Molecular Neurobiology with Dr. Crystal Dilworth
Ologies Podcast
November 12, 2019

Oh heeey, it's the lady who keeps candles in her wallet because you never know when you'll be in a pinch and it's going to be someone's birthday, and you'll be more excited about singing to them than they'll be excited about being sung to, Alie Ward, back with another episode of *Ologies*. You like brains? Does your brain like brains? It probably does. Right now, your soft squishy think-lump is just hanging out in your head, thinking about itself. How does it work? What's in there? Why do I want to eat Cool Whip out of the tub with my fingers? And why aren't I more excited about folding my laundry? The answer: molecular neurobiology.

But before we splish-splash into your mood juices, let's take care of some business up top and thank all the folks on Patreon.com/Ologies for being in the club. Y'all support the show and hear what topics I'm working on first and you submit your questions for the ologists. Thanks to everyone wearing *Ologies* merch from OlogiesMerch.com. Thanks to everyone who forwards an episode to a friend or who subscribes on their devices, and rates, and especially reviews, because you know I read your words and pick a freshie to put on blast, such as Dusqkee who said they're falling back in love with life and that:

> *… the ologists have shown me the light. The world is a beautiful place and with all these smart monkeys out there maybe, just maybe, we have a chance to share it with future generations! P.S. Thanks to Alie, I texted my crush and got some bangs! Boy howdy. Sincerely, Dusqkee*

And to that I say, "Haaaay!"

Also, side note: happy wedding Lizzyvette and hello to Kangaroo2, who left me a one-star review because they didn't like that I named so many patrons who asked questions. But Kangaroo2, isn't it nice to hear your name in a podcast you love? Isn't it, Kangaroo2? Just sayin'. Also, the bat episodes just got a lot of questions, okay Kangaroo2? It's fricken bats. I hope I have proven my point, that people like to hear their names. But I get it, and I'm going to read faster.

Okay, molecular neurobiology, let's get into it, let's break it down. 'Molecules', the word, derives from the Latin for 'tiny mass'; and 'neuro' comes from the Greek for 'sinew', or 'cord' or 'penis', because neurons are elongated, they look like strings or cords. Or, I guess, penises. Biology of course, the study of life. So molecular neurobiology: the study of the tiny masses that bring our dick-looking brain cells to life. I'm just reading facts here.

Now this ologist got a Bachelor's in Biochemistry at UC San Diego and later a PhD in molecular neuroscience at Caltech. She's also a dancer, a gymnast, a violinist, a TEDx Youth speaker, a tech strategist, and a TV host for *Voice of America*, *Al Jazeera America*, *Seeker*, *Discovery News*, and more. She's an IF/THEN STEM ambassador for the American Association for the Advancement of Science and Lyda Hill Philanthropies. Literally she is appointed a role model to other women and girls in science technology, engineering, and math fields. She also appears on segments of the new CBS show *Mission: Unstoppable*, where she is known, accurately, as Dr. Brain.

I've known her for five years and have adored her since we first sat down and shared a basket of sweet potato fries in 2014, and I was just straight-up giddy to have her on my couch and ask her one million questions about what a brain is made of, and white matter, and grey matter, and what makes us happy? And how do antidepressants work? And why are some substances addictive? And what happens on drugs? And can I have new habits? And what is anxiety all about? And how

depression works and caffeine hacks that may not work. So, get ready to fill your ears, and the thing between your ears, with all kinds of wisdom from wonderful person, neuroscientist, your new good friend and Molecular Neurobiologist, Dr. Crystal Dilworth.

Alie Ward: Let's start recording. Can you say your first and last name please? So, I pronounce it right? [*struggling to not laugh*]

Dr. Crystal Dilworth: Crystal Dilworth.

Alie: I know! [*laughs*]

Crystal: Do you want me to spell it for you?

Alie: No. [*laughs*] Docta Dilworth.

Crystal: Dr. Dilworth.

Alie: I always like to ask this question. What was it like when you came out of the room from defending and you were like, "I'm Dr. Dilworth."?

Crystal: I came out of the room and my committee was still in there deliberating, and normally that is one of the scariest moments in anyone's life because you're not sure what they're going to say, but I was pretty sure because my committee chair had been like, "We're just going to chat for a little bit, we'll be right out." They came out, and they shook my hand, and they said, "Congratulations Dr. Dilworth," [*Alie squeals*] and I got an entirely new lease on life!

Alie: Oh my god that's so exciting.

Crystal: Everything changed.

Alie: Did you know growing up that you were going to be a doctor or a neuroscientist? I mean, you are really good at a lot of things and I think that sometimes is difficult.

Crystal: No, I was going to be a dancer. I was going to be on stage at Lincoln Center, just like all of the books that I had read about how to be a professional ballet dancer. Had nothing to do with science really.

Alie: So, were you studying ballet and then sneaking into chem classes? How did it work? Who were you cheating on, scholastically?

Crystal: I think the decision to go to grad school, I was definitely cheating on my dance classes. I was in professional dance school in New York City doing the things that you have to do to be a professional dancer and I just wasn't fulfilled by the experience. I think it's really hard. I was lying about my age so that I could be in the school to begin with. And dancers, they're treated like empty vessels, right? The choreographer, the artistic director, these are the people that are filling the empty vessel with the intention.

When you have a bachelor's degree in biochemistry and you're used to doing independent research as an intern in a research lab, being treated like you have nothing personally to contribute is very difficult. And I was looking for an opportunity to be an adult and to be treated like I had something to intellectually contribute and I wasn't getting that in my artistic life. So, I started skipping my classes and taking the subway uptown to Columbia and attending the chemistry department lectures, which is insane now that I look back on it now. Nobody goes to those lectures voluntarily. The grad students are only there

because of the free pizza, but I was actually there for the intellectual stimulation, which is terrifying and awful.

Alie: Wait, they give pizza out at these things? [*laughs*]

Crystal: Otherwise nobody goes. Yeah, most of those weekly lectures are accompanied by some type of bribe.

Alie: So why neuroscience?

Crystal: Well, I guess I was always interested in people and their behavior maybe because, as a homeschooled kid, I didn't have a really diverse social network. I mean, I had a social network, but not the diversity that you would see in public school, for instance. Some people's behavior seemed unfathomable to me. I just don't understand, what is this programming and how does it work? And so, I thought, maybe I would study history, maybe I would study sociology or psychology. And my dad said no. [*"Hell nah."*] He was like, "That's not a real science. None of those are real sciences and you have to choose a real science."

Alie: What was your dad? Did your dad study science?

Crystal: Yeah, his background is in physics. My mom's background is in microbiology. That was what they understood. They were afraid of all the things that parents are afraid of. Like, "She's never going to get a job. She's going to be destitute. She's going to move back home." I live with my mom right now, by the way. So, FYI, best laid plans of mice and men. [*laughs*]

Alie: [*laughs*] Yes, but you're an international traveler and you're about to move to Sumatra.

Crystal: It's true. There are reasons also that I decided to move in with my mother to help take care of her as well. But like I said, this is their plan.

Alie: So, brains. Do you start with molecular biology? When you decide, "Okay, I want to figure out how this weird big lump of stuff in my bone bowl in my head works," where do you even begin with that? Do you start with neural anatomy? Do you start with the chemistry of it?

Crystal: For me, the Eureka moment was… I was taking organic chemistry because, typical freshman O-Chem, what everybody has to take. And I was also taking biopsychology, which is the closest I could get to a psych class and still have this be approved. I should clarify that I started college really young, so I was probably 14 or 15 at this time.

Alie: [shocked] Oh my god!

Crystal: My parents were still approving my course load, so I was restricted in what courses I could take based on their approval.

Alie: Oh my god, wait. I've known you for four years and I did not know that you started college at 14 or 15!

Crystal: Yeah. I started at a junior college, which your first two years are the types of courses you're able to take there. And I transferred to a four-year college much later.

Alie: Oh my god. I don't think I was wearing a bra at 14! [*laughs*]

Crystal: [*laughs*] I wasn't either.

Alie: Your parents would have obviously helped you figure out what courses you were going to take, so biopsychology?

Crystal: Yeah, it kind of backfired because I was in biopsych and they laid out, in the book and in the lecture, the pictures of the different neurotransmitters, the chemicals in our brain that determine the brain functionality that translates into behavior. And I would just learn from my organic chemistry class how to identify the critical chemical functionalities. Like, "That's an oxygen group, an OH group, hydroxyl, that's a benzene ring," and sort of start to understand how those things sort of fit with our biology. And that was like [*snaps her fingers*] the aha moment.

Alie: Eee!

Aside: If you're like, "Quick, Ward, what is a benzene ring?", it's not an oil gang, but more elementally it's six carbon atoms that are joined in a ring with a hydrogen atom stuck to each. And Crystal was like, "Aah! My brain loves this stuff!" Now her bachelor's is in biochem and so far most of her college courses were more generally about the human body chemistry and didn't focus on the thinky parts of the human body as much.

