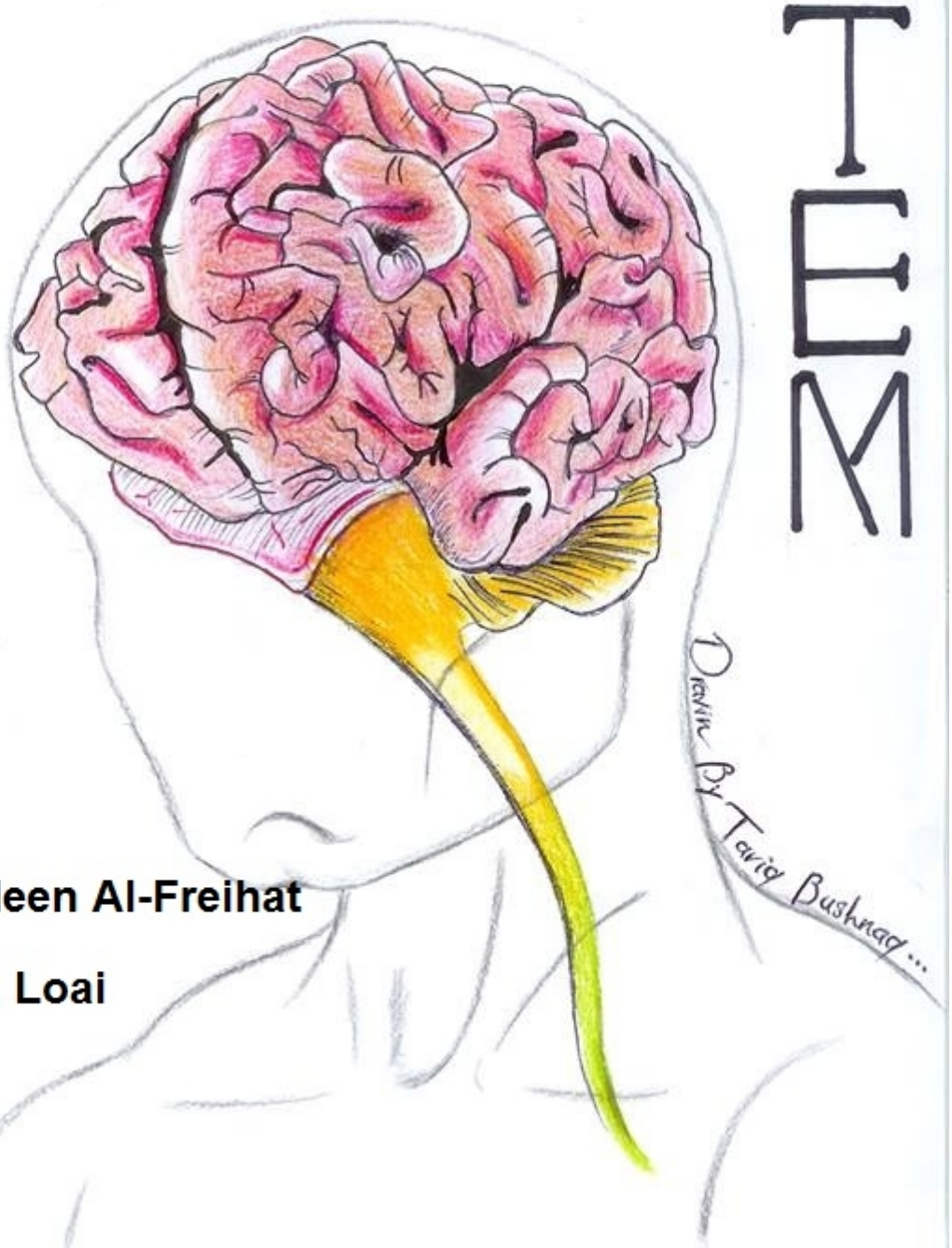
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ● Sheet
- ○ Slide

- ○ Anatomy
- ● Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
- ○ Pharmacology
- ○ PBL



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Lec #: **10**

Basal Ganglia

We talked about motor system. There are many motor functions of spinal cord, mainly reflexes. And, extrapyramidal control that comes from the sub-cortical region for REGULATION resulting in INVOLUNTARY actions. Also, there are orders come from the cortex resulting in VOLUNTARY actions. This motor system must be controlled and regulated.

