

Basal Ganglia

Motor system is complex interaction between Lower motor neurons (spinal cord and brainstem circuits) and Upper motor neurons (pyramidal and extrapyramidal tracts) plus two main regulators (Cerebellum and Basal Ganglia)

Today's lecture is about Basal Ganglia and it covers:

- I. Components of the basal ganglia
- II. Function of the basal ganglia
- III. Connection and circuits
- IV. Functional circuitry of the basal ganglia
- V. Symptoms and disorders discussed

I. Components of the basal ganglia

- Basal ganglia comprises multiple subcortical nuclei, most of them were supposed to develop from Telencephalon but only a small part of it does.
- Basal ganglia is divided into →Striatal Complex
 - ↳Pallidal Complex

-Striatal Complex components have the same type of neurons, same type and cyto-architecture of dendrites and the same neurotransmitters and it's furthermore divided into:

1. Dorsal striatal: Caudate and Putamen.
2. Ventral Striatal: Nucleus accumbens and Olfactory tubercle.

-Pallidal Complex is also divided into dorsal and ventral pallidal complex and it consists of: Pallidus and Substantia innominata

This Substantia innominata is part of Basal Nucleus (also called Nucleus Basalis/ Nucleus of Meynert), and from it Acetylcholine is released.

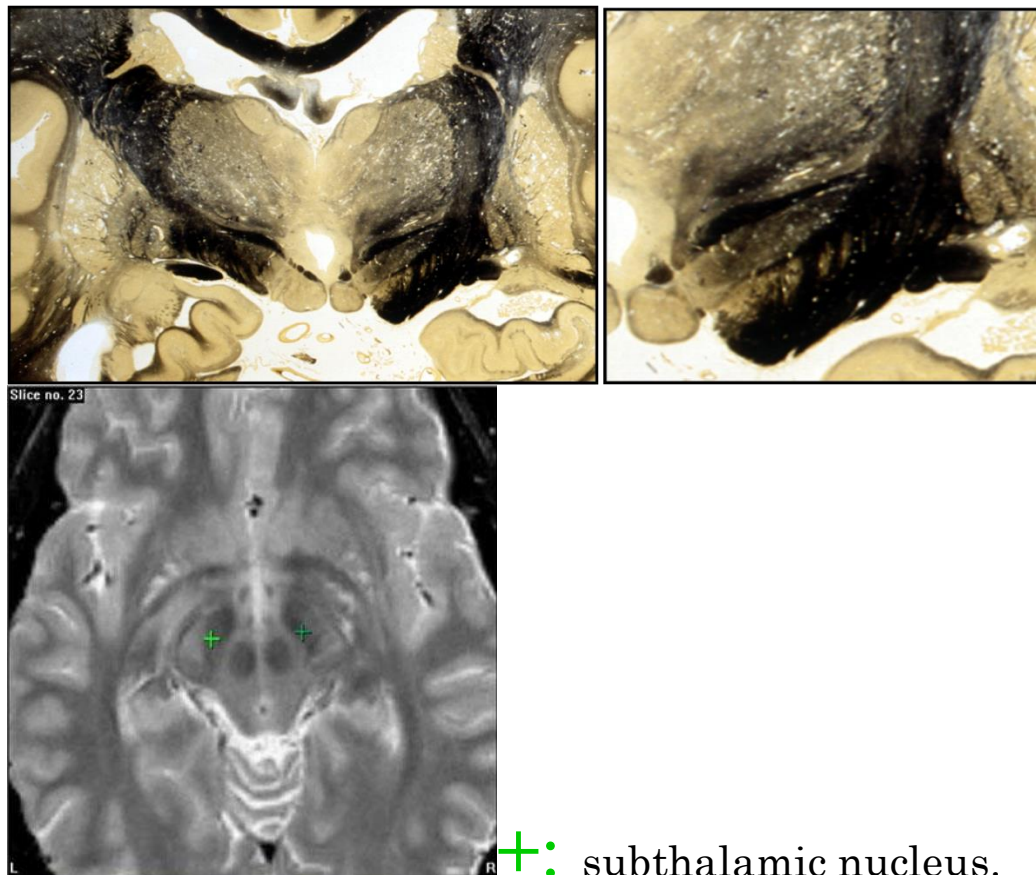
-Basal ganglia is functionally two parts:

- Ventral Basal nuclei (ventral pallidal –substantia innominata-, ventral striatal –Nucleus Accumbens and olfactory tubercle-)

- Dorsal basal nuclei (dorsal pallidum –globus pallidus-, dorsal striatum –caudate and putamen-)

Each part has its own circuit (Cortex part-striatum part-pallidum-thalamic- and cortical again)

If the cycle wasn't ending by cortex then the function of basal ganglia is lost.
-you can see in slides (5-10) MRI of the basal ganglia starting from a very rostral section moving caudally ending these images with an MRI showing the subthalamic nucleus which looks like a lense



+: subthalamic nucleus.

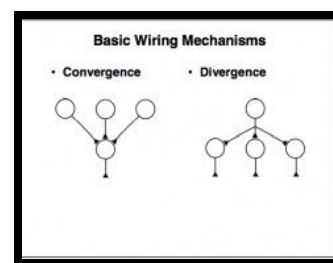
“It lies just above the rostral portion of the substantia nigra”

II. Function of the basal ganglia

Basal ganglia is a sequencer/regulator which acts like air traffic control towers that give airplanes the permission to land, it (basal ganglia) calculates the inputs and the outputs and decides which pathway to be activated and which to be

inhibited; accordingly, it has two circuits one for excitation the other is responsible for suppression .
(Direct and indirect pathways).

The most important component of these circuits is the striatal part which is the main balance keeper, it consists of crucial neurons: the **Medium Spiny Neurons**.



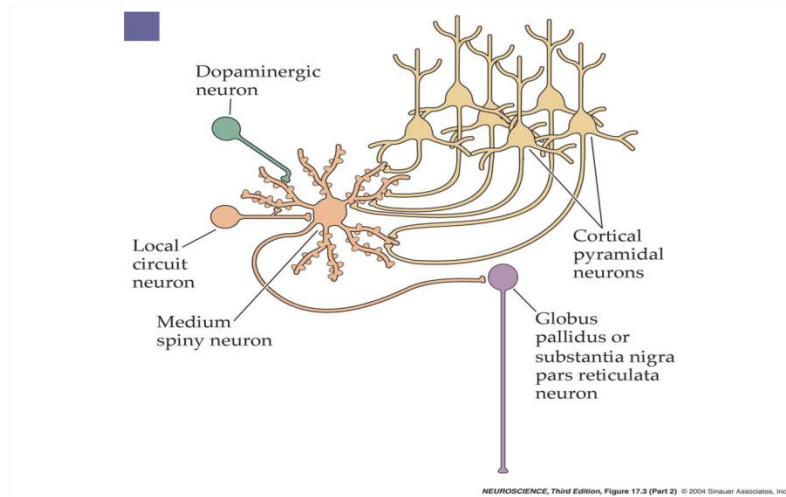
These neurons have a complex of dendrites with a lot of spines meaning that they have a lot of connections; sometimes we might have convergence of these spiny neurons from the cortex –Glutamatergic neurons-; many of cortical neurons from **layer 5** will converge on one or more of the spiny neurons depending on the distribution of the spiny neurons and the way the EPSP (Excitatory post synaptic potential) comes to the neurons , these medium spiny neurons are GABAergic neurons .

These spiny neurons are influenced by modulators two of them are:

1. Dopamine released from Substantia Nigra (regulated through feedback mechanisms from the organ it supplies)
2. Acetylcholine released in local circuits -from internal neurons within the striatum-(each part of basal nuclei supplies itself with Ach through local circuits plus a small part coming from substantia innominata).

*Substantia Innominata releases Ach mainly in ventral part of Pallidal complex.

cortical neuron → Glutamate → Medium spiny neuron within the striatum
(does the calculation) → GABA neurons to Globus Pallidus.



