Movement Disorders

WEEK 7, LECTURE 3

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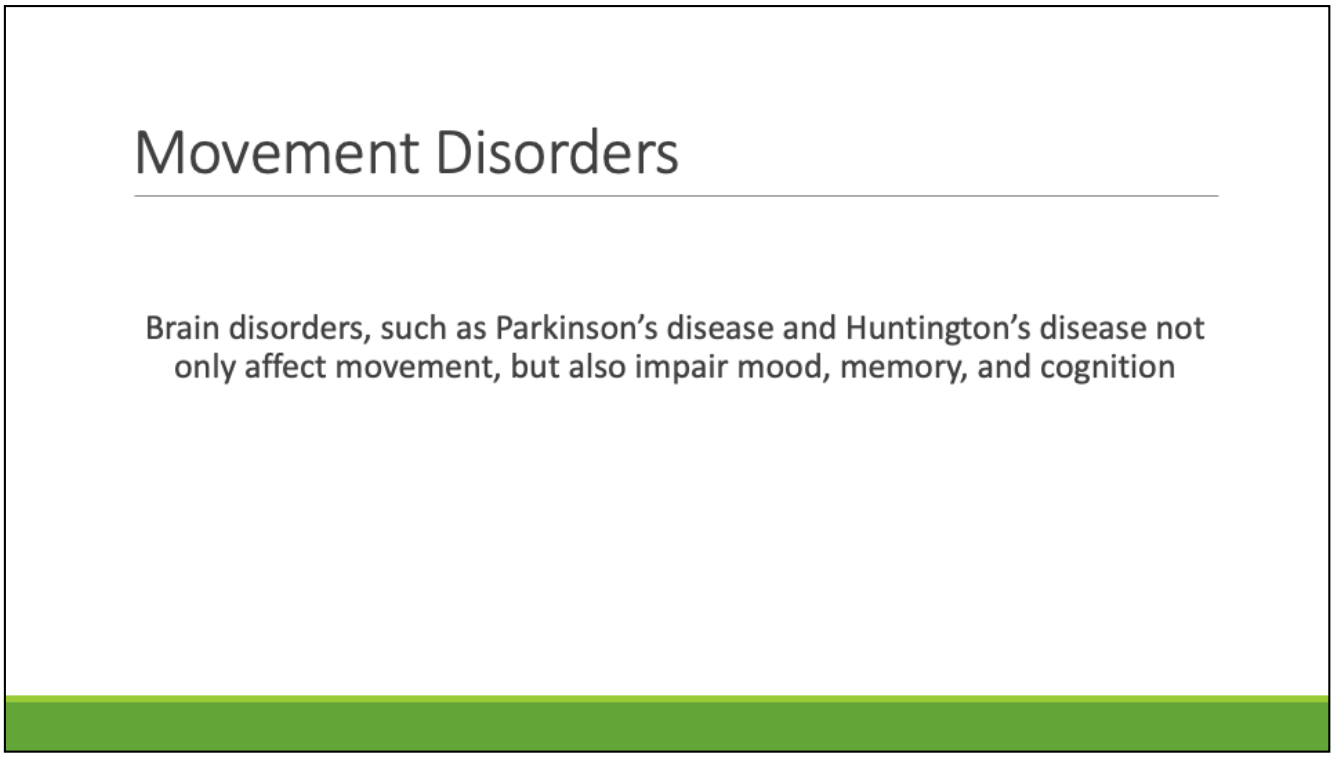
Welcome back! This is your last lecture series for this week. This lecture series is a little shorter, and I'm actually kind of happy about that, because this really isn't my preferred medium of getting the information out to you. If it has to be this way, at least it's for one of the shorter series, right?

In any case – in our last two lectures, we've been talking about movement under neurotypical conditions. This lecture will discuss cases in which movement can be impaired.



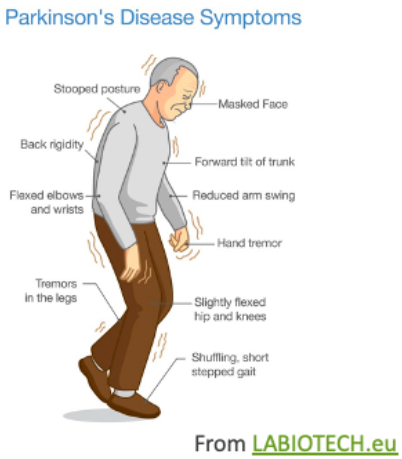
We'll mainly be focusing on two diseases: Parkinson's and Huntington's. Both of these are primarily considered movement disorders, but they effect much more than the ability to move: they also have effects on mood and cognition. There tends to be a lot of variance in cognitive and mood symptoms, but I should also note that these are both incredibly debilitating diseases, so mood disorder is an unfortunately natural companion to the other symptoms.

