Key:

J: Dr. Janes

J: If I were to ask the question, what is addiction? I'm sure you'll be able to answer based on what you've seen in the news, perhaps having watched a friend or a loved one struggle with an addictive disorder. But what isn't always readily apparent is that addiction is a brain-based disease and the changes in the brain that happen due to drug use cause this disorder to be chronic, relapsing and for it to continue despite no negative effects. But before I get into the brain's role in addiction, specifically, I need to talk about the brain's role and reward more generally, because the processes that underlie addiction and reward are quite similar. Because whenever we come into contact with a reward in our environment, whether it's going on a nice vacation, perhaps having a nice dessert at the end of a meal, we have a release of the neurotransmitter dopamine in our brain. And dopamine is going to be released by one cell and then it's going to bind to receptor of another cell, propagating that signal of reward that's going to make you want to do that behavior again and again. But we know we don't stay on vacation forever or only eat dessert other brain regions play a role in addiction as well because while the reward signal is being processed in the ventral striatum, the prefrontal cortex is playing a role in stopping these behaviors. So we can have flexible behavior, so we can plan for the future and so this is how we can switch easily from doing something we enjoy like having a nice dessert to eventually stopping having that dessert, or coming home from a vacation. The problem here is that addictive substances hijack this normal biological process. So if an individual is taking anything from nicotine, or cocaine, heroin or alcohol, this is still going to cause a rise of the neurotransmitter dopamine in brain regions such as the ventral striatum leading to those feelings of reward and enjoyment. The problem is, is that there are two main differences. One is that dopamine signal in the brain is going to come on much faster and there's going to be a lot more of it. And this is going to cause that reward signal to be much, much stronger for a drug of abuse. And this is why individuals are going to want to use a drug of abuse at the expense of other things that could be rewarding, like going on that vacation spending time with friends and loved ones. The other thing that happens is that prefrontal cortex that should be sending the stop signal will no longer be as effective. And so that signal becomes weakened and people continue to use drugs of abuse. And so overall, there becomes an imbalance in brain systems because in normal, healthy non drug users, we want a nice balance between reward and the ability to stop reward and plan for future things so we can enjoy life and we can eventually come back to work. But in people with an addictive disorder, the balance has shifted towards seeking those rewards, specifically towards seeking those drug rewards. So that individuals are unable to shift their behavioral way as easily as people who don't use drugs of abuse. The other change that occurs happens to do with how dopamine is functioning in the brain because normal healthy individuals are going to have that dopamine response to rewarding things in their environment, leading to those feelings of enjoyment. And a drug user is going to have that same process happen, but the reward signal is going to be much greater because there's much more dopamine in the system. But the brain is going to end up wanting to rebalance the dopamine system. And how this occurs is by lowering the amount of dopamine receptors in the brain. The consequence of this is tolerance, because lower dopamine receptors is going to lead to a weakened reward response to a drug of abuse. And this is why individuals who use drugs are going to end up escalating their use, why they're going to start needing more and more and more of that same drug to experience the same amount of rewarding feelings they did originally. And it's because dopamine system in the brain is trying to rebalance, it's compensating for the amount of dopamine being released. The other consequence of this reduction in dopamine receptors plays a role in withdrawal because when a healthy individual experiences reward to anything in their environment you get that dopamine response and the reward signal. But to a drug user the dopamine response is going to be weaker than when they're receiving a drug of abuse but also because of the tolerance effect, they're going to have lower dopamine receptors in their brain so now they're going to get a weakened reward signal just to everyday rewards. And this is going to play a role in withdrawal. Because the effects of withdrawal are very similar to those of the drug of abuse, except they're the exact opposite. So, if a drugs effect is to feel reward, you're going to end up feeling pretty lousy when you're no longer using that drug. You're also going to experience the inability to receive pleasure from everyday rewards. And so, this is how people end up getting caught in the cycle of abuse because there's feelings of negative affect in withdrawal, are going to end up causing people to become preoccupied and start to anticipate drug use. And those