Crystal: So, I didn't really go back to focusing on the brain until my senior year. So, all of my upper-division electives were in neuroscience and that's when I was like, "Oh, *this* is how I want to apply these things."

Alie: Okay, stupid question. What is the difference between neuroscience, neurology, neurobiology, molecular neurobiology? I feel like if you don't work with brains you're like, "Oh, kind of call it a neuro-something-or-other." What do those different fields mean?

Crystal: Okay, so I am going to take you on a little journey. [*"Storytime."*] I am a first-year graduate student. I have not yet chosen a lab. I'm at Caltech. Every single person that I'm meeting is smarter than me. I am incredibly intimidated and anxious and really, really need to do a good job otherwise I'm going to fail life. And I go into my first meeting with the professor that's going to be my PhD thesis advisor, but I don't know that at the time. And I'm trying to impress him with how smart I am, and I tell him I'm really interested in neurology and I'm really interested in brains and the things that brains do.

And he's like, "I'm going to stop you right there. [*"Imma let you finish"*] If you're interested in neurology, then you should be going to medical school. Oh, we don't do neurology here. *Neuroscience* is the science behind the brain. And we do research on how the brain works, and we get PhDs, and that's the type of science that we can do on the brain here. Are you still interested?"

Alie: [*lower pitch*] Oh my god.

Crystal: And so that is the difference. [*laughs*]

Alie: [*laughs*] Oh, god, I would have had immediate reactive diarrhea and just excused myself from life. I would have been like, "Oooops!"

Crystal: But you know when you're so anxious and your whole fight-or-flight system is engaged, and you're kind of too numb to it, and you're just like, "Okay, take the hit and keep rolling, keep going, keep going. There's nothing you can do about it."

Aside: So what is a neurologist, exactly? They are physicians, medical doctors with MDs and probably stethoscopes – I don't know – who treat neurological diseases and disorders that affect the nerves, spinal cord, and of course, the brain. You can show up in their office

and say, “Please doc, fix me.” That is a neurologist. I honestly don’t know about the stethoscopes, I just made that up, they might not even need ‘em. But you get the general aesthetic.

Alie: And a neuroscientist?

Crystal: Studies the science behind how the brain works and why the brain works. So, you have to have knowledge of some of that stuff. But it's mostly hypothesis-driven investigation.

Alie: Okay, so a brain, what is it? What is this big... is it mostly fat? What is it? Is it proteins? What is it made of?

Crystal: Yes, all those good things. It's all fats, and proteins, and carbohydrates all smushed together into a collection of different types of cells. There's like 80 billion neurons and they're all sort of smushed together, and there's different types of those neurons, those brain cells, and they're clustered together in different areas. And those different areas have specific functions that all have to work together. And that’s sort of what we think of as like the orchestra of the brain as an organ. But that's not even it. [*“But wait there’s more!”*]

There's like a whole other layer of cells, we call them glial cells or astrocytes, that help those neurons to function. So, it's not just neurons but there's a whole other set of support cells, and they're not even really support cells because they're doing really important stuff.

Alie: And what do the astrocytes and glial cells do?

Crystal: They do sooo many things. So, my favorite type of support cell is the cell that creates myelination around electrons. So that's like little wire insulators to help the electric part of the signal go faster down the axon of the neuron. So, if I'm a cell and you’re a cell, I could send my message to you way faster because of the insulation. And that's actually one of the last parts of brain maturation.

So, when we talk about brains not being fully cooked until our mid-20s and we're still developing, one of the last things that happens is that insulation process goes in, in that prefrontal cortex area, which is so important for decision making.

Aside: So glial cells are a support cell. And glial means ‘glue’ because it was thought that glial cells just kind of held all the neurons together, kind of like a bunch of mashed potatoes around a pile of yarn, but they do much more than that, and there are different types that do different things.

We won’t go into all of them, but the astrocytes are starry-shaped, hence ‘astro’, and they give nutrients to neurons, they help repair damage, and oligodendrocytes insulate the neurons in the brain by laying down this fatty cozy padding called myelin, which is like rubber around an electrical cord, or a Snuggie that protects you from live wires.

If you have multiple sclerosis, like my mom, aka our dear Fancy Nancy, who taught you the best insomnia hack ever in the Somnology episode, the immune system of folks with MS likes to eat away at that myelin and cause nerve and signaling troubles.

Just a side note, thank you to all the neuroscientists and neurologists working to find a cure for MS. We appreciate it and I want to interview you about it, please. Now, why is it important for these diva neurons to be so supported and so insulated? What do they look like? What do they do?

Alie: Now, neurons themselves, those are long and have fingers at one end kind of, can you explain what a neuron is?

Crystal: They can be long, they can be short, but the critical parts of the neuron are the cell body, which is where all the good stuff happens, like a normal cell. And the axon, which is like that long wire that connects one end to whatever other cell it wants to talk to. There's projections on each side of the neuron. Those would be considered dendrites, and those dendrites create the connections which we call synapses, that are how cells talk to each other. So, it's like the main parts.

Aside: So, neurons: they're a cell with a sometimes-long axon to reach out to other cells and little fingery dendrites at the end. You may remember the Dendrology episode with Casey Clapp about trees, so just think of those little branches at the end of the neurons. Those are dendrites. They also kind of look like if a bird had a bunch of toes, and then those toes had toes. That's your brain! Okay, so how are all these neurons chit-chatting, gabbing, they're shooting the shit and running the show up there? What are they doing?

Crystal: My favorite part of neuroscience is the fact that neurons use both electricity and chemicals as communication.

Alie: Oooh, tell me about this.

Crystal: So, the really important part of neurons is that there's all of these little gates that are regulating the ions flowing in and out of them. Ions are magnesium, calcium, sodium, chlorine, these are really important, and they're just constantly moving back and forth. But because all of those ions are charged, you get a little electrical field [*zapping*] from each of the different cells. And so, if I wanted to pass a signal to you, it would start as an electrical field that goes all the way down to my axon due to opening and closing, opening and closing, and the ions. But then it gets to the end and I can't transmit electricity to you cause there's a little gap. And so, what does the cell do?

The cell is like, "Okay crap, we have to communicate to the Alie cell. She likes serotonin. We're going to release serotonin into this little gap." And so that's when the electrical signal [*zapping*] gets converted into a chemical signal, [*splat*] which you can read because you speak the serotonin language, because you have little proteins on the ends of you on, like the end of your synapse, and you are catching all of those little serotonin molecules and bring them into you. And when there's enough of them, it generates another electrical signal that you can send.

Alie: Oh my god. How many cells are doing this all the time in our brain lumps?

Crystal: So, I don't know how many cells would be active at a given time, because that really depends on what we're doing. But if you think there's 80 billion neurons and then there's estimated, like, a hundred trillion synapsis, because it's not necessarily one synapse or two synapses per cell. You can have more connections. So, this is a lot.

Alie: Yeah, we're talking the final number is a shit-ton. [*laughs*]

Crystal: Many, many zeros. Yeah.

Alie: Okay. So, neurotransmitters, this is like a chemical messenger that cells are sending to each other?

Crystal: Yeah.

Alie: And what are the main neurotransmitters? I know we hear about dopamine, and serotonin, and maybe norepinephrine, but take me through some of the players here.

Crystal: Yeah. So, I think dopamine is like the media darling [*both laugh*] of the neurotransmitter world. You have a lot of specific chemicals, like the three that you mentioned that are involved in a lot of behaviors, but then there's other types of messengers as well. So, we have small peptides, like we would say oxytocin, which is not necessarily a formal neurotransmitter, but it's really critical in modulating brain function and behavior, for instance.

Aside: Oxytocin, you may have heard, is a neuropeptide – not to be confused with oxycontin, which is an opiate – but oxytocin can promote bonding and feelings of comfort and attachment with partners, members of a group, or with babies. And yes, it does increase when you pet a dog, which is why you probably would not follow around an unfamiliar goose in a park and pick up its poo, but you would for your dog and not think twice. Now, onto more neurotransmitters.

Crystal: We use acetylcholine a lot, so that's a neurotransmitter that I studied because of its relation to nicotine, which I'm sure we'll get to. And acetylcholine is really important because it's the fast-acting neurotransmitter in the brain, so if you need to get a cell to respond right away, acetylcholine might be the way to go. And it's so fast acting that it's used in the body as well to help with muscle contraction.

Alie: Oh my god, is it like the text message of neurotransmitters?

Crystal: Yes!

Alie: Get at me, so just send me a text. [*"Your phone is blowing up."*] And so, acetylcholine, can that do more than just make you happy or alert? Can that send all kinds of messages to you?