Parkinson's Disease

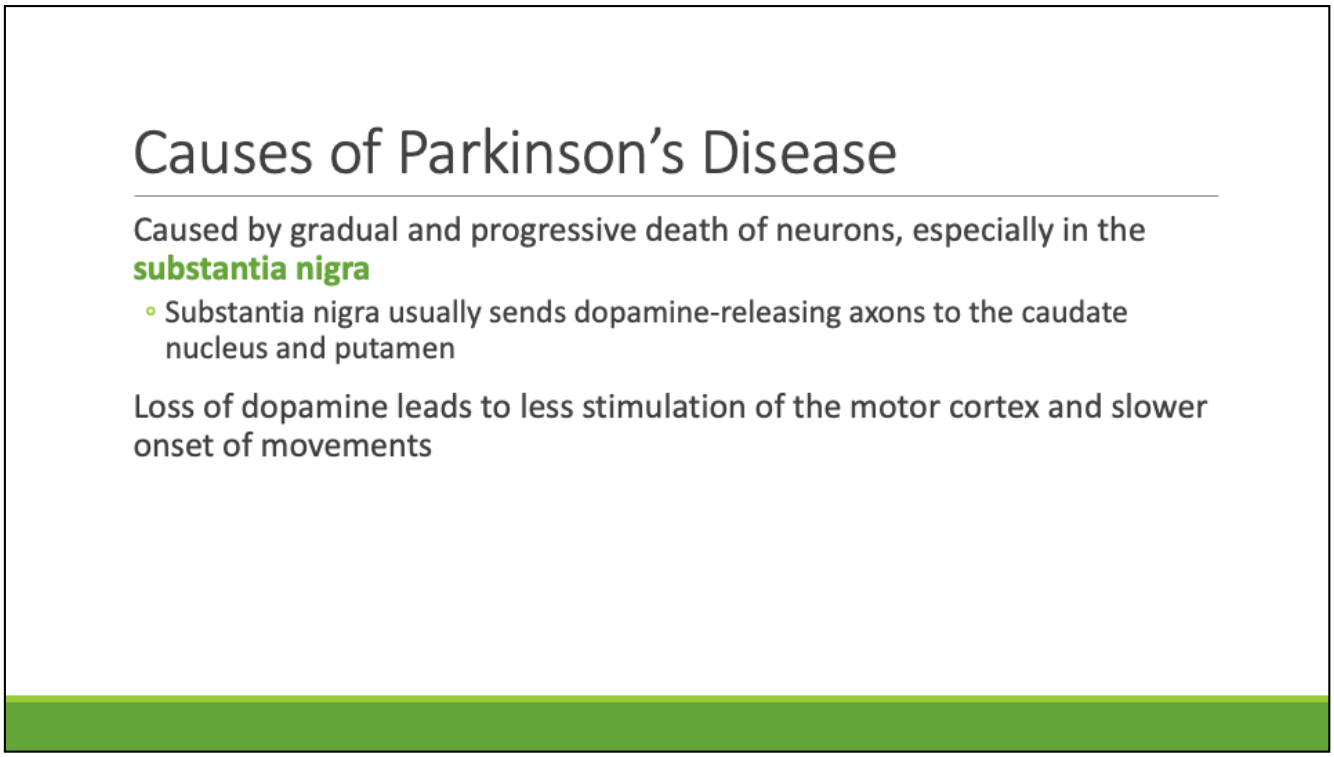
A movement disorder characterized by muscle tremors, rigidity, slow movements, and difficulty initiating physical and mental activity

- Associated with an impairment in initiating spontaneous movement in the absence of stimuli to guide the action

Symptoms also include depression, memory and reasoning deficits, loss of olfaction, and other cognitive deficits



