Modulation of movement by the basal ganglia

- Basal ganglia are a large set of nuclei that lie deep within the cerebral hemispheres
  - Consists of striatum (**caudate, putamen**) and the **globus pallidus**
- Together with the **substantia nigra** and the **subthalamic nucleus** comprises the **basal ganglia system** which links most areas of the cortex with upper motor neurons of the frontal cortex
- Basal ganglia influence movements by regulating the activity of upper motor neurons
  - Modulate the **initiation** and **termination** of movement
- Proper basal ganglia function required for normal voluntary movements
- Disorders of basal ganglia or associated structures result in upper motor neurons not switching smoothly between movement initation and termination commands

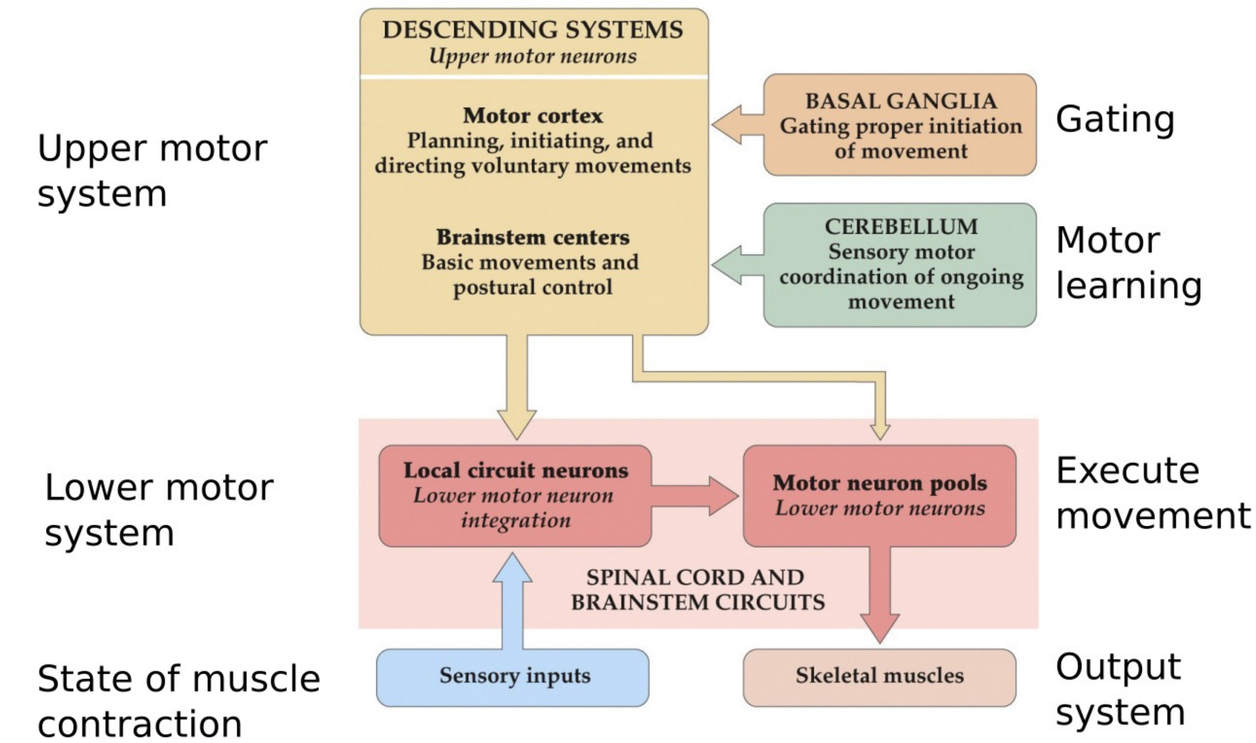
2021-11-30T10:07:14-08:00

Speaker notes

- Modulate the initiation, termination, amplitude, and selection of movement
- But basal ganglia also has varied non-motor roles:
  - also with "non-motor" circuits (limbic system class):
  - involved in learning, reward mechanisms
    - Response-outcome associations
    - Stimulus-response associations
  - and also non-motor prefrontal cortex loops to help in selection of conscious goals, decisions

modulate (wordnet, verb)
: vary the frequency, amplitude, phase, or other characteristic of (electromagnetic waves)
: adjust the pitch, tone, or volume of
: regulate

Overall organization of neural structures that control movement



Neuroscience 5e Fig. 16.1

Speaker notes

Today we will begin our examination of the pathways in the nervous system that modulate and give rise to volitional control of our skeletal muscles.

Basal ganglia and the control of movement– objectives

- Anatomical connectivity
- Function– modulation through disinhibition
- Neurotransmitters– dopamine, GABA, glutamate
- Diseases of the basal ganglia

Speaker notes

We will discuss…

- basal ganglia components
- inhibiting inhibition, "disinhibition" loops
- relevant neurotransmitter receptor signaling systems

Corpus striatum

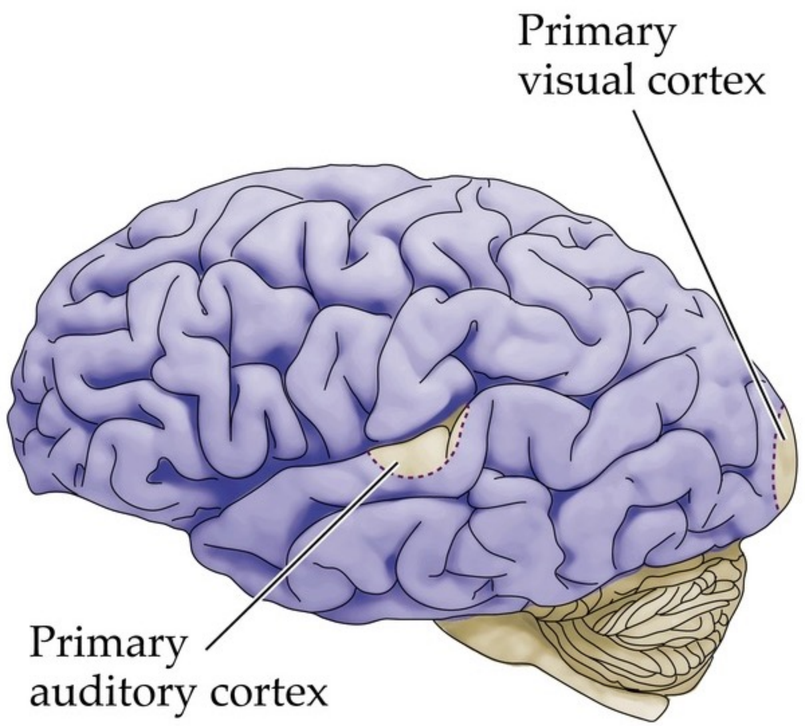
- Corpus striatum ('striped body') contains two portions– the caudate and putamen
- Function as the input zones for the basal ganglia
- Most regions of the cortex project to the striatum. Prominent innervation from the associational cortical areas of the frontal and parietal lobes. Collectively called the corticostriatal pathway
- Neurons in striatum that receive corticostriatal input are called **medium spiny neurons**. Large dendritic trees, integrate information from a variety of structures

Speaker notes

Caudate and putamen separated by white matter (internal capsule) in mid to caudal coronal view sections of the brain

Most cortical areas project to striatum

Most cortical areas project to the striatum, except for primary auditory cortex (A1) and primary visual cortex (V1).

