Lecture 20 - Basal Ganglia

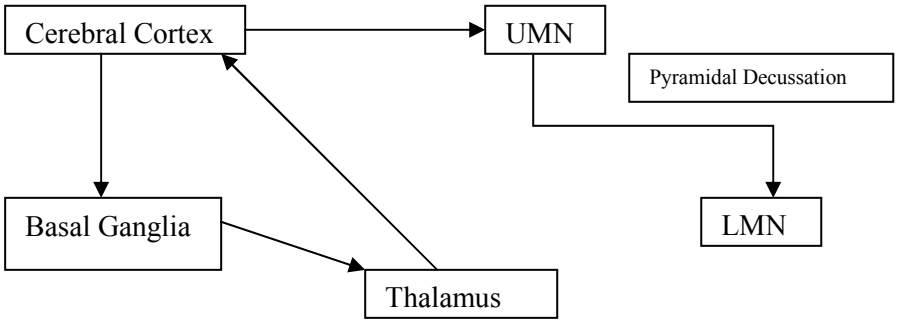
Basal Ganglia (Nolte 5th Ed pp 464)
Damage to the basal ganglia produces involuntary movements. Although the basal ganglia do not influence LMN directly (to cause this involuntary movements when damaged), they influence UMN systems – which in turn influence LMNs. The general function of basal ganglia is: regulation of movement.

Damage on one side….. (Notes)
Just remember: Unilateral damage to basal ganglia causes contralateral symptoms.

Overview of basal ganglia 1 (Nolte 5th Ed pp 464, Fig 19-1/2)
The basal ganglia facilitates wanted movements, and inhibit unwanted movements. Use of the term basal ganglia involves the following structure components: caudate nucleus (telencephalon), putamen (telencephalon), globus pallidus (internal / external segments – Gpi, GPe), subthalamus (diencephalon), & substantia nigra (compact and reticular parts – mesencephalon).

The caudate nucleus and putamen have the same embryological origin – hence together are referred to as the striatum (i.e.: coronal section shows striated appearance – Fig 19-4). Also, the putamen and globus pallidus are apposed anatomically – hence together are referred to as: lentiform nucleus. The substantia nigra (as illustrated in Fig 11-21) consists of neuromelanin (brown pigment).

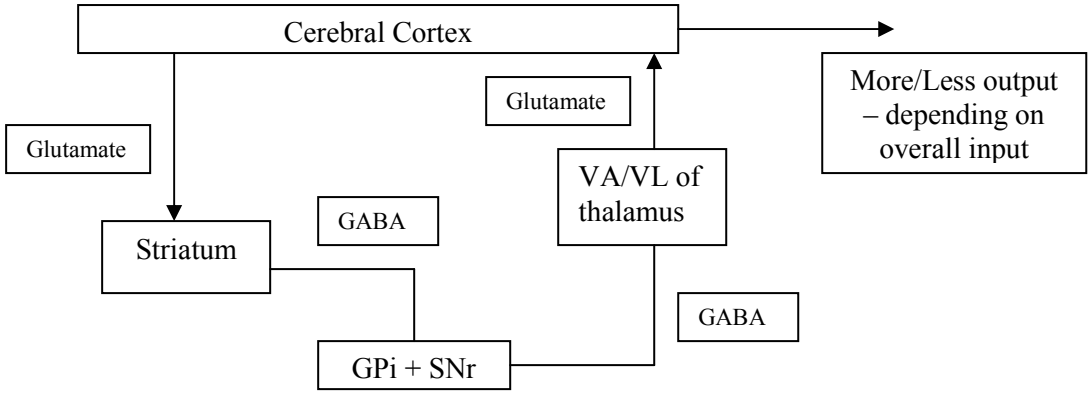
Overview of basal ganglia 2 (Notes, Fig 19-6)
It is important to note that the left basal ganglia affect the right side of the body. This is why; unilateral damage to the basal ganglia produces symptoms in the contralateral half of the body. **Remember this diagram.**



The principal circuitry outlined above is a loop that begins at the cerebral cortex. Fibres from an area of the cerebral cortex project to the basal ganglia, which in turn projects to the thalamus → en route to the cerebral cortex. The cortex integrates these signals and sends output to UMN systems that are involved in movement.

