MEET THE SCIENTIST WEBINAR FEBRUARY 2020

How Drug Dependence Impacts Decision Making

Presented by: Christina Gremel, Ph.D.
Moderated by: Jeffrey Borenstein, M.D.

Dr. Jeff Borenstein:

Good afternoon, and welcome to the Brain and Behavior Research Foundation's Meet the Scientist Monthly Webinar Series. I'm Dr. Jeff Borenstein, president and CEO of the foundation and your host for today's webinar. Today, Dr. Christina Gremel will present How Drug Dependence Impacts Decision Making. The Brain and Behavior Research Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include addiction, ADHD, anxiety, autism, bipolar disorder, borderline personality disorder, depression, eating disorders, OCD, post-traumatic stress, and schizophrenia. Since 1987, the foundation has awarded more than $408 million to fund more than 5,900 grants to scientists around the world.

Dr. Jeff Borenstein:

I'm delighted to introduce Dr. Christina Gremel. Dr. Gremel is assistant professor in the Department of Psychology and Neurosciences Graduate Program at the University of California San Diego. She was a 2015 Young Investigator grantee and a 2018 Friedman Prize winner honorable mention. Today's webinar will begin with her presentation. This will be followed by a question and answer period. To submit your questions please use the questions tab on the control panel on your screen. Feel free to submit the questions at any time. Following the presentations, I will ask as many as possible in the time allotted. Now, I'm pleased to introduce Dr. Gremel. Christina, the floor is yours.

Dr. Christina Gremel:

Great. Well, thank you for that very kind introduction. I would like to thank all the listeners who have tuned in for this. I know we have healthcare providers and folk working with mental health organizations, as well as families, and scientists, and students, and so I've tried to gear my talk in a broad way and hopefully provide a little bit more information about what we're doing. First off, I just want to start by thanking my funding sources. This work has been supported by the National Institutes of Health, NIAAA Institute, as well as Whitehall Foundation, and of course the Brain and Behavior Research Foundation. Without these funding sources a lot of this work would not have been possible.

Dr. Christina Gremel:

All right. Also, to kind of begin I want to also point people to useful links that hopefully could provide additional information on other topics or more in depth information about some of the things that I'm

going to speak about. Those are both NIH government websites, including NIAAA's and NIDA's, where there's a lot of useful information both for the lay consumer, as well as for the healthcare professional or researcher. All right.

Dr. Christina Gremel:

In my lab, we're really interested in trying to understand decision making, as well as how chronic drug dependence can lead to such drastic changes in how we make decisions. So, this is a figure of a bunch of schematics showing different human brains or showing a human brain. We're looking at ... all those wiggly parts are the cortex, the top part of your brain. You see all these different colored dots. You can see the label on the graph showing these little dots represent different things, with names such as attention, and working memory, or Q, or drug, or decision making, inhibitory control, and craving, intoxication. What these dots on these brains represent are long lasting changes seen in neural activity in subjects who have been dependent upon a drug.

Dr. Christina Gremel:

Now, some of these dots are seen while that person is still an active drug user, but a lot of these dots reflect neural activity that is still changed long into abstinence, even after someone has quit using and abusing. There have been long lasting changes seen in decision making circuits related to addiction, and so there is a lot of interest trying to understand what exact processes have been disrupted, with the hopes that perhaps gaining this understanding will help develop new ways of treatment or alleviate other problems that come along when someone is trying to abstain. All right.

Dr. Christina Gremel:

In our lab in particular, we're quite interested in investigating alcohol dependence. A lot of what I will tell you today may be extended to other types of drugs, as a lot of the phenomena have been seen with different types of drugs, but I'm going to really focus today on what we've been seeing and what others have been seeing with alcohol dependence. So, just a little bit of a brief recap. When we think about alcohol dependence, we also talk about alcohol use disorder. It's a chronic relapsing brain disease. Those suffering have a really hard time stopping or controlling their alcohol use, and this is even in despite of adverse social or family, problems with a job, and as well as a whole host of additional health consequences.

Dr. Christina Gremel:

Alcohol use disorders can range from being mild to more severe, but it appears recovery is possible regardless of that severity. This is a significant problem here in the United States. Just back in 2010, alcohol misuse caused the United States a little under $250 billion. More recent surveys on use suggested that about 26% of people within the US, adults, recorded that they engaged in a binge drinking episode in the past month, with about 6% to 7% reporting more heavier alcohol use in the past

month as well. So, this is a prevalent disorder. It has very negative and severe consequences, and it's quite common.

Dr. Christina Gremel:

When we think about alcohol use disorder and we think about deficits in decision making, work from the preclinical side has suggested that, sure enough, alcohol dependence can induce these long lasting effects even in abstinent alcoholics. So, what you're looking at here are these two different graphs. If we look at the X-axis or going along the bottom, you'll see three groups. One is a control, and then these other two groups reflect the number of detoxifications the patient has gone through. So, you have a single detoxification and then a multiple detoxification. In this particular study, what they were looking at was cognitive flexibility.