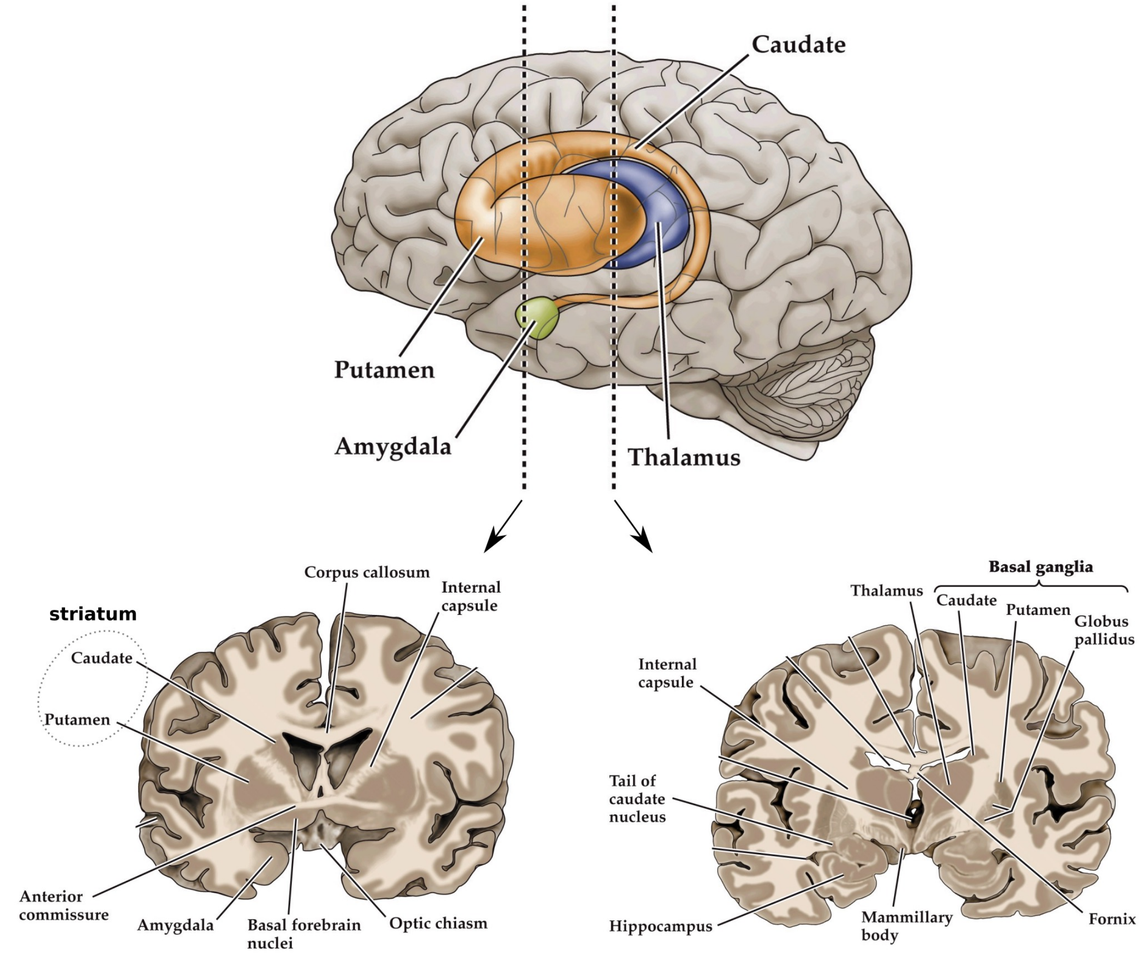


Neuroscience 2e 2001

Speaker notes

Axonal input to the striatum originates from all over the cortex, but with little input from the primary sensory areas of visual and auditory cortex

Anatomical location of the basal ganglia



Neuroscience 5e Fig. A14

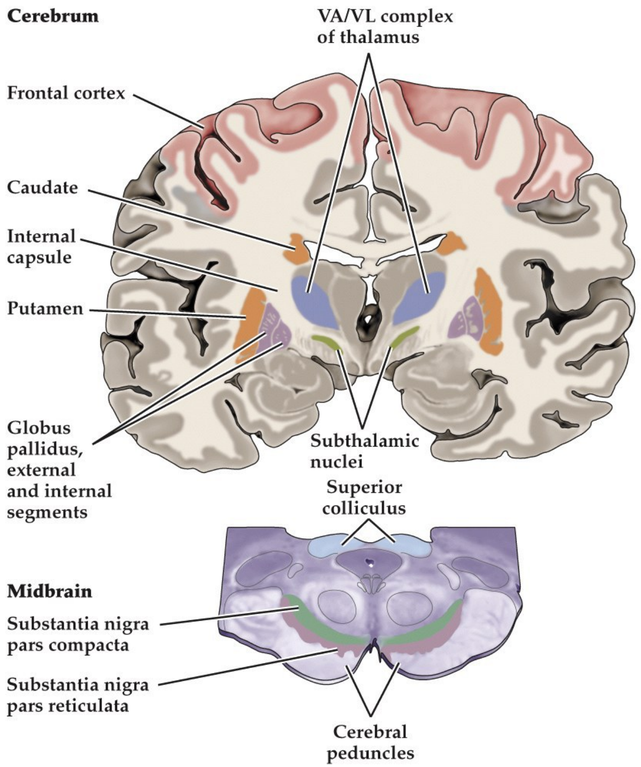
Speaker notes

mammillary body
: part of diencephalon, at junction with hypothalamus
: part of limbic system
: location at anterior end of the fornix
: relay from amygdala and hippocamus to thalamus by mamillo-thalamic tract
: role in recall of episodic memories

basal forebrain nuclei
: major source of acetylcholine input to cerebral cortex
: roles in attention, wakefulness, REM sleep

fornix
: latin for "arch"
: output of hippocampus
: hippocampal commissure in mid region
: mammillary body at one end of this tract

Anatomy of the basal ganglia: caudate and putamen



Neuroscience 5e Fig. 18.1

Speaker notes

Main input structures of basal ganglia system: Striatum– caudate and putamen

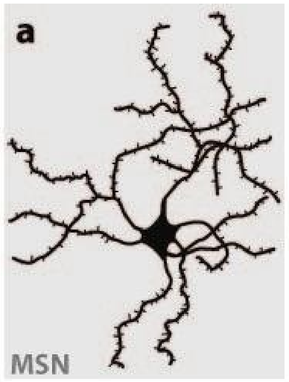
Main output structures of basal ganglia system: Globus pallidus interna (projects to thalamus) and substantia nigra pars reticulata (projects to superior colliculus; eye movements)

Intermediate nuclei in the basal ganglia system: Globus pallidus externa, STN, and substantia nigra pars compacta

TODO: human brain section

Striatum: medium spiny neurons

- Medium spiny neurons (MSNs) located in caudate and putamen
- ~90% of neurons in striatum. Project to globus pallidus
- GABAergic, inhibitory
- Very little spontaneous activity. Dependent on excitatory input for discharge
- Large dendritic trees



Speaker notes

Kreitzer Ann Rev Neurosci 2009

Medium spiny neuron in the corpus striatum

TODO: new image

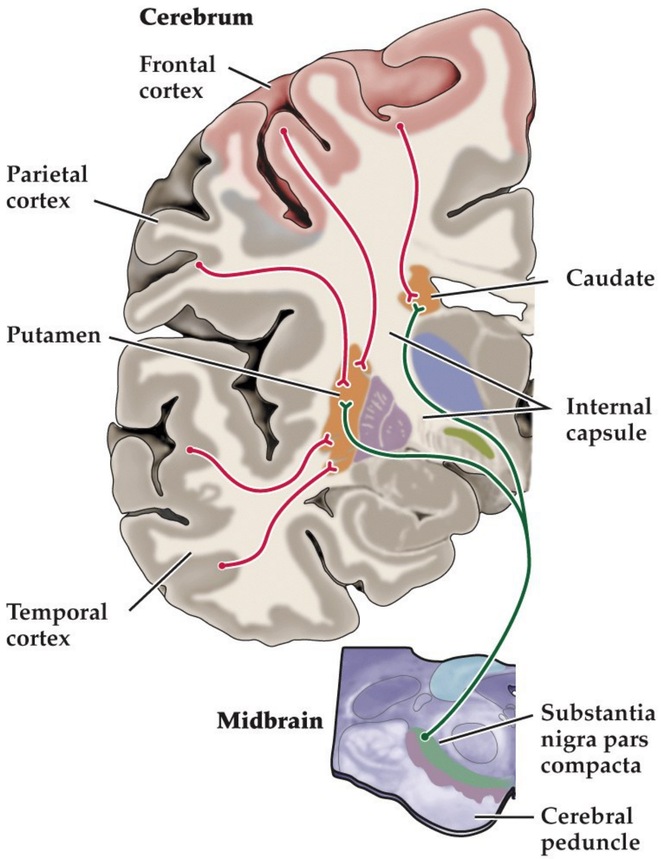
Cortical inputs to the caudate and putamen