Overview of Basal ganglia 3 (Notes, Fig 19-6)
We mentioned the basal ganglia in a circuitry loop. The particular areas of interest within the basal ganglia are the striatum, globus pallidus interna and substantia nigra pars reticulata. Outputs from the cerebral cortex reach these areas, and outputs from these areas reach VA/VL of thalamus. The thalamus (as mentioned above) projects back to the cerebral cortex (thalamocortical projections). **Remember this diagram (direct pathway).**

The neurotransmitters used in this pathway are highlighted in the diagram. Excitatory pathways have an arrow – while inhibitory pathways do not have an arrow.



Anatomy of basal ganglia (Nolte 5th Ed pp 465-467, Fig 19.1-19-5, Netter Plate 104)
The basal ganglia includes five major nuclei. The caudate nucleus and putamen together are a single anatomical unit → striatum. This is because when inspected in a coronal section, the internal capsule (located between them – Fig 19-1) appears striated. This is due to small strips of gray mater extending between these two structures.

The putamen is anatomically closely related to globus pallidus → together they are referred to as the lentiform (lenticular) nucleus. The globus pallidus is anatomically divided into two distinct regions namely: globus pallidus internal, globus pallidus (GPi) external (GPe).

The subthalamus is located near where the internal capsule becomes the cerebral peduncle. The substantia nigra is made up two components: pars compacta & pars reticulata. The pars compacta contains dopaminergic neurons (Fig 11-21) – it is this that degenerates in Parkinson's disease.

Blood supply of basal ganglia (Nolte 5th Ed pp 479, Netter Plate 132/133)
Thus the three main branches of blood supply to the basal ganglia is: **penetrating branches of posterior cerebral & posterior communicating arteries** (subthalamus, substantia nigra)**, lenticulostriate arteries** (striatum) **& anterior choroidal artery** (globus pallidus)**.**

Circuitry of basal ganglia: parallel inputs (Nolte 5th Ed pp 468 – 478)
Refer to the diagram I drew above for the circuitry of basal ganglia.

The circuitry of basal ganglia incorporates parallel inputs (see diagram from lecture → parallel inputs represented by numerous lines projecting from cortex) from most cortical areas to the striatum (putamen, caudate nucleus, nucleus acumbens). What is the *nucleus acumbens*? Note in Fig 19-4, the head of the caudate nucleus appears to be continuous with the putamen → This portion of continuity is referred to as **nucleus acumbens.**

Some points to consider:

- **Putamen** receives input from cortical areas such as: primary motor cortex, premotor cortex, supplementary motor cortex, primary somatosensory cortex
- **Caudate nucleus** receives input from cortical areas such as: association cortex, prefrontal cortex (frontal eye fields).
- **Nucleus acumbens** receives input from cortical areas such as: limbic cortex, hippocampus, amygdala.

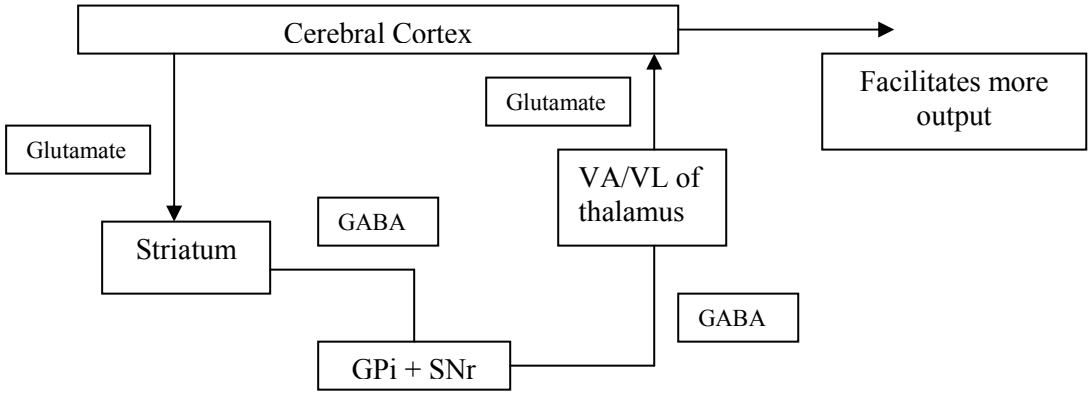
Note: we have only considered the cortical inputs to the striatum. *What about substantia nigra?* Well, the substantia nigra projects to all areas of the striatum by way of very fine axons (Fig 19-9). By far the most important inputs are the cortical ones. (**Note: This was not in the lecture notes).**