REGULATORS of the motor system

They don't send information to alpha and gamma motor neurons directly. These Regulators include:

1. **Basal Ganglia**
2. **Cerebellum**

BASAL GANGLIA

- Components of the basal ganglia
  - Function of the basal ganglia
  - Connection and circuits
- Functional circuitry of the basal ganglia
  e.g., direct and indirect pathways, transmitters
- Symptoms and disorders discussed

Structure

All Parts of Basal Ganglia are subcortical. Many parts are connected in specialized circuits. Their Functions include MOTIVATION and REGULATION of the cortex.

Basal ganglia is divided **FUNCTIONALLY** into:
1. Pallidal complex: has inhibitory effect.
2. Striatal complex: has activating effect.

The Balance of these two circuits determines the function of the cortex. The cortex receives many information, so it has to determine which is important, which to continue with, which must be activated or inhibited, etc. this can be done by Basal Ganglia (which is subcortical).

Usually, Basal ganglia (nuclei) has an inhibition effects on the cortex to reduce the basal line activities and activate the important actions. Basal Ganglia receives feedback from the cortex, if it needs something to be activated, it will be disinhibited. What does that mean?

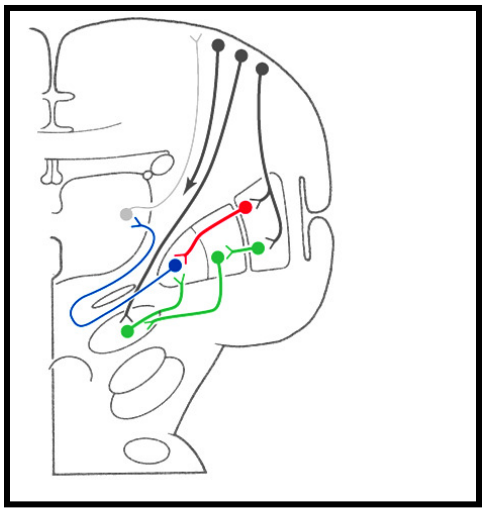
In Normal status, the basal ganglia inhibits the cortex. If there's a decision or action to be made, the cortex will check that with the basal ganglia. The connections within the ganglia will see if this action or decision is important or not and whether it should reach the cortex or not.
If YES → basal ganglia will be inhibited → NO inhibition on the cortex → actions.

"Basal Ganglia has TONIC inhibition on the cortex"

ANATOMICALLY, basal ganglia has 2 parts:

1. VENTRAL part 2. DORSAL part

And each has pallidal and striatal parts.



This diagram shows that there are different connections between the cortex and basal ganglia. (We'll not care about the details of these connections)

Anything that will go to the cortex must pass through the thalamus. The cortex is connected to all parts, but eventually the loop must end in the thalamus before reaching the cortex. The functions of the thalamus include PROCESSING and DECIDING if certain part must be activated or not!

AGAIN!

When there's NO order reaching the cortex → the cortex is inhibited by the basal Ganglia.

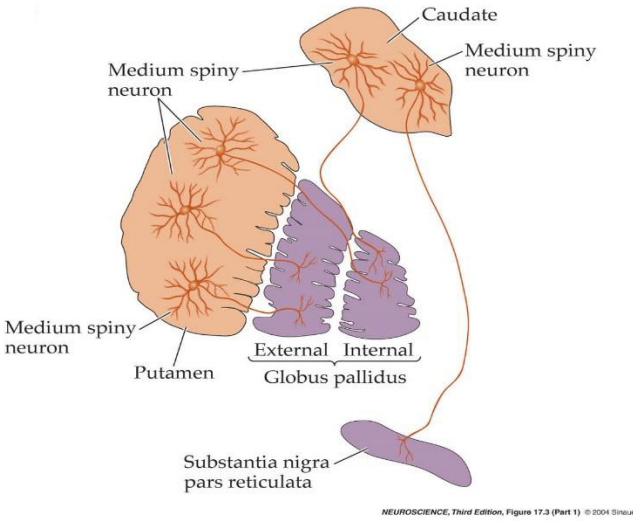
If the cortex sends an order, the basal ganglia will be inhibited.

