Basal Ganglia
and Dopamine

By Jakub Staniszewski

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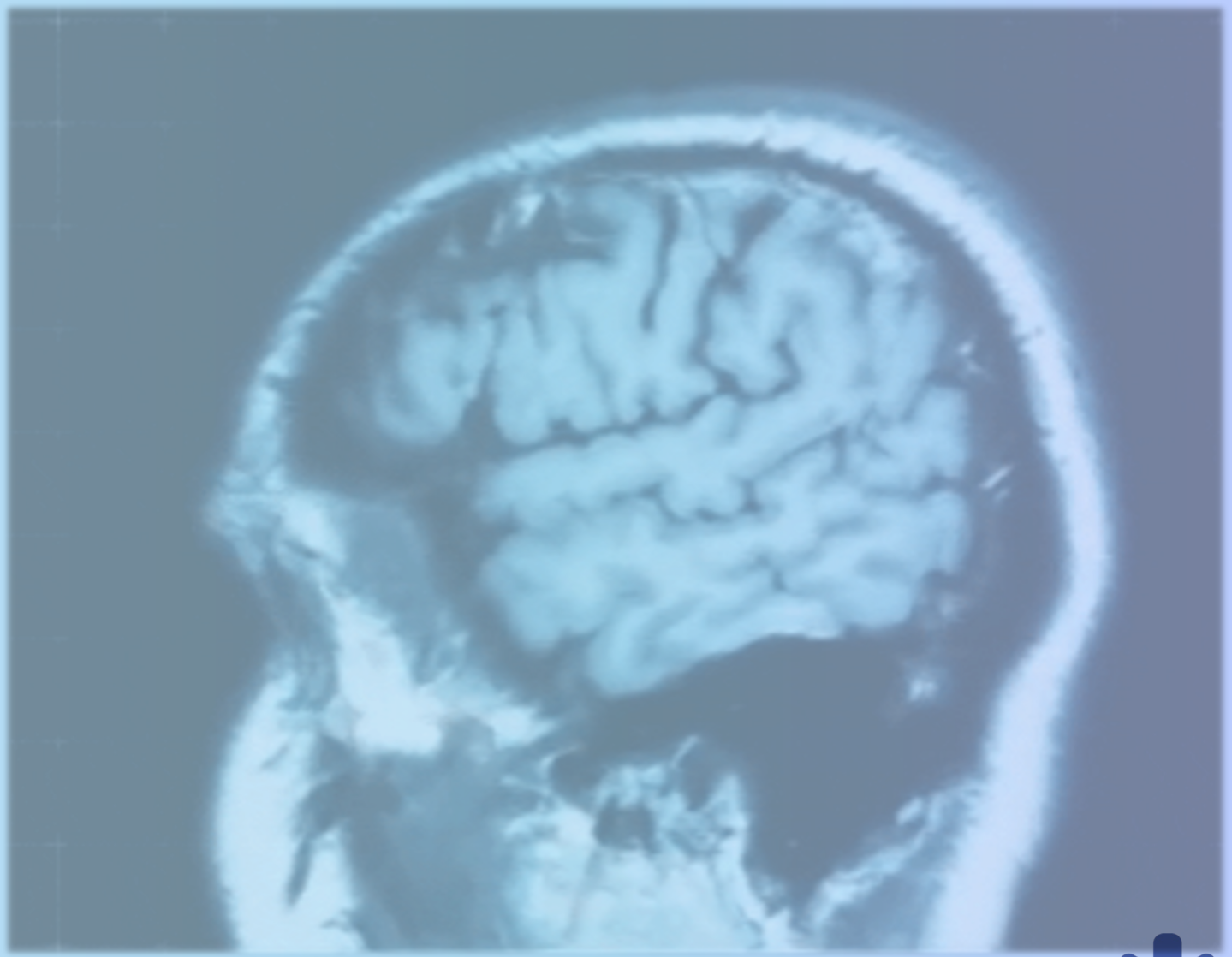


One of your patients enters the office…

Her symptoms have clearly worsened since her last visit; either she stopped taking her medications, or they no longer work.

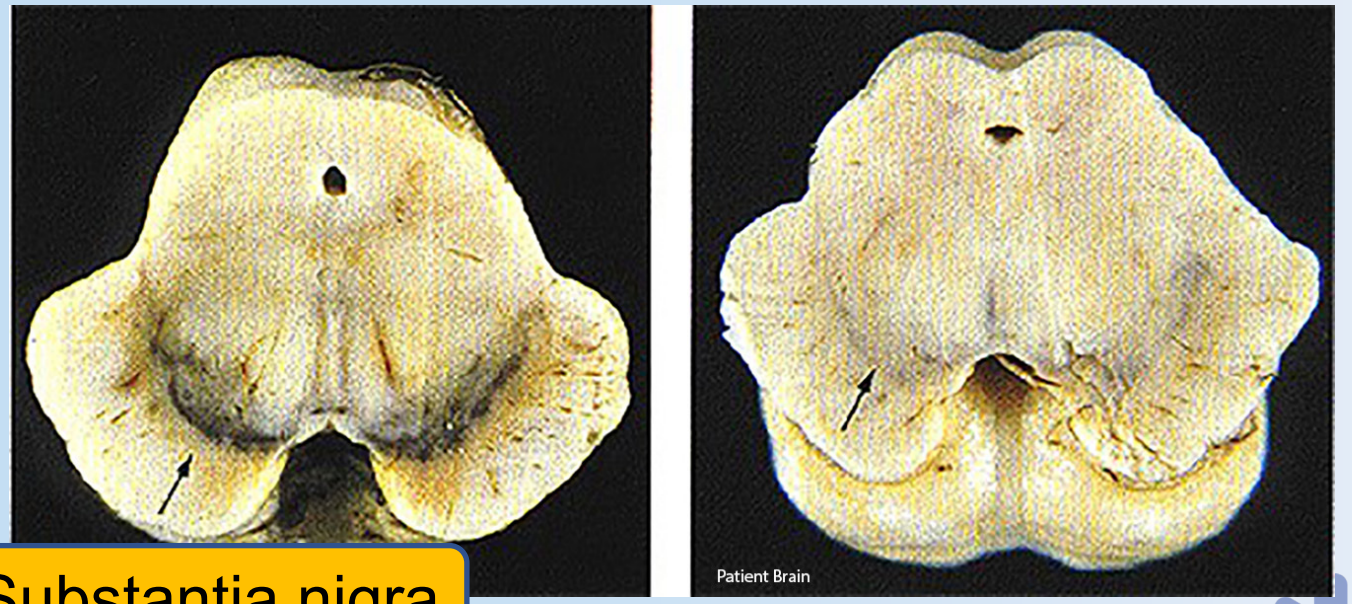
She slowly shuffles over to the chair across from you, hunching over and holding firmly onto her walker (she didn't have it last time).

While speaking with her, you notice she isn't taking notes as usual. You ask that she rest her hands on the desk to observe a worsening tremor. It seems to resemble rolling a pill between her thumb and index finger.

