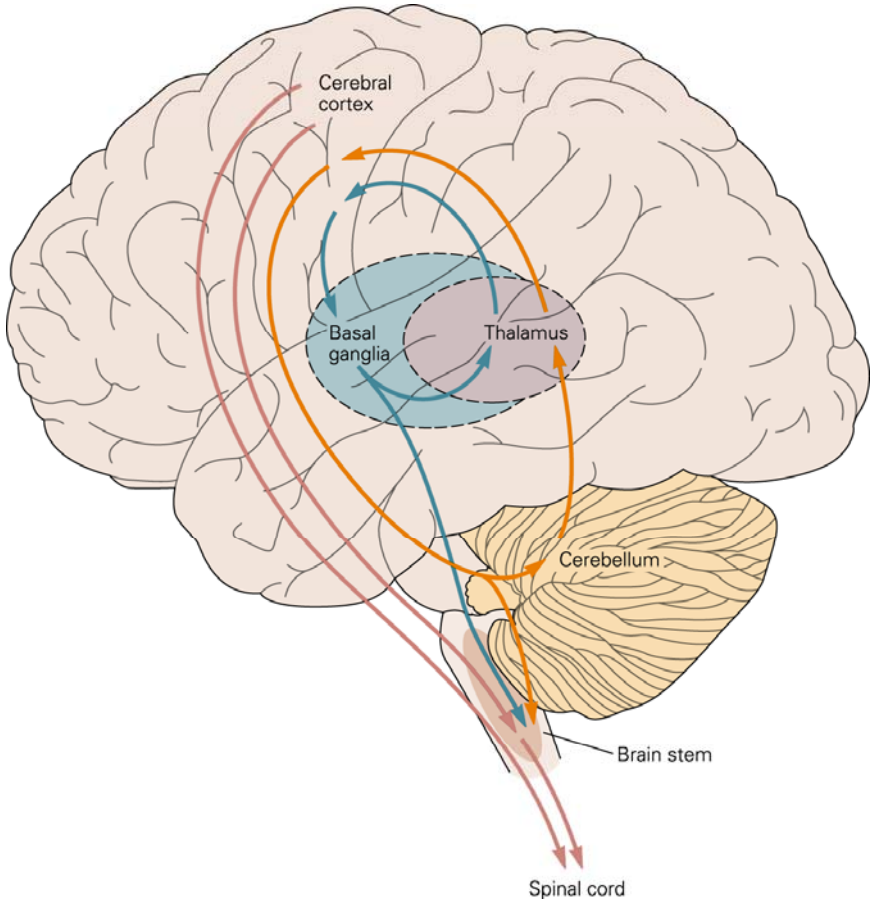
Basal Ganglia

1. Organization and functions of basal ganglia
2. Structure of striatum
3. Direct and indirect pathways
4. Parkinson disease
5. Hyperkinetic disorders