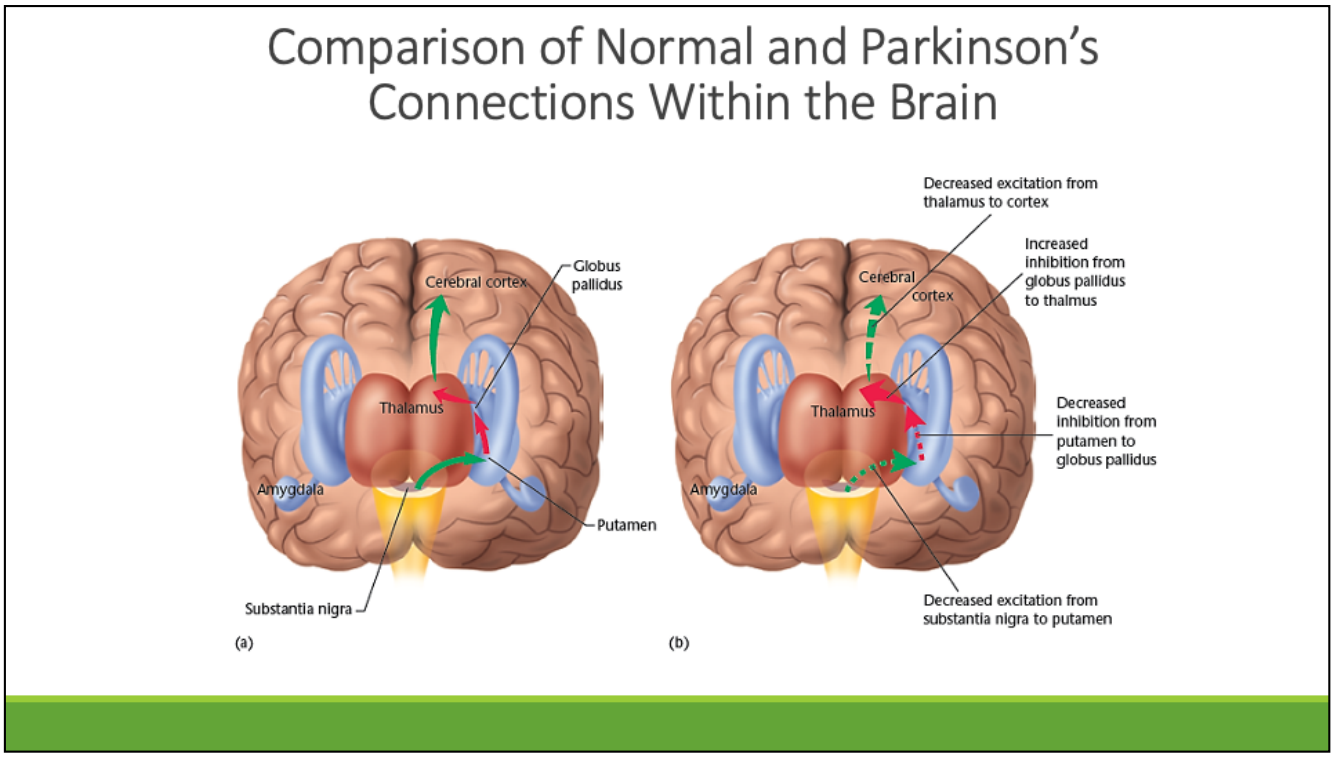
Let's start with Parkinson's disease. You can read about the general symptomatology above.



Parkinson's appears to be caused by the gradual, progressive death of dopaminergic neurons in the substantia nigra.

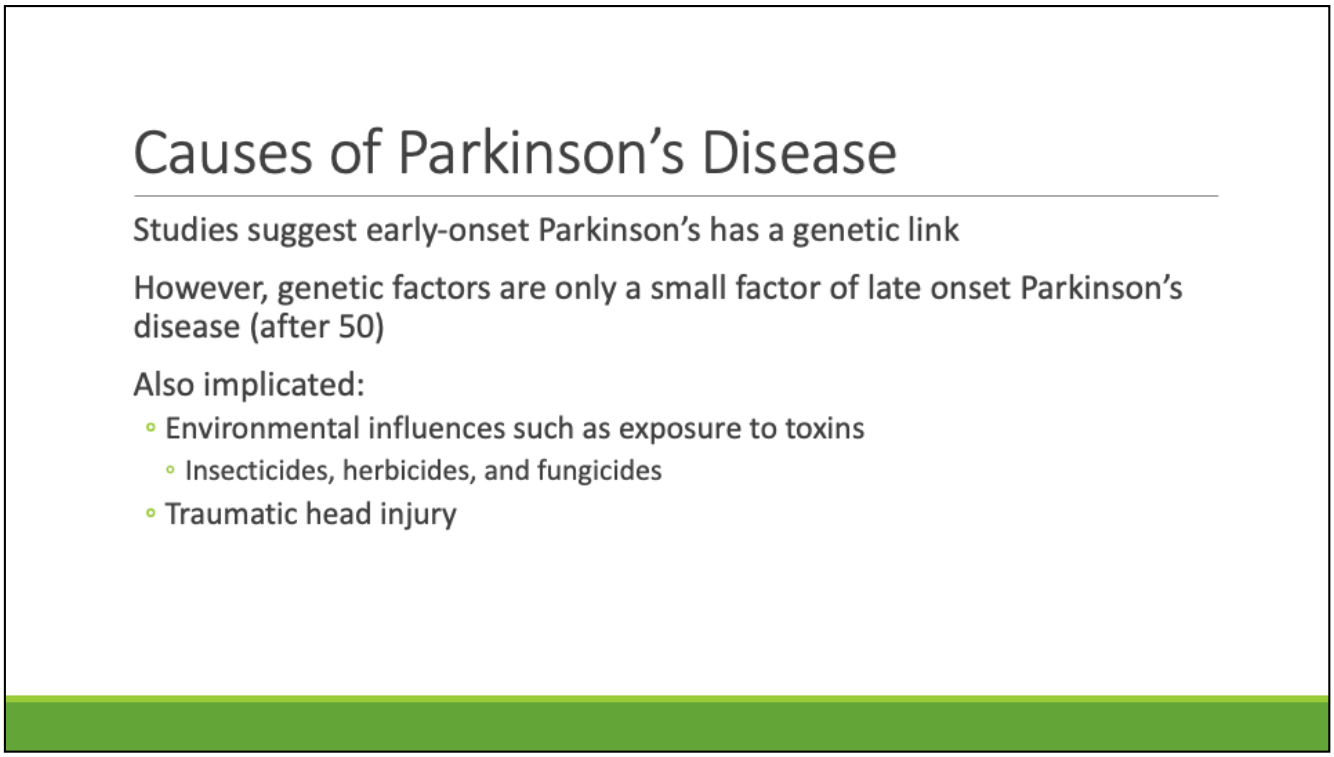
The substantia nigra is another part of the basal ganglia, and it typically sends dopamine and GABA to the striatum, which enables the initiation of movements – and specifically learned movements.

