Making Things Happen – 2: Motor Disorders

How Your Brain Works

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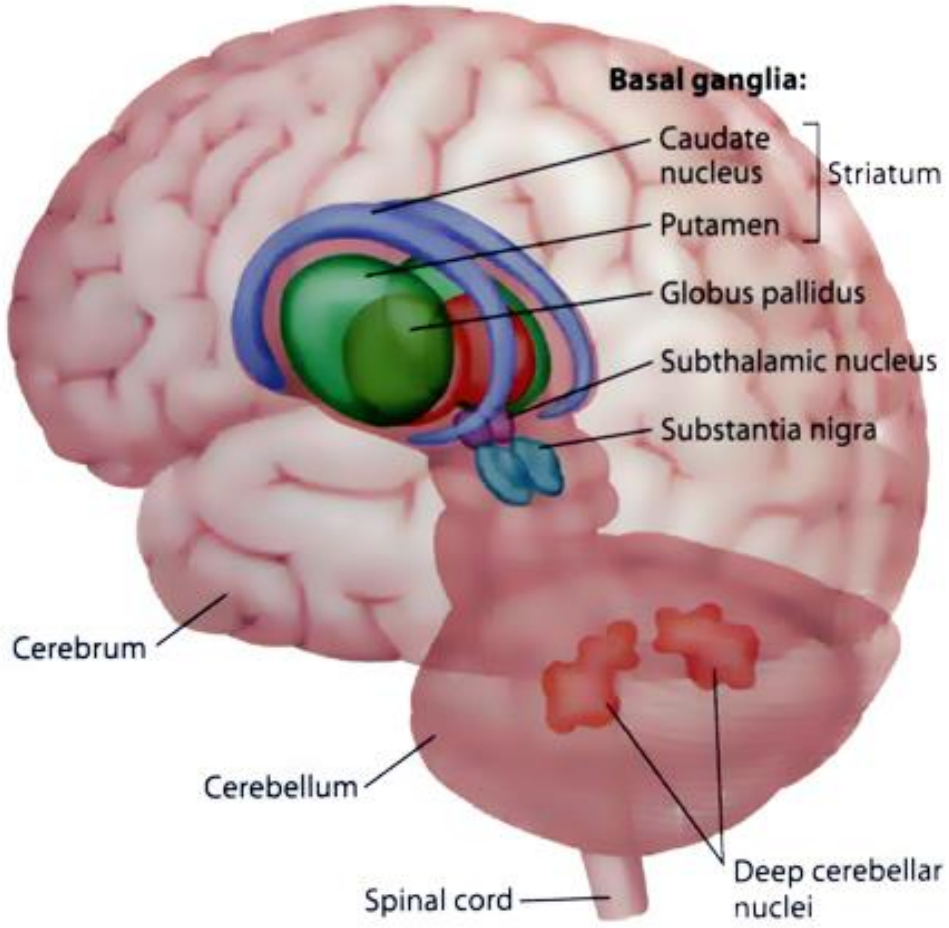
On the Menu in This Lecture

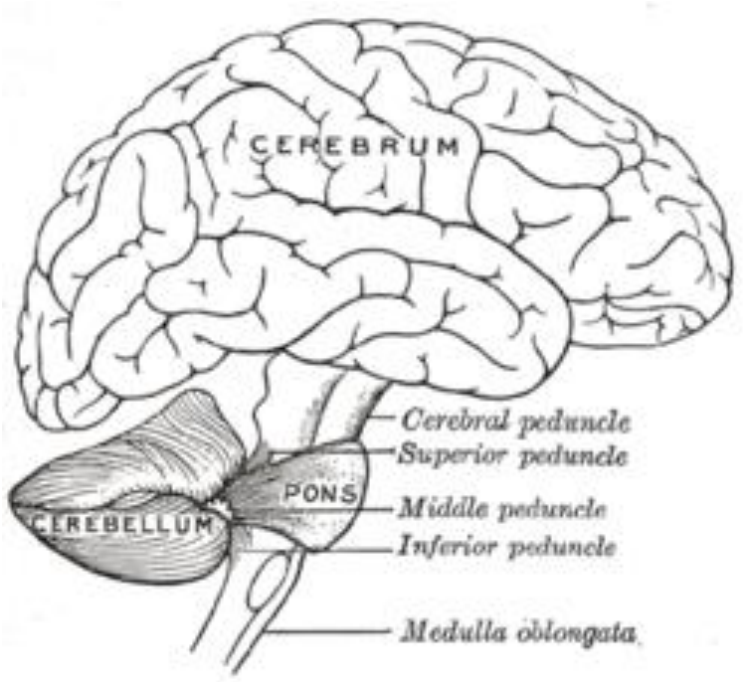
- In the previous lecture we saw how motor cortex and spinal cord control skeletal muscle movements.
- But cortex does not control movements all by itself it gets help from other structures, including:
- The **cerebellum**, which appears to be set up to learn associations between sensory inputs (and feedback) and motor intentions, making outcomes of motor commands more predictable and movements more coordinated.
- The **basal ganglia**, which appear to “filter” spontaneous, self-guided movements, and set overall activity levels.
- Think of the cerebellum as helping the brain answer the question: “How do I get my movements to achieve their desired result given my current environment?”, while the basal ganglia help answer the question “What, are the things that I want to do in the first place?”

