HABIT AND REWARD CIRCUITS IN THE BASAL GANGLIA

1. Introduction

To adapt behavior to a changing environment, the brain must maintain representations of where, when, and how to acquire the components necessary for survival. These representations are built from experience with sensory predictors in the environment and are constantly updated to facilitate survival. In the psychological literature, a reinforcer is an event that increases the future likelihood of behavior that preceded it. In the neuroscience literature, the term reward has come to represent discrete tangible reinforcers, including food, drugs, and forms of direct brain stimulation. While critical to action selection and the attainment of biological needs, the same trajectory from sensory predictor to reward achievement also underlies maladaptive behaviors and pathologies, including addiction. While important advances have been made in the identification of neural substrates of reward and reward-relevant sensory information, little is known about the integration of these signals and how cue-reward associations are learned and represented in the brain over time.

Abuse of a number of psychoactive substances can eventually control an individual behavior by producing dependence and/or addiction. There is increasing evidence suggesting that drug addiction represents a conditioning phenomenon that is largely dependent on associations between drug effect and environmental cues. An appropriate balance between neurotransmitters is necessary for the proper evaluation of stimuli associated with rewarding of aversive events. Imbalances can lead to maladaptive behaviors and pathologies, including addiction and mental illness (Lipton et al., 2019; Lüscher, 2013; Sulzer, 2011). After a 170% increase in drug abuse and suicide rates between 2009 and 2018, in 2020, the number of drug overdoses has hit an all-time high (Source: addictioncenter.com, 2020). Notably, the COVID-19 pandemic witnessed a sharp increase in alcohol and illegal drug use as well as opioid

overdoses (Source: addictioncenter.com, 2020), giving 2020 the title of “The deadliest year in drug history”. In 2024, we saw the steepest decline in drug overdose seen in decades. With over 100,000 drug overdose deaths still occurring every year, experts warn that the problem is still far from over and that this decline, while encouraging, should not downplay the significant need for continued harm reduction efforts. Scientists continue to encourage more focus and funding on addiction treatment and harm reduction strategies at both the national and state levels, specifically in underserved communities where overdose rates are still particularly high (addictioncenter.com 2024).

2. The striatum

While significant progress has been made in the identification of the brain structures involved in reward and habit processing, research is only beginning to uncover how the complex heterogeneity of the dopamine, glutamate and GABAergic systems influence motivated behaviors and how their interactions orchestrate complex behavior in health and disease.

The striatum is the major input nucleus of the basal ganglia, an evolutionarily preserved set of subcortical regions that facilitate action selection and voluntary motor control. It is often divided into two regions, the dorsal and ventral striatum (although further subdivision becomes relevant for specific functions of the striatum). It is generally thought that the dorsal striatum is mostly involved in movement, particularly automatized fine skills and micromovements embedded in an action (Thorn et al., 2010; Yin et al., 2009). The ventral portion of the striatum, containing the nucleus accumbens (NAc), receives projection from limbic cortices and amygdala and is more broadly involved in goal-related movements, a process by which the animal encodes values to the movement performance (Liljeholm & O’Doherty, 2012; O’Doherty, 2004). The ventral striatum plays a critical role in motivation and reward-based learning. This is a central hub that helps us make decisions based on what we’ve learned from previous experiences—particularly experiences tied to rewards like food, social interaction, or even

addictive substances. When we perform a task that leads to a reward, our brain releases dopamine, a chemical that reinforces that action so you're more likely to repeat it. The ventral striatum is heavily involved in this process, helping us connect actions with outcomes, particularly rewards.

The vast majority of the striatum is composed of spiny projections neurons (SPNs), accounting for up to 95% of all striatal neurons in rodents (DiFiglia et al., 1976; Kemp & Powell, 1971) and approximately 75% in primates (Fox et al., 1971; Graveland & Difiglia, 1985). Striatal SPNs form predominantly two distinct neural pathways. The direct pathway consists of GABAergic neurons D1 dopamine receptors (D1-SPNs, Gangarossa et al., 2013; Gerfen et al., 1990; Kawaguchi et al., 1990). This pathway receives glutamatergic input from the cortex (Wall et al., 2013), in particular sensory cortical and limbic structures, and from thalamus. Broadly, the indirect pathway neurons are also GABAergic but express D2 dopamine receptors (D2-SPNs, Gangarossa et al., 2013; Gerfen et al., 1990; Kawaguchi et al., 1990).