Crystal: Yeah, it can. So, if you think, we talked about the brain being groups of different types of cells, and each of those cell groups probably has different layers of cells as well. So, the complexity in the brain is really, really difficult to imagine. Each of those different functional groups of cells, or different parts of the brain, have connections to one, if not many, many others. And they're all talking to each other.

That's why I call it the orchestra because they're all working together. And if you think about each different system, like maybe the string system is dopamine system and the brass section would be your norepinephrine. Everybody sort of is talking to each other, but in different languages. And it might be that I'm a cell that releases acetylcholine, but you don't have any receptors for that. So, you can't see my signal, but somebody else can.

Alie: Did you use that metaphor in your PhD defense? Because I think it slaps, you should have. [*laughs*]

Crystal: I didn't, 'the orchestra of the brain', I'm sure it's not original. [*laughs*]

Alie: I think it's pretty good. I'm going to look it up and I'll tell you if anyone else has used it.

Aside: Okay, so other folks have used this and it turns out because it's a really apt, good analogy. Also, when it came to working on brains, Crystal used data from rodent brains to try to extrapolate what was happening in human brains, including I guess, her own.

Alie: Did you ever have any existential crises when you were like, "My brain is studying brains! Brains on brains on brains!"? Does it ever freak you out?

Crystal: Ah, no. I think there's the Carl Sagan quote like, "We are the way for the universe to know itself." And so, I think that that's kind of how I feel as a neuroscientist.

Alie: Do you ever think about certain reactions you have to life? Like if you're having a down day or an up day, are you ever thinking about your orchestra, like "The horn section's going off right now!"?

Crystal: [*laughs*] Absolutely, yeah, of course.

Alie: Does that help you at all when you're relating to other people thinking, "Okay, well this is not that this person's a jerk, or maybe this person isn't being sad for effect?" Do you think about them as like a concert of chemicals ever?

Crystal: Yeah, I can, that's when I'm rationally thinking and using that prefrontal cortex to try and compose a logical flow around why somebody is behaving the way that they are. But you know, in everyday life it's usually more emotion-driven, reactivity-driven. That's how our brains evolved, is to react to external stimuli, not necessarily to think and problem-solve about them as the first thing.

Because you don't want to be like, "Is it a snake? I'm not sure if it's a snake. I'm going to keep walking towards it until I'm absolutely sure. Ouch. Now I'm dying." Right? [*laughs*] That's not how our brains work. So, I think when I can step back and think rationally, "Why is this person yelling at me?" It is helpful, but I'm human just like everybody else. [*laughs*]

Alie: And that prefrontal cortex that's right behind our forehead, that's the kind of meatier chunk that's evolved more recently?

Crystal: Yeah, that's what we'd like to think of as one of the differentiating parts of human brains versus other animal brains. And I want to make a comment about animal brains in a second. But it's our ability to extrapolate, to use logic and reasoning to come up with creative solutions to problems, to not just react and to think about downstream effects. That's what the prefrontal cortex helps us do.

But what I was going to say, which is one of those mythbusting things… I was like, "I'm going to talk to Alie about neuroscience. What do I want people to know about neuroscience?" The pop culture reference to the lizard brain.

Alie: Yes, yes. Okay, okay, okay. Let's debunk this flimflam.

Crystal: It really bothers me.

Alie: Okay, I was going to ask about it. [*laughs*]

Crystal: Because it's often one used incorrectly. It's usually when people say, "Don't listen to your lizard brain," [*"It's just lizard brain, baby."*] I think what they mean is don't listen to your limbic system, or your midbrain, or the center of your brain in which emotions are generated and relevant.

But I think that quote – and I am blaming Sagan again for this – of there being an 'alligator brain around which everything else is wrapped' was put out there, he meant something even more basal, like your brain stem and the parts of the brain that control respiration, and heartbeat, and those types of really, really basic biological functions. But the fact of the matter is, is that lizards and reptiles actually have something similar to a cortex.

Alie: They do?

Crystal: Yeah, they do. It's nothing like the giant white matter that we have. It's nothing like the big prefrontal cortex that you would see in primates, but it's something that evolves similarly. And when I say evolve, I mean in gestational period. And you see very similar wiring.

Alie: Poor lizards.

Crystal: They're getting a bad rap.

Alie: [*laughs*] Oh no!

Aside: Also, are alligators even lizards? Back in the Saurology episode, I asked lizard scientist Earyn McGee about it.

[*clip from Saurology episode*]

Alie: Stupidest question. Alligators. They are lizards?

Earyn: No.

Alie: No?

Earyn: No.

Alie: Thank you for telling me that. I just realized, I was like, "How big does a lizard get?" Why isn't an alligator lizard? I'm sorry.

Earyn: They're just not. [laughs]

So much horsepucky flimflam debunked all at once.

Alie: So, you mentioned white matter and gray matter. What is the difference?

Crystal: So white matter is basically the wiring. So, when you would say there's a pathway between two brain regions, that's the white matter, it's the connections. And gray matter is like more the cell bodies and the gooier stuff. Put it that way.

Alie: Okay. Is there a skin on it? Is there like an apple skin on a brain?

Crystal: Not the way that you are describing it. But we do have a barrier between the brain and the blood system that provides the glucose and the other nutrients to the brain. And the blood-brain barrier is *critically* important to protecting the brain from all of the things that we're exposed to.

Alie: Can more things leak through that blood-brain barrier than we realize? Or are we finding that out?

Crystal: Probably. We used to think that it was impenetrable and now we know that there's evidence of a lot more transmission through that barrier than we think. But it really does protect us. I mean, think about all of the pharmacologicals that you've ever taken in your life. Some of them can slip through and that's good because we need them to regulate our behavior. And some of them are kept out by that barrier, which is great because they could be potentially toxic.

Alie: Oof. Okay. Well, getting back to neuro-transmitters…

Crystal: [*whispers*] Oh yeah, sorry!

Alie: Oh, no! I wanted to ask if you'd ever touched a brain before, so I had to get us off course!

Crystal: I have touched a human brain before!

Alie: What does it feel like!?

Crystal: It's very delicate. Like, you don't want to make a lot of really fast movements. And they're preserved brains. I haven't like touched a brain of a person. Some neurosurgeons have. I cannot speak to what it's like to touch a live brain, but one that's been preserved in formaldehyde. It's very delicate. It is as gooey as you think.

When you're holding it, if you're anything like me, just there's an oppressive sense of responsibility that happens when you're thinking about the life that brain was really responsible for guiding. I don't hold it for very long. [*laughs*] I held it, I kind of like felt the profound nature of what I was doing, and then I gave it back to the technician.

Alie: What was the setting?

Crystal: What was the setting? Honestly, this was in undergrad at a science fair, and that was just one of the really cool exhibits. Like there were mouse brains, and a human brain, and other brains that you could touch and play with.

Alie: Wouldn't it be crazy if you donated your brain to science and they're like, "You're just going to go to science fairs, recruit some people," you'd be like, "Okay, sweet." Shake some hands. Kiss some babies. Not shake some babies and kiss some hands, I almost said that backwards.

So, neurotransmitters, serotonin, dopamine – stupid question – but what do they do? Do they have different roles in terms of our emotions?

Crystal: They have very, very different roles. Dopamine, I'm going to start with, because everybody loves a good dopamine story, [*"I love it."*] and without dopamine we really wouldn't be motivated to do anything.

So, it's really interesting, in computer science, when they talk about computers having rewards so that you can teach it, like an artificial intelligence system, that "you're on the right track, keep going," we have similar rewards. You're on the right track, keep going. And dopamine is how our brains have been evolved to receive this reward. So, it makes us feel happy, but not really happy, more just like pleasure, like things are good. And anything that you would do that would keep you alive, elicits a dopamine response.

Alie: Really?

Crystal: So, eating, drinking, sleeping, hanging out with your friends, anything that you might enjoy, you get a little bit of a [*magical chimes*] dopamine hit. So it's basically to keep us doing things that are going to keep the human race alive. [*laughs*] Whereas serotonin is more nuanced. It's not just pleasure, but it's mood, and it's sleep, and really helping to modulate the way that those little dopamine hits are interpreted by the larger orchestra, if that makes sense.

Alie: Yeah. And what happens when they get off? Is there not enough to send a signal to the next neuron? Is there too much? And why does it seem like a very slim percentage of people have a good balance? [*laughs*] I feel like… Maybe it's just living in LA or internet culture, but I feel like everyone's like, "Oh yeah, my neurotransmitters are whack." I know mine are.

Crystal: I mean, unfortunately, I want to respond to you philosophically. When we first sequenced the human genome, the lead researcher on that project was the genome that they chose to sequence. Does that mean that he's the most normal genome and every other genome is going to be compared to his? Maybe. It was an arbitrary center for science to pick, right?

