CENTRAL NERVOUS SYSTEM

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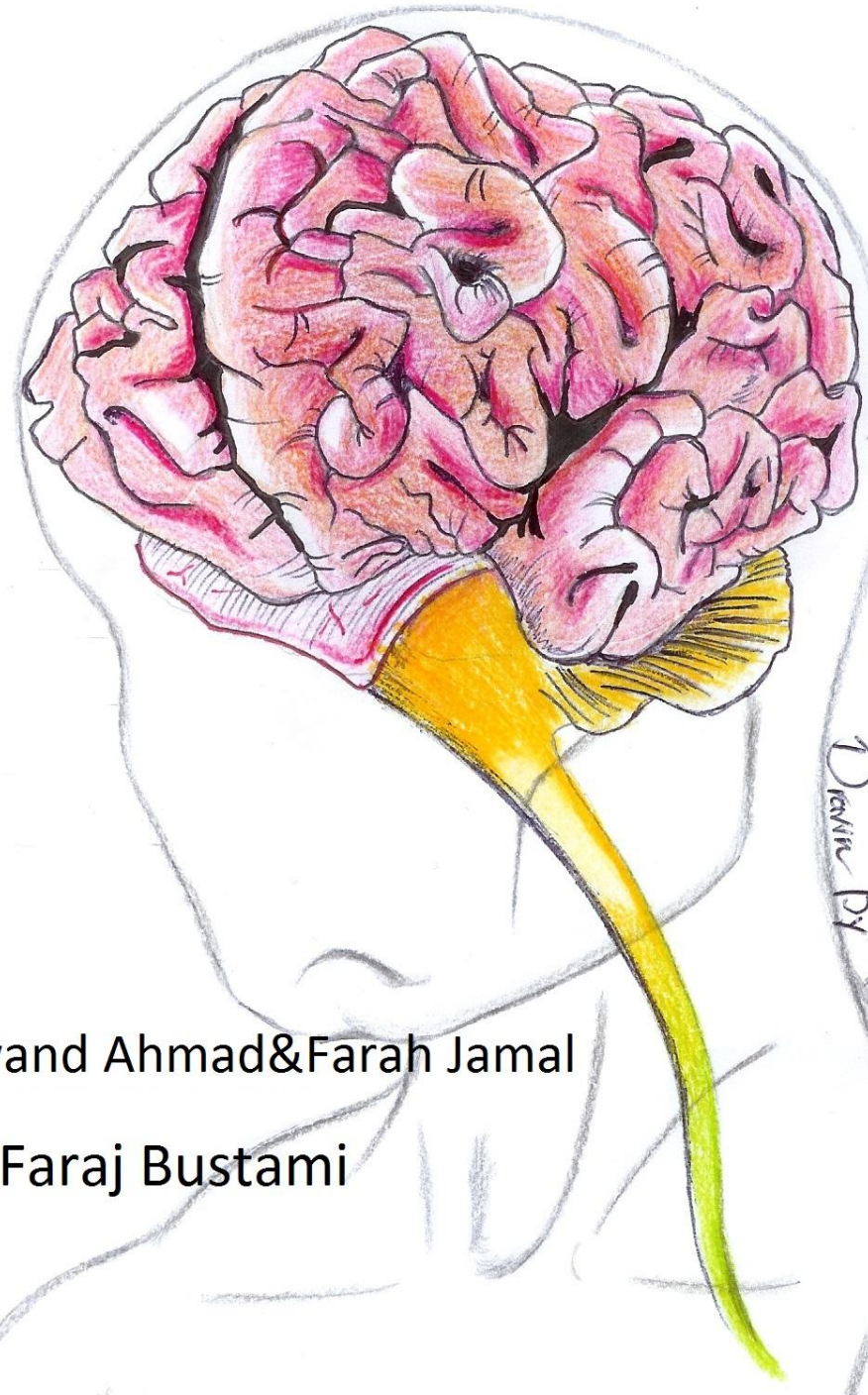

Drawn By Tariq Bushnaq...

Done By: Rawand Ahmad&Farah Jamal

Dr. Name: Dr Faraj Bustami

Lec #: 10

Basal Ganglia

Quick revision:

When we hear the term 'basal ganglia' we have to remember two words: **disinhibition** and **dyskinesia** (disturbance of movement), which could be **hypokinesia** which means lack of spontaneous movement and it happens in Parkinson disease (when you walk, your hands usually spontaneously and freely move as well, but this does not happen in Parkinson as they are very rigid.), Or **hyperkinesia** which means abnormal involuntary spontaneous movement and it happens in chorea disease.

We said that we have two pathways between the striatum and GPI: 1- **direct pathway** which facilitates movement, and 2-**indirect pathway** which limits movement, and there's always balance between them.

