11| The Human Microbiome and Mental Illness: The Gut-Brain Axis – With Dr. Tanya Nguyen

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Tanya Nguyen, Ryan Van Patten, John Bellone

Intro Music 00:00

Ryan Van Patten 00:17
Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior. I'm Ryan Van Patten...

John Bellone 00:24

...and I'm John Bellone. We'd like to wish everyone a very happy new year. Today's episode is a conversation with Dr. Tanya Nguyen, an Assistant Professor of Psychiatry at the University of California, San Diego. Tanya is very active both clinically and scientifically, and she is currently in the process of writing an NIH K award on the topic of the gut microbiome in schizophrenia. Ryan and I both find this topic to be really interesting. So this episode focuses on the human microbiome's relationship to cognition and mental illness.

Ryan Van Patten 01:01

Yeah, I think that the surge of empirical work in the microbiome that has been released in the last few years is both exciting and fascinating. We're learning a great deal about the functioning of the microbiome in the human body. I know that, as a kid, my mom would use the words bacteria and germs interchangeably to refer to these disease-causing pathogens and this really reflected a society-wide association between the idea of bacteria and the fear of an infection and illness. Fortunately, in more recent years, our eyes have started to become open to the fact that, although some microorganisms do cause disease, many are actually essential for our health and wellness.

The microbiome is a complex, multifaceted biological network that operates synergistically with our own body systems. Researchers are just now scratching the surface on its importance to our overall well being. Still, you may be wondering how all this relates to neuropsychology, and it's a legitimate question. First, I want to emphasize that John and I want NavNeuro to explore both topics that are right in the wheelhouse of neuropsychologists and areas that are more on the outskirts of the field. If neuropsychologists only spent time learning and thinking about ADHD, concussions, and dementia, we would be very narrow minded and we would miss important aspects of our patients' functioning. I think that we benefit a lot from having broad knowledge in psychology, biology, neuroscience and other related fields, which allows us to more effectively do research and treat a wide range of patients with a variety of brain diseases.

So our goal in this episode is to draw a roadmap between the microbiome, which resides primarily in the GI tract, and mental and cognitive disorders, which result from brain dysfunction. We hope to provide a compelling argument for why brain scientists such as neuropsychologists should be interested in these bacteria residing in the gut, rather than leaving this topic for biologists, nutritionists and gastroenterologists. So, now, we give you Tanya Nguyen.

Transition Music 03:16

John Bellone 03:25
Okay, so we're here with Tanya. Tanya, thanks so much for joining us.

Tanya Nguyen 03:29
Thanks for having me.

John Bellone 03:30
So why don't we just launch it off. Do you mind giving us a very brief overview of what the human microbiome is?

Tanya Nguyen 03:38
Sure. So the human microbiome is a dynamic ecological community of microorganisms and their genes that inhabit the human body. This includes mainly bacteria, but also archaea, microbial eukaryotes, fungi, and viruses. Then the metagenome is all of the genes and genetic material that's present in the microbiome as well. So the human metagenome consists of both the human genome, as contained in our DNA, as well as the genes associated with all of our microbiomes.

John Bellone 04:11
So it's really a diverse population of different bacteria and fungi and things like that.

Tanya Nguyen 04:15
Yes.

John Bellone 04:15
Okay. And maybe it's helpful just right off the bat to throw out a few stats that show the scope and the importance of the human microbiome. When I first started learning about this, I was really surprised to find that, on average, we harbor at least as many bacteria as our own human cells. So there are trillions of things living on and inside us that aren't our own cells. Hopefully, we don't have anyone with germophobia in our audience, that would be a terrifying realization. [laughs] But the microorganisms reside all over the human body, and the large intestine actually has the greatest microbial mass. Is that right?

Tanya Nguyen 04:52
Yes, that's correct.

John Bellone 04:53
Perfect. I've read that up to 20 million total unique genes make up that metagenome that you had mentioned. That's compared to just 20,000 genes in the human genome. So they outnumber our genes 100 to one. That's pretty surprising to find out.

Tanya Nguyen 05:13
Yeah, we are actually more bacteria than we are human, by those stats at least. [laughs]

Ryan Van Patten 05:18
[laughs]

John Bellone 05:20
I'm curious, why is the human microbiome such a popular topic of study right now? Why didn't we start studying it a long time ago?

Ryan Van Patten 05:28
If I could jump in. I'm going to give you my impression as to why that might be and get your feedback. In my mind, I'm thinking about technological advances that have happened in the past few decades and even more recent years. Something like Moore's law comes to mind - these exponential increases in computing power that we've had. So Moore's law being the idea that every two years, computing power, the ability of transistors to process data, doubles. And so that allows us statistically much more horsepower, right? When we think about the microbiome - anytime you have a microbiome data set, it's going to have a lot of data, right? Because there are so many microorganisms inside us. So is that the main reason why research has flourished in this area? Or are there other other reasons as well?

Tanya Nguyen 06:17
I think you hit the nail on the head. I think for centuries, decades, scientists and physicians have observed this link between the gut and the central nervous systems. There have even been publications that date as far back as the late 1800s and early 1900s suggesting that intestinal health was related to mental health and that somehow microbial manipulation could positively influence mental health. But

for all of those years, the importance of the human microbiome was elusive because of these technological challenges in studying unculturable microorganisms. So it's with the advent of these high throughput sequencing methods that we've been able to really characterize the rich and diverse ecosystem that resides in our gut. And then further, the cost of these methodologies has decreased dramatically over the years as well, particularly for what we call 16S rRNA sequencing.

