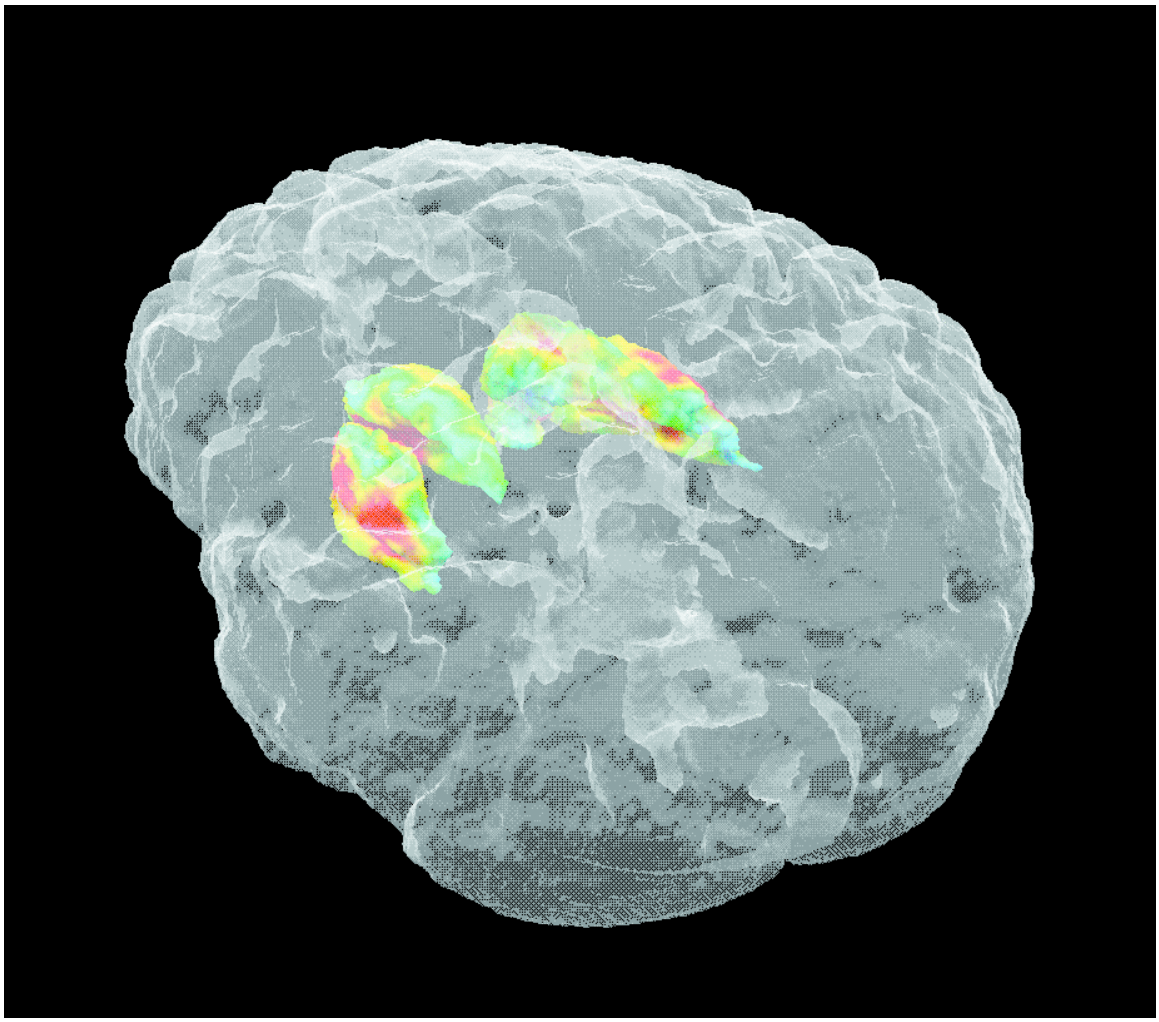
GABA AGONISTS
IN THE BASAL GANGLIA



CN540 FINAL TERM PROJECT

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KEY POINTS FOR TEACHERS

This lesson has four main ideas that should be reiterated throughout the lecture:

1) **Models Explain the Mind:** The class should come away knowing what a computational model is and what it is useful for, i.e. models help explain how the brain functions and make predictions about experimental data. In this case, basal ganglia models help us understand voluntary motor control and rewards-based learning due to findings from prior neuroscientific data.

2) **Learning Rewarded Behaviors:** The dopamine signal acts to help learn motor behavior based on rewards it can predict or expect by associating CS -> US -> UR.

3) **Dopamine as a Learning Signal:** The basal ganglia makes reward predictions, which create diffusive bursts of dopamine that as an "internal teacher" for the brain.

4) **Synaptic Connections = Learning Weights:** This learning occurs as biological changes at synapses between neurons and is acceralated by the presence of dopamine.

How does a limb movement happen? What process in the brain works in conjunction with our limbs to create a movement? One way of connecting these different parts of the puzzle is with the use of computational models of the brain. Today's lesson is geared toward helping you understand how a neural model works – with a special focus on the basal ganglia: an extremely important brain region that assists in learning for motor behavior.