In Parkinson's disease, the dopamine-releasing neurons in the substantia nigra start to die off. The loss of dopamine leads to less stimulation of the motor cortex, and slower onset of movements as a consequence.



This diagram highlights how Parkinson's disease affects normal brain functioning in the basal ganglia. Excitatory paths are shown in green, and inhibitory pathways are in red. The "normal" brain is on the left, and the one with Parkinson's is on the right.

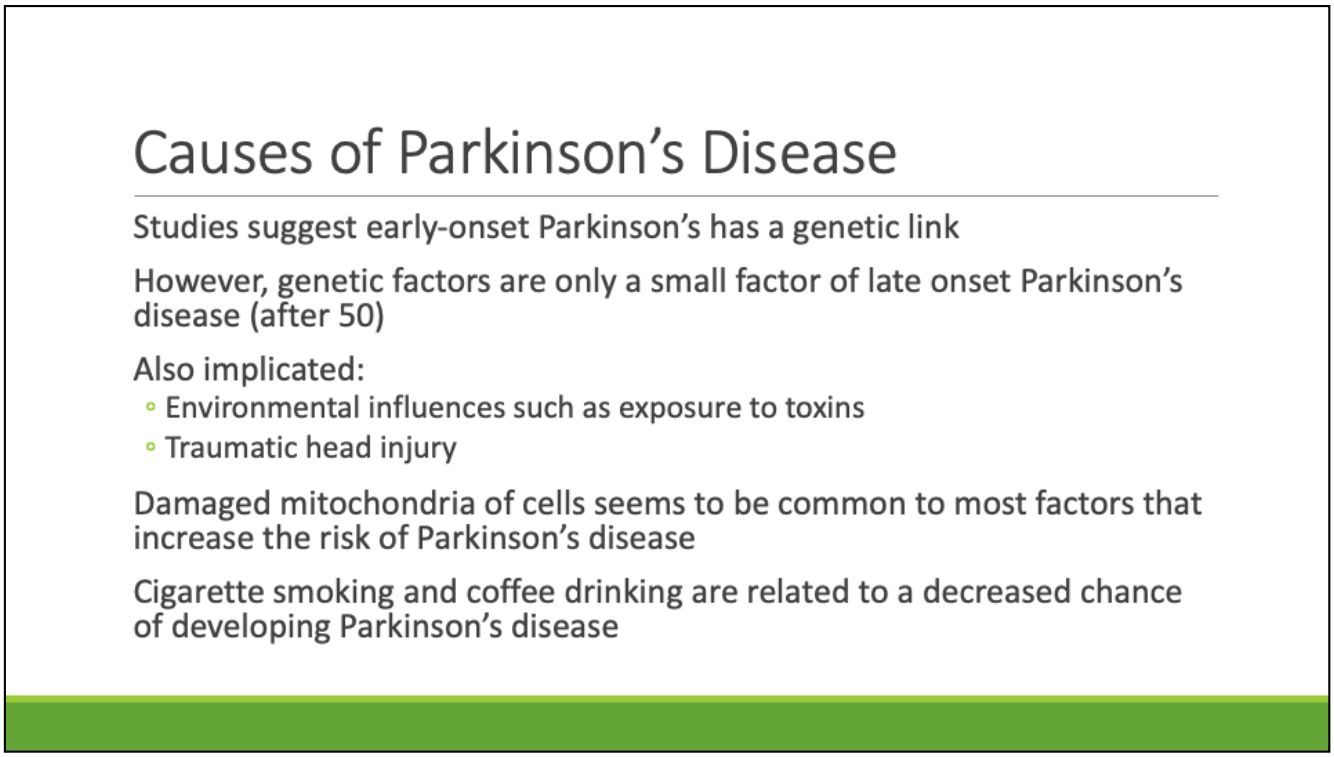
If you focus on the right image, you can see that there is decreased excitation from the substantia nigra. This leads to decreased inhibition from the striatum, and THAT leads to increased inhibition from the globus pallidus. The net result is a decrease in excitation, which leads to a decrease in motor functioning. This is another one of the many "X inhibits Y which excites Z" pathways. I do not need you to know this in detail, but I would like you to take a moment and compare this to the functioning of the direct and indirect pathways we discussed in our last lecture. The best way to wrap your head around these types of pathways is with lots of examples. So again, I'm not going to ask you about these pathways in detail, but the best way to gain a deeper understanding of them is to spend a little time going over examples (and of course I'm here if you have any questions).



When it comes to determining the causes of Parkinson's Disease… it's complicated. No one has been able to determine why neurons in the substantia nigra begin to die off.