III. Connection and Circuits

Basal ganglia receive from almost all parts of the cortex (neocortex and paleocortex);

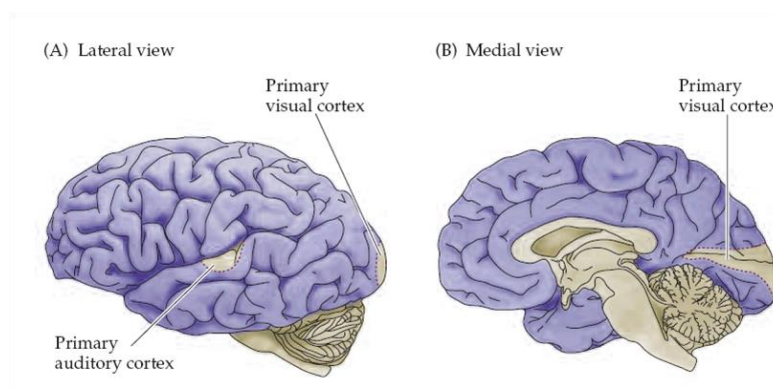
Rostral part of cortex → rostral part of Basal ganglia → Caudate (more involved with head of caudate)

Middle → Body of caudate + Putamen

Caudal → Tail of caudate (mainly) + (almost no Putamen at the caudal part)

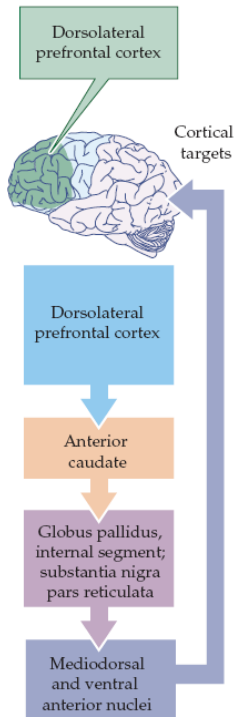
Two areas do not have connections with the Basal ganglia:

1. Primary sensory area of vision
2. Primary sensory area of audition



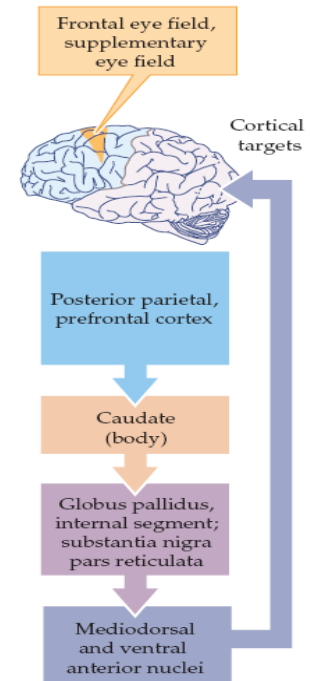
Circuits of the basal ganglia:

- a. **Motor Loop:** modulates the motor functions
Mainly from motor areas; motor cortex (M1 – primary motor area-, premotor area and supplementary motor area) sending signals to the body of caudate but mainly Putamen then going to Globus Pallidus → to Ventrolateral VL and Ventroanterior VA nuclei of the thalamus then ending in the cortex.

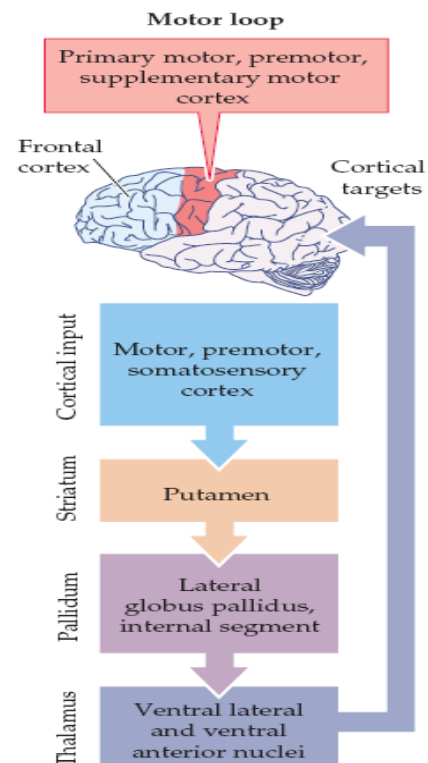


b. Visuomotor Loop:

Coming from visual associated cortices mainly, Frontal eye field (more rostral to the motor area) → Body of caudate → Globus Pallidus → Dorsomedial nucleus DM and Ventroanterior VA nucleus of Thalamus → ending in the cortex.