- Caudate receives cortical projections primarily from multimodal association cortices and motor areas from frontal lobe that control eye movements
- Putamen receives input from the primary and secondary somatic sensory cortex and extrastriate visual cortex in occipital and temporal lobes, premotor and motor cortex, and auditory association areas in temporal lobe
- These inputs are excitatory, glutamatergic synapses
- Each medium spiny neuron can receive input from lots of different cortical neurons

Speaker notes

Each cortical neuron synapses onto more than one MSN

Organization of inputs to basal ganglia



Neuroscience 5e Fig. 18.2

Speaker notes

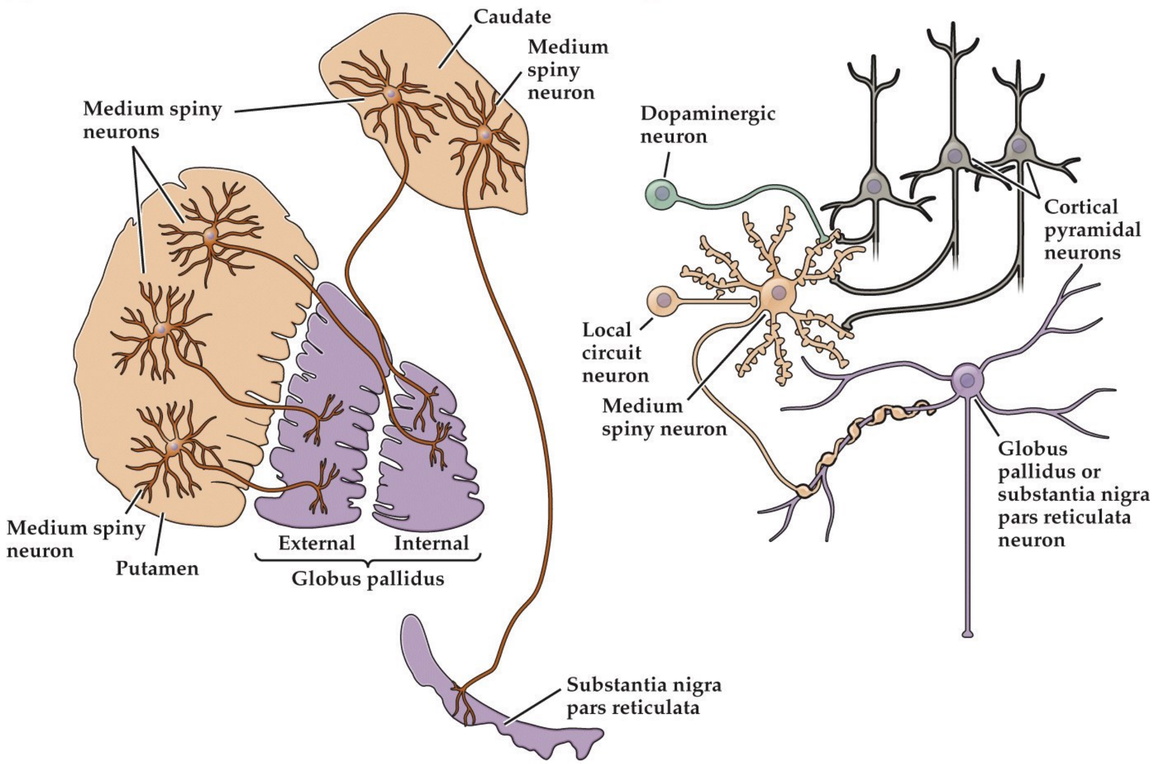
Projections from MSNs

- MSNs of caudate and putamen give rise to inhibitory GABAergic projections that terminate in a pair of nuclei within the basal ganglia called the globus pallidus (GP) and a region of the substantia nigra called the pars reticulata (SNr)
- Approximately 100 MSNs converge onto each neuron in the globus pallidus
- Globus pallidus contains two nuclei– GP externa (GPe) and GP interna (GPi)
- The GPi and the SNr contain the main output neurons of the basal ganglia
- Globus pallidus interna (GPi) neurons then convey information back to the cortex via the thalamus (ventral lateral and ventral anterior nuclei, VA/VL) to make a loop

Speaker notes

No notes on this slide.

MSNs send projections to the globus pallidus and pars reticulata



Neuroscience 5e Fig. 18.3

Speaker notes

No notes on this slide.

The direct pathway

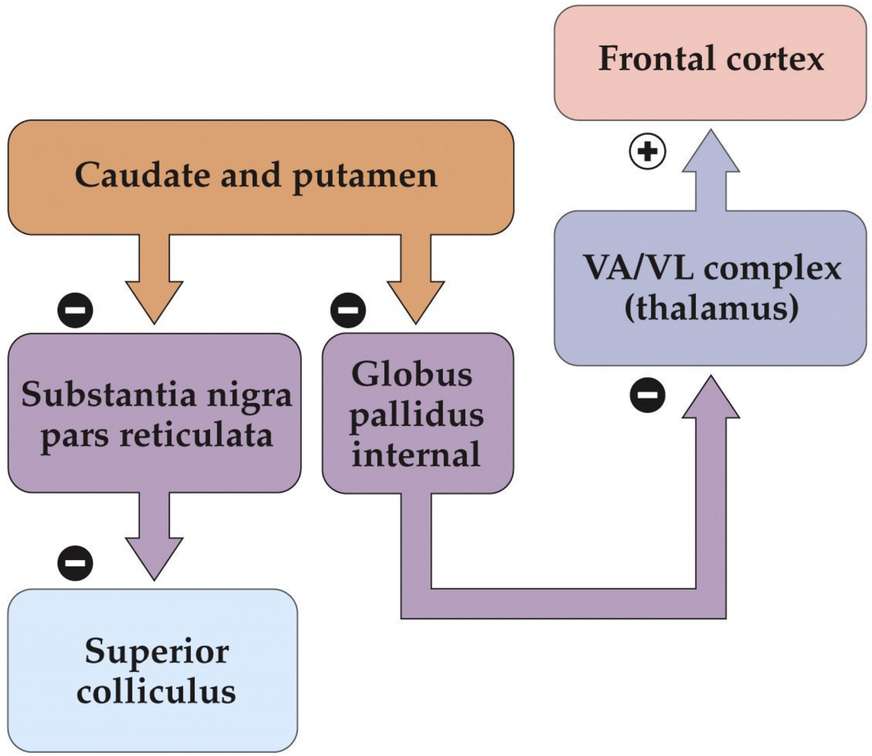
- **Globus pallidus and pars reticulata neurons are GABAergic**. Unlike MSNs they have high levels of spontaneous activity– they are tonically active
- Thus the output from the basal ganglia is normally inhibitory-- tonic inhibition
- When MSNs fire (in anticipation of movement) this inhibits the inhibition (**disinhibition**) and allows upper motor neurons (in cortex and superior colliculus) to send commands to local circuit and lower motor neurons that initiate movement
- Called the direct pathway

Speaker notes

- Substantia nigra pars reticulata (SNr) neurons project to upper motor neurons in the superior colliculus that command eye movements without going to the thalamus