Dr. Christina Gremel:

Cognitive flexibility, so the ability to change what you're doing if it's no longer the most adaptive behavior. If you're making one choice and that choice stops being rewarded or is no longer the best choice, you should switch and make the other choice. Normally, healthy people will do that. They will shift their behavior and make a more adaptive choice, but what was seen in abstinent alcoholics that had undergone either a single detox or multiple detoxification is that they made more errors and kept persisting making the wrong choice, instead of switching to the more adaptive choice. This could be seen in the number of errors they made, as well as the number of trials it took them to do this task. Those people who had gone through multiple detoxification just took a lot longer to try to acquire the best adaptive behavior. In alcohol dependence, increasing the number of detoxifications, it seemed to impair this ability for cognitive flexibility that's necessary for appropriate decision making.

Dr. Christina Gremel:

Now, when we talk about decision making and behavioral flexibility, one of the things we're talking about is being able to adjust your self-control. I want to define a little bit of what I'm talking about in terms of self-control. Probably most of you have heard of Skinner boxes, but some of the theory that has evolved from these types of works is termed instrumental learning theory. Instrumental learning theory has experimentally defined aspects of self-control in a couple of ways. We could think of decision making as being goal directed and that our self-control, our control, our choice is based on the consequences of our behavior.

Dr. Christina Gremel:

So, if our behavior is to get a certain goal, if we no longer want that goal or the value of that goal has decreased, then we're going to change our behavior. It's under our control. Likewise, if our behavior no longer produces the appropriate goal, we're also going to change our behavior. So, this is what we're talking about when we're talking about cognitive flexibility. We're talking about the ability to have goal

directed control over our behavior and change it based on the consequences of our behavior, as well as the relationship between our behavior and what it produces.

Dr. Christina Gremel:

Now, something else I'm sure most everyone has also heard of has been the idea of habits. Habits are talked about in a lot of different contexts. I just kind of want to define them in relation to how I'm talking about them here. So, habits is kind of like the counter of a goal directed control. Habitual control is when you're still initiating your behavior, there's some sense of control, but you're not really sensitive to the consequences of that behavior. If your behavior is producing a particular goal, even if I was to make that goal now negative or have an associated negative consequences, you're going to keep choosing to do that behavior. You're insensitive to the consequences of the behavior. Likewise, if you're doing a particular behavior and all of a sudden the behavior that normally produces the consequence doesn't anymore, you're still going to continue. You're more likely to continue doing that behavior, because it's just been habitual. It's been something that you've been doing for a long time and generally it has been good.

Dr. Christina Gremel:

So, these two different processes, this goal directed process and this habitual process, are thought to reflect different behavioral strategies we use to control our decision making, one more sensitive to the immediate consequences of our behavior and one that seems to be less sensitive and may persist even in the face of negative consequences. Now, these are psychological terms, but their behavioral controllers have been observed in humans, and nonhuman primates, and rats, and all the way down to mice. So, these are very evolutionarily conserved ways that our brain uses to control behavior, and we can measure these things across many different species and probe their function.

Dr. Christina Gremel:

Now, these definitions are really important, because they can be taken into preclinical and clinical studies and used to assess the degree to which someone is goal directed and look to see whether decreases in goal directedness are found across different psychopathologies. What is quite common is that across many types of disorders there are deficits in this goal directed decision making or in this type of self-control, where we're really sensitive to the consequences of our behavior, consequences of our actions. There's been a lot more work in this area as of recent looking at the disruption of goal directed control across different psychopathologies. I just wanted to bring your attention to this.

Dr. Christina Gremel:

The graph in B, along that X-axis you can see many different disorders that the BBRF directly funds investigations of. We have eating disorders, impulsivity, obsessive compulsive disorder, and alcohol addiction. All show this decrease in goal directed decision making. There are some deficits in the ability

for goal directed decision. On this graph it's referred to as model based learning. It's another way to talk about these types of self-control.

Dr. Christina Gremel:

A prominent hypothesis has been that a loss of goal directed control is found in addiction with a dominance of habitual control over drug seeking and drug taking behaviors, but I also want to point out that addiction pathologies of course also show many very excessive goal directed behaviors, where people spend a lot of time and a lot of resources on drug seeking, and they really know exactly which drug they want to take, and they're quite sensitive to the price of the drug. So, it's not that every single goal directed process may be disrupted in the addiction, but there may be particular ways that these decision making processes are disrupted. So, really trying to get in there and understand what components of this goal directed decision making are disruptive and perhaps identify some of the underlying neural mechanisms and molecular mechanisms that may bias away from using appropriate goal directed strategies at all times would be really useful in trying to target treatment of these diseases.

Dr. Christina Gremel:

All right. So, how do we identify behavioral control and decision making? I so far have shown graphs and figures coming from papers where they were looking in people, but for a lot of the type of neural mechanism and circuit and molecular identification that we want to do in the hopes of driving towards new therapeutic approaches we turn to animal models for this. Like I said, we can model these fundamental aspects of decision making in animal models. I'm going to give you a simple example that we're going to basically use throughout the rest of the talk to try to probe these deficits in decision making.