Aside: There was the publicly-funded Human Genome Project, and the first public genome came from mostly a single anonymous male donor – I think this would be a sperm donor? – from Buffalo, New York. But then a side, privately-funded genome research project was launched by geneticist J. Craig Venter who later admitted that his DNA was among the first donor pool to be fully sequenced. Tossing his own genetics into a research project was later addressed in the journal *Science* in an article bearing the headline, "Not Wicked, Perhaps, but Tacky".

Crystal: And so, when we say 'off', what is off, really? So, in the mental health profession, it's if you have a difference that's interfering with your ability to perform tasks in your personal or professional life, like your ability to be a part of society, then it's a difference that needs to be treated as abnormal. So, I don't know if we can say that they're necessarily off for us as an individual, but they're definitely off for us as a group of humans that all need to act together. Does that make sense?

Alie: Yeah, yeah.

Crystal: There's definitely differences. And those differences can come from genetics. It can come from environment, it can come from adaptations to trauma, or differences in our early environment as our brains were still developing. There are so many different ways that we can develop differences in the way that our neurotransmitters' systems function.

Alie: And what happens if we have too much dopamine? It seems like the more the merrier!

Crystal: It is the more the merrier, but it's also the way that it is dispensed. You described it in the Addictionology episode as this like sprinkler system. It's the intermittent release of dopamine that keeps us going. If you have too much dopamine, then you're probably not motivated to do anything because you've got everything that you need. So, it's kind of like what do you gift to the person that has everything? Your system is cool, so there's no reason to do anything.

In early experiments around the dopaminergic system, they allowed rodents to just self-administer stimulation to their dopamine whenever they wanted. So, this is basically a too-much dopamine situation because dopamine makes you feel good. So, you're just going to keep saying, "Yes please. Yes please. Yes please." [*"Yes please."*] And it basically interrupted all functions except for sleep, so they just didn't do anything.

But people have probably experienced this before. Like you're in a really good early stage of your relationship; you don't eat, your sleep's kind of disrupted, all you want to do is read your text messages over and over and over again, or check your phone to see if you've got another one. Your normal function is disrupted because you've got dopamine floating around in there at levels that you're totally not used to. And there's probably some oxytocin in there as well, really fucking things up. [*laughs*]

Alie: [*laughs*] Oh my god. Wait. So then, at what point does that decline? Is that like the two-year period of like, "No, I'm over this"?

Crystal: Yeah, I think we get used to it. And then we can sort of mellow out and become more normal. The rats, some of them died because they didn't eat or really do anything because they were just super happy pressing that lever for their dopamine hit. So, don't do that.

Alie: Oh no! Just pathologically fulfilled. [*laughs*]

Aside: Okay side note, I read one article that estimated four years was when dopamine starts to wane, but I really should ask a psychoneuroendocrinologist, or perhaps a

biological anthropologist about it, but if things are starting to feel a little stale with a partner, some researchers think that doing scary or novel things together – like, I dunno, ziplining, or going to haunted houses, or Costco on a Saturday – those things can get those new romance brain juices squirting again.

Alie: What happens if you don't have enough dopamine?

Crystal: If you don't have enough dopamine, it depends on what parts of your system are disrupted, but most of the classical symptoms that we see, for ADHD, or depression, or even anxiety in some cases, usually have to do with disruption of the dopamine system. That's why it gets all the media attention. The classic depression is lower levels of dopamine, which means that you're just not having the same response as someone that doesn't have depression, to your dog or to normal things in your life that would normally make you happy.

You're tired, you're lethargic, there's a lack of motivation, and you just aren't getting pleasure from the tasks that you normally would. So it's like that grayness, that lack of color, everything sort of seems blah, that would be what it would be like to not have enough dopamine in your system.

Alie: And is that because the dopamine isn't being produced at high enough levels or it's just not making the jump between the neurons?

Crystal: That's something that is sort of on an individual basis. But I would say overall, it's probably your system isn't able to produce enough dopamine. So, there's all these little packages of the dopamine chemicals that are sitting at the terminals near the synapse, just ready for the signal like, "Release us! We're ready to go." [*"All systems go."*] And someone that has lower numbers of those little vesicles, those little dopamine packets, even if the cell was like, "Okay, go release all the dopamine that you have!" it's going to be a lower level, less packages of dopamine released than what we would consider to be a normal cell.

Alie: What about serotonin, then? Does serotonin play a big part in depression, and anxiety, and ADHD as well? And all of the other things that all of us have? [*laughs*]

Crystal: Yes, the problem with the orchestra is that you can't just remove one section, right? [*laughs*] They all work together. So yes, serotonin is definitely implicated in pretty much everything, and norepinephrine is implicated in pretty much everything. But it's just a matter of what is the major contribution? So, serotonin and depression, we're used to thinking about SSRIs, which are Selective Serotonin Reuptake Inhibitors, which is the medication that we are giving to people with depression.

And why is that? We want more serotonin to be floating around in that synapse, in that space between the two cells. We want it to be sitting around longer. So that signal to continue elevating your mood is a bigger signal. So, there's usually these little Pac-Mans that live in that space between the two cells that collect all of the leftover molecules and bring them back into the cell. Like, "Okay, we don't need you anymore. So, you're going to come and live back in the cell again." And if we inhibit those little Pac-Man collectors, then you get more chemical in that synapse and then that raises the probability that the next cell is going to have a prolonged signal from that neurotransmitter.

Aside: So, by cockblocking the neurotransmitter gobblers, there will be more in the spaces between neurons to deliver messages. Kind of like if you cancelled a neurotransmitter's Lyft and you just kept him at the party longer. You're like, "Sorry.

What can I say? We love having you around. You're great at conversation, we love the signals you send."

Alie: This is a question that I have had for years, but I feel like I read somewhere that neuroscientists don't really know how antidepressants work?

Crystal: Yeah, no.

Alie: Is that true? [*laughs*]

Crystal: Look, there's so many medications… I'm sorry, big pharma. There's so many medications that we don't actually understand the molecular mechanism for. But if it works and there's the side effects aren't too bad, we're just like, "Put it out there and it'll help people."

Alie: Oh my god. Okay. So, we don't totally know how SSRIs work. We just know that a certain percentage of people, when they take them, are like, "Feelin' better!"

Crystal: We know exactly how they work. We don't know *why* they work. We don't know why keeping the serotonin, or norepinephrine, or the dopamine around in the synapse and increasing the signal leads to the behavioral changes. We can ask those molecular questions. That's a level I like to look at because it's a lot more concrete. We can get answers there.

But the multiple layers of complexity, which cells are getting the attenuated signal and what brain regions are those cells in? Oh, but it's this brain region, but it's only those brain layers of that brain region. And what are those particular active regions doing when they're working in concert? And how does that map to the genetic background of this individual and the external stimulus? And why does that mean that giving this SSRI, four weeks later, this person is willing to get off their couch? We don't know.

Alie: Yeah. I always wondered about the lag time there because that is the toughest. And I know that this is, like, a psychopharmacology question, but that is the toughest. If it's like, "Hey, you're depressed? Take this thing, man. Six weeks, there's a 20% chance you might feel better!" [*laughs*] You've got to have a lot of faith. And lucky for me… well not really lucky for me, I tried a few different medications for anxiety and depression before I found one that worked.

Aside: I've mentioned this in another episode, but I tried a genetic test to see which antianxiety or antidepressants would work better for me and I ended up going with something that was recommended, it was an SNRI, but you should do your own research. I did a ton of reading and decided I didn't have much to lose and I tried a company called GeneSight, which has a sliding scale, it's super affordable, they are not a sponsor. But it helped me out, but your mileage may vary. Anyway, let's move on to Crystal's research on nicotine addiction.

Alie: And what did you learn about how addiction works, having studied the mechanisms behind nicotine?

Crystal: So, for nicotine, it's super crazy. When you're exposing yourself to nicotine, you're actually changing the way that proteins in your brain are expressing. So, they're like, "Oh cool, I really like this. I would like it again, I would like it in a specific way. So, I'm going to change the way that I'm making the proteins in my cells so that they are better able to bind and respond to this drug that I have now been exposed to and know exists in the world."

Alie: And so, what does nicotine do? Does it wedge itself where a different neurotransmitter should be?

Crystal: Yeah, so nicotine looks a lot like acetylcholine. The receptors that bind nicotine also bind acetylcholine. They are called nicotinic acetylcholine receptors. They dominated my life for five years. [*laughs*] But what looks similar to a protein might not actually look similar to us.

Aside: So, acetylcholine is the one that's responsible for muscular contractions. It's super fact-acting and scientists think it may also affect memory and attention. Crystal produced from her purse two molecular models, as one does. She showed me that nicotine is a double-ringed molecule with two nitrogens, and acetylcholine has one nitrogen that's crowded with methyl groups, which are three hydrogens bonded to a carbon.

