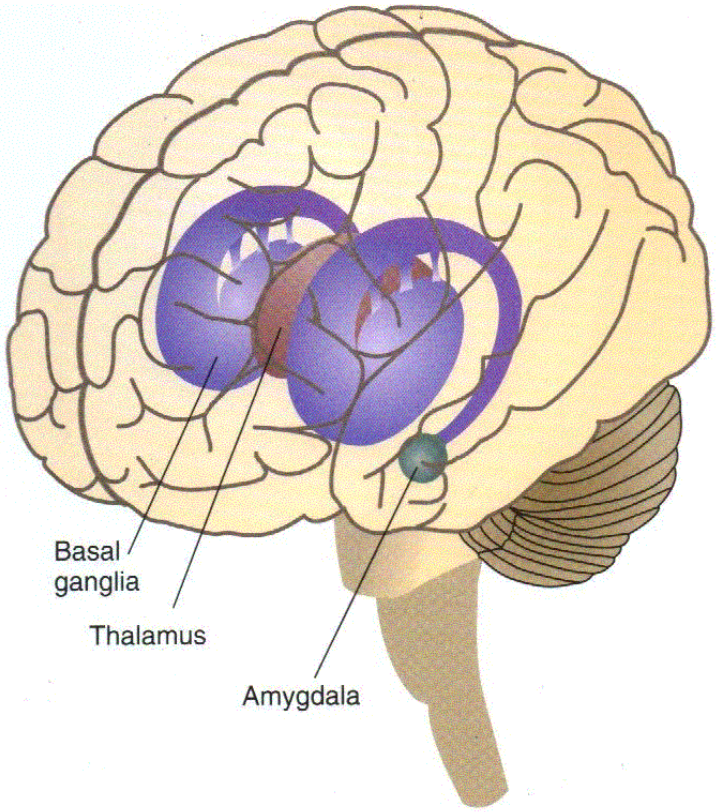
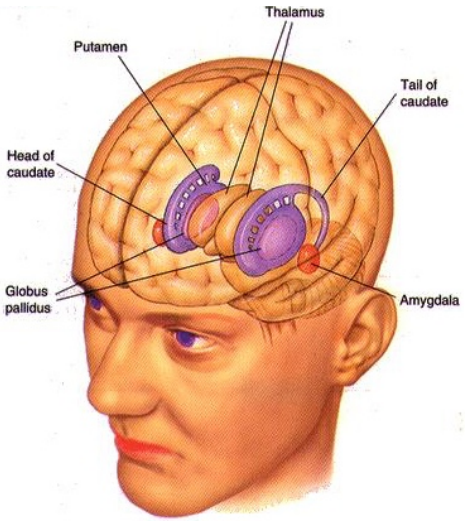
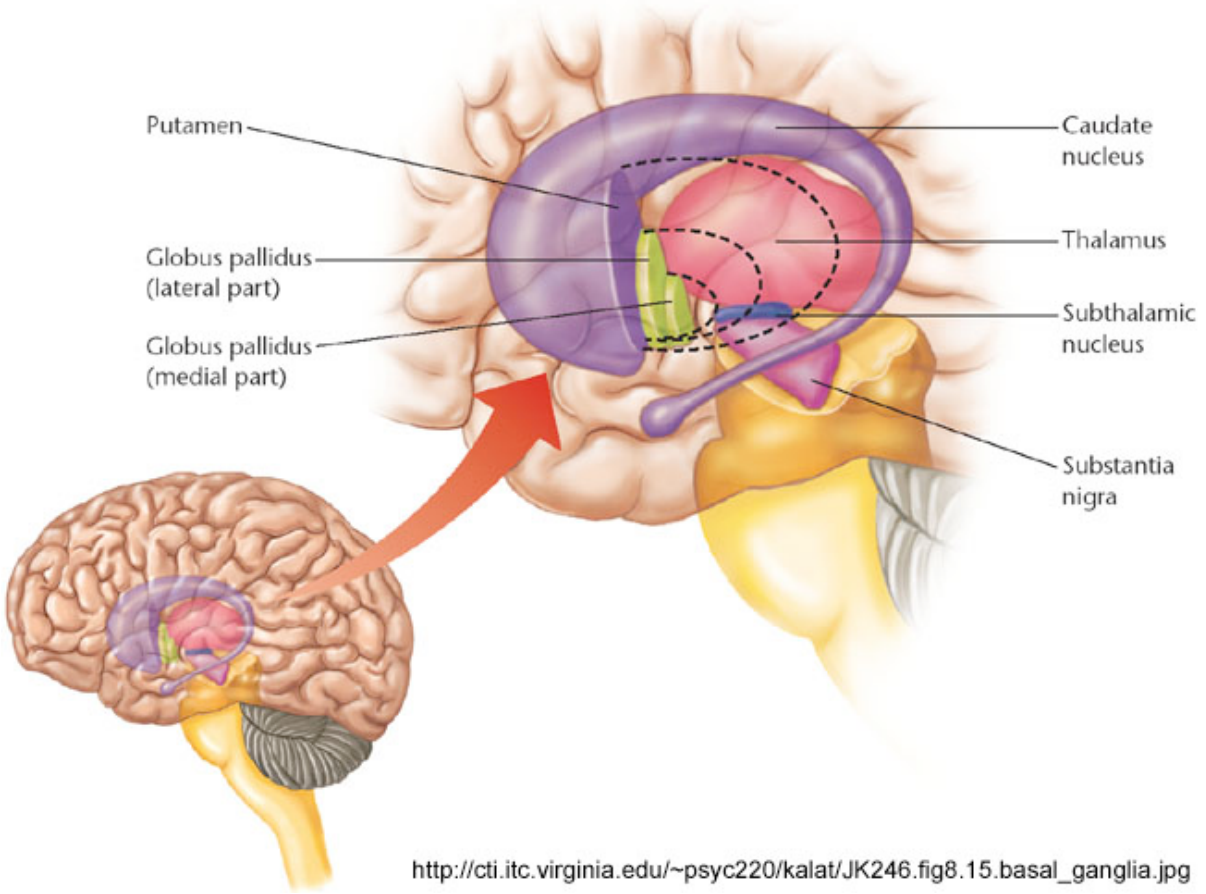
Introduction to Neuroscience: The Basal Ganglia

Michal Rivlin

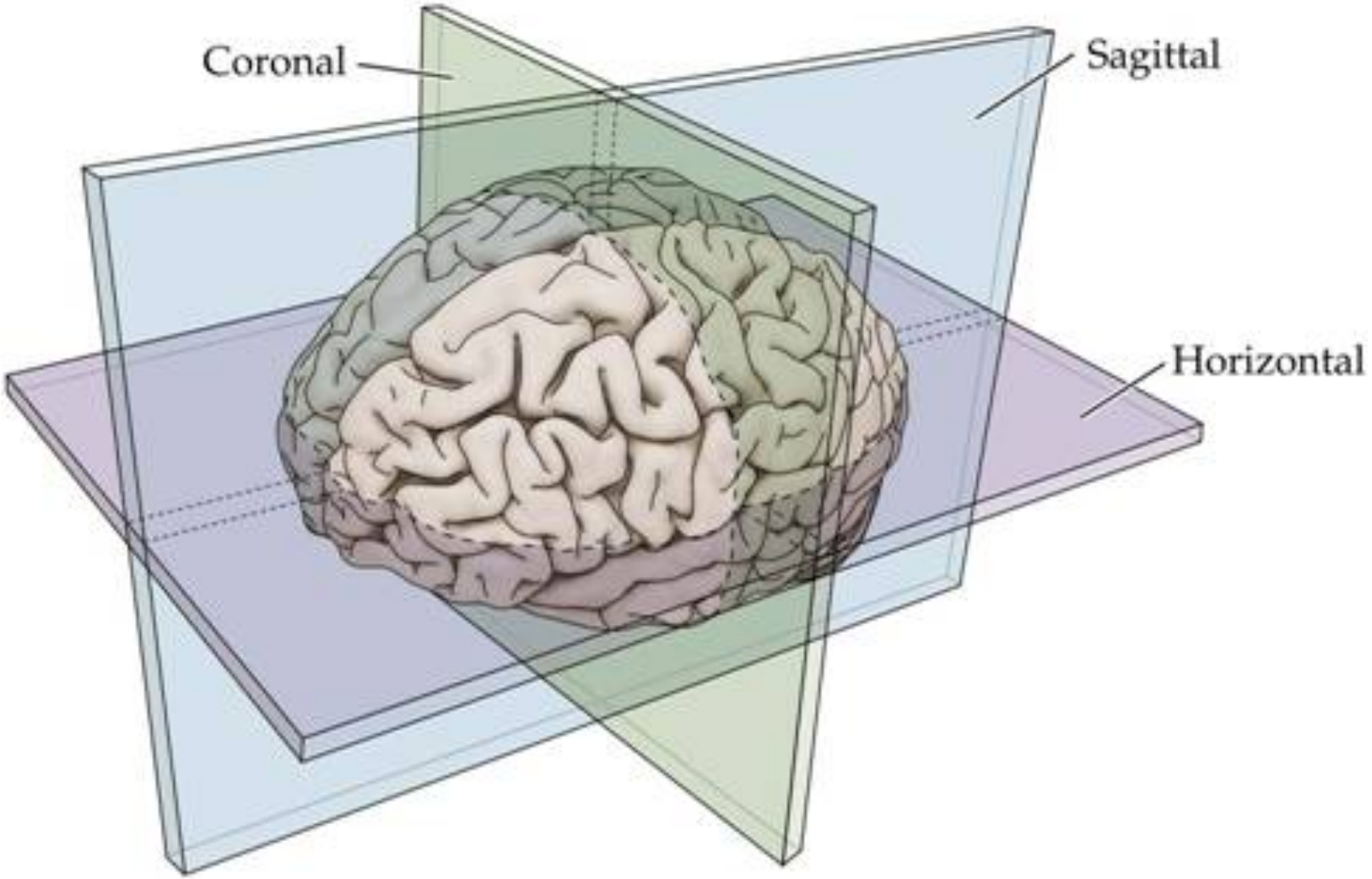


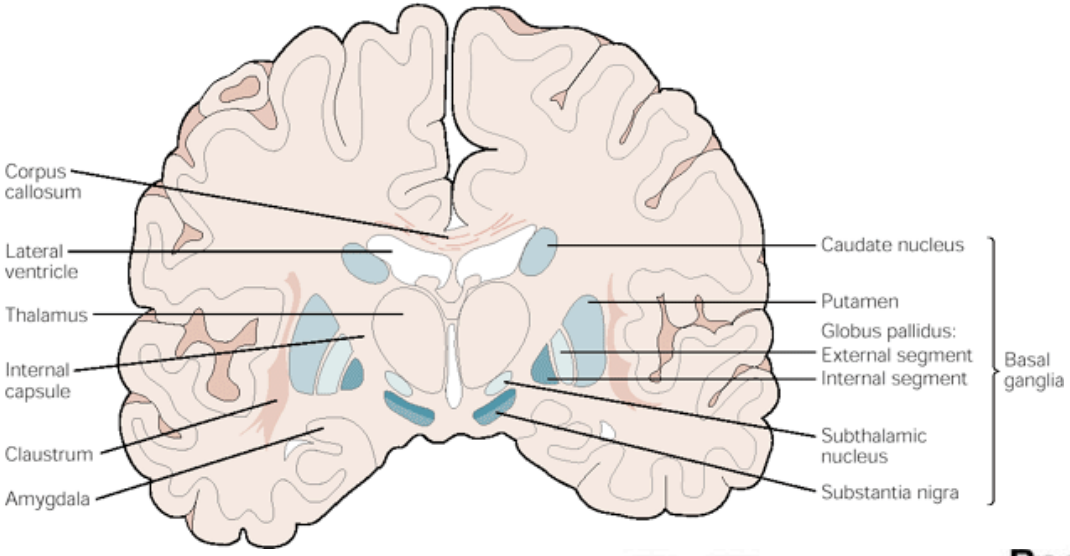
Basal Ganglia– a group of subcortical nuclei