Dr. Christina Gremel:

Imagine here we have a mouse or a rat and we can put them into a Skinner box. In a Skinner box, there is a lever that extends out into the chamber. When the animal presses that lever, they usually can get a food outcome, or a sucrose outcome, or a drug outcome, so they can make lever presses for food. Now, we can put different schedules on that lever press. Imagine that the animal has to press four times or eight times to get that outcome. What previous work has shown is that we could take two different groups of rats, a group reflected by the black diamonds and another group reflected by those red XS. What you're looking at here in panel A is you're looking at how fast they press the lever, their lever presses per minute, so the rate of pressing across different days of training. You see these escalating numbers. These are just the requirements on this lever press going up. So, we see two groups of rats, and they're learning to press the lever for food, and that increases across days.

Dr. Christina Gremel:

Now, if we just look at these two different groups, it's really hard to tell them apart. They look very similar, so at this point we'd say, oh, they maybe have similar types of decision making. They've learned

to press a lever for food. but what experimental psychologists have been able to do is develop experimental definitions to probe why the animal's actually pressing the lever. One of the ways they do this is through outcome devaluation testing. Outcome devaluation testing is a procedure that you can do ... usually it's done across two different days, and it's a fairly simple procedure, and it makes kind of some intuitive sense.

Dr. Christina Gremel:

Let's say we have on one day, which we call the devalued day, let's say we let that mouse or rat eat as much of the food as they want, and then we let them continue eating this food until they're satiated. Then we can put them back into that Skinner box and ask them to press the lever, and we can measure to see how much they actually want to press the lever. Now, we do this in extinction, where the food is not delivered, because the question we're asking is even though you just ate a whole lot of that food and you're no longer hungry for it, you've undergone what's called sensory specific satiation, will you continue to press the lever for food?

Dr. Christina Gremel:

We can compare that to a different day, which we call the value day, where they're able to eat as much of the other outcome, in this case sugar water, as they want to. So, they can become sated and they're no longer hungry, but they were sated on something other than the pellet that they normally press the lever for. Once again, after they're sated, we can put them back into the chamber, and they can press the lever, and we can examine how much they pressed the lever on that value day, when they were sated on the sugar water compared to how much they pressed the lever on the devalued day, when they were sated on those pellets that they normally press for. So, we're asking whether the pellets can exert ... if that outcome that they're normally ... their behavior is geared towards getting that outcome and we devalued the outcome, will they continue pressing?

Dr. Christina Gremel:

What has historically been seen is two different types of phenotypes. If you look at the group of rats in the black bars, on the X-axis, you can see that there's a valued state and the devalued state. What you see right away is that in the devalued state ... Sorry. We're looking at the lever presses per minute, so how fast they were pressing that lever. What you see in the group of rats reflected in black is that when they had that devalued state, when they got to eat as much of that food as they wanted to that they normally press the lever for, we devalued the consequence of their behavior, they reduced responding. However, if you look at the other group of rats in the red, you can see that they pressed very similarly between the value day, where they were sated on some other outcome, and the devalued day, where we've specifically decreased the value of their action, we've reduced the consequences of their behavior.

Dr. Christina Gremel:

Now, normally we'd talk about the group in the black, that type of behavior that's reflected in this difference between the valued and the devalued state, as reflective of goal directed control, while the bars in the red, they're more similar between the valued and the devalued states. We refer to this as habitual control, because in the black, the black bars shows that this behavior is sensitive to negative consequences, we no longer want the food, so we're going to stop responding, while the red bars reflected more of habitual, we're going to keep responding, even though that food now has some negative consequences or we don't want it anymore.

Dr. Christina Gremel:

Why is there this difference between these two bars? What these two bars reflect are two different groups of rats. One was just a control group that proceeded normally, had no experimental manipulation. However, the rats reflected by the red bars had undergone previous chronic, unpredictable stress. That previous chronic, unpredictable stress was sufficient to disrupt goal directed control and leave animals more reliant on habitual strategies. So, this is how we can identify some of the behavioral controllers mediating our self-control and decision making. We can do these types of lever press tasks, where we can change the value of the consequence that you're normally lever pressing for and examine the behavior. So, this is what we all term experimentally defined behaviors.

Dr. Christina Gremel:

Now, when we think about these two different behavioral strategies, we can ask whether they're similar, whether they emerge in the same way across time, if they're parallel processes. What many decades of research have now shown is that goal directed and habitual control are separate processes that have different time points perhaps of when they control behavior. So, when you first learn something ... If we look at this particular graph, we have sessions, so let's say the amount of learning across the X-axis, and what we're asking on the Y-axis is what's controlling behavior.

Dr. Christina Gremel:

Generally, it is thought is when you're first learning how to do something and you're first making decisions, you really rely on a goal directed strategy. However, over time there's also a habitual process, learning process, in your brain that is also emerging and that with continued time this process is strengthened and comes to control behavior. At the same time, goal directed processes seem to be less able to control behavior the longer we do something. But either one can be used to learn about things, so if we have these two different learning circuits, a goal directed circuit and habitual circuit, maybe the goal directed circuit dominates earlier on and may dominate earlier on in drug use, and then the habitual circuit can perhaps emerge and take over behavioral control.

Dr. Christina Gremel:

Now, what I've shown you so far is just how we've looked at these things in animal models, but we can then take these instrumental tasks in animal models and put them towards the investigation of disease

processes. These same types of questions have been examined in models of alcohol self-administration, where rats will actually self-administer alcohol and consume it orally. We can ask the question whether their self-administration is under goal directed versus habitual control. This work was done by Laura Corbit and Patricia Janak, along with other examples of this type of work. What they can do is put a rat into a Skinner box, where there is a lever, and the response, the lever press, is going to deliver alcohol. So, they can train an animal, a rat, to press the lever for alcohol, which the animal then consumes.