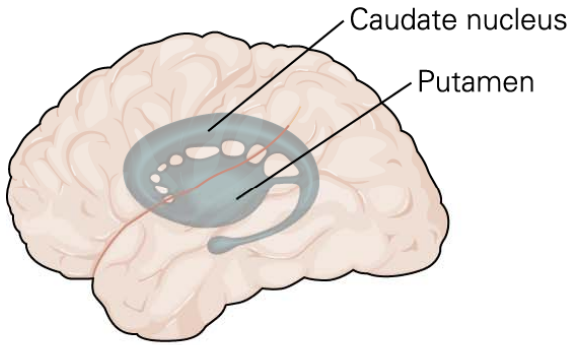
Basal ganglia

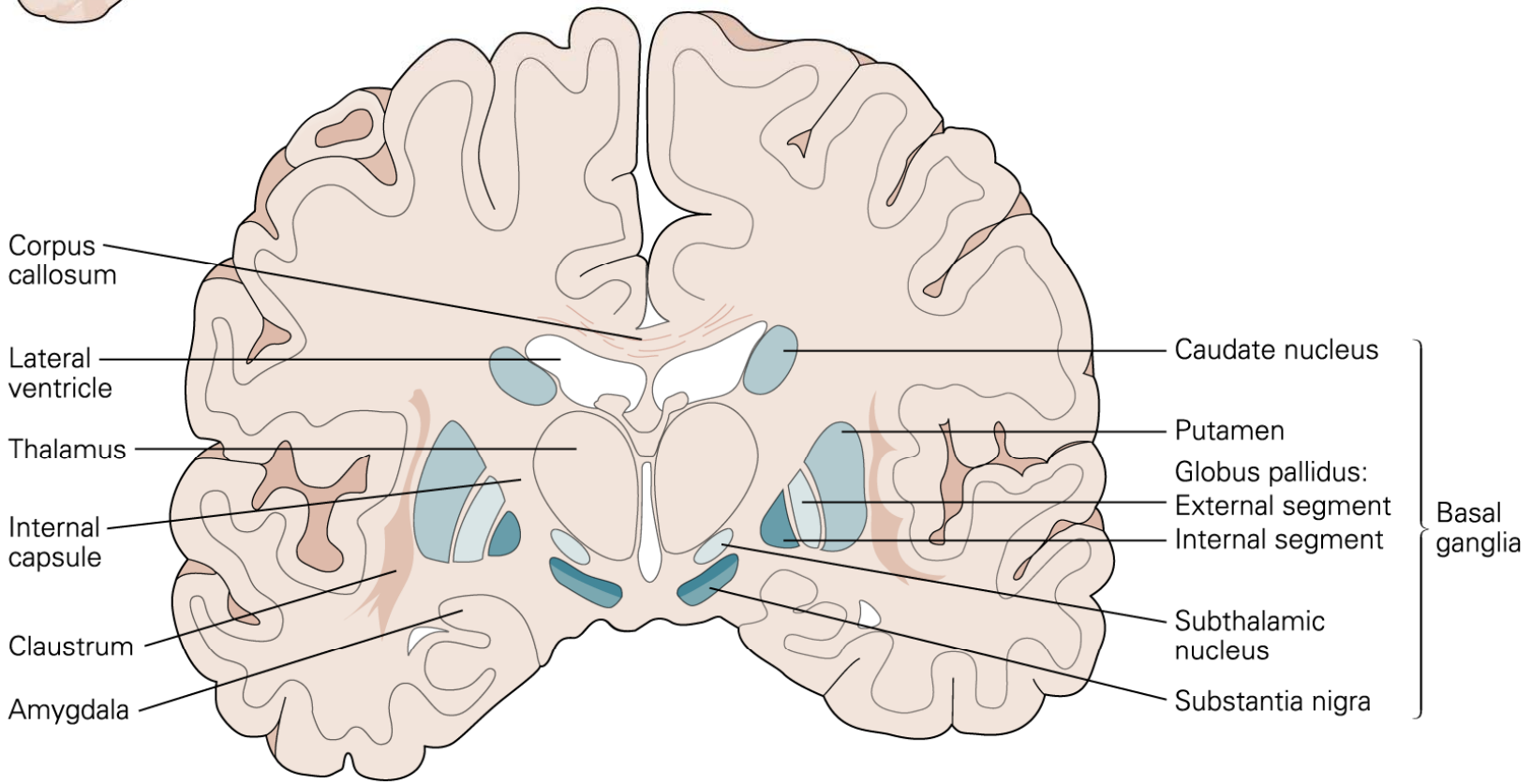
- Reentrant loop with cerebral cortex via thalamus (with output to brain stem)
- Consists of innerconnected subcortical nuclei with major projections to the cerebral cortex, thalamus, and brain stem nuclei.
- Functions: regulating voluntary movement via thalamus, also contributing to skeletomotor, oculomotor, cognitive and emotional functions.



Four principal nuclei:

1. Striatum (caudate nucleus, putamen)
2. Globus pallidus (pallidum, external and internal segment)
3. Substantia nigra (pars reticulata, pars compacta)
4. Subthalamic nucleus





Striatum

The largest component of the basal ganglia.

Three Subdivisions:

caudate nucleus, putamen, ventral striatum (nucleus accumbens, part of the reward system)

(separated by white matter “internal capsule”).