Circuitry of basal ganglia (Nolte 5th Ed pp 473, Fig 19-9)

We now have received all inputs from the cortex to the striatum (i.e.: caudate, putamen, nucleus acumbens). From here the projections can follow a DIRECT or INDIRECT PATHWAY.

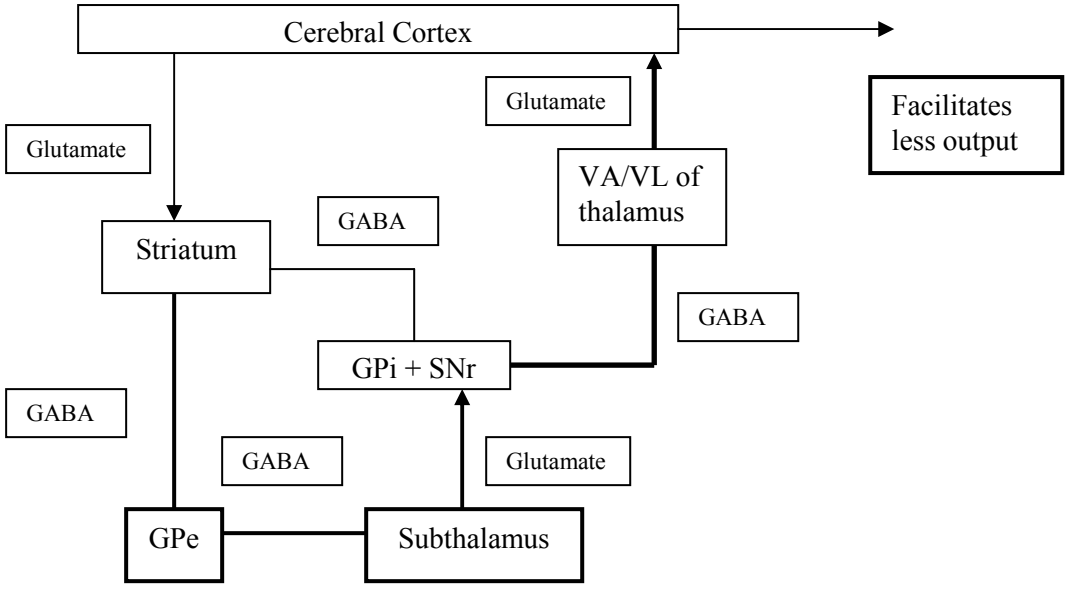
The DIRECT PATHWAY facilitates cortical output. The INDIRECT PATHWAY inhibits cortical output.

Direct Pathway (we are now at striatum level)
Striatal efferents converge on globus pallidus internal segment and also reach the substantia nigra pars reticulata. From here, the internal pallidal segment projects to the thalamus – via two collections of fibres: 1) lenticular fasciculus, 2) ansa lenticularis. The ansa lenticularis joins the lenticular fasciculus → in the thalamic fasciculus → this enters VA/VL of thalamus. This now projects to the frontal and other cortical areas completing the circuit.