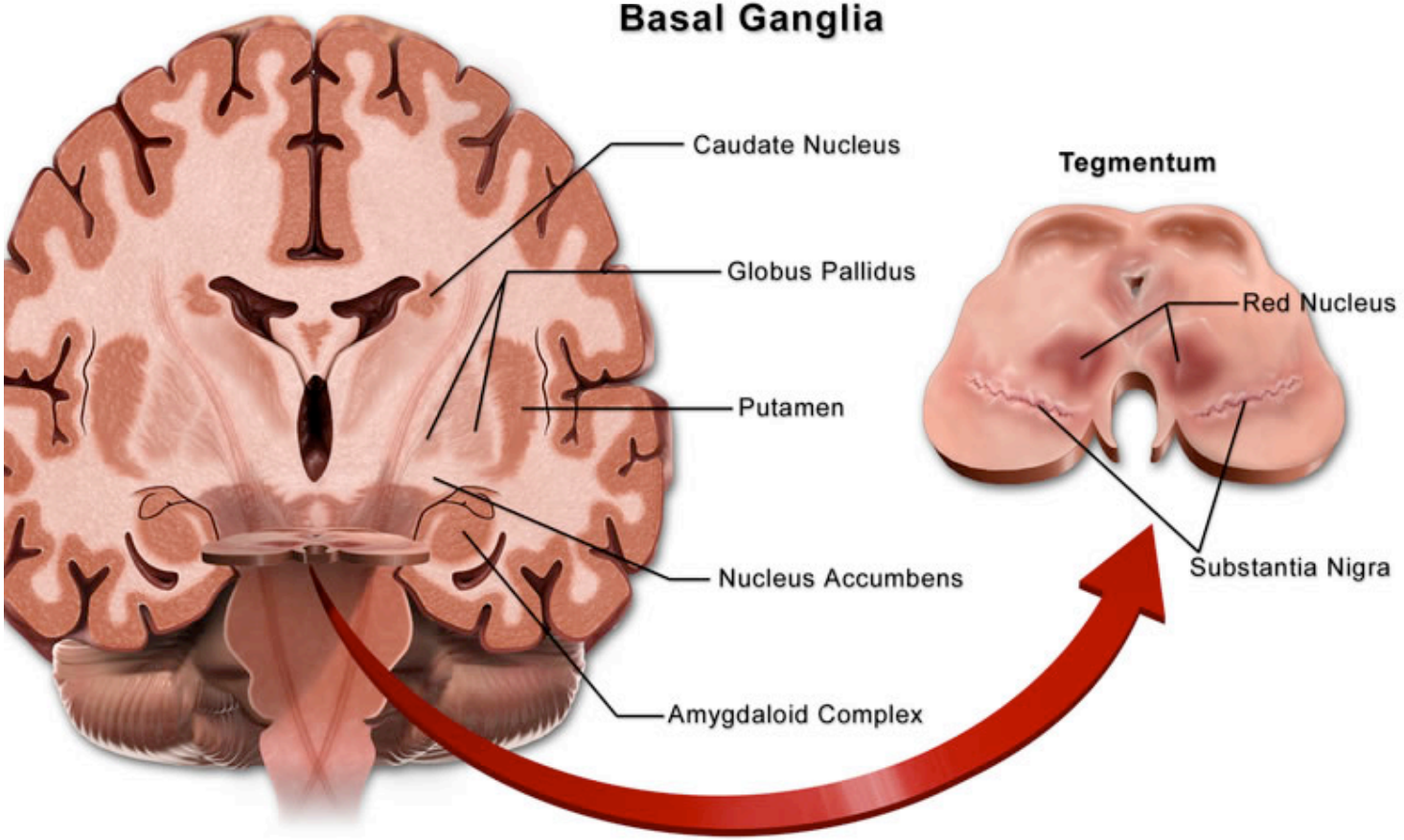


- Striatum: caudate & putamen
- Globus pallidus (external & internal segments)
- Subthalamic nucleus
- Substantia nigra (pars compacta & pars reticulata)


Coronal
Sagittal
Horizontal



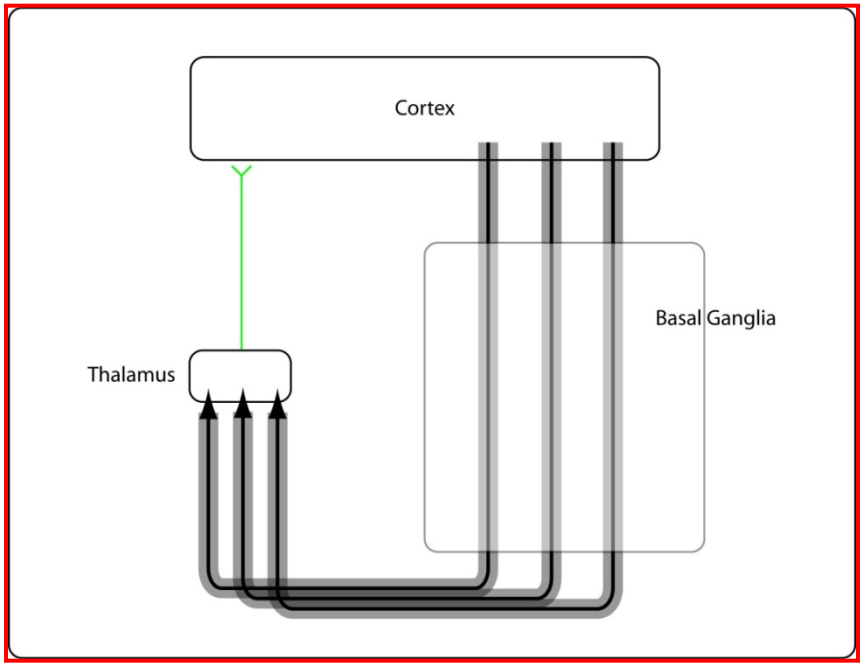
Basal Ganglia



Basal ganglia-thalamo-cortical loop

- Basal Ganglia receives robust input from the cortex

- Principal projection of the BG – via the thalamus back to cortical targets

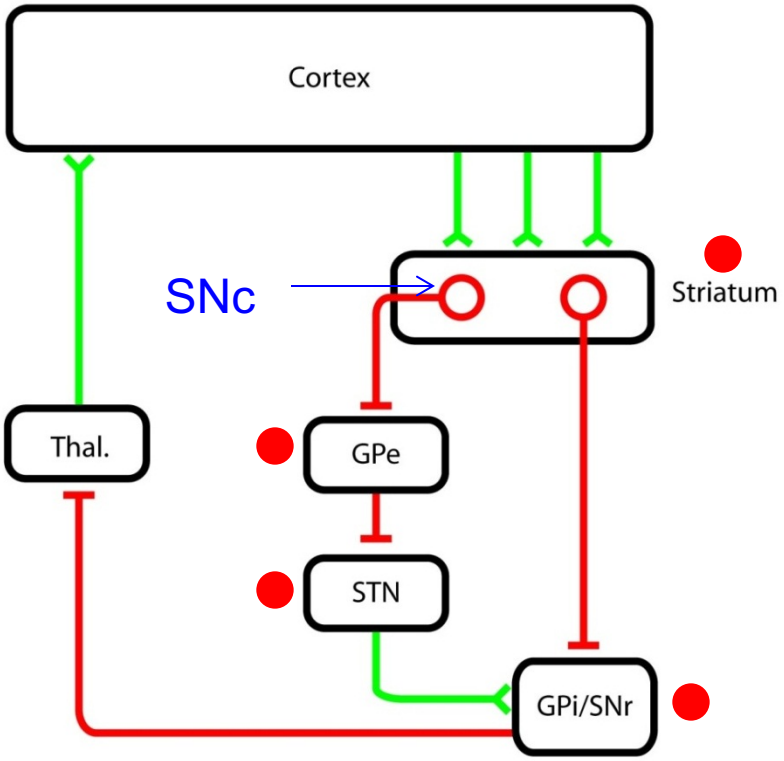


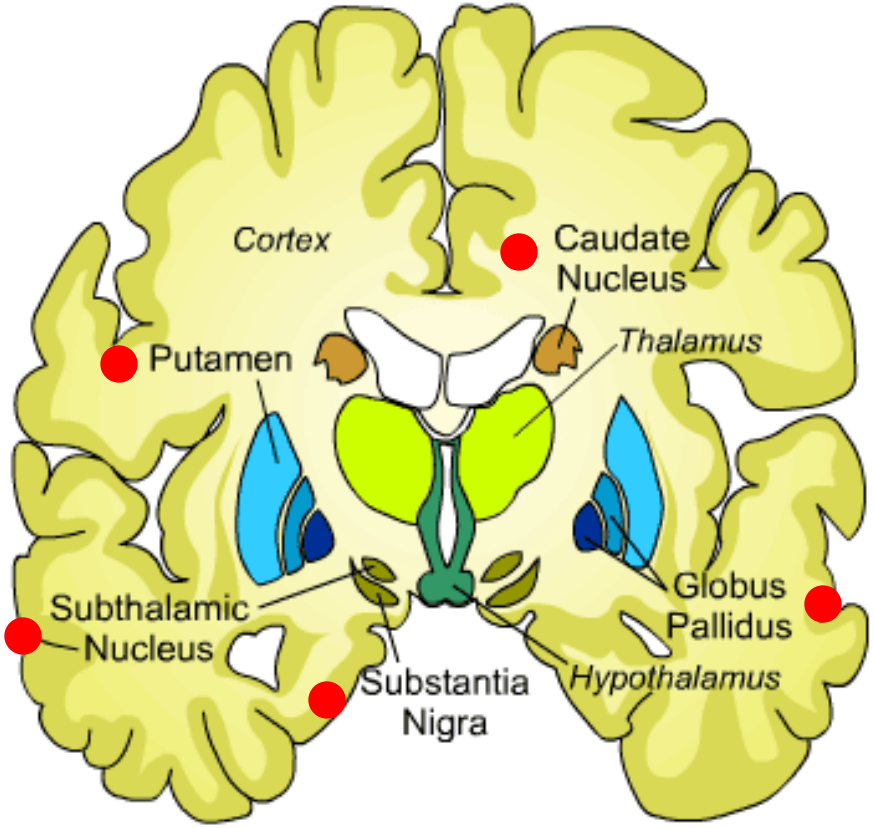
Overview of BG organization

- Input:
  - Caudate and putamen (together, the striatum)
- Intrinsic:
  - Subthalamic nucleus (STN)
  - External segment of globus pallidus (GPe)

Output:
Substantia nigra pars reticulata (SNr)
Internal segment of globus pallidus (GPi)

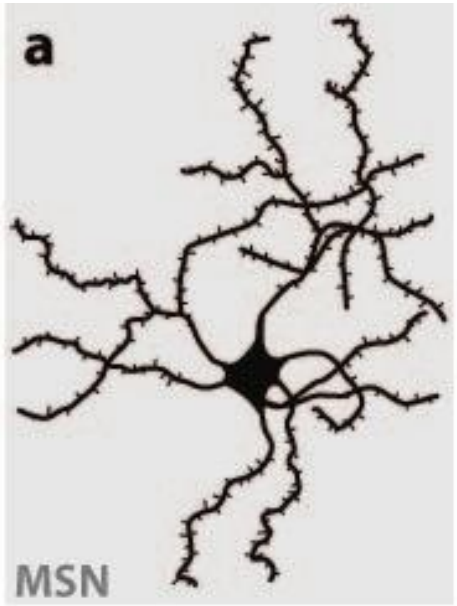
Neuromodulator:
Substantia nigra pars compacta (SNc)



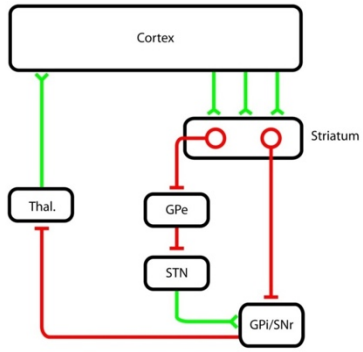


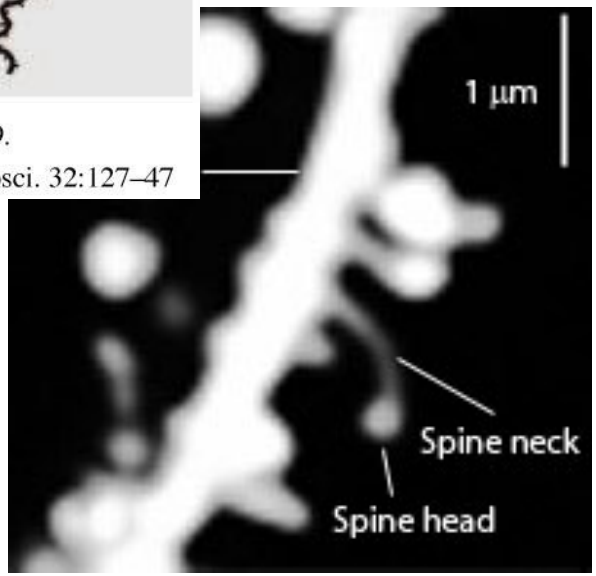
Striatum: Medium spiny neurons

- Caudate and putamen
- Medium spiny neurons
  - 95% of neurons; primary projection neurons
  - GABAergic; inhibitory
  - Very little spontaneous activity