At the end of your meeting you remind her to adhere to her medications. In leaving you see she struggles to lift her coat off the rack; her arms look stiff and her movements are jolty.

A few months later you get a call from the patient's sister. She informs you that her sister has recently passed away as a result of pneumonia.

When an autopsy is performed the brain stem is dissected, and the following can be seen.



Substantia nigra

Questions to ask

- What disease was the patient suffering from?
- What went wrong with the substantia nigra?
- How is the substantia nigra involved in movement?
- How could have medications helped this patient?

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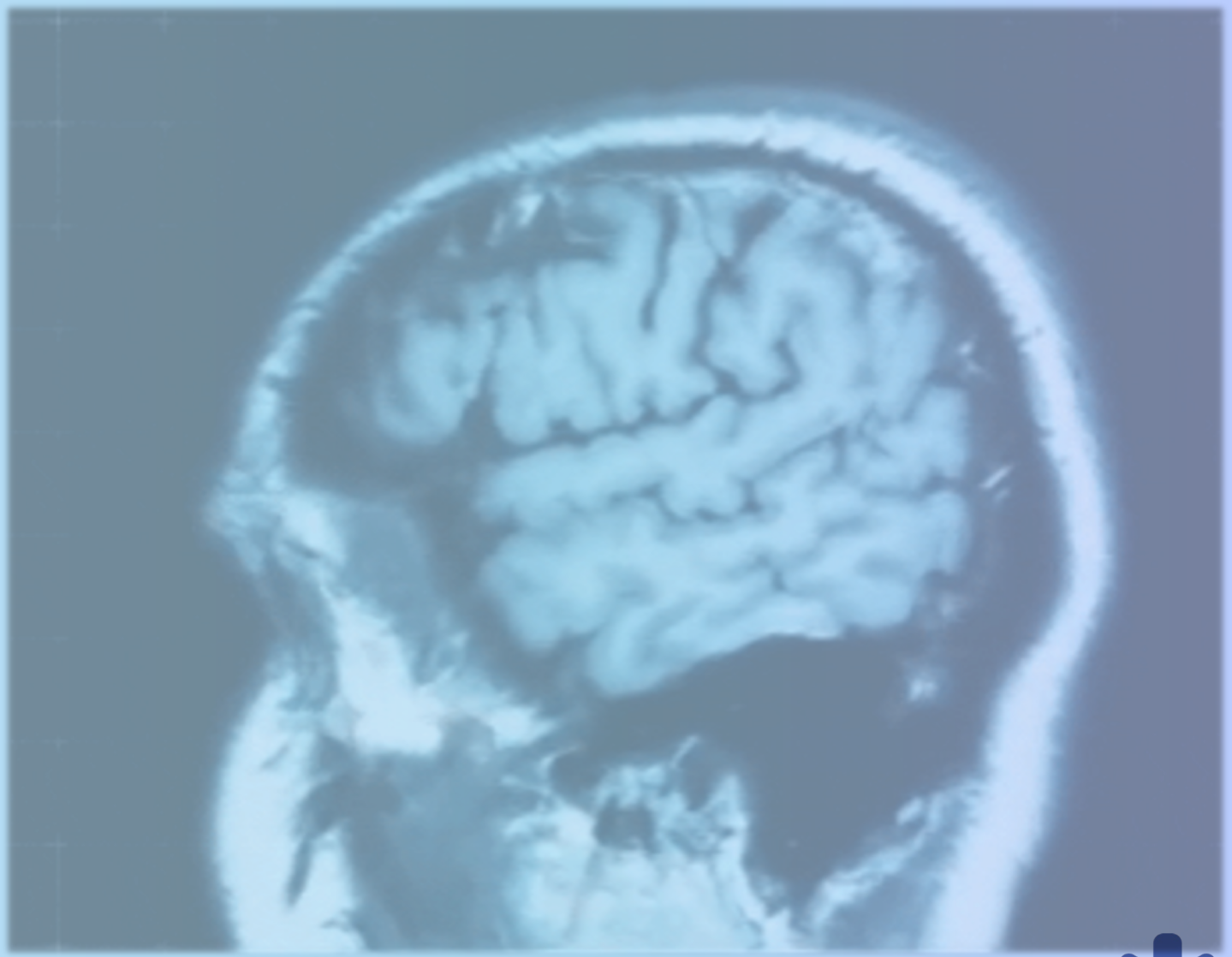
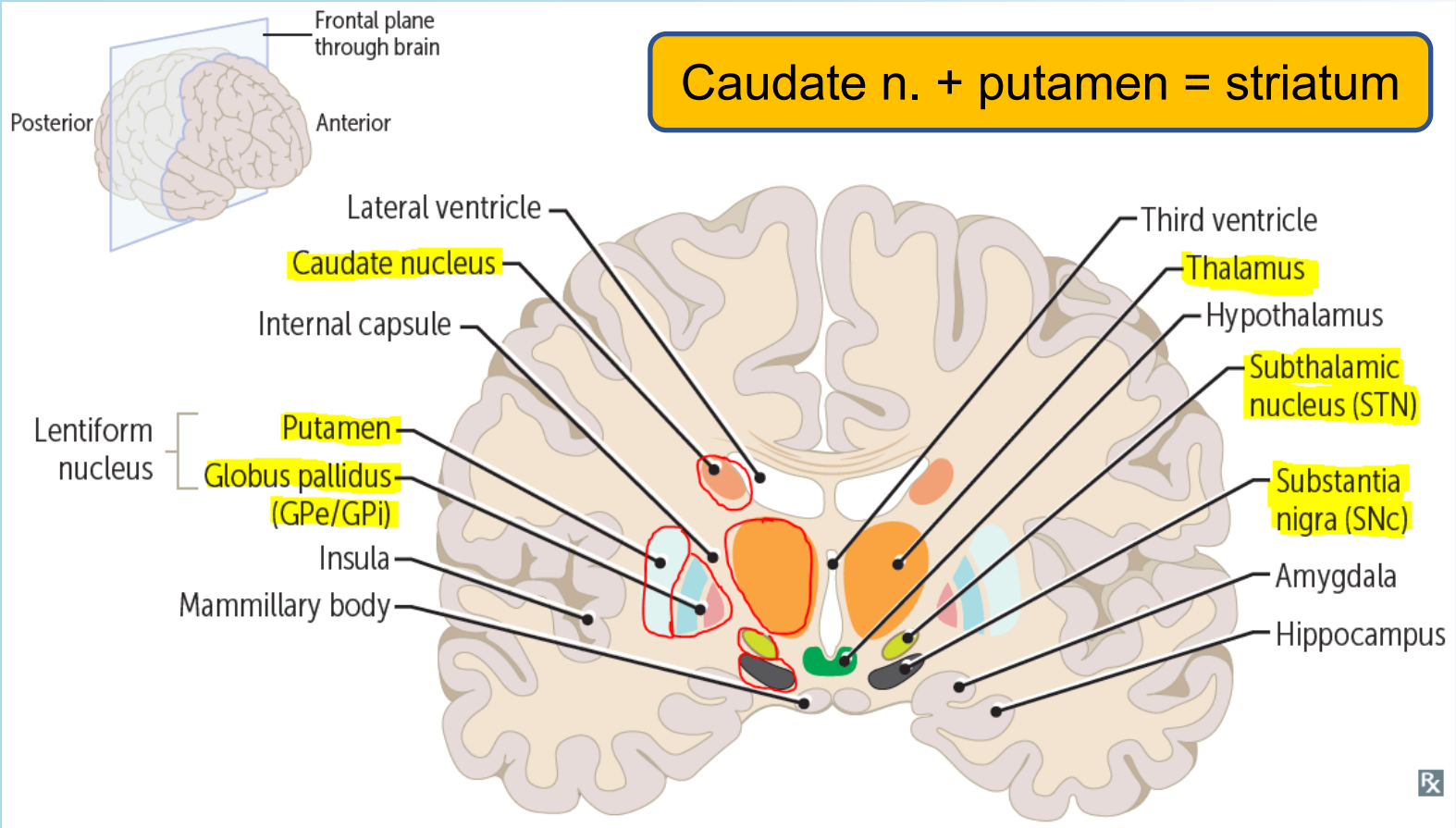


