PsychTalk

with Jose Drost-Lopez

Booze in the Brain

Interview with Dr. Donita Robinson

Kiersten Jeske: *You're tuned to 103.5, WCOM-LP, Chapel Hill and Carrboro's 100-watt wonder: listener-supported, community radio. You just heard a short tribute to Valentine's Day that, as you'll hear, also ties into today's topic. This is PsychTalk, bringing you interviews and stories that explore the mind. I'm Kiersten Jeske, here to introduce the show. Every week, we ask big questions about the way people think and act. Today we're asking about a problem shared by Whitney Houston and Amy Whinehouse. That problem is drug abuse. Whinehouse died of alcohol poisoning on July 23, 2011. Houston was found dead on Saturday, February 11 amid speculation that her history of alcohol and cocaine abuse played a part. Why did drugs take over their lives? There's a lot to be said about the role of culture and celebrity, but we're going to zero in on the brain. Neuroscientist Dr. Donita Robinson focuses on alcohol addiction, and she is in the studio to explain some of the basics, like why we enjoy alcohol in the first place. Here to speak with Dr. Robinson is your weekly host on PsychTalk, Jose Drost-Lopez.*

Jose: *Thanks Kiersten. I'll say a little more about Dr. Robinson; typically, her lab studies rats trained to press a lever to get alcohol. With these rats she monitors the striatum, a region known to be active in the pleasure and craving for things like food, sex and alcohol. Her work probes subtle aspects of brain activity, such as the timing of dopamine release and the specific role of small groups of neurons.*

Jose: Dr. Robinson, welcome.

Dr. Robinson: Thank you. I'm happy to be here.

Jose: It's so great; we were talking off-air about how you just love what you do. And that's exactly why we have this show: to have people who love what they do—the research they do—come talk about it.

But you will have to unpack what I just said; because I was talking about the striatum, and that sort of thing sounds scary—*is that an alien, or something*? So, let's start with the brain, and then we'll move more toward addiction. First of all, why does alcohol affect the brain? What's happening?

Dr. Robinson: Well, alcohol is a drug, and so it has a lot of actions on the brain. In fact, it has a couple of categories of actions. At low doses of alcohol it can stimulate the brain, so you feel kind of activated; you get a little more energy. It's often a really good feeling when you have your first drink.

But then there are biphasic effects. If you continue to drink, you can get the other side of alcohol, which is intoxicating and sedative, and it basically slows down the brain. So, you have to think that when you're drinking, it's going into your stomach. And your stomach is a pretty big place; and it can hold a lot of alcohol. But the alcohol kind of comes out slowly.

That's why, when you first start drinking you think, *this feels really good, I think I'll have another one; if one is good, two or three might be better*. But then, once you have that second or third one, the intoxication starts setting in, and maybe your speech gets slower, your thoughts get slower, your motor coordination is not as good.

Now, it's having those effects on the brain by acting at a lot of different chemical systems. Neurotransmitters are the chemicals in the brain that neurons (the brain cells) use to communicate with each other. And in fact, alcohol can affect many of the neurotransmitters of the brain: glutamate, GABA, and dopamine—which is one of the ones we're going to talk about today.

Jose: Glutamate, GABA, dopamine; so, these are all little chemical signallers. And somehow alcohol two-times us by first making these signals make us feel a little more excited, and then somehow making us feel miserable later.

Dr. Johnson: That's right.

Jose: That's the summary.

OK. Well, let's start with one of these little devious signalers that actually has a lot of effects on the brain. What is dopamine?

Dr. Johnson: If you look in the newspaper or in magazines, a lot of times you'll hear that dopamine is the pleasure chemical; and that comes from studies where animals would do things like press a lever to get their dopamine neurons activated. But it turns out that's not exactly what I think dopamine is doing. I think it's more accurate to say that dopamine is a brain signal of importance, or salience; it tells the brain when something important is out there that we need to get.

And, of course, those things that are important, we often interpret as being pleasurable. So, there's some overlap. These are things like food when we're hungry, or a potential mate and sex; also water when we're thirsty, or social affiliation. All of these things are good things, and dopamine is part of a system in the brain that is what you might think of as a 'seeking' system, or a 'go' system—like *go get that!*

Not only is dopamine released when you see those things, but also your brain is very efficient at survival, and at finding those things that help survival. And so, also cues in context, or other things in the environment that just predict the availability: like a refrigerator; when you're hungry, you know that the refrigerator signals food. The brain learns that these cues in context can predict rewards, and they also can start to stimulate dopamine systems, and cause dopamine release.

