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Intro to Parkinson's Disease

A. What is Parkinson's Disease?

Parkinson's Disease is a movement disorder. Primary symptoms include tremors, rigidity, slow movement (bradykinesia) or no movement (akinesia), and postural instability.

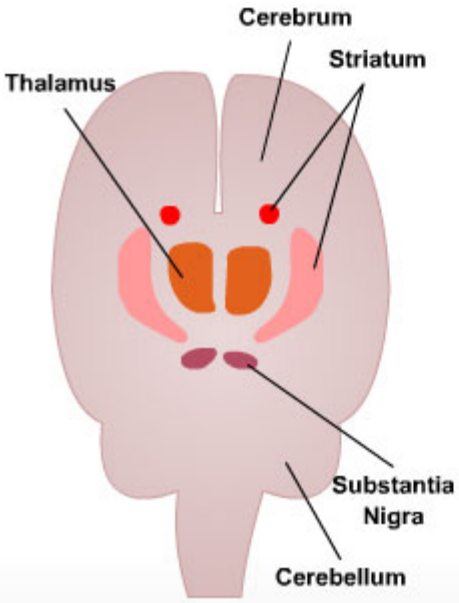
B. Who Gets Parkinson's Disease?

Left: Michael J. Fox
Above: Muhammad Ali

- The elderly primarily get Parkinson's Disease
- 1 Million sufferers in the US
- 2% lifetime risk
- Some young adults get Parkinson's Disease

C. How is the Brain Damaged in Parkinson's Disease?

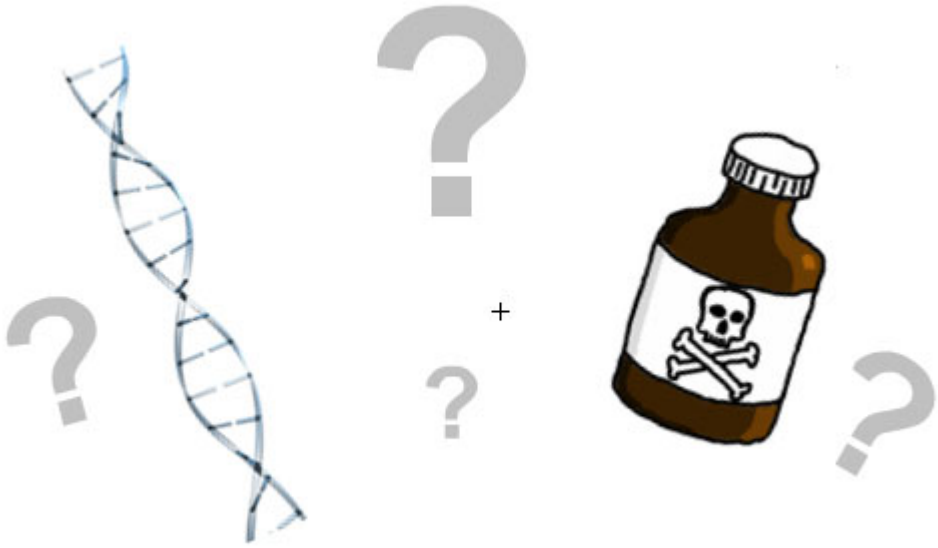
The brain loses the neurotransmitter Dopamine in the Substantia Nigra and Striatum.



Left: Conceptualized human brain top, **Right**: Real histology of human brain, normal brain on right side shows dark banding (dopamine) vs. brain on left w/ Parkinson's disease