Anatomy of basal ganglia

- Basal ganglia are a collection of **subcortical brain nuclei** (dense synaptic regions) that interact with each other to regulate movement of skeletal muscle.

- They form neuronal circuits with the motor cortex and the thalamus.
- They receive signals from the motor cortex and can send modified signals back.
- Functional anatomy is more important than actual anatomy!



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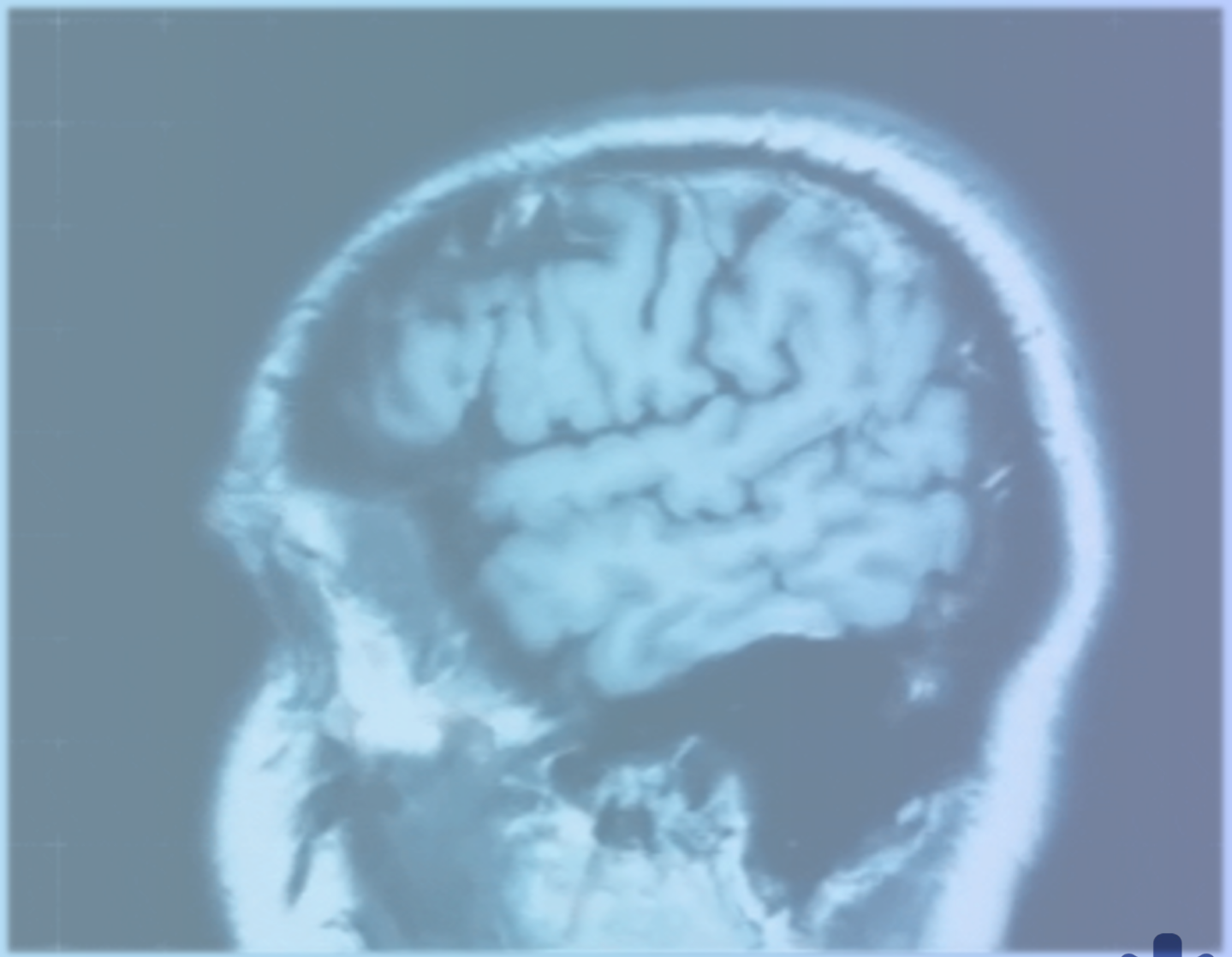
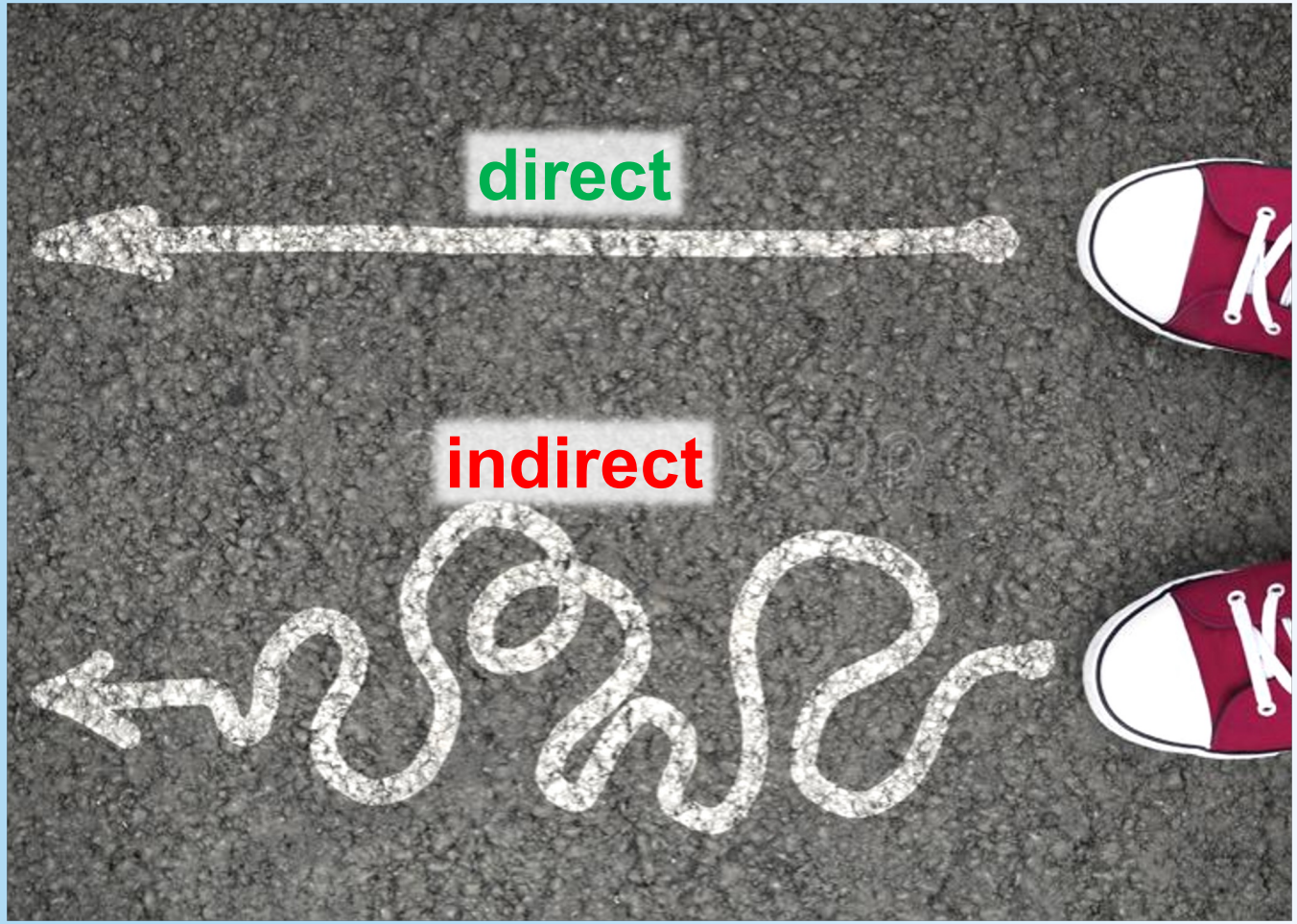