Ryan Van Patten 07:16
Okay, that's really helpful. Thanks for diving into the weeds a little bit for us. Before moving on, I think it'd be helpful if we define a few key terms that will come up in our discussion. So I'll take a stab at some of these and Tanya, give me feedback - let me know when I'm wrong.

First, as we mentioned, the human microbiome is referring to these microorganisms that operate in our bodies. A core concept in biology that will be important for the rest of our talk today is symbiosis or this lifelong relationship among organisms. So just to give a little bit of brief biology terminology, there are three basic symbiotic relationships. There's mutualistic, where both partners benefit; commensalistic, where one species benefits and the other is neither harmed or nor helped; and then parasitic, where one organism benefits while the other suffers. So with microorganisms residing inside of us, we can think about these different symbiotic relationships. Bad bacteria are likely to be parasitic, but not all bacteria are parasitic. So we can tweak this idea that bacteria or germs are bad and we should get rid of them because they help us.

Tanya Nguyen 08:27
Right. I'm glad you brought this up early in the conversation, because in neuropsychology, we tend not to forget about the fact that our brain lives in an ecosystem. And in the same way, our microbiomes really follow the principles of ecological biology. So that's something that I'm going to talk a lot more about throughout our conversation today.

John Bellone 08:49
We've co-evolved with organisms as well, right?

Tanya Nguyen 08:52
Exactly.

Ryan Van Patten 08:52
They're a part of us. We wouldn't exist without them. They're really part of our body in a way.

Tanya Nguyen 08:56
Right.

Ryan Van Patten 08:57
Okay, so let me run through a few of these definitions. So prebiotics, not probiotics, but prebiotics - these are non-digestible food components that are selectively fermented by intestinal microflora, these bacteria, and they're associated with health and well-being. Then we've all heard of probiotics in a lot of commercials and other advertisements. These are live microorganisms that, when they're administered in adequate amounts, confer a health benefit on the host. Another interesting intervention are fecal transplants, also known as poop pills.

John Bellone 09:33
Ryan just wanted to say that. [laughs]

Tanya Nguyen 09:34
[laughs]

Ryan Van Patten 09:35
I've been dying to get that out on the air. Having said that word…

Tanya Nguyen 09:38
They actually aren't pills either.

Ryan Van Patten 09:40
Right. That's what I've heard.

Tanya Nguyen 09:41
They're administered through enemas usually. So not as cool as a pill. [laughs]

Ryan Van Patten 09:46
Yeah. So what a fecal transplant is, it's an intervention that's designed to completely restore a dysbiotic microbial community through the administration, as Tanya said,

of a complete and complex microbiota from a healthy donor. So you have someone whose microbiome is sick or dysregulated in some way. You take a sample from someone who's healthy and share it, give it to that person in a nutshell. A few other terms that will likely come up a lot are alpha diversity and beta diversity. My simplistic understanding of these, Tanya let me know if you'd like to follow up. Alpha diversity refers to within sample diversity or variability, and beta diversity is between sample.

Tanya Nguyen 10:34
Yes.

Ryan Van Patten 10:35
Can you expand on that for us?

Tanya Nguyen 10:35
Sure, definitely. So alpha diversity, or within sample diversity, represents the number or richness and the evenness or distribution of specific bacteria or taxa within a single sample. The best analogy that I have is like a standard deviation, right? So if you have a group of bacteria, what's the standard deviation? What's the variability? The alpha diversity measure provides a single number or value that represents the total number distribution of the species or taxa within a single community. On the other hand, beta diversity measures the dissimilarity between different samples or communities. It indicates differences in taxa composition between samples based on either the presence or absence of quantitative abundance data.

Ryan Van Patten 11:28
Tanya, in doing some background reading for this, I've come across some terms. I'm curious if they are synonymous or interchangeable. Microbiome, I also read gut flora, gut microbiota, gastrointestinal microbiota - are these the exact same thing or used differently?

Tanya Nguyen 11:45
For the most part, they're all usually referring to the same thing. Yeah.

Ryan Van Patten 11:50
To move on, I'm wondering what constitutes a healthy versus an unhealthy microbiome. It's certainly more complicated than the idea of good bacteria and bad

bacteria. This is a very complex network of biological organisms inside of us. We need the microbiome to be in the correct balance. Can you talk about how researchers and experts in the field think about one person having a healthy versus unhealthy microbiome?

Tanya Nguyen 12:20

That's a really good question. The definition of a healthy microbiome is somewhat elusive. You know, I don't even like to describe food as healthy versus unhealthy. I like to think of it as food, as being nutritious. Because what defines health can vary a lot depending on a specific person, their overall lifestyle habits, and so on. But again, I want to refer back to the microbiome as being viewed from a perspective of ecology, that each microbiome is its own ecological system. If we think about ecology, the health of any community, whether it's our microbiome, whether it's the rainforest [or] the desert, the health of any community is really a function of its stability. Its ability to resist change and return to equilibrium after some type of ecologic stress. And generally, the more diverse or rich a microbial environment is, the greater its capacity to remain stable in the face of perturbations. So the prime example that I always like to offer is Clostridioides difficile infection.

Ryan Van Patten 13:25

C. diff?

Tanya Nguyen 13:26

Yes, C. diff infection. Exactly. Some readers who are familiar or have been in the hospital setting may be familiar with C. diff infection. You see signs posted all over. But C. diff is a parasitic bacterium that releases toxins that attack the lining of the intestine. It can cause symptoms ranging from diarrhea, life threatening inflammation of the colon. All humans are actually colonized by C. diff, but C. diff infection only occurs in a small proportion of the population, particularly older adults and individuals who tend to be more immunocompromised. The reason why it typically happens is that it occurs after long term antibiotic use. Older adults and people who are immunocompromised tend to more likely be on antibiotics. So when we treat infections with antibiotics, these drugs destroy not only all the bacteria that's causing the infection, but also the normal commensal mutual or symbiotic bacteria as well. So without enough healthy bacteria to keep C. diff in check, C. diff can grow out of control quite quickly and then overtake the rest of the bacteria in the gut.