But in a nutshell, Crystal describes both molecules as having similar friends, aka carbon atoms, that give them kind of an analogous bulk when it comes to fitting in to the same receptors.

Crystal: So, they look similar enough to the receptor that it responds in the same way.

Alie: Got it. So, it's like when you're doing a puzzle and you find a piece that doesn't quite fit but you can jam it in and then it fucks everything else up?

Crystal: Pretty much. It's exactly like that. I should have just said that. That's exactly what's happening. [*laughs*]

Alie: So how do some people who might be predisposed to that kind of addiction, how do they have a better chance at beating it if they want to? If they're like, "I'm done with you vaping, I'm done with you, cigarettes." What do they do?

Crystal: Look, beating addiction is really challenging because you have a learning and memory component and then you have a chemical dependence component, especially for smoking. Because you'll be like, "Oh, I'm done, I don't smoke anymore, I am successful." And then you'll have one drink too many and suddenly you've got a cigarette in your hand and you're not exactly sure why, and there's a chemical reason for that.

But there's also a learning and memory component. You definitely beat your addiction to smoking at work and at home, but you did not beat the addiction to smoking at the club [*"In the club we are all family."*] because you've learned that you have three drinks, then you go outside and you have a smoke. So, it's those behaviors that can really hang up recovery. Nicotine is actually one of the most addictive substances.

Alie: Ugh!

Crystal: I was listening to the Addictionology episode that you did, and yeah, there's a lot of really, really terrible withdrawal symptoms. Like withdrawing from alcohol is potentially lethal, so you need to be careful. We've seen media depictions of withdrawal from heroin, for instance, which is the one where everyone's like, "Oh my god, I'm being attacked by bugs and my skin is itchy. I need to get my skin off." That's awful.

You're not going to get that if you try to quit smoking. But once you go through those really, really awful, terrible withdrawal periods, you have a really good chance of not doing those drugs again. Whereas with nicotine, it can come back really at any time.

Aside: Okay, so what can one doooo?

Alie: Is there any promise when it comes to like meditation, and mindfulness, and breathing exercises? Can you retrain your brain through healthier behaviors at all?

Crystal: Yeah, you can definitely retrain your brain. You can also, through meditation, mindfulness, and cognitive behavioral therapy, reduce the reason that you are smoking at all. So, we see smoking behaviors, especially people that are addicted to nicotine oftentimes are in response to other things. Schizophrenics have a very specific smoking behavior. We think they're trying to self-medicate. Veterans come back, not even with PTSD, but just that have come back from really traumatic experiences. Possibly they're smoking in the characteristic way that they smoke to reduce activity in their amygdala.

Aside: You may remember the amygdala from the two-part Fearology episode. It is a brain nugget that I like to think of as the screaming almond of terror. [*Homer Simpson scream*] So some folks may self-administer nicotine to appease their shrieking almond. Does it solve problems? No, not at all. It only makes life worse. Blame your almond, and then try to outsmart it.

Crystal: There's lots of different indications that could cause somebody to smoke heavily that would make quitting harder.

Alie: Is that it all the same when it comes to anxiety, or depression, or ADHD? Are there any kind of situational triggers that might affect our levels of neurotransmitter?

Crystal: Yeah, that's a problem. We have that learning and memory component. We've learned something is dangerous to us, even if it's not, then our bodies are going to continue to respond to it that way. And you have to retrain. Some people are scared of dogs. Some people are scared of people [*laughs*] or snakes. My mom is terrified of snakes.

Alie: So is my brother-in-law, and he's a six-foot-four heavy metal guitarist with hair down to his waist and if he sees a snake on TV, he's like "Turn it off!" [*laughs*]

Crystal: Yup. My mom is exactly the same way. She gets like the chills and goes like "Ahhhh!" and then she runs out of the room. And so, if she decided that was something that she wanted to learn to not be afraid of, there are ways, through overexposure and other therapeutic methods that I don't know anything about but I know exist, to rewire the brain. Probably that direct signal of snake fear is never going to really go away. But you might be able to add a layer of regulation, like a snake checkpoint, "Okay, I'm going to react in a different way instead of reacting with my fear response."

Alie: And will your neurons form new pathways? Will they make new channels?

Crystal: You are referring to neuroplasticity.

Alie: I did it! [*laughs*]

Crystal: Yes, you did! [*laughs*] Yeah, you can definitely create new connections. We're doing that all the time. If we couldn't do that, we wouldn't be able to learn anything new, and we wouldn't be able to teach babies all the things that they need to learn in order to be competent humans. I mean, I've got to assume that there's some of those out there. [*laughs*]

So yes, through using particular pathways, particular connections in the brain, you can make those connections stronger. You can recruit other connections to make that pathway larger. I like to think of it as like, you start out with a hiking trail that you were told was a trail, and Google Maps doesn't really have it on there, and you need a machete,

and you're kind of like hacking through it. [*"It's a jungle in here"*] But if you walk that trail many, many times it eventually becomes much easier to use. It can eventually become a six-lane superhighway that's very, very fast to go down.

That's the preferred method because our brains are really lazy. They don't want to do new things; they don't want to think about anything. They just want to react because that's how we stay alive. And so, if you can train your brain that taking the path that you want it to take is actually easiest and allows it to be the most lazy, then you can influence the path that it chooses to take without you cognitively having to control it all the time.

Alie: So, practice makes a habit, kind of.

Crystal: Yes.

Alie: Oh, that's good to know. I have a gym membership that I have not used this month and I'm like, "I should make that a habit." [*laughs*] Okay, can I ask you questions from patrons?

Crystal: Yeah.

Alie: Okay.

Aside: Now, before we dive into the questions you submitted on Patreon, a few words about sponsors who make it possible for *Ologies* to donate to a different cause each week. Crystal is once again an IF/THEN STEM ambassador for the Lyda Hill Foundation, which works with a few nonprofits, so that's already amazing, but she chose her donation to go to The Geena Davis Institute on Gender in Media, founded by Geena Davis who has said: "What our children see sets the framework for what they believe is possible."

The Geena Davis Institute on Gender in Media is the only research-based organization working from within the entertainment industry to improve gender balance, to reduce stereotyping, and to create diverse female characters in entertainment and media for kids 11 and under. So, thanks Dr. Dilworth, a donation will go to them, and that is made possible by some sponsors of the show which you may hear about now.

[*Ad Break*]

Okay let's get to your molecular neurobiology questions, shall we?

Alie: I have questions from Patrons. And also, this definitely warrants a psychopharmacology follow up.

Crystal: Yes! Absolutely. I think that given all of the response and all the questions, you definitely need a psychiatrist on, like psychiatrist-ologist. [*laughs*]

Alie: [*super gently like a pharma ad*] This podcast is not intended to diagnose or treat.

Okay. A lot of folks had questions about this. Jack, Jennifer Alvarez, Elize, Anna Thompson, Grace Lauren, Rachael Thompson Panik, Donald MacGregor, Pandora II, Rebecca Lynn Weisselberg, Juliana, Aria Salan, Penny Lee and GenericNikki, all asked about ADHD. Jack said very, very plainly: I have ADHD. What exactly is wrong with my neurotransmitters? [*laughs*]

So yeah all those folks and I'm curious about it too, because sometimes I'm like, "Do I have ADHD? Maybe I do. I don't know."

Crystal: So classically ADHD is described as a disruption of the dopamine system. But I think that there's a lot to be said for the involvement of other neurotransmitters. We like to talk

about serotonin, but I actually think that norepinephrine is more relevant to ADHD specifically because norepinephrine is responsible for attention and alertness.

So, when your norepinephrine system is working, you're awake and you're alert. When it's really activated, it's telling you there is something you need to pay attention to right now and be very awake and maybe run. [*"You never know when you may have to jam."*]

And so, the attention needed to perform and complete a task is associated with norepinephrine cycling. So, there's a lot and then there's not so much. And then there's a lot, and then there's not so much; it's like just enough to kind of keep you on task and motivated. And that motivation also comes from dopamine.

But when it's tonic, when it's at an 'okay' level and just kind of like plugging along, there's really no reason for you to maintain attention because it's not telling you to do so. And so, you're like, "Huh, I want to feel good about something." And that's when you go looking in search of dopamine, because dopamine in ADHD people is a little bit lower, so they're constantly looking for stimulus that's going to pop that up so that they can feel good.

Alie: Oh wow. Why do you think so many people have ADHD or are getting diagnosed with it? I know so many people who are diagnosed later in life. Why do you think it's so prevalent?

Crystal: I don't have a good answer for that. There's a lot of discussions people have about our technology training us to have ADHD, about the fact that we have declared it a thing, kind of promoting the diagnosis of it and not being able to compare to 20 years ago to know if it really is increasing in prevalence because we've just started diagnosing it. This is an argument that is used for a lot of things.