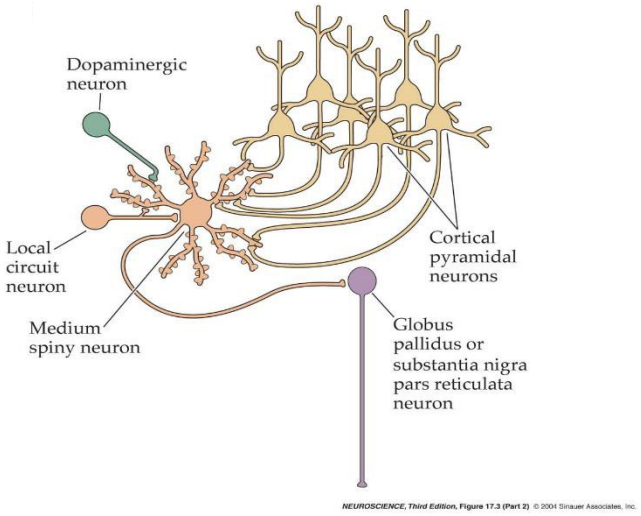
Some connections from brain stem will regulate basal ganglia and determine if this action is important. But SIMPLY…

If the cortex wants to do and order, the basal ganglia will be inhibited.

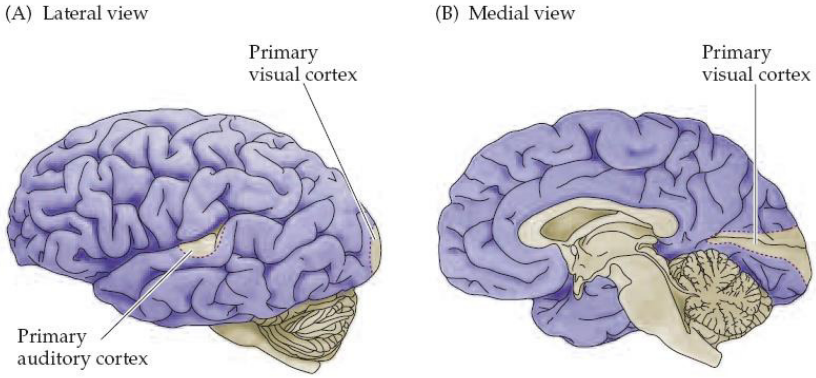
The circuit is going like that:
The cortex will send the order to the basal ganglia to be regulated. Then, it'll be sent to the thalamus that gives feedback to the cortex.

The regulation and processing in the basal ganglia require big neurons with multi dendrites. These neurons are called "**MEDIUM SPINY NEURONS**". These neurons are found more on striatal complex of ventral and dorsal parts of basal ganglia. They will take the information and make very complex processing due to their big spiny dendritic processes. They are similar to Purkinji cells of cerebellum. They have the ability to do complex processes and memory.