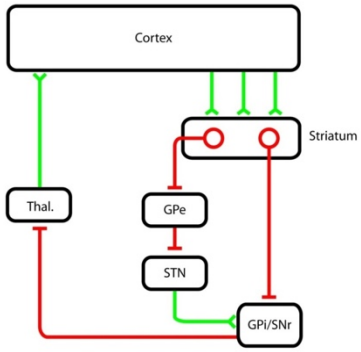


Kreitzer AC. 2009.
Annu. Rev. Neurosci. 32:127–47





Striatum: Intrinsic interneurons

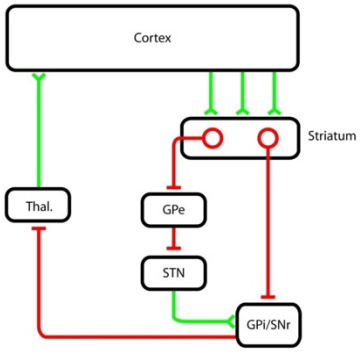


2 principle types

– 3 GABAergic interneurons

– Tonically active neurons (TANs)
  - Cholinergic
  - Large cell bodies

Globus pallidus

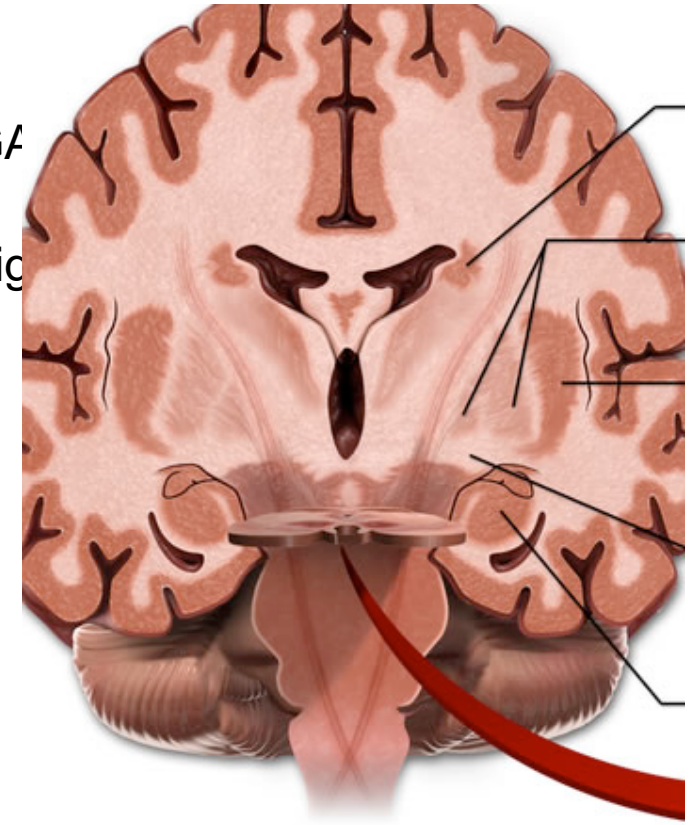


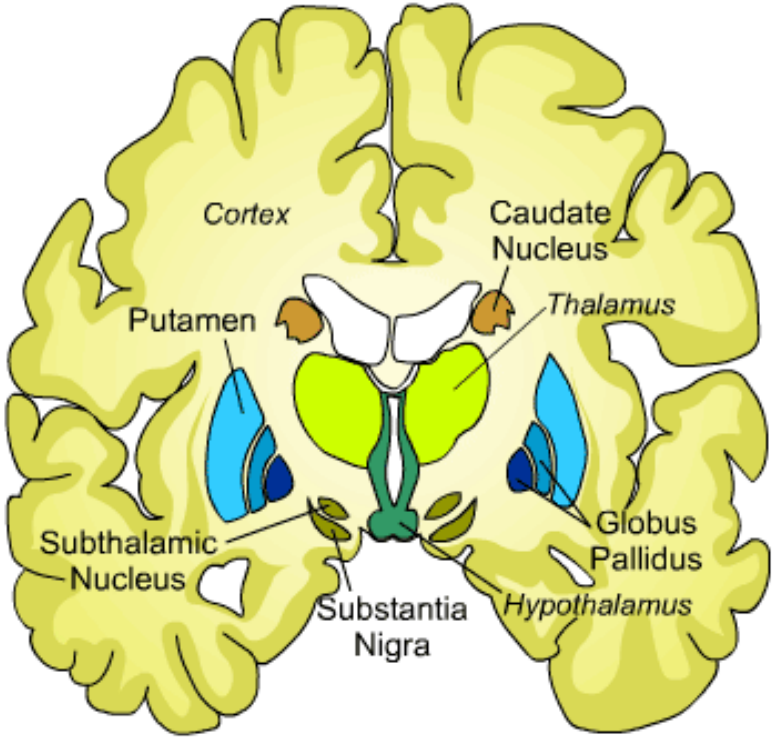
Two segments

Internal (GPi): Principle output nucleus
External (GPe): intrinsic circuitry

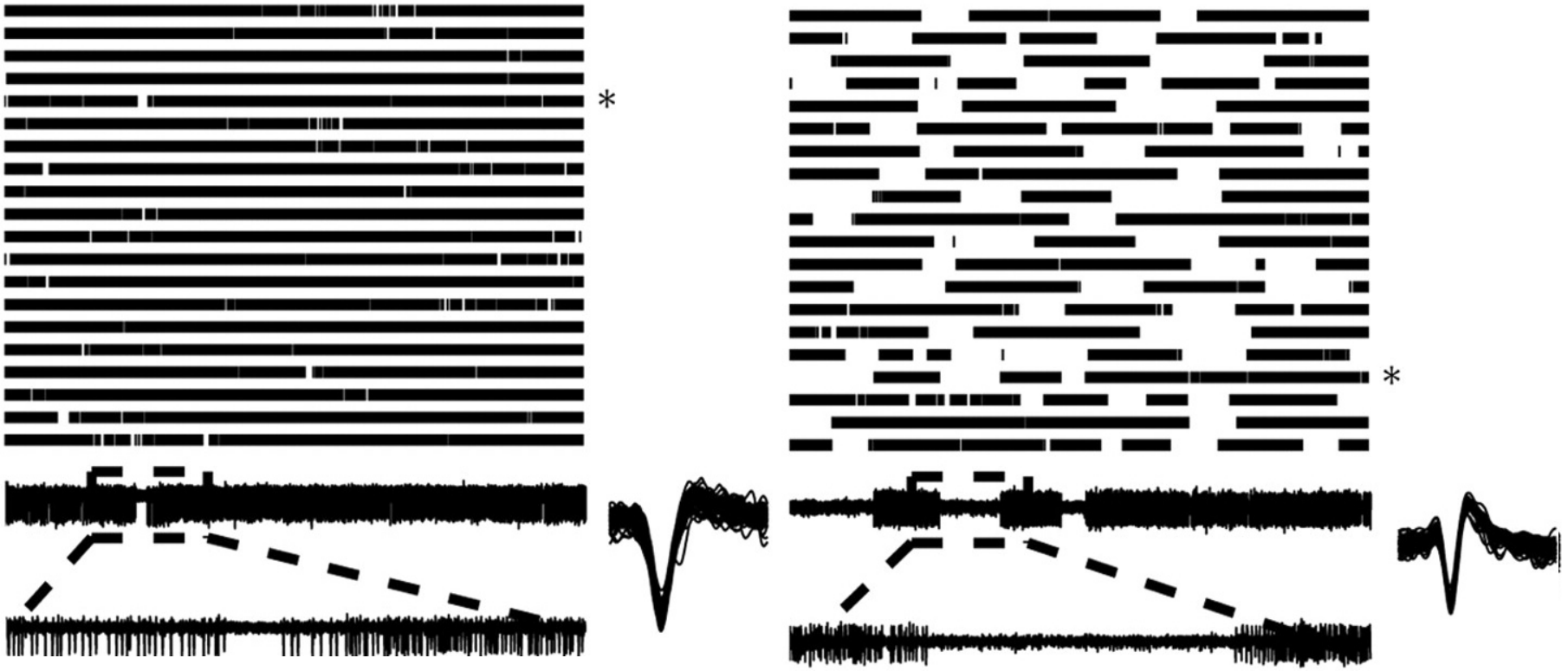
GA

hig





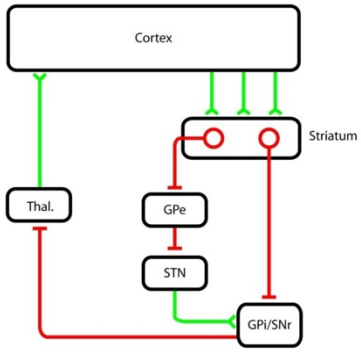
Globus pallidus

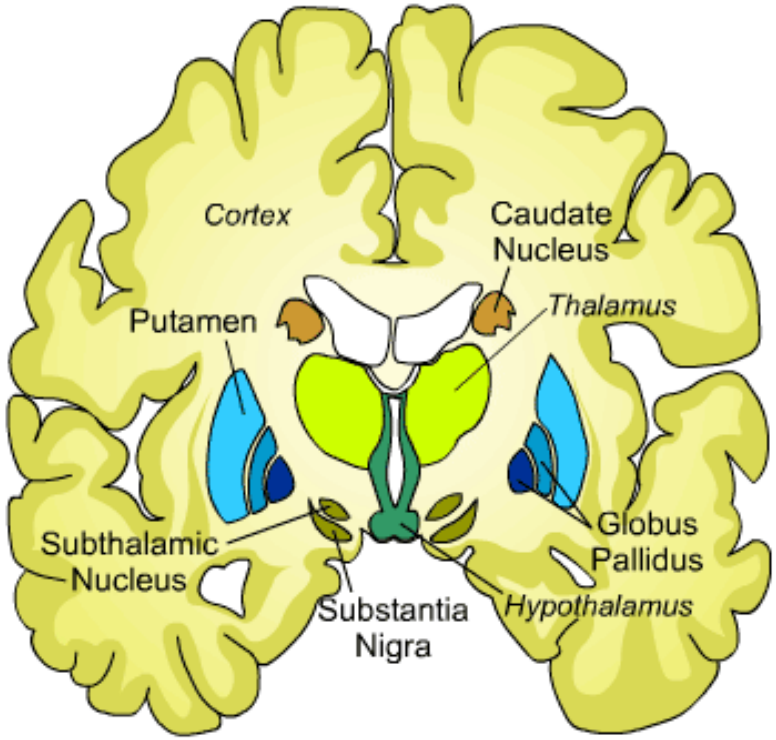


Elias et al. J. Neurosci. 2007

Subthalamic nucleus

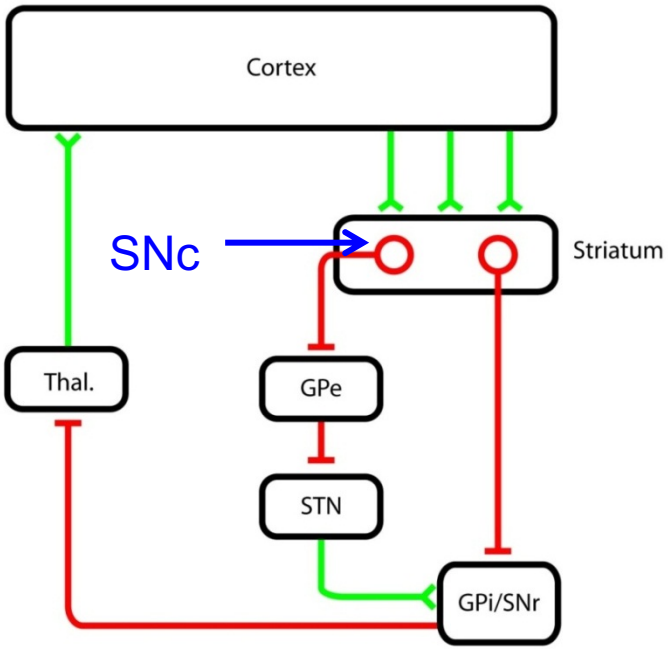
Glutamatergic;
excitatory

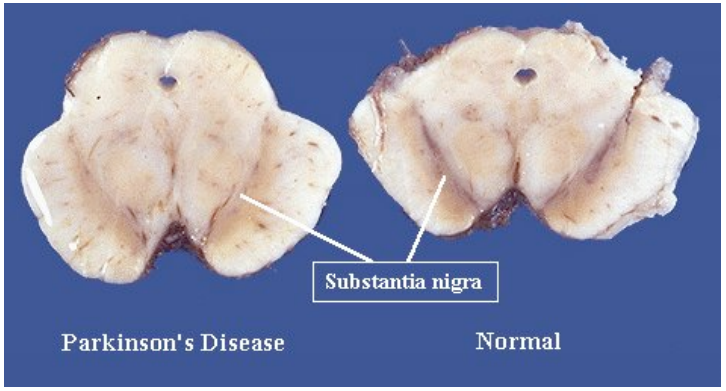




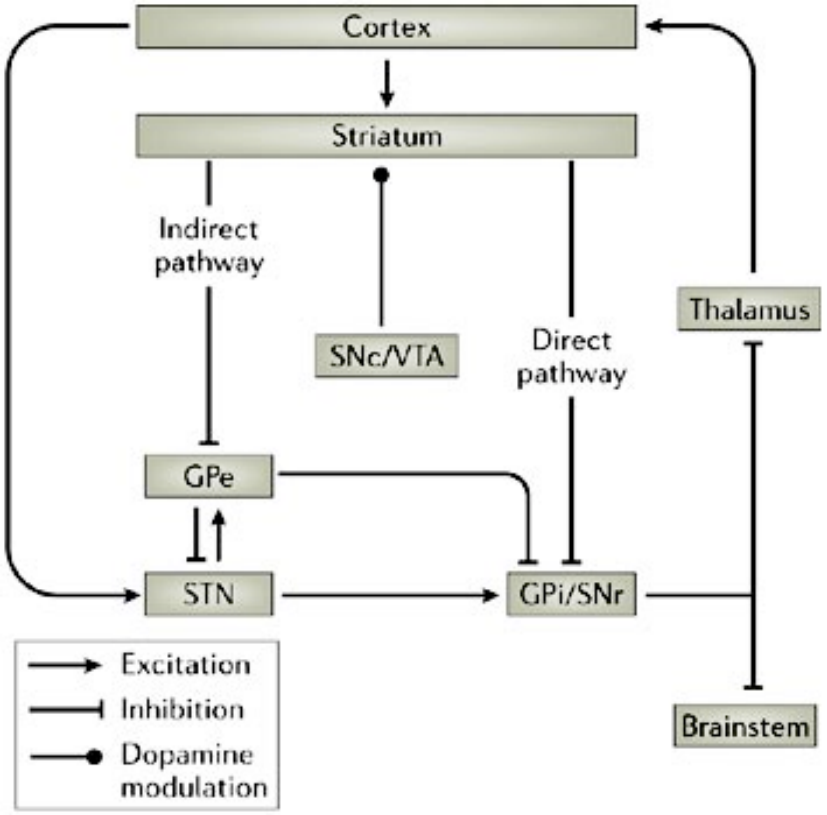
Substantia nigra

- Midbrain
- SN pars reticulata (SNr)
  - GABAergic
  - high tonic firing rates
  - Output of BG
- SN pars compacta (SNc)
  - Neuromelanin-containing cells
  - Dopaminergic
  - Tonic/phasic firing