There are many studies out there suggesting that there's some kind of genetic predisposition for it, although no one has been able to pinpoint what this is as of yet.

Moreover, as with many disorders with a possible genetic component, it seems like genes play much more of a role in early-onset Parkinson's. For those who start to show symptoms after age 50 (i.e. late-onset Parkinson's), it gets even *more* complicated. There's some research suggesting that individuals exposed to chemicals like pesticides are more likely to get it later in life. The same goes for people who have suffered a traumatic head injury at some point in their life. Again, though, it seems like a number of different factors lead to its onset. At this point, there is unfortunately no clear picture of the cause of this disorder.



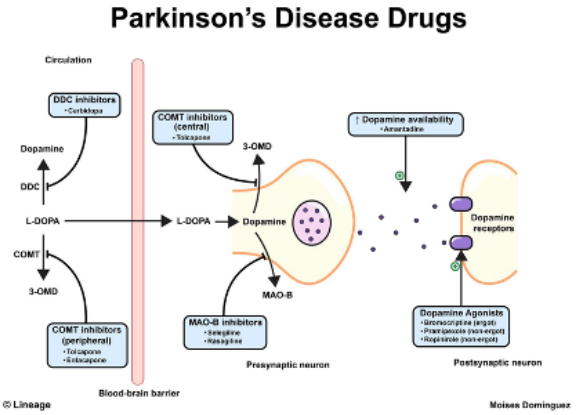
Regardless, it seems like these causes all lead to one common outcome: damaged mitochondria of cells in the substantia nigra.

Also, weirdly – cigarette smoking and coffee drinking are related to a *decreased* risk of developing Parkinson's. And this is a pretty robust effect – it even extends to those who have persistently been exposed to second-hand smoke! But it's really unclear what it is about smoking (and coffee drinking) that protects people against this disease. Researchers believe there might be some compound in nicotine that prevents damage, but the jury is still out on this one. I've done a little bit of research preparing for this lecture (Parkinson's is not my area of specialty, although I think it's fascinating) – and there really isn't a lot of research on this topic. At least not yet!

Treatment of Parkinson's Disease

The drug **L-dopa** is the primary treatment for Parkinson's and is a precursor to dopamine that easily crosses the blood-brain barrier

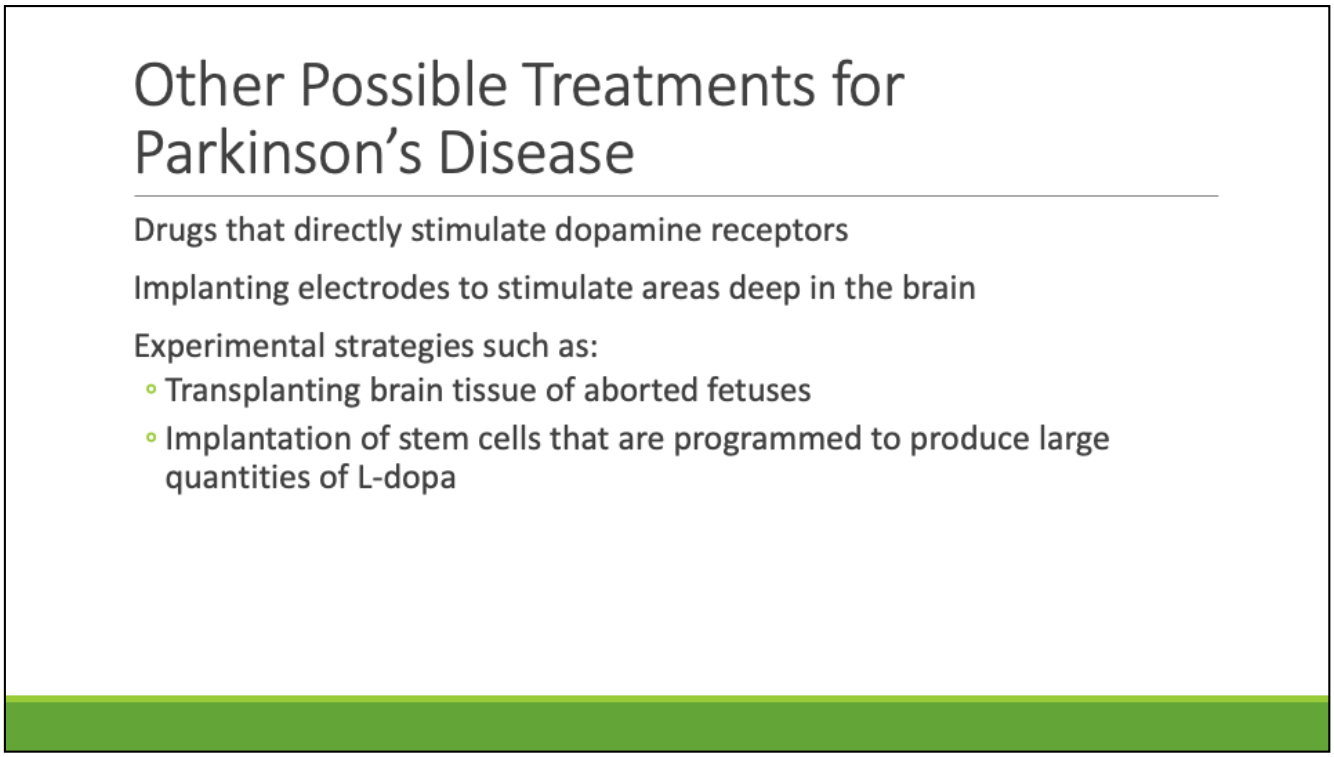
- Often ineffective, especially for those in the late stages of the disease
- Does not prevent the continued loss of neurons
- Can enter other brain cells and produce unpleasant side effects



