitatory
  - STN pathway is faster than striatal pathway
  - STN projections to GPI are divergent
  - Fast, widespread, divergent excitation from cortex through STN

• Cortex → Striatum → GPI & SNpr
  - Cortical input from virtually all cortex
  - Pathway is inhibitory
  - Striatal projection to GPI is focused
  - Slower, focused, inhibition through striatum.

Diagram of BG Circuits

http://en.wikipedia.org/wiki/Basal_ganglia
Summary

• Basal ganglia motor circuit is organized anatomically to receive input from virtually all of the cerebral cortex and to send inhibitory output via thalamus back to frontal lobe targets.
• Pathway through STN to GPi and SNpr is excitatory and divergent, thus, providing for broad excitation of these output structures.
• The pathway through the Striatum to GPi and SNpr is inhibitory and focused, providing for focused inhibition.
• Because the output of GPi and SNpr is inhibitory, the net result is focused facilitation and surrounding inhibition of thalamocortical and brainstem targets that are involved in the generation of motor patterns.

Summary Continued

• Neurons in most basal ganglia structures fire in relation to the preparation and execution of voluntary movement.
• Late timing and weak parameter coding suggest that basal ganglia neurons do not generate or program movements.
• BG neurons appear to act after the motor pattern is generated by cortical neurons, but before the movement begins, to facilitate the desired movement and to inhibit other motor patterns that might compete with the desired one.
• The net result of basal ganglia activity during a voluntary movement is the inhibition (“braking”) of competing motor patterns and focused facilitation (releasing the “brake”) from the selected voluntary movement pattern generators.