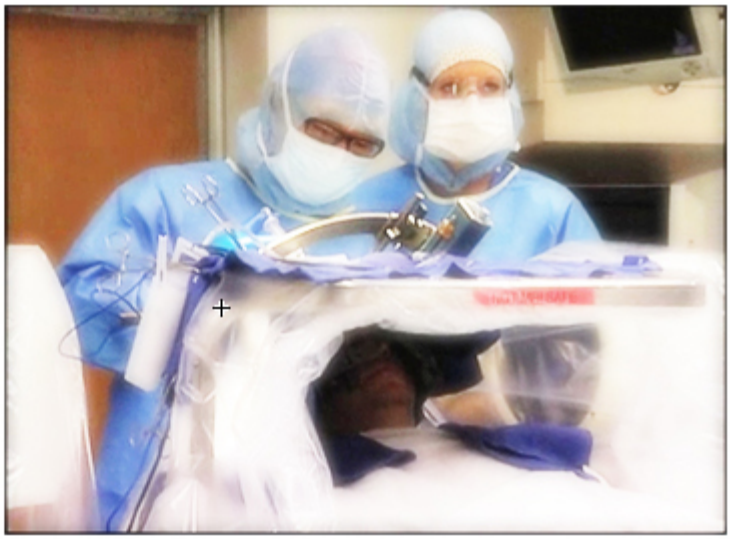
D. What Causes Parkinson's Disease?

- The cause of most cases of Parkinson's Disease is unknown
- Genes and chemicals have been implicated in some cases



E. Can Parkinson's Disease Be Cured?

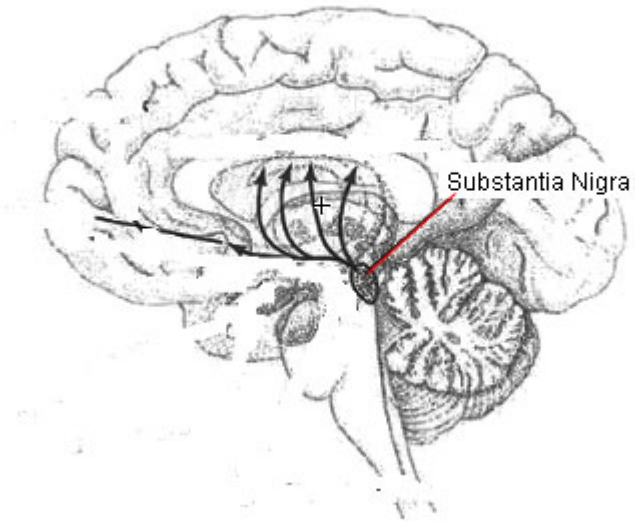
- No, but it can be treated with drugs and surgery
- Drugs that increase brain dopamine (levadopa) or mimic dopamine (agonists) are most commonly used
- The neurosurgical technique of Deep Brain Stimulation (DBS) is also being used more commonly



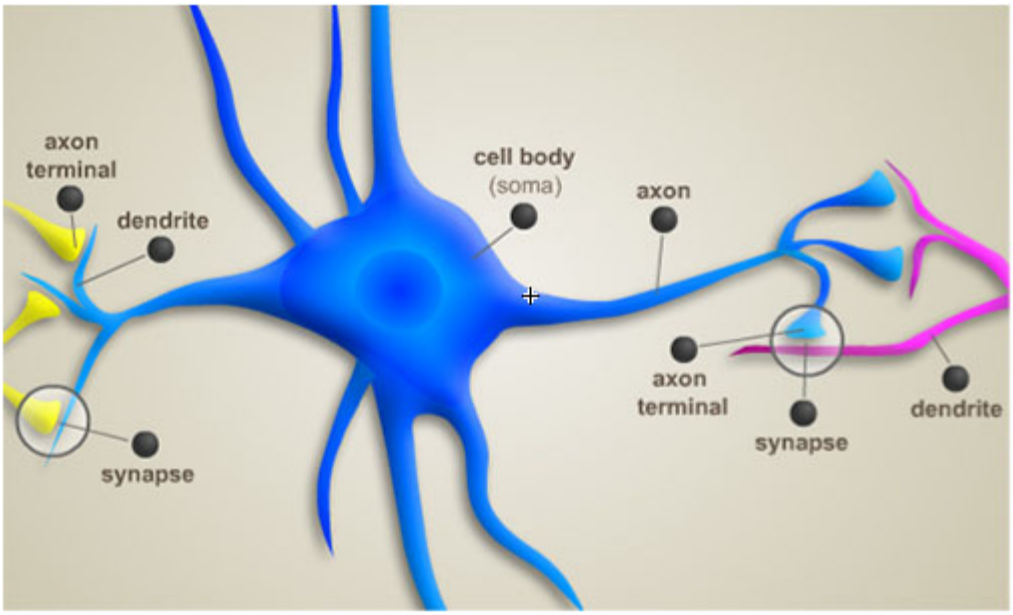
Intro to Dopamine Neurons

A. Where Are Dopamine Neurons in the Brain?

The dopamine neurons involved in movement and damaged in Parkinson's disease originate in the substantia nigra and terminate in the striatum, the so-called nigrostriatal dopamine neurons.