So, I don't really have a good answer for you, but I think that it might be that we're just becoming aware of our differences, and ADHD is a way for us to label those differences. Sometimes that's a good thing, but it isn't always. I know that there's a lot of really smart, really, really energetic and curious kids that get diagnosed with ADHD. And it might just be because we have a hard time handling that level of energy and curiosity.

Aside: Okay quick aside, I looked this up and adult ADHD diagnoses rose 123% between 2007 and 2016, and the prevalence of ADHD in kids went up 26%. Many researchers think it's just awareness of symptoms that's driving more people to get evaluated for it. I know so many folks with ADHD, some diagnosed in adulthood, that just wish they knew sooner.

Also, I just want to tell you, in the process of writing this aside, Jarrett was typing really loudly on his keyboard and I got distracted so I went and got the headphones that I'd lost for about six months but just found, and then in the process I wandered into the kitchen to make a matcha latte, and then I sat back down but I got an email, so I ended up checking my credit score for a while, anyway. Yes, ADHD awareness it is up! More people might have it than they realize.

Alie: And what about treatment for ADHD? I know like amphetamine salts are sometimes prescribed. What is that doing to the dopamine, or what is helping to level out?

Crystal: So, when I learned about this, which was a while ago, we were talking about the use of amphetamines in the concept of homeostasis. So, our entire system is designed to keep us in a certain region of activity, and alertness, and awakeness. We want to maintain that homeostasis, because when we get thrown out of it we get disease and a lot of terrible things. And so, when you take an ADHD brain and you give it amphetamine, you're

releasing a lot of norepinephrine, you're releasing a lot of adrenaline, you're releasing a lot of dopamine and that's like throwing you way up.

So, in a way it's compensating for the things that you might not have enough of, but it's also telling your body, "Hey, as a complete system, you've got to pay attention to what's happening here because something has gone crazy," and it's forcing your system to level you out. If you don't have those discrepancies though, a lower level of dopamine, and you take an amphetamine, then you've completely thrown your entire system into a whole other solar system, which for some people, is good. That's why we love cocaine because we love a lot of dopamine and we want that to hang around for a while. But usually ends up in really, really bad results.

Alie: Right? But if you are already low on the dopamine, then it just levels you off to where maybe a neurotypical person might be? Oh, that's fascinating.

Aside: So, the first line of therapy for ADHD is usually medication. Why is that? Well, it works, in up to 80% of folks suffering with ADHD, if the dosage is right. But the best strategy, doctors say, is combining strategies. Exercise, some supplements like fish oil and magnesium have been shown in some studies to improve symptoms, and being around nature every day can also be effective. Either way, there's no shame in the ADHD game: it's super common, and there are treatments out there. And yes, I want to do a whoooole episode on this. Besides, everyone wakes up and pours themselves a piping hot cup of stimulants anyway, right?

Crystal: One of the interesting things about homeostasis is that it's something that our body does naturally and it doesn't necessarily have to be drug related. Although there's a really great story about homeostasis and coffee. So, if you go through the same morning routine, when you wake up, and you go down, you're about to press the button on your coffee maker, and the sound of the coffee maker and the sound of the coffee going into the pot or the cup. Your body knows "I'm about to get some caffeine" so it will depress its system in anticipation of the stimulation from caffeine.

That's why replacing your coffee with decaf is a really terrible trick to play on people because you'll actually get more depressed than you would otherwise, because your body has depressed the system waiting for the stimulant and then it has not gotten it.

Alie: Oh nooooo! [*laughs*] Fuck, that sucks.

Crystal: So be really careful with your routine.

Alie: Oh my god. [*"I still say we use the routine we have."*] So, caffeine binds to the thing that makes you sleepy? It takes the place?

Crystal: So, caffeine interacts with adenosine receptors, and the adenosine receptors are open and waiting for the adenosine to come, and it comes and it binds them. And if enough adenosine binds enough of the receptors, then it's like, "Okay, we're sleepy now. We're going to go to bed." But the caffeine comes in and sits in that binding site and prevents the adenosine from binding the receptor, but doesn't activate them, so the adenosine can't get in. And the receptor's waiting for a signal that never comes. The caffeine is like, "Haha! You are awake now forever!" [*laughs*]

Aside: So yes, caffeine, it swoops in and takes the seat of the sleepy chemical like musical chairs and blocks the snoozy feelings. But what if you are staring at the ceiling and not even the Fancy Nancy trick – of thinking of a category like fruits or cities or *Star*

Wars characters and then going down the alphabet thinking of things in that category that start with each letter – is working?

Alie: Is it best it gradually taper off caffeine? Like if you need to?

Crystal: If you needed to? Why would you stop drinking coffee? I don't understand the question. [*laughs*]

Alie: [*laughs*] She says with a coffee cup.

Crystal: I don't know. I don't want to do that.

Alie: Okay. A lot of people had questions about the genetic levels of neurotransmitters like Radleigh, Joe Porfido, Corrie Navis, Kynley Wallace, Andrea, essentially asked, you know, anxiety, depression; hereditary, contagious? Radleigh asked: Are imbalances in neurotransmitters more likely due to genetics or environment? Speaking as someone with a whole slew of mental illnesses and addictive behaviors in my family, including myself.

And Radleigh, you're not alone. I feel like most of us are probably in the same basket.

Crystal: Going into Thanksgiving, everybody's going to know that they're in a family of nuts. Absolutely. All of us.

Alie: We all are.

Crystal: There's so many ways that neurotransmitter levels can be affected. Definitely genetics is one of them. Definitely environment is another, and things that we're temporarily going through can influence it as well. So, if you've just experienced a traumatic loss, you are going to have differences in your neurotransmitter release, but that is temporary and it will eventually go back to what for you is a normal level and you're able to cope.

But some people that have genetic differences, what does that even mean? It could mean we produce different amounts of neurotransmitter. It could mean that our receptors have different responses to those neurotransmitters than a neurotypical response. There's so many different ways that the amount or the reaction to a neurotransmitter can be affected by genetics or by environment. So, the answer is yes. Yes. That was a very long yes answer.

Aside: So, genetics can influence your neurotransmitter levels for sure, but before you blame your parents for everything: a whole bunch of factors are at play. So, it's not you, Fancy Nancy. It's me. Or Dad. Or how much caffeine I drink. Or maybe jet lag. Or the fact that I haven't been to the gym in a month. Anyway.

Alie: What about SSRIs versus SNRIs? I know Aurora, Heather Gentry, Gracie Zecha, Leanna Shuster, Rachel Polivka and Amelia H. all wanted to know: Do we know why different SSRIs and SNRIs have different effects on people? Amelia H. wanted to know: Is it just the molecular structure? Heather Gentry is a first-time question-asker, so is Gracie Zecha and they both kind of asked about increasing numbers of atypical antidepressants, and if the serotonin and depression model is not correct, if it's bigger than that.

Crystal: It's definitely bigger than that. It's *definitely* bigger than that. Especially when you're talking about the interplay between depression and anxiety. And that's what I think of when I think of a combination of SSRIs and SNRIs. So, we're still talking about reuptake inhibitors. We're still talking about the little molecules that go around collecting the neurotransmitters, and shoving them back into the cell that they originated from, and

waiting for the next opportunity to release them, and inhibiting this process. Keeping those neurotransmitters in the synapse longer so that you get a more prolonged signal.

Now we're talking about changing the amount of serotonin and norepinephrine and titrating those differences. That's why a lot of people have to try multiple different combinations of drugs until they find the one that works for them, because their problem might be more serotonin or less serotonin, it might be more about norepinephrine. And if it's anxiety related, it probably is or less.

Alie: Really? Ah, I wonder if that's why SSRIs didn't do much for me, but as a person with generalized anxiety disorder, thanks very much, an SNRI was helpful. What is happening with the norepinephrine when it comes to anxiety? Is it going off?

Crystal: Oh, yeah. I mean, like I was saying, norepinephrine is keeping you awake and it's telling you what to focus on. So, with generalized anxiety disorder, not only are you awake, but you're constantly having to focus on all the things that are chasing you. Your attention is on all the things that could potentially kill you because your brain is trying to keep you alive. [*feigning panic*] But it thinks that everything is trying to kill you, so you have to pay attention to everything. And then there's all the things and it gets really overwhelming because everything is trying to kill you and it's like living in Australia. [*laughs*] This is like a terrible cycle for brains to get into.

Aside: Australia: [*attempted Australian accent*] the land of sharks and snakes and spidahs and angry kangaroos. I guess an angry Kangaroo2, who gives you just one star. Oh look, Kangaroo2, I said your name again and you loved it!

Alie: I feel like perhaps you're very empathetic to this particular problem. [*laughs*]

Crystal: [*laughs*] It might be that I have experienced that before.

Alie: Does an SNRI… What exactly is it doing to norepinephrine if it's a selective norepinephrine reuptake inhibitor? Is it good to have more norepinephrine between the cells?