John Bellone 14:38
So it's not necessarily it being there in the first place that was the problem. It was when you wipe out the other stuff, then it's more opportunistic.

Tanya Nguyen 14:46
Exactly.

John Bellone 14:47
I see. Okay.

Ryan Van Patten 14:48
So going off this idea that antibiotics can have negative effects. Do you feel like - you may not have a great answer to this, but do you feel like the medical community appreciates that? So someone has an infection, and they could take an antibiotic, and that will be helpful. But now that we're learning more about potential negative effects of antibiotics, like that antibiotics are wiping out the good or helpful, at least the diversity of bacteria that would otherwise be protected for us, it should be a cost-benefit analysis every time an antibiotic is prescribed to someone. Do you feel like that is starting to be understood in the medical community? Such that we're making decisions...

Tanya Nguyen 15:30
Yeah, that's a great question. I'd like to think so. I know from my own personal experience, not too long ago I had an ear infection. So I went to my physician and asked for something to treat it. And they're like, "Well, let's try this anti-inflammatory medication instead because I don't like to prescribe antibiotics." And, you know, this was a while ago before I'd started studying the microbiome. I had never really thought about that. I was just getting into it, and I thought, "Well, yeah, that's a really great idea." Maybe I'll be less likely to take an antibiotic until it's really necessary.

Ryan Van Patten 16:03
Yeah. There's another related disadvantage of taking antibiotics that I think we've known about for quite some time, which is that over prescribing or people taking antibiotics too much essentially breeds superbugs. It breeds bacteria that are antibiotic resistant. So now we have at least two reasons to be very careful about prescribing and taking antibiotics. We want to only do it when it's absolutely necessary.

Tanya Nguyen 16:27
Right.

John Bellone 16:28
In addition to antibiotics, it seems like there's a slow but steady global homogenization in the gut microbiome. So we're losing the diversity of those different species, the different taxa. So in addition to antibiotics, it could be increased travel, globalization, longer lifespans, access to similar diets and therapies, things like that. I'm curious what impact that might have on overall health. Is this a good thing or a bad thing that we're all being more homogenized in our gut microbiome?

Tanya Nguyen 17:04
Yeah, that's an intriguing question. I certainly think that there's a homogenization of cultures and diets and therapies due to increased access. But I actually don't know if there's enough evidence to suggest at this time that there's the same homogenization in our gut microbiomes. Mostly because we haven't been studying the microbiome long enough to measure these large scale shifts. Now, I also think that this change can be good or bad depending on how you look at it. So unfortunately, the global homogenization of cultures has trended towards more Western-style diets, and as we've seen in general health trends that's led to increased obesity, metabolic disorders. I could imagine that this also leads to negative influences on the gut microbiome. Research has shown that people who adhere to primarily fast food style Western diets have decreased richness in species biodiversity compared to those who consume more traditional high fiber diets or Mediterranean style diets. But I actually don't know if the composition is actually more homogenous, as opposed to less diverse but still diverse from one another, if that makes sense.

John Bellone 18:19
I see. Okay.

Tanya Nguyen 18:19
Yeah.

John Bellone 18:20
Okay. So we're just not there yet.

Tanya Nguyen 18:23

Yeah. But then on the flip side, I think with increased technology and better health care, it also brings more access to novel interventions as well. So there's that potential for benefit on the microbiome - like these fecal transplants and probiotics and prebiotics.

John Bellone 18:39

That's true. Another thing that I'm curious about is how stable the microbiome is. Does it change across the lifespan? I've heard a couple of potentially conflicting things. One is that many factors like the method of birth, whether it's C-section or vaginal birth, whether there are pets in the home, whether the person was breastfed - that those can have significant effects on the microbiome of infants. I also read that the microbiome is relatively stabilized by a child's 1st birthday. But then I've also heard that there are significant changes that occur in older age. Certain life experiences, like traveling to a foreign country can impact the microbiome. So I was wondering if you could help me reconcile?

Tanya Nguyen 19:28

Yeah, it is conflicting. It sounds conflicting, and I think it is in a way partially conflicting. Dramatic changes in the gut microbiome do occur at early ages. Particularly in the first three years of human life you see a dramatic increase in diversity and stability of the microbiome. The maturation of the microbiome is actually a good example of ecological succession, in which communities undergo compositional and functional changes following initial colonization, until a relatively stable climax community is then established. So the human or the infant microbiome is relatively volatile. Antibiotics, breastfeeding status, like you mentioned, delivery modes all have an effect on how the infant is initially colonized, or the microbiome of the infant is colonized. Whether the microbiome differences in early life ultimately affect adult microbiome is actually not well understood. But the compositional differences driven by these factors in infancy can affect susceptibility to immune disorders later. So I think it's just as conflicting. I think we all have this core community and then there is some variability that is driven by our life experiences [and] exposure early on. I went to a conference not too long ago, in which a researcher looked at the microbiomes of children in more urban environments versus children from an Amish community and they had significant differences. The children in the Amish community, who spent every day in the hay with animals, had dramatically decreased prevalence of asthmatic disorders or other immune disorders compared to children in urbanized communities.