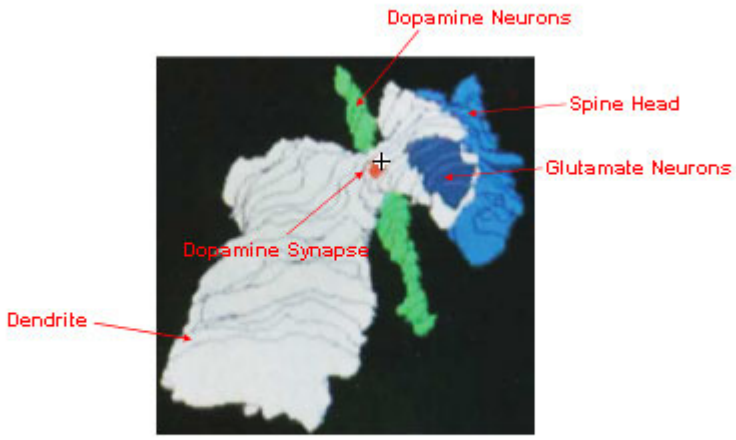


B. What is the Structure of Dopamine Neuron?



C. What is a Dopamine Synapse?

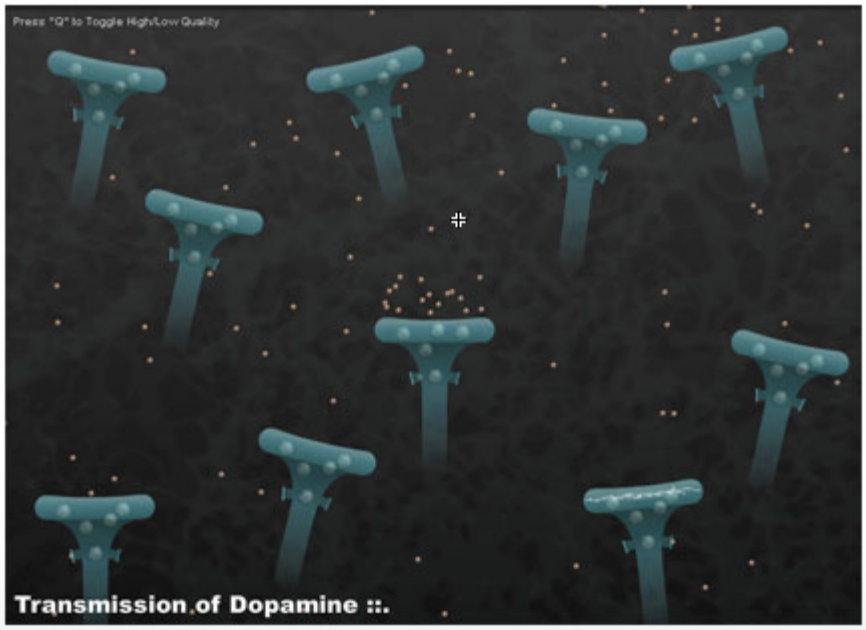
Dopamine neurons typically synapse onto the dendritic spine neck of medium spiny neurons in the striatum, adjacent to glutamate neurons coming from the cortex and synapsing on the spine head.