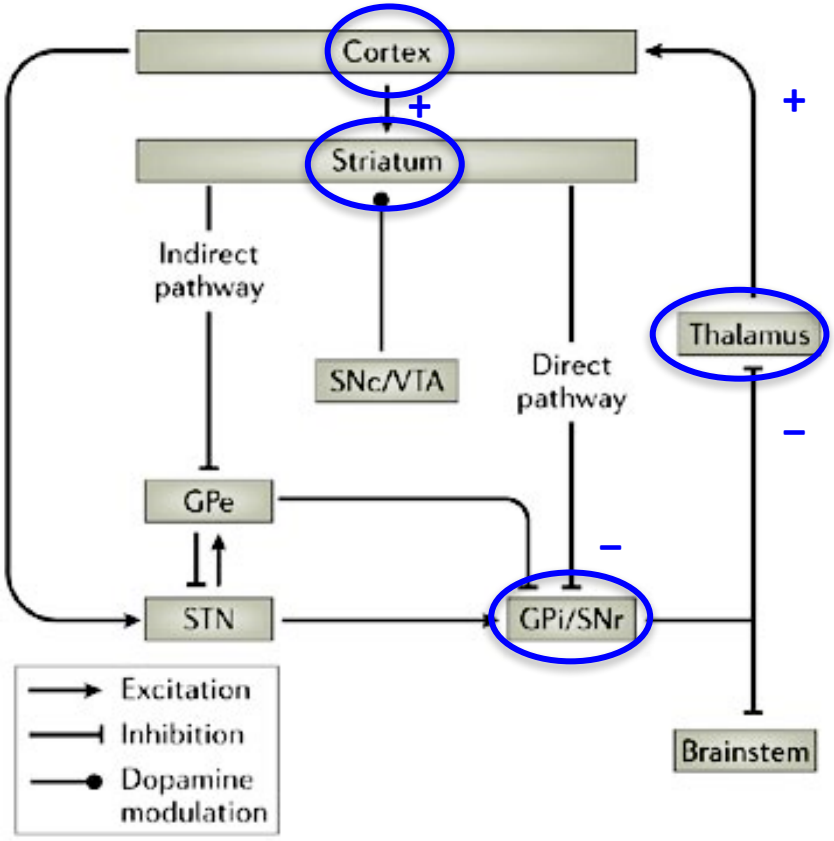




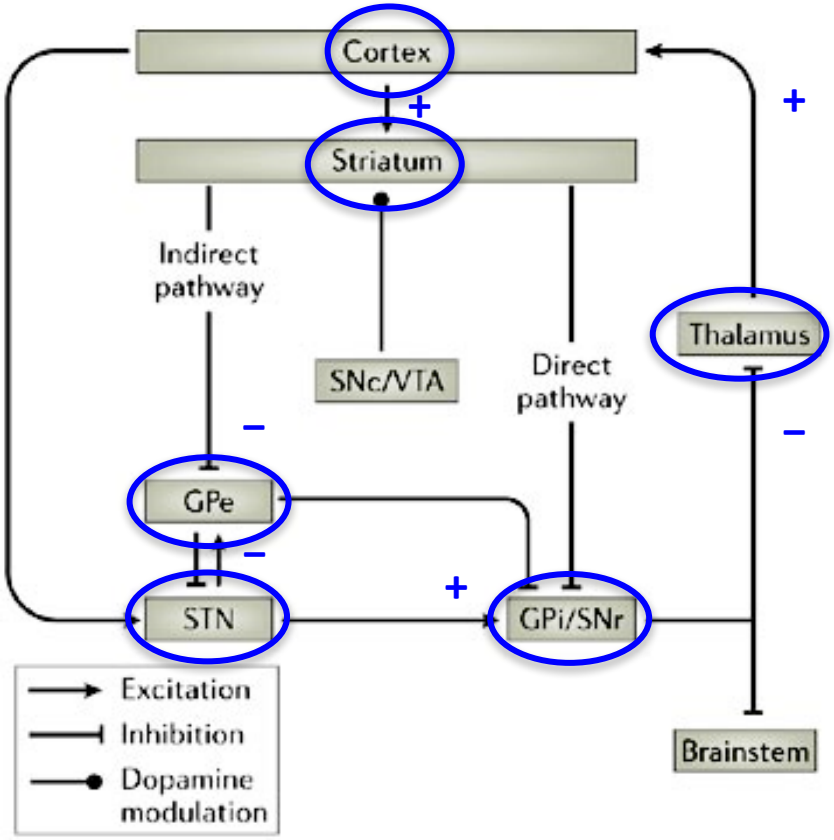
Direct and indirect pathways



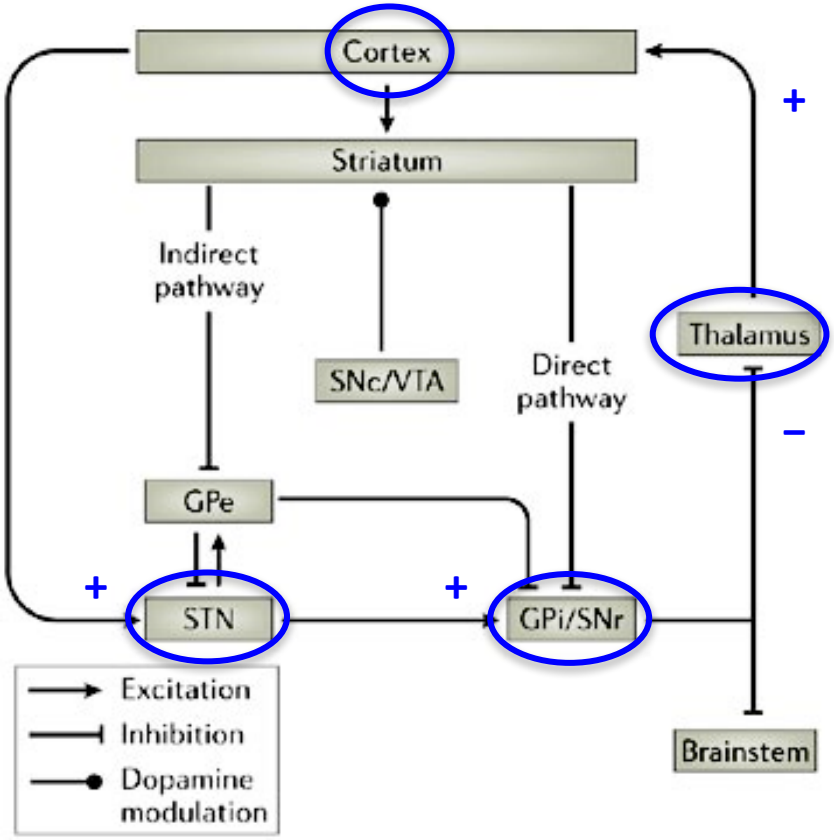
Direct pathway promotes action



Indirect pathway suppresses action



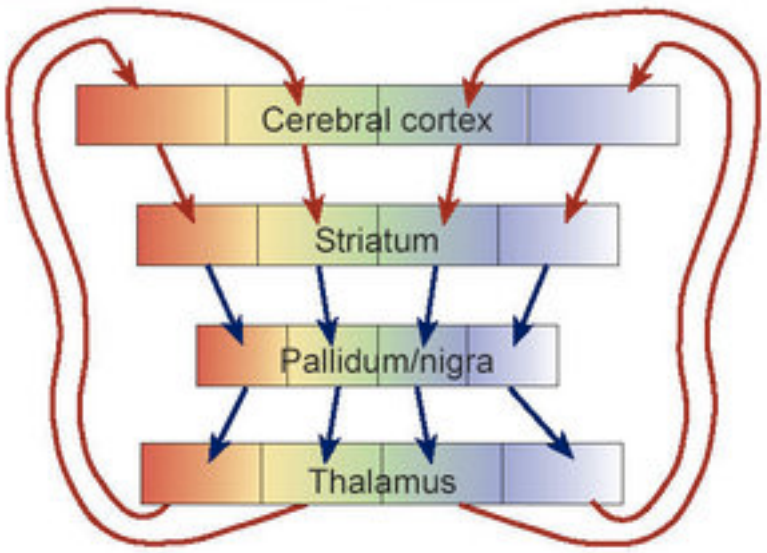
Hyperdirect pathway



Role of Basal Ganglia

BG dysfunction has been associated with numerous conditions including Parkinson's disease, Huntington's disease, Tourette's syndrome, schizophrenia, attention-deficit disorder, obsessive-compulsive disorder, and many of the addictions.

- Motor control
- Learning
- Motivation and reward
- Cognitive tasks



Reinforcement learning

- Supervised learning –

  All knowing teacher, detailed feedback

- Reinforcement learning –

  Learn and relearn based on actions and their effects (rewards)

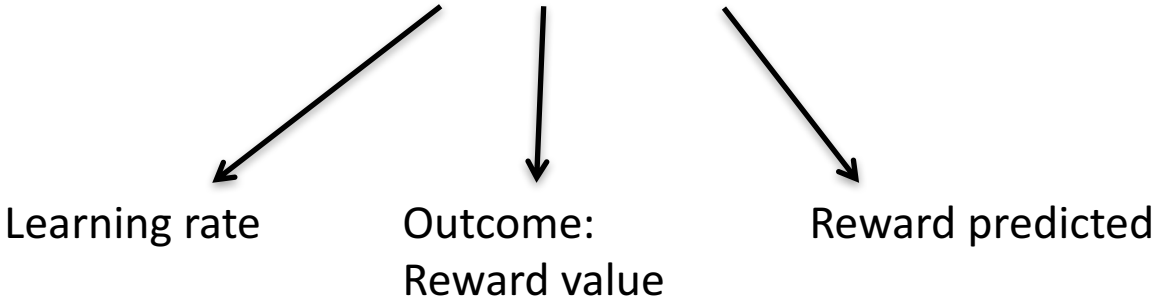
- Unsupervised learning –

  Self organization

Rescorla-Wagner rule (1972)

- The idea: error-driven learning
- Change in value is proportional to the difference between actual and predicted outcome

$$\Delta V = \eta[R - V]$$



TD learning

'truer' value of current state:
Reward at present state +
Estimated value of next state

Estimated value
of current state

$$V_t^{new} = V_t^{old} + \eta(r_{t+1} + V_{t+1}^{old} - V_t^{old})$$

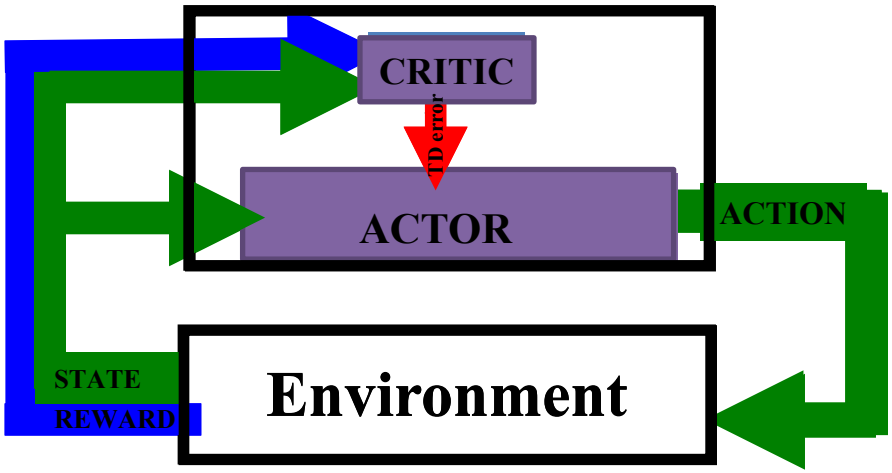
temporal difference prediction error δ(t+1)