Jose: So, when we see a Snicker's bar, or a very attractive person, it's the amount of dopamine fluctuating that's telling us *go get 'em*. And even the refrigerator is somehow triggering some changes in dopamine that are letting us know that what we want is in there.

Dr. Robinson: Probably so.

Jose: I guess we don't know everything about dopamine, right?

Dr. Robinson: Right. And that's one of the things where it's useful to have animal models; because we can measure dopamine directly in animal models, whereas it's harder to do that in people.

Jose: Right.

Well, let's jump to the next brain term. What are receptors?

Dr. Robinson: Neurotransmitters are the chemicals that the brain uses for communication; receptors are the detectors of those chemicals. An analogy is a lock and a key: the lock is the receptor and the key is the neurotransmitter, and when it fits just right, it can open the communication channels. And so, many drugs can have their actions in the body and in the brain by either enhancing activity at the receptors, or blocking activity at the receptors.

Jose: OK. So, we have dopamine affecting receptors that are causing neurons to react—to fire—and they're getting inhibited or excited. How is this working in the region called the striatum?

Dr. Robinson: The striatum is a really cool place in the brain. It's kind of a hub. If you think back to the dopamine as part of a 'go' system, it's sending a signal to the striatum— it actually sends dopamine release to the striatum—and it's encouraging the striatum…

Let me back up just one bit. The striatum is part of a circuit called the basal ganglia, that's involved in motor output, or making the decisions about what you want to do. When that 'go' signal of dopamine hits the striatum, it's encouraging the system to go get that reward.

But there are other things that come in to that system. The striatum—especially the ventral striatum, or the lower part of this area—also gets input from the prefrontal cortex. That's the part of the brain where you usually think of decision-making. And then, that part of the brain might say, *now is not a good time to go get that reward*. So, it can be thought of as kind of a 'stop' signal; or at least a 'stop and think' signal.

So, you have this 'go' signal and this 'stop' signal. You also have other things coming in to the striatum, like memories of maybe what happened last time; you have emotional parts of the brain sending inputs in to the striatum. And the striatum then integrates all this information to make the choice of *what am I going to do right now*, and make that decision.

So, that's why it's a really fascinating part of the brain to look at, because it's looking at that decision point—all of these factors coming together.

Jose: And with all those factors it's considering, it probably is a little too simple to just call it the 'pleasure center'—where the pleasure party is at.

Dr. Robinson: That's right.

And there are lots of parts of the striatum. There is the dorsal striatum, which, if you lose the dopamine input to the dorsal striatum, you get Parkinson's disease. And in Parkinson's disease you have a problem initiating movements. So, you can see how the dopamine is important to initiate movements.

One of the differences between the dorsal striatum (the top part of the striatum) and the ventral striatum (the more bottom part of the striatum) is that the ventral

striatum also gets emotional input, and some of that prefrontal cortical input, that makes it a little more tied to the emotional system, and then a little more important in things like drug addiction, where I think of the behavior as being really motivated, or really charged.

Jose: You mentioned the prefrontal cortex. That's the front part of the brain—sort of the front lobe; and there's an outer layer—that's maybe a source of a lot of our smarts and deeper thinking. Is that fair?

Dr. Robinson: Right. That's true; like planning and judgment, remembering consequences, and how things might value. You know, a tasty food might be more valuable when you're really hungry vs. when you're on a diet. And so, how do you remember that you have this other goal, which is to not overeat, or to lose a little bit of weight? That extra goal is then represented in the prefrontal cortex. And then it can send that 'stop' signal down to kind of mediate the 'go' signal of the dopamine release.

Jose: And that's cool, because I think it's tempting to say that we're slaves to the feelings in our brains, and we can't do anything about it. But there's a part of the brain that's also encoding our goals, and that's sort of the conscience, or the voice of planning. And that's also an influence that can affect our behavior, and our successful diet, or whatever else.

Well, let's get to the drinking component; how the drinking interferes with what's happening in there—what's happening in the brain while we're drinking—and especially over time. So, the first time it's fun, and then the next time maybe less fun. And then, over time, what does that do?

Dr. Robinson: The first times you drink, you have that activating feeling. And we think that dopamine is involved in that, in that some of the pleasurable feelings may be coming from opioids, or other neurotransmitters in the brain, and alcohol stimulating those.

So, you have those initial feelings that are very positive. And then, they can cause you to keep drinking, through positive reinforcement. 'Reinforcement' just means it's something that will continue the behavior. So, positive reinforcement means something good that will make it more likely that you will continue that behavior, or do it again.