Dr. Christina Gremel:

Then, once again, you can ask the question of why is the animal pressing the lever? Are they goal directed or are they habitual? They can do this again through one of the devaluation procedures. So, they can manipulate the value of alcohol either by allowing an animal to drink as much alcohol they want and thereby reducing the value of alcohol, or they can also pair alcohol consumption with some type of illness, such that there's a memory formed that alcohol produces illness, so they're reducing the value of the alcohol by associating it with a negative consequence. These two different types of tests are called either sensory specific satiety or a conditioned taste aversion. After an animal has been trained to lever press for alcohol, you can probe whether they're using a goal directed or habitual strategy when they're pressing for alcohol by using either sensory specific satiety or conditioned taste aversion.

Dr. Christina Gremel:

Then, after this devaluation, once again we can have a test procedure where you put them back in the box, they can press the lever, and what we're asking is whether the memory of alcohol, even though it's been devalued, will you continue to respond for that alcohol, or will you reduce your behavior, because that has now been paired with negative consequences? What others have seen is that if you let animals self-administer for just two weeks, and we're looking down here at the bottom of the slide on panel E, and we have our devalued state, where they either underwent sensory specific satiety or a conditioned taste aversion, and we compared how many lever presses they made in that devalued compared to a non-devalued state, if animals have only been self-administering alcohol for about two weeks, they still show a reduction in the devalued state. That means they're still goal directed. They now know alcohol neither is motivational as it used to be or it's now been paired with a negative consequences, and so they reduce responding when it's devalued.

Dr. Christina Gremel:

However, if you have animals who have been self-administering alcohol almost every day for eight weeks, so a long time in a rodent's life, what you see is their decision making is no longer goal directed. They continue to press the lever for alcohol, as reflected by no difference between the devalued and the non-devalued or the controlled state. They continue to press for alcohol, even though it's now associated with negative consequences. This suggests that long-term alcohol self-administration leads to a reliance on habitual control.

Dr. Christina Gremel:

Now, these animals, not only have they been drinking alcohol for eight weeks, but they've also been pressing a lever for eight weeks. So, there's two different things that may be both be contributing to the development of habitual control. One is just the level of lever pressing, and training, and learning that they've undergone has maybe biased them to start using more habitual processes. The other potential contributing factor is that they've also been exposed to just a lot of alcohol on its own. This leads to the question of does alcohol dependence itself, just having your brain be exposed to a lot of alcohol, is that sufficient to change the neural circuits and change decision making that we use in everyday life? The question would be is alcohol dependence induced changed in the brain to reduce our reliance on goal directed strategies and make us biased to use more habitual strategies independent of whether our decision is for going to seek out more alcohol or even just in our daily life?

Dr. Christina Gremel:

My lab set out to examine this question, and we needed to use a validated way of trying to induce alcohol dependence in mice. Mice, and rats, and rodents in general are sensitive to the bitter taste of alcohol, like many of us are. Oftentimes, you have to do little tricks to try to get them to drink, by adding in a lot of sugar, like we do with human alcohol, or maybe food restricting them, so they want to get more of their calories through alcohol. But even then it's hard to get animals to necessarily drink a lot, where we can actually induce a physical dependence like we see in humans. What the field has kind of coalesced around and has used is this well validated model of ethanol vapor dependence.

Dr. Christina Gremel:

What we do is we have mice breath ethanol vapor, and they do this at very high levels for a long time. What this does is it produces physical dependence on alcohol. So, they're never drinking alcohol per se, but they're breathing it in, and that vapor is raising blood alcohol levels in their blood stream, and it is changing their brain. This vapor procedure is they can stay in their home cage and put into a chamber, so they're still with their litter, their cage mates, and they are in this vapor chambers for 16 hours a day for four days a week for four weeks. Their blood alcohol levels are coming up to about twice the legal limit. So, we do this vapor procedure for a month.

Dr. Christina Gremel:

What I want to point out is there are these repeated withdrawal episodes in between each vapor exposure. So, they're in there for four days, and then they're going through withdrawal over the weekend. It's thought that this withdrawal component is very necessary to mimic the changes that have been seen in human alcoholics, so we can kind of mimic those changes down in this mouse model. Mice that are coming out of this model have been shown to have shown more withdrawal severity, so going through withdrawal they show more severe signs. They're tolerant to some other aspects of some other aspects of alcohol exposure. Mice coming through this vapor exposure will actually drink more, and they will seek more alcohol.

Dr. Christina Gremel:

This is a well validated model of alcohol dependence, and it's been widely used to try to examine the effects of alcohol dependence on the brain and behavior. So, what we do is we can put mice through this vapor procedure, and then after they're done in a Q withdrawal, we can put them in one of those Skinner boxes and train them to press a lever for food. We can do devaluation testing. The question we can ask is did this prior induction of alcohol dependence, does just making them physically dependent on alcohol, did that just change their decision making circuits? So, one of the tricks we want to be able to use to see if an animal is more goal directed or more habitual is that we can actually train each of these strategies in the same mouse, and we can get a mouse to shift back between being goal directed in one situation and habitual in the other.