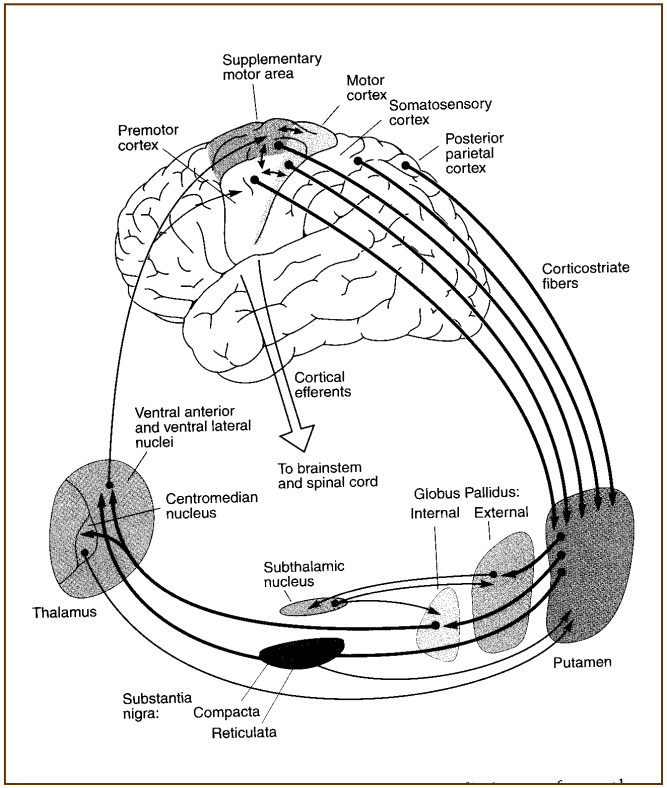
V_t = Estimated value of current state based on predicted future reward

r_t = reward given at time t

η = Learning rate

The computational machinery of the Basal Ganglia

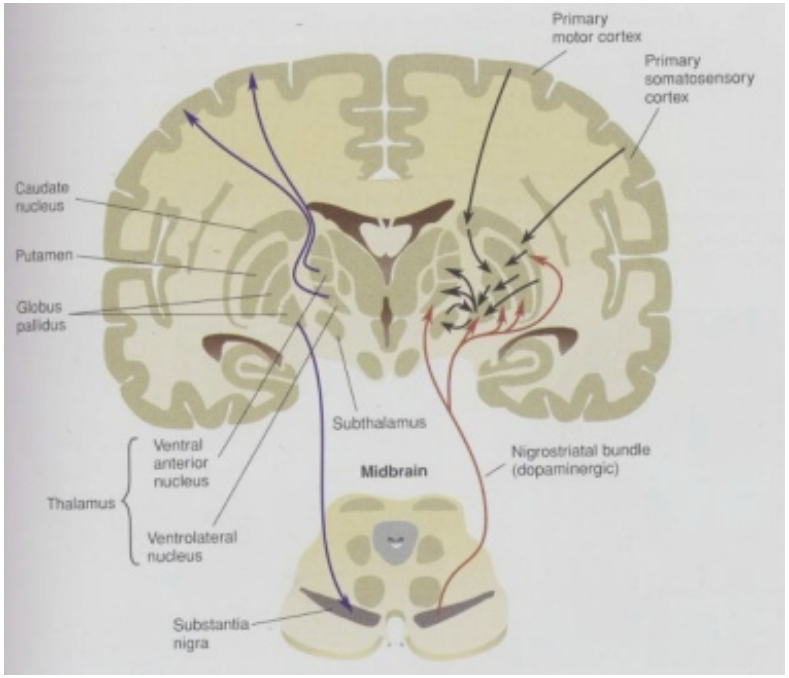


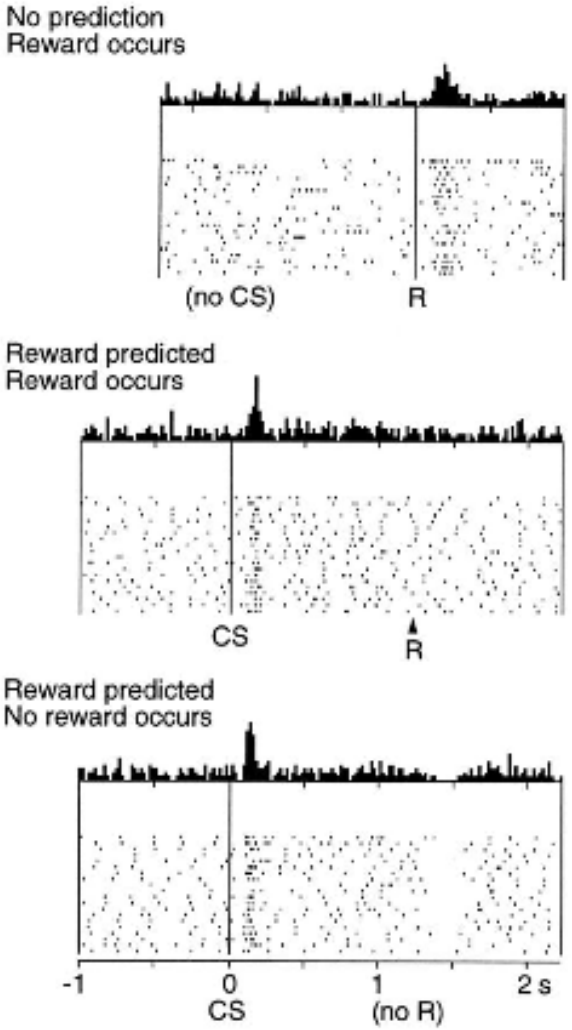


The basal ganglia networks are built as Actor-Critic network and employ temporal difference algorithms.

Dopamine provides the pleasure prediction error

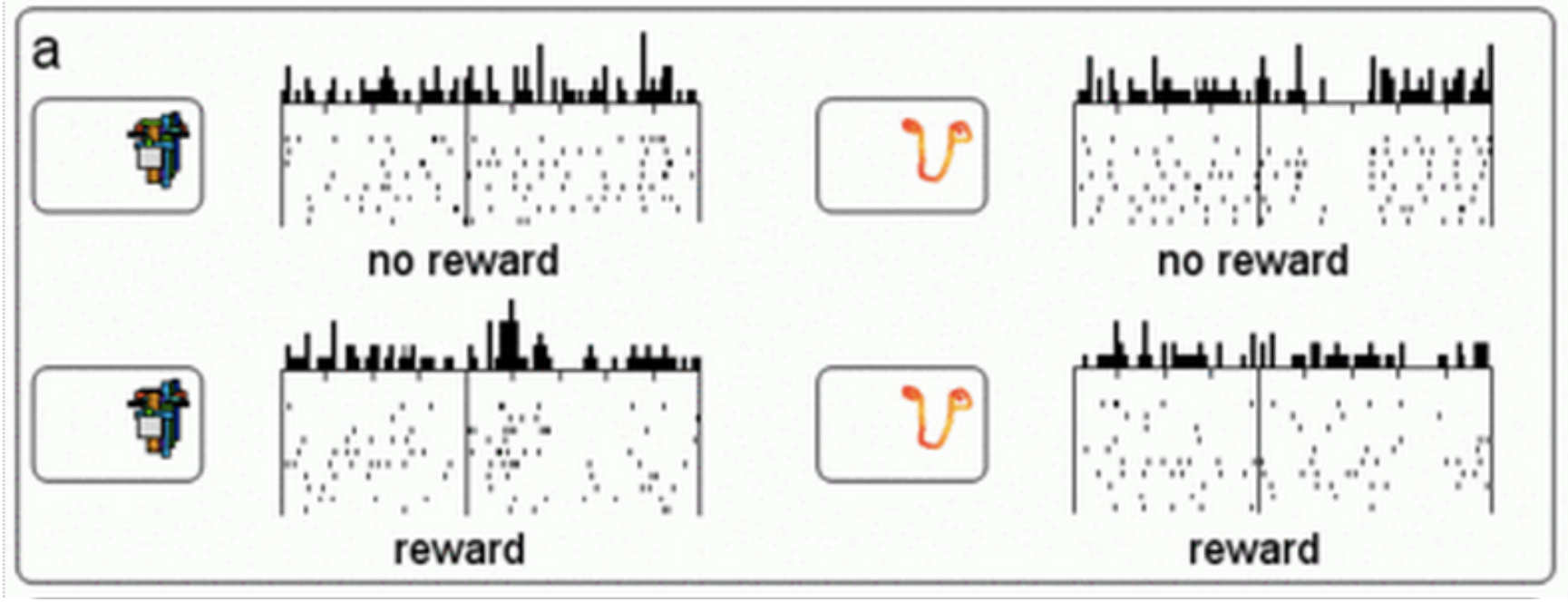
Dopamine match surprise signal





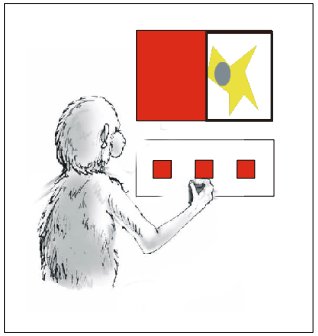
Schultz et al., 1997

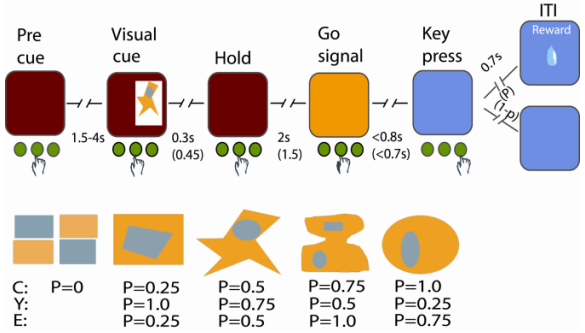
Dopamine match surprise signal

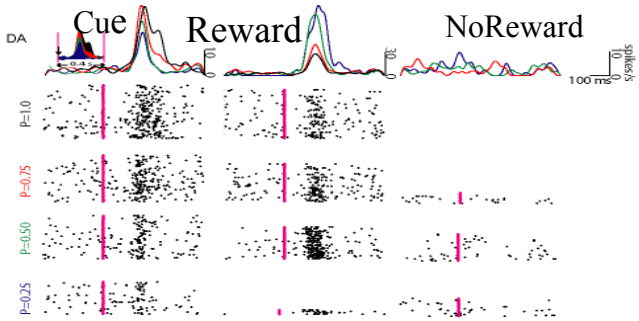


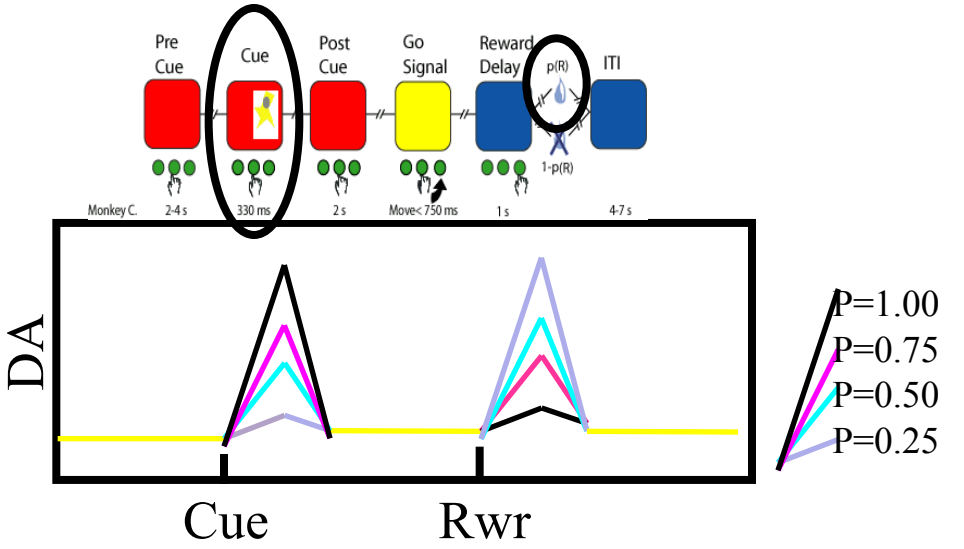
Dopamine signal = reward occurred – reward predicted