Caudate – receives inputs from **association cortex**

Putamen – receives somatotopically organized inputs from **SI** and **MI**

Both receive inputs from **intralaminar thalamic nuclei** and **substantia nigra**

Topographic connections between cortex and striatum –

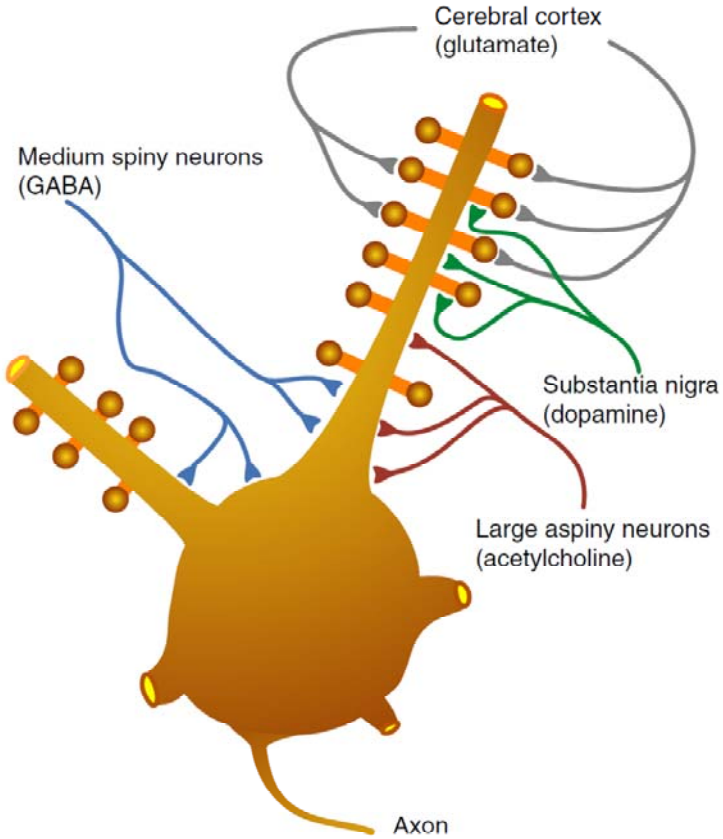
The loop from and to the cortex is structurally and functionally segregated - each area of the neocortex projects to a discrete region of the striatum in a highly topographic manner.

Neuronal types:

<u>Medium spiny neurons (inhibitory)</u>: Great majority (90-95 %) GABAergic projection neurons, covered with dendritic spines, receive synaptic input primarily from the cortex and thalamus, sends axons to globus pallidus and substantia nigra.

<u>Interneurons (inhibitory)</u>: 2% are large cholinergic neurons, with smooth dendrites and small interneurons containing somatostatin, neuropeptide Y. Reduce the activity of striatal output neurons, responsible for most of the tonic activity in the striatum.

