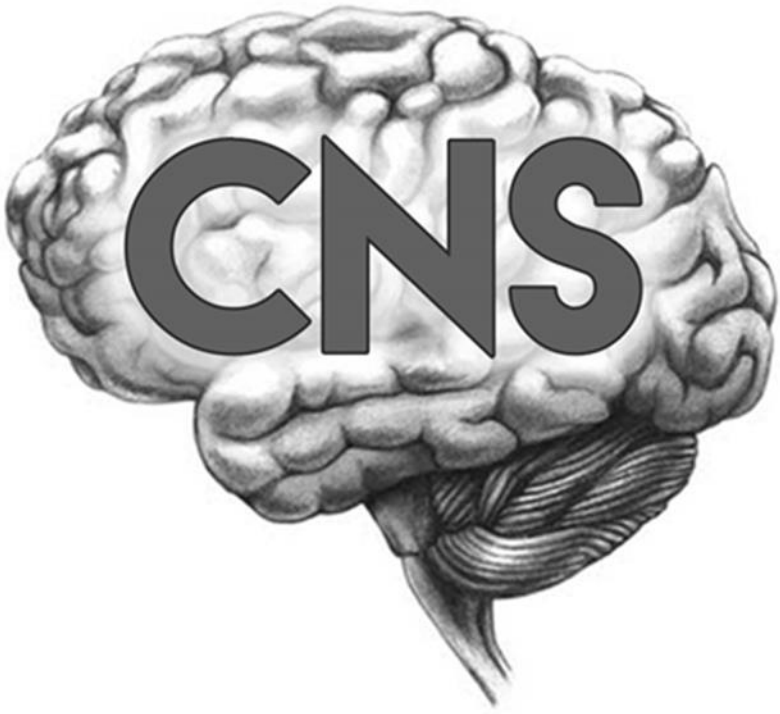

PHYSIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

7

Subject

Basal Ganglia

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Date: 00/00/2016

Price:

Notes:

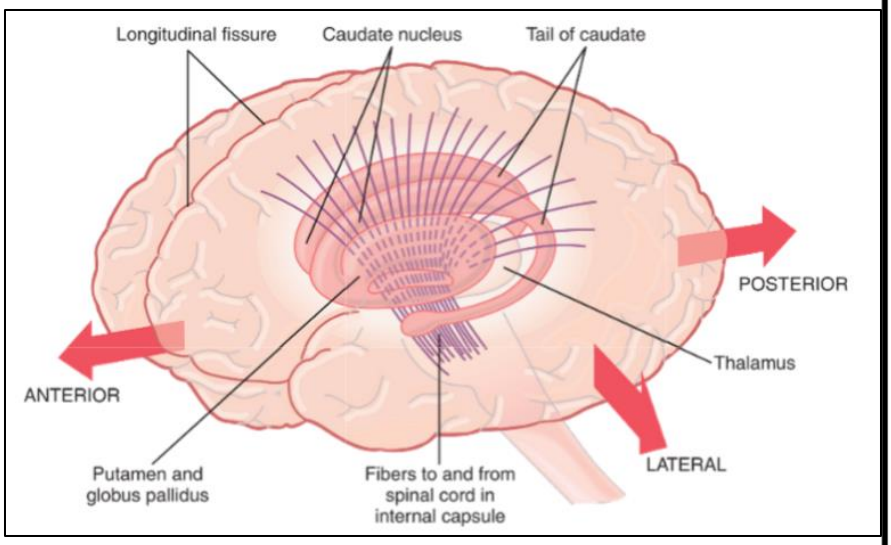
- This sheet is written according to the record of section 3.

- This sheet is not long. The material is only 13 pages (full of figures). There's a summary and 18 review questions at the end of the sheet (5 pages).

- It's recommended to study Dr. Faraj's lecture on Basal Ganglia before you read this sheet (the figures are better here, though).

- Contents:

Basal Ganglia (Nuclei):



- **Anatomy of the Basal Ganglia:**

The basal ganglia are the basal nuclei of the cerebrum that are present on each side of the brain and include:
1- Caudate nucleus
2- Putamen
3- Globus pallidus

And are associated(functionally) with other nuclei in the midbrain and diencephalon:
4- Substantia Nigra (in midbrain)

The substantia nigra ("black substance") derives its name from its content of melanin pigment.

5- Subthalamic nucleus (diencephalon).

- **Relations:**

- The basal ganglia are lateral to the thalamus.
- Between the thalamus and the basal ganglia is the internal capsule (consists of five parts: an anterior limb, posterior limb, genu, retrolenticular and subrenticular parts).
- The anterior limb of the internal capsule lies between the caudate and putamen (the fibers of the internal capsule give the putamen and caudate their striated appearance). → Striatum (Putamen & Caudate).

- **Motor Functions of the Basal Ganglia:**

Like the cerebellum, the basal ganglia are associated with the cerebral cortex in order to control the movement before its execution.

Unlike the cerebellum, the basal ganglia do not receive input from the spinal cord, but they do receive direct input from the cerebral cortex. In addition to their role in motor control, they contribute to cognitive and affective functions.

Very important: The basal ganglia act **reciprocally** (i.e. they receive most of their input from the cerebral cortex and also return almost all their output signals back to the cortex).

- Basal Ganglia efferents go to the cortex through the thalamus. Thalamic nuclei involved in BG circuits are the VA, VL and centromedian nucleus.

Before going through the details of basal ganglia circuits, it's convenient to mention the following:

A. Neurotransmitters in the Brain.

1- Glutamate: excitatory neurotransmitter.
2- GABA: inhibitory neurotransmitter.
3- Dopamine: could be excitatory or inhibitory, depending on the receptor (D_1 is excitatory, and D_2 is inhibitory).
4- Enkephalins and Substance P: act as neuromodulators.

From Wikipedia: Neuromodulation is the physiological process by which a given neuron uses one or more chemicals to regulate diverse populations of neurons. This is in contrast to classical synaptic transmission, in which one presynaptic neuron directly influences a single postsynaptic partner. Neuromodulators secreted by a small group of neurons diffuse through large areas of the nervous system, affecting multiple neurons. Major neuromodulators in the central nervous system include dopamine, serotonin, acetylcholine, histamine, and norepinephrine.