Intro to Pathways

- There are two pathways through the basal ganglia, direct and indirect.
- The direct pathway **increases** motor activity.
- The indirect pathway **decreases** motor activity.
- They share some structures, while some differ.
- The thalamus is the last stop before the cortex.



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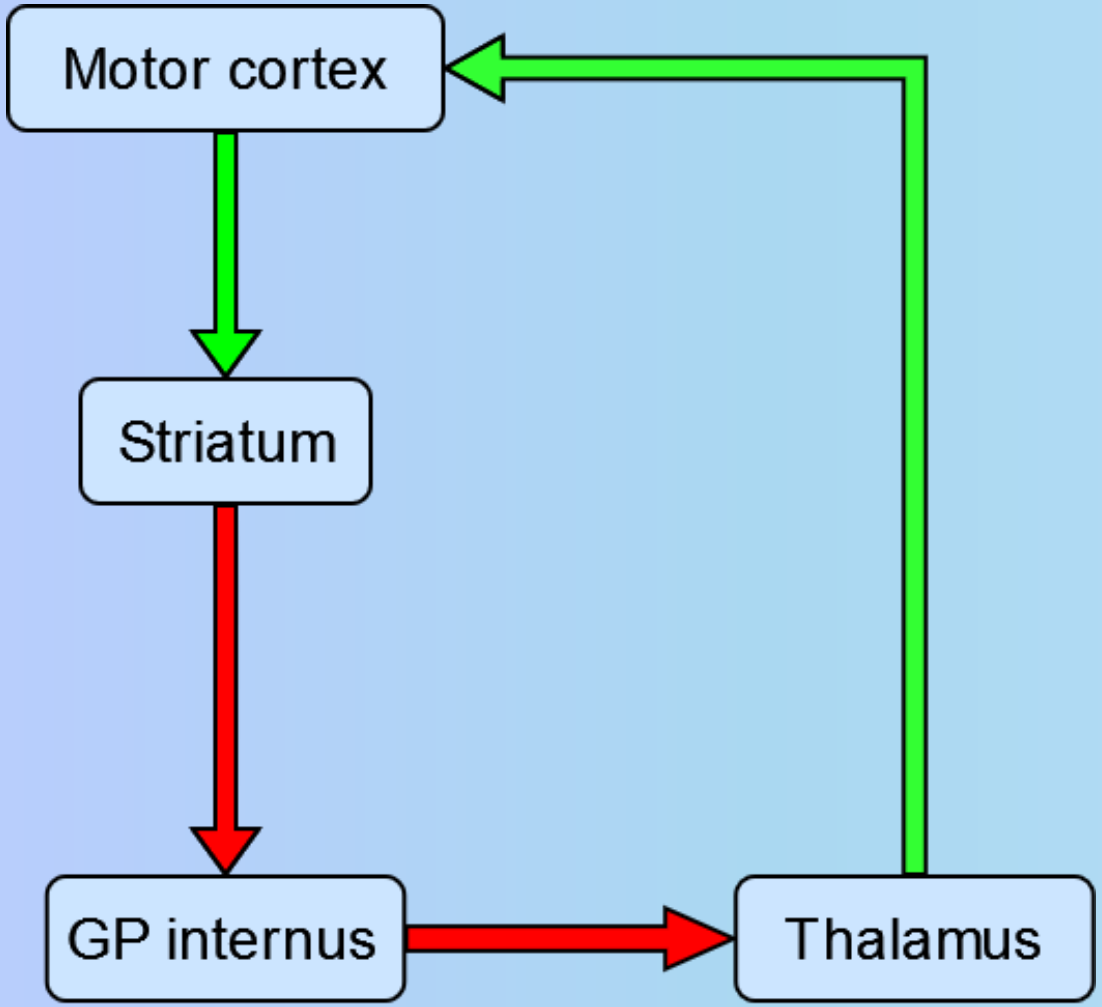
Direct pathway