Compensation of Dopamine Neurons

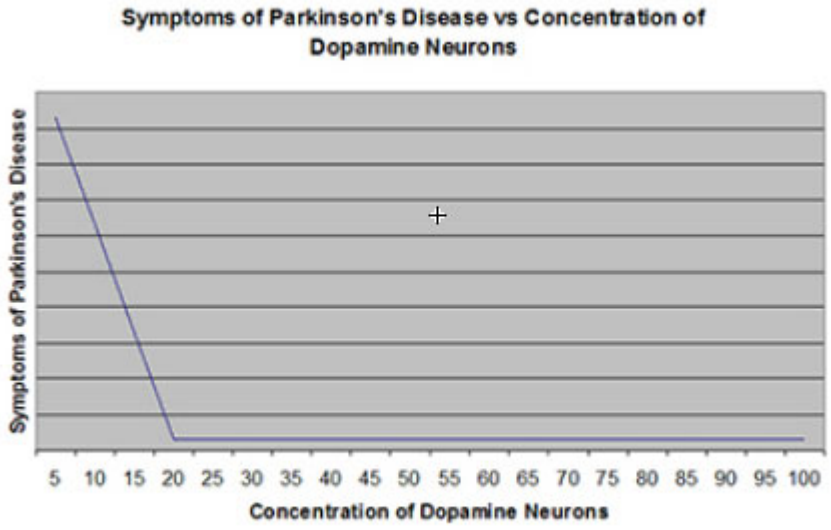
A. How is Dopamine Tone Maintained During the Pre-Symptomatic Phase of Parkinson's?

Dopamine tone is the constant level of extracellular dopamine in the brain. Normal movement requires a certain level of dopamine tone. In Parkinson's disease a drop in dopamine tone leads to motor dysfunction.



B. What is the Relationship Between Parkinson's and the Loss of Dopamine Neurons?

In Parkinson's Disease, dopamine tone stays at normal levels until the loss of dopamine terminals in the striatum exceeds 80%. Motor symptoms also emerge when terminal loss exceeds 80%.



C. What is the Relationship Between Dopamine Tone and Loss of Dopamine Neurons?

Dopamine neurons typically synapse onto the dendritic spine neck of medium spiny neurons in the striatum, adjacent to glutamate neurons coming from the cortex and synapsing on the spine head.

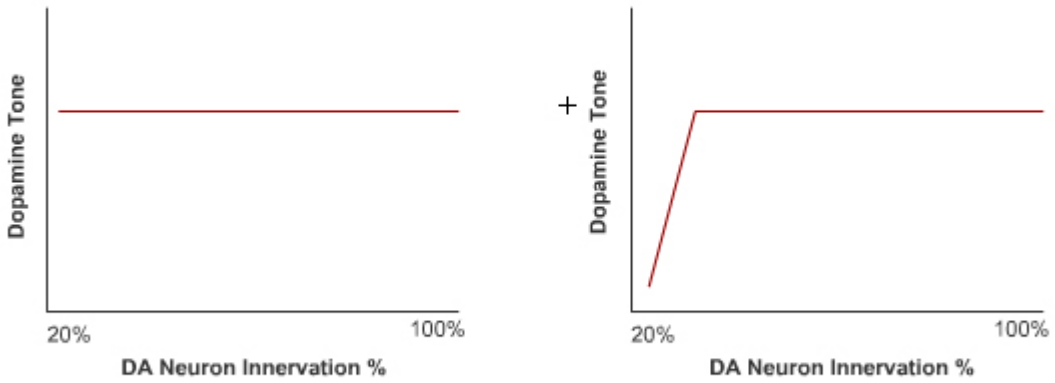
Designing Your Experiment

A. Scientific Methodology

1. Understand the available knowledge or make observations about the phenomenon.
2. Generate a hypothesis, or educated guess, about the phenomenon based on this understanding.
3. Make a prediction based on this hypothesis (i.e., if the hypothesis is true, I predict this should happen).
4. Design and perform an experiment testing the prediction.

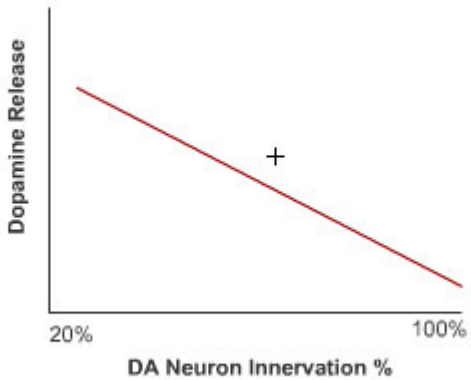
B. What Are We Investigating?