B. Basic Circuit between the Cortex and the Basal Ganglia.

- The input nuclei of the BG are the caudate and putamen (striatum), and the output nuclei is the GPi (i.e. anything coming into the BG comes to the striatum, and anything going out of it, goes from the GPi).

- The rule of thalamus in brain circuits: anything passing into the cortex has to pass through the thalamus.

With that in mind, can you anticipate the basic circuit of BG?

- The basic circuit:

Cortex →+ Striatum →- Pallidum →- Thalamus →+ Cortex

This forms the cortico-striato-pallido-thalamo-cortical loop.

Generalizations:

- Anything coming out, or into the cortex is excitatory (glutamatergic).
- Anything coming out of the BG is inhibitory (GABAergic).

- Dopaminergic fibers come from the pars compacta of the substantia nigra and affect two distinct groups of fibers in the striatum, one of which is carrying D_1 receptors and is thus excited, and the other carrying D_2 receptors and is thus inhibited (explained later).

Rule: All BG circuits start in the cortex and end up in the cortex.

(It's okay if things are confusing now. I will be explaining each of these things repeatedly throughout the sheet, just wait).

Note:
Each of the basal nuclei has topographical representation.

Motor Function of the Basal Ganglia: (Some were mentioned by Dr. Faraj, and others by Dr. Faisal).

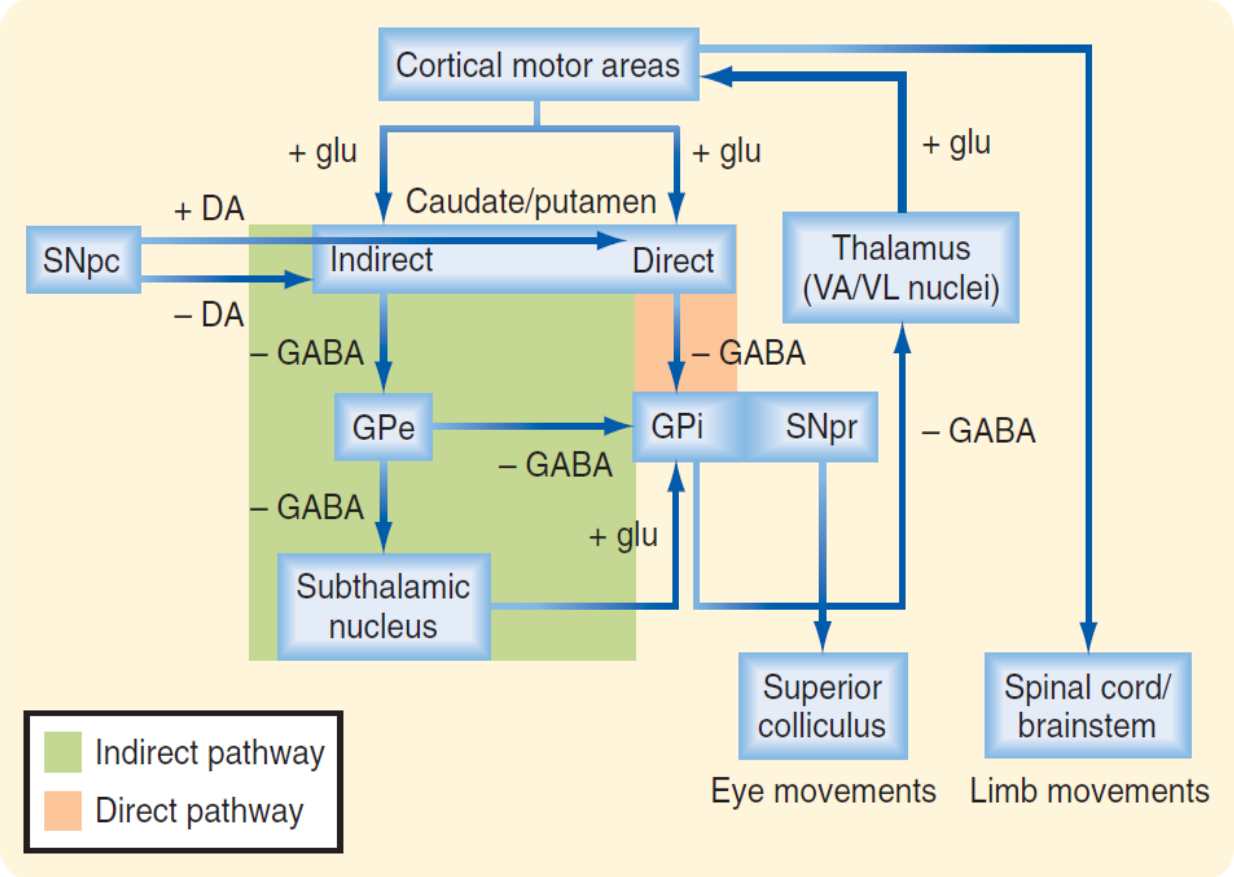
1- The basal ganglia are important in **initiation of movement** (including, the decision to move, and the direction and amplitude of movement). **What proves that?**
Neurons of the striatum begin to discharge before movement occurs.

2- **Control of complex patterns of motor activity**. Ex: Writing, using scissors, hammering nails, shooting a basketball through a hoop, passing a football, throwing a baseball, the movements of shoveling dirt, mist aspects of vocalization, controlled movements of the eyes, and any other of our skilled movements.

Functions of the Basal Ganglia:
Not much is known about the specific functions of each of the basal ganglia. Most of the information we have, were known by damaging one of these parts and then observing the resulting clinical abnormality. [Mentioned at the end of the sheet].

They are thought to function **in timing and scaling of motion**, as well as its **initiation of movement** (direction and amplitude of movement).

Basal Ganglia Circuits and Neurotransmitters



Functional connectivity of the basal ganglia for motor control. Connections between various basal ganglia components and other associated motor areas. The excitatory cortical input to the caudate and putamen influences output from the GPi and SNpr via a direct and an indirect pathway. Note that the two inhibitory steps in the indirect pathway mean that activity through this pathway has an effect on basal ganglia output to the thalamus and superior colliculus opposite that of the direct pathway. Note that DA is a neuromodulator that acts on D1 and D2 receptors on striatal neurons participating in the direct and indirect pathways, respectively

- The basal ganglia receive information mainly from the cerebral cortex, and then process these information by two major pathways: the direct pathway, and the indirect pathway.