Subcortical Motor Structures



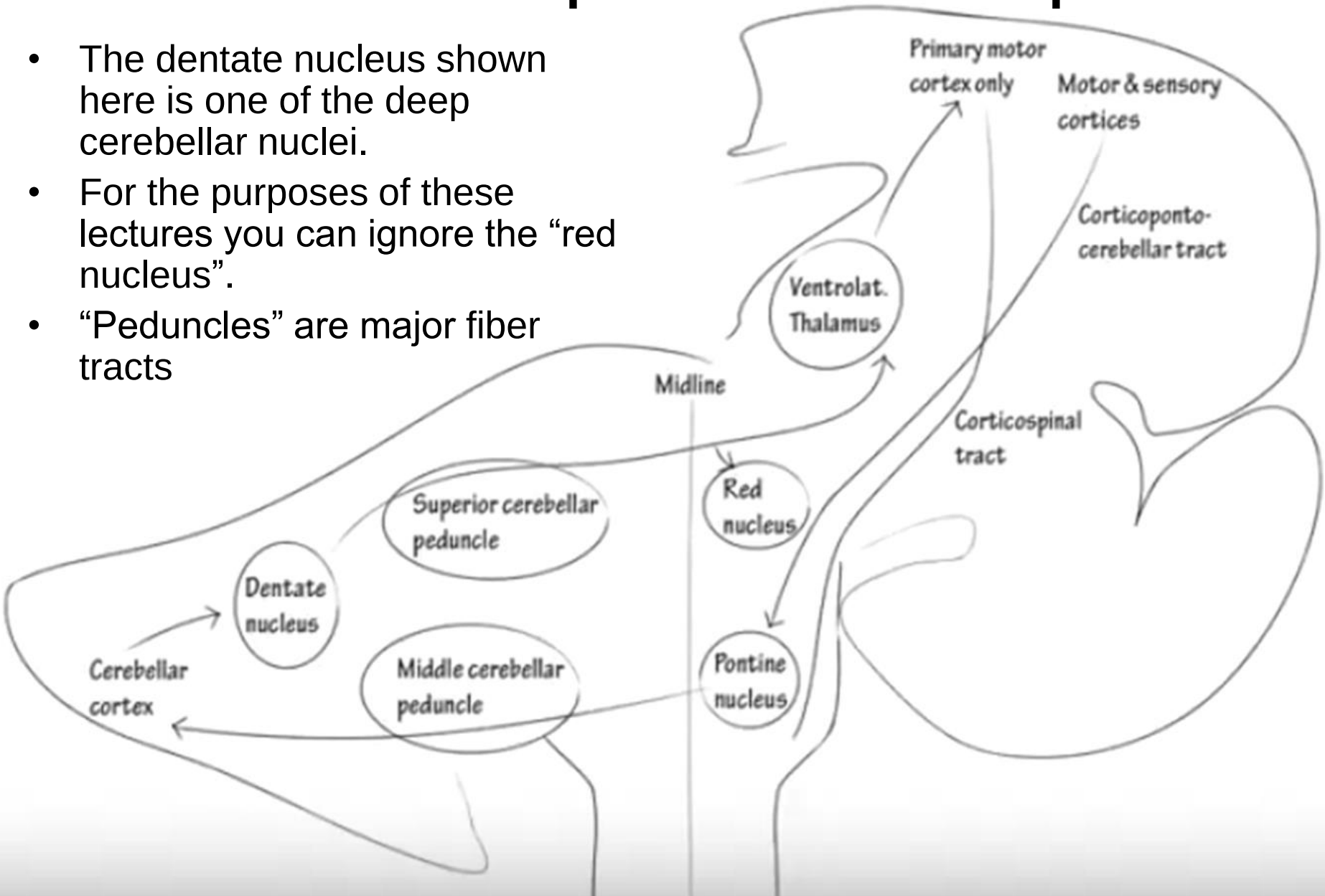
Cerebellum

- The cerebellum gets inputs from motor and sensory cortex (via the pons) as well as from spinal cord and the vestibular system (sense of balance).
- It sends outputs back to motor cortex via deep cerebellar nuclei and thalamus.



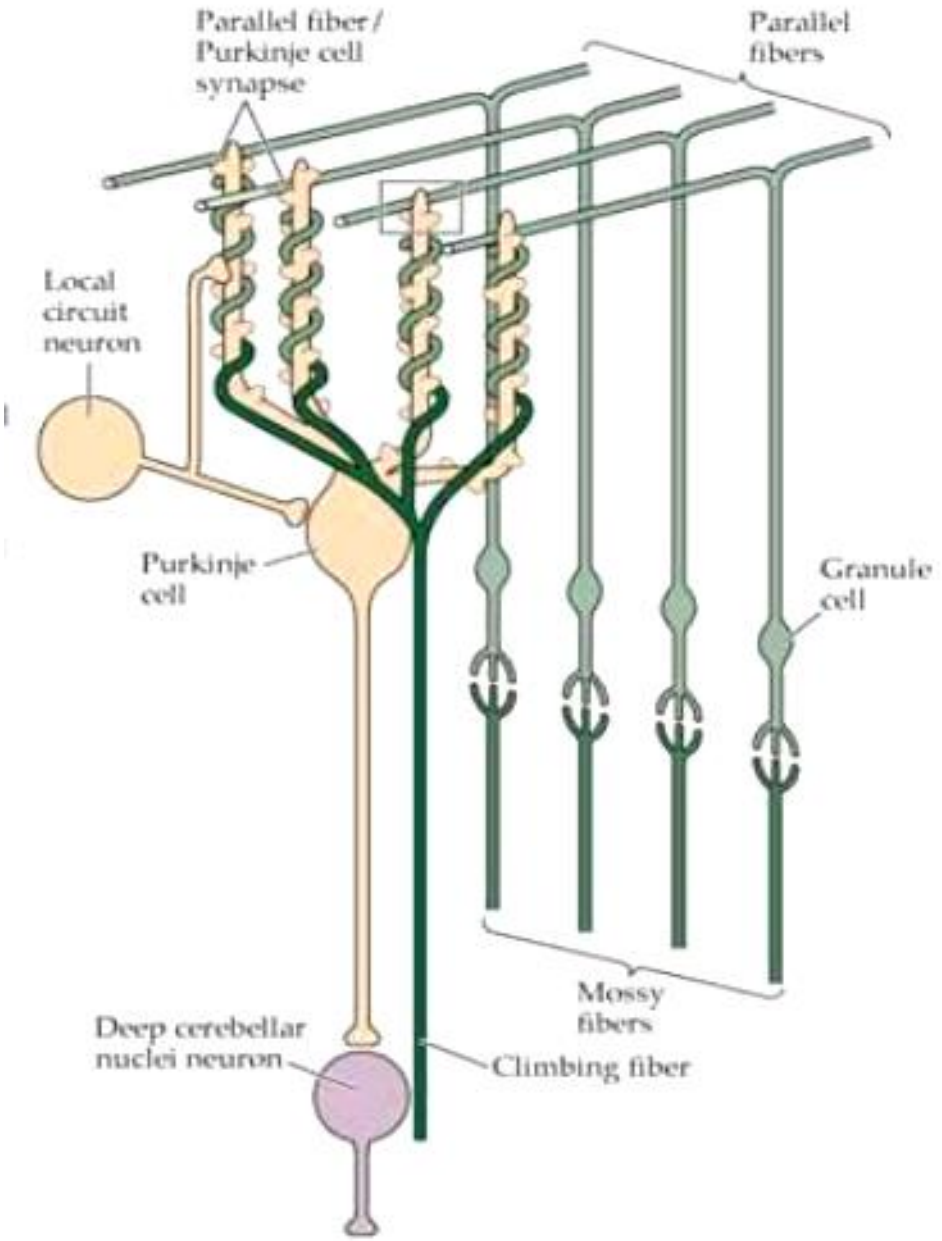
Cerebellum Inputs and Outputs

- The dentate nucleus shown here is one of the deep cerebellar nuclei.
- For the purposes of these lectures you can ignore the “red nucleus”.
- “Peduncles” are major fiber tracts