Parkinson disease:

Dopamine has an excitatory effect on the direct pathway and inhibitory effect on the indirect pathway.

Parkinson disease is a neurodegenerative disease characterized by lesions in the basal ganglia, predominantly in the substantia nigra. This lesion will result in loss of dopamine production by the pars compacta of substantia nigra ⇨ loss of dopamine in the striatum.

Loss of dopamine results in an imbalance between the direct and the indirect pathway, and will result in **overactive GPI**.

Signs of Parkinson disease:

1-rigidity (**gamma rigidity**): one of the most important signs of Parkinson disease. Which means *hypertonia* .and remember rigidity is different than spasticity:

Spasticity	**rigidity**
1-Affects either flexors of the upper limb or extensors of the lower limb (unidirectional)	1-affects both flexors and extensors (bidirectional)

2-Could be associated with hyperreflexia, babinski sign.	2- Is *never* ever associated with Hyperreflexia, babinski.

The mechanism by which we get rigidity in Parkinson disease is that overactive GPI results in more inhibition to the thalamus (recall that the thalamus is usually under tonic inhibition by the GPi), and disfacilitation to the cortex which results in hypokinesia. Recall that **hypokinesia** could be **bradykinesia** (slow movement) or **akinesia** (difficulty in initiating movement/hesitation to move).

Overactive GPI sends impulses to the **midbrain extrapyramidal area** and inhibits it, and then this region will send inhibition impulses to two regions:

1- **Pontinereticulospinal tract**, so inhibition of inhibition means **disinhibition** or excitation to the alpha and gamma motoneurons. Alpha and gamma will become hyperactive and the stretch reflex will become overactive, resulting in *hypertonia* in both flexors and **extensors**.
2- **Rubrospinal tract**, and again inhibition of inhibition means activation of alpha and gamma and the stretch reflex will become overactive and the result is hypertonia in the **flexors** mainly **distally** as well as proximally.

2-Rest Tremor (not always present): The patient will have something called pill rolling where he moves his fingers (especially the thumb and index) against each other as if counting pills. Keep in mind that many people have tremors due to other causes such as hepatic diseases or familial tremors.

We don't know the exact mechanism for rest tremor; some have assumed it happens due to overactive GPI; because if we surgically induce a lesion to the GPI by cauterization of the GPi (burning a part of the body), the tremor will be less intense or will disappear entirely. This is the only explanation.

When the patient suffers from rest tremors, we give him anticholinergic drugs, but if he/she doesn't respond, we treat him/her surgically by burning parts of GpI.

What is the difference between rest tremor and intention tremor?

Rest tremor: indicates basal ganglia diseases like Parkinson and it appears at rest.

Intention tremor: More coarse, indicates cerebellar diseases and it appears at the **end** of **purposeful** movements (when the patient tries to take a cup of tea for example).

3-**Staring look** (كأنو ببحلق): loss of spontaneous movements of the eye (the patient can't move his/her eyes to the right and left), and it is due to increased tone of muscles of the eye**.** We have two centers that control the movements of the eyes; one in the **frontal lobe** and the other in the **occipital lobe**.

What we care about here is the **frontal eye field** (area no. 8), which is located in the posterior part of the middle frontal gyrus .

Recall: When we stimulate area no. 8 on the right ⟶ the eyes will deviate to the left and when we stimulate area no. 8 on the left ⟶ the eyes will deviate to the right lesion to area no. 8 on the right ⟶ the eye will deviate to the right by the left area no.8

The frontal eye field as part of the cortex, has an input and output.

Input to the basal ganglia: we call it corticostriate , from the frontal eye field (part of the cortex) to the striatum and from the striatum to the GPI (direct or indirect).

Input: cortex ⟶ striatum ⟶ GPI

Output: from GPI to the thalamus (ventral anterior nucleus of thalamus) which in turn sends back to the frontal eye field.

Decreased Dopamine will result in absence of these connections and over activity of GPi, consequently, the patient will have a **staring look** and absence of spontaneous eye movement (it's very hard for him to move his eyes), often accompanied by **infrequent blinking** due to rigidity of eye muscles.

4-**Stooped posture**, or flexion of the trunk due to increased tone in the flexors (more than extensors) of vertebral column.

5- **Stiffness and resistance** to limb movement (loss of spontaneous movement)

6-**Loss of facial expressions** (We'll see later that nucleus accumbens, anatomically belonging to the basal ganglia but functionally related to the limbic system, is important in motor expression of emotions like posture and gestures, as well as facial expression related to emotions.)

7-**Difficulity in initiation of movement/Akinesia (**ما بقدر يقوم عن الكرسي)

8-**Shuffling (festinating gate):** in which the patient moves with short, accelerating steps, and his feet are fixed on the ground due to stiffness of legs يعني بمشي وقدمه ملزقة بالأرض.