The phenomenon is how dopamine tone is maintained at a constant level during the preclinical phase of Parkinson's disease. The flat line suggests that dopamine tone is compensated. A lack of compensation would be indicated by a falling line. In this lattercase, as dopamine neurons are lost, dopamine tone falls.



C. What are the Hypothesis and Predictions?

The hypothesis is that dopamine release increases to maintain dopamine tone during the preclinical phase of Parkinson's disease. The prediction is that dopamine release will increase with the loss of dopamine neurons.

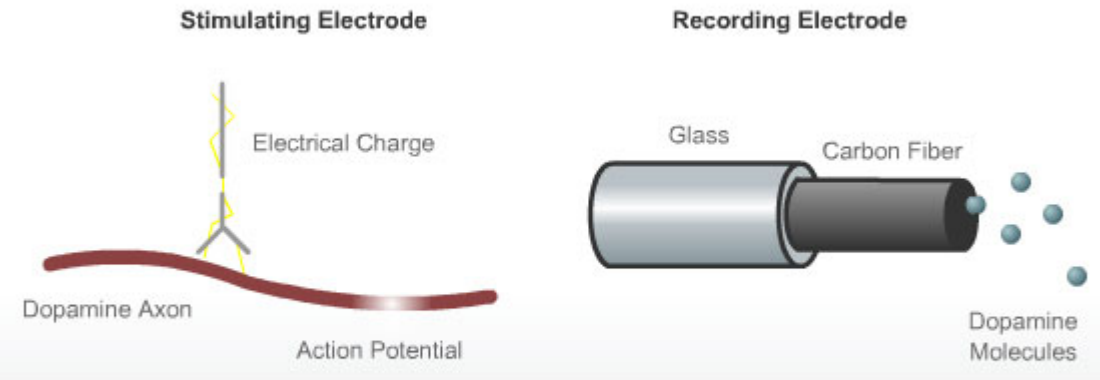


D. What is the Experiment?

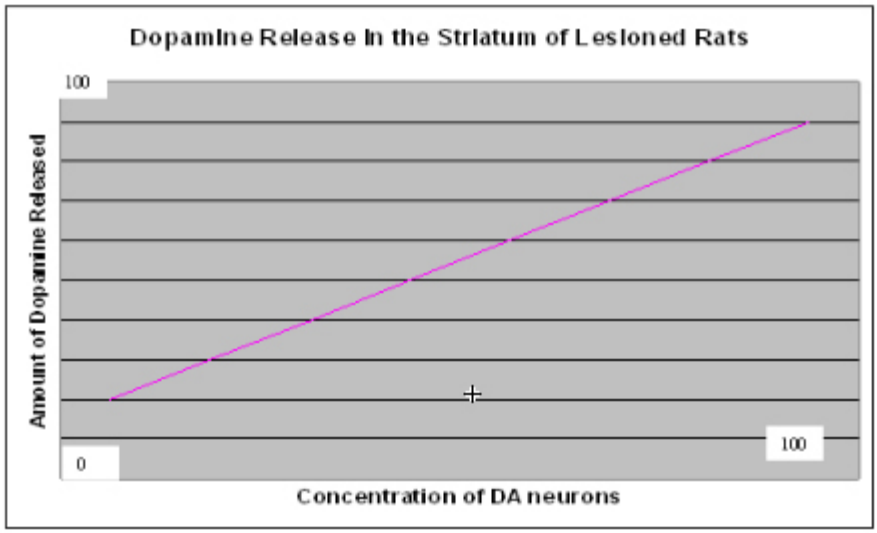
The experiment is to measure dopamine tone, dopamine release and dopamine uptake in a rat model of Parkinson's disease.

