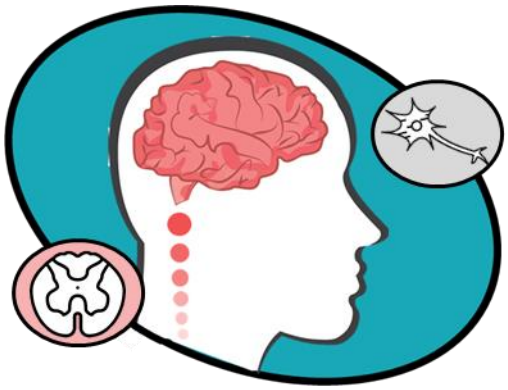


CNS

Physiology

Sheet Slide

Number

-

Done by:

-Hiba Rababah

Corrected by:

-

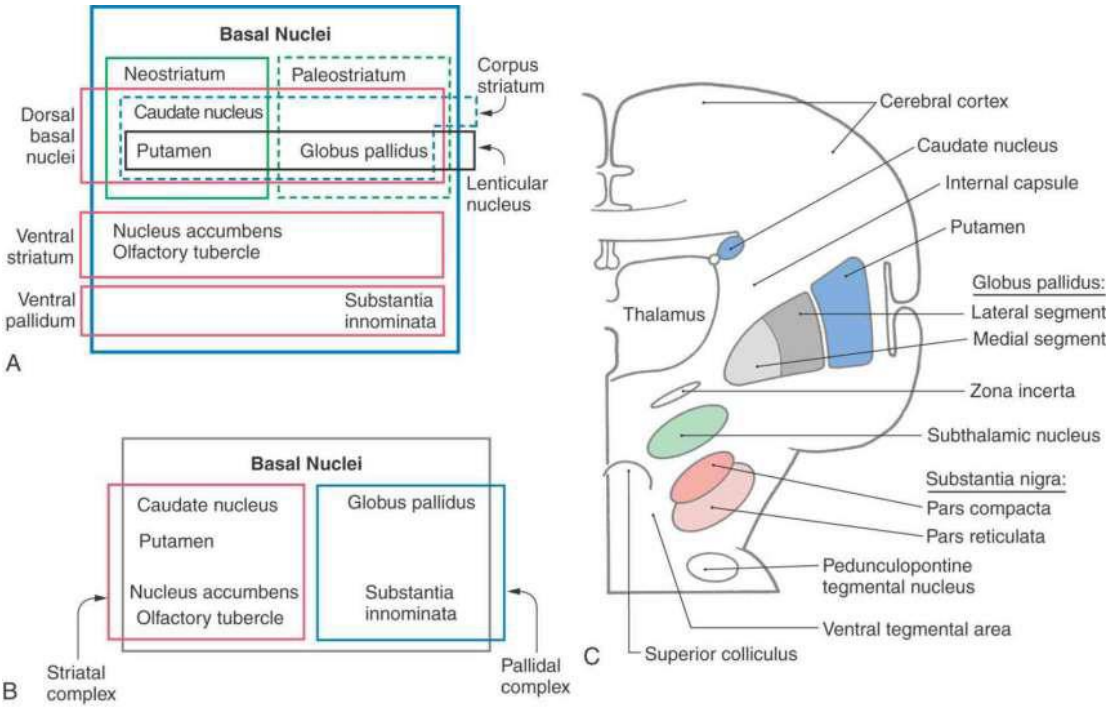
Doctor:

-Loai Al-zghoul

Basal ganglia (basal nucleus)

Note: what's written in blue wasn't mentioned by the doctor

Basal ganglia are composed of many structures that are heavily connected to each other to do one function. There're many ways to divide these structures, but in general, the basal ganglia are typically divided into **dorsal** basal ganglia and **ventral** basal ganglia. Each of these basal ganglia are composed of a group of structures, also these can be divided into **striatal complex** and **pallidal complex**, the importance of this division is related to their function as will be discussed later.



