

5. PARKINSON'S DISEASE

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PARKINSON'S DISEASE

The term 'Parkinson's disease' refers to a group of neurodegenerative conditions that affect several regions of the brain, including the pigmented nuclei in midbrain and brainstem, the olfactory tubercle, the cerebral cortex, and elements of the peripheral nervous system.

The earliest and most striking physical disabilities resulting from these changes are motor impairments that, together, are called 'parkinsonism'. These include paucity and slowness of movement (akinesia, bradykinesia), muscle stiffness (rigidity), and tremor at rest.

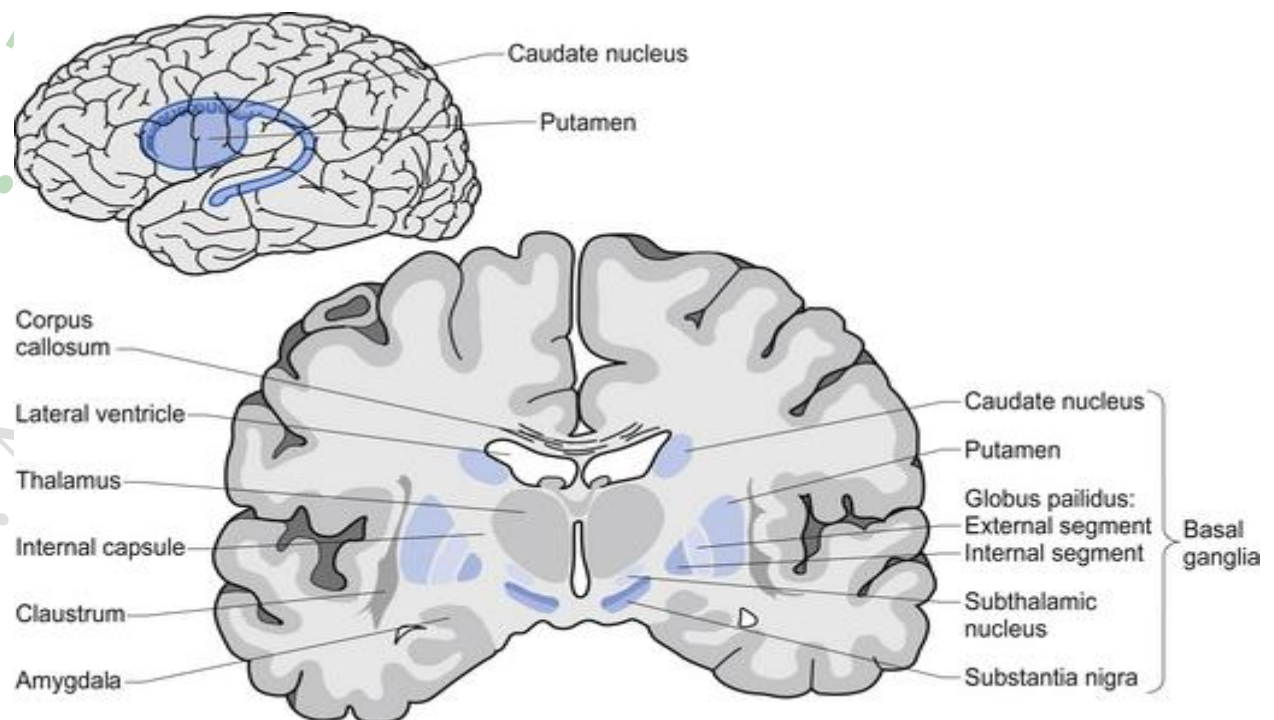
In large part, these problems result from the prominent degeneration of dopaminergic neurons in the midbrain, and the consequent deficiency of dopamine in brain areas that receive dopaminergic inputs from those neurons, specifically the post-commissural putamen and other basal ganglia regions. Dopamine loss in the basal ganglia, which may be responsible for the emergence of parkinsonism.

In the early stages of Parkinson's disease, your face may show little or no expression. Your arms may not swing when you walk. Your speech may become soft or slurred. Parkinson's disease symptoms worsen as your condition progresses over time.

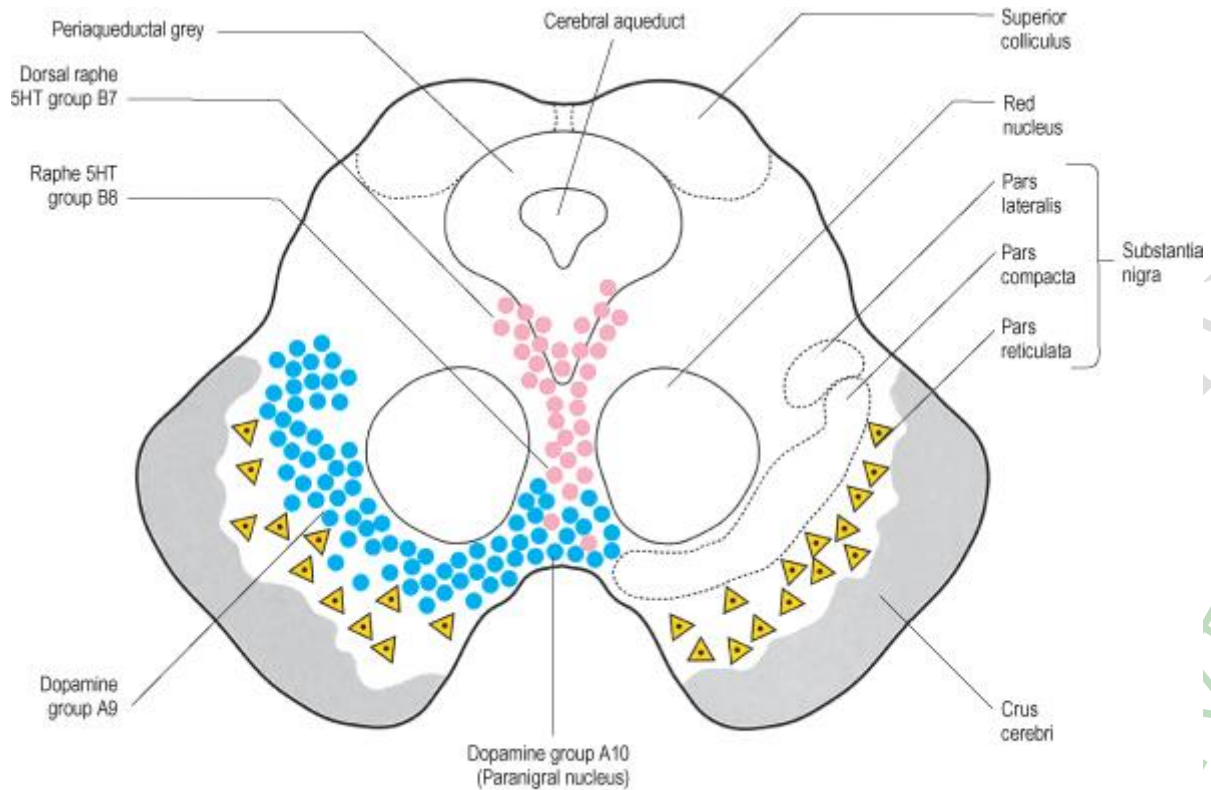
Although Parkinson's disease can't be cured, medications might significantly improve your symptoms. Occasionally, your doctor may suggest surgery to regulate certain regions of your brain and improve your symptoms.