Crystal: Yes, it can be, but it depends on the comparison levels to the other neurotransmitters. So, you're trying to balance dopamine, serotonin, norepinephrine, and get that right cocktail so that you get a harmony instead of a discordant dysfunction, if that makes sense.

Alie: That does make sense. I didn't realize that SNRIs and anxiety could be a good link; I always thought, "If I've got anxiety, why do I want more goddamn norepinephrine in my synapses?!" That was me screaming at my own brain. [*laughs*]

Crystal: [*laughs*] Yes.

Aside: So yes, SNRI affects both the norepinephrine and the serotonin and it's the balance that can be helpful, although the first few weeks on an SNRI can be rocky as hell and more stressy as your brain adjusts and *then* becomes more chill. My brain asked me to tell your brain that as a heads up.

Alie: Nikki, first-time question-asker, asked: Is the dopamine pathway activated when you eat an Oreo while studying? Like it would be when you smoke a cigarette?

What is that Oreo question?

Crystal: Okay, so I'm going to assume that the reason we're talking about Oreos is because there was a paper that showed that mice prefer Oreos to cocaine, and then it was used in mainstream media to promote many popular but scientifically irrelevant headlines like

'sugar is more addictive than cocaine' and a bunch of other things. So, I'm just going to substitute Oreo for Parmesan Goldfish, which is what I eat when I'm studying. And yeah, they're very, very different things.

So, we were talking about sugar and carbohydrates and feeding your brain in a certain way. There's definitely dopamine release when you're eating food because that's one of the things that are going to keep you alive and that's what dopamine is there for. Have we gotten this point enough? I'm not sure. Let me reiterate. Dopamine is released when you encounter things that keep you alive. The nicotine? Completely different. Nicotine is a cognitive enhancer, so it's probably helping your prefrontal cortex function and it's shown to help decrease anxiety. So, it's probably interacting in your amygdala to reduce stress and facilitating better studying.

Aside: Side note, just google Oreo+cocaine. That study is everywhere and was cited by every news outlet in the known universe. A professor who worked on the study stated in a 2013 press release that he "Hadn't touched an Oreo since the experiment," but it's unclear if that's because of their addictive implications or just because watching rats pick apart any food with their tiny clawed feet for years on end tends to tarnish its appeal. Now, speaking of full little bellies...

Alie: So, this is a good segue to the gut biome and Libbye Miller, Brigid, Emma Hoch-Schneider, Kaybeemaybee, Isabel, Christine Hottinger, Kira Gowan, MacKenzie Campbell, GenericNikki, Elize, Eileen, Steffen Williams, Jen Athanas, and Michelle Lee all asked about how many of our neurotransmitters are made in our guts. And do we have any leads yet on good foods for good neurotransmitters? Christine Hottinger asked: How do I eat myself happy?

Crystal: [*laughs*] Well, actually, there's been a lot of recent studies on the microbiome and the influence of food on mood. And we've always known, even before we identified that the microbiome was a thing, that diet had a huge impact on mood. And of course, we have always talked about blood sugar activity and how crashing after a lot of sugar can influence our mood and make us depressed.

But what I think that we're really asking about here is the chemicals that are released by the gut biome. One of those chemicals has been shown to be serotonin, which is like one of the really, really big findings in that field and in the neuroscience field too because we thought, "Oh, neurotransmitters are synthesized in the neurons." But yeah, I guess not always. I guess there can be serotonin and potentially other neurotransmitters just kind of floating around in your bloodstream. [*"Fancy meeting you here."*]

Does it influence mood? Yes, probably. Are there particular superfoods that you can eat to raise your serotonin? Probably not. But what we eat definitely does influence the different types of micro-organisms and the ratios of those micro-organisms in our gut. So, I can't tell her what to eat to make herself happy, but if she finds a particular type of diet that does make her happy, it's not all placebo.

Alie: Right, it's not just in her head, it's in her guts!

Crystal: Yeah, exactly.

Alie: I think that's so bananas that so much serotonin is made in our simmering poo tubes. Who knew? Who knew!?

Crystal: It is crazy. And I think about that too sometimes when I'm on a particular binge of very, very unhealthy food and I'm like, "How long am I going to have to eat healthy to readjust the ratios of gut bacteria?" because I know that I'm feeding it a certain type of sugar, or just a lot of sugar; that there's going to be overgrowth of one population in my microbiome. And I'm, like, apologizing to the potentially more valuable and rarer bacteria in my gut. Like, "I'm sorry. I know I'm overfeeding you."

Alie: I feel like if you like SimCity, you'll love the gut biome.

Crystal: Yes. That's so true.

Alie: It's like real-world consequences.

Aside: For more on this topic, see last November's Microbiology episode with Dr. Elaine Hsiao, who herself says she tries to eat a varied diet. Give your microbes natural foods that would help them thrive, i.e., not Oreos. Or cocaine. Which was in soft drinks until the early 1900s, which is just bananas. Speaking of guzzling up...

Alie: A few people ask about alcohol. Lindsey Defalco, Amelia H., Anna Thompson, and Emmanuel Sanchez asked: What's going on in the brain with different drugs and controlled substances like alcohol? And Amelia H. wants to know: Why is alcoholism an inheritable trait?

Crystal: Oh, alcohol is so interesting because there's no alcohol receptor. It doesn't act on a particular receptor the way that I was describing acetylcholine and nicotine. It sort of cozies up to the receptor and is, like, soft influence. We would call it allosteric modulation. So, it doesn't bind to the receptor and cause the receptor to do anything, but it affects the way that the receptor responds to the molecules that it's really supposed to be talking to. So, it can make it open easier so it needs less drug or less neurotransmitter before it responds. So, it's very sneaky and insidious in terms of the activity in the brain.

Alcohol, as anyone that has been drunk knows, affects your motor control and your muscles as well. So, it has more than just brain effects. But in the brain, it acts in that allosteric, sort of soft power, kind of a way.

Alie: And does it kind of mess with frontal cortex activity? In terms of loss of inhibition and maybe less control over emotion?

Crystal: Yeah, it disinhibits that inhibitory neurons. It's like the act of alcohol is a double negative. So, it works on your inhibitory neurons.

Alie: Oh, okay.

Crystal: So, they're normally like, "I'm inhibiting and I'm doing my job" and then alcohol is like, "Take a break, you'll be okay."

Aside: Crystal says that alcohol affects dopamine, serotonin, GABA – which is a neurotransmitter that helps maintain calm – and glutamate pathways, which affect memory. But just as your college roommate may have just lived for Friday Jager shots and you've never finished a beer; different people have different genetics that influence how receptors respond to alcohol. But the main point is: it doesn't have to affect just dopamine to become addictive and scientists are still figuring out how it all works. Neuroscience: it's compulkayted. Who knew? All of us. Literally all of us. On the topic of substances...

Alie: A bunch of people did ask about recreational drugs. Jess Bauzá de García, Rebekah Landry, Joe Porfido, Jimena Alonso, Kevin List, James Beaulieu, Cassie, Kari Brigham, all asked:

Hey, what's going on with recreational or ritualistic drugs like ayahuasca? Kevin List asks: What are your thoughts on micro-dosing for mental health issues like depression? And Jess wanted to know: Flimflam or not, is psilocybin an effective treatment for medication-resistant psychiatric conditions? So, what's going on with magical things?

Crystal: Magical things are as if one aspect of the orchestra completely went on steroids – if you showed up and there was like 37 cellos [*classical music with several cellos*] and, like, four of all of the other instruments – whatever that would sound like, that's kind of what recreational drugs do. They put things completely out of balance and we experience a new reality through that lens. Brains are basically making a guess at our realities anyway, and so we experience a brain's best guess at what is actually happening.

Aside: Right now, your whole reality is just a picture that your brain has painted based on what it's sensing. How weird is that? What is even real!?

Crystal: And so, when the predictions of the brain or the way that the system that is the brain tries to anticipate or interpret these completely out-of-whack situations, that's when we get the fun that is recreational drugs.

Alie: What happens with psychedelics? Is it a particular neurotransmitter that is just going off?

Crystal: A lot of them are acting on the serotonin system. Because serotonin is a modulation. It's more global than a lot of the other neurotransmitters. And so, when you get a bunch of serotonin dumped into the system, you have a lot of different brain regions that are all trying to cope with life.

Alie: Is that why people will take supplements like 5-HTP after they do molly or something like that?

Crystal: Yeah, you can deplete the amount… because your brain is synthesizing those molecules there's a limited number of them. If you think about a factory production line, it only goes so fast. So, you can only produce so many toys, or so many cars, or you can only produce so many molecules of your particular neurotransmitter.