The striatum receives dense innervation by dopamine neurons from the midbrain, which have long been shown to encode reward prediction error and salience. As animals engage with external stimuli, they associate cues with specific rewarding or aversive events. Dopamine activity eventually shifts from responding to the rewarding or aversive event to the presence of the associated cue. Most if not all drugs of abuse are modulators of dopamine signaling. Aside from dopamine, the ventral striatum receives excitatory innervation from prefrontal cortex, ventral hippocampus, and amygdala, regions shown to be important substrates for reward-related memory and sensory perception. Together, this collection of inputs as well as the striatum’s role in action selection and motor control make the ventral striatal SPN a key integrative locus for reinforcement (Cataldi et al., 2021).

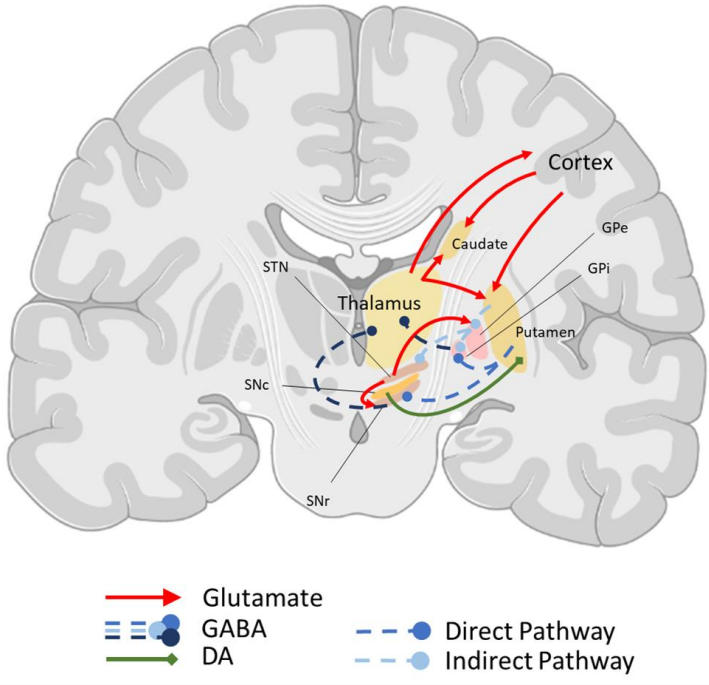

Fig. 2. Simplified schematic of the basal ganglia circuit involved in motor learning in the human brain. Connections to and from the dorsal portion of the striatum are indicated. The caudate and putamen receive glutamatergic projections (red solid arrows) from cortex and thalamus, while sending GABAergic projections (blue dashed lines) to downstream structures. The direct pathway is composed of GABAergic D1R-expressing SPNs from the striatum to the GPi and SNr. The inhibition of these structures by the direct pathway, and therefore disinhibition of the thalamus, promotes movement and is classically referred to as the 'go' pathway. In contrast, the indirect pathway via D2R-expressing GABAergic projections inhibits the GPe, which in turn causes disinhibition of the GPi and STN, leading to reduced activity of the thalamus and is known as the 'no-go' pathway. dopaminergic projections from the SNc (green solid line) modulates activity of both caudate and putamen. Location and size of each region are altered for presentation purposes. Figure created with BioRender.com. GPe, globus pallidus external; GPi, globus pallidus internal; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; DA, dopamine; SPNs, spiny projection neurons.

2.1 Dopamine and the striatum in health and disease

Dopamine plays a central role in the processes of learning, addiction, and mental health disorders such as schizophrenia and post-traumatic stress disorder (PTSD). The neurotransmitter is crucial in reinforcing behavior by linking actions or environmental cues to rewarding outcomes, a mechanism central to both addiction and the development of compulsive behaviors. In addiction, environmental cues, like specific places or sounds, can trigger cravings or drug-seeking behavior even after long periods of abstinence, demonstrating the power of these learned associations (Sulzer, 2011).

Addiction fundamentally alters how the brain responds to cues. The repeated use of addictive substances leads to changes in the ventral striatum, a key part of the brain's reward circuitry (Konova et al., 2013). SPNs in this area receive dopamine inputs that influence whether an action is perceived as rewarding or not. Over time, the brain begins to associate cues related to drug use (such as drug tools or places where drugs were taken) with the pleasure derived from the drug itself, leading to what is called cue-induced craving (Konova et al., 2013). This association can trigger compulsive behaviors where the mere sight or sound of a related cue provokes drug-seeking, even in the absence of the drug itself.

Moreover, operant conditioning plays a significant role in this mechanism. Animals and humans learn to associate certain actions (like pressing a lever or using a drug) with rewarding outcomes through repeated exposure. In laboratory experiments, animals have been shown to self-administer drugs when they are paired with specific cues, a method widely used to model addiction in animals (Olds & Milner, 1954). These studies demonstrate how strongly the brain ties actions to rewards, particularly in addiction, where the anticipation of a drug-induced reward becomes encoded in the brain's reward pathways (Koob & Le Moal, 2008).