Connections and circuits



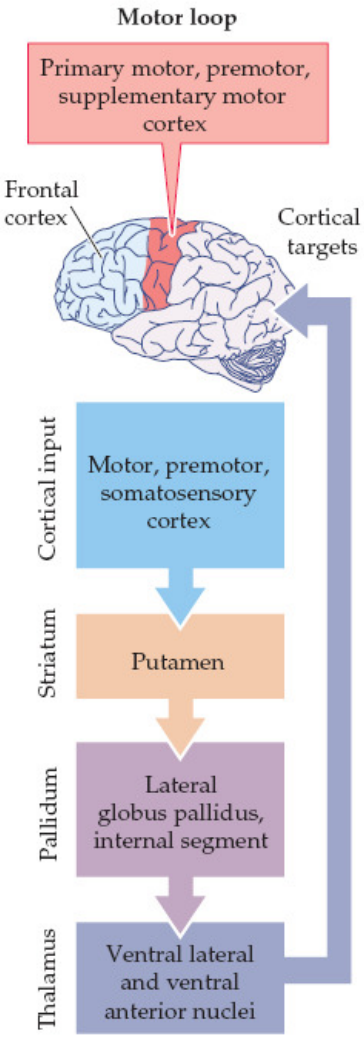
Basal Ganglia connects with and regulates the entire cortex, not only the motor cortex (**EXCEPT** the primary sensory area/the auditory and visual areas). It regulates ALL parts of cortex (motor activation, our emotions, our decisions, etc.) & this explains why who has deficit in the basal ganglia hasn't only motor symptoms, but later the patient will develop deficits in cognition and dementia.

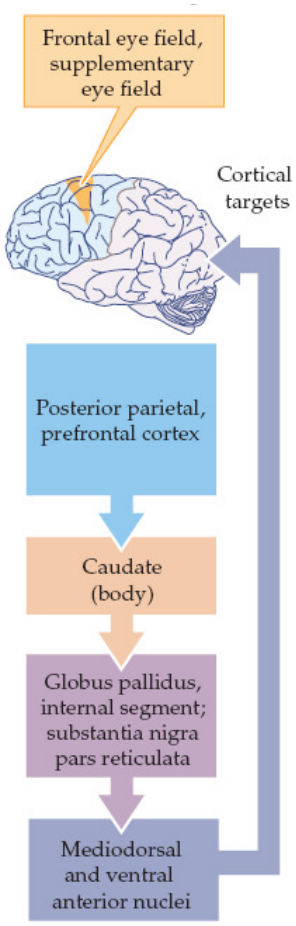
There are many loops because it has to connect all parts of the cortex. Each part of the cortex targets certain part or segment of basal ganglia.

ANATOMIC LOOPS:

1. MOTOR LOOP

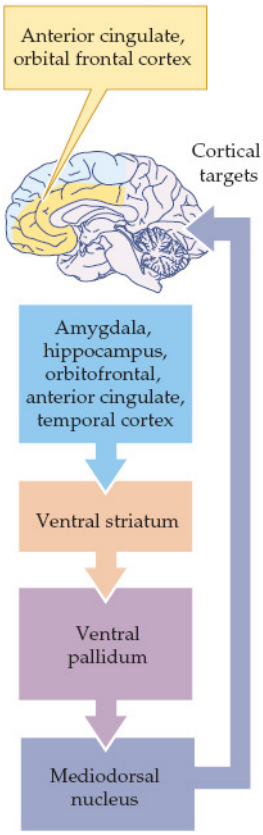
From motor cortex to basal ganglia to the thalamus (ventral lateral and ventral anterior nuclei) that send feedback to motor nuclei. Deficit in motor loop will lead to deficit in motor functions.





2. VISUOMOTOR LOOP

From visual cortical areas in frontal lobe mainly (& some in parietal) to basal ganglia to thalamus (mediodorsal and ventral anterior nuclei) that send feedback to the targeted area of the cortex.



3. MOTIVATIONAL LOOP

From the areas that are related to decisions and actions in prefrontal and rostral part of frontal cortex to basal ganglia and through the mediodorsal and ventral anterior nuclei in the thalamus to the related cortical areas.

4. EXCUTIVE LOOP (the dr.didn't mention it)

Notice that among all the loops, the main differences are: the area where it begins and which part of the thalamus is involved.

There're 2 types of the cortex:

1. **Neocortex**: 6 layers, in sophisticated animals.
2. **Paleocortex** or **allocortex:** 3-5 layers, old, less processing capacity.

