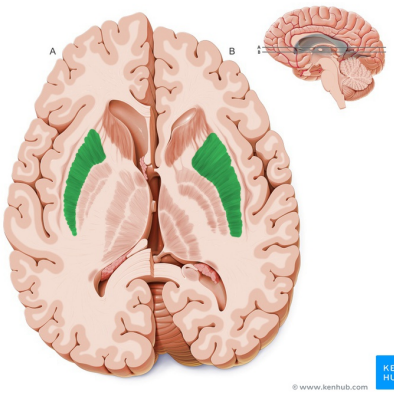
Connections of basal ganglia

Introduction

The **basal ganglia**, or basal nuclei, are areas of subcortical grey matter that play a prominent role in modulating movement, as well as cognitive and emotional functions, through a complex series of feedback loops to and from the cerebral cortex. Pharmacologic or pathologic disruption of these pathways results in a prominent motor, cognitive and emotional dysfunction.

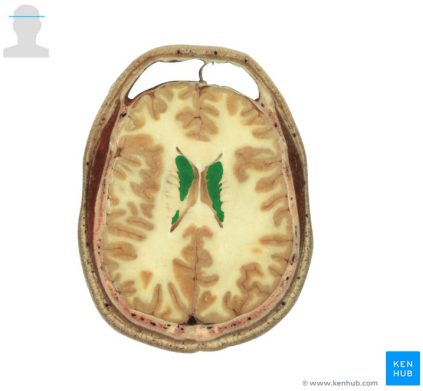
Anatomy

The **caudate nucleus** and **putamen** develop together and are functionally defined as the **striatum** (referring to the striped appearance exhibited by the bisecting internal capsule). Sensorimotor function is processed within the putamen, while limbic and associative functions are managed by the caudate nucleus. Approximating the putamen, but functionally distinct, is the **globus pallidus**, both of them are collectively known as lentiform nucleus.



Putamen - axial view

Lying lateral to the thalamus in the inferior aspect of each cerebral hemisphere, the caudate nucleus has a large **head** in the floor and lateral wall of the anterior horn of the lateral ventricle. The **body** and **tail** of the caudate nucleus follow the curve of the inferior horn of the lateral venetricle. The caudate nucleus is largely separated from the lentiform nucleus by the **internal capsule**, with the notable exception of prominent bridges through the anterior limb of the internal capsule.

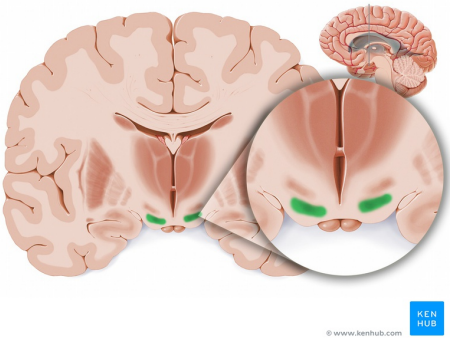


Caudate nucleus - axial view

The connectivity of the basal ganglia follows a predictable pattern that generally involves projections:

- from the cortex to the striatum
- from the striatum to the pallidum
- from the pallidum to the thalamus
- from the thalamus back to the cortex

Owing to a thorough integration with the striatum and pallidus, the **substantia nigra** and **subthalamic nucleus (STN)** are functionally grouped with the basal ganglia. Additional reciprocal pathways of the extrapyramidal system involve the cerebellum and the red nucleus.



Substantia nigra - coronal view

Neurotransmitters

Gamma-aminobutyric acid (GABA) is the standard inhibitory neurotransmitter in the human brain and **GABAergic** synapses are widespread throughout the basal ganglia. **Glutamate** is a common excitatory neurotransmitter and is present in cortical afferents to the striatum, STN afferents to the globus pallidus, and thalamocortical projections.

Dopamine, notably released by **substantia nigra pars compacta (SNc)** projections, has excitatory or inhibitory effects depending on the postsynaptic dopamine receptor subtype.