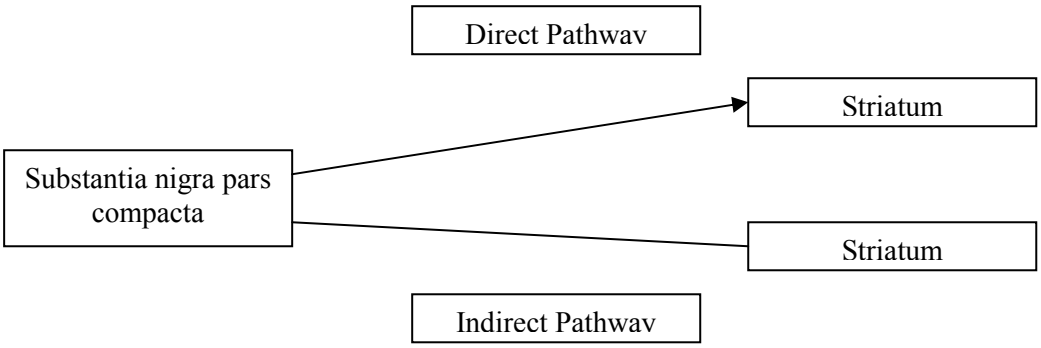


We mentioned: DIRECT PATHWAY → facilitates cortical output. How? Imagine an excitatory synapse is worth +1, while an inhibitory synapse is worth -1. Thus the above circuit will produce: +1, -1, -1, +1. Multiplying these will obtain = +1. Therefore direct pathway must have a +ve effect on cortical output → facilitate cortical output. Note also that excitatory pathways use glutamate and inhibitory pathways use GABA.

Indirect Pathway (we are not at striatum level)
Striatal efferents converge on globus pallidus external segment. The external segment projects to the subthalamic nucleus (excitatory nucleus) via the subthalamic fasciculus. The subthalamic nucleus now provides a powerful excitatory input to GPi/SNr neurons → project to the thalamus (VA/VL) → project to the cerebral cortex. Note: Indirect pathway in **bold.**



Effects of dopamine on direct & indirect pathway (Nolte 5th Ed pp 478)
The substantia nigra is composed of two parts. The pars reticulata is involved in both the direct and indirect pathway, and is composed of non-pigmented cells that are more loosely packed. The pars compacta, on the other hand, is composed of closely packed pigmented neurons. These neurons use dopamine as their neurotransmitter. These neurons project to the caudate nucleus and putamen (striatum). The **bottom line** here is: dopamine promotes movement altogether. How? Because dopamine **promotes** the **direct pathway**, hence **increasing** cortical output → therefore facilitating movement, while it **inhibits** the **indirect pathway (inhibitory pathway)**, hence **increasing** cortical output → therefore facilitating movement.



How can dopamine be excitatory and inhibitory? (Notes)
Notice that dopamine is excitatory to the direct pathway and inhibitory to the indirect pathway (also known as: inhibitory pathway). How can one neurotransmitter elicit two different functions? This is because: it depends on the type of receptor dopamine binds to on the target cell. Thus the target cells can express D1 or D2 receptors.

DI receptors: Dopamine binds to D1 receptors → stimulates adenylate cyclase
D2 receptors: Dopamine binds to D2 receptors → inhibits adenylate cyclase

Disorders of basal ganglia: Parkinson's disease (Davidson's Book of Medicine Chapter 14)

Parkinson's diseases is the most common disease of the basal ganglia. It results due to degeneration of dopaminergic neurons in the substantia nigra pars compacta region. About 70-80% of these neurons die.