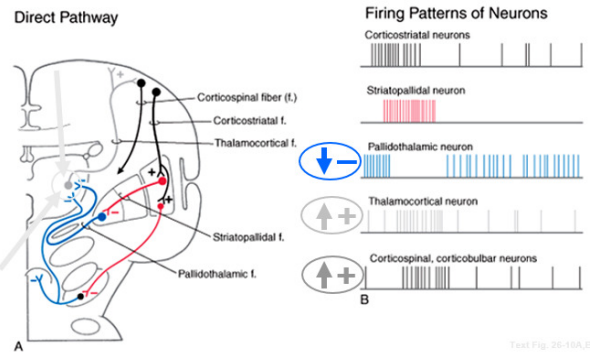
The motivational loop involves ventral part of dorsal nuclei in ventral lobe. Thus, it begins from paleocortex not neocortex and these 2 kinds of the cortex are found in the lower and inner part of the brain. This pathway is related to emotions.

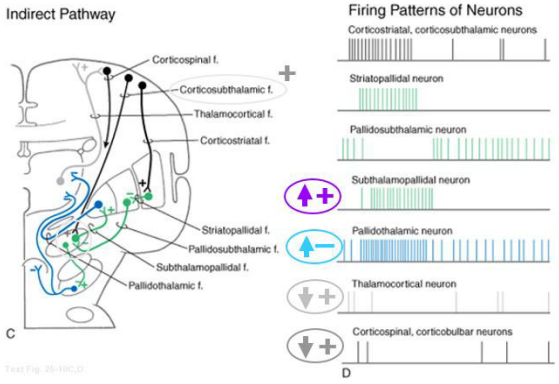
The neocortex requires processing by the thalamus but the paleocortex doesn't because it doesn't involve complicated processes. (This will be further explained in limbic system)

FUNCTIONAL LOOPS:

1. **Direct pathway**: inhibition of basal ganglia → activation of the cortex.
2. **Indirect pathway:** Activation of basal ganglia → inhibition of the cortex.

The balance between these 2 pathways determines the amount of activation of the cortex.





Modulators

They are small centers that work through 2nd messenger type of receptors to change the function and response of basal nuclei.

The balance between the activation and inhibition can be done mainly by the balance between **glutamate** and **GABA** neurotransmitters. The cortex releases glutamate and the basal ganglia contains many GABA neurons.

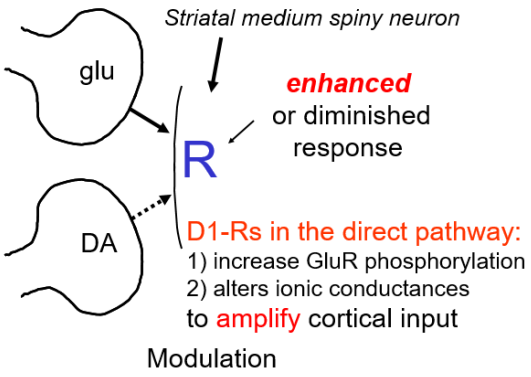
These modulators include:

1- Subthalamic nucleus: some people consider it as a part of the basal nuclei. It has an inhibitory effect (part of indirect pathway).
Active subthalamic nucleus → the indirect pathway is active → inhibition of the cortex.
2- Nigral complex
3- Parabrachial pontine reticular formation.
4- Zona inserta
5- Ventral basl nuclei

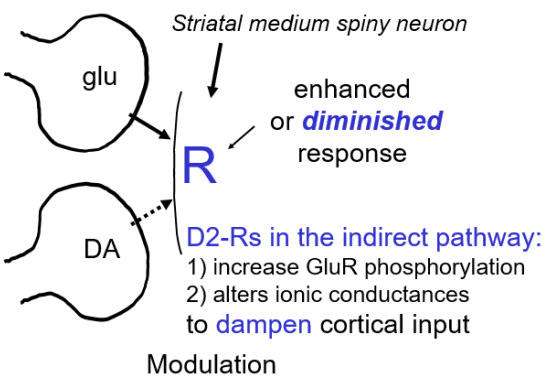
NIGRAL COMPLEX

It has modulation from the substance of basal nuclei to striatum mainly and flushes dopamine NT.
It works on 2 types of G protein receptors.