E. Lesioning and Stimulating/Recording

The model of Parkinson's disease is created by injecting neurotoxin in the substantia nigra of a rat, or "lesioning". This neurotoxin destroys dopamine neurons by generating hydrogen peroxide. The neurotoxin enters the dopamine neuron via a dopamine uptake site. Once in the cell, it reacts with vitamin C to make hydrogen peroxide, which then kills the cell body. Once the dopamine neurons have been destroyed, you will then need to stimulate the remaining neurons and record their dopamine release and uptake. This is achieved by implanting electrodes in strategic areas of the rat brain.

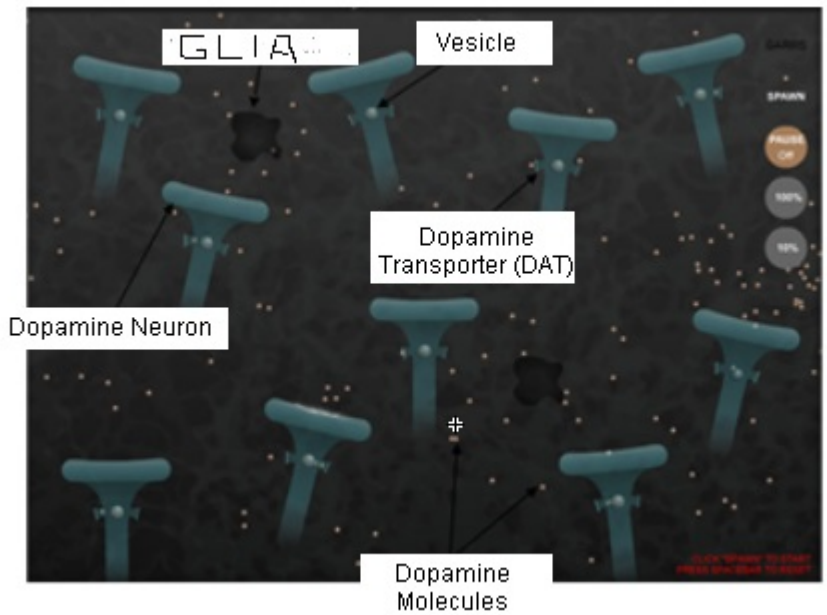


Interpreting the Lab Data



The data in the graph above was compiled from the data gathered during several experimental trials, including your own data. The results show that when there is a high concentration of dopaminergic (DA) neurons, the amount of dopamine released is also high (see upper right hand side of the graph). As the percentage of dopaminergic neurons decreases, so does the percentage of dopamine being released. According to this data, the remaining dopaminergic neurons do not increase dopamine output when dopaminergic neurons begin to die.

Interpreting the Passive Stabilization Animation



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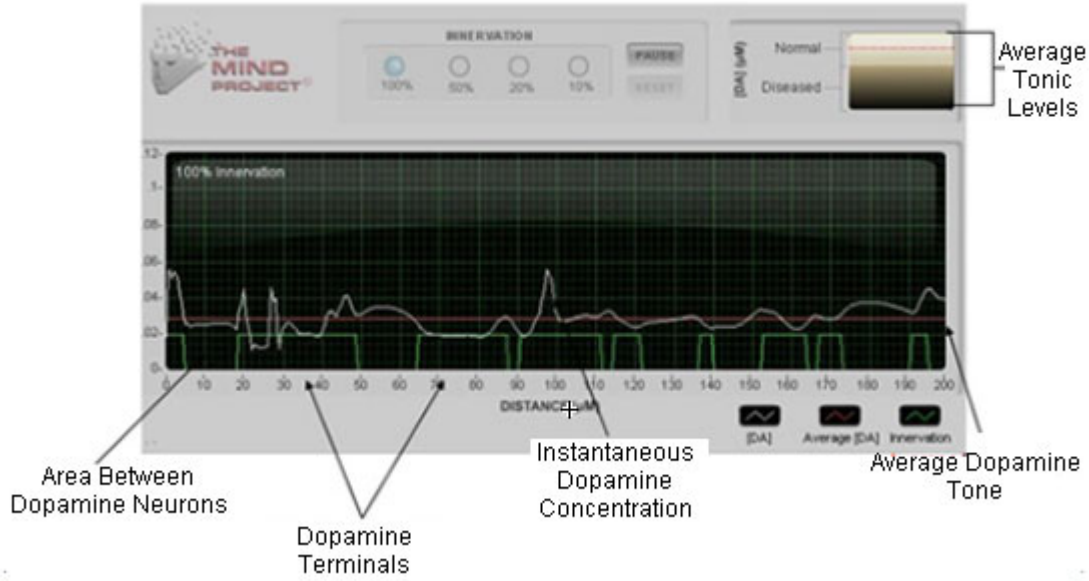
As you watch the animation, you'll see that with each action potential, a consistent number of dopamine molecules are released. After being released, a dopamine molecule will either be taken by a dopaminergic neuron or glial cell. If taken up by a dopaminergic neuron, it will be repackaged in a vesicle and eventually released again.