Function of the basal ganglia:

- In a few words, **Control cortical output.**

Let's talk a little bit about the cortex to understand the function of the basal ganglia:

The Cortex contains a lot of neurons and those neurons have **baseline activity,** which means that they can be activated and fires **without a stimulus**, or due to **a faulty stimulus**. So they could get excited by a stimulus such as thoughts or many other stimuli which are **not a real stimuli**. To understand this, imagine that there is a neuron located in the motor cortex and is heading towards spinal cord and from there to a muscle. As this neuron has baseline activity, it sends action potentials

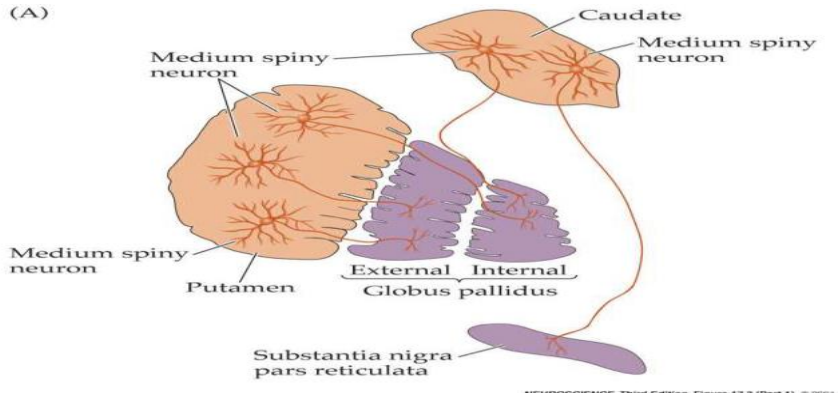
every 5 second, so this muscle will contract every 5 seconds!! We don't want this to happen, so we need a regulator for the cortical output that detects if this is a baseline activity or it is not a real activity so that this output gets inhibited or blocked. Or if this is a real desired order, it will allow the output to pass, this is the function of the basal ganglia.

How does the BG[1] do this?

Neurons of the basal ganglia (Medium spiny neurons)

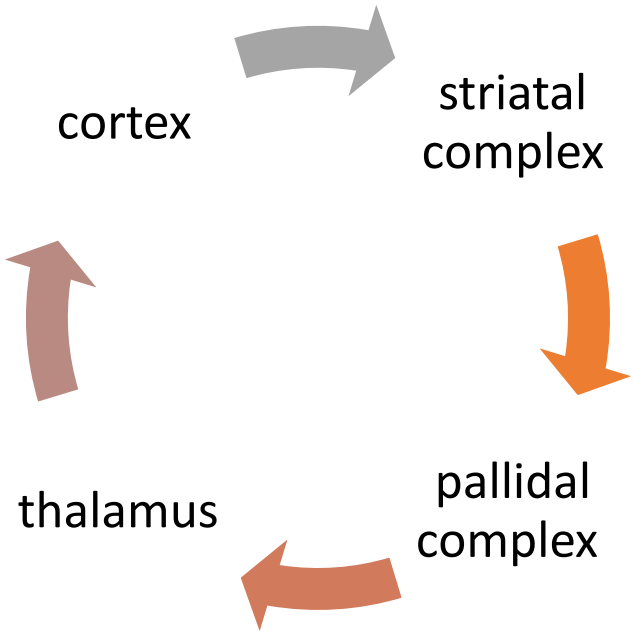
One of the important things that helps the basal ganglia to do their function is the presence of a specific type of neurons in the striatal complex which are connected to cortical neurons, they're called **medium spiny neurons (MSN)**. They are very large neurons with **extensive and large dendritic trees** that allow them to process and Integrate synapses from a lot of neurons from different areas in the cortex and do **complex processing**.

The connection between cortical neurons and medium spinal neurons is **unique** because there's a lot of **convergence**. Those spines will get activity from the cortex and calculate if this movement is real or not. They have excitatory and inhibitory pathways and the balance between those pathways is what determines if this activity is real (and activate the cortex) or not (and inhibit the cortex). In addition to these connections, there are a lot of modulators (associated nuclei); some of the most important are those from inside or outside BG which give Ach[2]. Other modulators are those that come from substantia nigra and give dopamine.



Connections and circuits

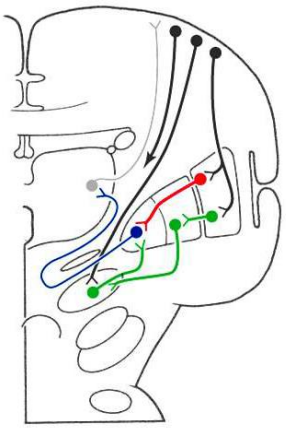
There are connections that come from the cortex to the basal ganglia and back to the cortex. Circuits involve fibres that descend from the cortex, enter the basal ganglia through striatal complex, then move to pallidal complex, then the thalamus, and after that return back to the cortex.