Dopaminergic inputs from SN contact both types

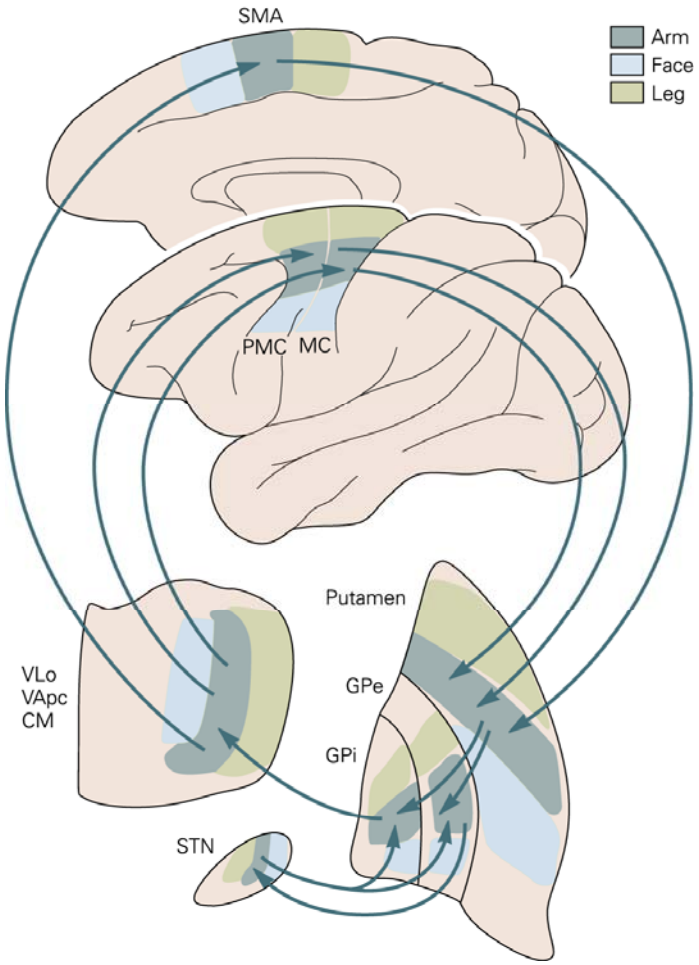


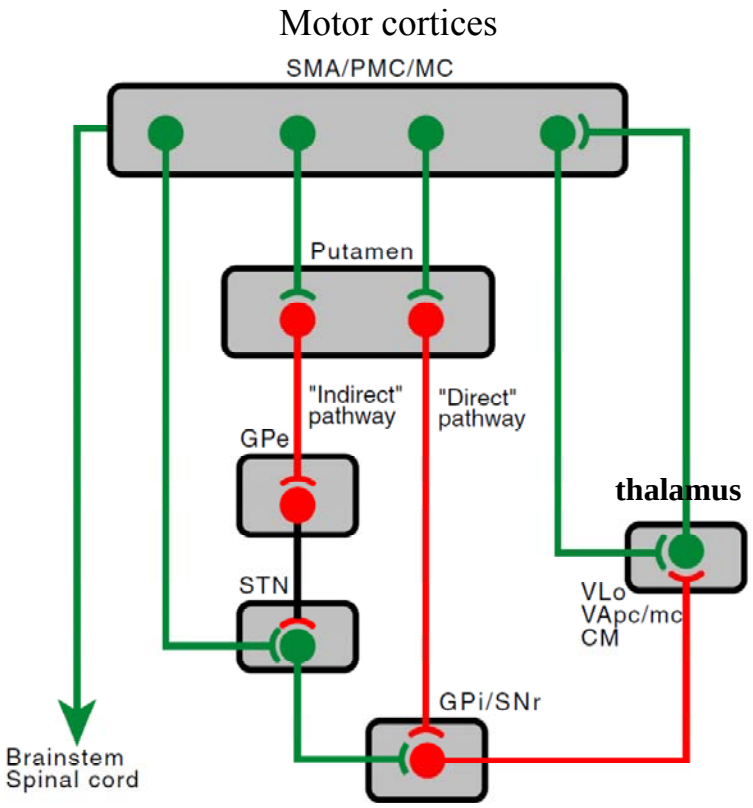
Output nuclei of the basal ganglia:

1. Internal pallidal segment (GPi)
2. Substantia nigra (pars reticulata)

Information from the striatum is processed in the pallidum and nigra in topographically organized manner before sent to the thalamus and brain stem (via modulation of the tonic inhibitory actions on thalamus and brain stem).

Synaptic actions in the cortex – basal ganglia – cortex loop: disinhibition of selective motor program.





GPe: globus pallidus (external segment)
GPi: globus pallidus (internal segments)

SN: substantia nigra (pars reticulata, pars compacta)
STN: subthalamic nucleus

Green: excitatory (glutamatergic)

Red : inhibitory (GABAergic)

Basal ganglia control of thalamocortical activity

Direct pathway:

cortex → striatum → GPi → thalamus → cortex.

\+ - - +

Activation leads to disinhibition of thalamocortical activity

Positive feedback - **facilitates movement**,

Dopamine modulation mediated by D1 receptors (facilitatory)

Indirect pathway:

cortex→striatum→GPe→STN→GPi→thalamus→cortex.