John Bellone 21:27
Sounds fascinating.

Ryan Van Patten 21:27
Yeah. So based on the evidence we have now, could we say that, are the recommendations at least tenuous that more natural behaviors - vaginal birth, breastfeeding, other things that are just more evolutionarily natural - tend to lead to more healthy microbiomes similar to what you described?

Tanya Nguyen 21:48
I think so. At this point.

John Bellone 21:49
Or at least there's a correlation there. Yeah.

Tanya Nguyen 21:51
There are a lot of books out right now, you know, popular media books, of course, that talk about how dirt is good because we're essentially exposing children at an early age to a large range of bacteria as opposed to raising them in a more sterile environment with limited exposure to different bacteria so that when they grow older, their core community of microbiome or bacteria is very different. They may be more susceptible to immune dysfunction because the gut microbiome is a big driver in the development of the immune system.

Ryan Van Patten 22:27
So we can quote Tanya, "dirt is good". Mud. Germs. [laughs]

Tanya Nguyen 22:33
You can actually quote some author. It's an actual book title. [laughs]

John Bellone 22:36
But that's a little bit in conflict with the idea that we should wash our hands quite frequently. I guess it depends on where you are. If you're in a hospital, it's a different setting. Okay.

Tanya Nguyen 22:49
Of course.

Ryan Van Patten 22:50
I'm sure it's ultimately to balance, right? We don't want to live in mud, but we don't want to go too far to the opposite end, which a lot of people these days, I think, are tempted to do, particularly with their children. Taking good care of them, keeping them in a bubble that's actually not good for their health.

Tanya Nguyen 23:05
Right, exactly.

Ryan Van Patten 23:08
So alterations to the gut microbiome, we know, are associated with a number of physical diseases, things like irritable bowel syndrome, or IBS, diabetes, obesity, cancer, pulmonary diseases. These relationships between the gut microbiome and some of these GI disorders, or disorders of the gut, are probably intuitive to some of our listeners. But would you mind just for the sake of thoroughness making the connection for us between dysbiosis and some of these disease processes?

Tanya Nguyen 23:41
Yeah, sure. So the most obvious physical diseases to be associated with the gut microbiome are gastrointestinal disorders as the gut microbiome is directly present within this organ. As you would expect, inflammatory bowel disorder or inflammatory bowel disease, or IBD, is the most studied human condition that's linked to the gut microbiome. Research within this disorder is arguably the most advanced in the microbiome field. Studies of IBD consistently report decreased intestinal microbiome diversity. It's characterized by specific taxonomic shifts, particularly in the direction of increased relative abundance of pathogenic bacteria, pathogenic and invasive bacteria as opposed to more commensalistic bacteria.

John Bellone 24:32
Bad versus the neutral?

Tanya Nguyen 24:33
The bad versus good, essentially. Yeah. There's a lot of experiments that have been done in animal models using fecal transplants, or FMT, as we call it, fecal microbiota transplantation. They've shown that the intestinal microbiome can also have a causal effect on obesity and metabolic disorders. Again, not surprising given that obesity is generally caused by poor food intake, poor metabolic regulation. So they actually use germ-free animals in these types of studies. These germ-free

animals are raised in a sterile environment, which eliminates the opportunity for colonization of the GI tract during development. So these animals ultimately have no gut microbiota. In these studies, both conventional and these germ-free animals are fed a high fat diet. The conventional mice become obese and show these typical metabolic alterations associated with obesity, including increased adipose tissue, insulin resistance, and increased intestinal permeability. But on the other hand, the germ-free animals show minimal weight gain. But then if you take fecal matter containing microbiomes from these obese conventional mice and transplant them into the germ-free mice who have been fed a high fat diet, you get obese mice. So this shows that at least some part of our health can be transferred from just the microbiome alone.

John Bellone 26:08

It's a pretty powerful study. So there's some evidence that some of these diseases like obesity or insulin sensitivity, let's say, or other physical maladaptations, there's a correlation there. But there's also been some research showing that cognitive abilities and emotional states can be affected. It seems like it might be even less clear the line drawn there. Can you tell us a little bit about the potential biological processes that are involved in this relationship between the microbiome and cognitive abilities or emotion?

Tanya Nguyen 26:47

The mechanisms by which the bacteria living in our gut are linked to cognitive and emotional functioning in the brain is not fully understood. But they're hypothesized to involve a number of different mechanisms, including the immune system through systemic cytokines, gut hormone signaling via cortisol in the HPA axis. So for example, the HPA axis regulates cortisol secretion, which can affect immune cells both in the gut and systemically. Then cortisol can also alter gut permeability and change microbiota composition. On the other hand, microbes and probiotic agents in the gut can affect levels of circulating cytokines, which we all know now to be able to cross the blood-brain barrier and impact brain function. Then also the vagus nerve and modulation of systemic tryptophan levels have been strongly implicated in relaying the influence of the gut to the brain. And then short chain fatty acids are probably one of the last mechanisms that is frequently discussed. These short chain fatty acids are bacterial metabolites of dietary fibers or prebiotics. And these can modulate the brain and behavior as well.

Ryan Van Patten 28:07

This is helpful to start going into some of the mechanisms. So we've laid out that there's a relationship [between] unhealthy gut microbiome [and] poor outcomes, physical and mental health. There's also some work elucidating what's underneath these mechanisms. You listed a number, which is helpful. Do we have a sense as to the pathway? Is it microbiome to vagus nerve to tryptophan to inflammation? Is this a linear progression like that? Or do we have a sense as to how that unfolds one after another? Are these all just correlates and we don't really know the direction or the ordering?