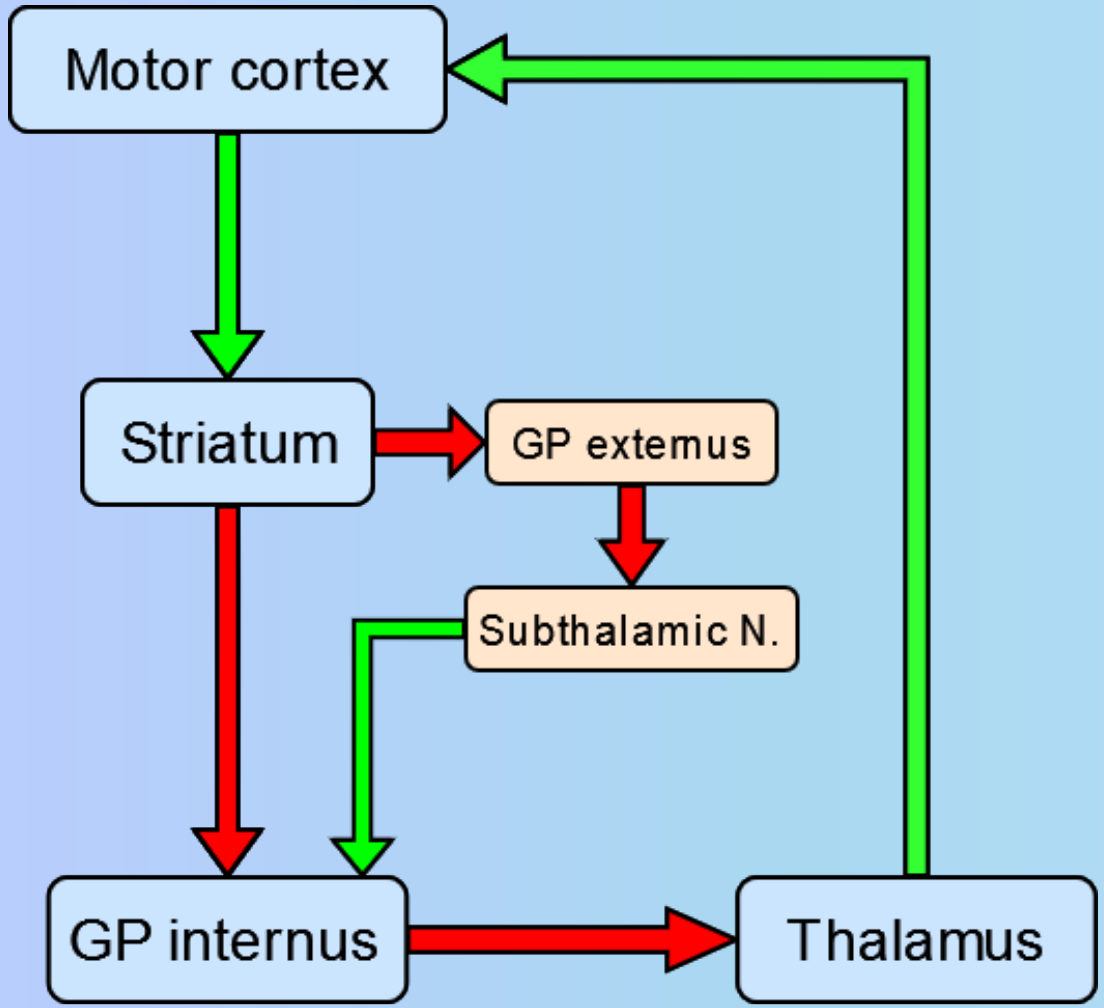
MSIT = **M**otor cortex, **S**triatum, **I**nternus, **T**halamus



- Stimulating signals are **green**, the neurotransmitter is **Glutamate**.
- Inhibitory signals are **red**, the neurotransmitter is **GABA**.
- The net result is **stimulation** of the motor cortex. More motor activity!
- Two negatives make a positive!

Indirect pathway

MSenIT = **M**otor cortex, **S**triatum, **e**xternus, **n**ucleus (subthalamic), **I**nternus, **T**halamus



- The striatum to GP internus pathway now has an extra minus.
- This inverts the signal, leading to inhibition of the thalamus.
- The subthalamic nucleus is the only stimulator among the basal ganglia (wants to be positive like the thalamus).
- **Less motor activity!**