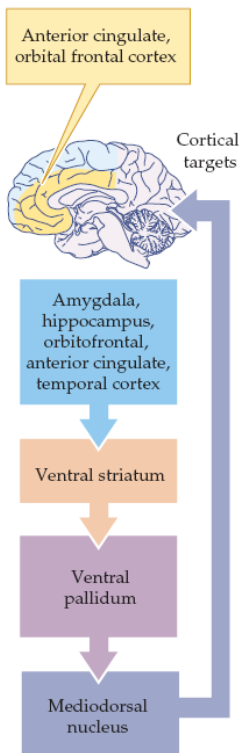
- c. **Executive loop:**
More in the rostral cortices; Prefrontal area → Head of Caudate → Globus Pallidus → Dorsomedial and Ventroanterior nuclei of the thalamus → cortex
Involved in Cognition and function of prefrontal cortex.
This explains why some people with basal ganglia disorders can have psychotic or cognitive dysfunction.



d. Motivational loop:

It's from the Non-Neocortical areas, -from the paleocortex or allocortex- mainly involved with ventral basal ganglia → ventral striatum (Nucleus Acumbens), Ventral pallidal complex (Substantia Innominata) → DM nucleus of the thalamus → neocortex

Usually the non neocortex is not related to the thalamus and when their tracts return into the neocortex they pass through the DM nucleus of the thalamus .



*“Based on the differences in lamination, the cerebral cortex can be classified into two parts, the large area of **neocortex** and the much smaller area of **allocortex**.” Wikipedia.

*Most of the cerebral cortex is neocortex. However, allocortex represents old functioning cortices such as **Hippocampus**, some parts of **Cingulate Gyrus** and cortices involved in emotion especially those with the olfactory function.

*Allocortex is related to emotion, limbic system and primitive functions. It (the allocortex) has two components: the *paleocortex* and *archicortex*.

*Neocortical area has **6** layers while Allocortical areas has **3-5** layers

*Less no. of layers → less processing → older in age

*Dorsal basal ganglia works in three loops (motor, visuomotor, executive) which controls Neocortices, while Ventral basal ganglia controls Allo, Pale and those are old, and related to emotion and limbic system

*Dorsal and ventral basal ganglia have interconnections → they do not function independently. These inter connections are also found in the three aforementioned loops

IV. Functional circuitry of the basal ganglia

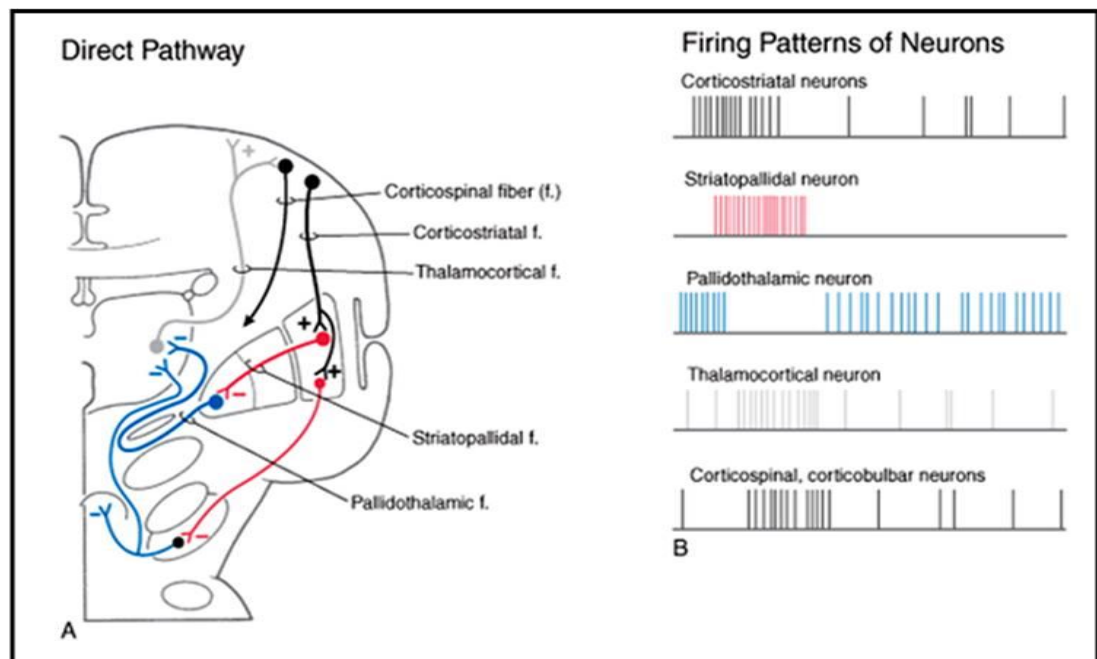
Functional organization of basal ganglia/ internal loops is the direct and indirect pathways.