Tanya Nguyen 28:50

I don't think that each of these mechanisms are necessarily linear. I think some of them can be independent of one another. I think cytokines and inflammation can be a bi-directional relationship, between the brain and the gut and vice versa. The other ones, I don't know if they're necessarily linked or not. I think the research or the jury's still out on these.

Ryan Van Patten 29:18

Right. Yeah.

John Bellone 29:20

Is the gut barrier dysfunction, that altered permeability, is that another potential mechanism?

Tanya Nguyen 29:27

Yes, definitely. The gut barrier dysfunction, or what is often referred to as leaky gut syndrome, is a situation in which there's increased permeability of the intestinal lumen. This intestinal inflammation so to speak can lead to the gastrointestinal barrier becoming compromised. When this happens, dwelling microbes are exposed to systemic circulation, some of which can be pathogens, and this gut inflammation can produce other systemic cytokines that are released into the blood that then travel up through the blood-brain barrier and impact cognition and behavior in that way. So, yes, the dysbiosis of the gut can impact this systemic physiological functioning. And so, in a way, that gut actually becomes a source of autointoxication.

John Bellone 30:23

I've heard some controversy with the leaky gut syndrome. There are some claims, it sounds like it's more pop psychology, but it sounds like there have been some claims made that gluten or carbs or other foods specifically cause autism or Alzheimer's disease via that leaky gut mechanism. I wasn't sure if you had thoughts about that.

Tanya Nguyen 30:47

Yeah, I have a lot of thoughts about popular media...

Ryan Van Patten 30:51

[laughs]

Tanya Nguyen 30:51

…and how it has skewed a lot of the research because a lot of the claims aren't really backed by research. There may be associations with a lot of these mental and neurological health disorders, with increased intestinal permeability, but I think the claim that it causes these disorders is quite far from any research at this point.

John Bellone 31:17

Yeah, that was my sense. It seems like we're far away from any kind of causative or even being very confident that these are significant driving factors.

Tanya Nguyen 31:27

Right. My guess is that - I mean, I don't know the literature on all of these disorders and the claims that gluten and carbs and these foods cause leaky gut syndrome. But we likely see an increased prevalence of leaky gut in these disorders. I mean, that very well may be true. But I don't know if it's the cause of or the result of these foods in particular, and the cause of the disorder. We do know, however, that some psychiatric disorders, including schizophrenia, are associated with higher serum antibody levels to fungal pathogens and other protein markers of bacterial translocation. So these are all markers within the systemic blood system that suggest that there's increased permeability because there's an increased antibody or immune response. So I think a lot of these disorders are associated with leaky gut syndrome. But, beyond that, we don't have a good understanding of how these are actually affecting the brain, although there's a high likelihood that they are.

John Bellone 32:28
This relates to the microbiome because when you have that leaky gut, then you have the microbiota spilling over.

Tanya Nguyen 32:35
Exactly, yeah.

Ryan Van Patten 32:38
So, Tanya, there's this term the gut brain access that's out there in the literature, and it's very trendy. In my mind, it builds off of the HPA axis, which in psychology we talked about a lot and you referred to earlier. I can imagine everything we've talked about thus far probably ties into the gut brain axis. Could you define it a little more concretely for us? Tell us what, if we read in a paper that someone is investigating the gut brain axis, what are they specifically looking at?

Tanya Nguyen 33:07
So the gut brain axis consists of a complex communication system that ensures proper maintenance of gastrointestinal homeostasis, but also has likely multiple effects on affect, motivation, and higher cognitive functions. So the overall role of the gut brain axis is to monitor and integrate gut functions as well as to link them to the cognitive and emotional centers of the brain, along with peripheral intestinal functions and mechanisms like immune activation, intestinal permeability, enteric reflex, and other types of signaling. So essentially it's this model or this concept that integrates how the gut functions with how the brain functions and all the mechanisms that I had previously mentioned before.

Ryan Van Patten 33:56
Right.

John Bellone 33:57
You throw out the term enteric, and I wonder if you know that there's the enteric nervous system. It's rarely talked about, but it's really like a second brain. It's this network of about 500 million or so neurons, over double the number of neurons in a dog's brain, that's just embedded in the lining of our gastrointestinal system and moderates our GI functioning. I'm curious if there's any link between that enteric nervous system and the microbiome?

Tanya Nguyen 34:25

Yes, definitely. The microbiome interacts locally with the intestinal cells and through that the enteric nervous system. Yeah, so it's interesting. My clinical work is focused on working with older adults, many of whom have advanced dementia syndromes, and from my experience in more advanced dementia syndromes, we also see a lot of gut dysfunction and gastrointestinal dysfunction. As we age, the GI tract or GI function starts to deteriorate as well, and that could almost be seen as happening in parallel with deterioration of neurons in the brain. So the enteric nervous system and the central nervous system kind of interact in that way. At the most end stages of dementia, many of my patients have what we call in which they forget or no longer know how to pass stool. Usually at that point, their cognitive functions are quite deteriorated as well. So it's a very interesting connection. Again, there's no data behind this, it's just my own clinical experience and observations.

John Bellone 35:34

I read a paper recently showing a link between Alzheimer's pathology, the A-beta tau proteins and the microbiome. It wasn't causative, but there was a correlation between both the diversity of bacteria and the abundance of bacteria and how that related to Alzheimer's pathology. I don't know if you've seen that study.

Tanya Nguyen 36:03

No, I haven't. But very interesting and not surprising. [It] seems to be in parallel with what we're seeing, at least in serious mental illnesses.