INTERNAL STRUCTURE OF BRAIN:

Before understanding the pathophysiology of Parkinsonism disease it is essential to understand the structure of brain.



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- Parkinsonism is considered to result primarily from abnormalities of basal ganglia function.
- The basal ganglia include:
 - The neostriatum (caudate nucleus and putamen),
 - the external and internal pallidal segments (GPe, GPi),
 - the subthalamic nucleus (STN), and
 - the substantia nigra with its pars reticulata (SNr) and pars compacta (SNc).
- They participate in anatomically and functionally segregated loops that involve specific thalamic and cortical areas.

PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

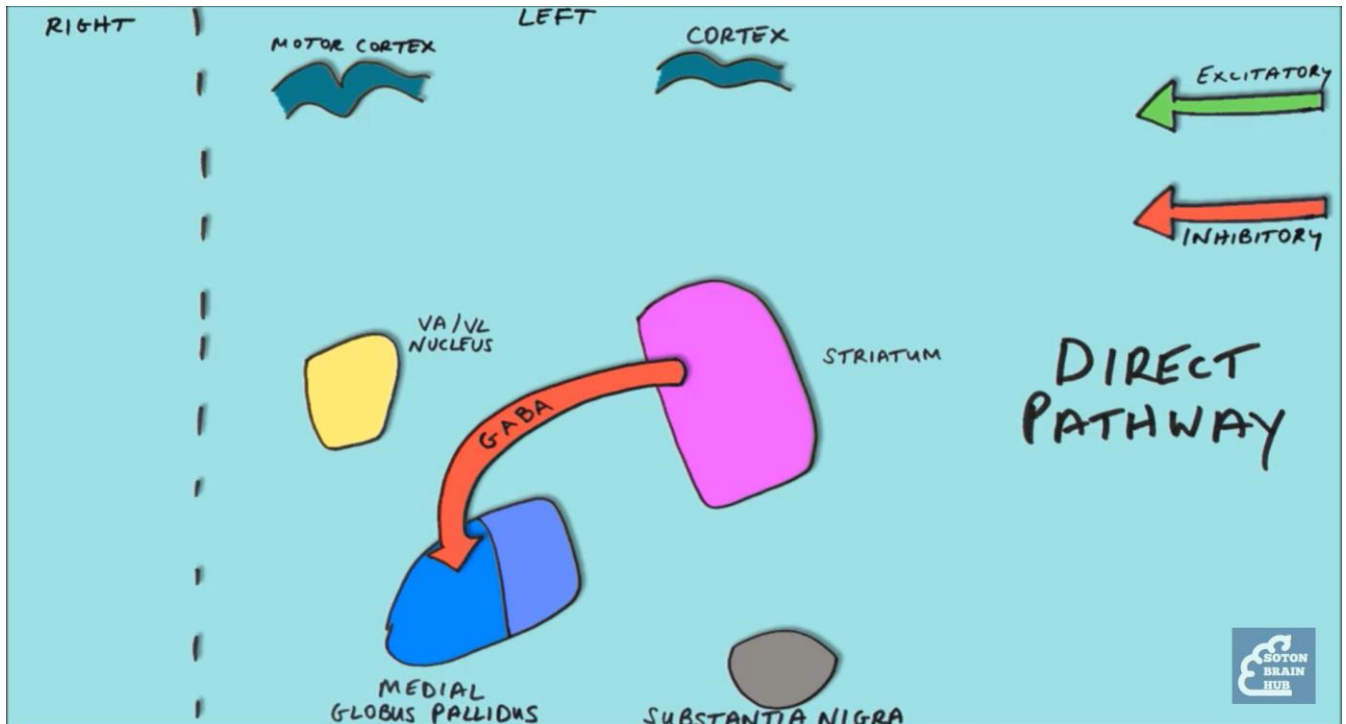
To understand the pathophysiology of Parkinson's disease it is essential to understand how the normal brain work:

Note:

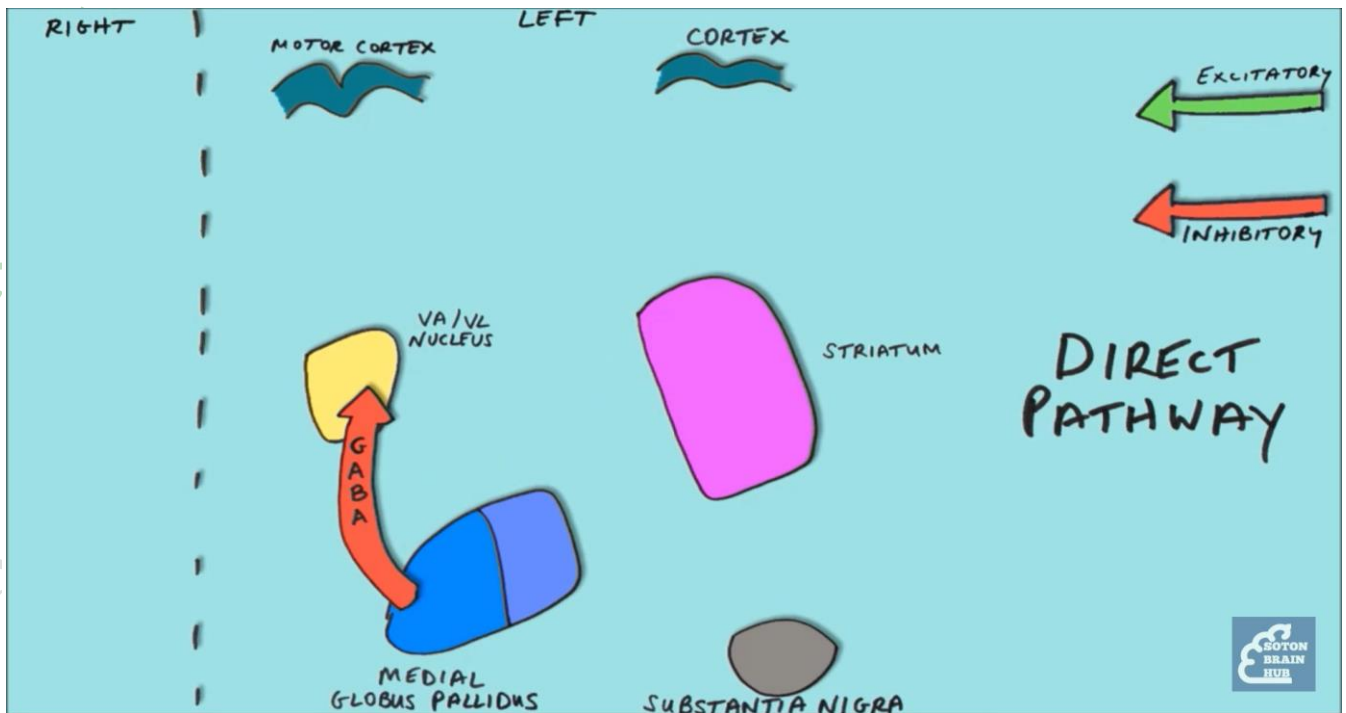
- Left side of the brain control the motor functions of right side.
- To understand the pathophysiology of parkinson's in this note take in consideration that green arrow always shows the stimulation and red arrow shows inhibition.
- As well as the **thickness of the arrow note down in each steps to understand pathophysiology more easy way.**