But as you keep drinking, over time you develop tolerance to some of those pleasant symptoms, and you're more likely to continue drinking for negative things. Like maybe if you take a drink in the morning because you have a hangover; that's drinking to alleviate negative consequences. So, it also reinforces the drinking behavior, but in a very different way than positive reinforcement.

Let's go back to the analogy of the 'go' system and the 'stop' system in the brain. Addictive drugs, one thing that they have in common is that they all seem to activate the 'go' system. They can all stimulate dopamine release in the nucleus accumbens. And so, that is thought to contribute to their positive reinforcing effects that make them addictive, and make you want to continue taking them.

But over time—and it might take a long time, because especially alcohol use disorder, or alcoholism, can take years to develop; sometimes decades—but over that time you have some brain damage. And some of that damage is in the prefrontal cortex, or just the area of the brain that you need to help moderate your drinking.

So, not only do you have drug effects enhancing the 'go' system, but you have drug effects that dampen your 'stop' system. And we think that contributes to the compulsive behavior that you see with alcoholism or drug addiction.

Jose: And what type of damage is it? Is it brain cells dying; or more subtle than that?

Dr. Robinson: There are certainly effects on circuits, and how the brain is functioning, well before you have problems with actual cell death. But after someone has died you can look at their brain, and if they have a history of alcoholism, their brain is smaller than someone else who is the same age and sex. And you can see that the prefrontal cortex is one of those places that's particularly hit; where the tissue is just thinner. And that's due to cell loss.

Jose: So, first the circuits sort of fire differently—neurons respond differently, the receptors don't trigger the same reactions—and then, over time, the brain also does shrink.

Dr. Robinson: Right.

Jose: OK. Well, there is a distinction here to make between just drinking, even a lot, and becoming addicted. What's the difference there?

Dr. Robinson: You can drink a lot, but still moderate your drinking. Lots of people will have occasions where they drink a lot, and maybe drink more than they expected. But then they learn, and the next time they don't drink that much. Addiction is typically medically defined by having negative consequences to your drinking, and having the desire to stop or reasons to stop, but being unable to.

So, that's really the difference. And to kind of illustrate that, there's a set of questions, called the CAGE Questionnaire, that doctors might ask their patients when they come in for a visit. It's four questions; and 'CAGE' is an acronym.

The first question is the 'C' question: *Have you ever felt like you should cut down on your drinking?* The 'A' question is: *Have people annoyed you by criticizing your drinking?* The 'G' question is: *Have you ever felt bad, or guilty about your drinking?* And then, the 'E' question is an eye-opener: *Have you ever had a drink first thing in the morning to steady your nerves, or to get rid of a hangover?*

The reason these questions are a good screen is because, first they get at kind of a quantity of drinking—*do you feel like you should cut down;* or, *do you ever drink so much that you have hangovers, and you might drink alcohol to relieve the hangover?* But they also get at some of the psychological aspects—*do you get annoyed because people are telling you that you're drinking too much;* or, *do you feel guilty about it?*—with the implication that you're unable to do anything about it.

This can identify when someone might have some problems with drinking. And then, to really diagnose an alcohol dependence you look for a number of factors, including quantity, as well as some of these negative consequences. So, my feeling is that the real hallmark of addiction is that it is compulsive use, despite negative consequences.

If you have no negative consequences, you don't have a problem. It's when you start having negative consequences—to your health, to your relationships, maybe with your job, maybe getting DUIs—and yet you're unable to do anything about it, or change the behavior.

Jose: Right.

Now, you mentioned this CAGE Questionnaire that gives you an initial sense, if you have this compulsive tendency that's causing negative effects in your life, that maybe you're addicted. But if you gave it to a rat, or to some other animal, they might not have the same sorts of answers, right?—*do you take an eye-opener in the morning?*

Dr. Robinson: That's right.

Jose: So, you do work mostly with rats. Let's compare what we've been talking about to how rats are affected by alcohol.

Dr. Robinson: In fact rats, in that way, are much smarter than people, in that they're much less likely to become alcoholic, and develop alcohol dependence. But they are useful, in that we can model a lot of the aspects of alcohol use and alcohol addiction in animals—not the whole picture that you would get in a human; but different aspects of it.

For example, someone who has alcohol use disorder drinks large quantities of alcohol, and those large quantities of alcohol have effects on the brain. Well, we can model that in animals by giving them large quantities of alcohol for a period of time, and seeing how the brain function or brain cells are changing.

Actually, 'eye-opener' is an interesting one, because that's something I feel like we can model in animals. We can train them to drink alcohol, and then over time they can learn to drink large quantities. And then, would they drink if they had a hangover? And you can set up the experiment to where animals will drink to relieve withdrawal symptoms. So, that's also something that we can set up in the lab.