1. VOLUNTARY MOVEMENT AND THE BRAIN

1.1 Voluntary vs. Involuntary Movement

First of all, what do we mean by voluntary movement? It might be best to start with what constitutes an *involuntary* movement – actions that include a doctor tapping your knee which causes your lower leg to spring up or jumping out of your seat when your best friend yells “BOO!” in your ear. These are both examples of body movement that are made without your “approval”. You didn’t volunteer to jump out of your seat. Conversely, *voluntary* movement implies we make a decision to act out a limb or eye movement.

So what happens when we make mistakes in a voluntary movement? In other words, what happens when our movements towards something are not accurate? One example might be when a restaurant waitress comes by the table and fills your empty water cup while you’re not looking. When you go to take a drink without looking, there’s a good chance you will spill water on your shirt. This can happen for several reasons: 1) not visually assessing the water height in the glass causes you to tip the glass too far based on prior visual cues (the water level was lower), 2) improperly assessing the weight of the glass based on prior arm movement, and 3) not voluntarily being aware or paying attention to the change that occurred.

1.2 A Few Reasons For Incorrect Movement

Muscle fatigue After lifting weights at the gym, limbs often become sore and fatigued after an extensive workout. In turn, this fatigue forces the limbs to re-adjust what they normally perform during a movement.

Fitts’ Law This law uses a mathematical equation to determine the relation between movement time, movement distance, and target width. For example, it takes a shorter amount of time to touch with your finger a large circle on a piece of paper than it does to touch a smaller circle based on the same initial starting point.

Movement-related diseases There are many disorders which cause a severe detriment to normal voluntary movement or what is called “motor control”. Some of these disorders include Parkinson’s or Huntington’s disease. Damage to the basal ganglia in the brain (which we will discuss later on) causes slow or excessive movement, respectively.

Alcohol So what happens to movement when a chemical substance such as an alcoholic beverage is introduced to the body? Anyone who has seen someone under the influence of alcohol knows that speech slurs, loss of refined motor control, difficulty walking, and slowed reaction times occur.

1.3 Brain and Body Regions Involved in Movement

In the last section we discussed how alcohol drastically affects motor control in a negative way. So what causes all these symptoms to occur? To understand this, first, we need to review some major areas of

the brain and body involved in the voluntary movement process. (Refer to the diagram below for a visualization of different brain regions)