Acetylcholine (ACh) is a neuromodulator promoting the release of neurotransmitters at the pre-synaptic membrane. Anticholinergic drugs such as atropine can improve parkinsonian and dystonic syndromes. Other neuromodulators identified in basal ganglia synapses include:

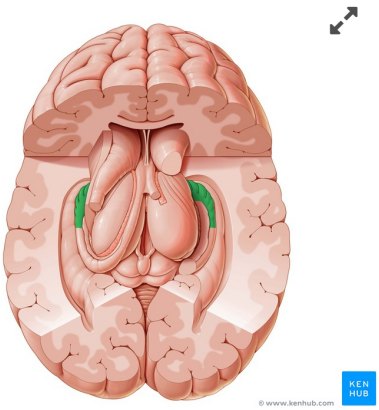
- cholecystokinin
- enkephalin
- neuropeptide Y
- somatostatin
- substance P

Neuropathways

Basal ganglia neurons are overwhelmingly GABAergic and maintain a **tone of inhibition** until acted upon by another inhibitory signal that withdraws that tone. Through a mechanism known as **disinhibition**, serial inhibitory signals lead to an excitatory signal. This occurs when an inhibitory neuron stimulates a second inhibitory neuron, thereby releasing its inhibitory activity on a third neuron, resulting in excitation. Excitatory **dopaminergic** and **glutamatergic** afferents may simultaneously influence GABAergic neurons, creating oscillations that fine-tune cortical signals.

Striatum

The striatum is the major site of **input** to the basal ganglia. Most striatal ganglia are GABAergic **medium spiny neurons** projecting to the **globus pallidus**. Large **aspiny cholinergic interneurons** occupy the remaining striatal mass. Excitatory glutamatergic afferents primarily originate from the cerebral cortex, but inputs are also received from the thalamus, substantia nigra, amygdala, and hippocampus.



Hippocampus - cranial view

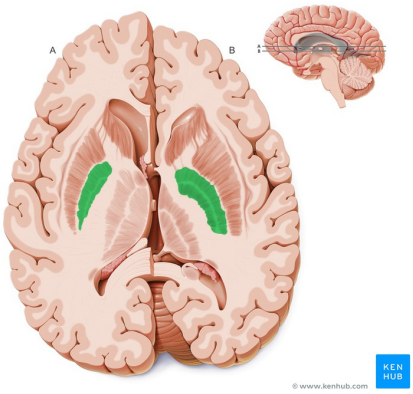
Cortical Inputs

Three major divisions of cortical afferents – sensorimotor, associative, and limbic – comprise distinct, closed loop systems that modulate motor, cognitive and emotional functions. **Sensorimotor afferents** from the motor cortex project to the putamen, and return to the motor cortices after processing within the basal ganglia.

Associative afferents originate from the frontal, parietal, temporal, or occipital cortices, project to the caudate nucleus, and complete the loop at the frontal cortex. The **limbic pathway** originates from the amygdala, hippocampus, orbitofrontal, cingulate, or temporal cortices, projects to the ventral striatum, and returns to the cingulate or orbitofrontal cortex, affecting emotion or motivation respectively.

Pallidum

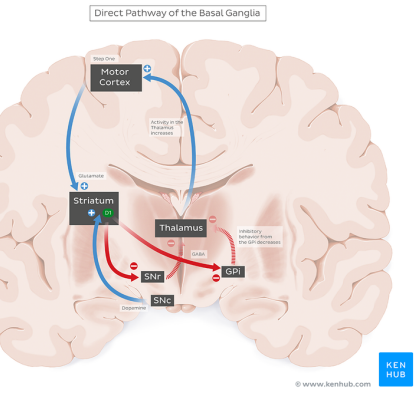
GABAergic striatal efferents project primarily to the **inner globus pallidus (GPi)**, the major site of **output** of the basal ganglia. The GPi and **substantia nigra pars reticulata (SNr)** are functionally closely integrated and seen as one unit. The SNr also sends modulating signals directly to the cortex and the limbic system. The **external globus pallidus (GPe)** is involved in an internal feedback loop that modulates the output of the GPi.