You can even look to see whether animals will choose to drink, despite a negative consequence. One of the things you can do with rats is to put something in the alcohol that makes it bitter—something like quinine, that they wouldn't normally want to drink. But if they persist in drinking, if they continue drinking despite that bad taste, then you know they're really motivated to drink.

And a normal rat wouldn't do that. So, to get a rat to do that, you might have to give them a lot of alcohol, and a history of alcohol, to change the brain in such a way that their drinking is then more like an addicted human.

What we can't model in rats, or course, are the psychological aspects; the desire to quit but inability to do so, and that conflict there, that you often see with people who have alcohol use disorder.

Jose: I'm curious how much rats like alcohol. If they've just tried it once or twice, will they start choosing it over water very quickly?

Dr. Robinson: Rats, like people, are all different. If you were to just look at 100 rats, maybe 5% of them would really like alcohol, 5% of them would never touch alcohol, and the rest of them would be kind of in the middle somewhere. You can actually take those rats that really like alcohol, breed them, and have a strain of rats that really likes to drink alcohol. We call those 'alcohol-preferring rats.'

So, that's possible. But the normal run-of-the-mill rat doesn't particularly like alcohol right away; but they do like sugar. So, what we do is train them to drink sugar—and maybe they'll press the lever to get a little bit of sugar—and then gradually add in the alcohol.

That gives them the opportunity to experience the effects of the alcohol; because they're drinking it for the sugar, but once they feel the effects of the alcohol, then a lot more of the rats kind of like that. Then, if you were to take the sugar away, some of the rats, they were only drinking for the sugar, and you take the sugar away, *no thanks*. But then, a good amount of the rats will continue to drink, now that they've experienced the effects of alcohol.

In fact, it's not that different from people, because very rarely do people start drinking Vodka and water. People start drinking wine coolers, and beer, and low-alcohol-content drinks that have a good flavor. And so, it's kind of analogous to that; we start the rats off drinking for the flavor, and then see which ones will continue to drink for the effects of the alcohol.

Jose: It sounds like you basically start them off with Piña Coladas, and then go to the whiskey later.

Dr. Robinson: That's right!

Jose: Well, let's go to the set-up of your experiments; which can be quite ingenious. First you have to put rats in a certain training regimen, so that they exhibit the behavior that suits your experiment. Tell us a little bit about their training.

Dr. Robinson: I should preface this by saying that in our experiments the rats aren't addicted, or dependent on alcohol. What we're really looking at is alcohol's ability to motivate them to work for it. And so, we have them press a lever to get the alcohol.

Like I said, we start by having them press a lever for sugar; over time we add in the alcohol and take out the sugar, so that they're pressing the lever for alcohol. But, depending on how we set up the experiment, we can get very different kinds of behavior.

To set this up, I'd like to give an analogy, to talk about the difference between what we call 'goal-directed,' 'purposeful,' or 'flexible' behavior vs. a habit. If you go into a room, and the room is dark and you want light, you flip the light switch. (I should tell you that this analogy, I heard from a professor up at Duke—Henry Yin—and I like this analogy.)

So, of course you're going to turn on the light switch, because you want light. That's goal-directed. And, of course, most everything we do, we think is goal-directed; we assume we have a purpose for what we're doing. But to show you that sometimes these behaviors can be habitual and unthinking, remember the last time your power went out in your house.

If you're like me, almost every time you walked into a room, you flipped the light switch—even though part of your brain knew that the power was out, and it wasn't going to work. If you were truly goal-directed, you wouldn't flip the light switch, because you would remember that information. But instead, that behavior was kind of habitual: *you go into the room, you turn on the light*.

When you think about drug-taking behavior or alcohol drinking, it can be the same way. There are many ways that the brain will do this behavior. One is goal-directed, when you think, *I want a drink*, and so you go get a drink; and another might be habitual, where, *this is the context where I drink,* or, *this is the time of day that I drink, and I'm going to drink*, but you're not really thinking about it.

We want to model that in rats; because I think there are different parts of the brain that seem to be more involved in goal-directed behavior, and other parts that are more involved in habits. And I think it will have important consequences on treating addiction, to see whether drugs have equal effects, or what are the relative effects on these two ways to motivate behavior. If you just block goal-directed behavior, but you don't do anything to habits, the drug is not going to be very effective to treat an addiction.

