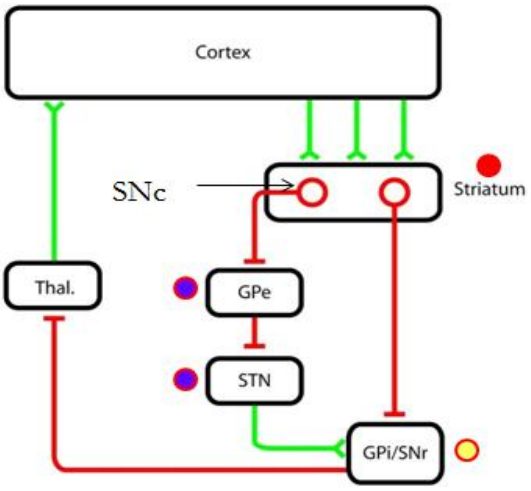
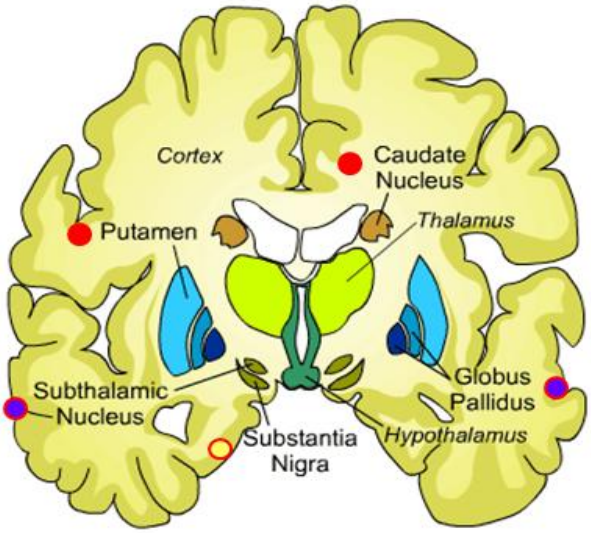
Unit VIII – Problem 5 – Physiology: Basal Nuclei

- **A simple way to explain how does movement occur:**
  - The program of the movement is present in the pre-motor area → from there it will be sent to the primary motor cortex → and it will travel through the spinal cord → to reach lower motor neurons which will terminate in the neuromuscular junction causing contraction of the muscle (movement).
    - ✓ Notice that there are other important actions occurring during this process which will be mentioned with more details in the points below.
- **The idea of movement is generated in the pre-frontal cortex** → then fibers will move from the pre-frontal cortex to supplementary area and pre-motor area which has a lot of programs for the same movement → these programs will be sent to the basal ganglia through a huge number of fibers → basal ganglia will chose one of these programs and send it back to the pre-motor cortex → then, fibers will go to the primary motor cortex → eventually resulting in movement (as it was mentioned above).
  - **Note: if there is any lesion to the basal ganglia:**
    - ✓ The basal ganglia will be unable to chose a program for the movement → resulting in hypokinesia (which is seen in Parkinson's disease).
    - ✓ The basal ganglia might chose more than one program resulting in hyperkinesia (and example is chorea disease).
- **The major player in the basal ganglia is globus pallidus** (which is usually inhibiting the thalamus (through the release of GABA: GABAergic neurons are always inhibitory in CNS) → resulting in further inhibition of the cortex (inhibition of movement).
- **If there is sufficient cortical stimulation** → this is going to excite the putamen → resulting in inhibition of globus pallidus internus → therefore, the thalamus will be stimulated → initiating the movement.
- **Notes:**
  - ↑ **inhibition of thalamus**: hypokinesia.
  - ↓ **inhibition of thalamus**: hyperkinesia
- **There are two types of inputs to the basal ganglia** (going mainly to the striatum which is composed of: caudate + putamen):
  - **More input is going to the putamen**: from motor and pre-motor areas.
  - **Less input is going to caudate**: from frontal eye field. Example: if you are looking to 3 persons at the same time, input from frontal eye field will travel to the caudate part of basal ganglia → so you can chose 1 person to look at or focus on.
- **Output:**
  - **Efferents from putamen will terminate in globus pallidus** → for body movements.
  - **Efferents from caudate will terminate in substantia nigra pars reticulata**→ for eye movements.
- **The main cells in striatum are called Medium Spiny Neurons (MSNs).**
  - **All input received by MSNs is excitatory** (there is release of glutamate).
  - **MSNs are always in a hyperpolarization state**. Fibers from these cells reach globus pallidus but they are silent (which means that they are not interfering with it).
  - **If the stimulation/input coming to MSNs from the cortex is strong enough** → they will fire (will be stimulated) → leading to removal of globus pallidus inhibitory effect on the thalamus → therefore, movement will occur.
- **There are direct and indirect pathways terminating in globus pallidus internus** (which is normally expressing inhibitory effect on thalamus to inhibit movement). As it was mentioned above, if globus pallidus internus is inhibited (its inhibitory effect on thalamus is removed), movement is initiated.
  - **Direct pathway**: it is causing movement by inhibiting globus pallidus internus.
  - **Indirect pathway**: causes no movement by stimulating globus pallidus internus.