Generalizations:

Direct Pathway: (Goes straight-forward cortex→ striatum → GPi → thalamus → cortex). Follow it in the figure above to check this.

- The direct pathway is **excitatory** (facilitates/ enhances movement).

Indirect Pathway: (Not straight-forward; goes from and into the cortex, just like the direct, but involves two extra accessory steps). Follow it in the figure above to check this.

- The indirect pathway is inhibitory (reduces movement).

- **In these pathways:**
  - Whenever there's **excitation** → **Glutamate** is involved (Signaling from and into the cortex).
  - Whenever there's **inhibition** → **GABA** is involved (Signaling from the basal ganglia).

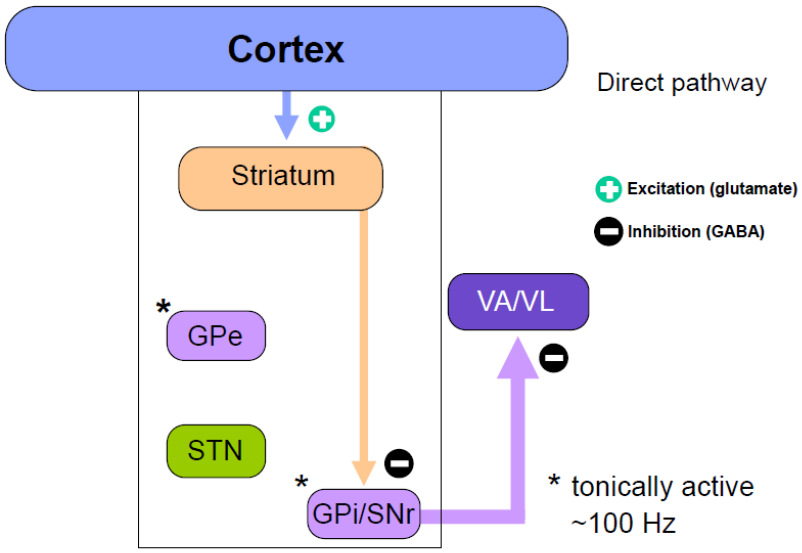
  - The **key part** of these pathways is the **thalamus**. Whenever we stimulate the thalamus, we enhance cortical motor activity, and whenever we inhibit it, we inhibit cortical motor activity.

Direct Pathway:

- The overall action of the direct pathway through the basal ganglia to motor areas of the cortex is to enhance motor activity.

Cortex → striatum → GPi/SNpr → VA/VL of the thalamus → Cortex.

Now, based on the generalizations we presented at the beginning of the sheet, you would be able to anticipate the effect of each step.



→ →

- The cortex excites the striatum (through glutamate) → Striatum inhibits GPi and SNpr → GPi and SNpr inhibit the thalamus (VA and VL).

The result of two successive inhibitory steps would be disinhibition. So, the activation of the direct pathway results in disinhibition of the thalamus that will excite the motor cortex and enhance motor activity.

Why do we say "Disinhibition" not "Excitation"?

Neurons of the striatum have little background activity (tonically inactive), while the GPi has a high background activity (tonically active).

→ When there's no movement (the cortex is sleeping), there's no strio-pallidal inhibition, but there's pallido-thalamic inhibition → the net effect is inhibition of the thalamus, and consequently the cortex.

→ When there's movement (the cortex is working), there's strio-pallidal inhibition, and pallido-thalamic inhibition → the net effect is excitation of the thalamus, and consequently the cortex (But because this excitation resulted from the removal of inhibition after the onset of movement, it's more conveniently called "Disinhibition".

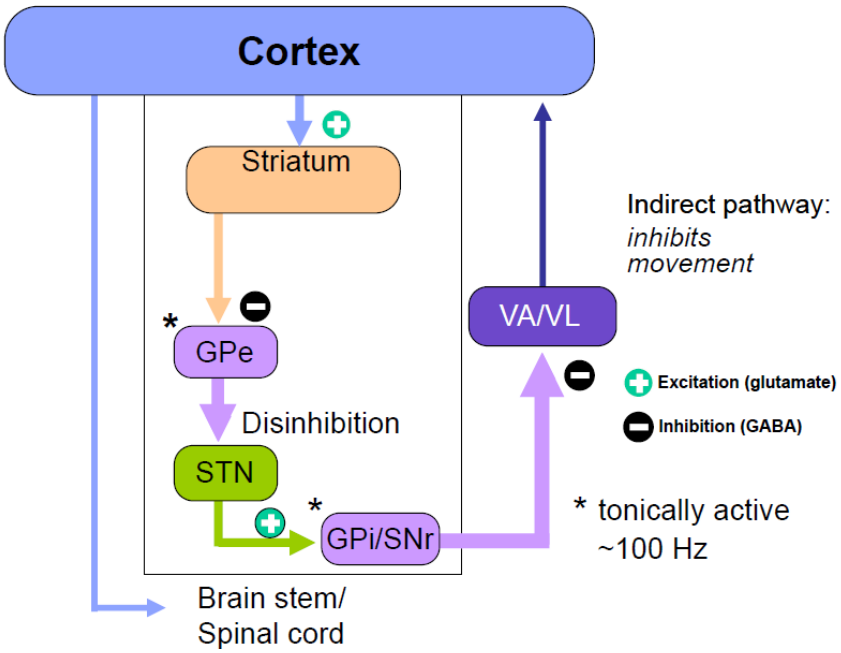
The doctor only said that GPi and GPe are tonically active, and the striatum is tonically inactive (So, this is what you have to know if you want to skip the confusing stuff mentioned above).

Indirect Pathway:

- The overall effect of the indirect pathway is to reduce the activity of neurons in motor areas of the cerebral cortex.