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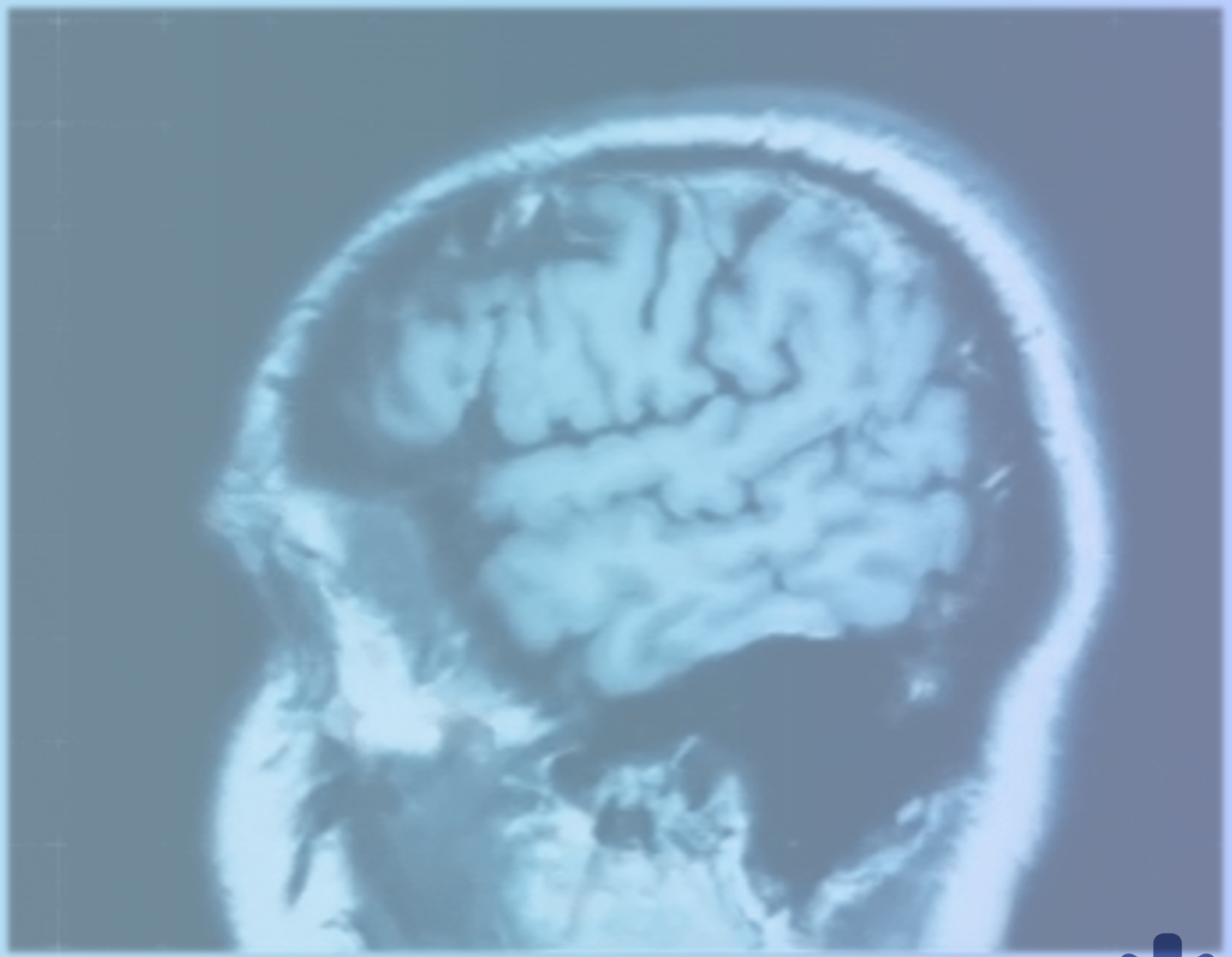
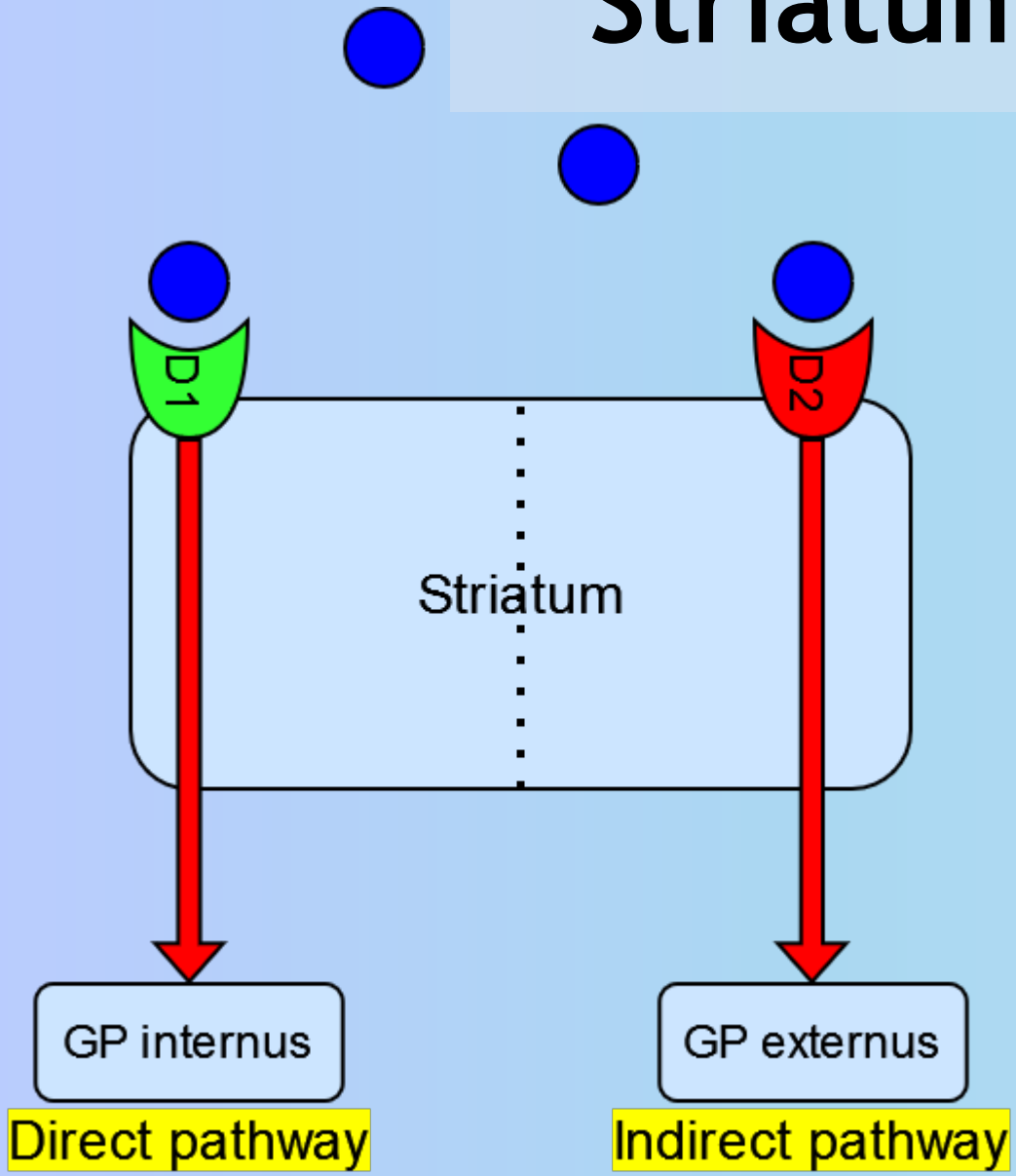


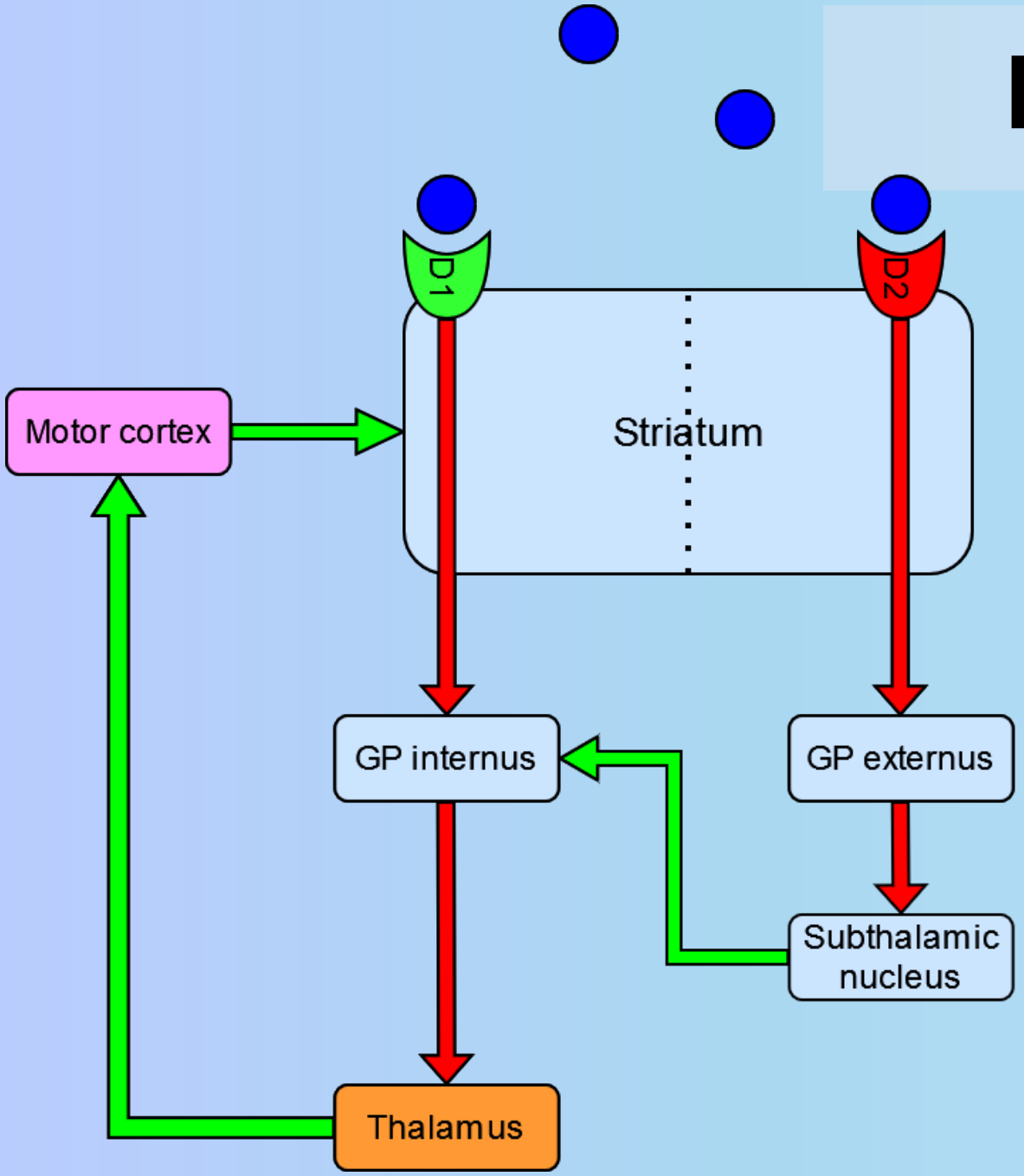
Striatum and Dopamine



- The striatum receives input from the motor cortex (via glutamate) and substantia nigra (via dopamine).
- Dopamine binds D1 and D2 receptors.
- The ligand is the same, but the outcome is different.
- D1 activated by dopamine
  D2 inhibited by dopamine
- Both lead to increased motor activity!