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- Striatum release inhibitory neurotransmitter (GABA) reduce the activity
- Medial Globus Pallidus (GPi) release inhibitory neurotransmitter (GABA) reduce the activity
- Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus release excitatory neurotransmitter Glutamate increase the activity.
- There are two types of dopaminergic receptors D1 stimulatory and D2 inhibitory in nature.

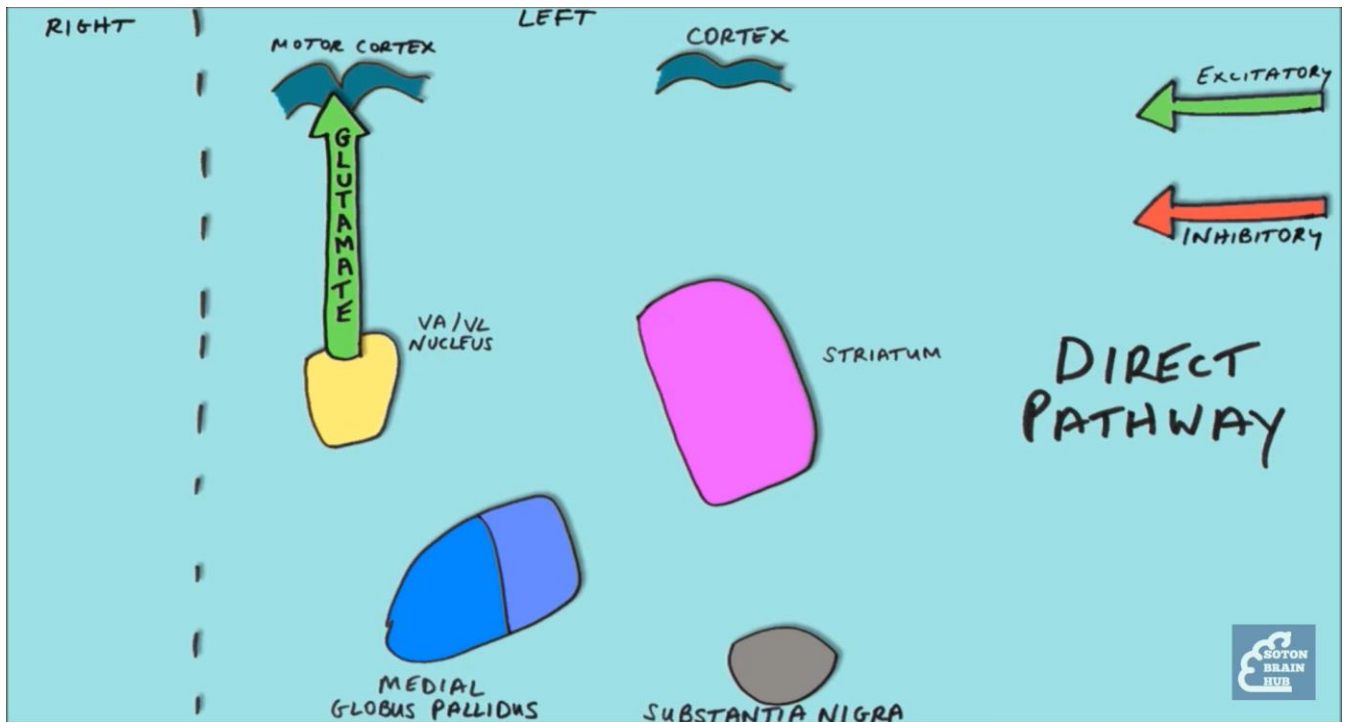


Striatum release inhibitory neurotransmitter (GABA) reduce the activity

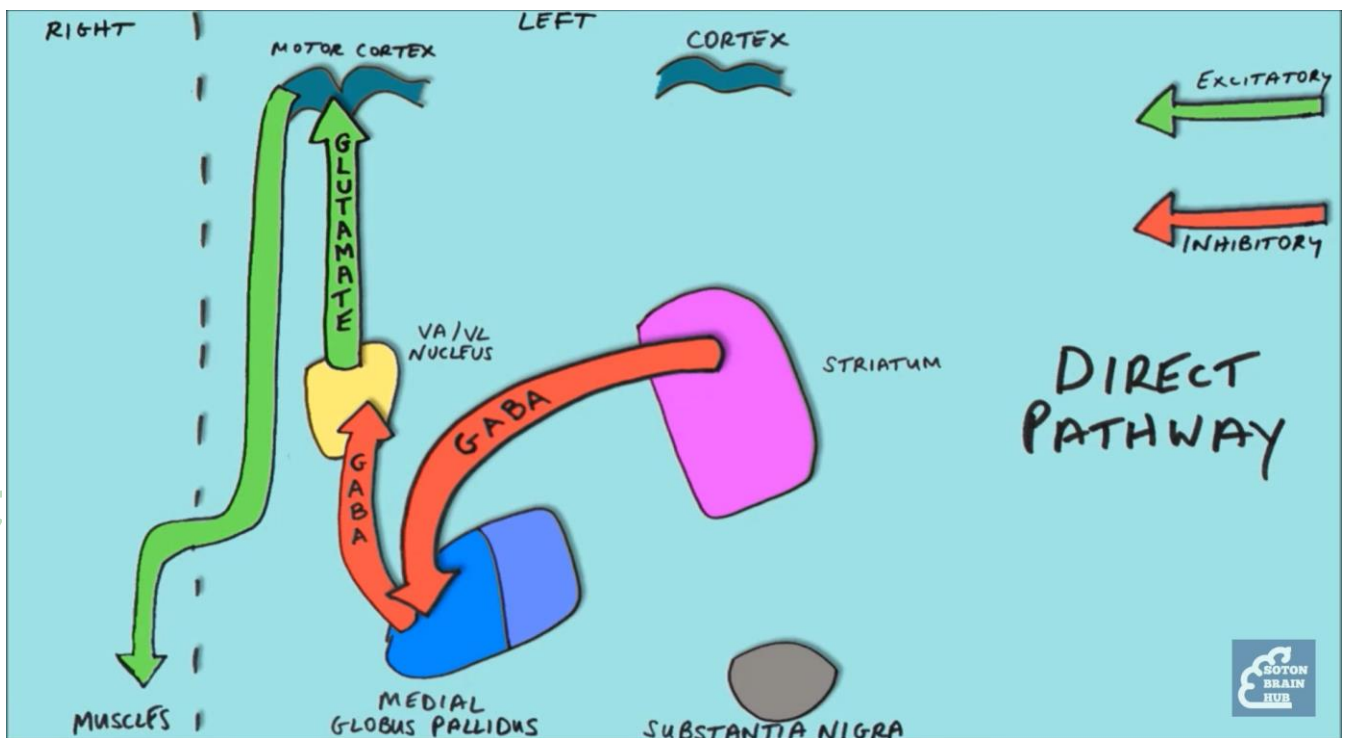


Medial Globus Pallidus (GPi) release inhibitory neurotransmitter (GABA) reduce the activity

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Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus release excitatory neurotransmitter Glutamate increase the activity.



Full pathway

1. DOPAMINERGIC PATHWAY

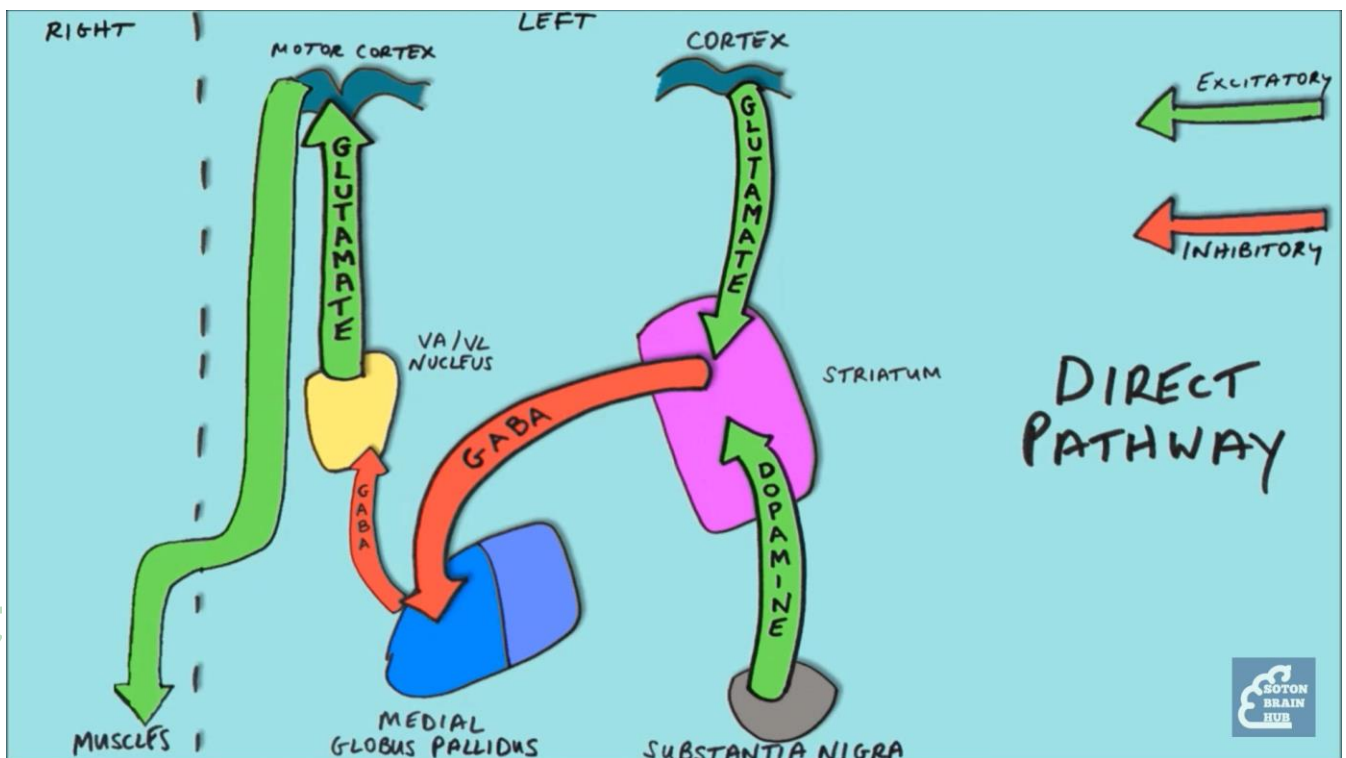
There are mainly two pathway involve in the parkinson's disease:

- A. Direct Pathway:
- B. Indirect Pathway:

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Direct Pathway in normal person:

- Cortex region of the brain secret the glutamate and substantia nigra release the dopamine in to the Striatum it act on D1 which is excitatory receptors. These effect excited striatum more.
- So, Striatum (caudate nucleus and putamen) project or release inhibitory neurotransmitter (GABA) which reduce the activity of medial globus pallidus so diminished the activity/release of inhibitory neurotransmitter (GABA) in medial globus pallidus.
- Due to reduce the activity of medial globus pallidus activate the Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus and it release excitatory neurotransmitter Glutamate.
- Excitatory neurotransmitter Glutamate activate the motor cortex region of the brain and it send message towards the spinal region to the muscle and this effect produce movement.
- This pathway suggest that if we increase the activity of striatum it inhibit the medial globus pallidus (GPi) at greater degree so more strongly excited the Ventral Lateral (VL) subthalamic nucleus which positively excited or stimulate the motor cortex.