Note:

In Parkinson disease we don't have any lesion in the upper or lower motor neurons, there is no hyperreflexia, Babinski sign or clonus.

Keep in mind that dyskinesia which occurs in Parkinson is NOT **apraxia,** which occurs following cerebral cortex lesions and affects the patient's ability to conceptualize what you ordered him to do; so something is wrong in **planning** or **execution** of complex movement. For example, when you ask a patient to hang a painting on the wall, he's supposed to plan holding a hammer and making a hole in the wall and so on, but this sort of planning is impaired in cerebral cortex lesions resulting in apraxia. (We'll talk about apraxia in subsequent lectures.)

The treatment for Parkinson disease is **L-dopa**, not dopamine, because dopamine cannot cross the blood brain barrier but L-dopa can.

The mechanism by which L-dopa is converted to dopamine is controversial: some people say it's unknown, others say that the remains of substantial nigra (remaining active cells) are responsible for converting L-dopa into dopamine.

Usually we combine L-dopa with **carbidopa**. Although carbidopa doesn't cross the blood brain barrier, it's very useful in preventing peripheral utilization of L-dopa (prevents tissue uptake of L-dopa).

Another new drug is **amantadine** (2in1), which **stimulates the release of dopamine** from what's left of the substantial nigra and it has a **anticholinergic effect.**

Therapy is not curative, as the disease progress in spite of treatment. It's just a replacement therapy!

Chemical changes in Parkinson disease:

Parkinson disease: ***Decreased dopamine to acetylcholine ratio.*** ↓dopamine , ↑acetylcholine .

Treatment for increasing dopamine: L-dopa (mainly treats rigidity)

Treatment for decreasing acetylcholine: anticholinergic drugs like Atropine (mainly treat tremors).

Another way of treatment, especially in resistant cases, is surgery. We make surgical destruction to part of from GPI (Cauterization) ⟶ the tremor will disappear and the rigidity will be less.

We have two types of neurons in the striatum: medium size spine neurons producing GABA, and next to GABAergic neurons are interneurons that produce acetylcholine (cholinergic neurons). Cholinergic neurons receive dopaminergic fibers from substantia nigra. These dopaminergic fibers inhibit cholinergic neurons.

In Parkinson disease there is no dopamine ⟶ so there is no inhibition on the cholinergic neurons ⟶ they will become hyper-excitable ⟶ making excessive stimulation to the GABA pathway (indirect pathway) ⟶ the indirect pathway will work excessivly ⟶ overactive GPI ⟶ signs of Parkinson.

That's why we give anticholinergic therapy .

L-dopa mainly treat rigidity

Anticholinergic mainly treats tremors.

*what we talked about in the last lecture and this lecture is the motor circiut (represented by direct and indirect pathways). Basal ganglia receive information from the cortex by what we call streams from the motor cortex, primary motor area, premotor supplementary area, somatic sensory area and association area.

Other circuits: **limbic and association circuits**.

` Note: all circuits within the basal ganglia start from the cortex, but what part of the cortex?

***Motor circuit** ⟹ primary motor cortex, supplementary motor cortex, premotor cortex, somatosensory and association cortex. Input will come from the cortex to the striatum (**mainly putamen**), then to the GPi through direct and indirect pathways, then to VA and VL thalamic nuclie to the cortex.

***Limbic circuit** ⟹-frontal association areas (anterior part of frontal lobe is called the prefrontal cortex; this area primarily controls social behaviors.)

-limbic lobe (cingulate gyrus, isthmus, parahippocampal gyrus, ancus)

-hippocampus

-amygdala

***Association circuit** ⟹ association areas (frontal, parietal and temporal lobes).

All these circuits receive input from the cortex and send their output back to the cortex (**reciprocal connection**). Recall that the cortex affects motor activity through pyramidal and extrapyramidal tracts.

Limbic circuit:

It starts from the cortex (frontal association areas, limbic lobe, hippocampus, amygdala) then it sends information to the striatum. Which parts of striatum? **Nucleus accumbens and ventral striatum.**

"Nucleus accumbens is formed by the union of ventral parts of head of caudate and putamen. Anatomically it belongs to the basal ganglia but functionally it's related to the limbic system."

After that, information is sent to the internal segment of globus pallidus (GPi), then to the thalamus (through pallidothalamic fibers). Which parts of the thalamus? **Ventral posterior nucleus and dorsomedial nucleus**. Then output returns back to the cortex (**anterior cingulate cortex (limbic system)** and **prefrontal cortex/orbitofrontal cortex (**the anterior part of the frontal lobe, responsible for social behavior).