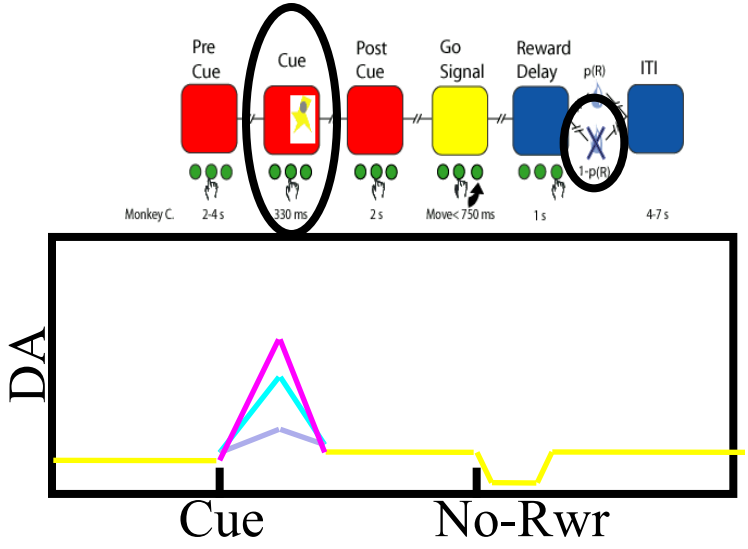
Dopamine neurons encode the (positive) mismatch between predictions and reality







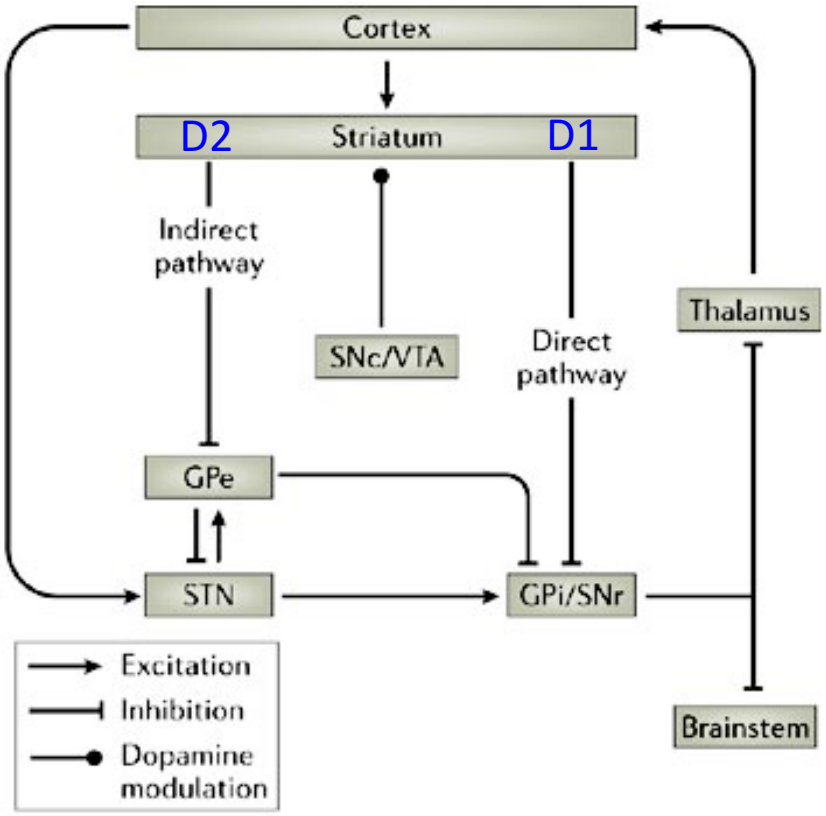




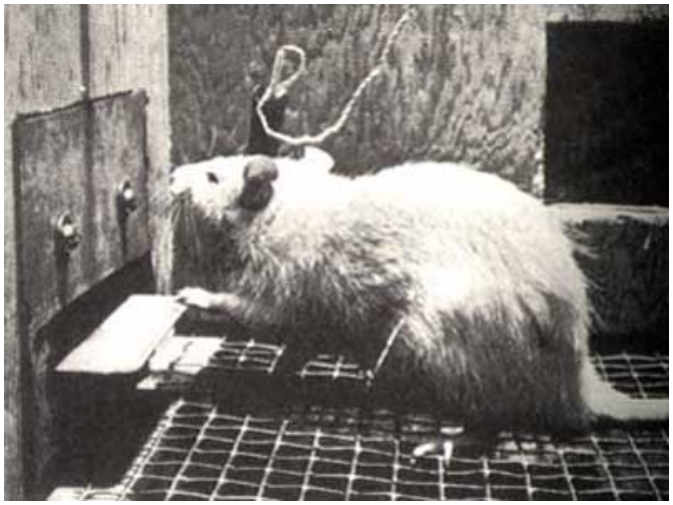
Genela Morris et al., Neuron, 2004

Effects of dopamine

- Learning = plasticity
- Teaching = modulating synaptic plasticity
- Cortico-striatal synapses are known to undergo long-term changes in synaptic efficacy.
  - Long-term potentiation (LTP) is mediated by activation of dopamine D1 receptors
  - Long-term depression (LTD) is mediated by activation of dopamine D2 receptors



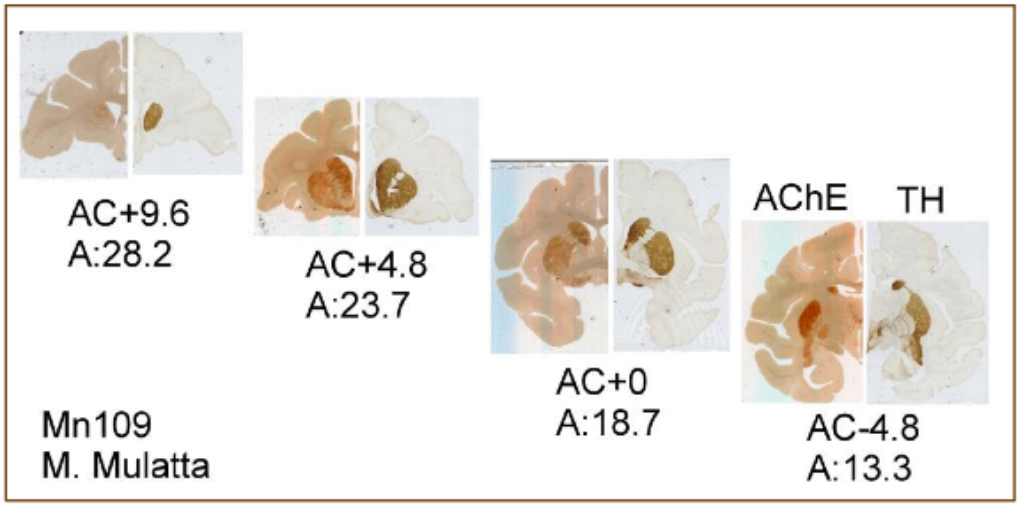
The strive for the dopaminergic reward

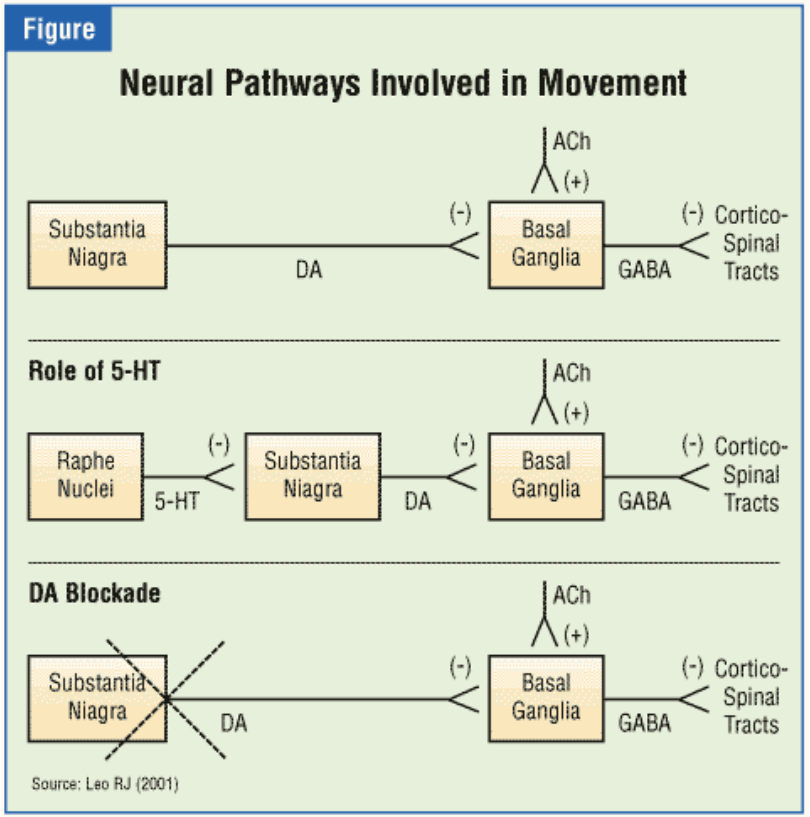


Electrical self-stimulation in neuronal pathways associated with dopamine.
Olds and Milner, 1954

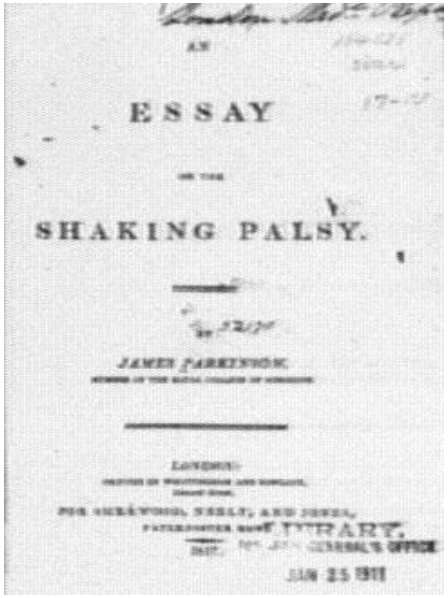
- Cocaine and amphetamines increase amount of dopamine by inhibiting its reuptake into the synaptic terminals.
- Opiate narcotics increase dopamine release by disinhibiting dopaminergic neurons.
- Nicotine increases striatal dopamine.
- A prolonged increase in dopamine levels may affect synaptic plasticity and provide the neural basis for drug addiction.

It’s not all about dopamine: balance between neurotransmitters





Parkinson's disease (PD)


AN

ESSAY

ON THE

SHAKING PALSY.

JAMES PARKINSON.

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW. TYRRELL,

James Parkinson, 1817

Clinical symptoms

- Akinesia/bradykinesia,
- Tremor,
- Muscular rigidity,
- Postural deficits
- Emotional and cognitive deficits

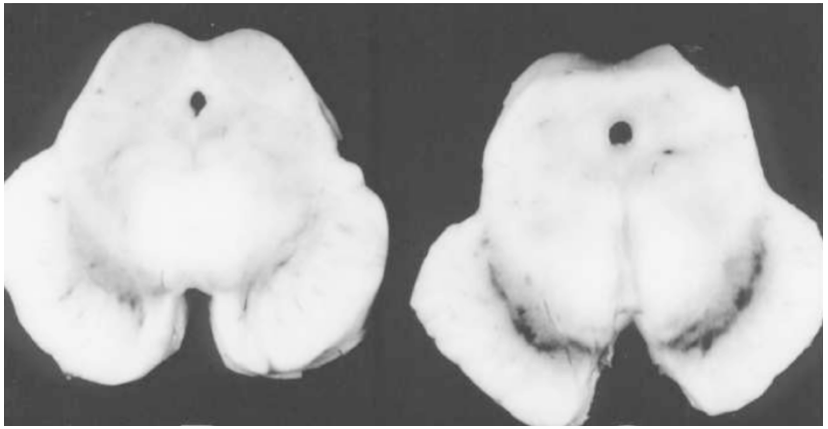
Epidemiology

- 3/1000 of total population
- Mean age of onset – 60 years
- 1/100 of >60 years

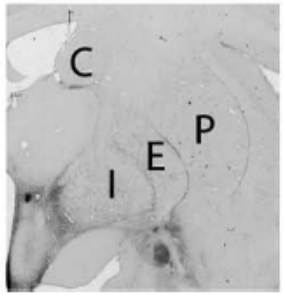
Parkinson's disease: depletion of dopamine