Cortex → striatum → **GPe → STN →** GPi → thalamus (VA/VL) → Cortex

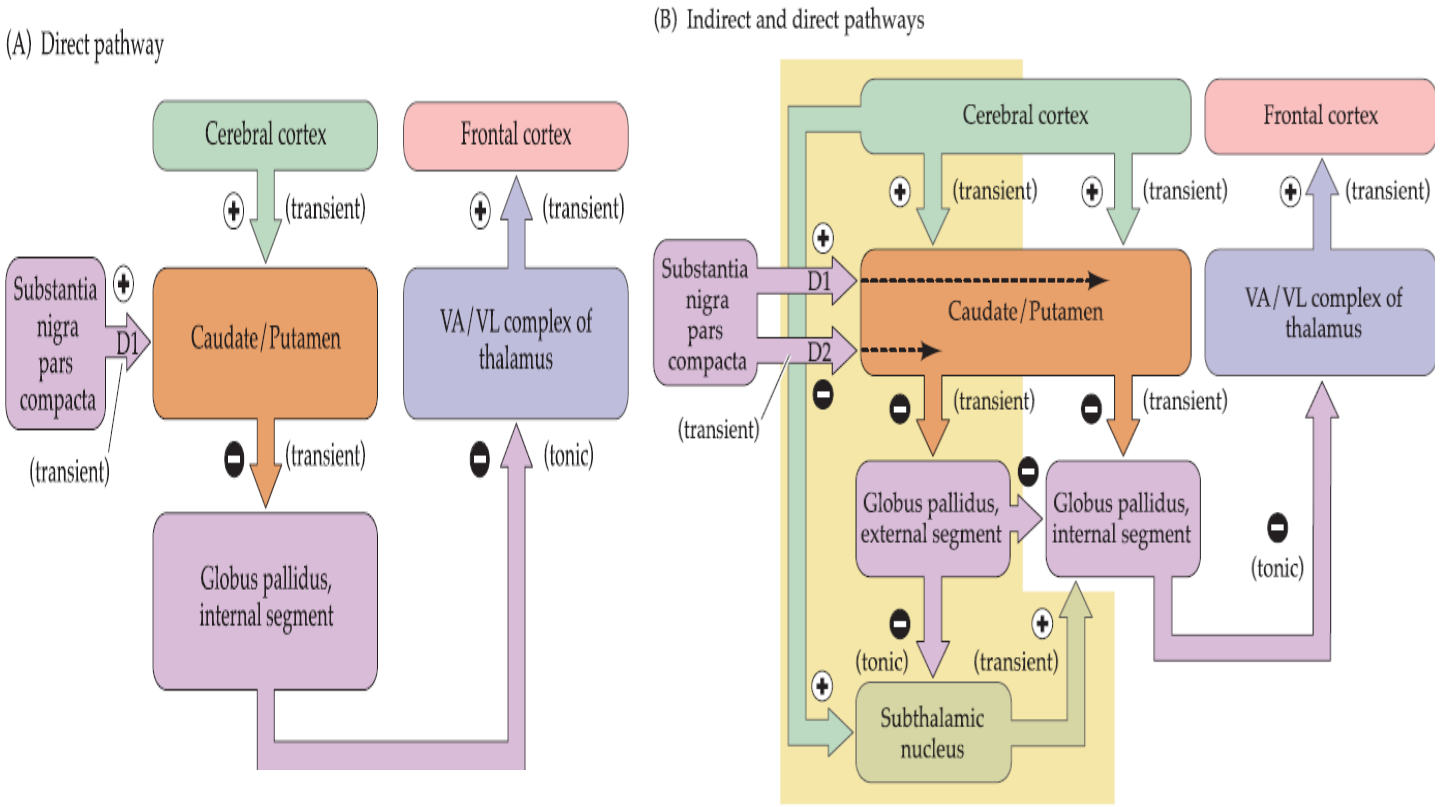
- "**GPe → STN →":** this is what makes the indirect pathway indirect.



- STN is excitatory to the GPi.
  This excitation is supposed to make the GPi more active → More inhibition of the thalamus → Reduction in movement. (This occurs without cortico-striatal signals).
- When there's movement, the cortex excites the striatum, that will inhibit GPe. So, the previously-inhibited STN, would be more active (i.e. disinhibition).

Conclusion:
Direct pathway: Disinhibition of the thalamus → enhancement of motor activity.
Indirect pathway: Disinhibition of the STN → reduction of motor activity.

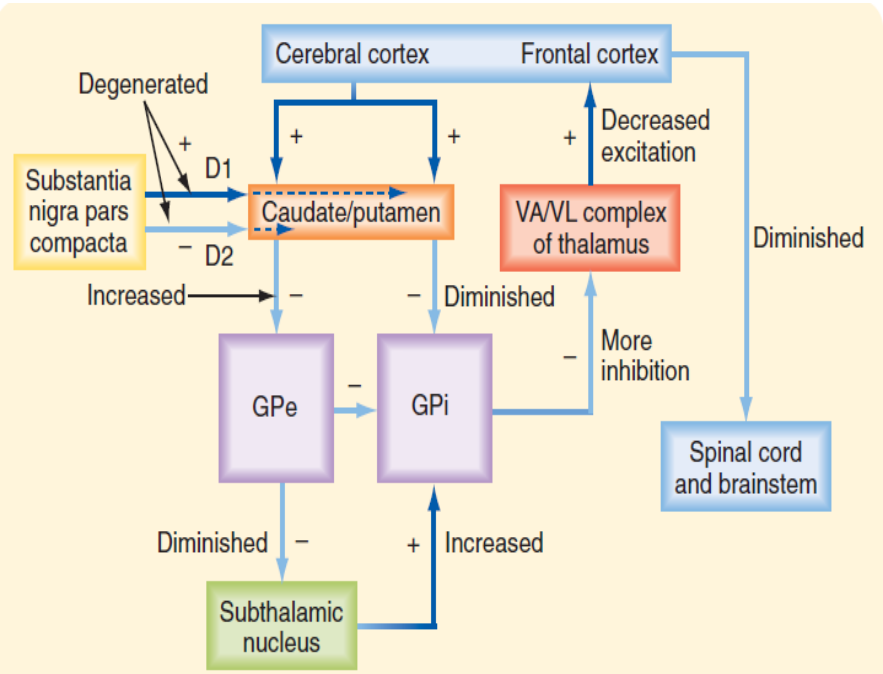
The Effect of Dopamine on the Direct and Indirect Pathways of the Basal Ganglia:



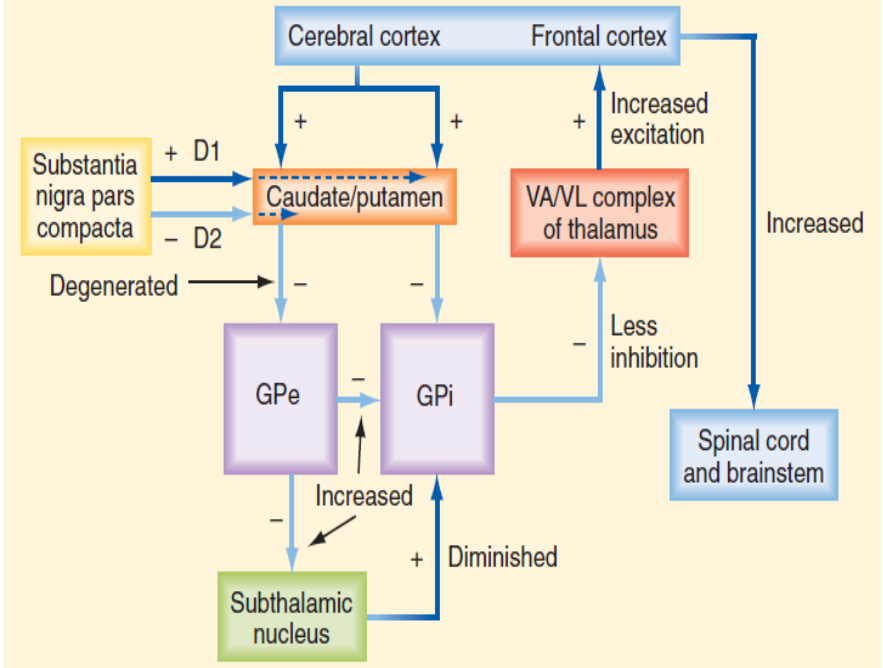
- Dopamine is one of the neurotransmitters in the brain, and is produced by neurons of the pars compacta of the substantia nigra.

- Dopamine has an excitatory effect on the direct pathway, and an inhibitory effect on the indirect pathway (depending on the receptors, with which it binds).
- The striatal fibers that project into the GPi (those of the direct pathway) have D_1 receptors, and dopamine here is excitatory.
- The striatal fibers that project into the GPe (those of the indirect pathway) have D_2 receptors, and dopamine here is inhibitory.
- Dopamine has a modulatory, rather than a direct effect on the striatum (i.e. it modulates the action of other neurotransmitters).
  Dopamine is excitatory = It makes other neurotransmitter more able to excite striatal neurons.
  Dopamine is inhibitory = It makes other neurotransmitters more able to inhibit striatal neurons.
- Extra information: D1 and D2 receptors are capable of excitation and inhibition, because they are coupled to Gs and Gi proteins, respectively.

- Motor behavior is determined by the balance between the direct and indirect pathways. If this balance is disturbed, we will end up with movement disorders, or dyskinesia.
- Dyskinesia (means bad movement) is different from bradykinesia (slowness in initiating movement). Dyskinesia may be: 1- Hyperkinesia, which is increase in involuntary spontaneous movements, or 2- Hypokinesia, which is lack of spontaneous movements and slowing of voluntary movement.



B Parkinson's disease (hypokinetic)



C Huntington's disease (hyperkinetic)

So, basal ganglia diseases fall into two categories:

1- Hypokinetic Disorders:
result from either insufficient direct pathway output (overactive GPi) or excessive indirect pathway output (overactive STN).
ex: Parkinson's Disease

How does that happen?
Dopamine is excitatory on the direct and inhibitory on the indirect → Loss of dopamine will cause activate the indirect and inhibit the direct → Less movement (Hypokinesia).

2- Hyperkinetic Disorders:
result from either excessive direct pathway output or insufficient indirect pathway output.
Ex: Huntington's Disease.
Loss of GABAergic inhibition of GPe → Overactive GPe → Underactive STN → Less inhibition to the thalamus → Increased excitation of the cortex → Chorea.

Follow these things on the figure.

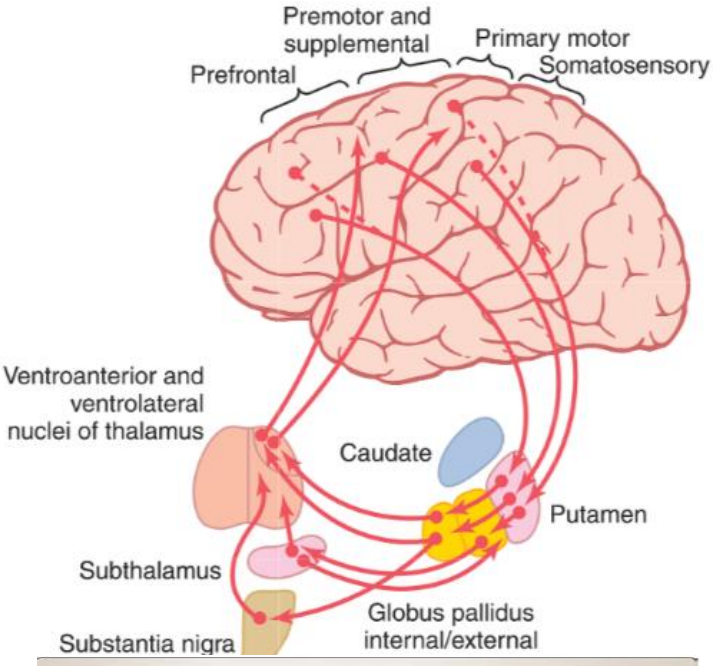
Neuronal Circuitry of the Basal Ganglia:

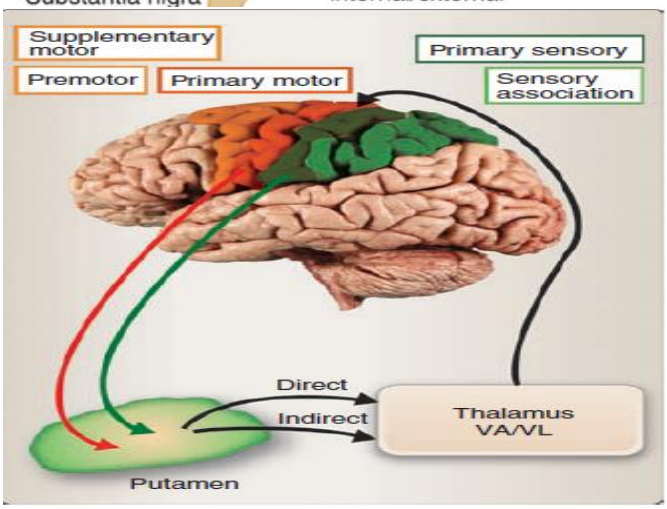
The neural circuits between the cortex and the basal ganglia are very complex. In this discussion we will concentrate on two major circuits, one of which is responsible for the motor functions of the basal ganglia (the putamen circuit), and the other is responsible for the cognitive functions (the caudate circuit).