Ryan Van Patten 36:13

Yeah, that actually piggybacks well, or transitions well into the question I have. In a few minutes, we're going to get into serious mental illness, Tanya, your research interest. But before that, I wanted to briefly touch on the literature on some other mental and cognitive illnesses with respect to the microbiome. In my reading, I've seen papers on depression, autism, Parkinson's disease, and a couple others that, at the very least, argue for a role of the microbiome. In my mind, integrating those together, the pattern that I was noticing was that people who have risk for - or I should say a lot of these are in mice as well - people or mice who have risk for the clinical syndrome, but who also have clean or healthy microbiome seemed to be relatively protected from the disease state. So I'll take Parkinson's disease as a model. In the paper I read, mice who had high alpha synuclein, thus at risk for PD motor symptoms, but whose microbiomes were otherwise healthy did not display the mouse version of PD symptoms. But then if microbiomes were transplanted from unhealthy mice into those healthy mice, then they would exhibit the PD motor

symptoms, which in my mind, argues for my healthy microbiome as a protective or moderating factor that may help stave off some disease syndromes. You could also look at it the other way - if it's an unhealthy microbiome, it's a risk factor. To your knowledge, can [you] summarize the literature on some of these other conditions and what we know?

Tanya Nguyen 38:03

Oh, yeah. That's a really interesting study. Most of the initial studies that directly assessed the microbiomes' impact on different aspects of behaviors related to psychiatric disorders were conducted in animal studies and using germ-free animals, like I mentioned before, within the context of studying obesity and metabolic dysfunction. So compared to conventional animals, germ-free animals generally show decreased depression or anxiety-like behaviors. And interestingly, if you use fecal matter transplantation of these germ-free animals with the microbiota derived from human patients with MDD, major depressive disorder, it actually induces both behavioral and physiological features characteristic of depression, including anhedonia, more anxiety-like behaviors, and alterations in tryptophan metabolism. So these experiments provide pretty compelling evidence that the gut microbiome can physiologically induce depression and anxiety-like behaviors, at least in animals. So I interpret these studies to suggest that one, the microbiome to some extent is necessary for some psychiatric or behavioral functions, and that two, perhaps there's some unique microbial signature or composition or functionality that's associated with specific disorders.

Ryan Van Patten 39:30

Yeah, that's really interesting. To zero in on one part of that, the translational piece if I heard you right [and] if I read this paper [right] as well, the transplant is from a human who has MDD into a mouse who does not.

Tanya Nguyen 39:45

Right.

Ryan Van Patten 39:45

From human to mouse. And then afterwards, the mouse exhibits some depressive symptoms, which shows a strong evolutionary grounding in the microbiome. It's been consistent across mammals, at least, to a big extent.

Tanya Nguyen 40:04
Yes, exactly. So it's pretty intriguing and a compelling study.

John Bellone 40:09
Some of our listeners might be wondering how you measure depression or depressive symptoms in a mouse. I've done some research in this area and there are a couple different ways. I don't know what this study used specifically. But there's a forced swim test, where you put a mouse or a rat in a cylinder, enclosed on all sides, and they're in water, and you see how long they struggle for. It's kind of sad, but you take them out of the water before they get hurt. You measure how long it takes them to stop struggling. It's kind of like a learned helplessness paradigm. Another way is for mice is a tail hanging test where you tape their tail up, and again, measure how long they struggle for. It just, again, sounds really sad but you take them off of there before they get hurt. You're just trying to measure how much they fight and that's again, a correlate of learned helplessness in a mouse.

Ryan Van Patten 41:07
I'm wondering if those same studies would work on Peruvian guinea pigs by chance, John. [laughs]

John Bellone 41:12
[laughs]

Ryan Van Patten 41:12
For listeners who don't know, John owns two Peruvian guinea pigs at home. So maybe you could do some experimentation…

John Bellone 41:19
I would never. [laughs]

Ryan Van Patten 41:24
[laughs]

John Bellone 41:24
No animals were harmed in the making of this podcast. [laughs]

Ryan Van Patten 41:26
[laughs]

Tanya Nguyen 41:26
[laughs]

Ryan Van Patten 41:28
Speaking of animal research, I want to ask one follow up about that. Probably because this literature in the microbiome is so new, a lot of the work is in animals. Also, obviously, there's more flexible ethics, there's more we can do, as John just described, [with] the animals [that] we can't do in humans. But I feel like, as

clinicians and clinical researchers, we're pretty far removed with some exceptions, like John, from basic animal research. But I feel very strongly that this is imperative to our understanding of diseases. There are a lot of models of Parkinson's, rat models, etc. that really give us a broader and more thorough understanding of these diseases. We wouldn't be where we are today without animal research. So Tanya, can you talk broadly about the contributions of animal work to the microbiome?

Tanya Nguyen 42:14
Yeah. I mean, the study that I had just mentioned, using the germ-free animals and transplanting with the microbiome from human patients with MDD just shows how much we're able to learn because we could never really do that in a human population. I don't think we would know nearly as much about the way and the mechanisms by which the microbiome impacts cognition or at least behavior without the studies.

There's another study that I just want to briefly mention and it involves autism. There's a pretty well established animal model for autism. It's maternal immune activation, or MIA, it's a mouse model for autism. These animals show changes in the microbiome composition in addition to defects in intestinal permeability, elevated inflammatory cytokines. They show, again, behaviors that are consistent with autism, which again, aren't exactly the same as autism but you measure them in an open field test, interaction with other animals, things like that. But these show that maybe intestinal permeability and inflammation may be that mechanism. Whereas in humans, we wouldn't be able to test that model at all, at least not at this point. That particular study also found that if you treat them with a commensal bacterium, it completely reverses all of the abnormalities, including the microbiome abnormalities, the inflammatory abnormalities, as well as some of the behavioral

abnormalities as well. So, again, really interesting studies are able to show these connections, that right now in humans, we've only been able to run correlations.