In addiction, the dopamine system's role extends beyond reward reinforcement. Dopamine also drives changes at the synaptic level that encode learned associations. For example, repeated exposure to drug-related cues can alter synaptic plasticity, a process where the strength of connections between neurons changes in response to activity (Sulzer, 2011). This plasticity, particularly in the striatum, strengthens the association between drug-related cues and reward. The cues eventually trigger dopamine release even in the absence of the drug, which is why individuals may relapse when encountering these cues.

Similarly, in schizophrenia, dopamine dysregulation plays a crucial role in abnormal behavior and cognition, particularly in how individuals process environmental cues. In schizophrenia, hyperactivity of the dopamine system, especially in the associative striatum, leads to impaired response inhibition and difficulties in distinguishing between relevant and

irrelevant stimuli (Frankle et al., 2022). This can result in auditory hallucinations where the brain misinterprets neutral sounds or thoughts as real, external voices, a symptom driven by overactive dopamine signaling (Howes & Falkenberg, 2011). These hallucinations demonstrate how excessive dopamine activity can amplify the brain's response to environmental cues, leading to maladaptive behavior similar to that seen in addiction.

In both addiction and schizophrenia, cue-response relationships are fundamental to understanding how behavior is shaped by dopamine. In addiction, cues related to drug use become potent triggers for relapse, while in schizophrenia, abnormal cue processing contributes to symptoms like hallucinations and delusions.

In PTSD, dopamine is also involved in the heightened sensitivity to environmental cues associated with trauma. Patients with PTSD may experience intense reactions to seemingly innocuous stimuli, like sounds or smells, that remind them of the traumatic event (van Rooij & Jovanovic, 2019). These conditioned responses are difficult to extinguish because the dopamine system reinforces the association between the cue and the fear response. As in addiction, the brain becomes wired to react strongly to specific stimuli, even when the actual threat is no longer present.

Overall, dopamine's involvement in cue-related learning and operant conditioning is fundamental in both normal and pathological behaviors. Whether it's the cravings triggered by drug-related cues in addiction, the hallucinations provoked by hyperactive dopamine signaling in schizophrenia, or the fear responses in PTSD, understanding these mechanisms helps to illuminate the neural basis of these complex disorders.

While dopamine's role in reward learning and addiction has been extensively studied, much less is known about the specific function of SPNs in the ventral striatum, particularly in relation to how they contribute to complex behaviors such as reward-seeking and habit formation. SPNs are integral to both the direct and indirect pathways that influence movement and reward (Gerfen & Surmeier, 2011). However, while dopamine modulates the activity of

these pathways, the precise contribution of SPNs, especially D1-SPNs, in mediating learned responses to cues and rewards is still unclear. Recent studies suggest that D1-SPNs are not merely passive recipients of dopamine signals but actively shape the brain's response to rewards and actions. Understanding the exact role of these neurons in processes such as reinforcement learning, addiction, and other mental health disorders could provide new insights into how the brain encodes habits and maladaptive behaviors

3. Our Experimental Approach

A central goal of systems neuroscience is to predict behavior based on neural dynamics. The recent development of neuron type-specific genetics and *in vivo* imaging techniques now allows us to probe the activity dynamics of these intermixed populations during naturalistic behaviors, even in ventral regions like the ventral striatum. Through fiber photometry and genetic calcium sensors I can record D1- SPN bulk dynamics during a sequence of reinforced behaviors that I use to determine the predictivity of neural signatures on behavioral performance. This analysis tests the classical notions of D1-SPN roles during behavior and more fully describes how this population encodes aspects of behavior during sensorimotor learning.

In my project, I outline a strategy to record cell type-specific activity during learning and execution of a sequence of cue-directed appetitive reinforcement tasks, and to evaluate the requirement of these neural dynamics for the transduction of reward predictive cues into locomotion and reward acquisition.

3.1 Animal model

Mice are a crucial model in neuroscience research due to their genetic and behavioral similarity to humans and the ease with which their genetics can be manipulated. In our experiments, we use genetically modified mice to express a calcium sensor, such as GCaMP6f, specifically in D1-SPNs of the ventral striatum. This enables us to measure the activity of these neurons with

high precision during tasks involving cue-reward or action-reward associations. Mice are one of the few species where these precise genetic tools can be used, allowing us to observe brain activity at the cellular level while still evaluating complex behaviors like operant conditioning.