Cerebellar Circuits

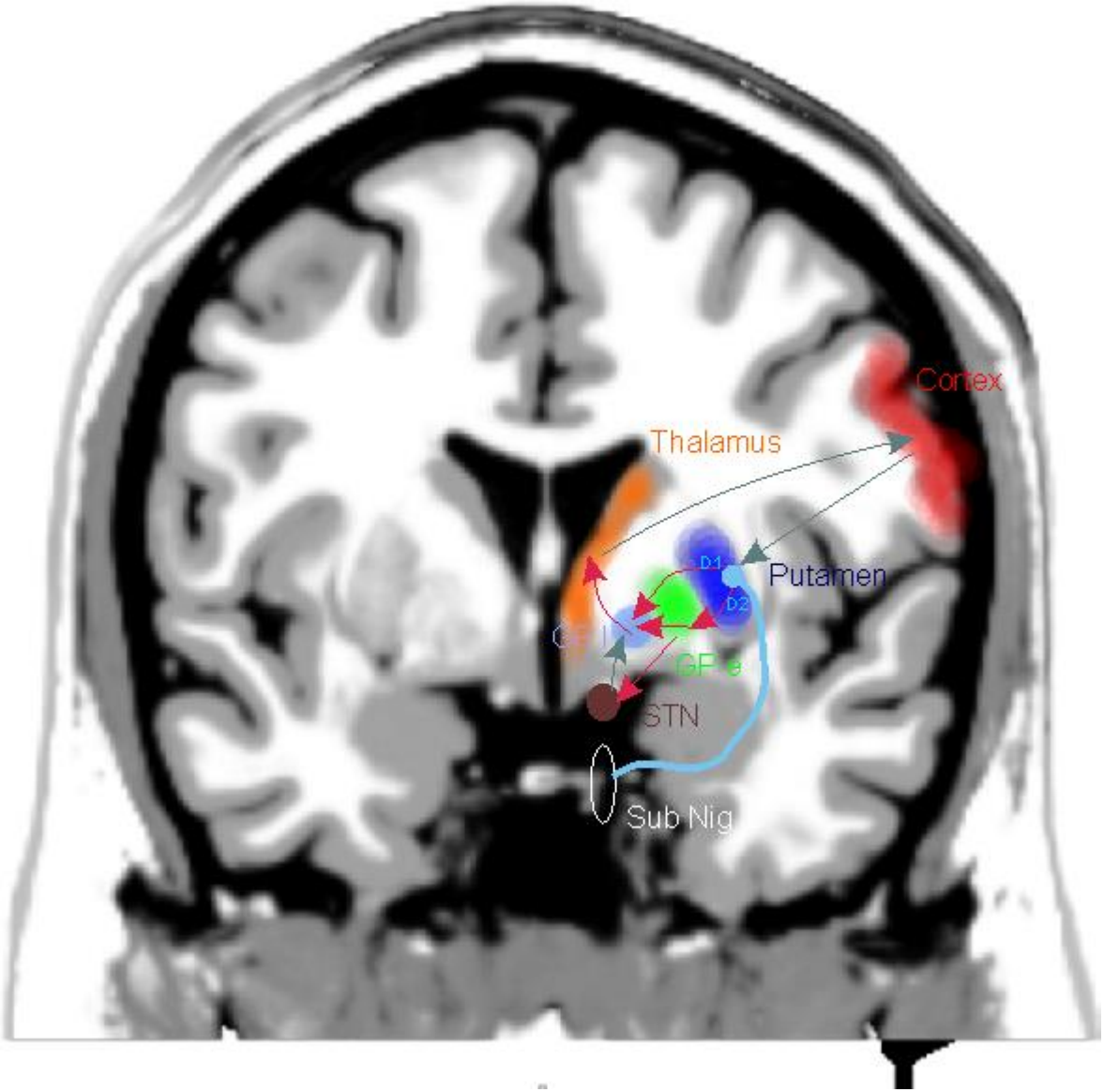
- Many more motor cortex neurons project to pontine nuclei and from there on to cerebellum than project directly to spinal cord.
- Input from the pons forms "**mossy fiber**" input onto **granule cells** in cerebellar cortex.
- Granule cells form **parallel fibers** which synapse onto **Purkinje cells**.
- Purkinje cells are thought to learn associations between parallel fiber inputs using **climbing fiber** inputs from the inferior olive as teaching input.



Cerebellar Ataxia and Intention Tremor

The Basal Ganglia

- GPi = globus pallidus internal segment
- GPe = globus pallidus external
- STN= subthalamic nucleus
- Sub Nig = Substantia Nigra (pars compacta)



Cortex – Basal Ganglia Loops

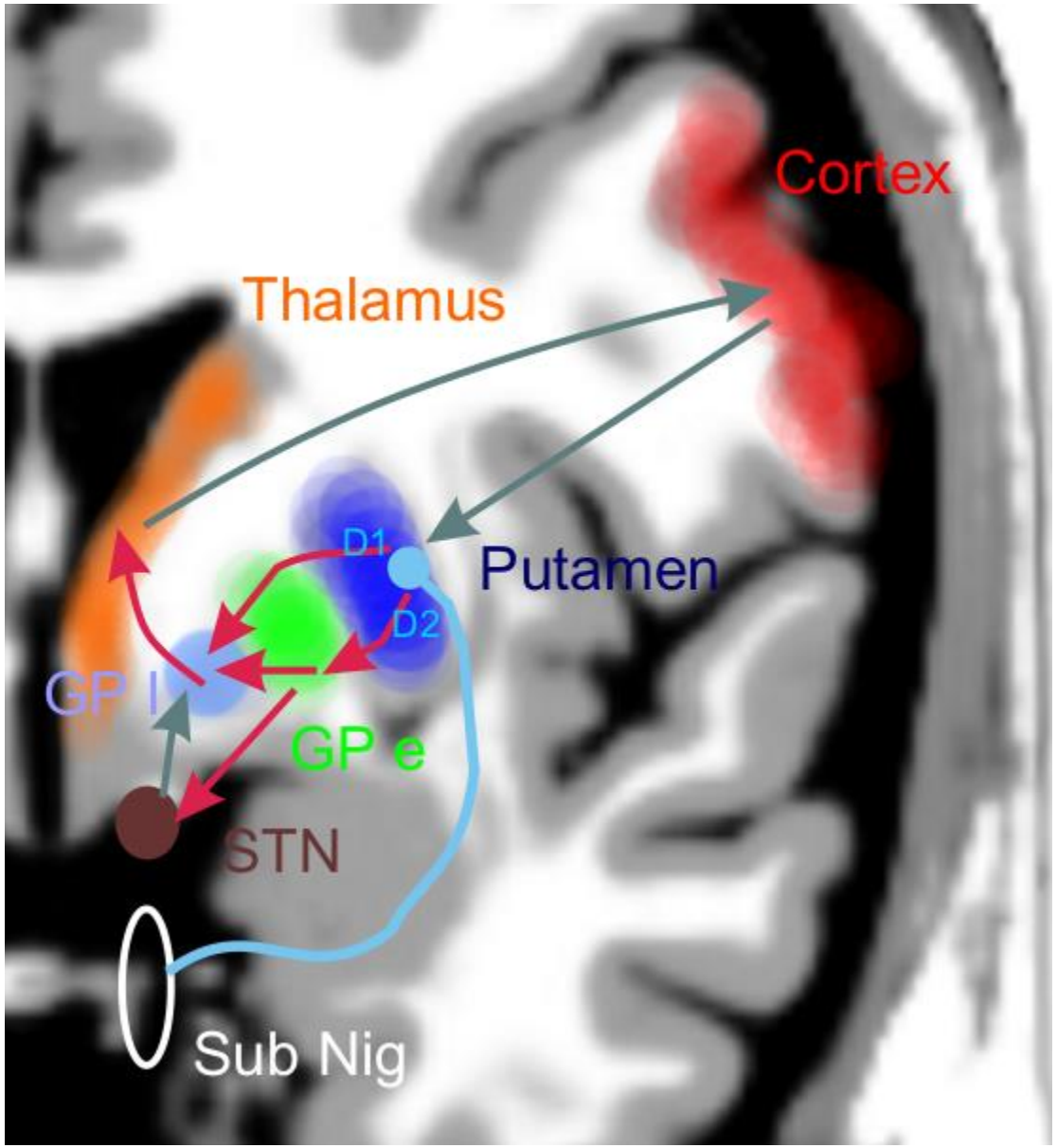
- Motor cortex (particularly the SMA) is closely coupled to a loop through the basal ganglia (BG)
- The BG comprise:
  - The **putamen** and **caudate** nucleus (collectively known as **striatum**)
  - The **globus pallidus**, which has separate **external** and **internal** segments.
  - The **substantia nigra**, which has a pars compacta (SNc, which we will focus on) and a pars reticulata (SNr, which we will ignore)
  - The **ventral tegmental area** (VTA), which can be thought of as an extension of the SNc
  - The **subthalamic nucleus** (ST).

Cortex – Basal Ganglia Loops 2

- In the BG “motor loop”, activity can pass from cortex through the BG to a nucleus of the thalamus, and from there back to cortex:
  - Cortex projects to putamen (excitatory, glutamate)
  - Putamen projects to GPi, either directly or indirectly, via GPe and (optionally) through STN. (Inhibitory, GABA).
  - GPi projects to thalamus. (Inhibitory, GABA).
  - Thalamus projects back to cortex (Excitatory, glutamate).
- These projections all occur in a somatotopic (homunculus) framework, i.e. activity starting from the hand region of motor cortex will return back to the hand region.