We have two **parallel** pathways:

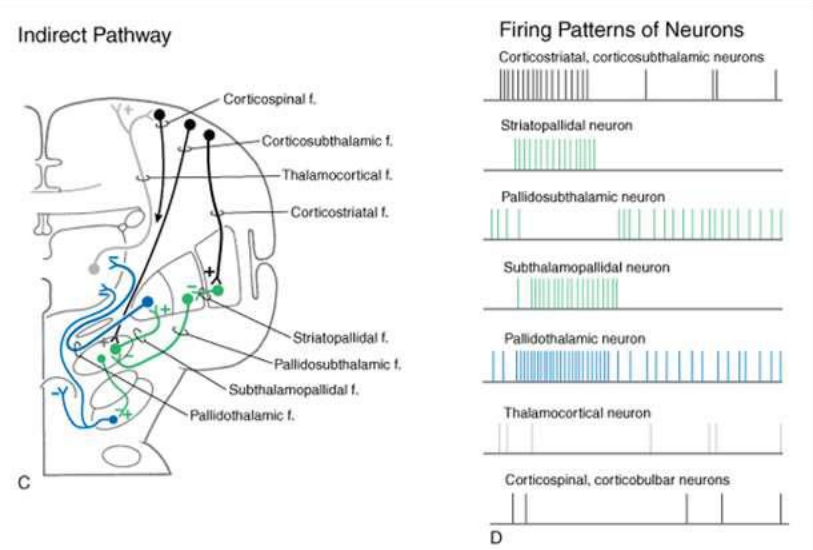
1. **Indirect** pathway which is the more important pathway that is **always active** because its goal is to **inhibit** cortical output.
2. **Direct** pathway that will be **activated only** when we need the **real cortical** output to pass so it **facilitates** and allows the cortex to pass the order to the desired destination.

Direct = Dark grey –Red –Blue–Light grey
Indirect= Dark grey –Green –Blue– Light grey
Text Fig. 26

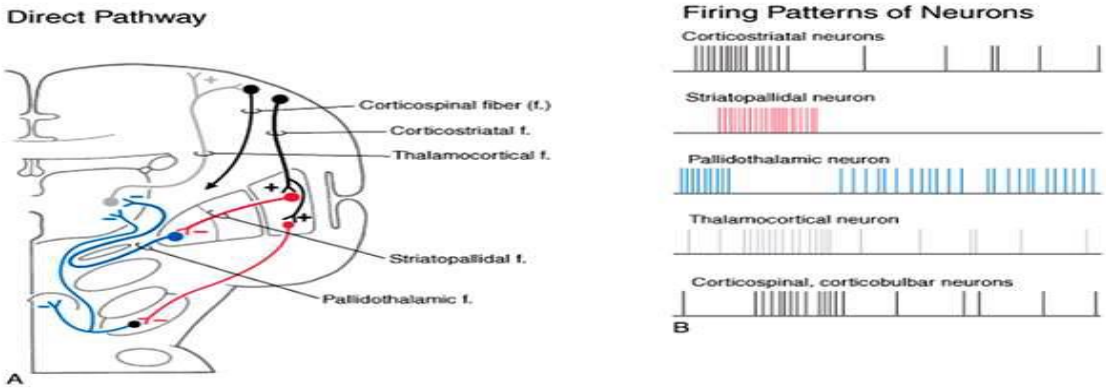


☒ In the Indirect pathway, **the cortical activity**- which is continuously active- is received by **striatal** complex then pass to **pallidal** complex then to one of the nuclei of **thalamus** then return back to cause inhibition of the cortex, so

activation of this pathway leads to inhibition of the cortex and blocking of the output.