\+ - - + - +

Activation leads to inhibition of thalamocortical activity

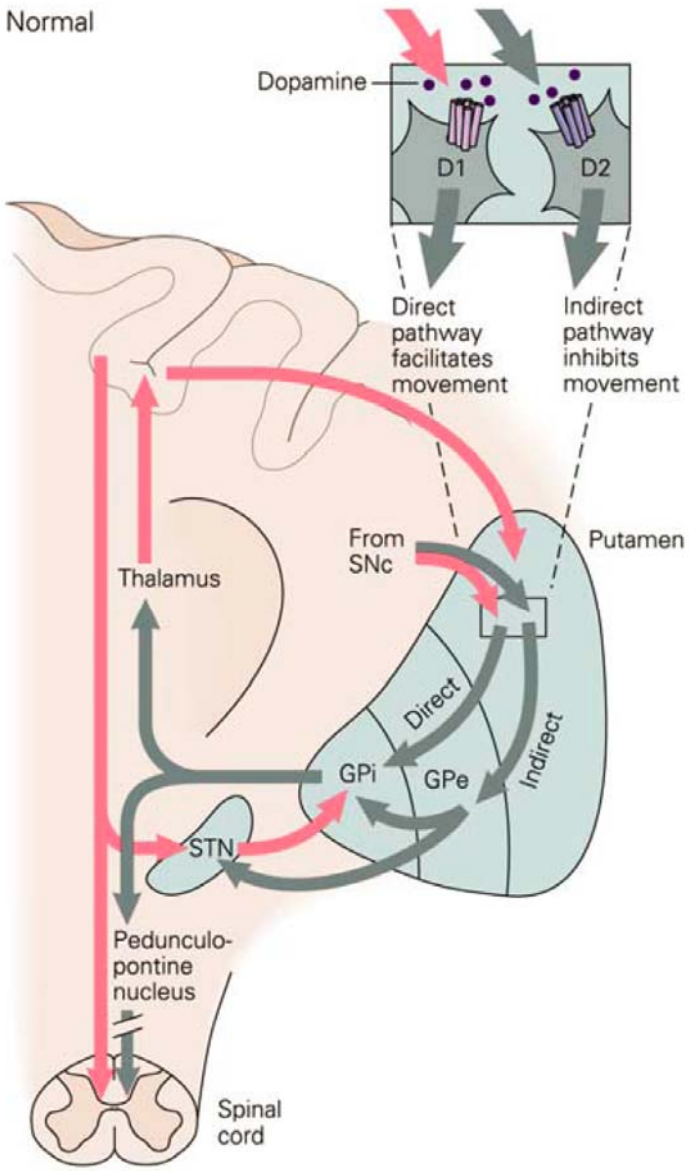
Negative feedback - **inhibits movement**

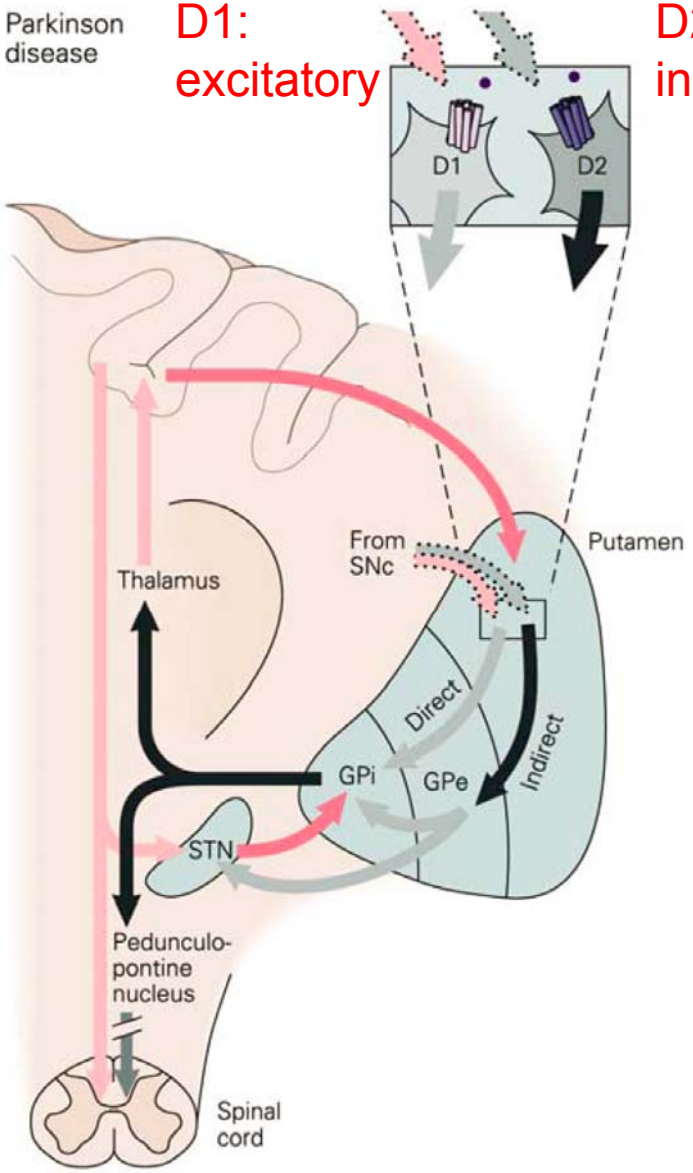
Dopamine modulation mediated by D2 receptors (suppressive)

NOTE: dopamine in both pathways facilitates movements

The effect of basal ganglia on the cortex results from a balance between the two pathways.