So, we try to model these in rats. And how we model this in rats is, for the goal-directed behavior, we can set it up to where every time the animal presses the lever it's going to get some alcohol. What that will do is to make a very flexible behavior. Every time the animal wants alcohol it will press a lever and it will get some. But then, if it doesn't want the alcohol—because say it's full, it's done; it just drank a lot of alcohol, and it doesn't feel like having it anymore—then it just won't press the lever.

This is kind of intuitive—it's what you think would happen anyway—but you can see the difference when I talk about the schedule that we use to train rats to be more habit-like. And that's called a 'variable interval schedule.' In that schedule, a certain period of time has to elapse. And it varies. In our lab we set it up to be around 30 seconds, but it could be as little as 3 seconds, it could be as long as 9 minutes.

It's just kind of randomized, how long that time is. And then, after that time has gone by, a lever press will get alcohol. But the rat doesn't know when that time has gone by. So, from the rat's point of view, it never really knows when a lever press is going to give it alcohol; it just knows that sometimes it does. What that

will do is it causes the animal to have a very steady, persistent pressing behavior; and it will just press very regularly, and for a long time.

Even if it doesn't want the alcohol (because you just gave it a lot of alcohol, and part of its brain knows that it's full), you kind of can't access that; just like when the power is out and you're continually flipping on light switches, you have that kind of automatic response. And I think of that behavior as being more persistent, less flexible.

And so, if we train the rats on the goal-directed schedule or on the habit-like schedule, and then give the animal a drug, we can see whether the drug is equally effective for both sets of rats, or does it work better in one set or the other set.

Jose: This is interesting. It actually was a little counterintuitive to me at first, because I thought that if you have a beer cooler that always has beer in it, always available, then somehow, in the case of rats, in their equivalent case they'd just continue to overdo it: like, *I like this; I'm going to keep going*.

But then I guess the analogy continues; and if you have a beer cooler, but it has beer once in awhile, and you might want beer sometime, so you just get in the habit of always opening it and checking, then that actually is closer to addictive, habit-forming behavior.

Dr. Robinson: Right. I think that's a good example.

Jose: So, we have that set-up. Now tell us, Dr. Robinson, how you monitor what's happening in rats' brains.

Dr. Robinson: We're interested in a couple of things. We want to look at dopamine release in the brain, and then we also want to look at the activity of neurons in the striatum.

I'll talk first about dopamine release, since the majority of our experiments are using that. That's one advantage of using an animal model; we can put a tiny

sensor right into the striatum of the brain, in the ventral striatum. The sensor is actually smaller than a human hair. So, it's very tiny.

On the surface of this sensor it can measure if there's any dopamine there. The sensor samples 10 times a second. So, we can see very fast changes of dopamine release; which would be important, because the brain, of course, works very quickly, and a neurotransmitter is released and then cleared very rapidly.

But what we found is that these fast fluctuations in dopamine can occur in this brain area when something important happens. And we call them 'dopamine transients,' because they're transiently there.

Jose: They're short bursts.

Dr. Robinson: Exactly.

We first saw dopamine transients in a male rat when we put a female into the cage. That's a very important cue for a male rat, or an important stimulus: a sexually receptive female. And sure enough, we saw a dopamine release that is consistent with the idea that dopamine tells the animal when something important is there, and kind of shifts the animal's behavior to go get it.

But we've also seen the same kind of signals for tasty food when an animal is hungry, and during drug self-administration. Professors at UNC, Dr. Gina Carelli and Dr. Mark Wightman, have shown that these dopamine transients occur when rats are taking cocaine, and they occur to the cues that tell the animal that cocaine is available.

In our lab we've seen dopamine release like that to alcohol drinking. In the goal-directed animal model I was talking about—where the animal just presses a lever, and every time, it's going to get alcohol—we have found that cues that tell the rat that alcohol is available will trigger one of these dopamine transients. So, the

dopamine is actually not released when the animal drinks the alcohol, but rather it's for that cue that tells the animal the alcohol is available.

Jose: So that, again, comes back to our initial clarification that dopamine is not just the squirt of pleasure, it's more about anticipating what we want, and pushing us toward it.

Dr. Robinson: That's right.

Now, the other thing we can measure in the brain is neurons firing. You talk about a neuron firing when it's being active, and sending a signal to the next set of neurons. If neurotransmitters activate a neuron enough at the receptors, then it fires what we call an action potential. That's actually a voltage change—it's an electrical signal—and we can measure that by a different kind of sensor we put in the brain that measures voltage.

In another set of experiments, what we do is look at how neurons in the striatum are firing. And those firing patterns then are reflecting all of that integration we talked about—the dopamine inputs, but also the cortical inputs, maybe from the prefrontal cortex and maybe from the emotion centers of the brain—and how those are all kind of integrated into the output.