Dr. Christina Gremel:

What we can do is we can put an animal into one box and have them press a lever. I told you that we can have different work requirements on lever pressing, like how many times they have to press it, or is there a particular schedule that they have to use? We can put a schedule on there that biases use of habitual behavior. We can put a mouse into context A, and they have to press a lever, that left lever, for food under a schedule that makes them more habitual. We can then immediately put that animal into a different context, but they have to press that same left lever for the exact same food, but now they're using a schedule that has been shown to bias goal directed behavior. Once we train an animal up in this, we can then ...

Dr. Christina Gremel:

Sorry. My apologies for jumping ahead. We did this with animals who have been exposed to this alcohol dependence induction. They're the group CIE. Then we have other animals who went to those same chambers every day, but just got air in their air. So, we can see that alcohol dependent animals and our control animals can learn to press a lever just fine. There's not a problem with being how to learn how to do this type of decision.

Dr. Christina Gremel:

We then wanted to probe, well, what decision making strategy are you using? Are you being goal directed, or are you being habitual? To do that, once again, we do one of these outcome devaluation testings, where we can feed them as many pellets as we want in that devalued state and compare it to control situation, where they can drink the sugar water, and then we can ask, when you're in the habitual context, how many times do you want to press the lever? When you're in the goal directed context, how many times do you want to press the lever? We do that in control animals. We can see these gray bars are when they're being habitual, and the black bars are when they're being goal directed, because you see that value bar is higher than that devalue bar. Our control animals can be habitual in the habitual context and goal directed in the goal directed training context.

Dr. Christina Gremel:

When we looked at our animals that had alcohol dependence induced a month ago, what we see is these animals rely on habitual strategies for decision making. This is just for food, and this is a one month out, after the last ethanol exposure. These animals are well into abstinence, but they do not show goal directed behavior. Those blue bars should be different, similar to the black, and they're not here. They're relying on these habitual type of strategies. This seems to suggest that prior alcohol dependence can indeed bias towards reliance on habitual behavioral strategies. We can see a loss of goal directed control.

Dr. Christina Gremel:

Now, we've been really interested in trying to understand some of the brain circuits that may be changed, and to understand the brain circuits that may be change, we need to think about which brain circuits are involved in this type of decision making. We know from a long literature that parts of the cortex and the basal ganglia or the striatum in your thalamus are all involved. So, this is kind of a nice schematic from a review paper, where they lay out what we call these different cortical-striatal-thalamic loops, so we have A, B, and C. You can say they have each of these kind of associated names of a motor circuit, associative circuit, and a limbic circuit. I want us to focus on our motor circuit and our associate circuit.

Dr. Christina Gremel:

The big human brain you're seeing in front of you, you can see where motor areas of the cortex are highlighted in orange. They send information down into the striatum, which is on these graphs labeled the putamen, and the GPE, and the GPI. Those are part of the globus pallidum. So, we have motor outputs from the motor cortex coming into the putamen and moving through the basal ganglia. If we move over to panel B, to the associative circuit, what you see is more of the front parts of the cortex, more up by your eyeballs, are shown in green. These green parts of the cortex also project out of the striatum, but they project to a different place in the striatum. They're projecting into what's called the caudate part of the striatum and then move through the system.

Dr. Christina Gremel:

You have these different parts of the cortex, the motor cortex and more of the associative frontal areas, projecting to different parts of the striatum. There's also a limbic circuit, where we have more eventually parts of the cortex projecting to different parts of the striatum as well, but we're going to really focus on this motor and associative circuit. This is found in people. All right? So, this is our human brain. While other species maybe don't have as large of a cortex or as involved as a cortex, there's still similar areas. So, we can take a human brain with, once again, the front of the part of the brain ... The frontal association areas are highlighted in blue. We know that monkeys, other primates still have these frontal cortices. Although the brain is a [inaudible 00:36:07] smaller, we also know that mice have some what we call homology to these frontal cortical associations, and they have structures that project to similar places of that striatum, like there is in humans and other non-human primates.

Dr. Christina Gremel:

We do our work in rodent models, and so I want to just tell you a little bit about what we know about how these cortical area project into the striatum in a rodent. This is kind of a busy graph, but what the big outline that you're looking at, straight ahead of you, that has the colors and the words, hindlimb, and trunk, and forelimb, those colored areas reflect the striatum in rodents. Up above that, on the left hand side, you have the rodent cortex. You see the SMC, which is some more of the motor areas, the motor control. Then you have frontal cortices reflected in blue, and purple, and pink, and red. What you can see is the frontal part of the cortices project into more medial or middle area of that striatum, and the motor areas project to the more lateral portions of the striatum.

Dr. Christina Gremel:

The reason why I'm bringing this topography up is because different portions of the striatum have been shown to differently control goal directed versus habitual decision making. This center or more medial part of the striatum is really important for goal directed control. If there are problems with this area in humans or if you lesion this area in other animal models, such as in rats and mice, they can no longer show goal directed control. They're always reliant upon habitual processes. Likewise, if you were to lesion the lateral part of the striatum, that green/blue color, you lose habitual control. You can only use these goal directed processes.