In the **direct pathway**, the cortical projections to the striatum use the excitatory transmitter **glutamate**. When they are activated, these cortical projections excite striatal neurons. This excitatory input is enough to turn on the

medium spiny neurons. Then medium spiny neurons use the inhibitory transmitter **GABA**, and they inhibit a cell in GP (internal). The cells in GP (internal) that project to **VA/VL** of the thalamus also use GABA.

So, the cortical signal excites striatal neurons, which results in **MORE** inhibition from striatum to GP (internal). More inhibition of GP (internal) means **LESS** inhibition of motor thalamus (VA/VL). leading in **the end to excitation of the cortex** through thalamocortical feedback neurons.

Since the motor thalamus receives LESS inhibition, the VA/VL cells will INCREASE their firing.



(↓ Pallidothalamic neuron, ↑ Thalamocortical neuron, ↑ Corticospinal, corticobulbar neurons.)

So the end result of cortical excitatory input to striatal neurons at the head of the direct pathway is

INCREASED FIRING OF VA/VL NEURONS AND IN TURN MOTOR CORTEX.

Now let's turn to the **Indirect Pathway**:

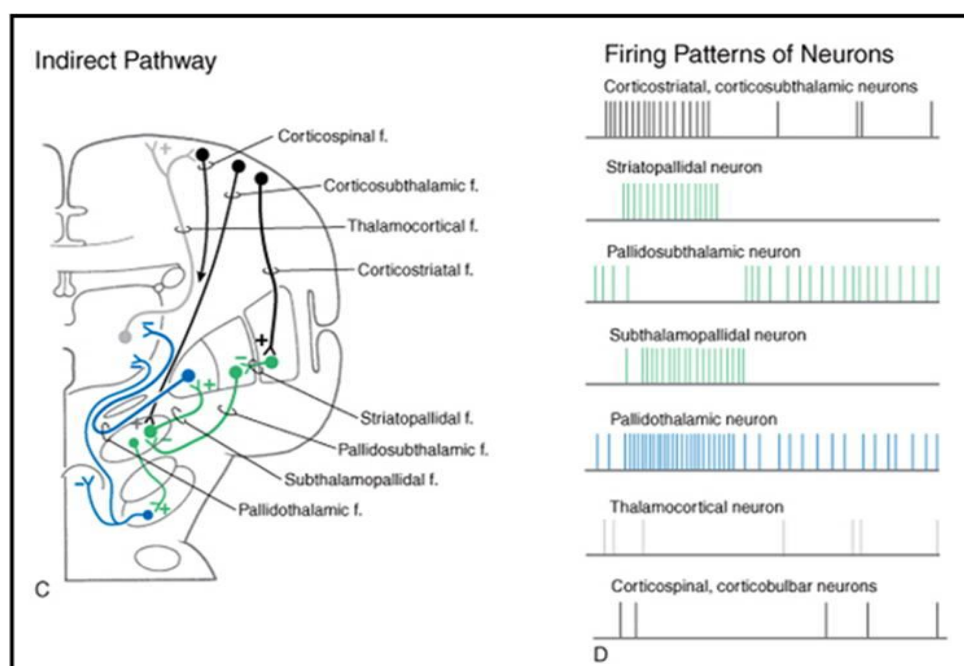
Instead of projecting to GP(internal), the striatal neurons of the indirect pathway project to GP(external).

In the indirect pathway, cortical fibers excite striatal neurons that project to GP(external). The increased activity of the GABAergic striatal neurons **decreases** activity in GP(external). The GABAergic cells in GP(external) inhibit

cells in the subthalamic nucleus, so the decrease in activity in GP(external) results in **less inhibition** of cells in the subthalamic nucleus. That is, subthalamic neurons are dis-inhibited and increase their activity. The “return” projection from the subthalamic nucleus to GP(internal) is **excitatory**, so the increased activity in the subthalamic nucleus results in more excitation to cells in GP(internal). Thus, the end result of actions of the indirect loop is an increase in activity of the GABAergic cells in GP(internal) that project to VA/VL or an INCREASE in INHIBITION of the thalamic neurons.