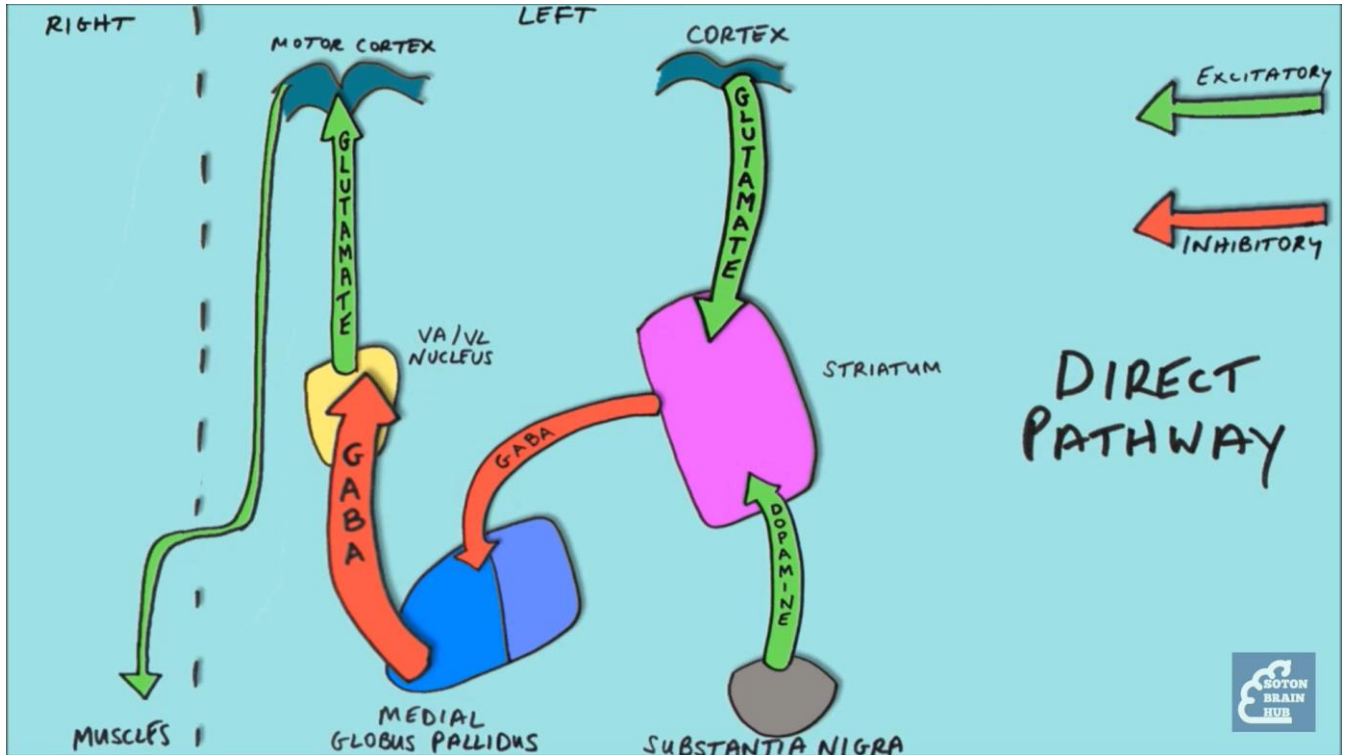


Direct Pathway in parkinson's disease:

- There is a degeneration of dopaminergic neurotransmitter (Locomotion activity) so the D1 receptor of striatum not get stimulate which is stimulatory in nature.
- This effect decrease/reduce the GABA related inhibitory activity in medial globus pallidus. So medial globus pallidus (GPi) inhibit more strongly the Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus.

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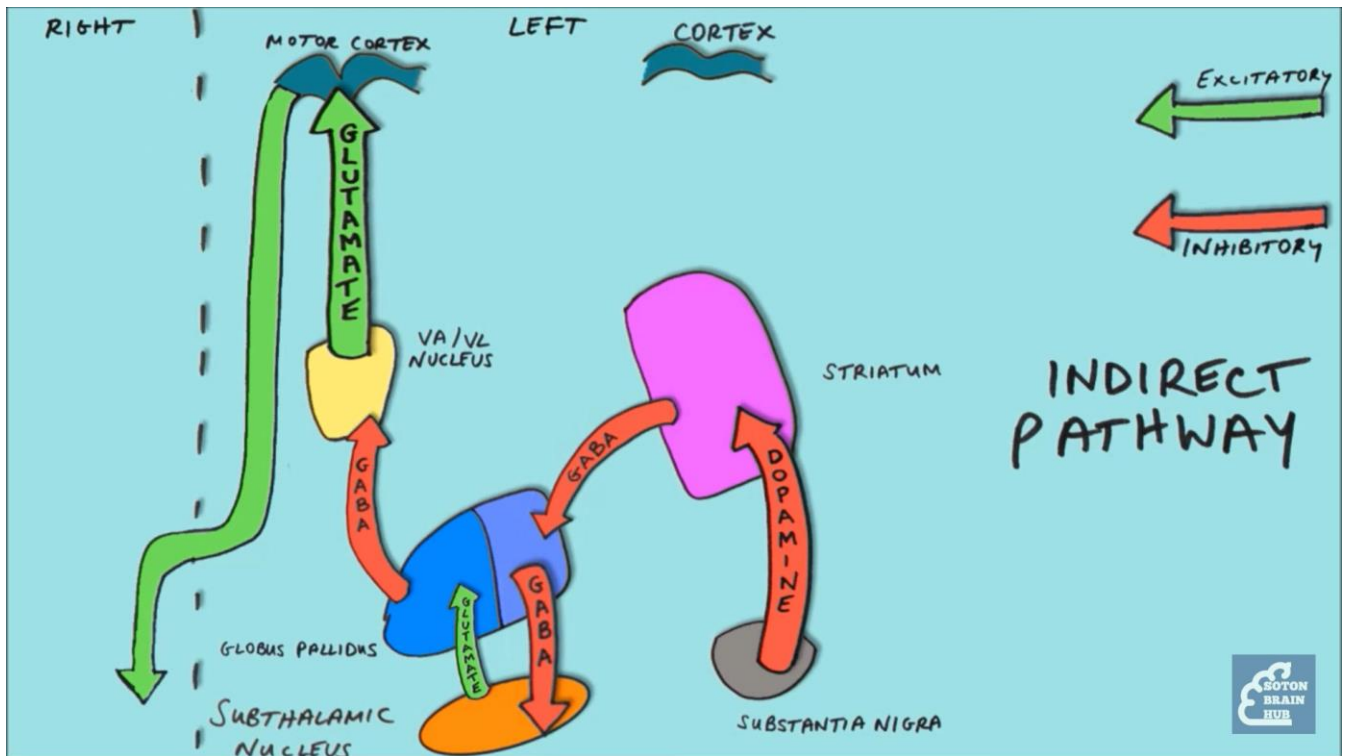
- Inhibition of Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus resist the excitation of motor cortex region and the muscles.
- This effect produce the hypokinetic symptoms such as bradykinesia may slow the movement of muscles or body.



Indirect Pathway in normal person:

- Substantia nigra release the dopamine in to the Striatum. If it bind on to the D2 receptor which is inhibitory in nature get activated. These effect reduce the excitation of striatum.
- So, Striatum (caudate nucleus and putamen) project or release less inhibitory neurotransmitter (GABA) which increase/stimulate the activity of lateral globus pallidus (GPe).
- So lateral globus pallidus (GPe) secret more amount of inhibitory neurotransmitter (GABA) in laeral globus pallidus. It produce the inhibition of subthalamic nucleus.
- This effect resist the excitation of medial globus pallidus and inhibit/decrease the release of inhibitory neurotransmitter (GABA) from medial globus pallidus.
- Due to reduce the activity of medial globus pallidus activate the Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus and it release excitatory neurotransmitter Glutamate.
- Excitatory neurotransmitter Glutamate activate the motor cortex region of the brain and it send message towards the spinal region to the muscle and this effect produce movement.