So how is Parkinson's treated? Right now, the most effective medication is something called L-dopa, which is a precursor to dopamine that can easily cross the blood-brain barrier.

However, it's by no means a cure, and also has several drawbacks, which you can read about above.

Now, you don't need to memorize anything about this chart, this is just here to show how L-dopa can cross the blood-brain barrier, be synthesized into dopamine, and the get released into the synapse.



The most promising alternative candidates for Parkinson's treatments are any drug that directly stimulates dopamine receptors (rather than providing a precursor for dopamine synthesis).

There are also other strategies in the works, such as implanting electrodes to stimulate dopamine release in the basal ganglia, or things like transplanting the intact brain tissue of aborted fetuses to replace the damaged tissue in the substantia nigra, or directly implanting stem cells that have been pre-programmed to produce large quantities of L-dopa.

All of these are in the works, but none has been proven effective as of yet. We are nowhere near a cure for this disease, unfortunately.

Huntington's Disease

A neurological disorder characterized by various motor symptoms

- Affects 1 in 10,000 in the United States
- Usually onset occurs between age 30-50

Associated with gradual and extensive brain damage especially in the basal ganglia but also in the cerebral cortex

Initial motor symptoms include arm jerks and facial twitches

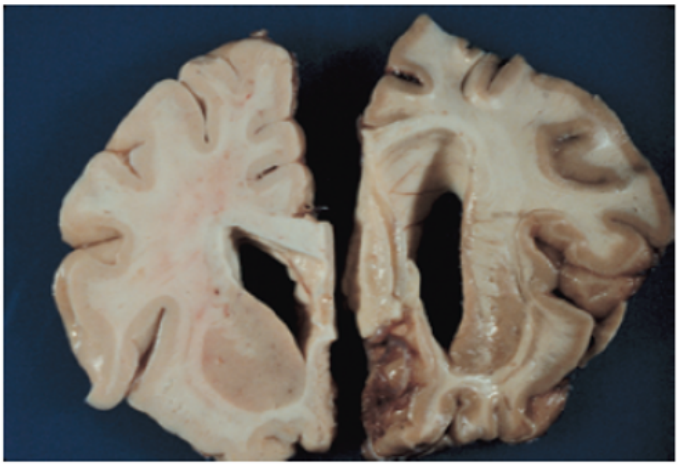
Motors symptoms progress to tremors and writhing that affect the persons walking, speech, and other voluntary movements

Also associated with various psychological disorders:

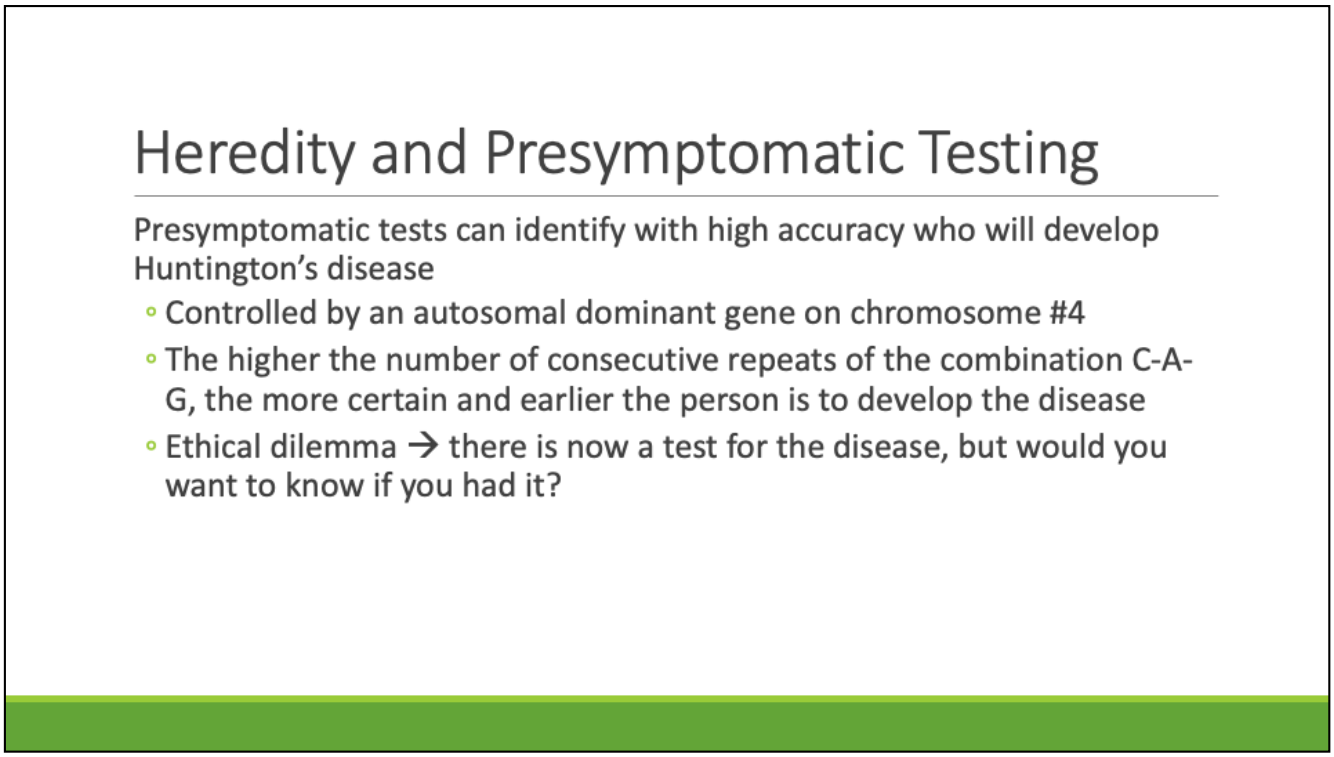
- Depression, memory impairment, anxiety, hallucinations/delusions, poor judgment, alcoholism, drug abuse, sexual disorders