Direct pathway of outputs from the basal ganglia

sign shows normal effect (excite or inhibit) at that synapse



Neuroscience 5e Fig. 18.4

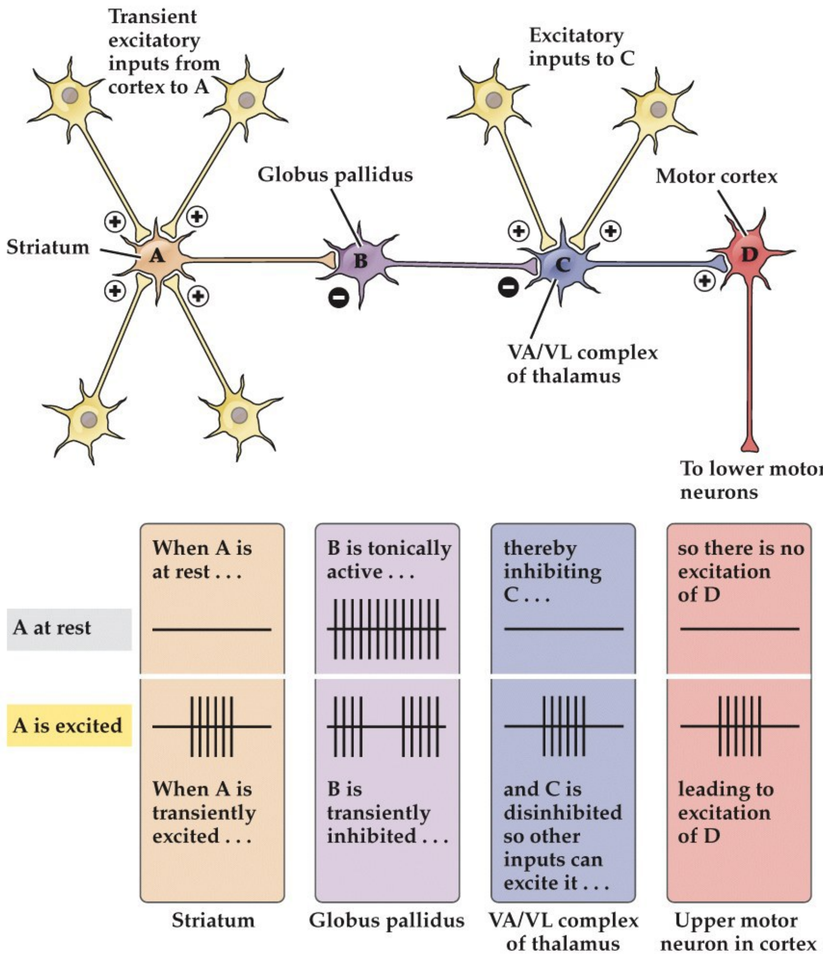
The GABAergic projection caudate/putamen medium spiny neurons are usually pretty quiet: they have a **low baseline spike rate.**

The GABAergic projection pallidus/reticulata neurons have a **high baseline spike rate.**

Speaker notes

No notes on this slide.

Example of a disinhibitory circuit



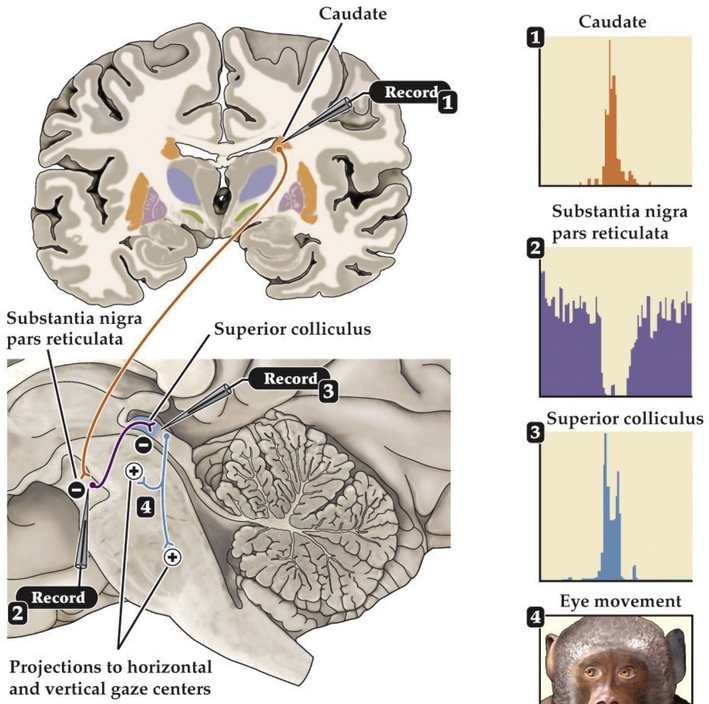
Neuroscience 5e Fig. 18.5

Speaker notes

No notes on this slide.

Basal ganglia disinhibition and the initiation of movement

Histograms of spike frequency in caudate, SNr, SC during eye movements



Neuroscience 5e Fig. 18.6

Speaker notes

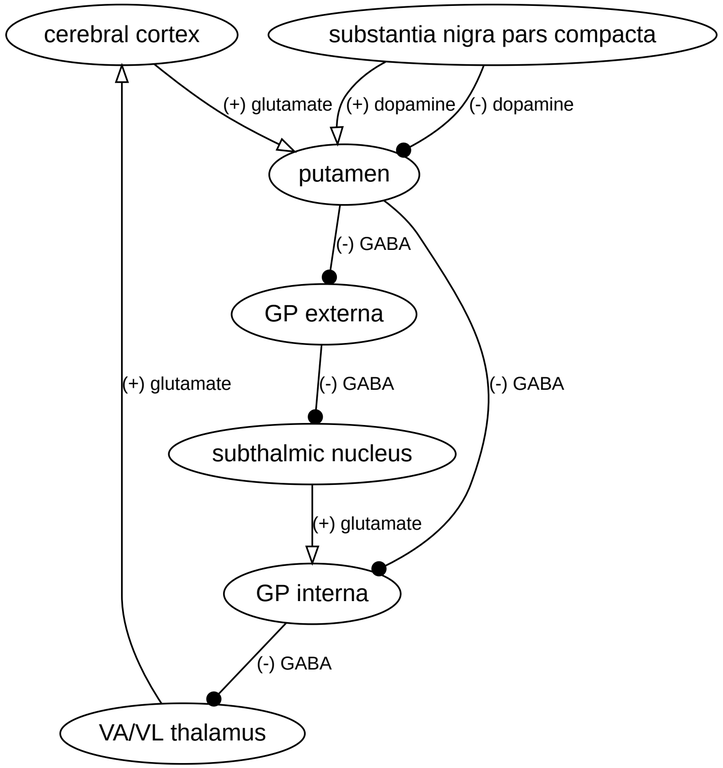
Recall that the superior colliculus contains upper motor neurons concerned with eye movements

Record spikes with microelectrodes inserted into caudate and SNr and superior colliculus.

Count spikes surrounding eye movement period, y axis is count (histogram), x axis is time (100s of msec to sec)

Disinhibition through the direct pathway increases activity in upper motor neurons

Direct pathway: ctx --> putamen --> GPi --> VA/VL --> ctx



Speaker notes

Overall effect of direct pathway on neocortex is excitatory by disinhibiting the upper motor neurons in the cortex (promotes movement, initiation of motor commands)

Indirect pathway circuits

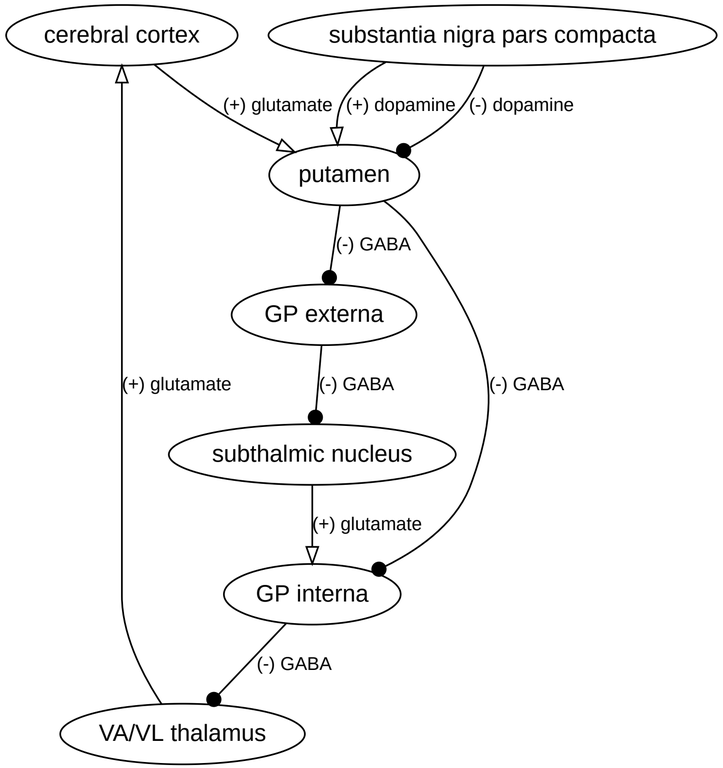
- Provides a second route of influence via a loop back to the direct pathway
- MSN neurons also project to the globus pallidus external (GPe) nuclei which then project to the subthalamic nucleus (STN) of the ventral thalamus
- STN neurons project back to GPi which then projects out of basal ganglia to the VA/VL complex of the thalamus
- **Subthalamic projections are excitatory which increases the inhibition of GPi**. Opposite/antagonistic of the direct pathway. Acts as a brake to prevent too much disinhibition of upper motor neurons
- Decreases upper motor neuron activity

Speaker notes

No notes on this slide.