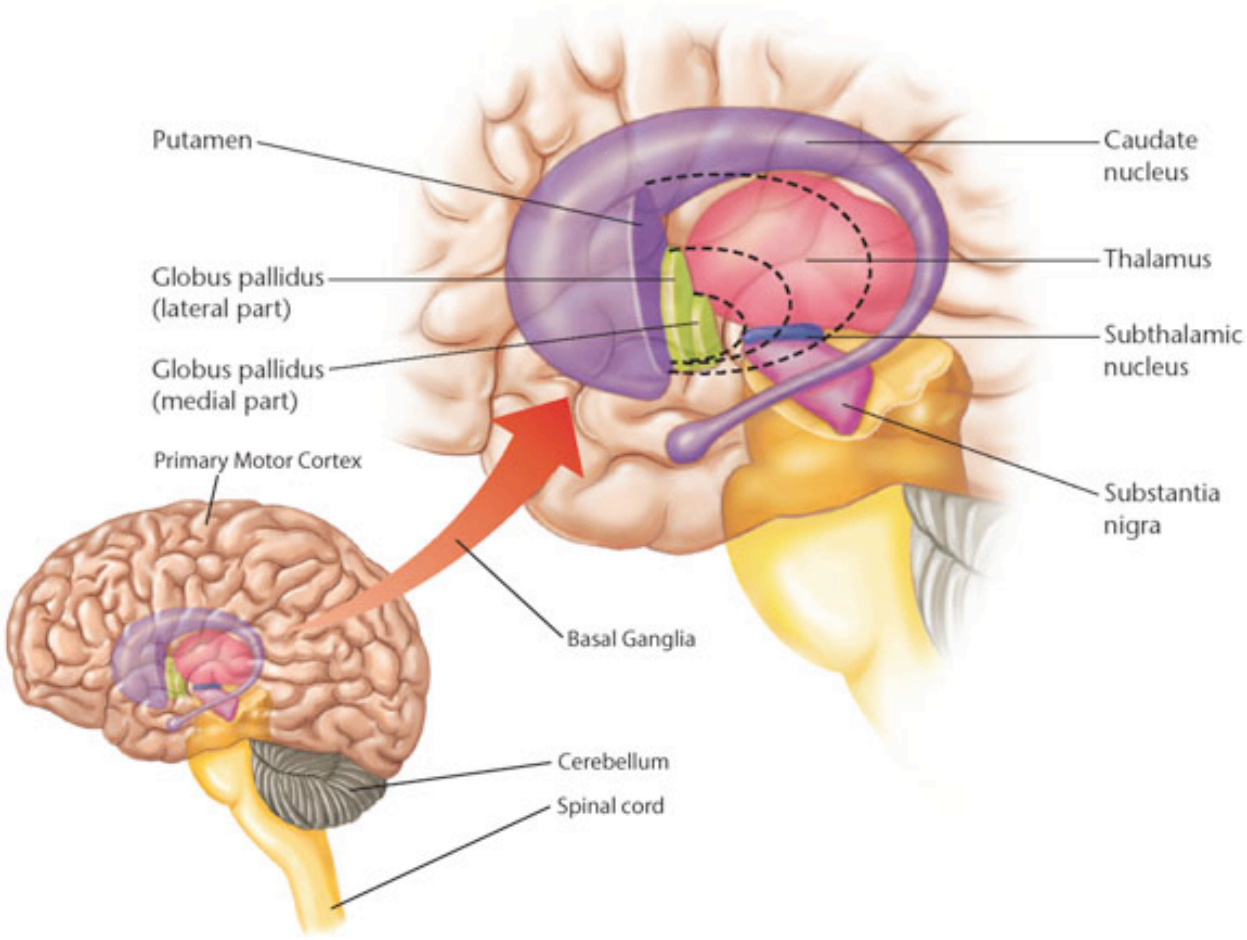


Figure adapted from http://cti.itc.virginia.edu/~psyc220/

Motor cortex This area of the cortex (the outer "crinkly" realm of the brain that we see) is known to control motor performance. Even though voluntary movement requires several areas such as motor cortex, cerebellum, basal ganglia and spinal cord working together, many executive "GO" commands to make a movement start in the primary motor cortex and descend to lower areas such as the cerebellum. Anterior to (towards the front) the primary motor cortex is the premotor cortex which is important for planning of movements in response to what we see, feel, smell, hear or touch.

Basal ganglia This area is comprised of several pieces: the striatum (caudate and putamen), globus pallidus, substantia nigra, and subthalamic nuclei. The basal ganglia receives many neuron inputs from the cortex as well as other areas such as the thalamus and are important for movement selection, perhaps by providing a gating signal back to cortex to cause a planned movement to be produced, and by

inhibiting the gating signals for unwanted movements (from CN510 Lecture 3, 19). As we mentioned earlier, damage to certain areas within the basal ganglia causes Parkinson's and Huntington's diseases.

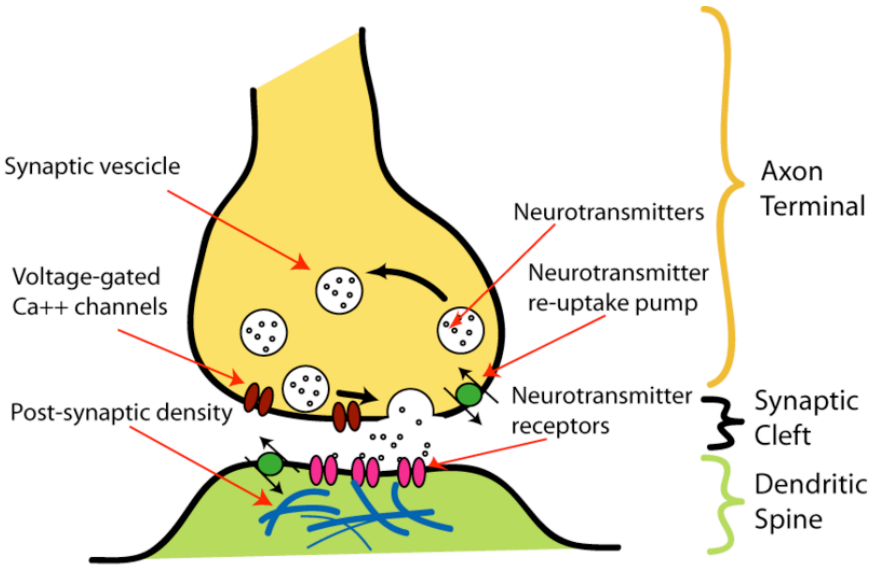
Cerebellum The cerebellum is located in the posterior (rear) part of the brain and is important for correction and coordination of a movement. The cerebellum acts as a "side loop" to assure smooth, well-coordinated movements. Both the cerebellum and the basal ganglia act as a sort of gate where only a fine-tuned motor command to the limbs is allowed to flow through once the gate is opened.

Spinal cord The spinal cord is an important area for sending sensory and motor information from the brain to the limbs and vice versa. Neurons collect near the spinal cord and are then sent up or down the spinal cord through the brain stem and to various brain areas or body parts.

Limbs Even though the limbs may not be part of the central nervous system, important *sensory neurons* are located in the limbs which send signals to the brain through the spinal cord to update the brain on what is occurring in the external/internal environment. There are also *motor neurons* in muscles which allow for voluntary and involuntary movements to occur based on commands sent from the brain as well as from the spinal cord.

1.4 Neurotransmitters

So how do these neurons in different areas communicate with one another? At the end of a neuron's long output known as an *axon* is a knob-like structure called a *synapse*. Two neurons "talk" at the junction of their synapses. When Neuron 1 sends an electrical signal down its axon there are chemicals called *neurotransmitters* which travel through its synapse and attach to receptors on Neuron 2. When neurotransmitters cling to the receptor of Neuron 2 the electrical signal continues onto the next neuron target. Below is a diagram of how neurotransmitters work at the synapse.