And on that note, let's move on to our next topic. The next disease we're going to talk about is one that is quite rare but also quite devastating. Huntington's disease is characterized by a wide range of motor symptoms, which you can read about in detail above.

A Normal Brain vs. a Brain w/Huntington's Disease



The brain section on the left is a normal brain, and the one on the right is one that was affected by Huntington's disease. The angle of cut through the normal brain makes the ventricle look larger in this photo than it actually is… but even so, you can see how much larger the ventricle it is in the patient with Huntington's disease. The ventricles expand because of the loss of neurons, and CSF fills in the missing areas. You can also see that there is substantial neural tissue loss in the patient with Huntington's.

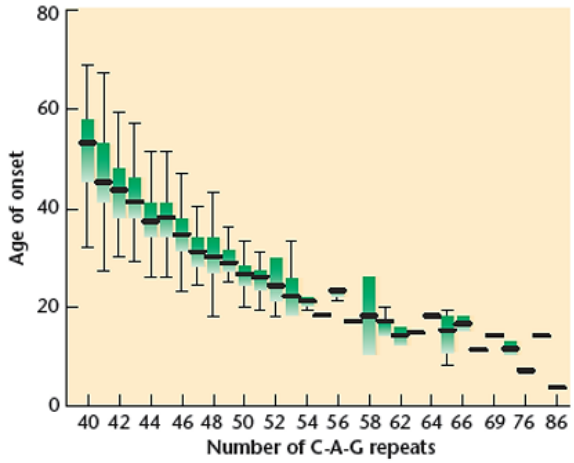


Most disorders don't have a single genetic cause, but Huntington's is unique in that it does. The gene for Huntington's is located on chromosome 4, and it's actually a dominant gene – so if you have it, it's much more likely that the disease will manifest (as opposed to you being a carrier for it).

This gene codes for a specific sequence of nucleotides: C-A-G. And it actually codes for repeats of this sequence, basically telling this sequence to repeat over and over again. The more consecutive C-A-G repeats of this sequence one has, the more likely one is to develop the disease. A higher number of C-A-G repeats also indicates an earlier onset of the disease.