Indirect pathway

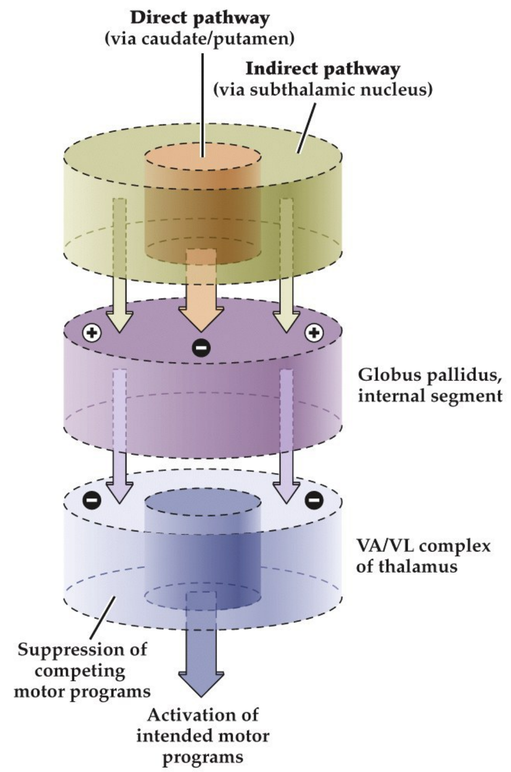
Indirect pathway: ctx --> putamen --> GPe --> STN --> GPi --> VA/VL --> ctx



Speaker notes

Overall effect on upper motor neuron activity in neocortex is inhibitory. Serves to modulate the disinihibitory actions of the direct pathway

'Center–surround' functional organization of the direct and indirect pathways



Neuroscience 5e Fig. 18.8

Speaker notes

Importantly, there is more spatially discrete connectivity in the converging input from MSNs onto selective patches of microcircuits in the GPi for the direct pathway. For the indirect pathway, the input is much broader from MSNs onto patches of microcircuits in the GPi-->STN-->GPe. Results in greater upper motor neuron excitation in center of microcircuit (channel of information) due to the direct pathway overriding a diffuse broader inhibition for competing surround circuits (different motor programs for example) from the indirect pathway.

think about center-surround receptive fields for luminance contrast in retinal ganglion cells mediated by synaptic interactions between photoreceptors, bipolar cells, and horizontal cells in the outer plexiform layer.

-difference of Gaussians is a feature enhancement algorithm

-'mexican hat' distribution (shaped like a sombrero) (normal distribution with a postive central tendancy and negative side saddles)

-multidimensional generalization of this wavelet is called the Laplacian of Gaussian function

-frequently used as a blob detector

-automatic scale selection in computer vision applications; see Laplacian of Gaussian
https://en.wikipedia.org/wiki/Mexican_hat_wavelet

Attentional field has a 'Mexican hat' distribution:

http://www.sciencedirect.com/science/article/pii/S0042698904005735

Dopaminergic neurons modulate direct and indirect pathways

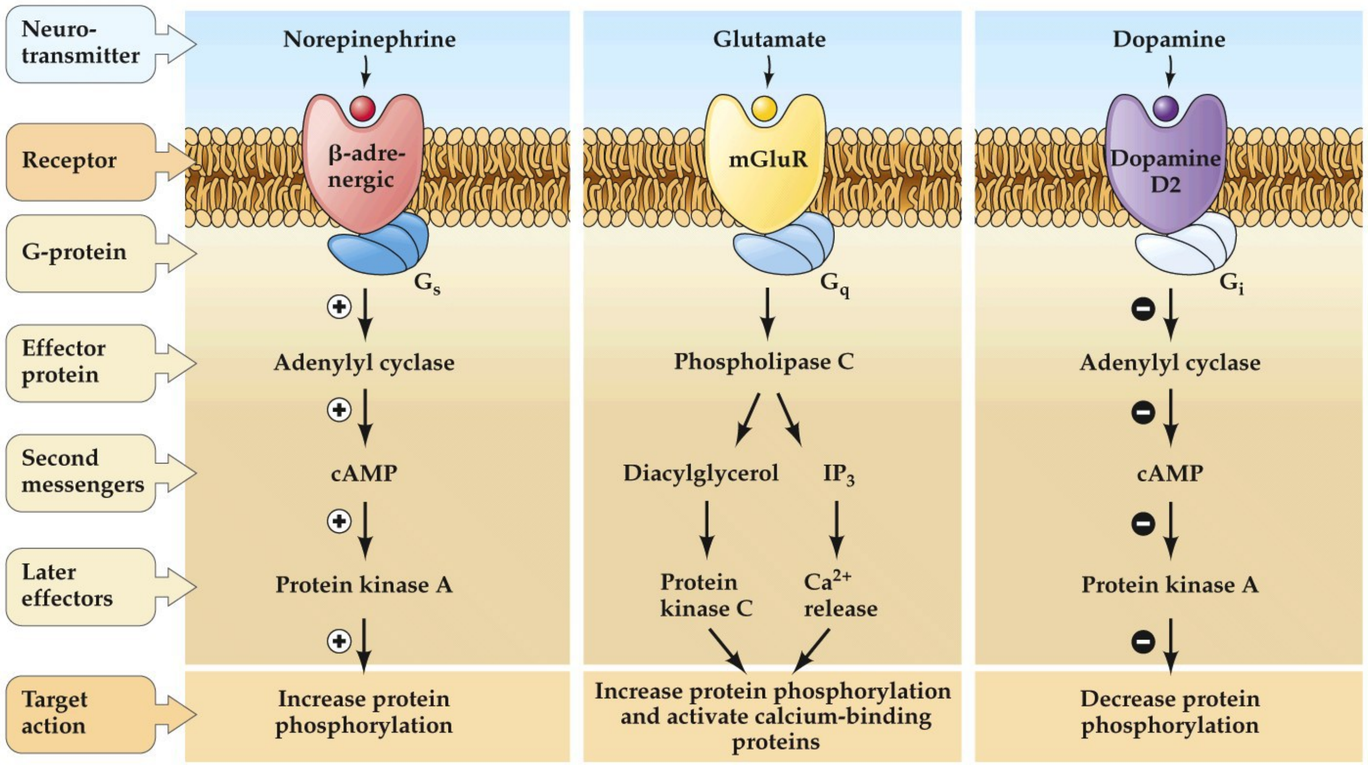
- Medium spiny neurons (MSNs) in striatum project to the substantia nigra pars compacta (SNc), which in turn projects back to MSNs
- Both MSNs that project to GPe and GPi receive these inputs
- Those that project to GPi have type D1 receptors (coupled to a Gαs, excitatory) and those that project to GPe use type D2 receptors (Gαi, inhibitory)
- Dopamine excites the direct and inhibits the indirect pathway

Speaker notes

No notes on this slide.

Effector pathways associated with G-protein-coupled receptors

Specificity at the level of the G protein α subunit. D1 uses Gs, D2 uses Gi G-proteins