Dopamine increases motor activity

Effects of dopamine



- Dopamine at D1 leads to disinhibition of the thalamus.
- Dopamine at D2 blocks inhibition of GP externus. The result is the same on the thalamus.
- Multiply all the minuses!

(-) x (-) = (+)
(-) x (-) x (-) x (-) = (+)

D1rect = D1 – r
Indirect = inhibitory

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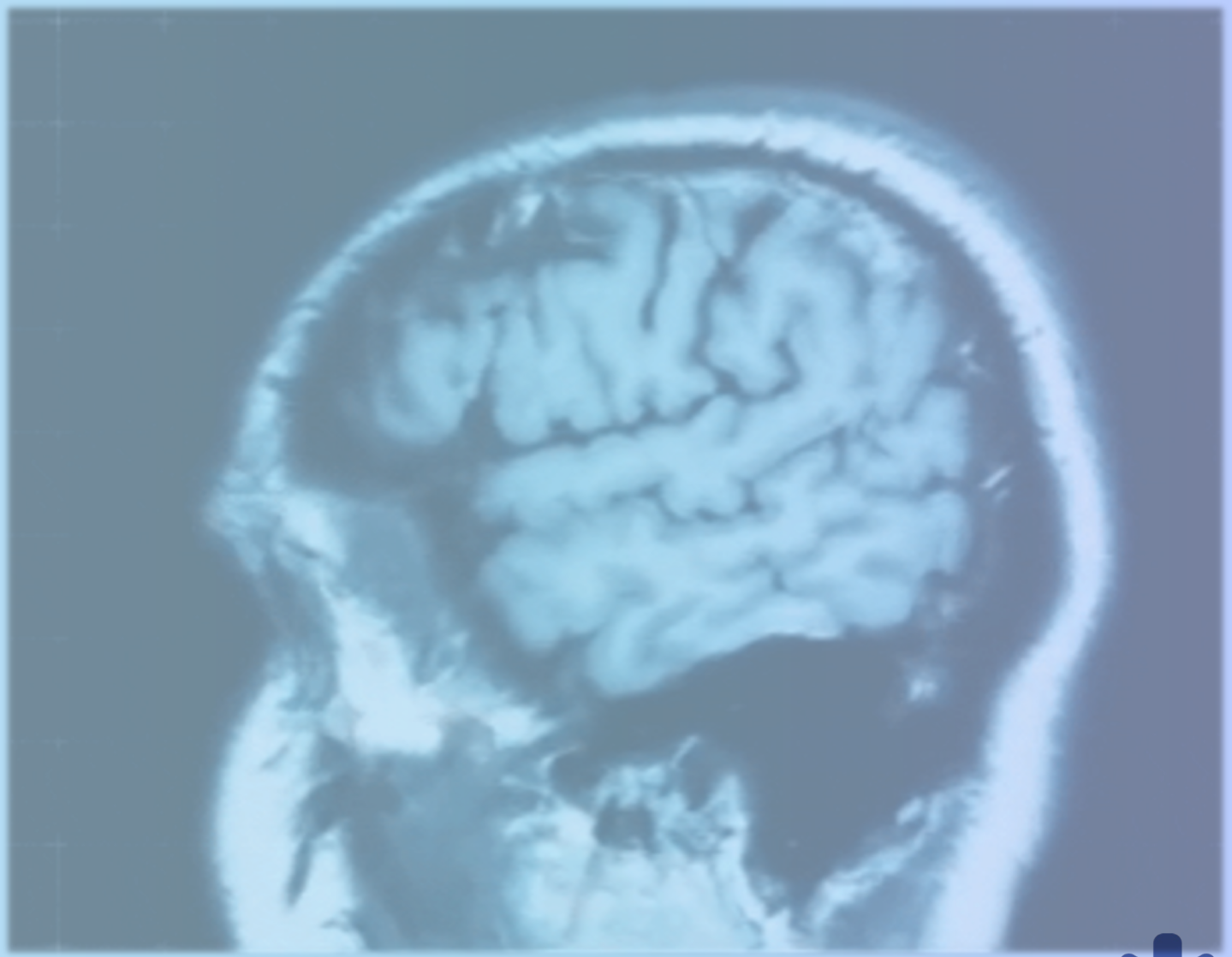