The Motor Loop

- Excitatory (Glutamatergic) connections shown in dark green
- Inhibitory (GABAergic) connections shown in red
- Dopaminergic connections shown in sky blue



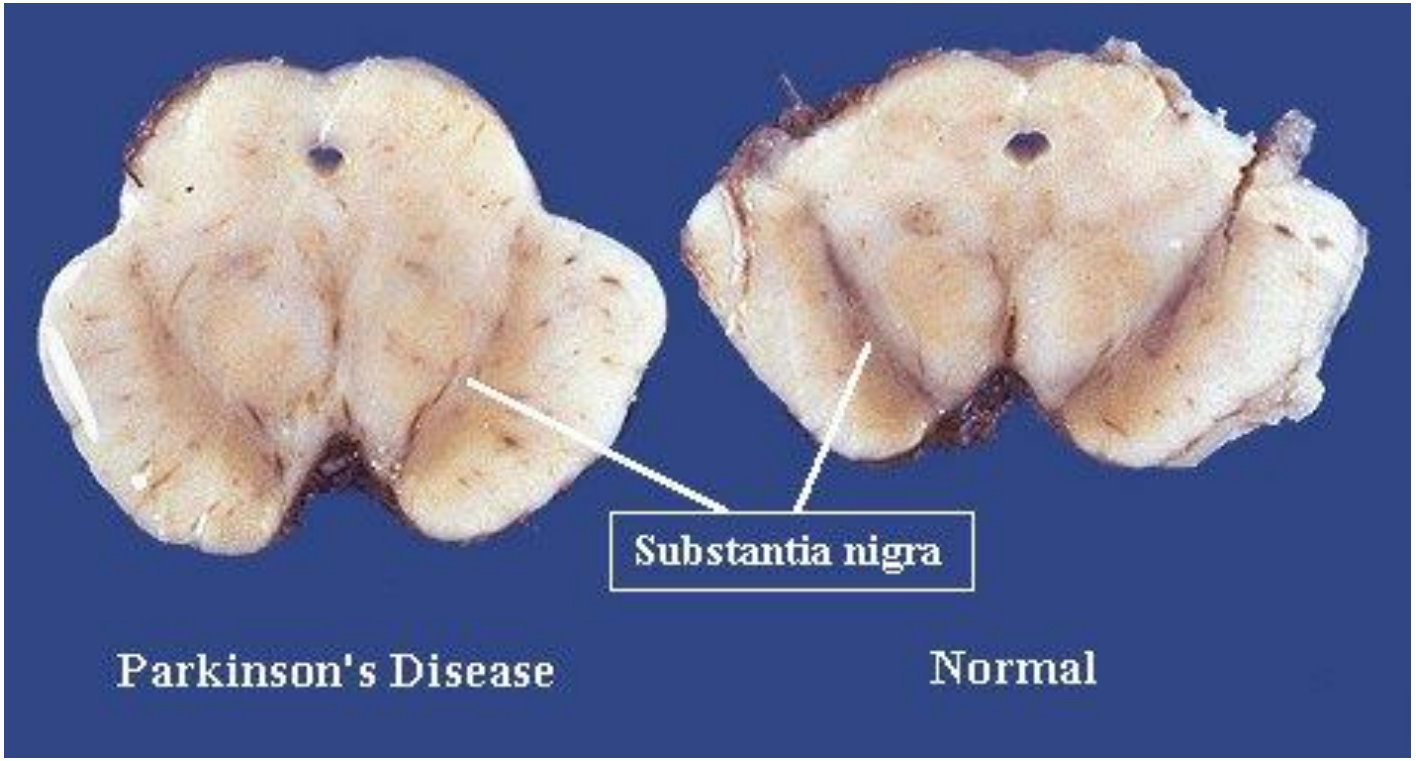
Cortex – Basal Ganglia Loops 3

- Paths through the BG motor loop which have an even number of inhibitory connections in them are called the "**direct pathway**":
  Ctx → Put → GPi → Thal → Ctx.
- Even numbers of inhibitions mean that "inhibition is inhibited" or taken away, so the direct pathway will amplify activity.
- Paths through the BG motor loop which have an odd number of inhibitory connections in them are called the "**indirect pathway**":
  Ctx → Put → GPe → GPi → Thal → Ctx or:
  Ctx → Put → GPe → STN → GPi → Thal → Ctx.
- Odd numbers of inhibitions mean that "disinhibition is inhibited", so there will be more inhibition, less activity in Ctx, if the indirect pathway is more active.

Cortex – Basal Ganglia Loops 4

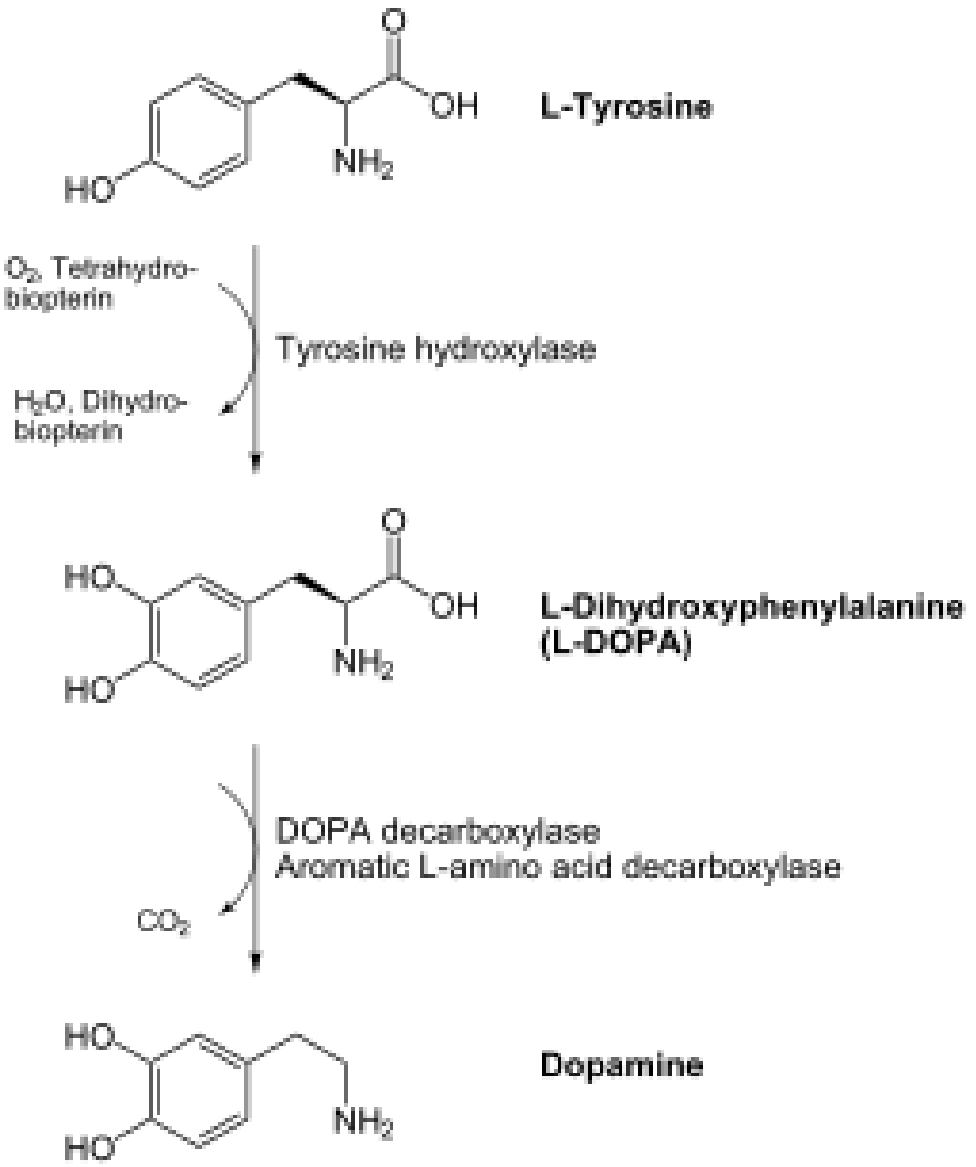
- Remember from the last lecture that motor cortical neurons represent movement intentions, and that they are spontaneously active. Think of that spontaneous activity as being “filtered” through the direct and indirect pathways, which can “up-vote” or “down-vote” that activity as it runs through the loops.
- Dopaminergic input from the SNc plays a big role in regulating and shaping the pathways through the BG. “Tonic” dopamine release from the SNc into Put will make the neurons of the direct path more active through “D1” dopamine receptors and will make neurons of the indirect path less active through “D2” dopamine receptors.
- Consequently, the more dopamine release, the more direct pathway activity and the more motor output.