Additionally, their relatively short life cycle, well-characterized genome, and the ability to control environmental variables in the laboratory make them an ideal model for studying the neural circuits underlying reward learning, addiction, and other cognitive processes (Crawley, 2007). Moreover, mouse models allow for longitudinal studies, enabling researchers to track changes in behavior and brain function over time, which is critical in understanding how these circuits adapt or become dysregulated in conditions like addiction or schizophrenia.

D1-Cre mice are genetically modified to express Cre-recombinase under the control of the D1 dopamine receptor gene, allowing for targeted expression of proteins, like calcium sensors, specifically in D1-SPNs. This enables precise measurement of activity of this subset of neurons in response to stimuli.

Since mice are nocturnal animals, they are kept on a reversed light cycle, where lights are off during the day to align their awake phase with daytime experimental conditions. Experiments are conducted in the dark to minimize stress and ensure natural, relaxed behavior.

3.2 Classical and Operant Conditioning: How We Learn

To study how the brain learns to associate actions with rewards, we use two main learning concepts: classical conditioning and operant conditioning.

Classical conditioning is a simple form of learning. It happens when we associate two things: one that naturally triggers a response (like food) and a neutral signal (like a sound). Classical conditioning is used to train people or animals to respond automatically to certain triggers. The most famous example -- Pavlov's dogs. Ivan Pavlov was a Russian psychologist. He observed that dogs salivated when food was put in front of them. That's natural, or what's called an unconditioned response. But then Pavlov noticed that the dogs began to salivate shortly before

their food arrived, possibly because the sound of the food cart triggered their anticipation of mealtime. In his experiment, at mealtimes, he sounded a bell shortly before the food arrived. Eventually, the dogs began to salivate when they heard the bell. That was a trained, or conditioned, response to the sound of the bell.

Operant conditioning is different because it involves learning from the consequences of our actions. If you press a button and receive a reward, you'll learn to press the button again when you want that reward. Operant conditioning involves active participation from the subject—in our case, mice pressing a lever to receive a reward.

Operant conditioning is a method of learning that uses rewards and punishment to modify behavior.

Through operant conditioning, behavior that is rewarded is likely to be repeated and behavior that is punished is prone to happen less. In this context, reinforcers are responses from the environment that increase the likelihood of a behavior being repeated. They can either be positive or negative. In our experiments we use a solution containing sucrose as a reward (positive reinforcer), which is highly valuable for mice.

3.3 Our Experimental Setup: A Custom-Made Operant Box

To observe this type of learning in real time, I built a custom operant box that allows mice to press levers and receive rewards while we monitor their brain activity. The box is made of a type of acrylic plexiglass that allows us to track the mice's movements even in the dark using infrared light and an infrared camera. We control various elements of the experiment—like the lights, sound cues, and levers—using an Arduino, which is a small programmable microcontroller.

An Arduino is like the brain of the box. It allows us to precisely control when things happen, such as turning on the sound or dispensing the reward. The Arduino is programmed to execute these tasks automatically using custom codes, in the Arduino coding language.

The Arduino code also provides inputs at each time the mouse is licking from the spout to acquire the reward or pressing the lever to access the spout. The code records each individual lick and the actual physical force applied to the lever.

I developed python codes, another useful programming language, to analyze the information provided and establish the engagement of the mouse with the different components of the test and the level of learning over multiple trials.

3.4 Fiber Photometry: Measuring Brain Activity

To measure the activity of the D1-SPNs in the ventral striatum, we use a technique called **fiber photometry**.

This method allows us to track changes in calcium levels in the neurons, which is an indicator of their activity. When neurons are active, calcium flows into them, and we can detect this because we have induced in the brain region of interest genetic expression of a special protein called GCaMP6f. This protein glows when calcium is present, and using fiber photometry, we can capture this glow and monitor it over time.

The mouse has a tiny fiber optic cable implanted in its brain, specifically targeting the ventral striatum. This cable shines a specific light into the brain, and when the neurons are active, the GCaMP protein glows. A detector captures this glow, and the amount of light emitted tells us how active the neurons are.

This gives us a way to directly measure neural activity in real time, allowing us to see when certain neurons are involved in actions like pressing a lever or receiving a reward. Using D1-cre mice, we can specifically record from D1-SPNs neurons.

3.5 DeepLabCut: Tracking Movements with Precision

One of the challenges in studying behavior is tracking the animal's movements with high precision. For this, we use a tool called **DeepLabCut** (Mathis et al., 2018), which uses

advanced machine learning to analyze videos and detect specific body parts, such as the mouse's paws or head, as they move around. DeepLabCut allows us to track these movements in fine detail, without needing to attach physical markers to the animals.