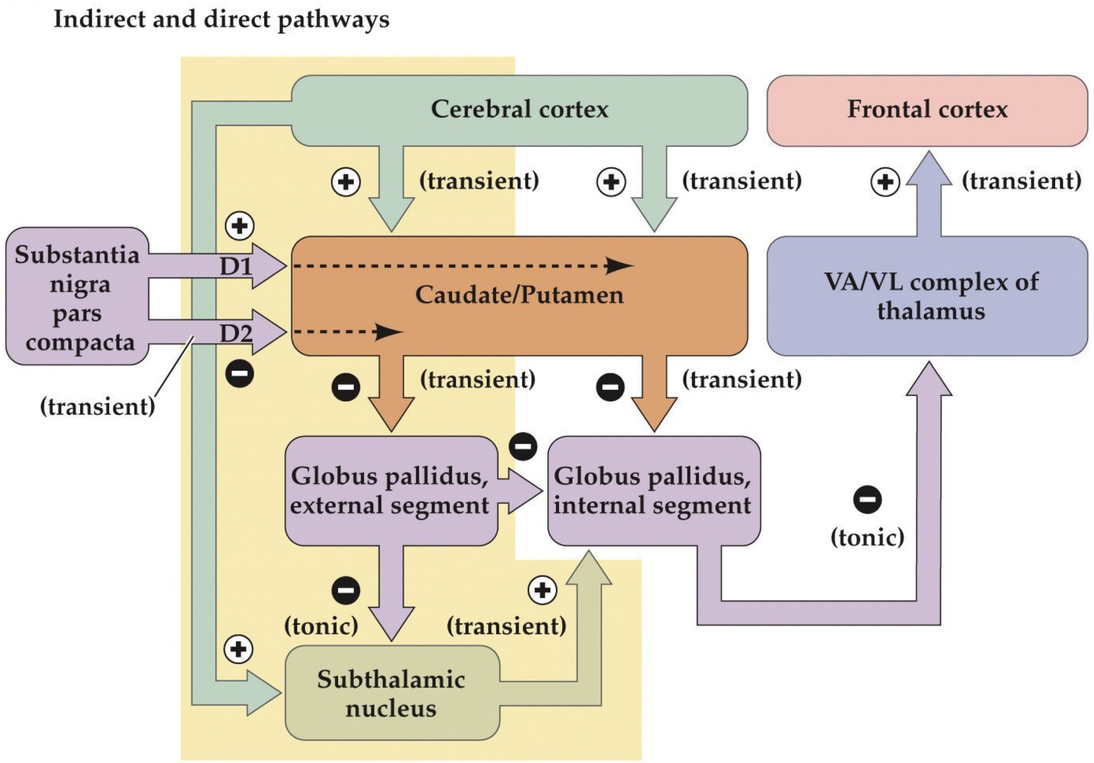
Neuroscience 5e Fig. 7.6

Speaker notes

No notes on this slide.

Direct and indirect pathways through the basal ganglia

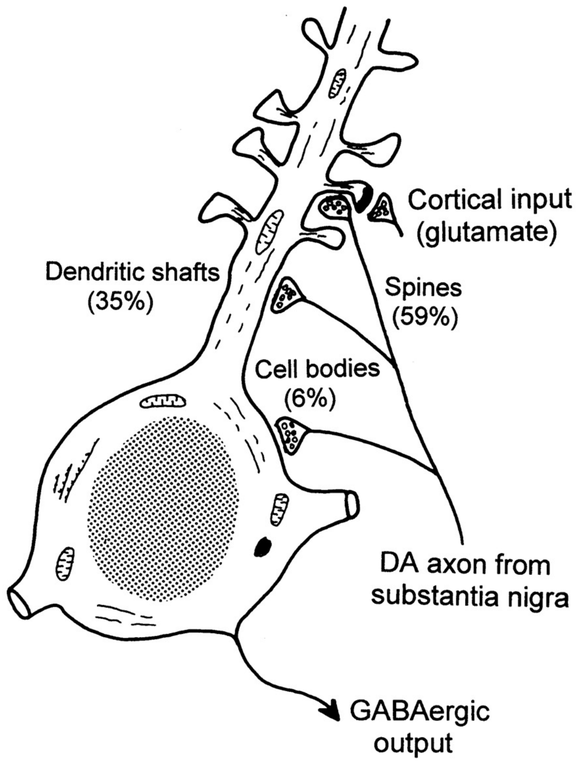
Dopamine excites the direct and inhibits the indirect pathway.



Neuroscience 5e Fig. 18.7

Speaker notes

Synaptic input to striatal medium spiny neurons



Smith and Bolam, 1990

Speaker notes

No notes on this slide.

Motor behavior is determined by the balance between direct/indirect striatal outputs

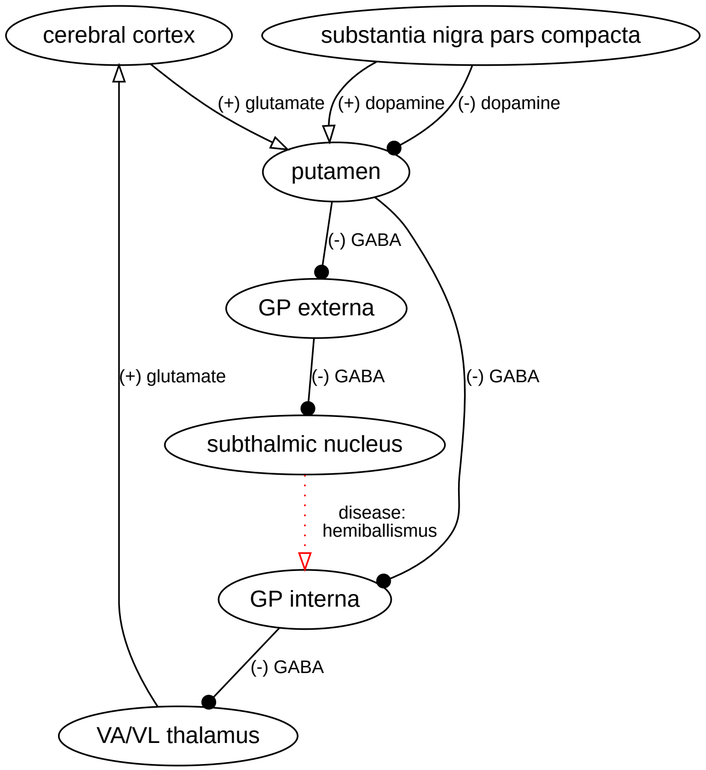
- Hypokinetic disorders (decreased movement)
  - Insufficient direct pathway output
  - Excess indirect pathway output
- Hyperkinetic disorders (excess movement)
  - Excess direct pathway output
  - Insufficient indirect pathway output

Speaker notes

No notes on this slide.

Hemiballismus: violent involuntary movements of the limbs

Defects in the subthalamic nucleus contralateral to the involuntary movements. Reduced indirect pathway function.



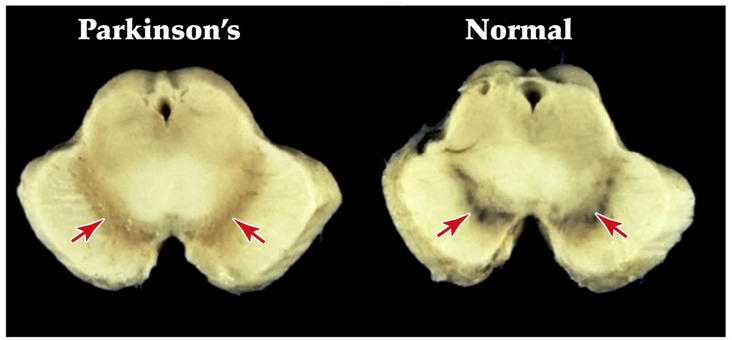
Speaker notes

damage to STN results in violent involuntary movements of the limbs.

rarer than Parkinson's (500x less common).

Parkinson’s disease

- Due to the degeneration of dopaminergic neurons of the substantia nigra pars compacta
- Leads to tremors, slowness of movements, rigidity of extremities and neck, minimal facial expressions
- Slowly progressing disease
- Some success in slowing the progression comes from the use of Levadopa (L-DOPA)– gets converted to dopamine and gets to dopamine receptors in basal ganglia



Neuroscience 5e Fig. 18.9

Speaker notes

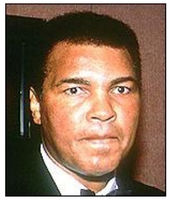
from https://en.wikipedia.org/wiki/Substantia_nigra

> *Substantia nigra is Latin for "black substance", reflecting the fact that parts of the substantia nigra appear darker than neighboring areas due to high levels of neuromelanin in dopaminergic neurons.*

Parkinson’s disease

Pathophysiology is the loss of nigrostriatal dopaminergic projections from SNc


Michael J. Fox

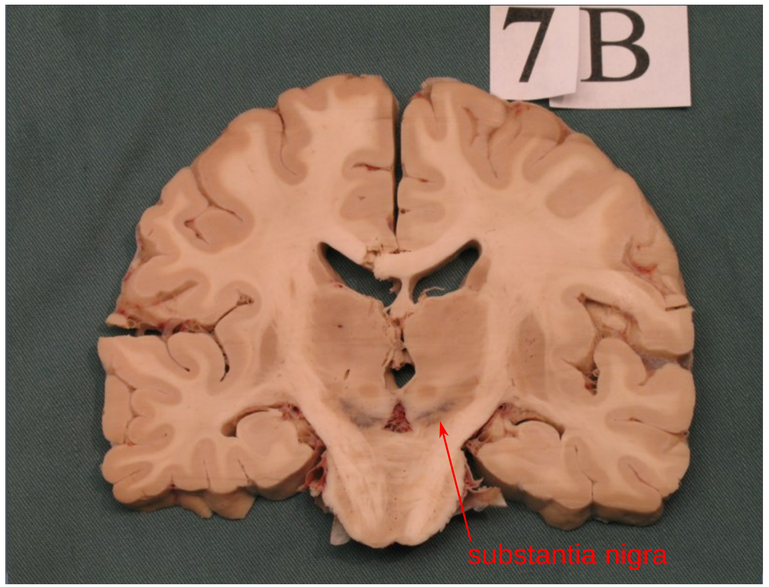

Muhammad Ali


Katherine Hepburn

Speaker notes

hypokinetic, failure of disinhibition. dimin facial expressions, slow shuffling movements, no arm swinging during walking