1. D1 receptor → ↑ glutamate from basal nuclei → excitation of the circuit.



2. D2 receptor → ↓ glutamate → inhibition of the circuit.



D1 receptor activates the direct pathway and D2 inhibits the indirect pathway. So the net effect of dopamine:
↑ direct pathway and ↓ indirect pathway → Excitation of the cortex.

Again: the balance between the direct and the indirect pathways determines if the cortex will be activated or inhibited.
↑ direct → ↑ cortex
↑ indirect → ↓ cortex

DISORDERS

Insufficient direct output or excess indirect output → inhibition of the cortex → ↓ the motor output from motor complex → **hypokinetic disorders.**

Excess direct output or insufficient indirect effect → activation of the cortex → ↑ motor output → **hyperkinetic disorders.**

The cortex will be very active without control or regulation in the hyperkinetic disorders → ↑ motor orders even if the order isn't chosen by the basal ganglia → involuntary & undesirable movements in different forms depending on which parts of the body that are affected.

HYPERKINETIC SYMPTOMS

1. Chorea (dance-like)
2. Ballismus (usually hemi-ballismus): sudden / repetitive / lower and upper limbs
3. Dystonia: ↑ tension / in trunk and neck usually
4. Athetosis: can be
   A- chorea like athetosis (Choreoathetosis)
   B- athetotic dystonia

These types are classified depending on the location mainly because the symptoms are very similar.

If Ballismus is severe, it appears like chorea. Chorea includes increase of the voluntary movement in comparison to Ballismus.

PARKINSON'S DISEASE

- Loss of dopamine cells in substantia nigra→ ↓ dopamine modulation on basal nuclei → the cortex is inhibited → hypokinetic

Notice that in normal person (the right), the substantia nigra appears black. But in parkinson's disease (the left), the pigment is lost (loss of the neurons).

SYMPTOMS

- At the beginning, it affects the motor loop so the symptoms include:
  tremor (distal muscles), bradykinesia, rigidity and loss of postural reflexes.
  If more and more dopamine is lost → the tremor will affect the proximal muscles also.
  The rigidity increases and the movements become very slow → curves of the shoulders and back.
- Then, other loops will be affected like the visuomotor loop →↓blinking of the eyes → dry eyes. Also, the motivational loop might be affected→ less processes in prefrontal lobe → loss of cognition and dementia.

At first, we have slow responses and activation → no feedbacks from the basal ganglia→the cortex will try to compensate, → more active (initially, the patient is moving slowly, and then his movements become faster.

- Depression and dementia may occur due to less processing in the prefrontal lobe.

TREATMENT (to compensate the lost dopamine)

1- L-Dopa (dopamine precursor) and drugs that increase dopamine functions. But they cause increase in dopamine in all parts → the cognition will be affected → psychiatric disorders (side effects)
2- Deep brain stimulation:
   because in Parkinson's disease, the neurons are lost. So here we're trying to stimulate the small number of the neurons. It's powerful in treating Parkinson's disease because dopamine

modulation back to normal. The problem is that the neurons will die with time and age and with more stimulation by Deep brain stimulation more neurons are going to die. To solve this problem, we can activate of the indirect pathway by increasing the activity of substantia nigra or GP.

3- New Novel drugs

A- Anti- Ach: very common. If Ach is decrease, the basal ganglia will be inhibited → ↑ activity of cortex

B- Anti-glutamate

C- Anti-AMPA

HYPERKINETIC DISORDERS

1. Huntington's chorea
2. Dystonia
3. Tardive dyskinesia
4. DOPA-induced dyskinesia
5. Hemiballismus
6. Tourette's syndrome

Most of these disorders are genetic. Others are either environmental or drug-induced.

Chorea	Ballismus	Athetosis
Rapid	Rapid	Slow
Involuntary	Involuntary	Involuntary
Non-stereotypical	Non-stereotypical	Non-stereotypical
Semi-purposeful / non-purposeful	Non-purposeful	Non-purposeful
Dance-like	violent flinging movement	writing
More on distal	More on proximal	Has propensity affecting upper limb

SORRY for any mistake

GOOD LUCK!

This sheet is dedicated to Riham Al-Hindi and RaghdaYasin :P.