Degeneration of nigrostriatal dopamine pathway





Parkinson Disease

- Most common movement disorder (1 million in the U.S.)
- Key symptoms:
  - Tremor – 4-5 /s at rest
  - Rigidity – increase muscle tone
  - Bradykinesia - slowness in executing movement
    (difficulty in selecting or activating motor programs)
  - Akinesia – loss of movement
  - Postural instability (impaired reflex and balance)
  - Cognitive dysfunction and speech defects

- Cause: Decrease stimulation of motor cortex by basal ganglia, due to deficiency of dopamine (in striatum, putamen in particular)

<u>The MPTP Model of PD</u>

Drug addicts exposed to MPTP develop PD symptoms
MPTP-treated monkey – a PD model of drug development

Pathogenesis of PD:

Degeneration of dopaminergic neurons in the substantia nigra (pars compacta)
→ loss of dopaminergic inputs to striatum (putamen in particular)
→ increased activity in the indirect pathway and reduced activity in the direct pathway
→ increased activity in the internal pallidal segment
→ increased inhibition of thalamocortical and midbrain tegmental neurons
→ (hypokinetic) movement deficits

Treatment:

Durgs: oral administration of L-DOPA (precursor of dopamine), dopamine agonists (activating dopamine receptors), MAO-B (monoamine oxidase-B) inhibitor (preventing dopamine breakdown)

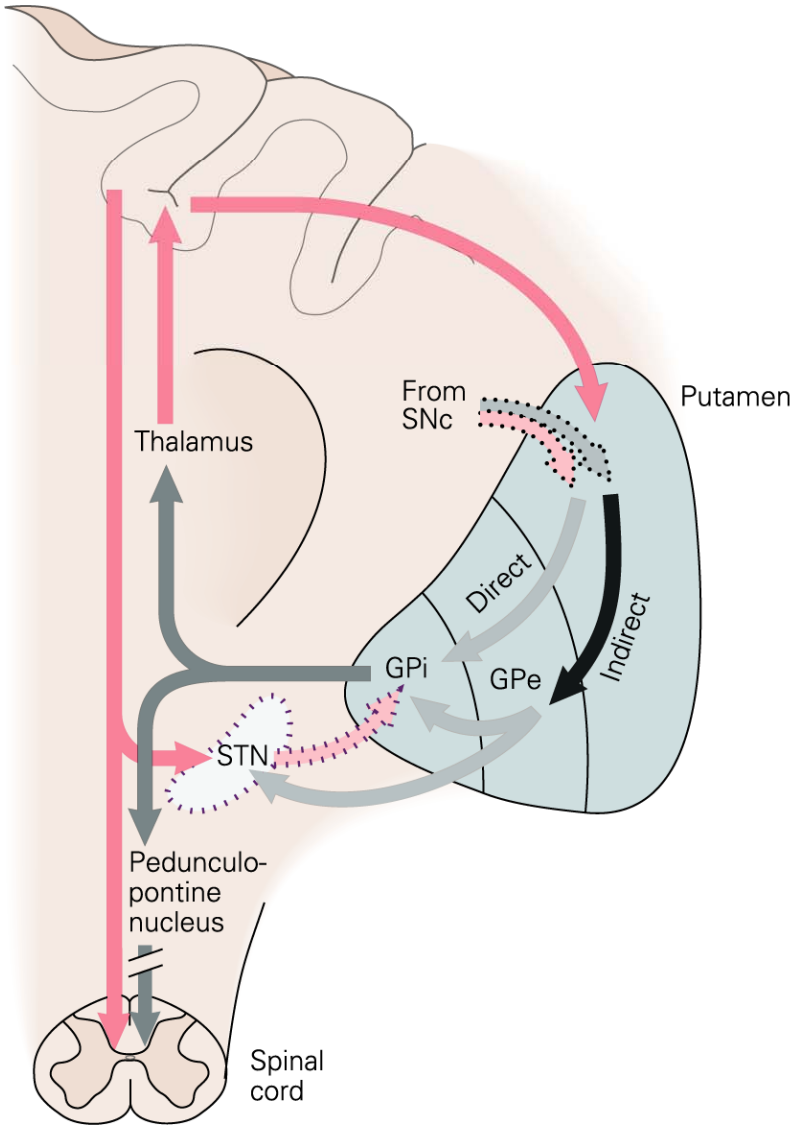
Deep brain stimulation: currently the most used surgical treatment