Parkinson’s- loss of dopamine making neurons in the midbrain's substantia nigra



B. Crawford and K. McBurney, Univ. of Victoria

Speaker notes

substantia nigra pars compacta, a nucleus containing neurons making the neurotransmitter dopamine that are important for regulating motor movements via their connections with the basal ganglia and which are devastated in parkinson’s disease.

dark appearance due to high levels of dark pigment neuromelanin in dopaminergic neurons
Neuromelanin is directly biosynthesized from L-DOPA, precursor to dopamine, by tyrosine hydroxylase (TH)

What causes dopaminergic neurons to die?

- Most cases are late-adult onset without a clear inheritance pattern
- Small fraction are familial
- α−synuclein a synaptic protein that when mutated can lead to aggregation and cause the formation of Lewy bodies. Autosomal dominant mutations
- Aggregates may spread from neuron to neuron
- Two other autosomal recessive mutations Pink1 and Parkin block mitochondria function in dopaminergic neurons-conserved from fly to humans

Speaker notes

from https://en.wikipedia.org/wiki/Parkinson%27s_disease

-mostly idiopathic, having no known cause

> *These genes code for alpha-synuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2.[7][37] In most cases, people with these mutations will develop PD.*

Models: mptp, insecticide rotenone, herbicide paraquat and the fungicide maneb.

> *proportion in a population at a given time is about 0.3% in industrialized countries. PD is more common in the elderly and rates rises from 1% in those over 60 years of age to 4% of the population over 80*

alzheimers:

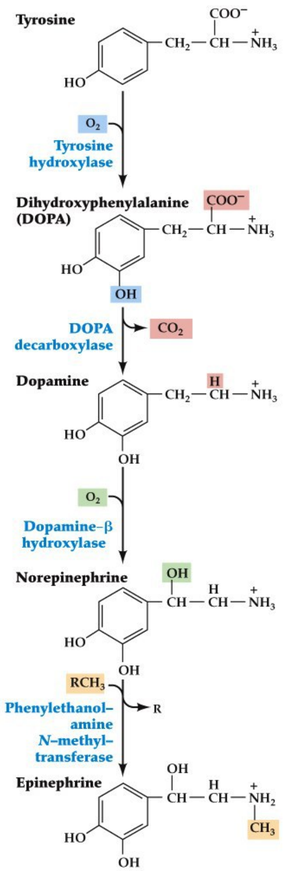
http://www.alz.org/facts/

2/3 women

6.4% dementia over 60 & 4.4% with AD over 60

Treatments for Parkinson’s

- Dopamine can’t cross the blood brain barrier but L-DOPA can
- Deep brain stimulation
- Cell replacement therapy– implant dopamine making neurons into the striatum



Neuroscience 5e Fig. 6.10

Speaker notes

deep brain stimulation– bypass the circuit by inhibiting the STN output

http://www.youtube.com/watch?v=mO3C6iTpSGo

http://www.laskerfoundation.org/awards/2014_c_description.htm

https://www.youtube.com/watch?v=JAz-prw_W2A

from: http://www.ncbi.nlm.nih.gov/books/NBK28180/

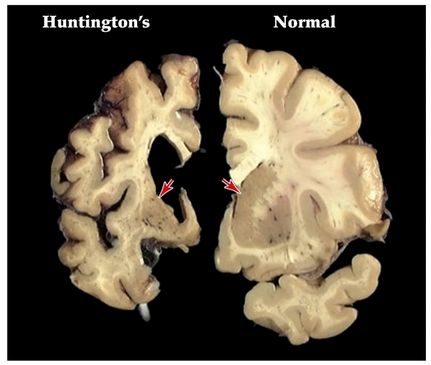
> *Neutral l-amino acids have various rates of movement into the brain [13,14]. Phenylalanine, leucine, tyrosine, isoleucine, valine, tryptophan, methionine, histidine and l-dihydroxy- phenylalanine (l-DOPA) may enter as rapidly as glucose. These essential amino acids cannot be synthesized by the brain and, therefore, must be supplied from protein breakdown and diet (see Chap. 33)*

L-DOPA is transported across the blood brain barrier by LAT-1 (L or Large amino acid transporter). Dopamine is too polar to be lipid soluble and has no specific transporter

non-polar: symmetric distribution of charge.

Huntington’s disease

- One of the most common inherited neurological diseases
- Progressive deterioration of the caudate and putamen that project to the GP externa (indirect pathway)
- Leads to a movement disorder consisting of rapid jerky motions with no clear purpose



Neuroscience 5e Fig. 18.9

Speaker notes

- George Huntington, physician long island 1872
- 1 in 10000 people will have Huntington's disease in the US
- death in 10-20 yrs
- autosomal dominant inheritance, chromosome 4. Gene called Huntingtin
- if disease begins in childhood rigidity, seizures, dementia, and rapid progressive course can ensue
- atrophy of striatum is pronounced. Some associated degeneration of frontal and temporal cortices

Function of huntingtin gene product unclear. Null expression in mice lethal

evidence that huntingtin interacts with 19 different proteins

Huntington’s disease

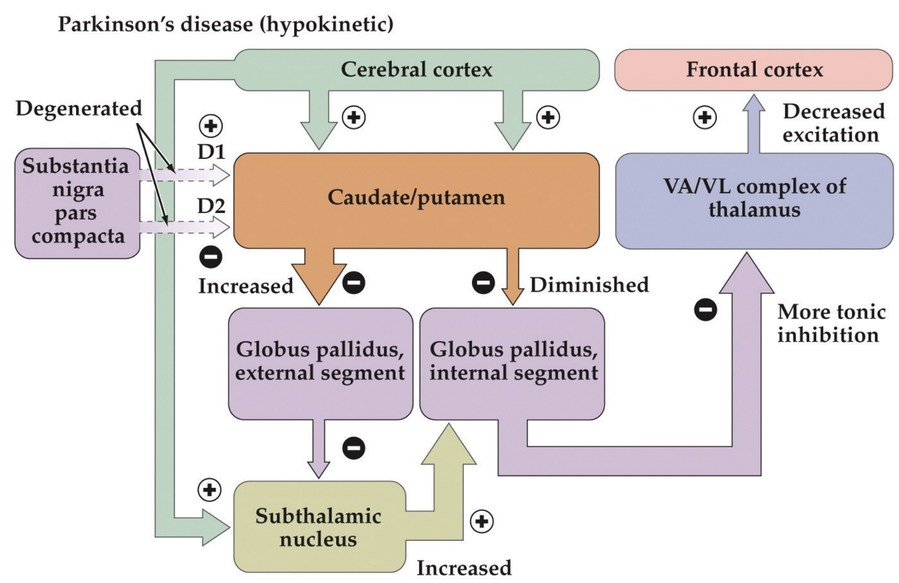
- Dominantly inherited– strikes around midlife
- Patients develop depression, mood swings, and abnormal movements (striatum)
- Caused by alterations in a single gene that encodes the huntingtin protein
- Huntingtin protein has an expansion of a CAG trinucleotide repeat, resulting in an extended polyglutamine repeat. Leads to aggregation of proteins and cell death