Ryan Van Patten 44:01
Right.

John Bellone 44:03
Ryan, maybe we should do a whole episode soon about animal testing and the costs and benefits of it, the ethics of it. I think our listeners - so I did a lot of the animal types of research. They had fun with me. They would swim in the open, you know, in the water maze, or do that kind of thing. They exercised with me. I didn't do any of the other stuff. But I got that question a lot, of the ethics involved in animal testing, and I think our listeners should know that there is an ethical review board, the IACUC, Institutional Animal Care and Use Committee. It's like the IRB, the Institutional Review Board, that makes sure all the ethical standards are upheld. We limit the number of animals that we use. We don't expose them to unnecessary amounts of suffering or if you do use suffering, you have to really, really justify it and take all measures to reduce it. So I just wanted to mention that. We should cover it more thoroughly, though.

Ryan Van Patten 45:04
For sure.

John Bellone 45:05
So, Tanya, can you walk us through - we talked a little bit about some mental health conditions like depression, but can you maybe walk us through the thought process behind studying the gut microbiome in more severe mental illness? Schizophrenia is a particular interest of yours. Why is the gut microbiome likely relevant here?

Tanya Nguyen 45:29
I think there are a lot of parallels between medical health disorders like inflammatory bowel disease and obesity, diabetes, with mental illness, and particularly severe mental illnesses such as schizophrenia and bipolar disorder. My specific research interests are in accelerated aging in schizophrenia and bipolar disorder and how that impacts mental health and cognitive symptoms. Compared with the general population, people with schizophrenia and bipolar disorder have higher rates of chronic medical illnesses and conditions and they tend to die younger. If you want to think of a popular media example is Carrie Fisher, who we

all knew to have bipolar disorder and she ultimately died of heart disease. Most of the excess deaths in schizophrenia in particular are not due to the mental disorder itself or suicide, but actually metabolic and cardiovascular conditions, cancers and other chronic comorbidities. These tend to occur at earlier ages. In fact, following cardiovascular and cerebrovascular disorders, gastrointestinal disorders are the third leading cause of death in patients with schizophrenia. So for this reason, it got me thinking, "Well, could this be part of the physiological changes that occur in serious mental illness? Or could the microbiome be one of the mechanisms that contribute to a decline in physiological functioning? And how does that impact cognitive functioning as well?"

John Bellone 47:05

Can you maybe summarize for us what we know to this point about dysbiosis, that microbial imbalance in schizophrenia? Just get a little more into the weeds here.

Tanya Nguyen 47:15

Sure. So, to date, there are only five published studies of the gut microbiome in individuals with or at risk for psychotic disorders. There's one in patients with high risk for schizophrenia, two in patients with first episode psychosis, and then two in adults with chronic schizophrenia. We know that the gut microbiome in patients with high risk for these disorders is significantly different than healthy individuals. So that's the beta diversity measure, right? There's a significant difference in the composition between these two groups. However, the specific composition or taxa that drive these differences vary across studies and the findings can be at times conflicting. Some of these studies show a relationship of specific taxa and clinical presentation. So for example, severity of psychotic and depressive symptoms have been shown to be associated with specific taxa. There's one study that actually looked at the gut microbiome in patients with first episode psychosis, and then followed them up at one year to see how many of them are re-hospitalised. They found that patients who had the greatest abnormalities in microbiome composition from healthy controls at the time of hospitalization showed a lower rate of disease remission at one year follow-up. So even though the findings are limited, they're still pretty compelling and suggest that somehow, the gut microbiome can impact clinical presentation in these disorders, even though we don't know exactly how they impact cognition specifically, at least not quite yet.

Ryan Van Patten 48:59
But it's really intriguing. Where that takes me is to wonder [is], where do you think we're going from here in terms of microbiome and severe mental illness? What's on the horizon? I know you have a stake in this.

Tanya Nguyen 49:09
Yes, definitely. Well, the good news is that there's a lot left to learn. I mean, there have been so few studies. But there's also a lot of inherent challenges to doing research with psychiatric populations to any mental health or neurologic population, as many of us are very familiar with. For me in particular, schizophrenia is a very heterogeneous disorder. Patients have so many comorbidities, many of which impact the gut microbiome. So how do you know if they have altered gut microbiomes because they just have higher rates of obesity, metabolic disorders, heart disease, versus the mental illness itself. I think the first issue at hand is replication using larger sample sizes. Larger sample sizes will give us better power for some of the high throughput sequencing that's really needed and allow for more complex models that can account for all of these factors other than disease state. Other relevant variables of interest would be age, how does it change with age? Diet. Medication use, particularly antipsychotic medication use, many of which cause a lot of metabolic dysfunction and obesity itself.

John Bellone 50:24
You just submitted an NIH K award, right? To study the microbiome in schizophrenia.

Tanya Nguyen 50:29
I did. Yes.

John Bellone 50:29
So you're actively contributing to this progression.

Tanya Nguyen 50:32
I am. I'm trying to at least.

Ryan Van Patten 50:34
NIH willing. [laughs]

Tanya Nguyen 50:36
Yes. [laughs]

John Bellone 50:39
Can you tell us a little bit more about your proposed project?