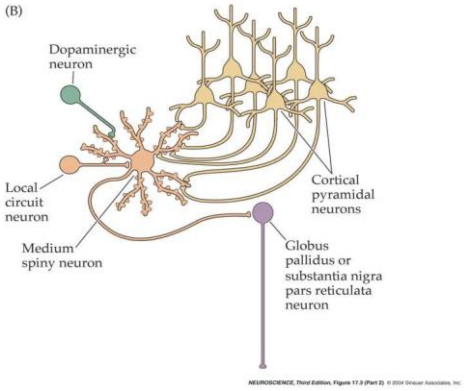


☒ In the direct pathway, the **cortical activity** also enters the striatal complex then to pallidal complex, thalamus, but this pathway will lead *to activation of the cortex.*



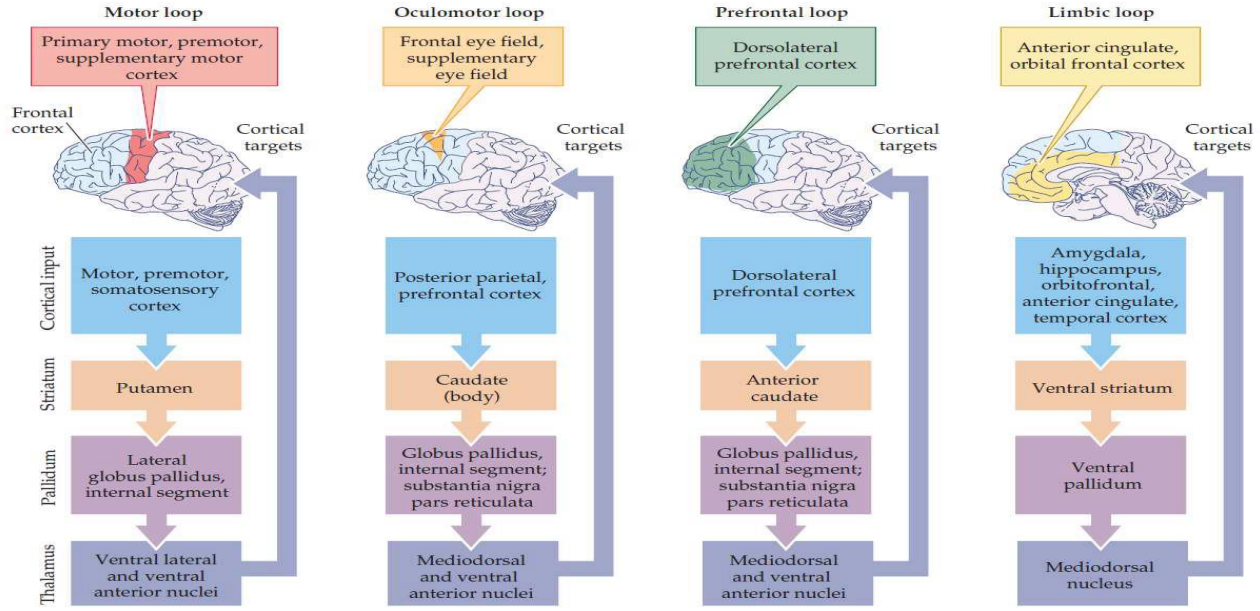
☒ Because the **indirect** pathway is always active, it has a **tonic activity**, it is always inhibiting the cortex output until a real output or real thoughts from the cortex are generated, the **phasic activity** of the direct pathway turn on, this means that the direct pathway will be active for certain moments allowing the removal of inhibition of the indirect pathway. So you will hear that direct pathway or basal ganglia works by **<u>disinhibition</u>**. Disinhibition means that there is always inhibition of cortical output until the real order needs to pass, here, the direct pathway interferes to stop this inhibition for a certain moments and allow passing of that order.

☒ In the two different pathways, the direct and indirect, both have connections between MSN and cortical neurons, but the way in which connections are arranged is what leads MSN in indirect pathway to be always active and send feedback inhibition to cortical output, the different connections in the direct pathway leads to activation of this pathway and disinhibition of basal ganglia and cortex and allow output to pass.



Functional loops

As we said that the function of the basal ganglia is to **regulate cortical output**, so most areas in the cortex are connected to the basal ganglia except **primary sensory cortices** such as the primary visual area. So we can divide the basal ganglia into functional group depending on the region of the cortex that they are connected to. In general there are five famous functional groups, note that in each functional group, there is a part of the cortex that sends impulses to striatal complex then to pallidal complex then to a certain nucleus in the thalamus then return back to the same area in the cortex. And it is important to notice that the anterior(rostral) parts of the cortex are connected with the anterior(rostral) parts of the striatum, and the posterior parts of the cortex are connected with the posterior parts of the striatum, and so on.(you should memorize specifically these connections, as they will help you to predict the sequences of lesions within the striatum, they are mentioned below in red).