Parkinson's Disease

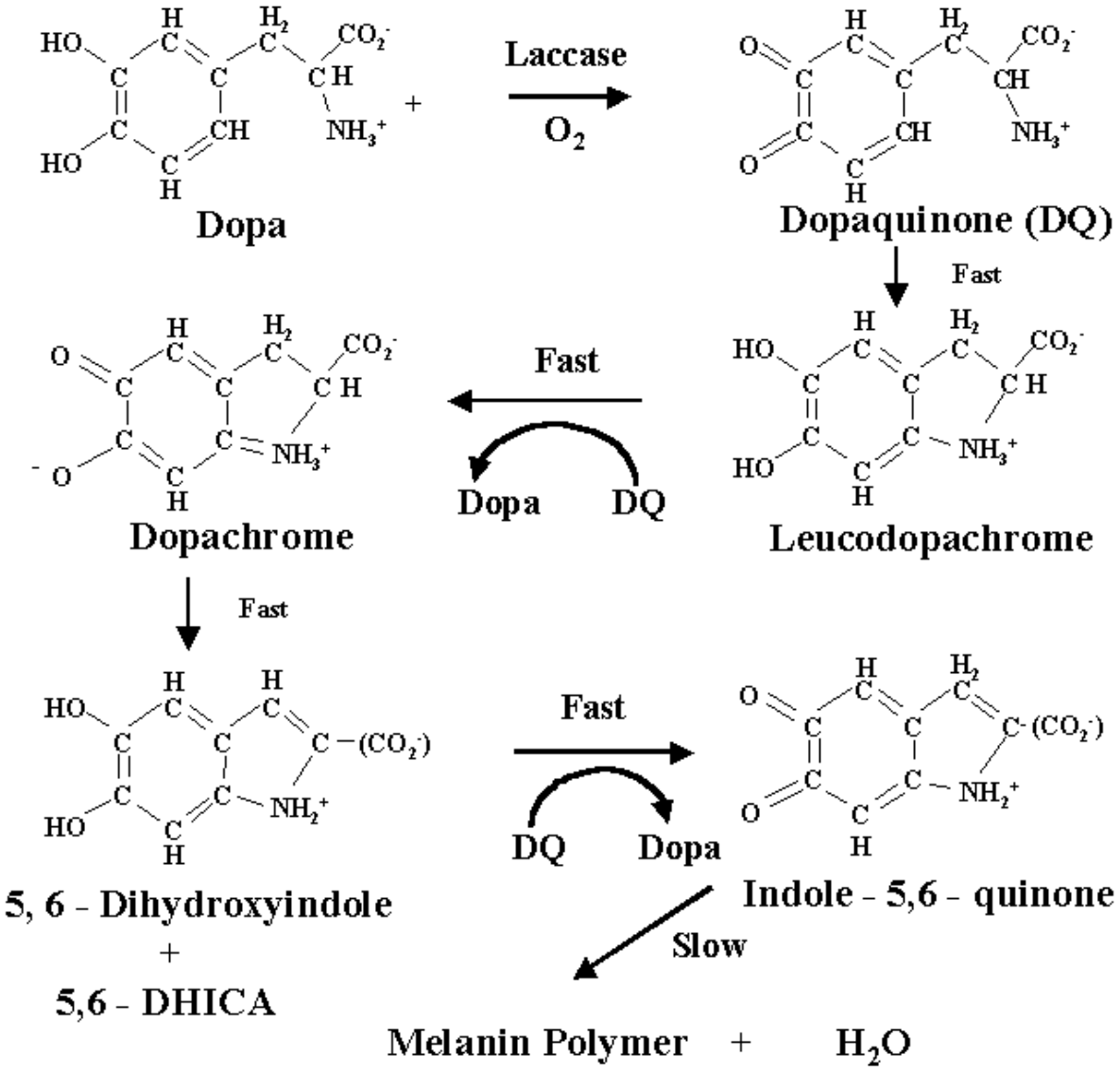


- The cause of Parkinson's disease is a degeneration of dopaminergic neurons in the substantia nigra pars compacta.
- The most prominent symptoms are slowness of movement (bradykinesia), difficulty in initiating movements, and tremor.

Dopamine Biosynthesis and L-DOPA



An aside: Why Substantia Nigra neurons are Black: common biochemical pathways for dopamine and melanin.



Parkinsonian Resting Tremor & Bradykinesia

- http://www.youtube.com/watch?v=jclJVrLODQA

Parkinsonian Gait and L-DOPA treatment

- To treat Parkinsonism, patients are given L-DOPA to make the remaining SNc cells produce more dopamine.
- That can work quite well as long as the degeneration of the SNc is only partial.
- http://www.youtube.com/watch?v=sf1N0Zf5IqA