When we measure the cell firing, we're looking at that output. So, that's another way that we monitor how the circuit is working.

Jose: So, you're looking at chemical messengers; you're looking at electrical firing, essentially. And this leads to some interesting results and insights.

So, let's start with the angle of drugs and medicine that can help people not relapse. There are drugs that help abstinent addicts, such as naltrexone, which you've worked on. What does naltrexone do?

Dr. Robinson: Naltrexone is an opiate receptor antagonist. Opioid release is triggered by morphine and heroin, but also alcohol can enhance opioid release.

And if there is any feel-good system in the brain, I think it's going to be the opioids. And so, naltrexone would then block their actions.

Naltrexone is FDA-approved to treat opioid dependence, as well as alcoholism. The idea is that it would block some of the pleasurable effects, or some of the rewarding or activating effects of the drugs.

One of the things we are interested in doing in our lab is to test the effect of naltrexone in animals that were trained in that goal-directed way—that very flexible way—to drink alcohol vs. animals that were trained in that more habit-like way.

Our hypothesis was that naltrexone would be more effective in the rats that were trained to be goal-directed drinkers; because the whole idea of a flexible behavior is that if you decrease the reward, the animals are going to press less for it—they're able to change their behavior—but with the habit-trained animals, you can change the reward value of what they're getting and their behavior is less flexible.

And, in fact, that's what we found. We're just finishing up that study, and our results are consistent with that.

Now, one thing that's interesting is that's not the whole story; because naltrexone has some effects, even when you don't drink the alcohol. And in our animals what we found is that naltrexone seems to kind of slow down the animal's motivation or lever-pressing behavior, just in general. It seems to have a couple of effects. There's a lot of research suggesting that it does seem to decrease alcohol reward, but it also can decrease some of the motivation.

And that's consistent with people. If you give clinical trials where people have been given naltrexone, sometimes people are reporting that naltrexone decreases craving. And it's doing that. They're not actively drinking; but it decreases their desire to drink. I think that's analogous to what we're seeing in the animals, where they might seek the alcohol less, even if the alcohol is not right there.

So, it seems to have a couple of effects: It's decreasing alcohol reward; but you only experience that if you drink the alcohol. It also seems to decrease some of the motivation to seek alcohol, that you can observe even when the animal doesn't have alcohol to drink.

I think these kinds of distinctions can be important when you want to develop medications to treat addiction and alcoholism; because right now we have a handful of medications—we have naltrexone that you can take in a pill or you can get as a shot (long-lasting naltrexone); we have acamprosate, which acts to block some of the glutamate activity in the brain; and we have Antabuse, or disulfiram, which makes you sick if you drink alcohol while you're taking it—and that's really it.

That's all that we have that's approved. And none of these work for everybody. Naltrexone might work in about 20% of the people. So, we really need to get a handle on how these drugs are working, so that we can better design new drugs to help fill in the holes.

Jose: So, I guess the idea is that we want drugs to be as sort of surgically precise as possible, rather than a shotgun approach where it affects a lot of the brain; it doesn't affect everyone the same way.

Dr. Robinson: That's right. You could have a drug that keeps someone from drinking alcohol, but it might also keep them from enjoying life, or holding down a job. And that's not acceptable. So, you're right; you want precision to treat the disorder, but not have a lot of side effects.

Jose: Right. Well, we're all glad you're working on that; and hopefully we'll see some good developments from neuroscience in the future.

Let's jump to another set of results that you've looked at with your work in rats, which is the difference between adolescents and adults—teens and adults. And

this gets a lot of attention, this contrast. There are headlines like 'Your Teen's Defects Have Been Found in the Brain.'

And you actually have an advertisement with you, if you want to describe it. It can also give this sense that the media helps us understand—between teens and adults.

Dr. Robinson: A year or two ago, Allstate came out with an advertisement that has a picture of a brain with a hole in it; an automobile-shaped hole in the front part of the brain—in the frontal cortex. The title of the advertisement is "Why do most 16-year-olds drive like they're *missing a part of their brain*?" And then it says, "BECAUSE THEY ARE."

And it goes on to talk about how, during adolescence and during the teen years, the prefrontal cortex is still developing; and in fact, that judgment part and decision-making part of the brain is one of the last parts of the brain to fully mature. And I think there is more and more appreciation of that development that's still ongoing during adolescence.

The brain is probably the last organ to really mature; and the prefrontal cortex seems to be the last part to mature. And it doesn't seem to be adult-like until you're in maybe in your mid-20s, even—so, later than what we would normally think of.

