Summary of Saunders et al. Nature Neuroscience, 2018. "Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties"

We are interested in how cues in the environment – sights, sounds, and places - guide behavior, in particular for the acquisition of things we need for survival, like food, or water. You can imagine when you move through your environment, you're presented with lots of information that can spur thoughts and motivations and guide decisions. How do we make sense of all this? A simple example that I like to give is a fast food sign. For me, the In-N-Out burger sign is a really salient cue in the environment - because I've come to associate the sign with the experience of eating food at in and out, if it pops up while I'm walking down the road it might trigger thoughts of previous in and out experiences, hunger, and even make interrupt what I'm doing to actually go to In-N-Out and get a cheese burger. But if you think about the sign itself, stripped of these past experiences, it's just some colors and symbols and letters, it doesn't really have innate value or meaning. So, we're interested in this process - how something neutral like a sign, can acquire complex motivational value to trigger and guide complex behaviors.

How do we figure out what is important in our environment, in order to seek out things we need for survival, or other things we want? We know that one set of neurons in the brain that make the chemical dopamine are important in general in both learning about the world, and in movement. Dopamine neurons are the ones that degenerate in Parkinson's disease, for example. Dopamine release from these neurons surges when you experience a reward, like food, or drugs of abuse.

We wanted to know if dopamine neurons are actually responsible for assigning that value, that meaning, to cues. For establishing neutral sensory information as important.

In these studies, we asked two basic questions:

1) Do dopamine neurons play a causal or generative role in assigning meaning /value to sensory cues in the environment?

2) If so, do different groups of dopamine neurons serve different functions within this process? Are there dopamine circuit-specific motivational functions?

To ask these questions, we used a research technique called optogenetics. In this method, we inject a virus into the brain of rats that modifies neurons so that they become sensitive to light. This gives us control over how those neurons function. We can turn them on, turn them off, etc, in various patterns, and we can time this manipulation to other events, like the presentation of sensory cues, to an animal while it behaves, and then see how that behavior changes. In this case, we targeted dopamine neurons, making them sensitive to blue light, which we then shined onto those neurons during our experiments.

The main experimental detail that is critical to understand is, in order to isolate the function of dopamine neuron activity in these processes, it was important to not present our research subjects with a "real" reward, like food, or water. We did a simple experiment - rats who had their dopamine neurons modified to become sensitive to light were placed in a chamber. Periodically, we presented a cue on the wall of the chamber, something that the rats had no experience with before, and then a couple seconds later, we shined light on the dopamine neurons of the animals, to turn them on. This is a form of Pavlovian conditioning, similar to the classic example with Pavlov's dogs, where he rang a bell and then presented hungry dogs with a bowl of food. For Pavlov's dogs, the bell initially had no meaning, but after a few pairings with food, they started salivating just in response to the bell.

We wanted to see if cues that predicted dopamine neuron activation, would, through this conditioning process, trigger behaviors on their own. We found that this was indeed the case, after a few days of conditioning, our rats started moving around when the cue turned on, **before we triggered the light activation of their dopamine neurons.** Because our rats never received a "real" reward, like food, this tells us that dopamine neurons are one of the brain's fundamental systems for creating meaning and value in sensory cues, that then allows those cues to guide behavior. Now, you may be wondering what behavior our rats do. Since there is no reward to collect - no food pellet (or cheeseburger!) - for example, we found that our rats simply moved around the chamber, in response to the cue, and this behavior became more intense as training progressed.

Given these results, the answer to our first question is yes, dopamine neurons play a causal role in establishment of conditioned cues during Pavlovian learning. Indeed, our results show that the basic computation that underlies Pavlovian learning is prediction of dopamine neuron activity - cues that predict it are assigned conditioned value, and they can promote behavior on their own, even in the absence of food, drugs, and other innately rewarding substances. Dopamine neurons are one important way our brains give the world around us meaning.

To address the second question, we conducted our optogenetic conditioning experiment again, but this time, we targeted specific subpopulations of dopamine neurons. Some of these neurons, located a part of the brain called the **substantial nigra (SNc), send projections the dorsal striatum – this is where dopamine is released**. Another set of these neurons, located in an area called the **ventral tegmental area (VTA), send projections to the ventral striatum**. Historically, these two populations have been studied in different disease research fields - SNc neurons in Parkinson's, and VTA neurons in reward and addiction science.

We found that for both of these dopamine systems – SNc and VTA, cues paired with their activation evoked behavior, in the form of simple movement, but the patterns of that movement were drastically different. Cues that predicted activation of SNc dopamine neurons, which are the ones that degenerate first in Parkinson's disease, triggered really intense movement in our rats. When the cue light turned on, rats ran around in circles within the chamber, reaching a high velocity.

Cues that predicted VTA dopamine neuron activation, in contrast, promoted movement, but this movement was not intense, and was instead directed at the cue itself. Literally, rats approached the cue and sniffed it, sometimes even biting the light. In a sense, the cue had taken on reward-like properties, which made it intensely attractive and exciting to our rats. The VTA dopamine predictive cues had become “incentives”.

This distinction was striking to us, because it means that the motivational content that dopamine neurons assign to sensory cues varies, depending on the specific dopamine neuron circuit involved. Some dopamine neurons allow sensory cues to invigorate movement (“get up and go”). Others make sensory cues attention grabbing and give them reward-like properties that draw animals in close (“where to go”). You can imagine that in a real-world situation, both forms of motivation are critical - you have to be motivated to move and behave, and you also have to know where to go, in order to get things you want and need.

And so, our studies show that cue-triggered motivation is created by dopamine neurons, and different facets of motivation, which result in different behaviors, are controlled by different dopamine neuron circuits.

It is important to discover more detail about the biological basis of cue-triggered motivation, to define more specific brain targets that create it - because exaggerated motivational value attributed to drug cues is one important component of addiction. If a cue - a sign, an alley, your favorite bar - takes on this powerful motivational value, they will be difficult to resist triggers of relapse and binging. Similar processes underlie other compulsive behaviors, like problem gambling, binge eating, etc. Thus, an essential goal for future studies is to understand how normal, healthy cue-triggered motivation differs from dysfunctional motivation that occurs in humans with addiction and related diseases. **Building on these results we hope to identify brain targets that could be studied for disease intervention, to potentially alter cue-triggered motivation, to boost, or dampen it, to meet therapeutic goals.**