- The input to the basal ganglia comes from wide areas of the cerebral cortex (motor, sensory, association, limbic areas), into the striatum. Motor inputs come into the putamen and form the Putamen Circuit. Inputs from association areas come into the caudate and form the Caudate Circuit.

Putamen Circuit (Motor Circuit):

- Responsible for the motor functions of the basal ganglia.
- Cortex (primary motor, premotor, supplementary motor, and somatosensory areas) → Putamen → VA & VL of the thalamus → Cortex (the same parts).
- The input is mainly from premotor area and SMA.
- The output is mainly to the primary motor area.
- The figure shows that the direct and indirect pathway work together for control of motor activity.
  [Arrows going out of GPi represent the direct pathway, and those going out of the GPe represent the indirect pathway].
- The putamen receives input from many areas of the cortex, and it then integrates these inputs and sends its output through the direct and indirect pathways within the basal ganglia.
  It's the balance between these two pathways that determines motor performance (motor behavior).





- The specific functions of each part of the basal ganglia is known when lost. So, let's see what happens in BG lesions.

Lesions of the Basal Ganglia:

1- Globus pallidus → Athetosis
Athetosis consists of slow, but continuous writhing movement of the distal parts of the limbs (the hand, and the arm), the neck and the face.

2- Putamen → Multiple small lesions in the putamen lead to flicking movements in the hands, face and other parts of the body (Chorea).

Remember: Huntington's disease results from loss of GABAergic inhibition from the striatum.

Note: Chorea is seen in adults in cases of Huntington's disease, and as a complication of acute rheumatic fever (especially in young girls). In case of acute rheumatic fever, chorea is reversible.

Sydenham's chorea in acute rheumatic fever: https://www.youtube.com/watch?v=-Os3T6Yz7w0

3- Substantia Nigra → Parkinson's Disease
(Rigidity, resting tremor, and bradykinesia).

Note: Rigidity in Parkinson's disease is called cogwheel rigidity.
Rest tremor: Tremor at rest, seen in Parkinson's disease.
Intention tremor: Tremor during movement, seen in cerebellar diseases.

4- Subthalamic nucleus → Hemiballism: sudden involuntary, violent flailing movements of an entire limb on one side of the body, contralateral to the lesion.

Remember: Ballistic movement = Rapid movement.

Hemiballism (if it occurs on one side).
Ballism (if it occurs on both sides).

Important Note:
In all **basal ganglia disorders**, the motor dysfunction is **contralateral** to the diseased component. This is understandable because the main final output of the basal ganglia to the body is mediated by the corticospinal tract.

Cerebellar diseases cause **ipsilateral** motor dysfunction.

Notes about Basal Ganglia Disorders:

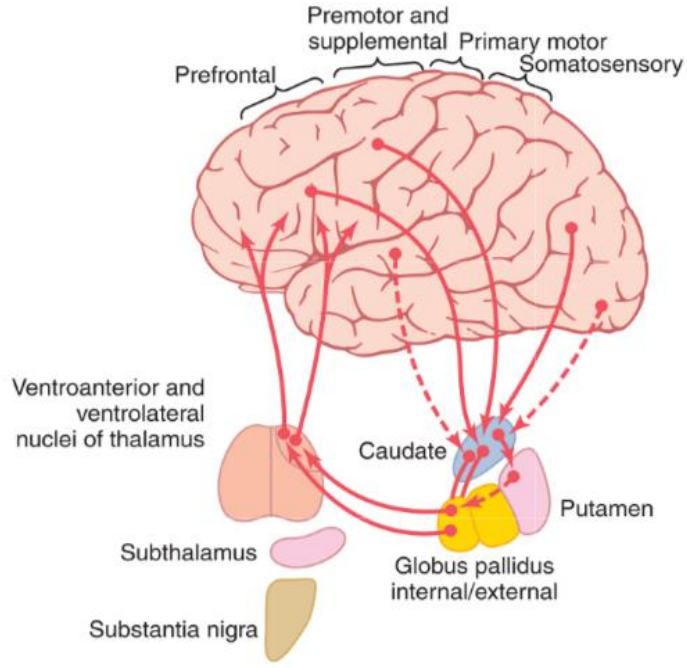
- The deficits seen in the various basal ganglia diseases include abnormal movement **(dyskinesia),** increased muscle tone **(cogwheel rigidity),** and slowness in initiating movement **(bradykinesia).** Abnormal movement includes tremor, **athetosis, chorea, ballism,** and **dystonia.**

- The tremor of basal ganglion disease is a "pill-rolling," 3-Hz tremor that occurs when the limb is at rest.

Caudate Circuit (Associative Circuit).

- Responsible for planning of complex motor activity (motor activity that require cognitive control).
- Cognition means the thinking processes of the brain, using both sensory input to the brain plus information already stored in memory.

Note: None of our recommended textbooks explains this point well enough. So, I'll try to explain it as clear as I can.



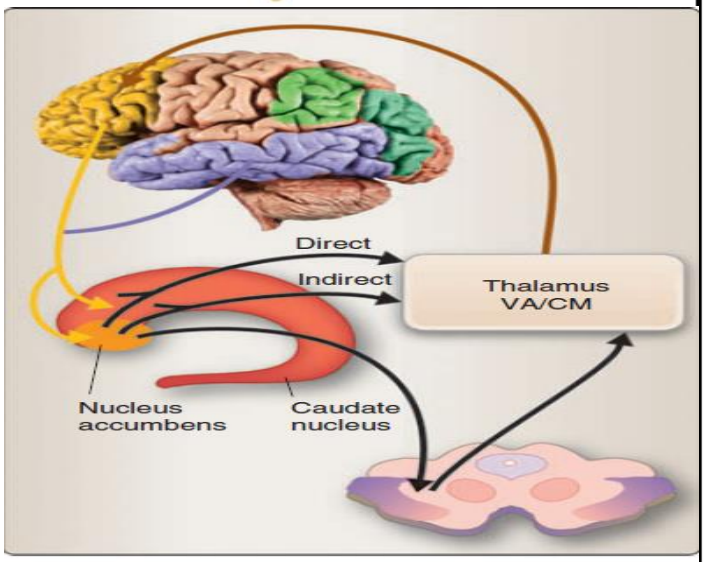


Figure 16.15
Schematic representation of the associative circuit. VA = ventral anterior nucleus; CM = centromedian nucleus.