Jose: And another recasting of the way teens were, compared to adults, is that they have a different risk/reward balance, where they're more willing to take risks and seek big rewards, even though there are punishments that adults might not tolerate.

That's just another way of saying that the dopamine circuits are different, their brain is set up a little differently; and when we grow up, the brain matures, and leads to different behavior.

Dr. Robinson: Yes. There's model I like to use to guide my thinking on this, by Monique Ernst—who is a scientist at the National Institutes of Health—that she calls the Triadic Model of Motivated Behavior.

When you think about *what behavior am I going to choose to do*, your prefrontal cortex is making that decision; and it's weighing the 'go' system with maybe a 'stop' system. Or you can think of it as the 'good' or—I usually use the word 'appetitive,' but I think that's kind of…

Jose: That's a fancy word.

Dr. Robinson: That's a fancy word, so I want more like…

Jose: Approach/withdraw; go/no go?

Dr. Robinson: Yes, 'approaching' behavior—that's a good word—vs. an 'avoiding' behavior.

So, you can think of something like alcohol, where there are reasons to drink it, but there are also reasons not to drink it, and your brain weighs those reasons. During adolescence the approach and the aversive aspects are not in the same balance that they are in adults, in that the approach aspects are dominant and the avoidance aspects are less dominant.

And there's biology underlying that; because the 'go' system and the interaction of the prefrontal cortex with the 'go' system is different in adolescence than the interaction of the prefrontal cortex with that avoidance system. You can see that, even in the effects of drugs—say something like alcohol—where there are some pleasant effects, and there are some intoxicating effects. Adolescents (and you see this in rats and people) are more sensitive to the good effects of alcohol, and less sensitive to the intoxicating effects.

There's a study by Linda Spear, who is a researcher on this at Binghamton University, where she looked at intoxication to alcohol in adolescent vs. adult

rats; because adolescents also might metabolize faster, so it could be that they're drinking alcohol, and then they just clear it. Maybe their livers are faster, and they're just clearing it more quickly.

With rats, if you get them intoxicated, they'll go to sleep, basically. And if you put them on their back, it will take them longer to get back on their feet. You call that the 'righting reflex;' or the ability to go from their back, back onto their feet.

Jose: What's that called?

Dr. Robinson: The righting reflex; so, they're righting themselves.

Jose: Oh, I see; they're righting the position of their body. OK.

Dr. Robinson: Exactly.

You can look at the righting reflex after giving a high dose of alcohol. And what she found was that the adolescents would recover their righting reflex—they'd be able to move themselves back into the position they wanted to be in—at much higher concentrations of alcohol still in their body, than the adults.

They have less intoxicating effects of alcohol than the adults do. And so, you couple that with an increased reward, and basically the things that would limit your alcohol drinking—say getting drunk and falling asleep—aren't happening nearly as quickly or effectively in adolescents; and that can make them very vulnerable to drinking large quantities of alcohol.

Jose: Yes, the righting reflex is interesting. I'm thinking, as an analogy in humans, maybe the DUI tests that police do; maybe if someone is close to some threshold, they might actually be able to walk the straight line more easily as a teenager.

Dr. Robinson: Right. That's a good analogy.

Jose: And so, that would set up an unfortunate pattern of reinforcement, where there are higher rewards and seemingly less negative consequences—at least, at the moment.

Dr. Robinson: That's right.

So, it turns out that adolescence is a really vulnerable time for a lot of psychiatric disorders. Addiction is one of them; but it's also the time when schizophrenia might emerge, and anxiety disorders, and depression.

And so, what my lab is interested in is how is the brain developing during that time; how is it different than the adult brain? The goal is to try to figure out how those developmental changes are contributing to this vulnerability; why are the animals so vulnerable to addictions and other psychiatric disorders?

We're just beginning this line of research. It's so exciting! And one of the things that we did at the very first was to look at dopamine release. What I find just so interesting is that rats are like people, in that during adolescence, peers are super important.

We know that human adolescents, that's a time when friends are important; and the opinions of friends are usually much more important than the opinions of parents, and there's an increase in social interaction and social influences. What's fascinating is that rats are the same way. They really like to be with other adolescent rats at that time; and they do a lot of play behaviors, and that's very motivating to them.

Well, our lab has shown that in adults, a brief social interaction, whether it's a male with a female or two male rats, is a way that you can trigger dopamine release, or these dopamine transients. So, we were wondering if dopamine transients would be different in adolescents, because social interaction is so important. And we did find a difference.