Dr. Christina Gremel:

Within our brains, and this has been seen in neural activity in humans as well, that these different parts of the striatum, the medial striatum or the caudate striatum in people is involved in goal directed control, and the lateral part of the striatum, or the putamen in primates, is involved in habitual control. Either system can control the behavior. What scientists think is likely is that both of them are contributing to kind of a gradient of control, where in some situations we may be more goal directed and in other situations we may be more habitual.

Dr. Christina Gremel:

The question is does alcohol dependence change this striatal control? One way that it may change striatal control is by changing how the cortex talks to striatum. Up in the cortex, those blue and purple colors are projecting down into striatum, and it could be that alcohol dependence changes how the cortex functions and what kind of information it's sending to the striatum to control our decision making. One of the regions that we know is really important for decision making in the cortex is called the orbital frontal cortex. This is a part of your cortex that sits kind of right ... if you think about your eyebrow bones, right behind your eyebrow bones, kind of up above your nose, a little bit more medial. The OFC has been heavily implicated in value based decision making in people, as well as rodents.

Dr. Christina Gremel:

On the left is just a scan, a cartoon scan of a brain and kind of where the OFC would sit within that scan, as well as then a picture of a rodent OFC, where those yellow dots are a genetic tool that we put in the animal's brain, and it's in the region of this orbital frontal cortex. We're able to look at neural activity of the orbital frontal cortex in humans, as well as monitor and manipulate neural activity of the orbital frontal cortex in rodent models.

Dr. Christina Gremel:

In humans, we've seen this orbital frontal cortex does seem to change in alcohol dependence. So, once again, we can ask the question whether OFC activity has changed in abstinent alcoholics, depending upon the number of detoxes they've gone through, a single detox or multiple detox. What you're looking at in panel C is the three far left bars reflect neural activity in the orbital frontal cortex. This is activity of the OFC in response to looking at fearful or emotional stimuli and being able to disambiguate between them. What has been commonly seen is that in alcoholics who have undergone multiple detoxes is that their OFC is just less active. It's not as responsive when viewing these fearful or emotional stimuli.

Dr. Christina Gremel:

In another study, preclinical researchers reported that the OFC is less active than it should be, and this decreased OFC activity was associated with impaired decision making. Abstinent alcoholics were asked to choose between a small, immediate reward or whether they could wait for a delayed but larger reward. Abstinent alcoholics were more likely to go with the small, immediate reward. This behavior was tied to reduced OFC activity. So, the less activity in OFC, the more likely they were going to choose the small but immediate reward. This choice of small but immediate reflects not the best adaptive decision making that they could be making in terms of waiting for a larger reward that may be a little bit delayed. Work in human alcoholics and in humans in general has implicated OFC in value based decision making and that this seems to be impaired in alcohol dependence.

Dr. Christina Gremel:

We also know that OFC neurons can change their activity during decision makings, so it's possible for scientists to record from single neurons in the brain and what all these little, black dots are on these schedules or these raster plots, so every little, black dot is a neuron firing action potential, which is the way neurons communicate with other neurons. They send an action potential, which is electrical and chemical information. We know that OFC neurons can increase or decrease their activity during decision making, implicating them in this type of value based decision making.

Dr. Christina Gremel:

We also know that if we damage the OFC, we can disrupt decision making. We, once again, use this lever pressing outcome devaluation task to have animals press the lever for food, but in one group of animals we had actually lesioned the OFC. A lesion is when we can kill those neurons just selectively within the

OFC. When we did that, we found that animals no longer made goal directed information. When we induce damage to the orbital frontal cortex, mice and others have shown rats do not use goal directed strategies to control their decision making.

Dr. Christina Gremel:

In the past decade, two decades, there's been large advances in neuroscience techniques, which allow us to get really specific in the questions we ask about the neural circuits involved. While previous decades we've used lesions and other types of drug approaches, some of those can have long term consequences or there can be compensation by other brain areas. So, modern techniques now allow us to ask questions about neural activity in a very temporally precise way. One of those ways we can do that is through the activation of designer receptors exclusively activated by designer drugs. These were developed by Bryan Roth at UNC. But the basic idea is that we can take these modified receptors that scientists made that are only going to be activated by a particular drug. We can take the instructions or the gene for this receptor and we can put them into particular neurons in the brain and only where we want to.

Dr. Christina Gremel:

What that means is that when we want to change the activity of this neuron, either turn it on or turn it off, we can give this drug to selectively activate just those neurons that we want to in the brain. Now, we wanted to do this in the orbital frontal cortex to make sure that this part of the brain was really contributing to value based decision making. So, we put this tool into neurons in the orbital frontal cortex, such that when we have the drug to the animal we turned off these neurons, so that they're no longer working. That's only for a couple of hours, but we were able to test these animals. Once again, we saw that, sure enough, they did not use goal directed strategies. There should be a difference between those two last bars and there is not, suggesting, once again, that inhibiting, that quieting down the orbital frontal cortex leads to a loss of goal directed control and that we need to have more activity in the OFC, in the orbital frontal cortex, for goal directed control.