Guyton:
Most of our motor actions occur as a consequence of thoughts generated in the mind, a process called *cognitive control of motor activity.* The caudate nucleus plays a major role in this cognitive control of motor activity.

Dr. Faraj's Notes:
The associative circuit is responsible for planning of complex motor activity. So, when a new task has been practiced and well-learned, the activity in the associative circuit decreases and the motor circuit becomes active instead.

Ex: When you drive a car for the first time, you need to perform motor functions, that also need practicing, learning and perception of the environment (the street in front, and other cars around you). This complex movement needs cognition. However, when it becomes well-learned and practiced, less cognition is needed (re-read Dr. Faraj's note again now).

[This is my own explanation, so forgive me if shown to be wrong later].

- **The neuronal circuitry of the caudate circuit:**
  Cortex (Association areas of the frontal, parietal and temporal lobes) → Caudate → GPi and GPe → VA and VL of the thalamus → Cortex (premotor area, SMA, and prefrontal cortex).

  The main things to remember from this circuit are:
  - Inputs come mainly from association areas (the parts that integrate the different types of sensory and motor information into usable thought patterns).
  - Output into the cortex mainly goes to the prefrontal, premotor and supplementary motor areas not to the primary motor area. Why?

  Let's make things logical:

  - The main function of the caudate circuit is cognitive control of movement (determining the patterns and sequence of movements to achieve a complex coordinated movement).
- Area 6 and SMA → Planning for complex movements, Area 4 → excitation of single muscles.

➔ So it's logical for the circuit to terminate in area 6 and SMA rather than area 4, isn't it?!

Example from Guyton [The Importance of Cognitive Functions in the Motor System].
A good example of this would be a person seeing a lion approach and then responding instantaneously and automatically by (1) turning away from the lion, (2) beginning to run, and (3) even attempting to climb a tree. **Without the cognitive functions, the person might not have the instinctive knowledge, without thinking for too long a time, to respond quickly and appropriately. Thus, cognitive control of motor activity determines subconsciously, and within seconds, which patterns of movement will be used together to achieve a complex goal**

Note: Differences between Guyton and Dr. Faraj.
Dr. Faraj:
Information comes from the VA nucleus to the motor and prefrontal cortices, and from the CM nucleus to wide cortical areas to affect the arousal (wakefulness of the cortex).

Guyton:
Information comes from the VA and VL to the motor and prefrontal cortices.

Dr. Faraj notes are taken from a specialized neuroscience textbook, and are supposed to be more accurate.

Summary of the Afferent and Efferents of the Basal Ganglia:

Afferents:

- Cerebral cortex to caudate and putamen
- Substantia nigra pars compacta to putamen and caudate
- Subthalamic nucleus to globus pallidus and to substantia nigra pars reticulata
- Centromedial nucleus of the thalamus to putamen and caudate
- Raphe magnus nucleus to putamen and caudate

Effetrents:

- Putamen and caudate to globus pallidus
- Putamen and caudate to substantia nigra pars reticularis
- Globus pallidus to subthalmic nucleus
- Globus pallidus to ventroanterio and ventrolateral nuclei of the thalamus

Centromedial nucleus is concerned with sensation, especially pain sensation. Pain sensation is associated with emotions.

Summary: (This if from Lippincott Illustrated Reviews of Neuroscience, from which Dr. Faraj explains the basal ganglia).

Skip it if you want.

- The basal ganglia nuclei are large masses of gray matter deep within the cerebral hemispheres. They include the caudate, putamen, globus pallidus, substantia nigra, and subthalamic nucleus. These nuclei are interconnected with each other and with other nuclei within the diencephalon and the midbrain. The basal ganglia function primarily as components in a series of parallel circuits and have a complex role in the control of movement and in encoding cognitive processes and their behavioral output.
- Input to the basal ganglia is to the striatum (caudate nucleus and putamen). The caudate nucleus and putamen each receive input from distinct cortical and subcortical regions. A single cell in the striatum receives input from multiple sources, which makes every cell in the striatum an **integrator**. This integration of input allows the basal ganglia to encode for the decision to move, the direction of the movement, the amplitude of the movement, and the motor expression of emotions. The output from the basal ganglia arises from the internal part of the globus pallidus (GPi) and the substantia nigra and projects to the ventral anterior and ventral lateral nuclei of the thalamus.
- The thalamus is under tonic inhibition. The *output* from the basal ganglia can either decrease or increase the tonic inhibition of the thalamus via two internal pathways. The direct pathway releases the thalamus from tonic inhibition. Removing this tonic inhibition leads to more excitation of the cortex and in turn more cortical output. The indirect pathway inhibits the output from the thalamus, leading to less excitation of the cortex and less cortical output. Thus, the indirect pathway counterbalances the effects of or puts "brakes" on the direct pathway. An imbalance of this system underlies motor disorders, such as Parkinson and Huntington diseases.
- The *input* to the basal ganglia can be described as three parallel streams of information from the cortex: motor, associative, and limbic. The motor circuit is the best known and plays the key role in motor performance and in the regulation of eye movements. The associative circuit plays an important role in cognitive processes and learning. The limbic circuit is involved in the regulation of emotional, motivational, and affective aspects of behavior. The striatum integrates these inputs and determines the activity of the thalamus via the direct and indirect pathways. The basal ganglia therefore integrate sensory, motor, emotional, and motivational inputs that result in a final common pathway, which determines the complex behavior we display.

Review Questions:

1- Which statement about lesions to the basal ganglia is correct?

A. Degeneration of dopaminergic neurons in the substantia nigra leads to inhibition of activity in the indirect pathway, which increases the inhibition of the thalamus.

B. A loss of the subthalamic nucleus leads to decreased inhibition of the thalamus, which results in hyperkinetic movements on the ipsilateral side.

C. Degeneration of the striatum (caudate and putamen) leads to increased inhibition of the thalamus.

D. Degeneration of dopaminergic neurons in the substantia nigra leads to decreased inhibition of the subthalamic nucleus and, therefore, increased inhibition of the thalamus.