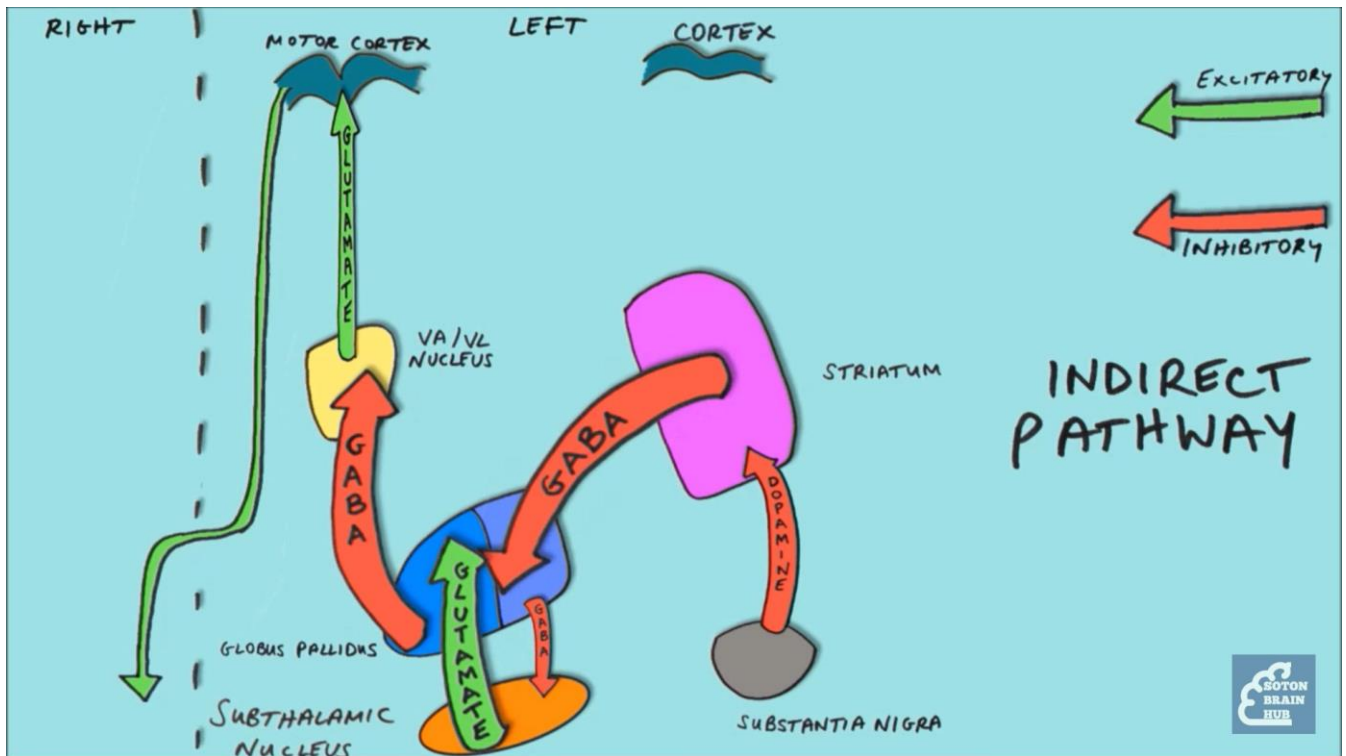
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Indirect Pathway in parkinson's disease:

- There is a degeneration of dopaminergic neurotransmitter (Locomotion activity) in substantia nigra so it inhibits the activation of inhibitory dopaminergic neurotransmitter D2 so it resists the inhibition of striatum.
- Striatum releases inhibitory neurotransmitter GABA and inhibits the activity of lateral globus pallidus (GPe). It produces stimulation of subthalamic nucleus.
- Stimulated subthalamic nucleus releases the excitatory glutamate into the medial globus pallidus (GPi).
- Activated or stimulated medial globus pallidus (GPi) inhibits the Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus through the over-activation of GABA.
- Inhibition of Ventral Anterior (VA) and Ventral Lateral (VL) subthalamic nucleus resists the excitation of motor cortex region and the muscles.
- This effect produces the hypokinetic symptoms such as bradykinesia, which may slow the movement of muscles or body.

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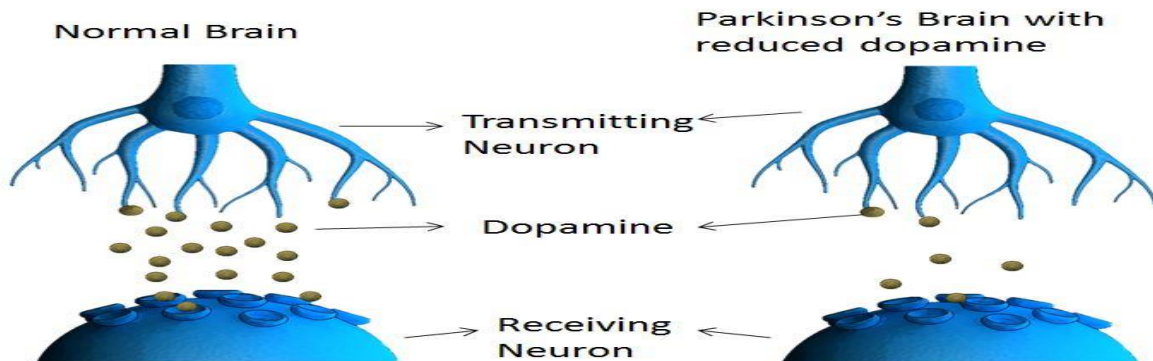


Refer below link for more understanding:

1. <https://www.youtube.com/watch?v=I4XXoiWwoNc>
2. <https://www.youtube.com/watch?v=Hu5KVfFnrh0&t=610s>