Dr. Christina Gremel:

To test that more directly there's another great, new tool that scientists, neuroscientists, often rely on. It's a way to use light to control brain activity, as crazy as it sounds. What scientists were able to do is take a protein that was sensitive to light from algae, and this protein, it's a channel that basically passes a positive charge into a cell, and it can make neurons fire these action potentials, and that's how they communicate. So, once again, we can take the gene for this protein, we can insert those instructions into specific neurons in the brain, and then we can shine light down onto those neurons and cause them to fire these action potentials. This is how they communicate with other neurons around them. So, we can use this to control the neural activity in the orbital frontal cortex.

Dr. Christina Gremel:

What we can do is when we put this tool, this optogenetic tool, in the orbital frontal cortex and we shined light down onto these neurons and made them become active, we can actually increase the amount of goal directed control that we see. So, while the previous technique with DREADDs we showed that we could reduce the activity of OFC and lose goal directed control, with this optogenetic approach we could increase the activity of the orbital frontal cortex and increase goal directed control. Together these suggest that the orbital frontal cortex is really governing this goal directed control. This provides us with a really strong target through which alcohol dependence may be exerting its effects, because remember, in alcohol dependence we have a loss of this goal directed control.

Dr. Christina Gremel:

So, we wondered, does alcohol dependence affect the function of the orbital frontal cortex? Work from preclinical studies in humans would suggest that the OFC is quieter overall, so we had the hypothesis that alcohol dependence reduces the activity of the OFC, of the orbital frontal cortex. So, to test that what we did, once again, was we put animals into vapor chambers. Then afterwards, almost a month later we can euthanize the animal and take out their brain, and we can record from OFC neurons. So, we can kind of poke the OFC neurons, and keeping these brain slices functional and alive, we can ask these neurons how they work now. When we did that, in this middle graph, our black is our control animals and then our reds are our mice that underwent the induction of alcohol dependence. You can see there's less activity in these neurons or there's a reduced excitability of these neurons following alcohol dependence. So, alcohol dependence just made these neurons less active.

Dr. Christina Gremel:

I brought up the cortex, because it sends information to the basal ganglia, which we know controls these decision making processes as well. So, what's really interesting is that our parts of our cortex, including the orbital frontal cortex, project down to the basal ganglia and they talk to two different streams of information. There's a stream of information moving through the direct pathway, which we can genetically label in mice now, as well as moving through the indirect pathway, which, once again, we can also target with mice. For those of you who have heard more about the basal ganglia and these direct and indirect pathways, they're thought to reflect kind of a little bit of a push and pull system over the control of our behavior, but we know that the orbital frontal cortex can come down and can perhaps talk to these two different pathways. So, we wanted to look at whether alcohol dependence affected that communication.

Dr. Christina Gremel:

Does alcohol dependence change how the orbital frontal cortex talks to the direct pathway, which is thought to promote wanted behaviors, and does it change how it talks to the indirect pathway, which is thought to reduce unwanted behaviors? Now, how the orbital frontal cortex talks to these two different downstream basal ganglia pathways is by releasing a neurotransmitter called glutamate. It's an excitatory neural transmitter, for those of you more in the knowledge about neuroscience. What we did is we put animals through the vapor procedure, once again, to induce physical dependence, and then

we can record downstream in this direct pathway or this indirect pathway, and we can directly probe just the contribution of these orbital frontal cortex terminals down into the striatum.

Dr. Christina Gremel:

Now, when we did that ... I know this is a little bit busy graph. For those of you who are not scientists or don't do any of this neuroscience, I'll just kind of walk you through this. Up in the left hand corner, what we're asking is how much neurotransmitter are you releasing when I ask you to release, when I make you active? What we're asking is how much transmitter the orbital frontal cortex is releasing onto that direct pathway. Kind of not intuitively, the black line, when you're below one, it means you're releasing more neurotransmitter, and when you're above one, you're releasing less. So, what you see in our air controls is that they have a high probability of releasing glutamate. However, in alcohol dependent mice, that is reversed, and there's actually a really low probability of them releasing glutamate or another way of thinking about it is of them passing information down into basal ganglia circuits.

Dr. Christina Gremel:

What was interesting is that this was really just onto that direct pathway of the basal ganglia and not the indirect pathway, suggesting that there is an impairment in alcohol dependence in the ability of a part of the cortex known to control value based decision making, its ability to tell that information to the pathway in the basal ganglia that helps promote wanted behaviors. Our work has suggested that alcohol dependence not only reduces the activity of these orbital frontal cortical neurons, but it also reduces the amount of information that it sends down into basal ganglia.

Dr. Christina Gremel:

Now, if these changes that we're observing just in a brain slice, if they have any relevance for the behavior, we should be able to manipulate the activity of these neurons in alcohol dependent mice and try to restore this goal directed decision making. So, to do that what we can turn to is that DREADD or that designer receptor exclusively activated by a designer drug, and we can use a variety of that receptor that's going to actually increase the activity of these orbital frontal cortex neurons. So, we can put this tool into these neurons in mice, and then we can have these mice be induced into alcohol dependence, and then we can ask, using our Skinner boxes and our devaluation procedures, we can then ask whether when we activate these orbital frontal cortex neurons, can we restore proper goal directed control.