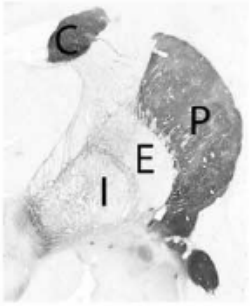
Parkinson Normal

Substantia nigra



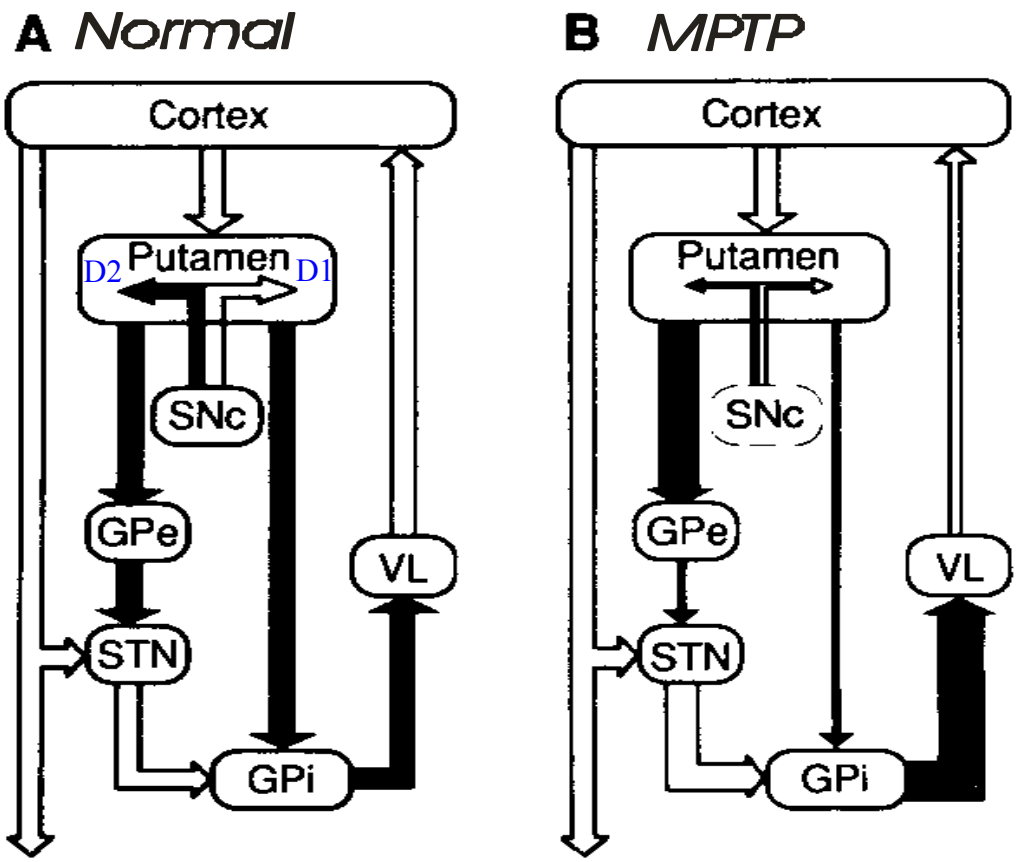
Striatum





Tyrosine hydroxylase catalyzes L-DOPA, a precursor for dopamine

Effects of dopamine depletion on direct and indirect pathways

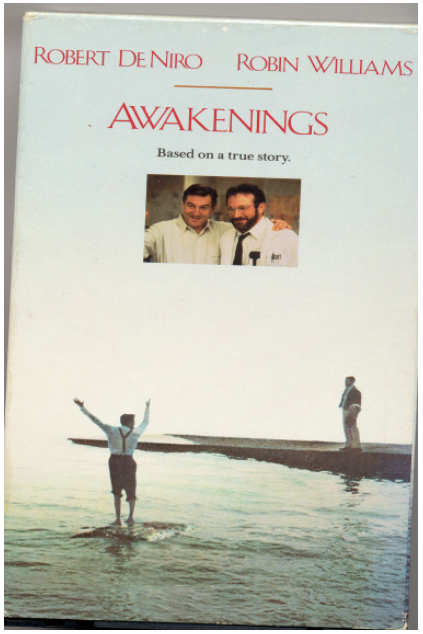


Direct pathway promotes action
Indirect pathway suppresses action

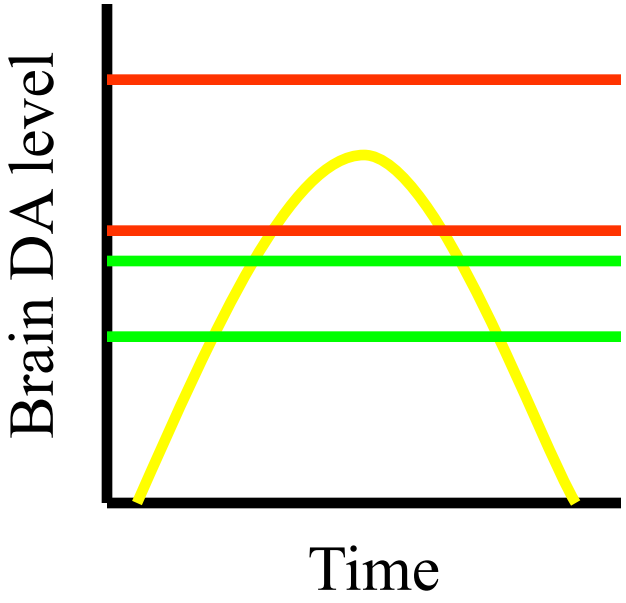
Dopamine replacement therapy of Parkinson's disease

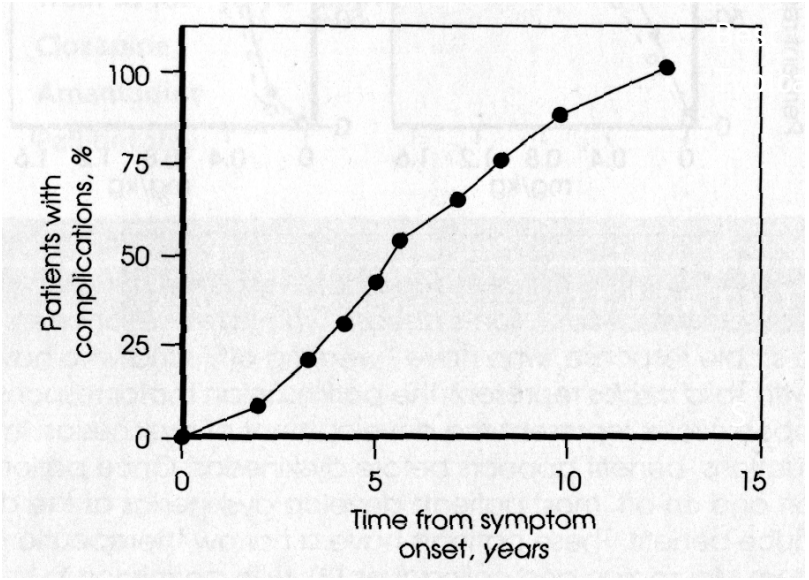
1967-9, George C. Cotzias: L-DOPA (a precursor of dopamine that cross the blood brain barrier) is established as the gold-standard therapeutic agent for Parkinson's disease.

1970 – today: Dopamine replacement therapy (L-DOPA, post synaptic agonists, etc)



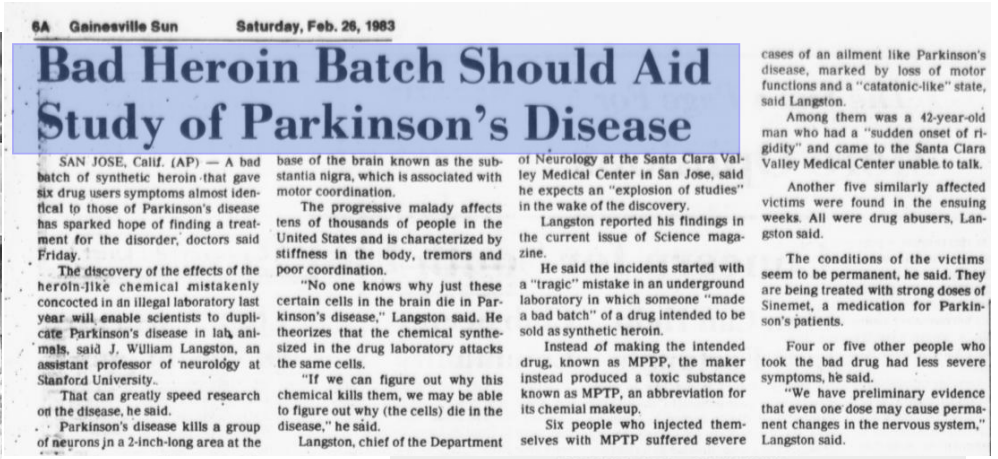
The limits of dopamine replacement therapy





Levodopa-induced dyskinesia
Dystonia

The MPTP model of Parkinson's disease



6A Gainesville Sun Saturday, Feb. 26, 1983

Bad Heroin Batch Should Aid Study of Parkinson's Disease

SAN JOSE, Calif. (AP) — A bad batch of synthetic heroin that gave six drug users symptoms almost identical to those of Parkinson's disease has sparked hope of finding a treatment for the disorder, doctors said Friday.

The discovery of the effects of the heroin-like chemical mistakenly concocted in an illegal laboratory last year will enable scientists to duplicate Parkinson's disease in lab animals, said J. William Langston, an assistant professor of neurology at Stanford University.

That can greatly speed research on the disease, he said.

Parkinson's disease kills a group of neurons in a 2-inch-long area at the base of the brain known as the substantia nigra, which is associated with motor coordination.

The progressive malady affects tens of thousands of people in the United States and is characterized by stiffness in the body, tremors and poor coordination.

"No one knows why just these certain cells in the brain die in Parkinson's disease," Langston said. He theorizes that the chemical synthesized in the drug laboratory attacks the same cells.

"If we can figure out why this chemical kills them, we may be able to figure out why (the cells) die in the disease," he said.

Langston, chief of the Department of Neurology at the Santa Clara Valley Medical Center in San Jose, said he expects an "explosion of studies" in the wake of the discovery.

Langston reported his findings in the current issue of Science magazine.

He said the incidents started with a "tragic" mistake in an underground laboratory in which someone "made a bad batch" of a drug intended to be sold as synthetic heroin.

Instead of making the intended drug, known as MPPP, the maker instead produced a toxic substance known as MPTP, an abbreviation for its chemial makeup.

Six people who injected themselves with MPTP suffered severe cases of an ailment like Parkinson's disease, marked by loss of motor functions and a "catatonic-like" state, said Langston.

Among them was a 42-year-old man who had a "sudden onset of rigidity" and came to the Santa Clara Valley Medical Center unable to talk.

Another five similarly affected victims were found in the ensuing weeks. All were drug abusers, Langston said.

The conditions of the victims seem to be permanent, he said. They are being treated with strong doses of Sinemet, a medication for Parkinson's patients.

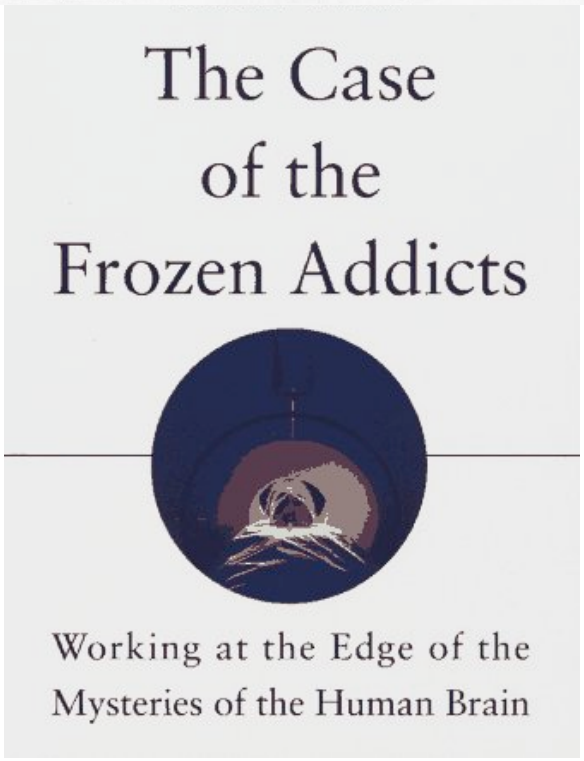
Four or five other people who took the bad drug had less severe symptoms, he said.

"We have preliminary evidence that even one dose may cause permanent changes in the nervous system," Langston said.

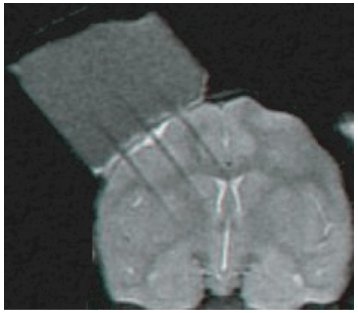
MPPP (1-methyl-4-propionoxypiperidine)
- a reverse ester of meperidine and a potent narcotic
- easy to synthesize
- synthesis typically results in MPTP as byproduct.

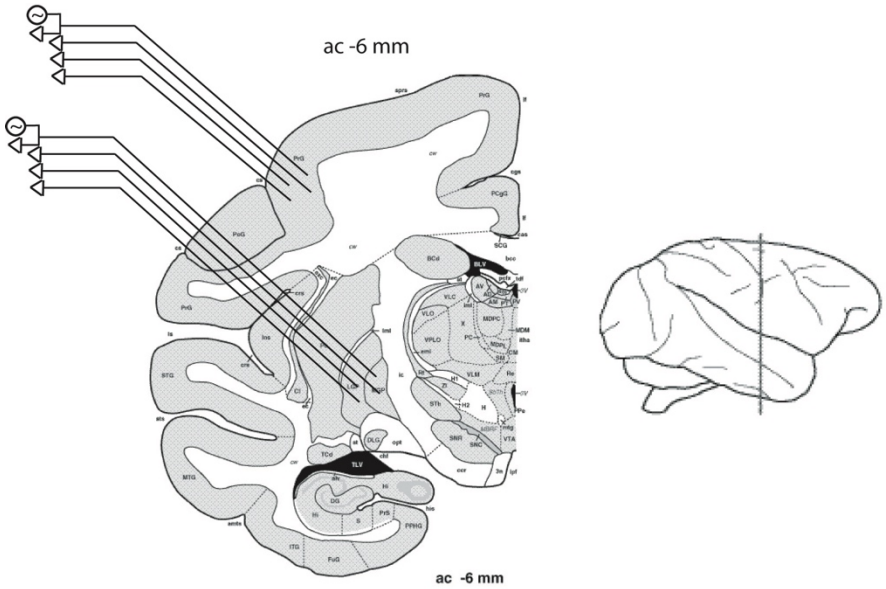
1976: A college student synthesized and abused MPPP for 6 months.
- made a 'sloppy batch', and became severely Parkinsonian.
- Pathology: severe cell loss limited to the SN (Davis et al. 1979).