- **Overview of basal ganglia organization:**
  - **Input**: caudate + putamen (together called striatum).
  - **Output**: substantia nigra pars reticularis (SNr) and globus pallidus internus (GPi)
  - **Intrinsic**: subthalamic nuclei (STN) and globus pallidus externus (GPe).
  - **Neuromodulator**: sabstantia nigra pars compacta (SNc).





- **The cortex has 150 million fibers (1 million of them are composing the pyramidal tract) → going to striatum which has 30,000 fibers → going to globus pallidus externus which as 100 fibers.**
  - **So there is a process of convergence (large dendritic trees and decreasing cell number).**
- **Normally when there is no movement:**
  - **MSNs in striatum are silent** → substantia nigra pars reticulata and globus pallidus internus are releasing the inhibitory neurotransmitter GABA → thus superior colliculus and motor cortex are inhibited → no movement.
- **When there is movement**:
  - **Cortex is releasing stimuli which are strong enough to → stimulate MSNs →** which will release GABA to inhibit substantia nigra pars reticulata and globus pallidus internus → removing their inhibitory effect on superior colliculus and motor cortex → movement.
- **Basal ganglia is also regulating our behavior and emotions (not only the motor function).**
- **Remember that the main function of basal ganglia is inhibition of excessive unwanted movements**. Therefore, only desired movements are allowed to happen. In addition, basal ganglia is inhibiting all unwanted ideas so we can focus only on one thing or issue.
- **As it was mentioned above, the output of basal ganglia is represented by:**
  - **Substantia nigra reticulata (SNr).**
  - **Globus pallidus internus (GPi).**
    Notice that normally they are tonically active and tonically inhibiting thalamus and superior colliculus (by releasing the neurotransmitter GABA) → thus suppressing movement.
- **If we want movement to occur** → GPi/SNr must be inhibited → so there will be removal of their inhibitory effect on the thalamus → thalamus is stimulated → eventually activating thalamo-cortical fibers → and thus movement occurs.
- **GPi/SNr are under 2 controls from striatum:**
  - **Direct pathway**: which is going directly from striatum to globus pallidus internus. Stimulation of the direct pathway results in movement.

- **Indirect pathway**: which is passing to globus pallidus externus → then to subthalamic nucleus → and eventually to globus pallidus internus. Stimulation of the indirect pathway results in inhibition of movement (no movement).

- **Action selection:**
  - If a lot of stimuli and programs are present (ex. Looking to 3 persons at the same time) → the direct pathway will inhibit globus pallidus internus for the desired action (e.g. choosing only one of those persons to look at) → while the indirect pathway will stimulate globus pallidus internus for the undesired action (e.g. looking at other persons) → eventually there will be strong stimulation of the cortex to cause accurate eye movement toward the desired person.
- **The indirect pathway has 2 parts:**
  - **One which will reach GPi by passing through subthalamic nucleus.**
  - **Another which will directly pass from globus pallidus externus to GPi.**
- **When substantia nigra pars compacta is stimulated** → dopamine will be released to reach MSNs (which are present in striatum).
  - **In the striatum, dopamine will bind to its receptors:**
    - ✓ D1-receptor: which is stimulating the direct pathway.
    - ✓ D2-receptor: which is inhibiting the indirect pathway.

      Note: the outcome from the actions of these 2 receptors would be → enhancement of movement.
  - **Dopamine deficiency**: it will result in hypokinesia (because normally dopamine is enhancing movement → Parkinson's disease).
- **Acetylcholine effects:**
  - **Ach function is opposite to dopamine:**
    - ✓ Inhibition of the direct pathway.
    - ✓ Stimulation of the indirect pathway.

      Note: the outcome from these 2 actions is inhibition of movement.
- **Cardinal signs of Parkinson's disease:**
  - **Tremor at rest**: usually unilateral and then progresses to bilateral.
  - **Rigidity and bradykinesia** → leading to mask-face and making the patient fall easily (there is loss of associated movements).
  - **Micrographia**: because of the presence of tremor → the minimum power/force is used for writing otherwise tremor will occur during writing.
- **In Parkinson's disease** → dopamine is not produced (there is deficiency of dopamine) → therefore, there is no movement.
- **In Huntington' chorea** → there is a lesion in the indirect pathway → so the direct pathway will be predominant → and this will result in stimulation of movement.
- **In hemiballismus** → there is a lesion in the subthalamic nucleus resulting in loss of indirect pathway → sudden violent movements.
- **Surgical treatment of Parkinson's disease:**
  - **Destroying subthalamic nucleus** (removing the indirect pathway). Therefore, movement will be increased.
  - **Destroying the globus pallidus internus.**
  - **Transcranial cutaneual stimulation** → which is enabling the patient to cause repeated stimulation of the basal ganglia.
    - ✓ Electrodes will be implanted in subthalamic nucleus → repeated stimulation will cause neurons of subthalami to enter a refractory period → where they will not be active → and they will act as if there is a lesion in subthalami (lesion of indirect pathway) → resulting in improvement of movement.