E. Degeneration of the striatum leads to decreased inhibition of the subthalamic nucleus and, therefore, decreased inhibition of the thalamus.

2- **Parkinson disease is a motor disorder characterized by hypokinesia or akinesia. This effect on movement is due to:**

A. Increased excitatory input from the substantia nigra to the striatum, which increases the amplification of the cortical input to the striatum.

B. Reduced inhibition of the globus pallidus (GPe), which results in greater inhibitory input to the subthalamic nucleus.

C. Inhibition of the globus pallidus (GPi) results in less inhibitory input to the thalamus, thereby decreasing the tonic inhibition of the thalamus.

D. A loss of dopaminergic signaling from the substantia nigra to the striatum, which results in increased stimulation of an inhibitory neuron
projecting to the globus pallidus (GPe).

E. A loss of dopaminergic input to the cholinergic interneuron in the striatum (caudate and putamen), which results in decreased stimulation of the globus pallidus (GPi).

3- Neurological disease associated with the cerebellum produces which of the following types of symptoms?

A) Resting tremor B) Athetosis
C) Rigidity D) Ataxia
E) Akinesia

4- Which of the following neurotransmitters is used by the axons of substantia nigra neurons that project to the caudate and putamen?
A) Norepinephrine B) Dopamine C) Serotonin D) Acetylcholine
E) GABA

5- Which of the following structures <u>is not</u> considered to be part of the basal ganglia?
A) Caudate nucleus B) Dentate nucleus C) Substantia nigra D) Putamen
E) Globus pallidus

6- Hemiballismus, the sudden flailing movements of an entire limb, results when damage occurs to which area of the brain?
A) The subthalamic nucleus B) The ventral basal complex of the thalamus
C) The globus pallidus D) The red nucleus
E) The lateral hypothalamus

7- Which structures in the cerebellum have a topographical representation of the body?
A) The dentate nucleus B) The lateral hemispheres C) The flocculonodular lobe
D) The vermis and intermediate hemisphere E) The cerebellar peduncles

8- The condition of athetosis results when which area of the brain is dysfunctional?
A) Globus pallidus B) Substantia nigra
C) Ventral anterior complex of the thalamus D) Putamen
E) Purkinje cell layer of the cerebellum

9- Which component of the basal ganglia plays the major role in the control of cognitive (memory-guided) motor activity?
A) Globus pallidus B) Substantia nigra C) Caudate nucleus
D) Putamen E) Subthalamic nucleus

10- A wide variety of neurotransmitters have been identified in the cell bodies and afferent synaptic terminals in the basal ganglia. A deficiency of which of the following transmitters is typically associated with Parkinson disease?
A) Norepinephrine B) Dopamine C) Serotonin D) GABA E) Substance P

11- A 72-year-old man visits his physician because he finds it difficult to hold his hand steady when painting. Examination reveals a resting tremor and rigidity. The symptoms are relieved by a single dose of levodopa. This patient's neurological signs are most likely related to a lesion within which of the following?

a. Caudate nucleus and putamen b. Cerebellum c. Hippocampus
d. Premotor area e. Substantia nigra

12- A 78-year-old man is evaluated by a physiatrist after a stroke. The patient is observed to suffer from dysmetria, ataxia, and an intention tremor. These neurological signs are most likely related to a lesion within which of the following regions of the brain?

a. Basal ganglia b. Cerebellum c. Cortical motor strip
d. Eighth cranial nerve e. Medulla

13- A 59-year-old woman with an inherited neurodegenerative disease is admitted to the hospital because of agitation and aggression. Three years prior to admission, her irregular, flinging movements had become so severe that she could not walk or assist in her own care. Within which of the following areas of the brain the neuronal degeneration results in this presentation?

a. Anterior cerebellum b. Limbic system c. Striatum d. Substantia nigra
e. Subthalamus

14&15: A patient presents with violent involuntary ballistic movements that are jerky and irregular and mainly involve the upper extremity on one side of the body.

14. The lesion was most likely located in the:
a. Neostriatum b. Paleostriatum c. Subthalamic nucleus
d. Pars reticulata of the substantia nigra e. Claustrum

15. The motor dysfunctions characteristic of this disorder can best be accounted for in terms of loss of:
a. Inhibitory input to the caudate nucleus
b. Excitatory input to the medial (internal) pallidal segment
c. Dopaminergic input to the caudate nucleus and putamen
d. Gamma aminobutyric acid (GABA)-ergic input to the lateral (external) pallidal segment
e. Glutamatergic input to the caudate nucleus

16&17: A patient presents with reduced facial expression, spontaneous movements (slower than normal) that are revealed most clearly when walking, monotonous speech, an increase in muscle tone in the arms, and a rhythmic tremor (4 to 7 Hz) in the fingers, including a pill-rolling tremor.

16. This disorder can be directly linked to loss of:
a. Glutamatergic inputs from neocortex to the neostriatum
b. Gamma aminobutyric acid (GABA)-ergic input to the lateral (external) pallidal segment
c. Glutamatergic input to the medial (internal) pallidal segment
d. Dopaminergic inputs to the neostriatum
e. Cholinergic inputs to the neostriatum

17. Which of the following pharmacological treatment strategies would be most appropriate for this patient?

a. Cholinergic (muscarinic) agonist (Pilocarpine)
b. Gamma aminobutyric acid (GABA)A agonist (Muscimol)
c. L-3, 4-hydroxyphenylalanine (L-DOPA) plus a dopamine-decarboxylase inhibitor (Sinemet)
d. Serotonin reuptake inhibitor (Prozac)
e. Gamma aminobutyric acid (GABA)B agonist (Baclofen)

18. A 55-year-old man was recently diagnosed with Huntington's disease. This disorder may best be understood in terms of the loss of which substance with which result?

a. Serotonin in the globus pallidus, increased excitation of ventral anterior thalamic nucleus

b. Substance P in the neostriatum, increased inhibition in the medial pallidal segment

c. Gamma aminobutyric acid (GABA) in the neostriatum, reduction of neostriatal inhibition on the lateral (external) pallidal segment

d. Acetylcholine and gamma aminobutyric acid (GABA) in the neostriatum, reduction of inhibition on the medial (internal) pallidal segment

e. Dopamine in the neostriatum, a reduction of neostriatal inhibition on the medial pallidal segment.