For our discussion of alcohol effects on the basal ganglia we need to focus on two neurotransmitters: dopamine and GABA.

Dopamine (DA) This neurotransmitter has a high concentration in the substantia nigra of the basal ganglia and project globally to the striatum. “Dopamine plays a critical role in motor and cognitive function through actions mediated by specific receptors (Huntley et al, 1992).” These receptors have two major types: an excitatory receptor **D1** and an inhibitory receptor **D2**. If DA is depleted, then severe motor dysfunction can occur stemming from the basal ganglia.

GABA This is an inhibitory neurotransmitter found primarily in medium spiny neurons of the striatum. There are many types of GABA receptors but the one we will discuss for our purposes is **$GABA_A$**.

GABA agonists A GABA *agonist* is a substance that binds to a receptor in order to trigger a response – helping GABA receptors open. In our model, **ethanol**, the active ingredient in alcoholic beverages, provides an example of a commonly consumed substance which is believed to be a $GABA_A$ agonist. $GABA_A$ in conjunction with ethanol (or other $GABA_A$ agonists) is known to cause behavioral effects such as muscle relaxation or sedation.

2. THE BASAL GANGLIA

2.1 The Parts

Striatum The basal ganglia’s input structure. It consists primarily of the caudate and putamen. The striatum sends inhibitory GABA signals to both globus pallidus segments.

Globus pallidus The basal ganglia’s output structure. It has two major parts: an external segment (**GPe**) an internal segment (**GPi**). This area sends inhibitory GABA projections to the thalamus.

Substantia nigra Another basal ganglia output with two parts: the substantia nigra pars compacta (**SNc**) and pars reticulata (**SNr**). The SNc is a primary source of DA to the striatum and the SNr primarily sends GABAergic signals to the superior colliculus for controlling eye movements.

Thalamus The thalamus is at the heart of the brain and sends relays back and forth between subcortical and cortex areas. With regards to the basal ganglia, inhibitory signals from the substantia nigra and globus pallidus are sent to the thalamus, which then sends signals to motor cortex.

Subthalamic nucleus (STN) This area also plays an important in control of basal ganglia output by preventing premature interruption of plan execution by another plan entering the basal ganglia.

2.2 How the Parts Interact

The basal ganglia controls behavior with normally-closed gates as we discussed earlier. To enact this plan the basal ganglia is known to have two primary pathways (see the diagram below):

Direct pathway Activation of this pathway usually *releases* plan execution. The path goes like this: cortex → striatum → GPi/SNpr → thalamus

Indirect pathway Activation of this pathway enables *deferral* of a chosen plan. The path goes like this: cortex → striatum → GPe → STN → GPi → thalamus

Notice that the indirect pathway chooses the GPe, thus adding an extra step! Also note from the diagram below that D1 receptors work for neurons projecting to the direct pathway whereas D2 receptors work for neurons projecting to the indirect pathway.