feelings of preoccupation and anticipation might then lead the individual to use drugs again, eventually bingeing and becoming intoxicated. And then after a period of withdrawal, you experienced the withdrawal and negative affect again. So, people get stuck within the cycle that they're unable to escape from. So far, we've really been talking about how the act of using a drug of abuse impacts the brain. And then it has a cyclical effect, where drug use causes the brain to change, which perpetuates drug use. We can actually see these changes measure using techniques like Positron Emission Tomography. With this technique, we're able to measure dopamine D2 receptors in the brain. And what we're seeing here is in the red region where there are a lot of dopamine D2 receptors, but when we look to individuals who are using cocaine, methamphetamine or even heroin, what we see is that red region is gone. There's just not as many dopamine D2 receptors in the brains of drug users and this is a consequence of drug use. What we also know is that there's a relationship between the amount of dopamine D2 receptors in the brain and how well that prefrontal cortex is going to function, such that individuals who have more dopamine D2 receptors are going to have better function in the prefrontal cortex. And the opposite is also true, weaker dopamine D2 receptor expression, weaker prefrontal function. So, we're able to really very directly measure that balance between our reward system and the functioning of our prefrontal cortex. The other take home message from this is that we can in fact, measure the biological effects of drug use in the brain. And this is no different than other medical issues. What I'm showing you here with the white arrow is where in the brain there is reduced metabolism in a cocaine user, specifically, it's pointing out the prefrontal cortex. And we can see the same reduced metabolism in the diseased heart relative to the healthy heart. So just like heart disease, we're able to measure a biological change in the brain that's associated with addiction. Which brings up a good question, which is whether the brain actually ends up recovering. And unfortunately, the answer to this is, it's complicated because there are many brain systems that play a role in addiction. If there's recovery in one system, there may not necessarily be recovery in all systems. But there's still hope, because there is examples of recovery in certain brain areas. So, going back to our story of the D2 receptor, when we look at drug users, they're going to have less dopamine D2 receptors than healthy non drug users. And after a period of about 14 months of abstinence we can start to see recovery of those dopamine receptors, such that the ex-drug user starts to look more and more like a healthy individual. So, there can be recovery but as I mentioned, drug use is a complicated disorder that involves many different brain systems from those involved in reward, decision making reason, memory, and emotion. So even if there's recovery in one brain system, in one brain area with one neurotransmitter, it doesn't necessarily mean that all systems are going to recover. And there's also going to be variants between different people because things like severity of drug use, longevity of drug use, are also going to impact whether someone who's able to maintain abstinence in the long run. Now, so far, we've really been talking about how drug use impacts the brain and how that then leads to more drug use in the future but we know there are many different factors that can impact the brain and then subsequently drug use. I want to give three different examples, these are just examples, because there are many different factors that can impact brain function and subsequently drug use. But I would like to touch on genetics, environment, and then mental health issues. And when talking about genetics, again, I could talk about many different examples because there are many different genetic factors associated with addiction. But for this I want to stick with our story of the dopamine D2 receptor because as we talked about earlier, the dopamine D2 receptor becomes downregulated in those who use drugs of abuse chronically. But we can look to healthy individuals who are genetically predisposed to have lower dopamine D2 receptors in the brain. And these individuals don't learn as well from negative consequences in fact, their brains have weaker responses to negative feedback stimuli. So even though they've never used a drug of abuse, their brain is set up in such a way that they can't learn effectively from negative consequences which helps us understand addiction a little bit better because we know that addiction continues despite known harmful effects. We also know that dopamine receptors are downregulated in people with addiction. So, the consequences of drugs of abuse are making it more difficult for individuals to learn from negative consequences, such as health issues, disruptions and the relationships with others. We also know that genetics may play a role in who ends up becoming addicted because having a genetic predisposition, like a reduction in dopamine receptors, is actually linked with a higher likelihood of developing an addiction. So how the brain is functioning even