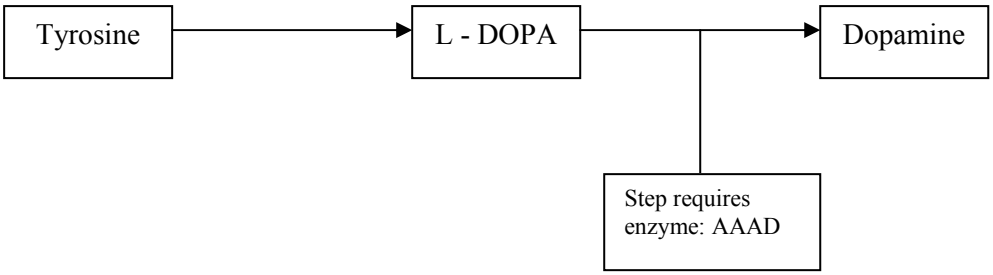
Aeitology
The cause is largely unknown, although genetic inheritance of a-synuclein is being investigated. Also MPTP (methyl-phenyl-tetrahydropyridine) has proven to cause severe parkinsonism in drug abusers – it is a chemical injected by drug abusers – chemical taken in by dopamine neurons → affects mitochondria → neurons die.

Symptoms
Remember: TRAP.

- T – resting tremor
- R – rigidity
- A – akinesia / hypokinesia / bradykinesia
- P – postural instability

Degeneration of SNc in Parkinson's disease (Davidson's Book of Medicine Chapter 14)
So why does death of SNc cause Parkinson's disease. Remember: SNc is composed of dopaminergic neurons → dopamine has excitatory effect on direct pathway (facilitates movement) and inhibitory effect of indirect/inhibitory pathway (facilitates movement). Thus, dopamine on the whole **facilitates movement**. Now → dopaminergic neurons die → no dopamine → direct pathway not activated as much (decreased output) / loss of inhibition to indirect pathway (increased output) → overall: **movement is lost!**

Treatment of Parkinson's Disease (Davidson's Book of Medicine Chapter 14)
Pathway that makes dopamine:



Treatment regime includes:

- L-DOPA / carbidopa (decarboxylase inhibitor)
  - L-DOPA is given orally. But L-DOPA is converted to dopamine in the peripheries by AAAD. But to reduce this carbidopa (decarboxylase inhibitor) is given → inhibits the enzyme → more L-DOPA remains.
  - Therefore more L-DOPA actually enters the brain via the BBB.
  - Once in the brain, it gets converted to → Dopamine (by AAAD) → Dopamine binds to dopamine receptors on striatal neurons.
- Dopamine agonists (bromocroptine D2 agaonist):
  - These directly bind to dopamine receptors on striatal neurons
- MAO-B inhibitors (selegiline, deprenyl):
  - This reduces dopamine metabolism outside the neuron, so more dopamine is available to bind to striatal neurons.
- Experimental:
  - Here, they don't treat "dying neurons", rather they let them die. Apparently treatment causes more death. **Treat Parkinson's by letting dopaminergic neurons die!**

Disorders of basal ganglia: Huntington's Disease (Davidson's Book of Medicine Chapter 14)
Huntington's disease results due to degeneration of striatal neurons (GABAergic neurons). This degeneration is because the lateral ventricle enlarged, therefore caudate and putamen

are affected (Note: These are right next to lateral ventricle). These neurons produce GABA – which has inhibitory effects.

Aeitology: The cause is genetic – autosomal dominant (50% chance of offspring getting it) – expanded CAG repeats in huntingtin gene.
Symptoms: Chorea (dance like movements), Personality change (ugly + abusive), ↓ cognitive function.
Treatment (to inhibit chorea): dopamine antagonists (haloperidol), dopamine depletion (reserpine). Basically trying to reduce cortical output → chorea stops.

Degeneration of striatum in Huntington's disease (Nolte 5th Ed pp 479)

Huntington's disease is characterised by chorea movements. This seems to occur due to underactivity of the indirect/inhibitory pathway. Note the subthalamus is involved here. So damage to one subthalamic nucleus causes contralateral hemiballismus (i.e.: the reason for contralateral is because basal ganglia projects to ipsilateral cortex → which controls contralateral body). That is: subthalamus does not stimulate SNr + GPi → therefore thalamus is not inhibited enough → therefore increase cortical output → ballistic movements.

Bottom line: Damage to one subthalamic nucleus causes hyperactivity of the contralateral side of body.