Dyskinesia

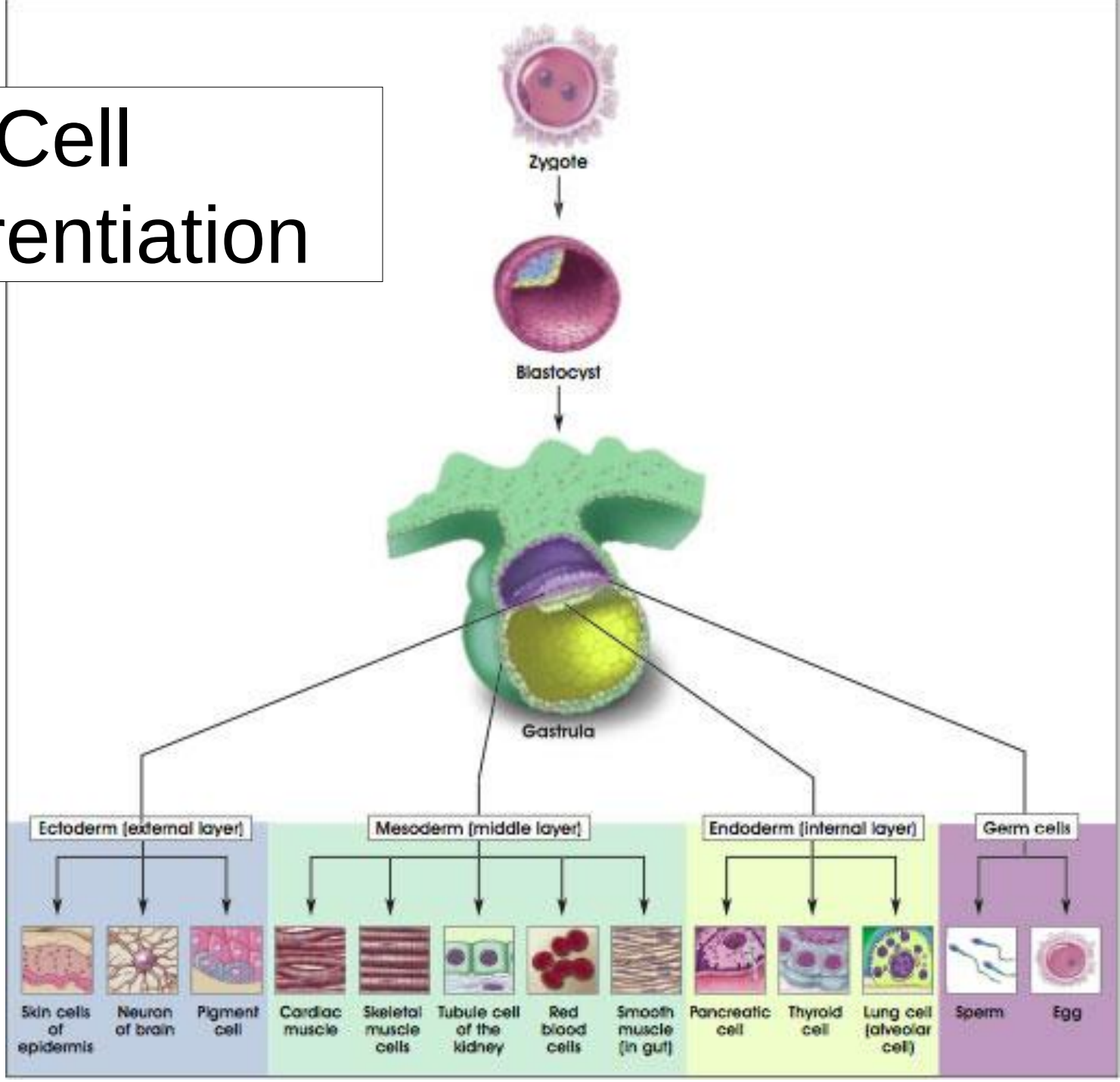
- A common side-effect of L-DOPA therapy
- Too much dopamine produced: bad spontaneous “motor ideas” are also executed unfiltered.
- The case shown here is quite severe

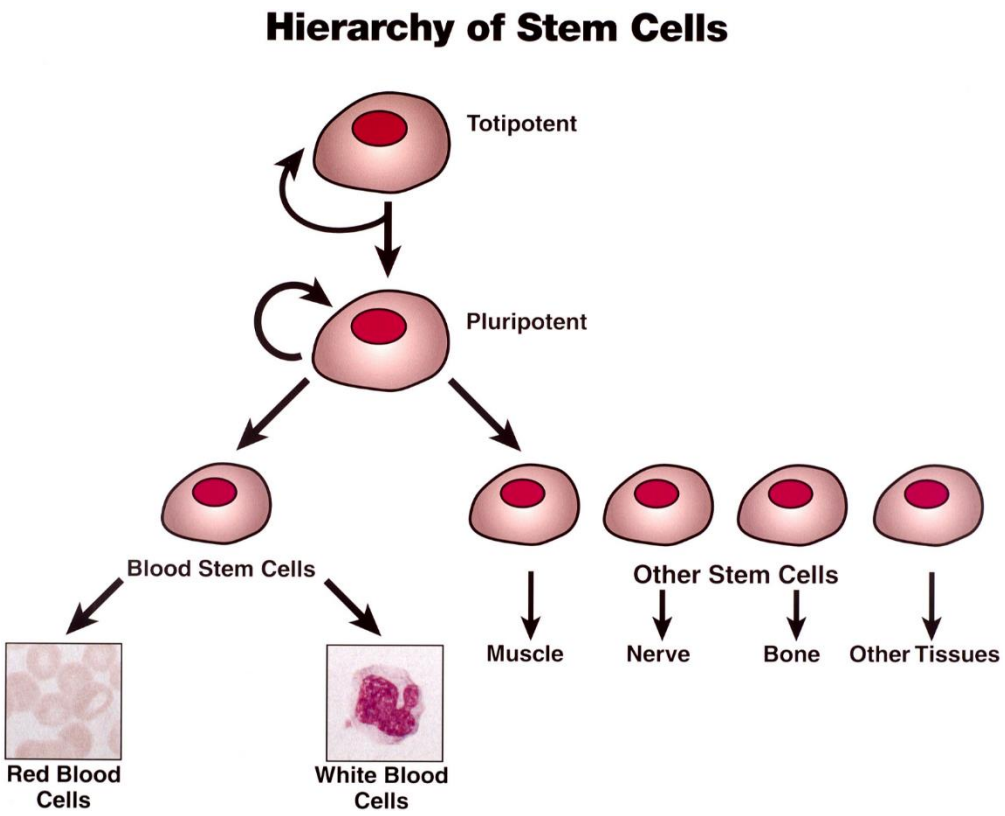
Break

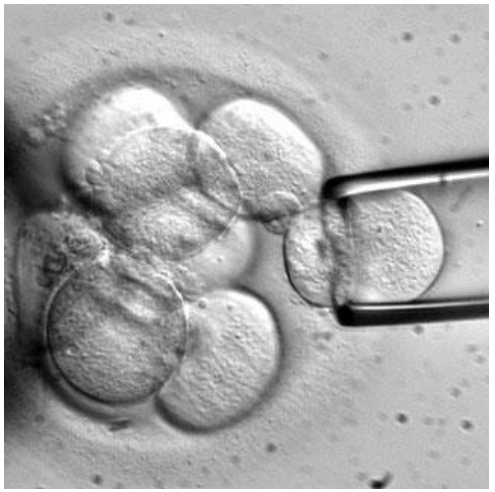
Michael Fox backs stem cell research

- The “back to the future” star suffers from quite severe early-onset Parkinsons.
- He would like to see stem-cell treatments developed to replace dead SNc neurons.

Cell Differentiation

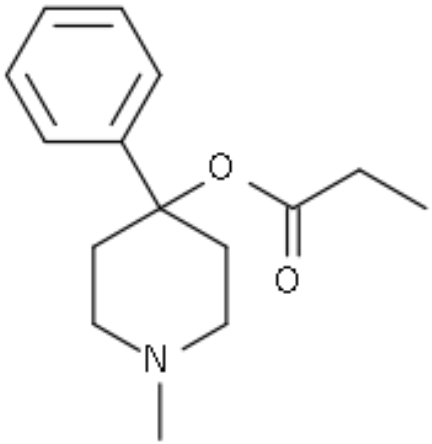


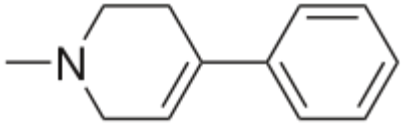




- The idea of stem cell therapy for PD is to make new dopaminergic neurons from stem cells to inject into the BG.
- But undifferentiated stem cells are rare in adults but very common in embryos.
- Religious pressure groups who (bizarrely) think of human embryos as people lobby hard to suppress research into human embryonic stem cells. Luckily scientists are getting better at re-differentiating adult human stem cells.