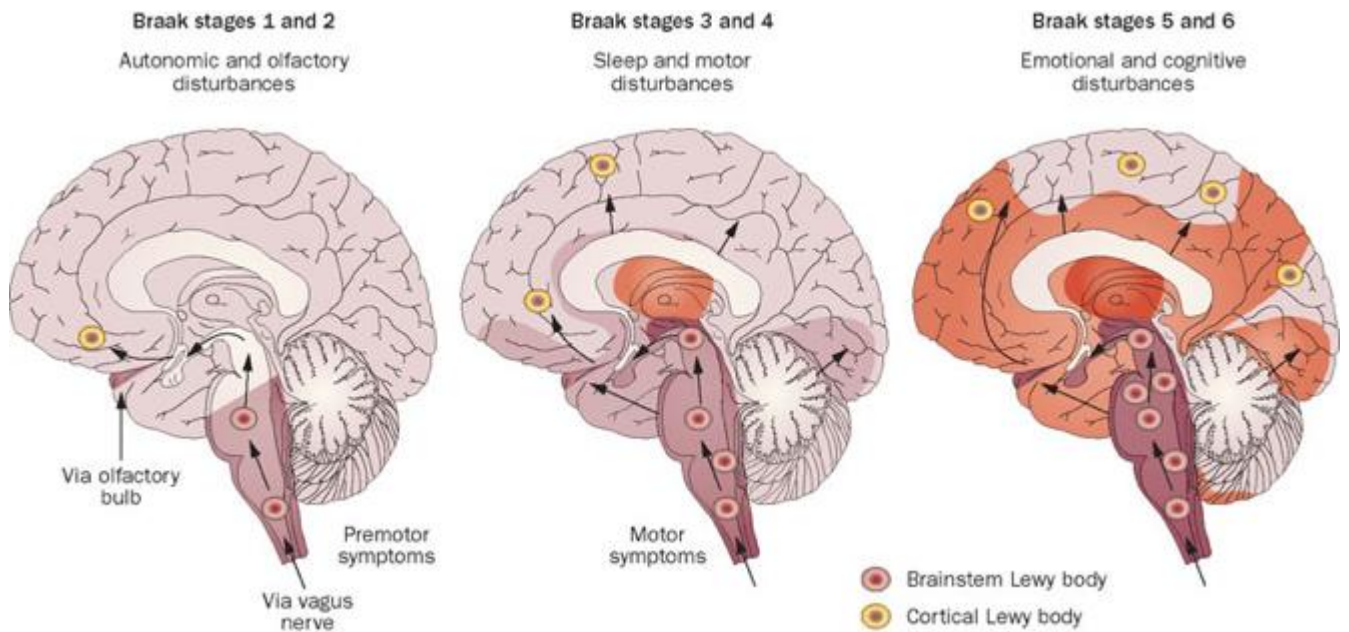
Direct and Indirect Pathways

- | | |
|--|--|
| <ul style="list-style-type: none"> • Direct pathway <ul style="list-style-type: none"> - Disinhibits motor thalamus - Activates thalamo-cortex - Activates motor cortex - Facilitates movement | <ul style="list-style-type: none"> • Indirect pathway <ul style="list-style-type: none"> - Inhibits motor thalamus - Inhibits thalamo-cortex - Inhibits motor cortex - Inhibits movement |
|--|--|



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2. PROTEIN AGGREGATION:



- The first major proposed cause of neuronal death in Parkinson's disease is the bundling, or oligomerization, of proteins.
- The protein alpha-synuclein has increased presence in the brains of Parkinson's Disease patients and, as α -synuclein is insoluble, it aggregates to form Lewy bodies in neurons.
- Traditionally, Lewy bodies were thought to be the main cause of cell death in Parkinson's disease; however, more recent studies suggest that Lewy bodies lead to other effects that cause cell death. Regardless, Lewy bodies are widely recognized as a pathological marker of Parkinson's disease.
- Lewy bodies first appear in the olfactory bulb, medulla oblongata, and pontine tegmentum; patients at this stage are asymptomatic. As the disease progresses, Lewy bodies develop in the substantia nigra, areas of the midbrain and basal forebrain, and in the neocortex.

3. AUTOPHAGY

- The second major proposed mechanism for neuronal death in Parkinson's disease, autophagy, is a mechanism by which inner components of the cell are broken down and recycled for use. Autophagy has been shown to play a role in brain health, helping to regulate cellular function. Disruption of the autophagy mechanism can lead to several different types of diseases like Parkinson's disease.
- Autophagy can also clear aggregated protein; however, in neurodegenerative diseases autophagy sometimes cannot break down oligomers fast enough to clear them and maintain regular cell

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function. Without clearance of protein bundles or other harmful molecules, cells start to alter their function and eventually undergo cell death.

- Autophagy dysfunction in Parkinson's disease has also been shown to lead to dysregulated mitochondria degradation.

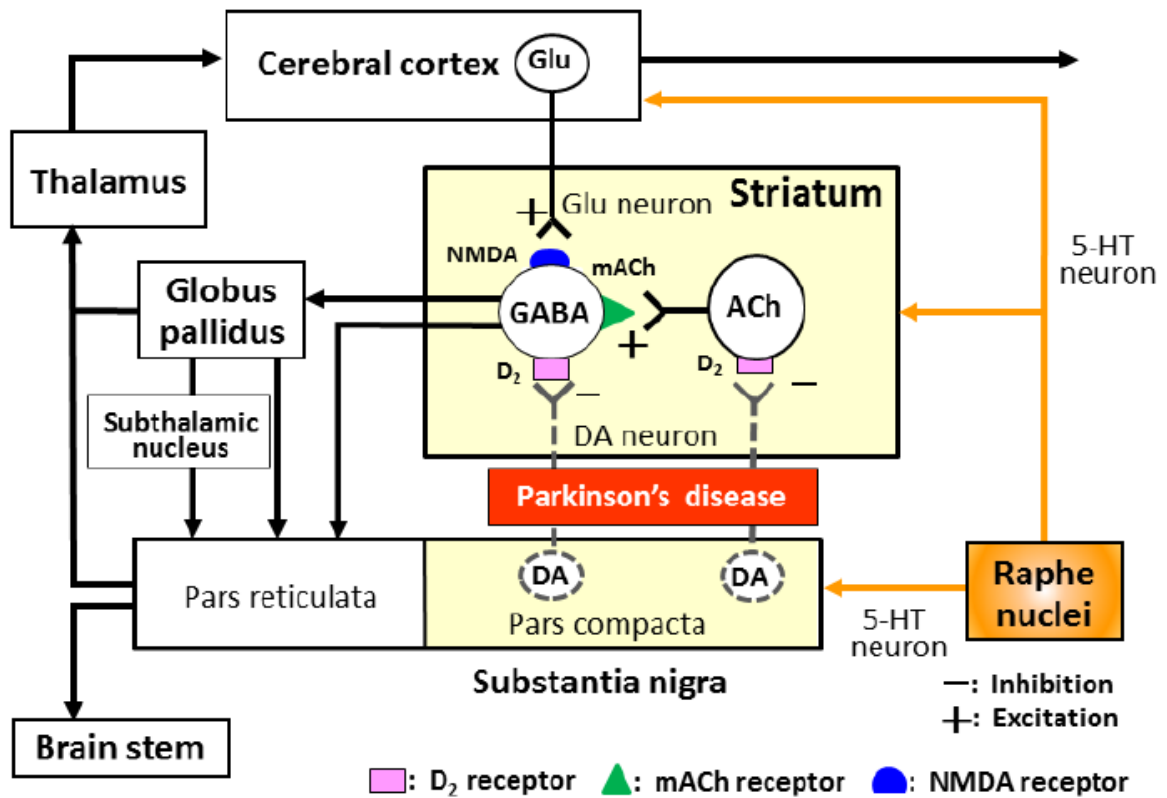
4. MUTATION IN GENE:

- INK1 is a protein normally transported into the mitochondrion, but can also accumulate on the surface of impaired mitochondria.
- Accumulated PINK1 then recruits Parkin; Parkin initiates the break down of dysfunctional mitochondria, a mechanism that acts as a "quality control".
- In Parkinson's disease, the genes coding PINK1 and Parkin are thought to be mutated, therefore preventing the breakdown of impaired mitochondria, causing abnormal function and morphology of mitochondria and eventually cell death.
- Mitochondrial DNA (mtDNA) mutations have also been shown to accumulate with age indicating that susceptibility to this mechanism of neuronal death increases with age.

5. ROLE OF ACETYLCHOLINE:

- In Parkinson's disease, dopamine depletion blocks autoinhibition of acetylcholine release through muscarinic autoreceptors, leading to excessive acetylcholine release which eventually prunes spines of the indirect-pathway projection neurons of the striatum and thus interrupts information transfer from motor command centers in the cerebral cortex.

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In patients with Parkinson's disease, the nigro-striatal dopaminergic neurons are degenerated, which causes hyperexcitation of both GABA and ACh striatal neurons.

SYMPTOMS

Parkinson's disease signs and symptoms can be different for everyone. Early signs may be mild and go unnoticed. Symptoms often begin on one side of your body and usually remain worse on that side, even after symptoms begin to affect both sides.

Parkinson's signs and symptoms may include:

- **Tremor.** A tremor, or shaking, usually begins in a limb, often your hand or fingers. You may a rub your thumb and forefinger back-and-forth, known as a pill-rolling tremor. Your hand may tremor when it's at rest. (<https://www.youtube.com/watch?v=0-t4RTQ0EsM>)
- **Slowed movement (bradykinesia).** Over time, Parkinson's disease may slow your movement, making simple tasks difficult and time-consuming. Your steps may become shorter when you walk. It may be difficult to get out of a chair. You may drag your feet as you try to walk.
- **Rigid muscles.** Muscle stiffness may occur in any part of your body. The stiff muscles can be painful and limit your range of motion.

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- **Impaired posture and balance.** Your posture may become stooped, or you may have balance problems as a result of Parkinson's disease.
- **Loss of automatic movements.** You may have a decreased ability to perform unconscious movements, including blinking, smiling or swinging your arms when you walk.
- **Speech changes.** You may speak softly, quickly, slur or hesitate before talking. Your speech may be more of a monotone rather than with the usual inflections.
- **Writing changes.** It may become hard to write, and your writing may appear small.

CAUSES

In Parkinson's disease, certain nerve cells (neurons) in the brain gradually break down or die. Many of the symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes abnormal brain activity, leading to symptoms of Parkinson's disease.

The cause of Parkinson's disease is unknown, but several factors appear to play a role, including:

- **Your genes.** Researchers have identified specific genetic mutations that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease.

However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.

- **Environmental triggers.** Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is relatively small.

Researchers have also noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:

- **The presence of Lewy bodies.** Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.
- **Alpha-synuclein is found within Lewy bodies.** Although many substances are found within Lewy bodies, scientists believe an important one is the natural and widespread protein called alpha-synuclein (a-synuclein). It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers.

RISK FACTORS

Risk factors for Parkinson's disease include:

- **Age.** Young adults rarely experience Parkinson's disease. It ordinarily begins in middle or late life, and the risk increases with age. People usually develop the disease around age 60 or older.

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- **Heredity.** Having a close relative with Parkinson's disease increases the chances that you'll develop the disease. However, your risks are still small unless you have many relatives in your family with Parkinson's disease.
- **Sex.** Men are more likely to develop Parkinson's disease than are women.
- **Exposure to toxins.** Ongoing exposure to herbicides and pesticides may slightly increase your risk of Parkinson's disease.

COMPLICATIONS

Parkinson's disease is often accompanied by these additional problems, which may be treatable:

- **Thinking difficulties.** You may experience cognitive problems (dementia) and thinking difficulties. These usually occur in the later stages of Parkinson's disease. Such cognitive problems aren't very responsive to medications.
- **Depression and emotional changes.** You may experience depression, sometimes in the very early stages. Receiving treatment for depression can make it easier to handle the other challenges of Parkinson's disease.
You may also experience other emotional changes, such as fear, anxiety or loss of motivation. Doctors may give you medications to treat these symptoms.
- **Swallowing problems.** You may develop difficulties with swallowing as your condition progresses. Saliva may accumulate in your mouth due to slowed swallowing, leading to drooling.
- **Chewing and eating problems.** Late-stage Parkinson's disease affects the muscles in your mouth, making chewing difficult. This can lead to choking and poor nutrition.
- **Sleep problems and sleep disorders.** People with Parkinson's disease often have sleep problems, including waking up frequently throughout the night, waking up early or falling asleep during the day.
People may also experience rapid eye movement sleep behavior disorder, which involves acting out your dreams. Medications may help your sleep problems.
- **Bladder problems.** Parkinson's disease may cause bladder problems, including being unable to control urine or having difficulty urinating.
- **Constipation.** Many people with Parkinson's disease develop constipation, mainly due to a slower digestive tract.

YOU MAY ALSO EXPERIENCE:

- **Blood pressure changes.** You may feel dizzy or lightheaded when you stand due to a sudden drop in blood pressure (orthostatic hypotension).
- **Smell dysfunction.** You may experience problems with your sense of smell. You may have difficulty identifying certain odors or the difference between odors.

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- **Fatigue.** Many people with Parkinson's disease lose energy and experience fatigue, especially later in the day. The cause isn't always known.
- **Pain.** Some people with Parkinson's disease experience pain, either in specific areas of their bodies or throughout their bodies.
- **Sexual dysfunction.** Some people with Parkinson's disease notice a decrease in sexual desire or performance.

PREVENTION

Because the cause of Parkinson's is unknown, proven ways to prevent the disease also remain a mystery. Some research has shown that regular aerobic exercise might reduce the risk of Parkinson's disease. Some other research has shown that people who drink caffeine — which is found in coffee, tea and cola — get Parkinson's disease less often than those who don't drink it. However, it is still not known whether caffeine actually protects against getting Parkinson's, or is related in some other way. Currently there is not enough evidence to suggest drinking caffeinated beverages to protect against Parkinson's. Green tea is also related to a reduced risk of developing Parkinson's disease.