Cortex (frontal association areas, limbic lobe, hippocampus, amygdala) ⇨ striatum (nucleus accumbens and ventral striatum) ⇨ Gpi ⇨ Thalamus (ventral posterior nucleus and dorsomedial nucleus) ⇨ back to the cortex.

What are the functions of the limbic system?

1- Regulation of emotional, motivational and affective aspects of behavior (السلوك).
2- Motor expression of behavior (التعبير عن الانفعالات) by facial expressions, posture and gesture (إيماء).
3- Memory.

Note: As mentioned above, patients will lose facial expressions (**mask face**) in Parkinson's disease. This indicates that the basal ganglia has a role in controlling limbic system not only a motor activity.

Caudate nucleus is related to **C**ognition, while the putamen is important for motor activities.

Association circuit:

It starts from cortical association areas (where ideas, plans and the desire of COMPLEX movement are generated and include: frontal, parietal (area 5 and 7)

and temporal), then it sends information to **caudate (mainly)** and nucleus accumbens.

After that, information is sent to GPi then to the thalamus. Which parts of the thalamus? **Ventral anterior and Centromedian**. Output then returns back to the cortex (ventral anterior send output to the motor cortex and prefrontal association areas while centromedian sends to wide areas of the cortex, that's why centromedian is considered as a part of reticular activating system that keeps you fully conscious).

Cortex (frontal,parietal,temporal) ⇨ caudate(mainly) and nucleus accumbens ⇨ GPi ⇨ thalamus(Ventral anterior and centromedian) ⇨ cortex(VA:Motor cortex and prefrontal association areas, centromedian: wide areas of the cortex).

What are the functions of association areas?

1- Allow you to perceive (recognize) what you feel, for e.g.: visual association areas 18/19 in the occipital lobe allows you to understand what you see.
2- Cognition (planning for complex motor activities).

Important note:

"When a new task has been practiced and well learned, activity in the association circuit decreases and the motor circuit becomes active instead".

So again, what are the functions of basal ganglia?

1- Motor function 2- emotional, motivational..(Limbic system) 3- cognition.

Note that Rigidity is the most disabling symptom of Parkinson's as it's responsible for ataxia.

Dyskinesias (other basal ganglia disorders resulting in abnormal movements):

1-**Athetosis**:

Athetosis

Is a symptom characterized by slow, involuntary winding movements (snake like movement). It affects the extremities (distal muscles) in particular as windings, continuous abductions and adductions.

You might think that the patient is mentally disturbed, but in fact these are involuntary movements as a result of basal ganglia disorders (particularly putamen lesions).

It might follow trauma, injury at birth or loss of blood supply to the brain.

2-**Hemiballism** (ballism ⇨ throwing):

Violent abnormal movements originating mainly from the proximal muscles, caused by lesions in the subthalamic nucleus.

Symptoms are contralateral to the lesion; (lesion on the right ⇨ symptoms appear on the left half of the body)

Most hyperkinesia disorders follow this mechanism:

(Recall that the subthalamic nucleus activates GPi)

Suppression of subthalamic nucleus ⇨ underactive Gpi ⇨ disinhibition of ⇨ thalamus ⇨ greater facilitation of cortex ⇨ Hyperkinesia

However, in cases of chorea and **athetosis**: the problem starts at the beginning of the indirect pathway (destruction of striatum cells ⇨ over active globus pallidus external segment ⇨ suppression of subthalamic nucleus ⇨ no glutamate ⇨ underactive GPI), in contrast to hemiballism in which the lesion directly affects the subthalamic nucleus and reduces its activity.

3-**Tardive dyskinesia**:

Iatrogenic disorder which occurs as a result of long term use of anti-schizophrenia drugs. Tardive dyskinesia is characterized by abnormal reflexes (abnormal tongue movements, unusual facial expressions and so on…).

4- **Wilson disease** (or hepatolenticular degeneration):

Is a rare inherited disorder of **abnormal copper metabolism** that causes copper to accumulate in your liver, brain (particularly in the lentiform nucleus) and other tissues. Manifests as psychiatric disturbances and liver disorders (liver cirrhosis).

Signs and symptoms:

-Parkinson-like symptoms (tremors, rigidity..) due to destruction of the lentiform nucleus.

-psychiatric disturbances

-Copper deposits forming a brown-yellow ring that appears to encircle the cornea of the eye (**kayser-Fleischer ring**).

-An MRI of a patient with Wilson disease could show cavities in the lentiform nucleus as a result of copper deposition.

-Aminoaciduria (copper deposits in kidneys).

Dedication to:

Asil Habash,Ghaydaa Hwamdeh,SireenAlkhateeb,Salsabeela Banihamad,Dania Tobasy,shatha khader.

“Life isn’t about waiting for the storm to pass; it’s learning to dance in the rain.”

Done by:

Rawand Ahmad&Farah Jamal