Back to our patient

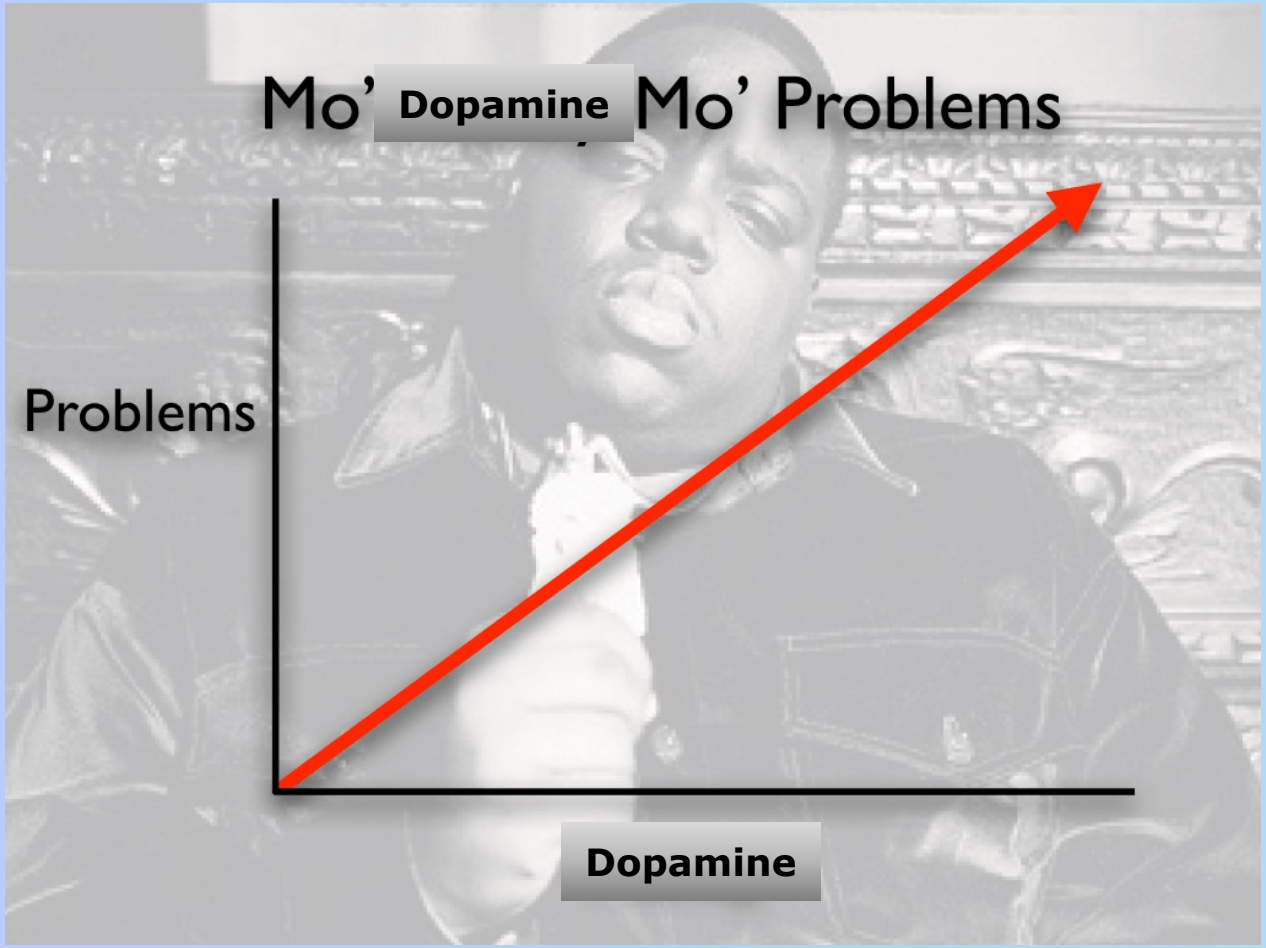
- The **nigrostriatal pathway** (substantia nigra → striatum) is a dopaminergic pathway.
- **Less dopamine = less movement** (rigidity, difficulty initiating movements).
- We can suspect a problem with the substantia nigra producing dopamine.

- **Parkinson disease** results in loss of dopaminergic neurons in the S. nigra.
- Typical symptoms are:
  - Pill-rolling tremor
  - Rigidity
  - Bradykinesia
  - Shuffling gait
  - Postural instability
  - Small handwriting

Treatment of Parkinson Disease

- **The main goal of treatment**: more dopamine reaching the striatum.
- **The compromise**: increase levels of dopamine in the CNS.
- **The solution**: give levodopa, an exogenous form of dopamine.
- **Side note**: Adjunctive medications may eventually be needed.

Huntington Disease



- A complex neurological disease with many symptoms.
- Motor symptoms are related to increased levels of dopamine.
- Patients often present with chorea (random contractions, hyperkinetic) and athetosis (slow writhing movements).
- Treatment for chorea uses drugs (VMAT-2 inhibitors) that inhibit release of dopamine.

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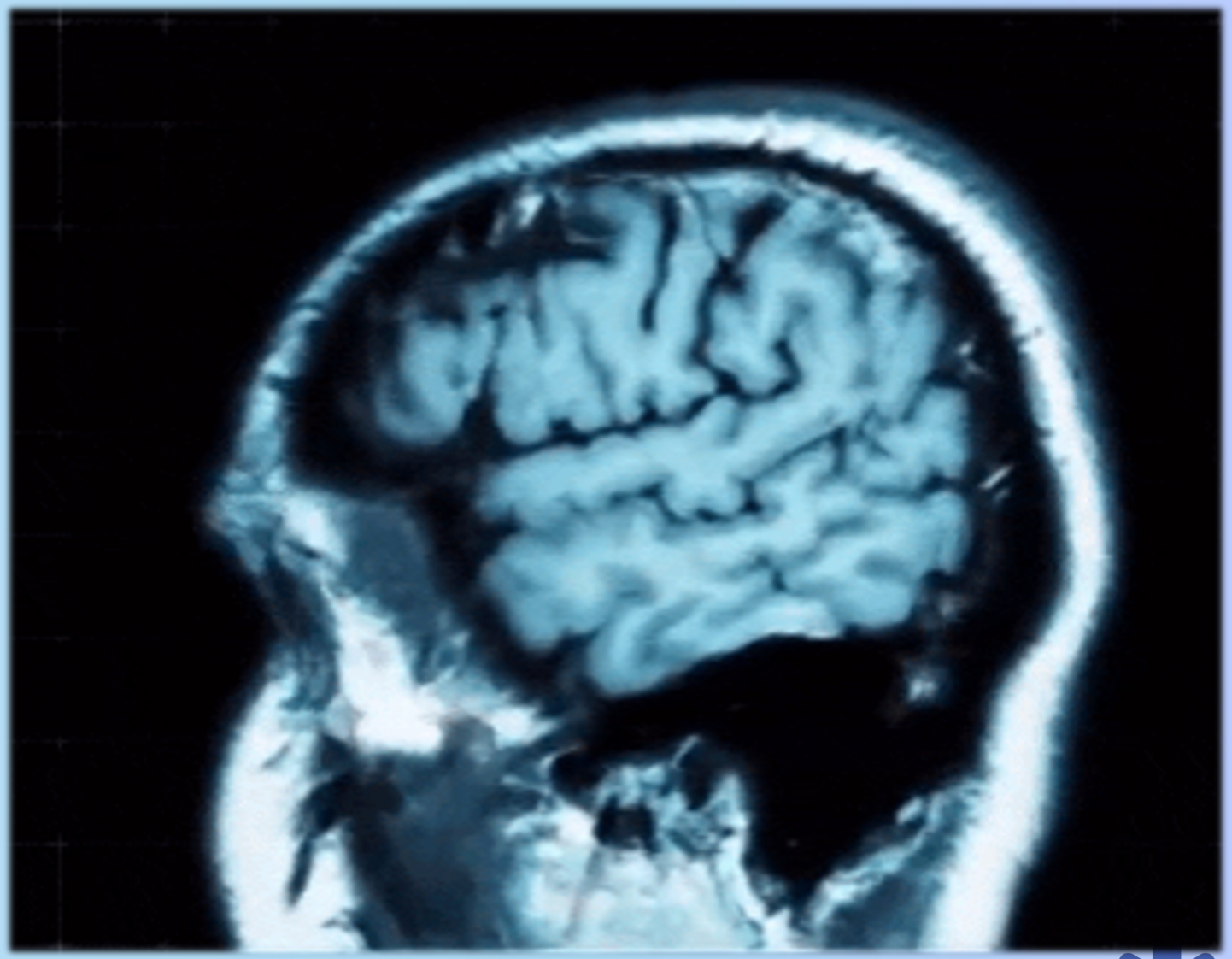

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Thanks for listening!

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