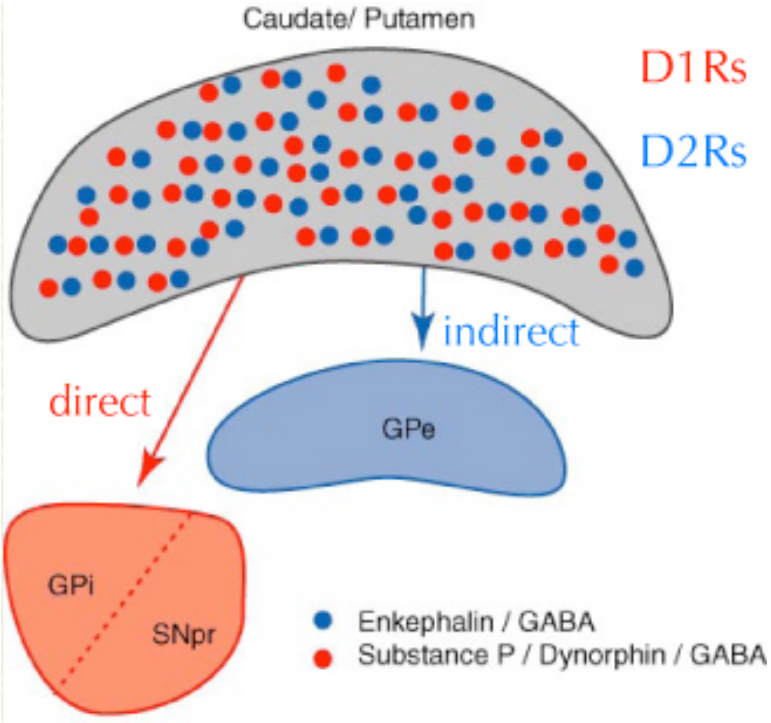


Figure adapted from *Fundamental Neuroscience, 2ed*

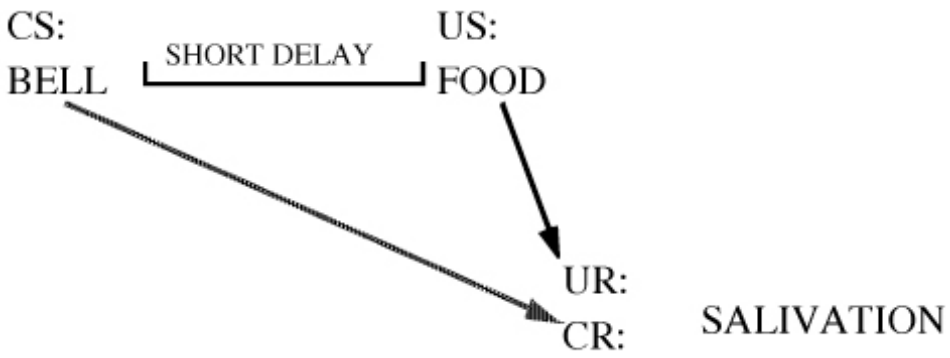
2.3 The Normally-Closed Gate

The basal ganglia works by interaction between *excitatory* and *inhibitory* neurons. For example, an excitatory neuron synapsing on an inhibitory neuron makes the inhibition even greater whereas an inhibitory neuron synapsing on an inhibitory neuron *disinhibits* the neuron. Momentarily removing this tonic (constant) inhibition permits action and this is why the basal ganglia acts as a normally-closed gate.

3. CLASSICAL CONDITIONING

3.1 Pavlovian Stimulus-Response

In the Brown et al 1999 model, dopamine acts as a signal of *unexpected reward* in behavioral tasks such as classical conditioning. So what is classical conditioning? The Russian psychologist, Ivan Pavlov, associated a conditioned stimulus (CS) with a conditioned response (CR) through the presence of an unconditioned stimulus (US). In the famous Pavlov's dog experiment the CS is a bell, the US is a piece of food, and the CR is a salivating dog. This is known as a **stimulus-response** theory.



Classical conditioning as performed by Pavlov

3.2 Conditioning and the Basal Ganglia

So how does associative learning behavior relate to the basal ganglia? In the Brown 1999 model, "learning enables the SNc cells to respond immediately to unexpected cues (CS) but to omit responses in an adaptively timed fashion to expected rewards (US). Because these firing patterns also act as learning signals in the striatum and elsewhere, they have been suggested to play a key role in both addictive

behavior and reinforcement learning (Brown 1999, 10502).” In this model, DA is used as the signal for unexpected rewards in behavioral tasks such as classical conditioning.
Brown et al propose that the primary reward signal after hearing the bell ring comes from the hypothalamus and the excitatory reward-prediction signals which generate the CS-induced DA burst travel from the striatum to the globus pallidus by receiving inputs from the limbic system. What is most important here is that the striatum acts as a main pathway of excitatory reward predictions.

This means there are two distinct pathways in conditioning – one for initial excitatory reward prediction and another for timed reward prediction – which control SNc behavioral responses such as salivation. “The excitatory pathway generated CS-induced excitatory SNc dopamine bursts. The inhibitory pathway prevents dopamine bursts in response to predictable reward-related signals (Brown 1999, 10502).” This is the basis of how the basal ganglia predicts a CR by modulating dopamine.

4. THE MATHEMATICAL MODEL

4.1 Using and Understanding the GABA Agonist GUI

The GUI has several parameters which you can vary:
ISI (Interstimulus Interval): This is the time between when the CS comes on and the US comes on.
ITI (Intertrial Interval): This is the time between trials.
US Length: This is the amount of time the US is on.
CS Length: This is the amount of time the CS is on.
Training GABA level: This is the amount of external GABA that the model will train on.
Testing GABA level: This is the amount of external GABA that the model will test on.

NOTE TO TEACHERS

Run the model now so that you can discuss the model details while the simulation is running. Ask class members to choose parameters. We recommend varying *only* the GABA parameters from their set values. In order to see anything interesting, the US and CS need to overlap. The default values in the GUI provide that situation. Also, the model can take awhile to run, so it’s probably a good idea to run fewer than 10 training trials.

Now that the parameters are set, it is important to understand what these parameters are doing. We can alter parameters in order to get different GABA effects, then compare them to experimental results from

neurobiological information. Since ethanol can act as a GABA agonist, this model is one possible way of looking at alcohol's effects on motor control and learning.

4.2 A Brief Overview of the Brown et al 1999 Model

We have already discussed the conditioning aspect of how the Brown model of the basal ganglia works, so now we can understand how the DA signal acts as an "internal teacher" or learning model.