Pallidotomy: removal of internal pallidal segment (PGi) or STN (for advanced cases)

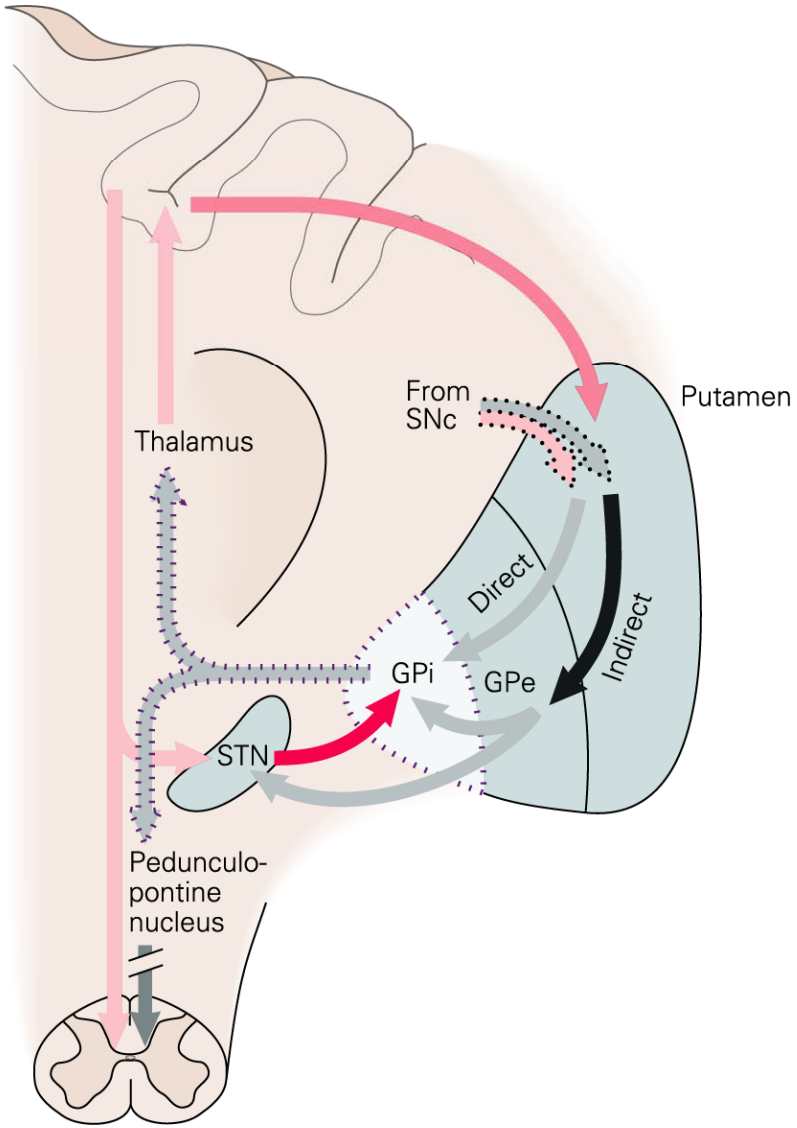
(Recording from MPTP-treated monkey: decreased tonic activity in PGe but increased in subthalamic nuclei and PGi, reversed by dopamine receptor agonist (apomorphine). PD symptoms eliminated by STN lesion or inactivating PGi)

Parkinson disease + surgical therapies

STN lesion



GPi lesion



Causes of PD

Genetic

Specific genetic mutations have been associated with PD in a very low percentage of cases of Parkinson's disease.

Common gene defect may contribute to the susceptibility to both PD and AD.

Toxins

A combination of genetically determined vulnerability to environmental toxins (pesticides, heavy metals, especially those that generate reactive oxygen species (ROS).