1. **Motor loop**: This loop originates in the primary motor area, supplementary motor area. The corticostriatal projections terminate in putamen part of striatum, which also receives projections from the somatosensory cortex. Efferent from the putamen terminate in the globus pallidus interna then return back through ventral lateral and ventral anterior nuclei of the thalamus to motor cortex .
2. **Oculomotor loop:** the connection from **frontal eye field** and **supplementary eye field** goes to body of caudate (dorsolateral part) of striatum to pallidum to thalamus then return back to control oculomotor cortex to **control eye movement and gaze**.
3. **Prefrontal loop**: This loop originates in the **dorsal lateral prefrontal cortex**, and goes to the head of caudate. It's called the **Executive loop** because it controls and regulates **cognitive** functioning such as planning and attention.
4. **Limbic loop:** This loop has a diverse set of telencephalic regions including **anterior cingulate and orbital frontal cortex**, from there, it goes to the nucleus accumbens part of stratum. It is called the Motivational **loop** since it regulates our **motivation go/no go**. Motivational phenomena include such things as drive, pleasure, desire and emotions.
5. Ventral loop (not shown in the picture):it starts from the **lateral orbital frontal cortex** and goes to the ventromedial part of streatum. It's called the **Social loop** as it is responsible of our social behaviour and empathies

☒ The role of thumb here is that the **anterior cortex (rostral cortical** area) will be connected to the **rostral part of striatal complex.** For example, in prefrontal loop, **dorsolateral prefrontal cortex** is connected to the **anterior part of caudate (head)** while **oculomotor loop** Is connected to **body of caudate** more specifically dorsolateral part of it, **motor loop** is connected to **putamen** as it's in the middle part of striatal complex, **ventral loop** (social loop) is connected to **ventromedial part of striatal complex** and **limbic loop** is connected to **ventral ganglia** mainly striatal complex of it **nucleus accumbens** (not dorsal ganglia)

☒ These loops will be discussed in next lectures, in this lecture we are concerned about motor loop, but what you really need to know is that certain regions in cortex will go to striatum to pallidum to distinctive thalamic nuclei then return back to regulate cortical function, in addition, in each functional loop there is indirect pathway that will inhibit cortex and prevent passing of output and direct pathway that will facilitate cortical outputs.

Motor loop

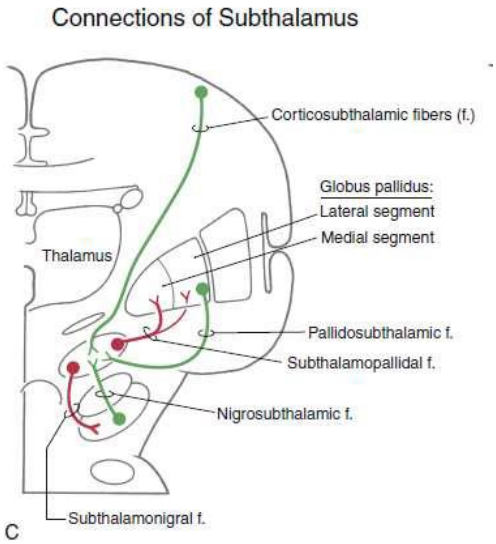
As we said earlier, tonic activation of the indirect pathway leads to inhibiting unwanted movement that can be activated by baseline activity of neurons or if I thought to do a movement but I don't want to do it (not a real stimulus), but if I want to move my hand consciously for example, the direct pathway in the muscle that is responsible for my hand movement will be activated to disinhibit indirect pathway and allow action potential to pass to move my hand.

Modulators (associated nuclei)

In addition to the circuits we've talked about, there are certain **modulator nuclei** that **associate** with the basal ganglia in order to modulate their function helping to process more in direct or indirect pathway which will help increase inhibition or facilitation of the cortical output.

These modulator are:

1. **Subthalamic nucleus**: although it's involved in the subthalamic ganglia, there are some books that account it as part of the indirect pathway due to its huge role there, its function is to facilitate and activate **indirect** pathway which leads to more inhibition of the cortex.



2. **Nigral complex**: it uses neuromodulator (dopamine). Substantia nigra especially "pars compacta" sends fibers to basal ganglia to release dopamine.
   - ☒ **Dopamine** is a type of **neuromodulato**r that uses **second messenger**, as we said previously, second messenger modulates and changes the response pattern of neuron more than just excitation or inhibition.