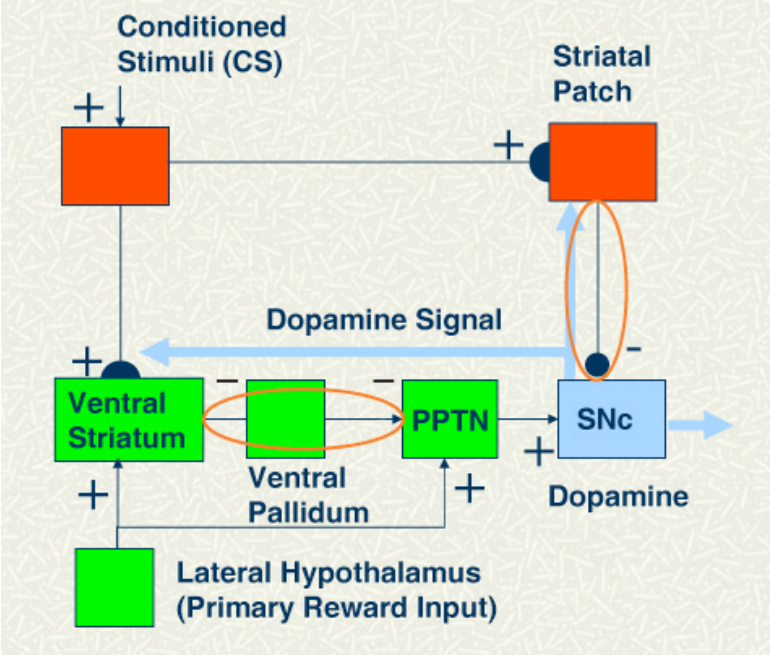


Figure from Brown et al 1999 model

Green: immediate excitatory predictions of reward (leads to dopamine increase at CS)

Red: delayed inhibitory expectations of reward (leads to dopamine decrease at US)

Blue: dopamine (DA) cells signal novel events, especially reward prediction timing errors

Orange: inhibitory (GABAergic) connections

Each of these connections are given a mathematical equation which allows scientists to simulate various task situations for DA cells. We replicated this model and modified a bit in order to see what, if any, effects GABA agonists have on this basal ganglia model. **Now let's see some results!**

4.3 Results from Conditioning Tests on the Model

The figures show results for a few tests of the model. Before each test, the model was pretrained with 8 trials of CS-US parings either under normal conditions (first figure) or under a slight GABA (0.05) conditions (second figure). This graphs display when the CS and US occur in the trial, and the level of dopamine output with these colors:

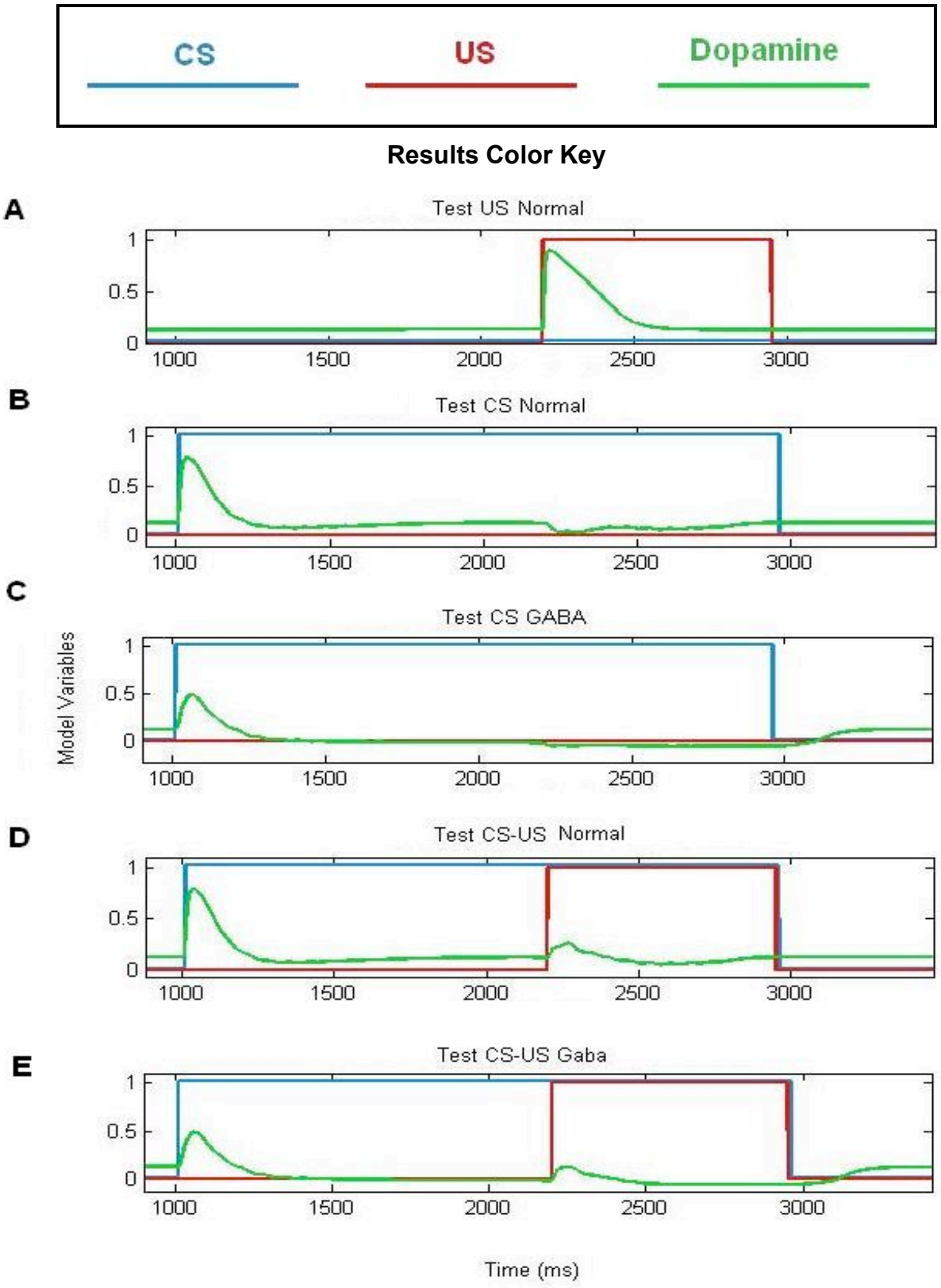


Figure of Results for Normal Subject: **A** shows a burst of dopamine in response to an unexpected reward (US alone); **B** shows the burst of dopamine shifted to the CS and a dip in dopamine when an expected reward is omitted (CS with no US); **C** shows that the dopamine dip is less temporally prominent (than B)