Dr. Christina Gremel:

That's exactly what we found. While our CIE control animals, the ones who didn't have that tool activated in them, while they were habitual, if we put this tool that activated these orbital frontal cortex neurons and we activated them during devaluation testing, we could restore goal directed control in these mice. So, mice that otherwise would be left reliant on habitual processes, just by increasing the activity of the orbital frontal cortex we are able to restore goal directed control in them.

Dr. Christina Gremel:

So, why would this be useful? Well, our findings of the types of neural activity and how we could restore it provide necessary and important information to preclinical research groups. They can use these findings to try to help investigate molecular mechanisms and potentially identify targets for drug therapies to help aid in recovery. It's also pertinent to the design of recent transcranial magnetic studies, TMS in other words, that have been used to try to examine cortical perturbations to change different types of decision making. Perhaps it could be that you could use these findings to help guide TMS studies that would try to restore cognitive behavioral flexibility in the orbital frontal cortex.

Dr. Christina Gremel:

When we start thinking about future ways to alter circuit function in humans, while I've talked to you about DREADD technologies and optogenetic technologies that we've used in rodent models to change brain activity, in humans, in addition to cognitive behavioral therapy, it could be that TMS, or transcranial magnetic stimulation, could be used to modify the activity of these types of cortical areas. It's perhaps a promising, new venture that scientists are exploring. All right. With that, I would like to say thank you for listening, and I look forward to your questions.

Dr. Jeff Borenstein:

Well, let me say, on behalf of all of us, thank you for the work that you've been doing and for a really excellent presentation that gives a sense of the breadth of approaches to understand how the brain works, how that relates to a particular condition, and then how that can potentially lead to new treatments. So, thank you for really sharing all that.

Dr. Christina Gremel:

Oh. No. You're welcome. It's been fun.

Dr. Jeff Borenstein:

I want to ask when you look at what you're going to be doing in the next five years, next 10 years, where do you see your research going, and then if you came back in five years from now, what would you be telling us?

Dr. Christina Gremel:

So, we're really interested in trying to understand how dependence affects the cortex's control over decision making in general. We're looking across different parts of the cortex. To try to answer this question we needed to identify how different parts of the cortex are contributing to our decision making, such that when it goes awry, we can then look at different parts of the cortex. Now, not every part of the cortex is going to change in the same way in drug dependence, and so we think there's a lot of work that needs to be done to try to understand how different portions of our cortex are disrupted, what the disruption means for our decision making, and are there particular ways we can target that

neural activity to try to help restore more adaptive decision making to just help people make better decisions about their daily lives and drug use.

Dr. Jeff Borenstein:

Thank you. Thank you. One question I have relates potentially to prevention, which in the work looking at small, immediate rewards versus large, delayed rewards, can you describe any work that's been done looking at people who aren't yet addicted, maybe adolescence, people at risk, and is there any work that's been done to help improve the ability to figure out who may be at greatest risk and therefore take steps to avoid the chemical dependency?

Dr. Christina Gremel:

Yeah. This is a really hot topic in terms of trying to do these exact same things, as trying to understand some of these perhaps more impulsive behaviors we're seeing. Are those really produced by dependence, or are people maybe have these impulsive characteristics prior to dependence, and does that make them more susceptible to some of these dependence type factors? So, people are actively looking at that, both in preclinical and clinical work, as well as in animal models. In adolescence in particular we know is quite sensitive time, that a lot of these circuits that control impulsive types of behaviors, our cortex especially, are still developing into your mid-20s. I always tell my undergrads, "Be careful. Your brain is still changing." But a lot of drug use during these time periods can really ... it seems to affect how these circuits occur and then the ability to use these circuits to control these types of impulsive type decisions. That is an area that a lot of people are pursuing, so hopefully we'll get further with that and get more information soon.

Dr. Jeff Borenstein:

Good. Thank you. I think I'm going to emphasize an important point you just made, that the brain continues to develop through the mid-20s, so especially as marijuana's being legalized in locations around the country, this is something that people should be aware of, that their brain is still developing and you don't want to negatively affect the development of your brain.

Dr. Christina Gremel:

Yes. I tell my children and my students, "Please protect the brain." As long as-

Dr. Jeff Borenstein:

Absolutely. Absolutely. Well, I want to, again, say thank you so much for the work that you do, for the presentation.

Dr. Christina Gremel:

Thank you for inviting me.

Dr. Jeff Borenstein:

I also want to thank everybody who joined us today. 100% of all donor contributions for research are invested in our grants to scientists. All of the research we fund is made possible through supporters like you, so please consider making a gift by visiting our website, BBRFoundation.org, or call 1-(800)-829-8289. This webinar has been recorded. If you missed any portion of the presentation or would like to share it with family or friends, please visit the events and webinars page on our website.

Dr. Jeff Borenstein:

I hope you'll join us again in March, when Dr. Christopher Pittenger, associate professor of psychiatry, assistant chair for translational research, director of the OCD Research Clinic, and co-director of the Neuroscience Research Training Program at Yale University School of Medicine will present **Brain and Behavior Based Strategies in the Treatment of OCD**. This webinar will take place on **Tuesday, March 10th at 2:00PM Eastern time**. Once again, thank you for joining us. Have a great day. Take care. Have a great day. Take care.

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