Modulation could be toward excitation and it's called **excitatory** modulation or modulation could lead to the decrease of possibility of generation of action potential and called **inhibitory** modulation. So the cortical neurons come to MSN and give **EPSPs** which either generate action potential or not, while dopamine modulates but don't **give EPSP,** instead dopamine increases or decreases the possibility of the EPSP to generate action potential. Dopamine supply both direct and indirect pathways.

- ☒ in the **direct** pathway, we have dopamine **type 1** receptors (D1-Rs) which are **excitatory** modulators, so in case of presence dopamine in direct pathway, it's easier to excite so dopamine increase activity of direct pathway and leads to increased cortical activity and cortical output.
- ☒ In the **indirect** pathway, we have **dopamine type 2** receptor (D2-Rs) which have **inhibitory** modulation so it decreases activity of indirect pathway so dopamine decrease activity of indirect pathway which leads to **<u>decreased inhibition</u>** of cortical output allow cortical activity to increase.
- ☒ **Thus, the action of dopamine is, overall, excitatory as it decreases the activity of the indirect pathway and increases the activity of direct in order to increase cortical activity of the cortex.**

Note: doctor mentioned that connections are complicated, what he really wants you to understand is the net effect and the general idea.

3. **Pedunculopontine nucleus (Acetylcholine)**:
   Nuclei in the region of the parabrachial pontine reticular formation are intimately connected with all portions of the basal nuclei and their associated nuclei. The parabrachial pontine nuclei are connected with motor centres in the brainstem. The nucleus and its neurons release neurotransmitter **(acetylcholine) which** have modulatory effect on direct and indirect pathways. In the **direct** pathway, neurons have muscarinic receptor type 4 **(M4-Rs)** which are **inhibitory m**odulators so acetylcholine will cause inhibition of the direct pathway and leads to **decreased activity of the cortex**, while **in the indirect** pathway, neurons have muscarinic receptors type 1 **(M1-Rs)** which are **excitatory**, hence acetylcholine will increase and facilitate the indirect pathway leading to **increased inhibition** of the cortex and **decreased activity**, thus the **overall** effect of acetylcholine is **inhibitory** through increased activity of the indirect pathway and cortical inhibition while decrease direct pathway and cortical activity hence as a net result decrease cortical activity and its output .

Disorders of basal ganglia

Any disorder in the basal ganglia will affect cortical output that is connected with it, these disorders involve increase or decrease output or affect the function itself.

Disorders in the Motor loop

1. Hypokinetic disorders (decrease in movement): result from either insufficient direct pathway output or excess indirect pathway output (more inhibition).
2. Hyperkinetic disorders (increase in movement): result from either excess direct pathway output (more activation) or insufficient indirect pathway output (less inhibition) collectively lead to more activation of the cortex.

Parkinson's disease

One of most common Hypokinetic disorders that result from degeneration and loss of dopamine modulation of the striatal complex. As we said, dopamine works by exciting direct pathway and inhibiting the indirect pathway, thus loss of dopamine causes a decrease in direct pathway and less inhibition of the indirect pathway, so the net effect is more inhibition of the cortex which leads to decreased movement and hypokinesia. As we have studied in pathology, the hallmark of this disease is a motor problem, why? Because the degeneration in substantia nigra will affect mainly Putamen part of the striatum and involvement of the motor loop causes bradykinesia and movement problem that will continue and progressively cause more neuronal death. Degeneration in substantia nigra begin **lateral to medial** so in the end, this will involve other functional loops in the basal ganglia, hence in progressive stages this will affect visual motor loop and executive loop in prefrontal loop causing cognitive problem and dementia in these patients in the future.

Note: Dementia in Parkinson's patients differ from other types of dementia.
Treatment of Parkinson:

1. Increase dopamine levels.

2. Decrease acetylcholine level (because acetylcholine inhibit direct pathway and stimulate indirect pathway, so drugs that decrease Ach try to re-establish the balance between direct and indirect pathway). Exact drugs will be explained in pharmacology. Many times we use anti-acetylcholine drugs instead of increasing the dopamine dose if more degeneration happen in substantia nigra to avoid side effects of dopamine.