and a weaker CS dopamine burst, when tested under a GABA agonist; **D** shows the dopamine burst burst partial shifted from US to CS (compared to A); finally **E** again shows a weaker dopamine response in the CS-US pairing under the GABA agonist.

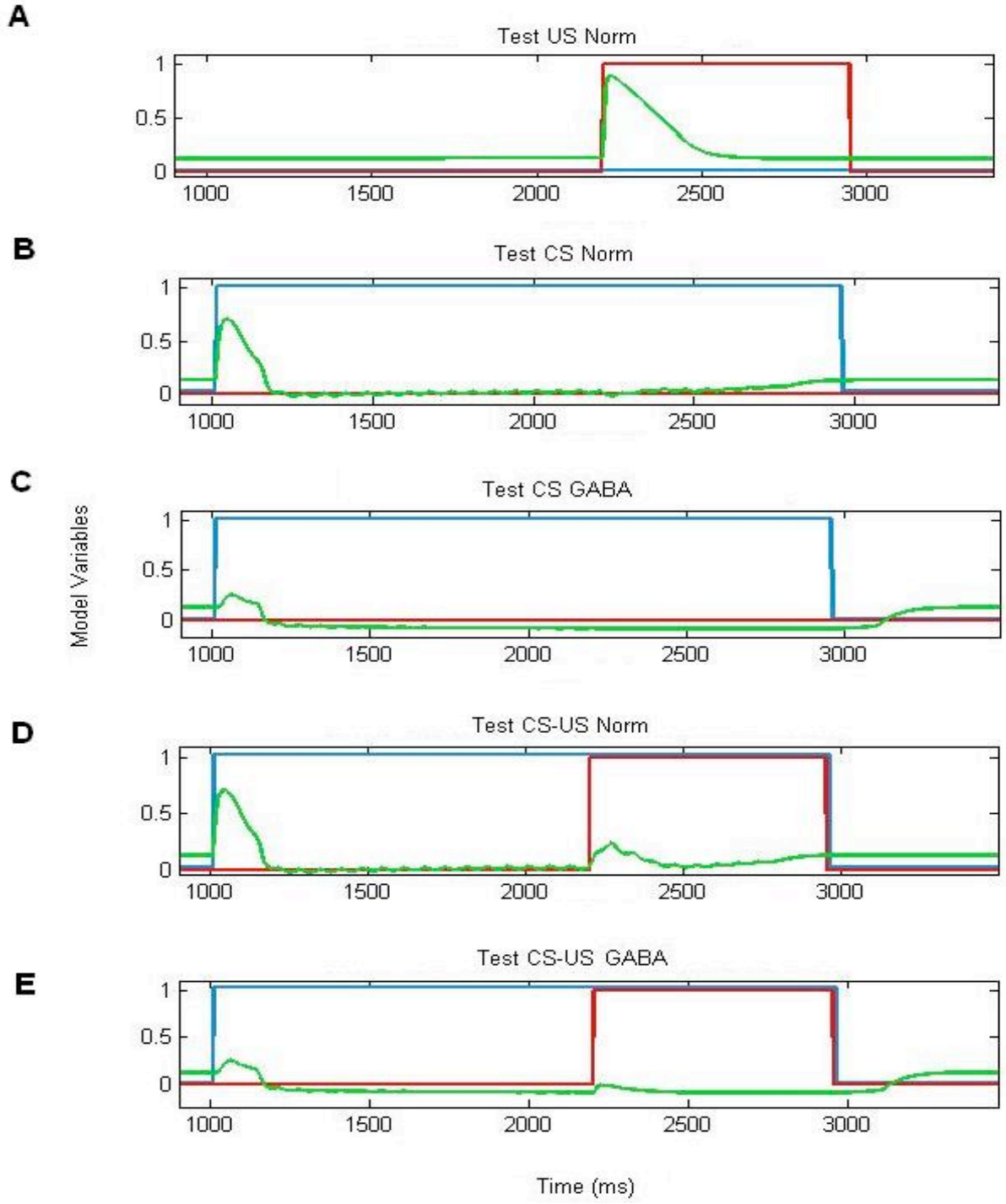


Figure of Results for Subject trained under GABA agonist (level of 0.05): **A** shows a burst of dopamine to an unexpected reward remains the same; **B** shows the burst of dopamine shifted to the CS followed by a

lowered baseline dopamine that nearly masks the dip in dopamine when an expected reward is omitted; **C** shows that a weakened CS dopamine burst, and lower baseline eliminates any the US dopamine dip, when tested under a GABA agonist; **D** shows the dopamine burst burst partial shifted from US to CS (as normally observed); finally **E** shows greatly diminished dopamine response in CS-US pairing under the GABA agonist.