Speaker notes

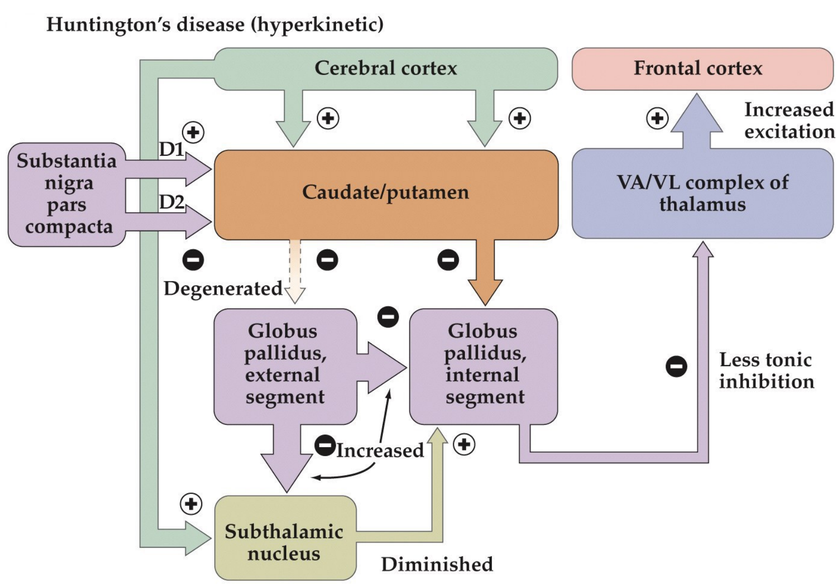
15-34 cytosine-adenine-guanine (CAG) DNA repeats normally, 42-66 in Huntingtin's disease resulting in an unstable triplet repeat in coding region of gene. Polyglutamine

Hypokinetic and hyperkinetic disorders summary

- Parkinson's– hypokinetic disorder. More tonic inhibition of thalamus and decreased excitation of frontal cortex
- Huntington's– hyperkinetic disorder. Less tonic inhibition of thalamus and more excitation of frontal cortex



Neuroscience 5e Fig. 18.10



Neuroscience 5e Fig. 18.10

Speaker notes

Parkinson's– hypokinetic disorder. More tonic inhibition of thalamus and decreased excitation of frontal cortex.

Huntington's– hyperkinetic disorder. Less tonic inhibition of thalamus and more excitation of frontal cortex.

See also fig 18.9, 18.10 Neuroscience 6e.

Movement disorders

Movement disorders

Speaker notes

schizophrenia:
https://www.youtube.com/watch?v=OjM9GI_MLyQ

Non-motor loops of the basal ganglia

- Basal ganglia are also involved in loops that modulate non-motor behaviors
- Work in a similar way to suppress outputs
- The limbic loop regulates emotional behavior and motivation
- Tourette’s may be a problem with limbic loop (no longer have inhibitions with language selection?)
- Drugs of abuse affect dopamine release
- Schizophrenia, may be due to aberrant activity in limbic and prefrontal loops resulting in hallucinations disordered cognition

Speaker notes

- prefrontal loop may regulate initiation and termination of cognitive processes like planning, working memory, attention
- limbic loop could initiate and terminate emotional and motivated behavior, transitions from one mood state to another
- deterioration of cognitive and emotional function in Parkinson's and Huntington's disease may be result of disruptions to these non-motor loops
- antipsychotic drugs that act on dopaminergic receptors support hypothesis that schizophrenia involves disruption of basal ganglia non-motor loops
- drugs of abuse that affect dopamine neurotransmission
  - methylphenidate, amphetamine, meth, cocaine as well as those of nicotine [#Volkow-2000]

from [#Volkow-2000]:

> *drug abusers have marked decreases in dopamine D2 receptors and in dopamine release. This decrease in dopamine function is associated with reduced regional activity in orbitofrontal cortex (involved in salience attribution; its disruption results in compulsive behaviors), cingulate gyrus (involved in inhibitory control; its disruption results in impulsivity) and dorsolateral prefrontal cortex (involved in executive function; its disruption results in impaired regulation of intentional actions)*

- obsessive-compulsive disorder, depression, chronic anxiety all could involve dysfunctions of the limbic loop
- nucleus accumbens is a component of the limbic loop in ventral division of striatum and implicated in addiction to drugs of abuse expression of addictive reward-seeking behavior

[#Volkow-2000]: Volkow, N. D., Fowler, J. S., Wang, G. J., Baler, R., & Telang, F. (2009). Imaging dopamine’s role in drug abuse and addiction. Neuropharmacology, 56(Suppl 1), 3–8. http://doi.org/10.1016/j.neuropharm.2008.05.022

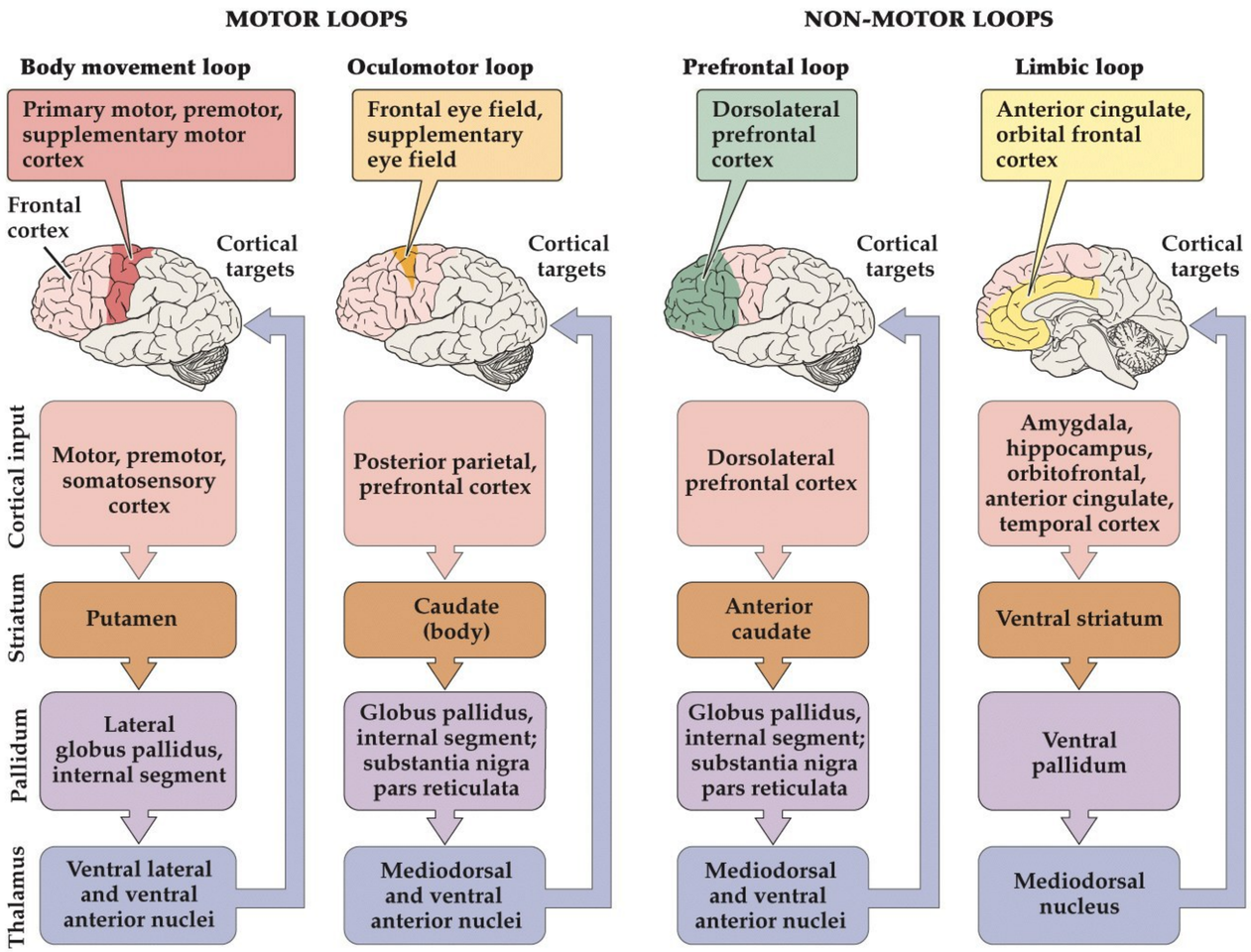
Tourette's example

Tourette's

Speaker notes

schizophrenia:
https://www.youtube.com/watch?v=OjM9GI_MLyQ

Types of corticostriatal loops



Neuroscience 5e Box 18D

Speaker notes

Tourettes may be a disruption to non-motor corticostriatal loops.