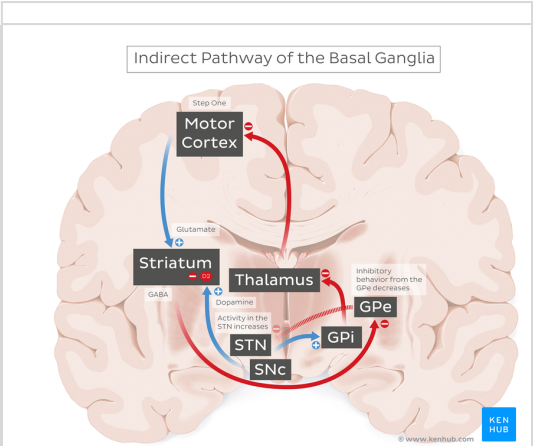
Globus pallidus - axial view

Direct and Indirect Pathways

Outputs from the striatum to the GPi/SNr are divided into two opposing pathways, regulated by dopaminergic efferents from the SNc to the striatum. The **direct pathway** involves activation of monosynaptic GABAergic afferents from the striatum to the GPi/SNr and is important in initiating and maintaining movement through disinhibition of corticothalamic efferents. The **indirect pathway** is important for suppressing extemporaneous movement through inhibition of corticothalamic efferents. This involves an internal loop of polysynaptic signals from the striatum to the GPe, disinhibition of the STN, and glutamatergic excitation of the GPi/SNr.



Direct Pathway of the Basal Ganglia



Indirect pathway of the basal ganglia

The balance of signals via the direct or indirect pathway is influenced by the subtype of dopamine receptor expressed on a striatal ganglion. Dopaminergic afferents of the **substantia nigra pars compacta (SNc)** promote excitation of **D1 receptors** of the direct pathway and inhibition of **D2 receptors** of the indirect pathway. The uniquely glutamatergic fibers of the subthalamic nucleus form a bundle called the **subthalamic fasciculus** which traverses the internal capsule to the globus pallidus.

Pallidothalamic Output

The GPi projects inhibitory GABAergic neurons to the ventrolateral and ventral anterior nuclei of the thalamus via fascicles of myelinated white matter known as the **fields of Forel** (or H-fields). These bundles of neurons traverse the internal capsule and are organized into three distinct bundles: the **thalamic bundle (H1)** includes the fibers of the **ansa lenticularis**, the **lenticular fasciculus (H2)**, and fibers projecting from the **cerebellum**. Field H3 is a distinct zone of grey and white matter associated with the **red nucleus**. The thalamus subsequently returns the modulated signals to the sensorimotor cortex via glutamatergic neurons, completing the feedback loop of the cerebral cortex and the basal ganglia.

Clinical Notes

Symptoms of Disordered Movement

Pathologic or pharmacologic disruption to pathways of the basal ganglia may result in a variety of disordered movements, though not frank weakness or paralysis. Defective movement may be characterized by:

- **hypokinesia** (reduction in spontaneous movement)
- **akinesia** (complete loss of spontaneous movement)
- **bradykinesia** (abnormally slow movement)

Excessive movement may be characterized by:

- tremor
- rigidity
- **dyskinesia** (unwanted involuntary movements)

- **athetosis** (slow involuntary rhythmic movements of extremities and face)
- **ballismus** (quick involuntary movements of face and extremities)
- **dystonia**

Parkinson's Disease

The resting tremor, bradykinesia, and rigidity of Parkinson's disease (PD) is a result of degeneration of the **SNc** resulting in depletion of **dopamine** at the nigrostriatal synapse. The decreased activity in the direct pathway and increased activity in the indirect pathway result in excessive inhibition of thalamocortical signals manifesting as **bradykinesia**.

Symptomatic treatment for PD involves a variety of drugs that augment dopaminergic effect in the striatum. Levodopa is a precursor to dopamine, and a first-line therapy in PD. It is typically administered with a decarboxylase inhibitor (carbidopa) that prevents conversion to dopamine outside of the brain causing unwanted effects. Dopamine agonists (i.e. bromocriptine) and drugs that slow dopamine metabolism are also used.

Chorea

In contrast to parkinsonian symptoms, chorea (Latin choreus, meaning "dance") refers to a collection of **hyperkinetic symptoms** due to degeneration of **basal ganglia neurons**. Degeneration may be a result of a variety of syndromes including hereditary disease (i.e. Huntington's disease, Wilson's disease), lacunar stroke, infection (i.e. AIDS), drug (i.e. levodopa) or heavy metal exposure (copper), to name a few. Treatment of chorea symptoms involves removal or treatment of the offending agent; which is not often possible. Dopamine receptor antagonists (i.e. antipsychotics) may be effective to reduce symptoms.

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Illustrations:

- Putamen - axial view - Paul Kim
- Caudate nucleus - axial view - National Library of Medicine
- Substantia nigra - coronal view - Paul Kim
- Hippocampus - cranial view - Paul Kim

- Globus pallidus - axial view - Paul Kim
- Direct and Indirect Pathways of the Basal Ganglia - Stefanie Schultz