So, the indirect pathway is striatum to GP(external) to subthalamic nucleus to GP(internal) to VA/VL to motor cortex .

The Indirect Pathway turns DOWN the motor thalamus and, in turn, motor cortex. Thus, it TURNS DOWN motor activity.



(↑ Corticosubthalamic, ↓ Pallidosubthalamic, ↑ Subthalamopallidal, ↑ Pallidothalamic, ↓ Thalamocortical, ↓ Corticospinal, Corticobulbar.)

Modulators (associated nuclei):

Modulators receive input from other areas or cortices of the brain to modulate the pathway consequently their basic circuit either activate direct pathway or inhibit the indirect pathway

- **Subthalamic Nucleus**: it doesn't matter whether we consider it a modulator or part of the indirect pathway.
- **Nigral Complex**: it gives two inputs: a Dopamine input to the striatum and the second input is GABA to other parts/ other modulators.

- **Parabrachial Pontine Reticular Formation;** a subpontine nucleus – motor loop
- **Zona inserta:** is found in the basal ganglia just below the thalamus
- **Ventral Basal Nuclei**

Nigral complex:

Dopamine works through Second messenger subtypes of receptors;
Now, if we have Glutamate we will get a direct fast effect leading to an EPSP while in case of dopamine NO direct effect is observed; it only modulates the effect.

Dopamine receptors are either:

D1-Receptors in the direct pathway:

- 1) Increases Glu receptor phosphorylation
- 2) Alters ionic conductance to amplify cortical input.

} **enhanced** response

OR

D2-Receptors in the indirect pathway:

- 1) Increases Glu receptor phosphorylation
- 2) Alters ionic conductance to dampen cortical input

} **diminished**
response

So the end result is that the direct pathway is activated and indirect pathway is inhibited leading to excitation (increase firing) of the thalamocortical neurons.

Remember that dopamine's function is related to motivation and planning (intention of doing things).

V. Symptoms and disorders discussed

Whenever the balance between direct and indirect pathways is lost disorders are found.

For instance, if we have

- **insufficient direct** pathway output
- **excess indirect** pathway output

} loss of function
Hypokinetic Disorders

in hypokinetic disorders the motor function of the body is under the control of extrapyramidal tracts –excessive extrapyramidal symptoms.

These hypokinetic disorders occur if the part of putamen involved in the direct pathway or substantia nigra were damaged.

While if it was

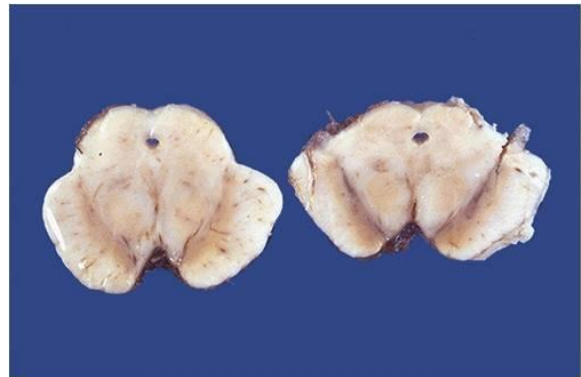
- | | | |
|---|---|---|
| <ul style="list-style-type: none">• excess direct pathway output• insufficient indirect pathway output | } | Hyperkinetic Disorders
more excitation |
|---|---|---|

Usually signs of hyperkinetic disorders are seen as:

- * **Chorea** (dancing like movement),
- * **Ballismus** which most of the time occurs on one side of the body (hemi-ballismus),
- * **Dystonia** (torsion spasm) means increased tension in the muscles with generalized or partial contraction “leading to involuntary movement and the slowing of intentional movement” Wikipedia.

In Parkinson's, cortex stops functioning → Rigidity is only seen here (not in dystonia)

* **Athetosis**: small movement of the hands (distal regions) and it has two types either Choreiform type: CHOREATHETOSIS –dance like-, or Dystonia type: ATHETOTIC DYSTONIA.



The most well known hypokinetic syndrome is **Parkinson's disease**, in Parkinson's there is loss of Dopamine from substantia nigra.