In our experiments, this is particularly useful for analyzing how mice approach the lever, how quickly they press it, and how their body posture changes over time as they learn the task. It also helps us align their movements with the neural data we collect through fiber photometry, giving us a complete picture of how behavior and brain activity are connected.

3.6 The Role of Python Coding

A significant part of our research involves analyzing large amounts of data, which comes from both the behavior of the mice and their brain activity. To make sense of all this data, we write custom Python code that processes it automatically. This code allows us to:

- Synchronize the behavioral data (like when the mouse presses the lever) with the neural activity data.
- Identify patterns in the data, such as how quickly the mouse learns to press the lever or how its brain responds to different phases of the task.
- Create visual representations of the data so that we can easily interpret the results.

Python is a flexible and powerful programming language, which is why it’s widely used in both research and industry for tasks like data analysis and machine learning.

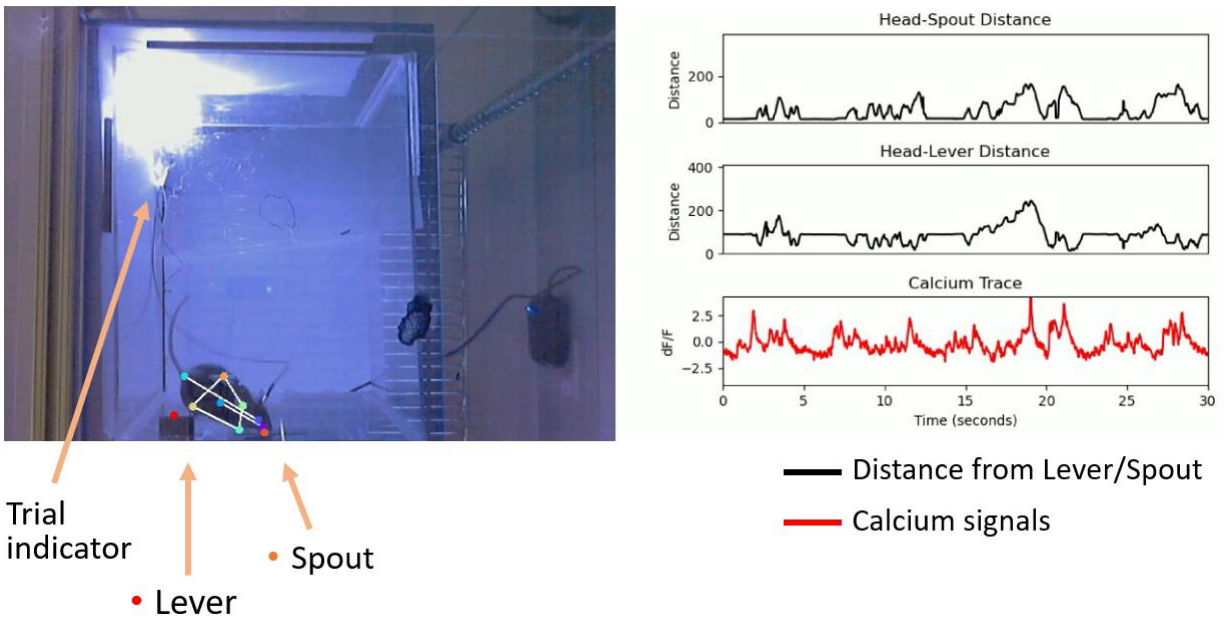

Figure 2. Example of analyzed behavior video. Videos are recorded in the dark, using an infrared camera placed below the operant box. **Left.** In this picture the mouse is seen licking from the spout at the center-bottom of the image. Using DeepLabCut, the lever is labeled with a red dot, while the spout is labeled in orange. The infrared LED light at the top right corner of the picture indicates that the mouse has pressed the lever and the trial has started. **Right.** At the top is a sample trace (black) indicating the distance from the mouse head to the spout. The middle plot (also black) shows the distance from the head of the mouse to the lever. The bottom trace (red) corresponds to the calcium signals as recorded using fiber photometry while the mouse is performing the experiment.

4. Conclusion

In summary, my research uses a variety of advanced tools and techniques to study how the brain learns from rewards. By combining **operant conditioning** with **fiber photometry**, **DeepLabCut**, and **Python programming**, I can precisely measure how neurons in the ventral striatum respond during learning. The ultimate goal is to gain a better understanding of how reward-based learning works, which could provide insights into conditions like addiction, as well as Parkinson's Disease, Schizophrenia, and other neurological disorders where these processes go awry.

This sophisticated combination of techniques gives us a comprehensive view of the learning process in the brain, and our results may pave the way for new approaches to treating mental health disorders.

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