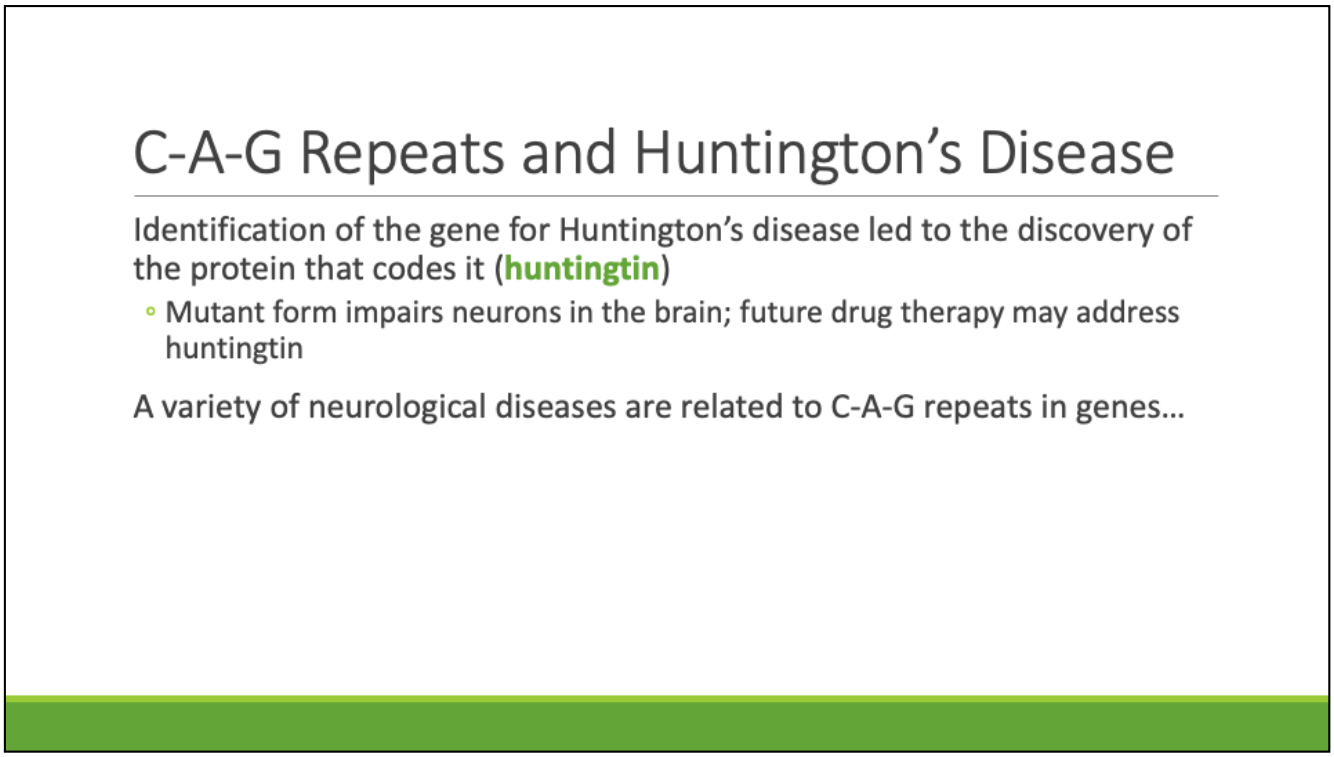
Because so much is known about the genetic underpinnings of Huntington's, individuals who think they might be at risk can actually take a test for it even before they start showing symptoms. But the fact that testing exists raises a kind of scary ethical dilemma for people. Would you want to know if you had it? It can be an incredibly difficult choice for individuals who know they're at risk.

Example: Base Pair Repeats and Onset of Huntington's Disease



So this graph is based on a study that looked at the number of CAG repeats (on the x-axis) and the age of onset of Huntington's (on the y-axis). You can see that, first and foremost, as the number of repeats increases, the age of onset decreases (and vice versa). Notice also that there is a lot more variability (indicated by the black lines above and below each marking on the graph) for age of onset in people with fewer C-A-G repeats. This tells us that C-A-G repeats are a good predictor of age of onset, but there are other factors at play here as well.

In any case, the take-home from this is that the more C-A-G repeats one has, the more likely one is to have the disorder, and the more likely it is to manifest earlier in life (around age 40 or so).



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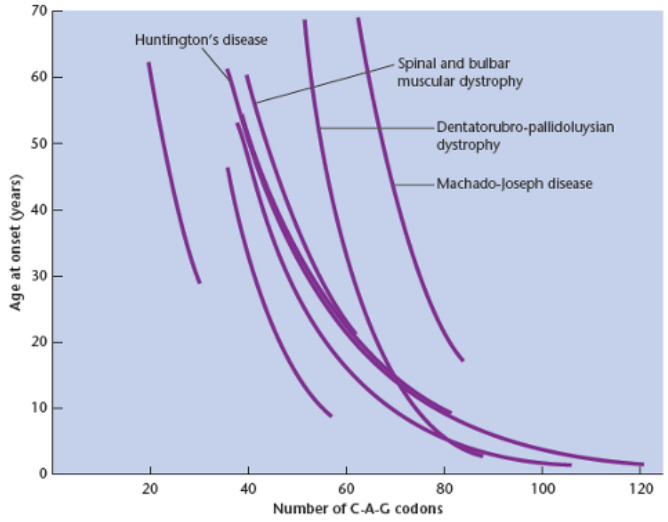
CAG repeats are actually not limited to Huntington's disease: they're also found in a number of other neurological diseases...

C-A-G Repeats and Other Diseases



Here's another graph, which speaks to this last point. So, the x-axis here shows the number of C-A-G repeats, and the y-axis shows the average age at onset of different neurological diseases, including Huntington's. The key point is that for each disease, the greater the number of C-A-G repeats, the earlier the onset of symptoms.

So C-A-G repeats are a good way of assessing the potential manifestation of *many* neurological disorders, not just Huntington's.

Questions for your discussion groups…

1. What is the (general) cause of Parkinson's Disease?
2. What is the (general) cause of Huntington's Disease?

That does it for this week's lectures! Here are some last discussion questions to round out the week.

Thank you all for working with me this week. Hopefully by next week I'll be back at it again with my scratchy voice.