We found that if you keep putting the rat in to interact, with an adult you'll get dopamine release the first time, but then it starts to go away. We call that 'habituation;' where the response goes away over time. But in the adolescents, we didn't see that habituation. So, the dopamine transients associated with social interaction appear to be enhanced during adolescence.

Jose: So, from rats we get the impression that teenagers just really enjoy hanging out, persistently, over a long time. That's why they always want to be out of the house…

Dr. Robinson: It could be, yes.

Jose: …and hanging out with the cool kids.

Dr. Robinson: That's right.

Jose: That's so fascinating that we can look at animal models—we can look at rats—and find so many things mirroring ourselves; and learn things about what's really happening in the brain at this subsecond level, that give insights into ourselves.

And that brings me to this broader question about the value of animal research, or what it gives us that other types of research don't. What does it give us that we can't necessarily find in researching with people, or with computer simulations?

Dr. Robinson: Some aspects of research, you can use computer simulations, or you can use cell lines, or things like that. A principle of medical research is that we want to use the lowest system available. I think that's ethically the right thing to do. The problem is, when you're researching a psychiatric disorder, or something about the brain, it's really hard to get down to that level.

Now, a goal of research is to be able to model the brain with a computer, and simulate brain activity; but we don't know how it works. So, there's a lot to be done before we're going to get there. And if we want to look at brain activity

during these motivated behaviors, and compulsive behaviors, and maybe dysregulated behaviors, we have to look, right now, in an animal model.

But the animal model then allows us to probe neurotransmitter release, and brain activity, and how the different parts of the brain are working together; things that are much harder to do in people. We can do some of it in people. With imaging techniques we can look at brain structure and we can look at brain function, but it's on a slower time scale, and we can't pinpoint areas of the brain like we can in animal models.

But the goal of a lot of animal research, including my lab's, is really to model the human disease. We want to be able to understand the neurobiology underlying human disease. And in my lab we're interested in addiction; and that will be valuable in learning how to treat it, and also to prevent it.

Jose: Yes. That's great.

And can you paint us a quick picture of what that treatment and prevention could look like in the future? Is it that we're going to just have drugs that really target receptors very carefully? What's going to happen—we hope—that's going to be a breakthrough?

Dr. Robinson: A lot of research to date has focused on particular receptors, and if we get to a very specific receptor type, can we get the effects on the disease, without having so many side effects. For psychiatric diseases that really hasn't been very successful.

And that's probably because psychiatric diseases aren't typically a problem with one receptor or one cell type, but rather most psychiatric diseases seem to be developmental in nature, and they also seem to be diseases of circuitry. And some of the promising drug treatments that are being tested right now—at least for alcohol use disorders—are things that have actually more global effects, but might change the balance of brain circuitry.

The way I like to think about it is, if you have this brain circuit that's driving compulsive alcohol drinking, that's super activated and pathologically activated, if you give the brain a drug that kind of dampens everything down, it might selectively dampen down that overactive circuit, whereas letting other circuits continue to function more normally.

Jose: And I guess we also have some more futuristic hopes, aside from drugs. For example, I've heard of genetic engineering that would let us activate cells with light (that's far off in the future maybe); or something like transcranial magnetic stimulation, or electrical stimulation of the brain, that would affect circuits, too. That would be interesting if you could just plug a cap into your iPad or your phone, and it would start helping you tune your brain function.

Dr. Robinson: That's right. And the optogenetics, or the light stimulation, is going on at UNC in animal models. So, maybe someday that could be used for people.

Jose: Very cool!

Well, Dr. Robinson, I am going to end with a sort of silly personal question. You have a background in biological psychology and chemistry. So, I'm wondering, when you're looking around at people every day, do you think of them in terms of brain tissues and chemical cascades? Are you imagining my dopamine fluctuations and spike trains right now?

Dr. Robinson: Well, no; I can't say that I do.

But I think that by studying the brain and brain circuits I do have appreciation that brain diseases like addiction aren't character defects, but rather they are problems with the way the brain functions. And I think that the more we understand that, the more compassion we might have for each other.

So, a little different than what you suggested.

Jose: Well, that's great; a very human response. So, neuroscience can ultimately let us be more understanding and compassionate with others. I like that!

Dr. Robinson: Oh, yes!

Jose: Well, thank you, Dr. Robinson.

Dr. Robinson, by the way, for our listeners, is a neuroscience researcher at UNC Chapel Hill, who specializes in addiction. She looks at animal models, like rats, to try to understand how alcohol and other potentially addictive cues affect brain activity.

Thank you so much for coming on.

Dr. Robinson: Thank you for having me.

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