Drug addicts in California who consumed a contaminated batch of synthetic opiate developed PD symptom – toxin identified to be **MPTP** (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). MPTP acts by generating ROS

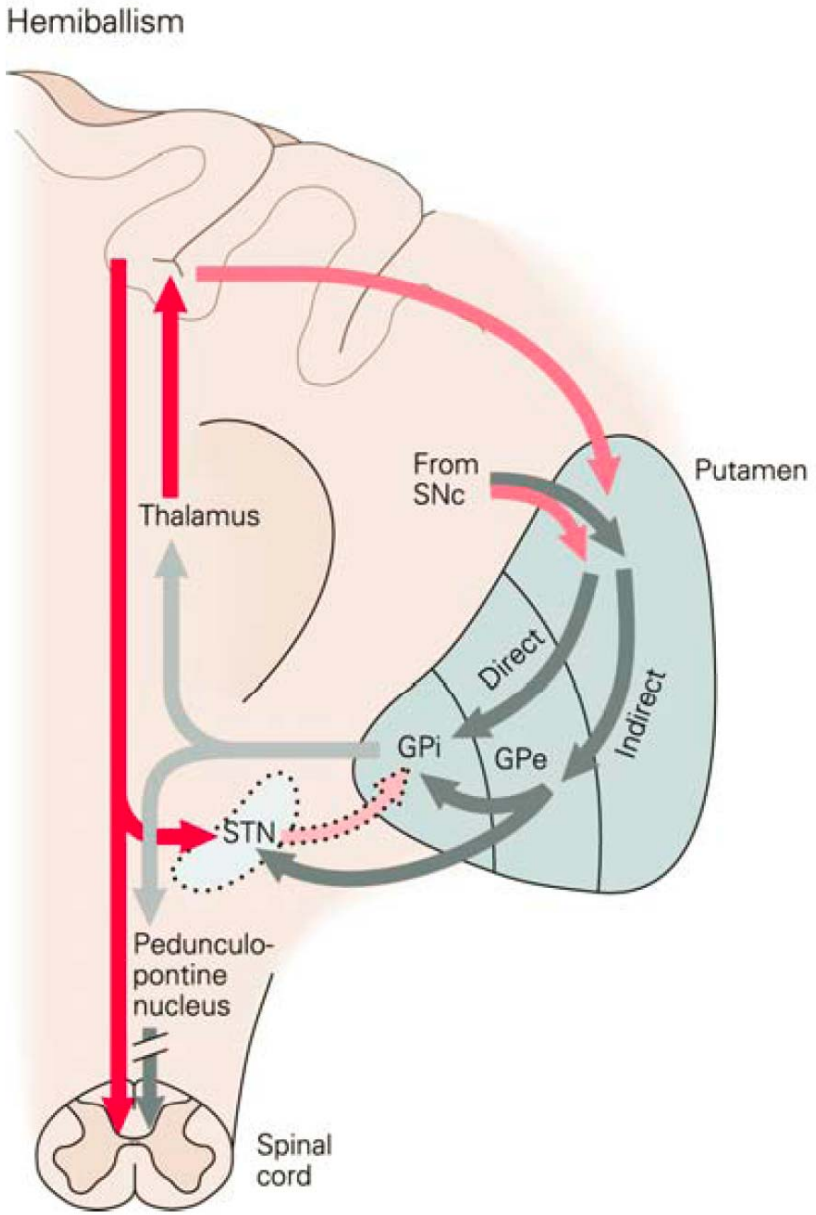
Head trauma

Past episodes of head trauma are reported more frequently by individuals with PD

Hyperkinetic Disorder I

- Hemiballism – involuntary movements of limbs (“ball-throwing”-like) due to lesion (stroke) of subthalamic nucleus.

  Reduced tonic output of internal pallidal segment causes disinhibition of the thalamocortical circuits and spontaneous discharges that trigger the abnormal movement.



Hyperkinetic disorders II – Huntington Disease

- Frequency – 5-10 per 100,000
- Key symptoms:

  Chorea - abnormal involuntary writhing movements

  Behavioral or psychiatic disturbances

  Cognitive impairment (dementia)

  Death 15-20 years after onset

Cause: Single gene defect

Huntington Disease (HD)

An autosomal dominant disorder (A single, abnormal gene on non-sex chromosome 4 from either parent can cause the disorder).

Gene: huntingtin (function unknown)

Normal: 40 CAG (glutamine) repeats in the first exon

Disease: 70-100 CAG repeats, cause neuronal degeneration

Pathology:

Preferential lost of striatal neurons of the indirect pathway

→ reduced inhibition of GPe

→ Increased inhibition and functional inactivation of STN

→ Reduced excitation of GPi

→ Reduced inhibition of thalamocortical pathway

→ spontaneous motor activity