1982: MPPP was distributed en-mass in California as 'synthetic heroin'
- young drug abusers arriving in ER with advanced Parkinsonism.
- typical Parkinsonian rest tremor in about half (3-4/7) of MPTP patients (Langston et al. 1983, 1987, 1995).



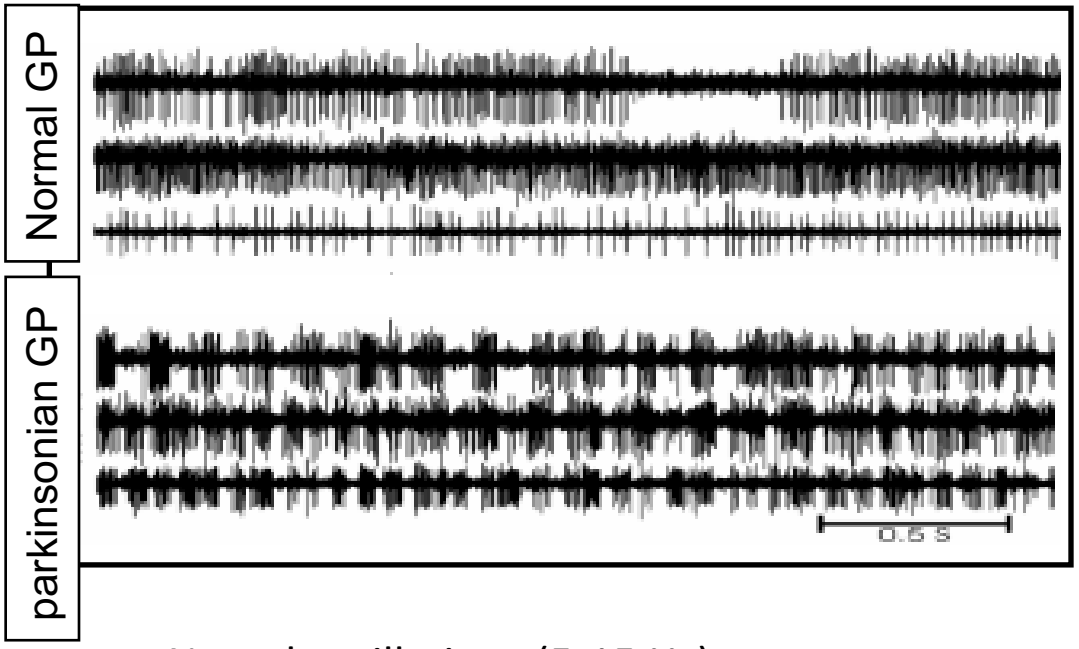
The MPTP model of Parkinson's disease





Appearance of neuronal oscillations

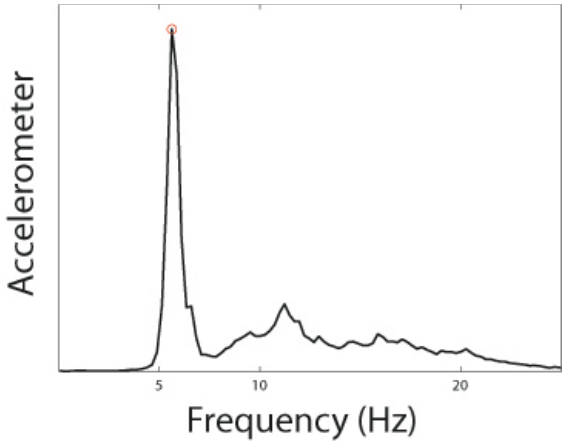
- The parkinsonian brain demonstrates oscillatory activity:
  - PD patients during brain surgery
  - MPTP primates



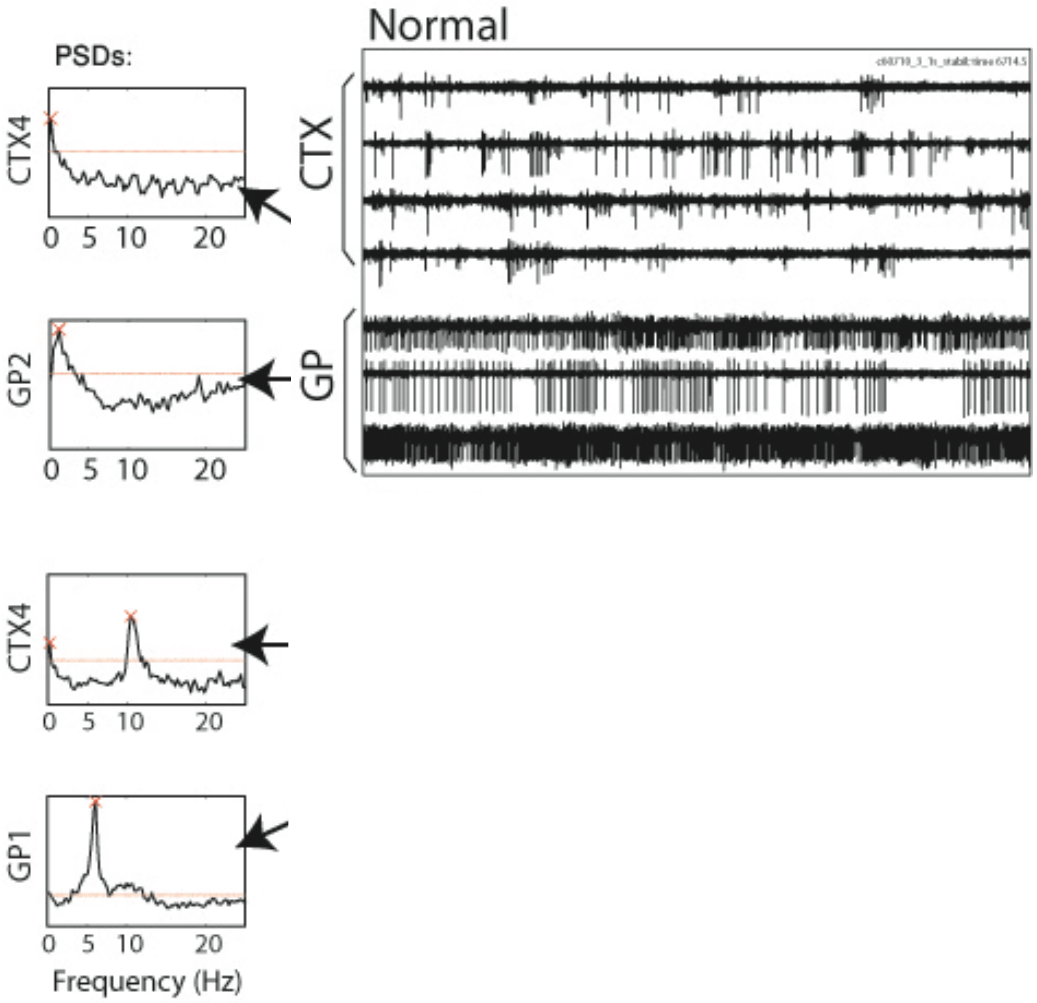
Neural oscillations (5-15 Hz)

Spontaneous activity

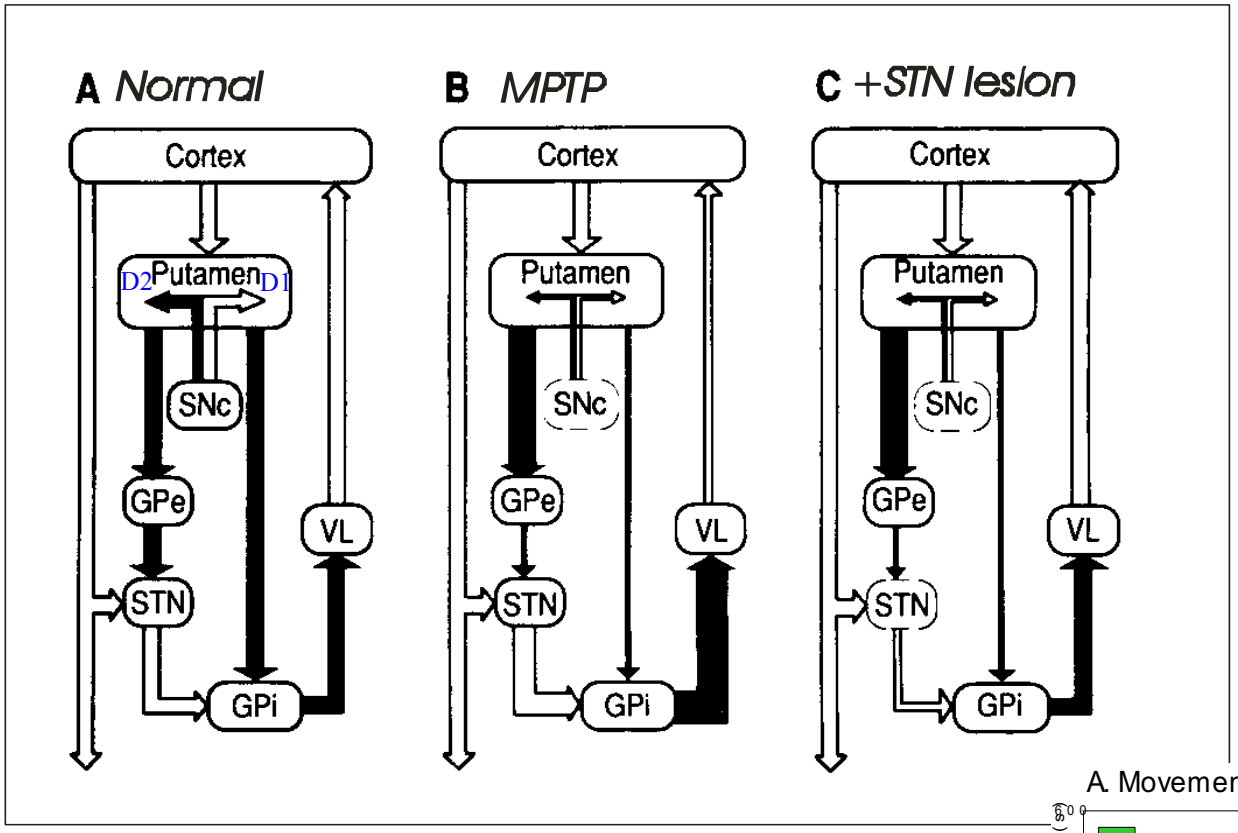
- Neuronal oscillations appear in the GP as well as in MI

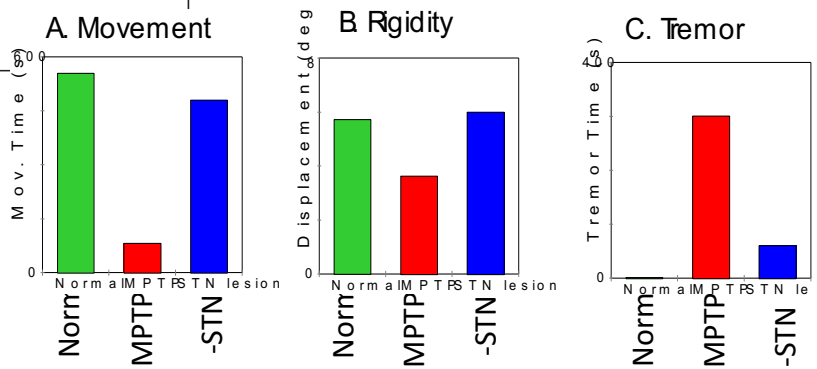


  - Tremor frequency differs from cortical frequency



Inactivation of the subthalamic nucleus ameliorates Parkinson symptoms of the MPTP monkey





Bergman, Wichmann and DeLong, 1990

Deep brain stimulation (DBS)

- Deep brain stimulation (DBS) is used as a treatment for advanced PD.
- An electrode is located in the STN/GPi and high frequency stimulation (~130 Hz) is given through the electrode.

BG hyperkinetic disorders

- Huntington's disease
  - striatal projection neurons become dysfunctional and degenerate
  - causes defects in behavior and uncontrolled movements.
  - hereditary disease
- Hemiballismus
  - Reduced activity in the subthalamic nucleus
  - Repetitive, large amplitude involuntary movements of the limbs

BG non-motor disorders

- Tourette syndrome
- Obsessive-compulsive disorder
- Attention-deficit hyperactivity disorder (ADHD)
- Addiction