- Substantia nigra (the black area) is called so because it appears black without staining (due to melanin).

No substantia nigra → no excitation/inhibition modulation → ↑ Pallidothalamic neurons → ↓ cortex activity → cortex will not be influenced much by extrapyramidal pathway → muscle tension (especially muscles of the hand).

In **mild** cases of Parkinson's some parts work and others not → contraction at times and others no → Parkinson's will start as tremor.

This tremor will be at rest and disappears during movement.

In **severe** cases patient will suffer from Bradykinesia, Rigidity, and loss of postural reflexes.

If degeneration continued to involve more loops, it will cause Depression and Dementia and cognitive problems.

Treatment:

- Patient lacks dopamine→→ we give him L-Dopa
- Loss of neurons→→ Deep brain stimulation
(in deep brain stimulation we either activate substantia nigra OR we inhibit the indirect pathway through inhibition of Subthalamic nucleus or Globus pallidus internal by electrode.(this is more common))

Nowadays,

Internal circuits include Acetylcholine→→ Anticholinergic drugs
In some cases we mix dopamine and anticholinergic drugs for treatment.

Anticholinergic drugs target **AMPA** (glutamate receptor) and **A2** (alpha 2 receptor). (Commercially available)

- Also basal ganglia contain substance P which is also targeted nowadays in treating Parkinson's.

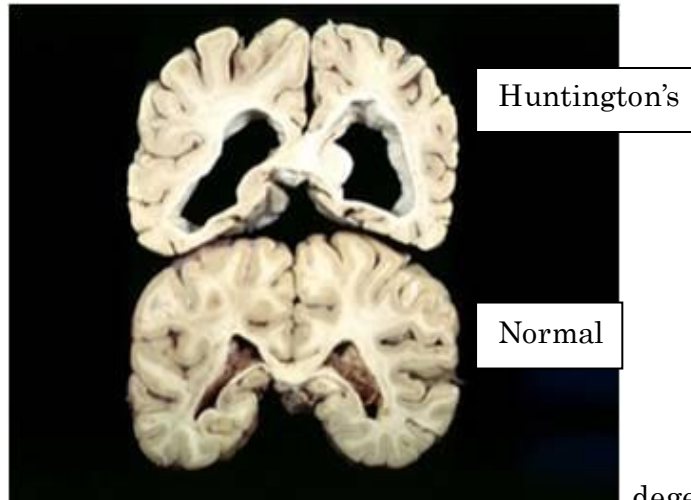
Hyperkinetic disorders :

Disorder	Causes
Huntington's chorea	Genetic (autosomal dominant)
Dystonia	Genetic or idiopathic
Tardive dyskinesia	Chronic use of neuroleptic drugs
DOPA-induced dyskinesia	Parkinson's therapy (antipsychotic therapy)
Hemiballismus	Unilateral vascular accident, typically subthalamic nucleus
Tourette's syndrome	Excessive D2-subtype DA receptor expression Genetic or idiopathic but mainly genetic

Huntington's chorea: caused by degeneration of GABAergic neurons (atrophy of striatum), there would be excessive direct pathway and insufficient indirect pathway; it starts rostral and medial then caudal and lateral.

Rostral part of basal ganglia (head of caudate) is affected first, accordingly early symptoms of Huntington's chorea are **psychotic** (depression) before motor, then motor is affected and it ends by the death of the patient within 10-15 years.

Rostral motor signs are: chorea (brief, involuntary movements) and dystonia (abnormal postures).



degenerated head of caudate

Dystonia: involuntary movement in one or more of the limbs (proximal and not distal – unlike Athetosis). It's mostly idiopathic although it might be caused by trauma, ions concentration imbalance or infection (bacterial/viral)

If it is a bacterial infection specifically strep type A. infection that is causing dystonia, then it's called **Sydenham Chorea**

Sydenham chorea occurs in children, its symptoms appear 3-4 weeks after the infection, usually it resolves within 6 months but sometimes it doesn't.

REMEMBER, If a lesion was found in:

Head of caudate → Huntington's chorea

Lenticular nucleus → Wilson disease (AKA hepatolenticular disorder)

Subthalamic nucleus → Hemiballismus

Substantia Nigra – Parkinson's disease