As dopmainergic neurons are lost, you will notice that the action potentials do not increase in frequency nor are more dopamine molecules released with each action potential.

Interpreting the Passive Stabilization Computer Model

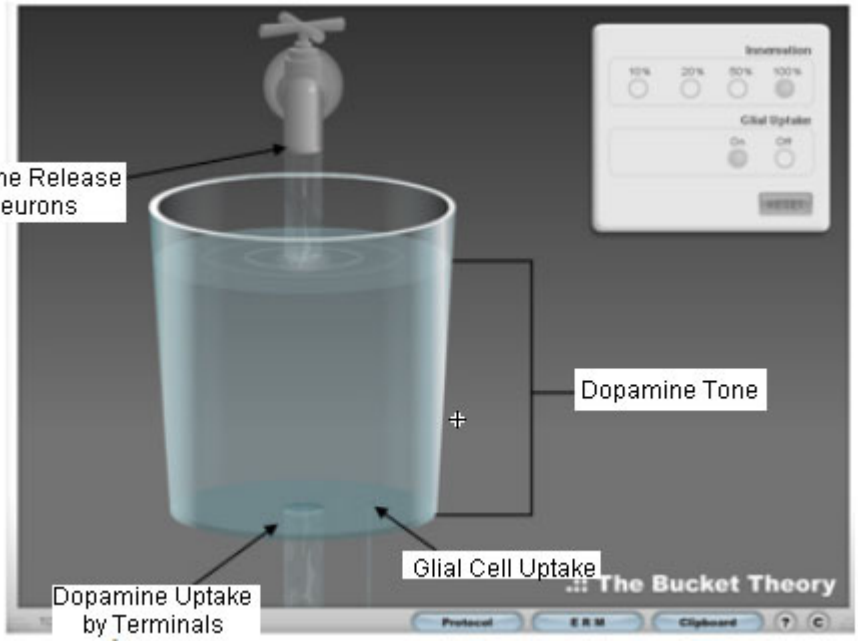


The computer model of the Passive Stabilization Theory can be confusing when you first look at it but, once you understand what the different elements actually represent, it can help to demonstrate how it works. In the diagram above, you can see that the different elements have been labeled.

Starting at the bottom of the diagram, you will see green bars with spaces in between. The green bars represent dopamine neurons and the spaces in between them are the areas between the dopamine neurons. Moving further up, you will see a white, wavy line. This white line represents the dopamine concentration that results from release and uptake by individual neurons. Notice that there is dopamine present even in the areas that don't have a dopamine synapse. Finally, the red line represents the average concentration of dopamine in the extrasynaptic (outside of the synapses) space. This concentration is also known as dopamine tone.

Unlike the other animations you've looked at, this computer model is not intended to only conceptually represent the passive stabilization theory but is based directly on data generated in experiments in Dr. Garris' lab.