before someone uses a drug of abuse can end up impacting whether somebody becomes addicted but we know that it's not just genetics, we know there are other factors as well, things in the environment, and by environment, I could mean anything from growing up in a home where drug use is prevalent to early childhood trauma, or even the classic story of peer pressure. But what I mean by environment here is the idea of cue reactivity. And by cue reactivity, I mean, when a person who's trying to quit using a drug comes into contact with anything in their environment that reminds them of their prior drug use. So, this can be the story of somebody who is an ex-alcoholic, and they go past that bar where they used to drink and all of a sudden they find themselves relapsing. Or someone who is an ex-opiate user goes to their friend's home, where they used to use heroin and they find themselves using again. Or in our lab, we've looked at people who are wanting to try to quit smoking and what we found was that individuals who are more likely to relapse relative to those who didn't had the most brain reactivity to smoking cues, even before they tried to quit smoking. So how the brain is responding to environmental stimuli is somewhat individualized and these individual differences then can impact relapse vulnerability. And this brings up the question of whether relapse really does mean failure. I did give an example of how relapse can actually be in part linked with individual variability in brain function, but I also wanted to point out that relapse in addiction is quite comparable to other medical issues. Because the relapse rates of addictive disorders are about 40% to 60%, which is similar to other diseases like type one diabetes, hypertension, as well as asthma. And in all of these cases, people could benefit both from a medical intervention like a medication, as well as from a change in their behavior, such as eating better, exercising, no longer using a drug. So, this is just again, another example of how drug use shares a lot of similarities with other medical issues. But again, we know that it is not just genetics and not just environment that are going to impact relapse we know there's a strong comorbidity between relapse vulnerability and having a mental illness. In fact, there's high comorbidity between having a mental illness and addiction in general. And again, I could talk about many examples here from schizophrenia to post traumatic stress disorder, but I want to use the example of the link between nicotine dependence and major depressive disorder. And this is because when we look at the healthy non psychiatrically ill population, only about 22% of people smoke tobacco cigarettes. When we look at people with major depression, what we find is that number almost doubles, which really begs the question, what is going on neurobiologically in those with major depression that might make someone more vulnerable to develop an addictive disorder? What we know about major depression is there's actually weakened communication between brain regions that play a role in reward. Specifically, the ventral striatum and the ventral parts of the medial prefrontal cortex don't communicate with one another as strongly. And this contributes to some symptoms of major depression. But if we were to give that individual with major depression, nicotine, what we see is the connectivity between these regions starts to strengthen starts to look more and more like a healthy individual. And this is an example of one theory about why there is so much comorbidity between addiction and mental health. And that's the idea that individuals with mental health issues may actually be self-medicating, they might be using a drug of abuse to fix an underlying neurobiological problem that's actually really related with their mental illness. And I'm not advocating drugs of abuse as a way to treat mental illness but I am saying that this initial beneficial effect of the person might actually get them stuck, and then get them stuck within that cycle of abuse and experience. Seeing all of those negative effects that we know can happen from using any drug of abuse. It also points out the idea that we can't necessarily treat one disorder from the other. And in order to account for addiction we might also need to account for the underlying psychiatric issues that a person is faced with. So, now if I were to ask once again, what is addiction? Hopefully, your answers changed a bit to include the idea that addiction is a brain-based disease that has biological effects like any other medical health issue. Hopefully, you also understand that addiction is a complex disorder and it's difficult to treat in part because there is the involvement of many different brain system. And also, while it's important to understand the commonalities across addictive disorders, and how certain neurobiological changes occur across addictions, there's going to also be individual variability that needs to be taken into account things like differences in genetics, environment, and psychiatric health. And it's all these individual differences that are going to play a role in why it is someone may have a hard time maintaining abstinence and why they may have even started using drugs in the first place.