4.4 Results of Learning Rates from the Model

The model allows us to look at how the basal ganglia learns over a history of trials. Then, we can compare differences between training under normal conditions against training under the presence of a GABA agonist (see figure below).

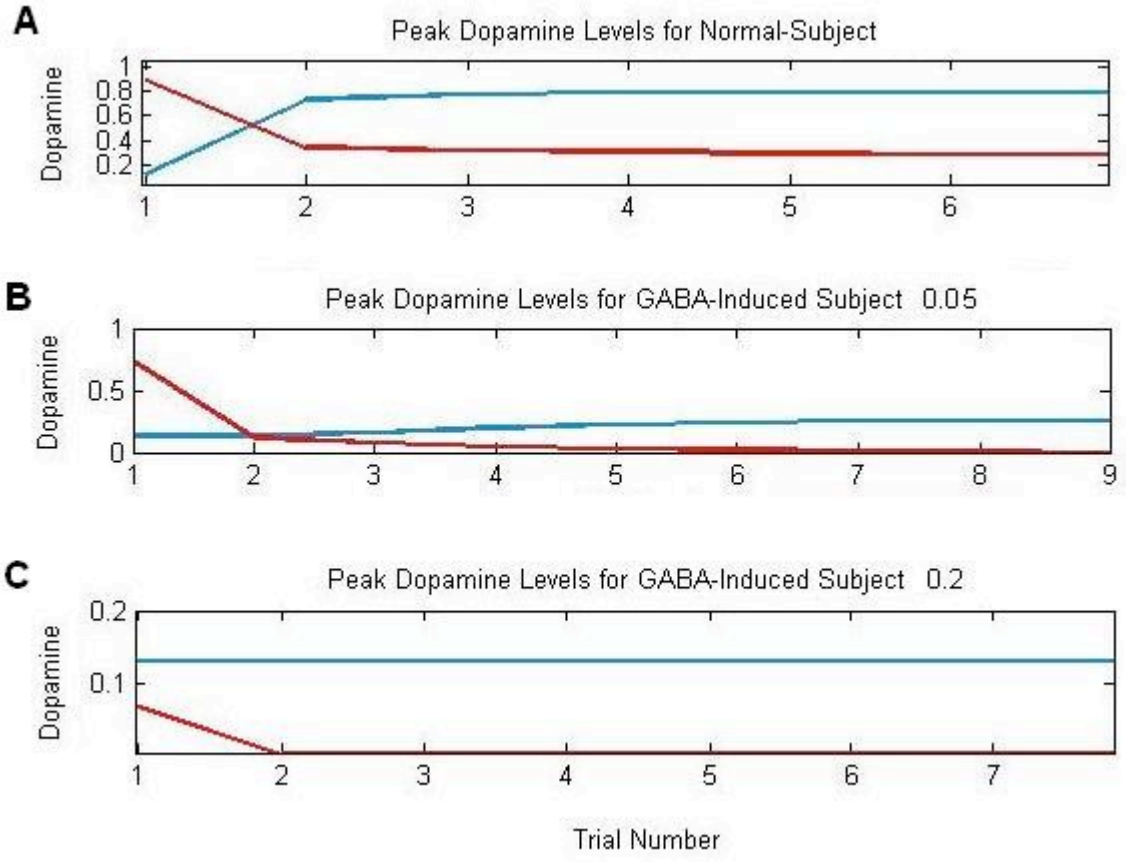


Figure of Peak Levels of Dopamine following CS and US onset: Here the blue line represents the peak level of dopamine following the CS and the red represents the peak level of dopamine following the US. **A** shows the shift of dopamine from US to CS under normal training; **B** shows that dopamine following the US declines, while CS dopamine increases more slowly during training under a GABA level of 0.05; **C** shows that only levels of dopamine CS change over training under a GABA level of 0.2.

These results suggests that learning supported by the basal ganglia may be greatly impaired beyond certain levels of GABA agonist. More generally, the results show that the increased presence of GABA can lead to diminished output of dopamine from the basal ganglia and thus impairment in voluntary motor behavior.

5. QUESTIONS FOR STUDENTS TO DISCUSS

1) What else could you make a model of?
2) What other variations could you make to this kind of basal ganglia model to get different behavioral results?
3) What happens when you inhibit a tonically-active inhibitory cell?

A Refresh of the Key Points

The lesson should return to the four main ideas at the end.
(and recalled at the start of the next session)

1) **Models Explain the Mind:** Computational models help explain brain functions such as voluntary movement and make predictions about experimental data.
2) **Learning Rewarded Behaviors:** The brain learns motor behavior based on rewards it can predict or expect by associating CS -> US -> UR.
3) **Dopamine as a Learning Signal**: The basal ganglia makes reward predictions, which create bursts of dopamine that act as an "internal teacher" to the brain.
4) **Synaptic Connections = Learning Weights:** This learning occurs as biological changes at synapses.