3. Novel treatment ways is based on decreasing indirect pathway activity and decreasing the inhibition on the cortex by a surgical procedure called **deep brain stimulation**, in which an electrode is put over the subthalamic nucleus (STN) - which are modulators of indirect pathway and have inhibitory effect on the cortex- then we give a high current frequency stimulation to cause exhaustion in indirect pathway to decrease inhibition of the cortex. Other surgical procedures involve Globus pallidus interna but STN is more famous.

Hyperkinetic disorders

The symptoms of the involuntary unwanted movement take different forms such as:

1. Chorea: dance like movement, usually in distal parts of the limbs, semi purposeful since these patient try to appear as if they move voluntarily movement on purpose.

2. Ballismus: appearance of flinging, violent and rapid involuntary movement of the limb usually in proximal part of limbs so the whole limbs move and the patient is unable to mask his movements so nonpurposeful.

3. Dystonia: it's either sustained contraction or continuous repeated contraction involving one or a group of muscles which will cause twisting of the limb if it happens in the arm or twisting in torso muscles if it happens in the core muscles, leads to abnormal posture.

3. Athetosis: slow involuntary movement usually convulsions involving hands, fingers, feet and toes, rarely involve arms and legs.

- **Choreatic disorders**

Huntington's disease

Genetic disorder caused by loss of striatal neurons usually starts in rostral part then progresses to medial part and Putman then finally goes to caudal and lateral, hence usually the first affected pathway is dorsolateral prefrontal pathway causing early symptoms such as mood changes, cognitive disability, depression, then when degeneration progresses to involve other parts, symptoms like Hyperkinesia appear. Usually starts with Chorea like movements, which worsen with time as more neurons are lost, then Chorea movement may develop to Dystonia and lead to death. Patients usually die before the

degeneration reaches the caudal part and cause dementia except in few patients who actually develop dementia.

Sydenham chorea

A disease that affects children after certain infections commonly due to group of streptococcal infections. Pathophysiology suggest either due to the bacterial antigen that stimulates the release of autoantibody against certain receptors including dopamine receptors, or due to fever that leads to death of neurons or decreased supply to neurons and leads to chorea. Because this disease has an underlying treatable cause, once treated, symptoms resolve completely in most children. Unfortunately, in some children, symptoms alleviate but not completely.

Dystonia

Possible causes:

1- Most common is genetic disorder.
2- Idiopathic.
3- Trauma.
4- Certain drugs or metal poisoning.

As most causes are due to a genetic problem, they are hard to treat. Drugs have no receptors, they don't respond well even we might use anti-Parkinson drugs or some sedatives. In these patients we might intervene surgically in an attempt for a deep brain stimulation. The best case scenario is a local dystonia where we can use botulinum toxin -BOTOX- to relax the muscle.

HemiBallismus

Ballismus is flinging of the body with rapid, involuntary movement that affects all the limb, most common cases are one side of the body which are called HemiBallismus. Most common cause is a stroke in the subthalamic nucleus which functions to facilitate indirect pathway, so there will be excitation and increase in movement.

Tardive dyskinesia

Result from some antipsychotic drugs which are dopamine antagonist. Use of dopamine antagonist for a long time will block dopamine receptors which will stimulate sensitization and over expression of dopamine receptor especially D1_Rs leading to over activation of direct pathway causing this Hyperkinetic

disorder. Jerky involuntary movement which appear mostly on the face but also can involve hand, arm or even the trunk. Lip smacking, continuous fast eye blinking, protruding the tongue are all examples of facial involvement.

Tourette's syndrome

Genetic cause, the pathophysiology is not well known but it's believed that it is a mutation in dopamine receptors in the prefrontal cortex and basal ganglia. Present with a motor or sound tics. Tics are sudden repetitive movements, not rhythmic. At least one sound and one movement must be present to say that this patient has Tourette's syndrome. The patient is able to control these symptoms and attempt to hide these symptom but this may lead to more urge to do them. This urge may be induced by stress or certain emotions. These tics don't cause a problem as he can control them so don't cause a major problem in his life, but in some cases unfortunately the tics are so severe because either the tic itself is severe or it is very frequent (he has to repeat it too many times) so will affect his life. Most cases resolve with adulthood because they usually appear in the late childhood early teen and rarely stays after 18 but yes some cases stay and even worsens.

[1] basal ganglia [2]acetylcholine