So if you have taken molly or one of these recreational drugs that has dumped a whole bunch of neurotransmitter into your brain and you've been backstroking through those happy molecules for a while, [*"Aaah the water's great!"*] and when it's time for your brain to go back to normal because it's no longer getting those signals, it has nothing left to give, literally. So giving it some precursors for the molecules that it needs to replenish is sort of a way of helping it get back to normal because you're skipping a few steps in the assembly line.

Alie: Got it. So, you're not left high and dry.

Aside: Literally high, and actually dry of the good brain juices. Now this next topic was on the minds of patrons Giannina Rokvic, Graham Tattersall, Maria, GenericNikki, Sydney van Zyl, Dawn Ewald, first-time mindfulness-question-asker Jennifer Tran, and first-time question-asker Ashley Beatty, who wondered about the impact of meditation on anxiety and depression specifically.

Alie: And now what about meditation, yoga, things like that? Do you ever use any of it? Do you feel like you should be using it?

Crystal: I think that it's definitely a good place to start. I'm one of those people that is like, "Why would you pay for a gym membership if you could just go outside and run?" And then I

just stay inside and watch Netflix the entire time. And that's kind of how I feel about mindfulness. It's something that you can do quite easily. You know there's positive effects. There's been scientific papers that have shown that there are positive effects of meditation practice, of mindfulness practice that really does help quiet some of the overactivity and the amygdala that we see in Western society for instance. So why not do it? I don't do it. I probably should. It would definitely help me a lot. So, do as I say, not as I do.

Alie: Okay, doctor. [*laughs*] What is your least favorite thing about neuroscience, about brains, or about your life as Dr. Brain, essentially, on TV and all over the world?

Crystal: Neuroscience is really hard to do without actually touching the tissue that you're trying to study. And so, we use a lot of model brains in order to learn the things that we learn, which is really challenging because even the information that I was sharing with you today, we know this to be true for mice and rats, and we assume that it is also true for humans to the best of our possible ability. But as far as I know, we aren't able to do the same types of experiments on humans. So, a lot of what we know is inferred.

Alie: Right. Would you ever donate your brain to science? What do you think?

Crystal: I think I would be a terrible test subject. Like I'm always the outlier. I never feel that I am a good representation of the mathematical average of a human anything. So, I feel like my brain would give wrong data or not accurate data. [*laughs*] And I think that actually speaks to the earlier question about why don't we know how these things work? And it's like, we can know things pretty accurately for a particular breed of mouse or particular breed of rat because they're all exactly the same, they're all clones of each other. So, it's really easy for us to know what's going on there. We can't clone humans, we can't do research on humans. So, all of the genetic background, all of the environmental differences, all of those things mean that we're really just kind of guessing at what's going to work for the average population.

Alie: Isn't it kind of crazy? We just have clones, like animal clones running around? Isn't that kind of weird? Does that ever creep you out?

Crystal: It doesn't really creep me out, but I guess because I mostly work with bacteria and mice. And it's easy to not see them as necessarily having personalities. But I never raised mice. I was the beneficiary of people that did mouse experiments, but I never actually had a colony of mice that I was raising. And I know that neuroscientists that do work directly with live behaving animals would absolutely tell me that I'm crazy, that they have personalities and differences even though genetically they're the same.

Alie: Wow. Did you hear that Barbra Streisand cloned her dog and she thought she was getting one and they're like, “We've got four.” And she's like, “Fuck.” She had to give them away to her assistant’s daughter or something. She's like, “I didn't think I'd get four of them.”

Aside: It’s true, Barbra Streisand missed her dog Samantha so much that she had four more made from a swab of her cheek. The runt of that litter, sadly, died. But she kept two of them and the third she says, [*radio filter*] “The 13-year-old daughter of my A&R man bonded with one of the clones, so I gave them that puppy.” So, there you go. Clones: they’re all over the place and it’s just like, not a biggie. Shrug.

Alie: What's your favorite thing about your job, or neuroscience, or the brain?

Crystal: I mean, I think that we are inherently selfish and that we really like to know things about ourselves. And neuroscience is my way of trying to understand the human condition. Brains are really intense, and they want everything to have meaning, and they will ascribe meaning to things that really there is no purpose to. So, I think that that's probably what I'm trying to do with my meaningless life, is to figure out, "Why humans? Why me?"

Alie: That's the best title for a biography: *Why Humans? Why Us?*

Aside: As for neuroscience movies, Crystal says pretty much none of them get it right, like none, and they all try to make things way too spiritual. That 'using only 10% of your brain thing' is a big, hairy, smelly myth and that the Scarlett Johannsen vehicle *Lucy* was wall-to-wall flimflam and egregious. She thinks writers and directors should focus on the real neuroscience because it's bananas and mysterious enough.

Crystal: Reality is stranger than fiction. Let's figure out what's actually going on and how can we tell that story in an epic but accurate way, because it really is enough to blow your mind.

Alie: Your *actual* mind. Thank you so much, Dr. Dilworth.

Crystal: Thank you for having me.

Alie: Of course.

So now that you are fully enchanted by the knowledge of Dr. Brain, Crystal Dilworth, you can head to CrystalDilworth.com for links to her social media and her LinkedIn page. There's a link to that in the show notes of this episode. And special thank you Casey Handmer for making sure she got that domain name. That's CrystalDilworth.com. So go there and follow her on Twitter and on LinkedIn and on Instagram. You can also check her out on *Mission Unstoppable* on CBS every Saturday. Links will be up at AlieWard.com/Ologies/MolecularNeurobiology, including to the charity supported and to the sponsors making that possible.

We are @Ologies on Instagram and Twitter; I'm @AlieWard on both. If you have a picture of yourself in merch, on Merch Mondays we repost it so just hashtag #OlogiesMerch. I'm also on CBS every Saturday morning on *Innovation Nation* with Mo Rocca, and I have my own science show on CW called *Did I Mention Invention*, which is on Saturday or Sunday depending on where you live in the country. Thank you to Erin Talbert and of course Hannah Lipow for adminning the Facebook Ologies Podcast group and for being amazing people. Special love going out to the brain of Hannah Lipow this week. Also, thank you to Boni Dutch and Shannon Feltus of the comedy podcast *You Are That* for handling merch at OlogiesMerch.com and also for being wonderful.

Transcripts and bleeped episodes are at AlieWard.com/Ologies-Extras. There will be a link in the show notes. Thank you to all the *Ologies* transcribers in the Ologies Transcribers Facebook group and Emily White for working on those. Assistant editing was done by Jarrett Sleeper of Mindjam media and the mental health podcast, *My Good Bad Brain*; he talks about ADHD a lot on that, so check out *My Good Bad Brain.*

And thanks, as always, to the brain that stitches all these pieces together each week, Steven Ray Morris, who also hosts *The Purrrcast* about cats and the dino podcast, *See Jurassic Right*. The theme music was written and performed by Nick Thorburn of the band Islands. And that cello music you heard was The Cello Song by The Piano Guys, and they're on YouTube.

Now if you stick around until the end of the episode you know I tell you a secret. This week's secret is that I had a nightmare that I was getting shot into space, and I was like, "Oh, I'm an astronaut, I

guess," and beforehand they had to weigh everything that went into or came out of my body and let's just say it was a little too close for comfort in my dream, and I woke up so relieved that I didn't have to pee in a bucket in front of anyone.

Also, another secret: I actually do keep candles in my wallet because honestly it happens so often, it's someone's birthday and being able to shove a candle in a piece of toast or a Snickers, it's such a day-maker. They don't take up much room, I just put 2 or 3 wrapped up in a little piece of tinfoil and I wedge 'em in my wallet. I'm pretty sure it looks like something illegal. But I promise, keep a few birthday candles in your bag and you're going to use them sooner than you think. They come in handy all the time. Also does NASA even make you pee in buckets, or did I make that up in a dream? Let me know.

Okay berbye.

Transcribed by Saira Manns, your anxious Australian friend who's been singing the praises of store-bought neurotransmitters since 2014.

Edits by Kaydee Coast, who reminds you don't lick toads, check your crevices, milk your thumbs, and to never apologize for asking questions. Kthxbi.

Some links you may enjoy:

J. Craig Venton being a DNA donor: "Not wicked perhaps, but tacky"

The brain is an orchestra

Neuroglial cells: not just mashed potatoes

Roles of glial cells

The Paint Guys' "The Cello Song"

Oxytocin

Genesight tests efficacy

Love, attachment, relationships and dopamine

Nicotine molecule

Wonderful video about acetylcholine

Rising prevalence of ADHD

SNRIs and anxiety

ADHD treatments

Fish oil and ADHD?

Dopamine and romantic love

Cocaine, cookies and rats

Researcher's Oreo aversion

Non-pharma interventions on serotonin

Alcohol and neurotransmitters

Is booze a depressant?

Caffeine and ADHD

Barbra's cloned doggos

For comments and enquiries on this or other transcripts, please contact OlogiteEmily@gmail.com