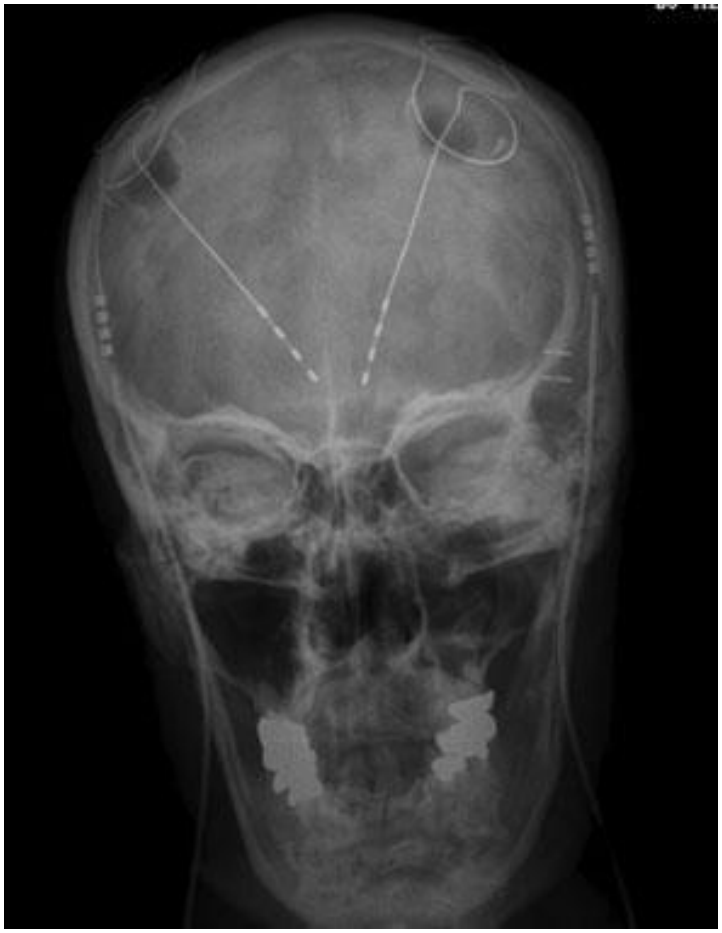
MPPP and MPTP

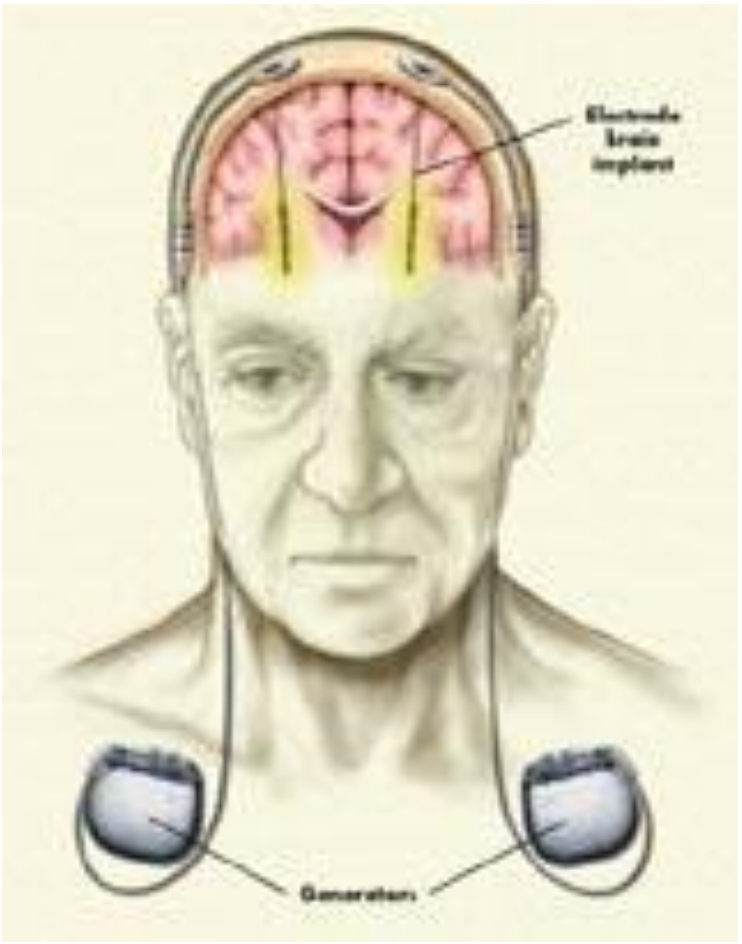




- MPPP is a synthetic heroin substitute
- MPTP is a contaminant that can arise from MPPP synthesis. It kills dopaminergic neurons and makes people (and animals) instantly severely Parkinsonian.
- Some successes have been reported in treating MPTP poisoned addicts with embryonic tissue grafts.

Deep Brain Stimulation





- DBS most commonly targets the subthalamic nucleus

Treating Parkinsonian Tremor with DBS

- http://www.youtube.com/watch?v=g5Y9f4Xr42o
- DBS can be very effective at suppressing Parkinsonian tremor even when drug treatments no longer work.
- Attempts to use DBS for other disorders, including chronic depression or chronic pain syndromes have so far failed to give consistent positive results.

Huntington's Disease

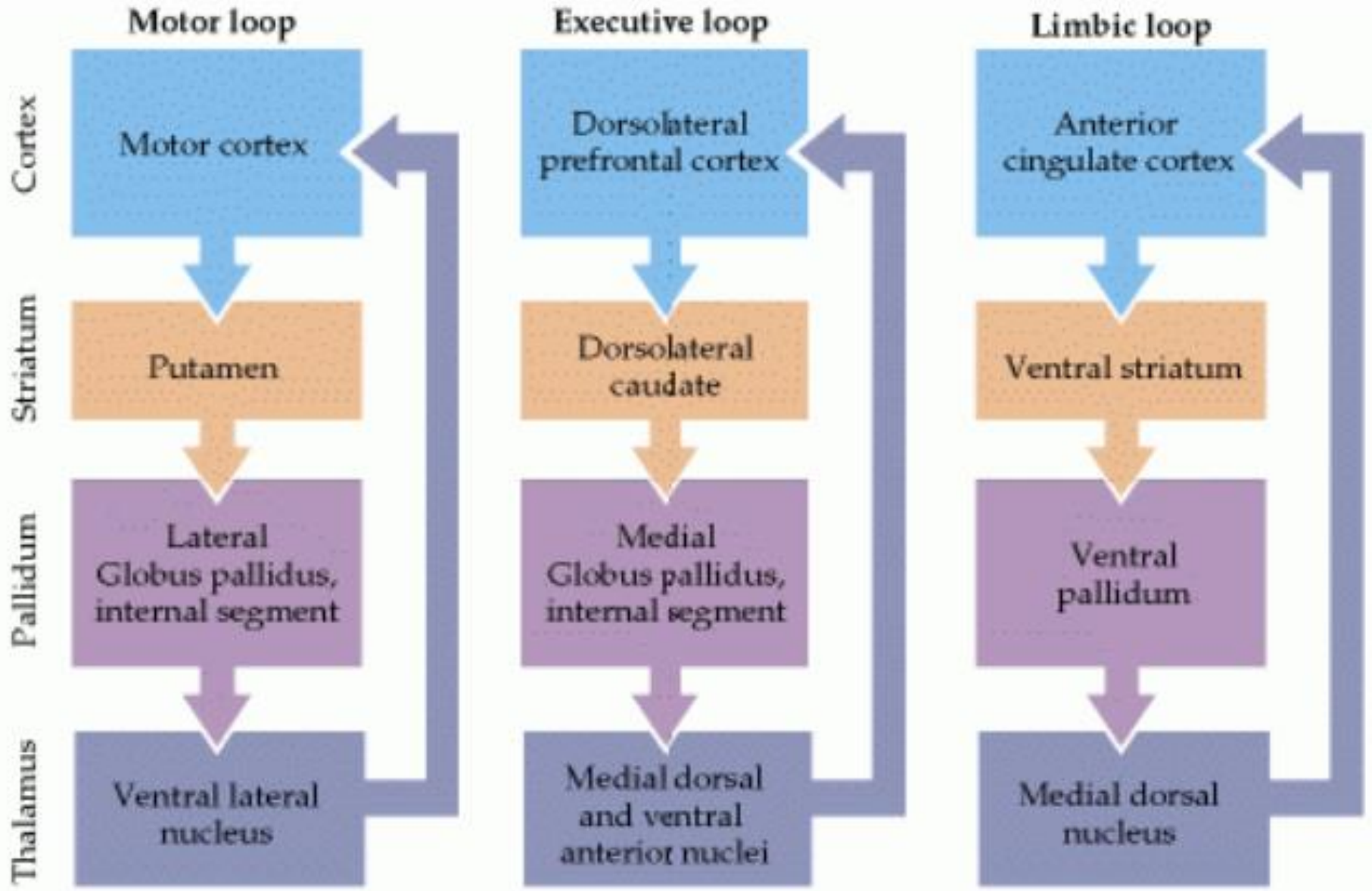
- A genetic mutation of the HTT gene on chromosome 4 causes premature neural cell death in homozygous carriers.
- Spiny stellate neurons projecting from putamen to the GPe are the first affected.
- Damage to the indirect pathway: not enough inhibitory control on spontaneous movement.
- As the disease progresses, damage is more widespread.