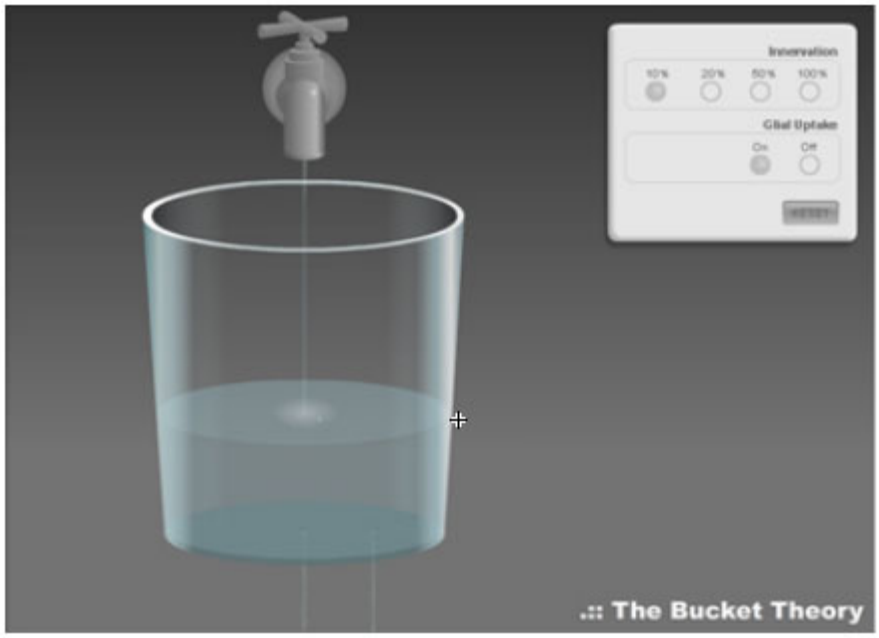
Interpreting the Bucket Theory



The bucket in the Bucket "Theory" is an analogy as to how passive stabilization works in the striatum. Because it is an analogy, it is designed to examine passive stabilization conceptually and not quantitatively. This why there are few numbers associated with the animation.

As can be seen above, each part of the bucket analogy represents a main component in the passive stabilization theory. The faucet represents the release of dopamine by dopaminergic neurons, the central drain represents the uptake of dopamine by dopaminergic neurons, the small drain on the right represents dopamine uptake by glial cells and the liquid in the bucket represents dopaminergic tone.

As the level of innervation decreases, you'll notice that the faucet and central drain also decrease in diameter, representing the loss of dopamine neurons to both release and take up dopamine. The small drain to the right, however, does not change in size.



As can be seen in Figure 2 above, by the time innervation reaches 10%, the rate of dopamine uptake by the glial cells, combined with the dopamine uptake by the remaining dopamine neurons, begins to overcome the amount of dopamine released by the dopamine neurons. The result is a decrease in dopmaniergic tone in the striaum.

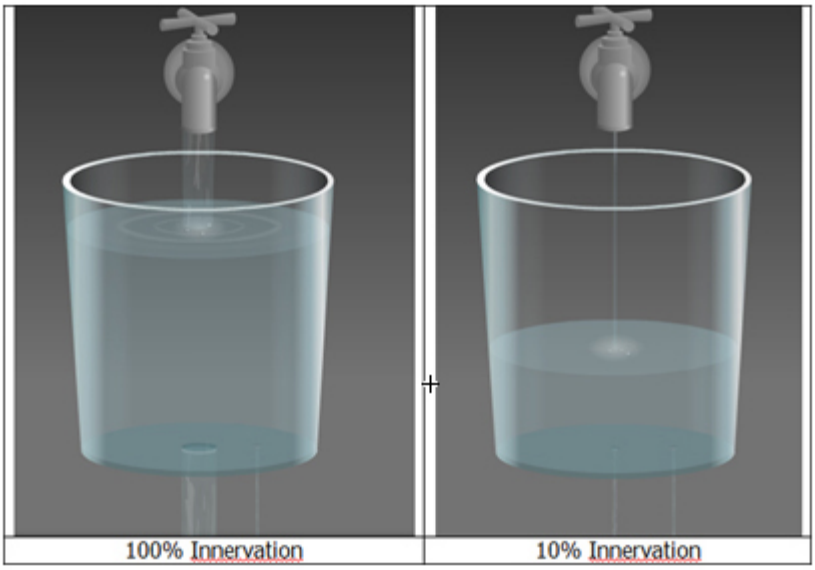


Figure 3 above provides a side by side comparison of 100% innervation and 10% innervation and the impact on the dopaminergic tone as well as the relative levels of dopamine input and output in the striatum.