Huntington’s Chorea

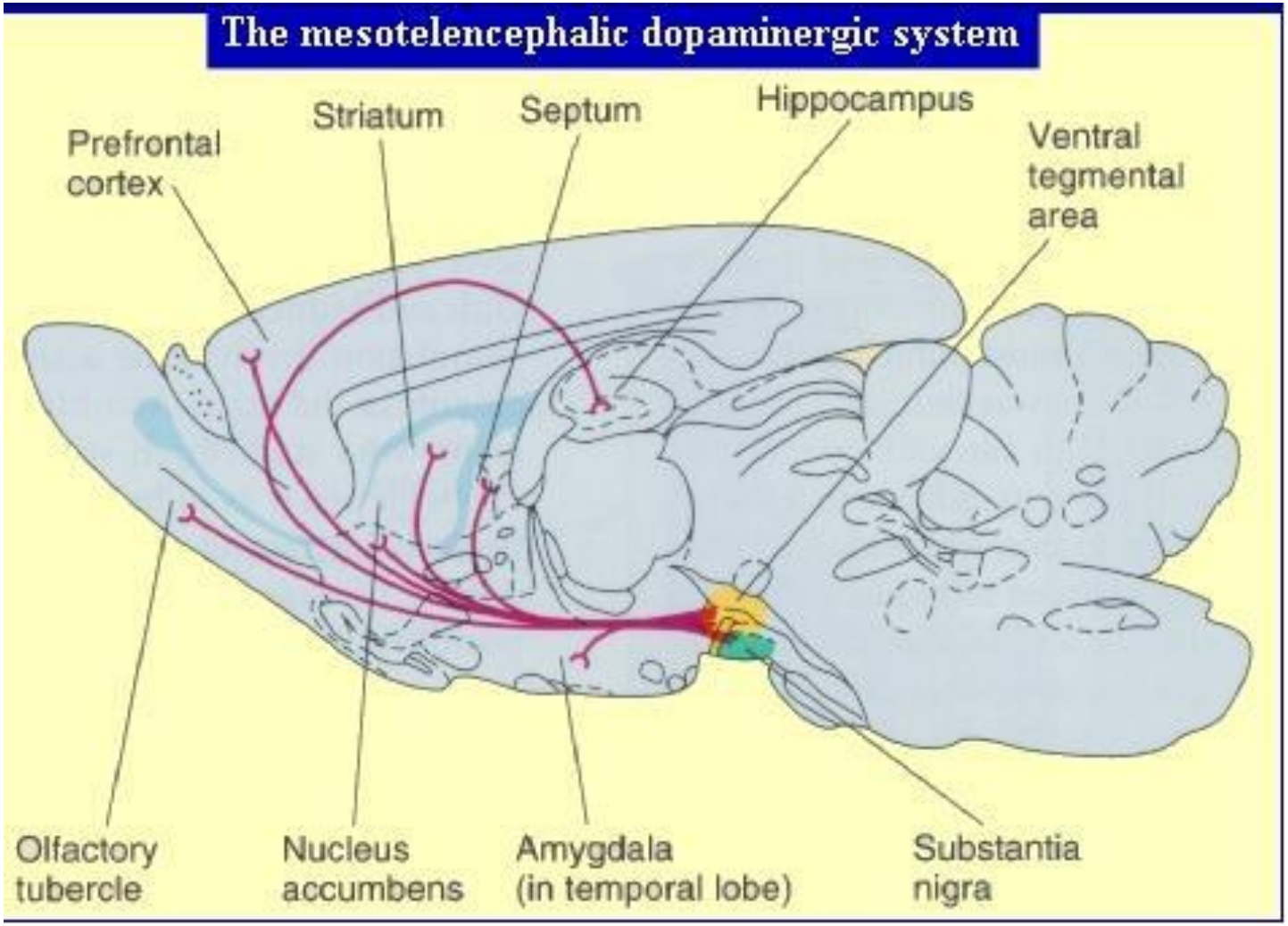
Generalizing the Motor Loop Idea Beyond Low Level Motor Control

- Remember from last lecture that, as we go more “frontal” from primary motor cortex to prefrontal areas, we find neurons that appear to encode increasingly “abstract” motor intentions. (E.g. “mirror neurons”).
- These more anterior structures, as well as limbic parts of the brain, also form loops through the basal ganglia (cognitive and limbic loops), which are also under dompaminergic control, in a manner that is quite similar to the motor loop.

The Forebrain: Loops Upon Loops



Mesolimbic Mesocortical Dopamine Pathways



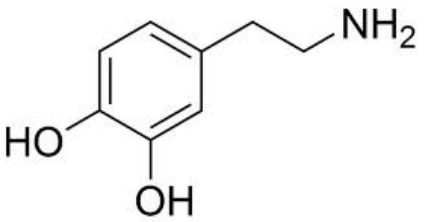
Reported Prevalences of Behavioural and Psychiatric Symptoms in Huntington's disease[

Irritability	38–73%
Apathy	34–76%
Anxiety	34–61%
Depressed mood	33–69%
Obsessive and compulsive	10–52%

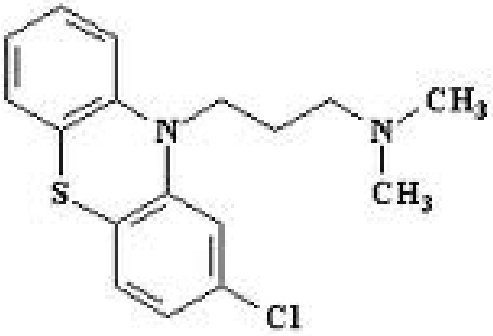
- Cognitive and limbic loops and their possible malfunctions gives us a theoretical framework which allows us to think about likely underlying causes of many psychiatric conditions, from OCD and mania to addiction.

Dopaminergic Antagonists

- Dopamine



- Chlorpromazine



- Numerous **dopamine antagonists** are used to treat a wide range of psychiatric diseases including obsessive-compulsive disorder, Tourette's syndrome, anxiety disorders and psychotic states.
- Parkinson-like symptoms are common side effects.

A Look Ahead

- Today's lecture revolved around the role of "*tonic"* Dopamine levels as a sort of "thermostat" of activity levels in motor, cognitive and limbic loops around the brain.
- However, the activity of dopaminergic neurons in the SNc and VTA also changes in a "*phasic"* manner that appears to predict how "rewarding" a particular activity is likely to be.