Tanya Nguyen 50:42
Sure. So my K proposal aims to identify microbiome and metabolome alterations in patients with chronic schizophrenia, and how they relate to important demographic and clinical characteristics. So this aim is really to provide that basic foundational knowledge about the gut microbiome because so little is known at this point. Another aim is to examine age-associated changes in the gut composition, and identify sensitive biomarkers of aging within the microbiome. As I mentioned before, I'm really interested in accelerated aging and how the microbiome can mediate or moderate this relationship. Then the third aim is to elucidate the association between the microbiome and cognitive functioning, and how inflammation specifically can moderate this relationship. So throughout the podcast today, I've talked a lot about inflammation, intestinal permeability, gut inflammation, things like that. I really think that one of the mechanisms by which the microbiome impacts cognition is through inflammation. So understanding this can help us identify potential intervention factors that we could manipulate to improve cognitive function in this population because we know most treatments for schizophrenia, or at least biological treatments for schizophrenia at this point, aren't really effective in improving cognitive function, and that cognitive functioning is the greatest predictor of functional outcomes.

Ryan Van Patten 52:10
Right. Right. I'm glad you mentioned intervention. That's a perfect segue because I'd like to talk a little bit about what we know currently, and where you imagine the field going. There's this up and coming research and the microbiome, and we have these mental health conditions and cognitive functioning, what might interventions look like? How might we capitalize on our increasing knowledge of the microbiome to develop interventions that improve prognosis and potentially early detection of disease states? Where do you think [we] are going?

Tanya Nguyen 52:40
There's so many potential avenues. I have to say that it is actually my personal long term interest to develop interventions to modify the gut microbiome in a way that it can improve psychiatric and cognitive functioning. As a side note, prior to doing the

work that I do now, in graduate school, my research was actually in nutritional interventions. I had an F31 looking at how nutritional interventions could improve cognitive functioning in a pediatric population - so children with fetal alcohol spectrum disorders. That's actually how I became drawn to the microbiome. Before going into microbiome, I was interested in inflammation, then I was like, "Well, diet...inflammation." Then there was this field that got microbiome, and so that's ultimately where I wanted to go. I think my mentors had to really kind of halt me from actually proposing [an] intervention study, because they're like, "We don't know anything for you to even do an intervention study." So that's kind of how I backtracked into just understanding the gut microbiome.

So having said that, going back to your question about interventions, I think there's so many ways. We talked about probiotics and prebiotics, those are potential intervention factors. I think way, way, way, way, way down the road, maybe fecal transplantation. But even before that, we can start thinking about how to [use] behavioral modifications. How can we use diet, exercise nutrition, to impact cognitive function? I know that there are some studies. I think one group at UCLA is currently looking at how diet and nutritional interventions impact schizophrenia and cognition. So I think there's a lot of potential there and now just adding in the gut microbiome piece to see how that might mediate or moderate that impact or effect.

Ryan Van Patten 54:34
You said fecal transplantation being way down the road, but don't we do that now in certain circumstances? Like people with C. diff could get a fecal transplant.

Tanya Nguyen 54:43
Yes.

Ryan Van Patten 54:43
But you're saying way down the road in terms of mental health?

Tanya Nguyen 54:46
Yes, that's what I mean. Yes, I should clarify. Yes. So fecal matter transplantation is the method, the standard treatment for C. diff infection. There have been a number of studies in IBD, but the literature is still mixed when you actually do a meta-analysis, it's kind of hit or miss for IBD. So it has potential in the future. But I think right now, we don't know enough.

Ryan Van Patten 55:09
Sure. Yeah, that makes sense.

John Bellone 55:11
There's been a few popular media outlets that have suggested that these psychobiotics, as they call them, are the future of mental health. And maybe they will be, but it sounds like we're so far from that unfortunately. There's so many questions that pop up in my mind when I think about this. Like, wouldn't probiotics be just a drop in the bucket compared to the trillions of other microbiota already in us? And how do we know which are the right types of microbiota bacteria for different individuals who will likely have different microbiomes? How do we know the probiotics are going to actually get to where they need to go? And whether they're going to thrive there in the long term? It just seems like so many questions come up here, and I doubt that there are any specific answers to these.

Tanya Nguyen 56:01
No, but what you're saying, those are exactly my thoughts as well. We just don't know enough about the human microbiome right now to answer those questions. So when you see those ads of those companies claiming to be able to improve happiness by giving you this small pill of bacteria, it's likely not true. There's still so much work that needs to be done in characterizing and understanding variability in the microbiome before we can reliably start manipulating and developing treatments. What we need to know include [is] how do probiotics change the microbial environment?

You'd be surprised to know that most studies looking at probiotics don't actually measure the gut microbiome. So we don't actually know whether or not these bacteria are actually colonizing the gut, if they're making it past the stomach and then the proximal intestine. We also need to know which types of microbiomes or people who would most likely benefit and then what the mechanisms are. I actually have a colleague who recently published a review on probiotic studies in improving neuropsychiatric outcomes, and she concluded that studies both in animals and in humans of probiotic treatments is inconclusive. Most of these studies use different formulations with different strains. Like I said, most don't report confirmation of intestinal colonization. The routes of administration vary. And no trials actually include follow up to determine whether or not these results are long lasting.

Ryan Van Patten 57:34
Yeah. So clearly, the mass marketed probiotics we see commercials for, there's not yet evidence that that does any good.

Tanya Nguyen 57:41
No.

John Bellone 57:41
So we shouldn't just down as much kombucha and yogurt as we can? [laughs]

Ryan Van Patten 57:46
[laughs]

Tanya Nguyen 57:47
Actually, some of the experts in the field actually really do support eating fermented foods. Kombucha, kimchi, because, again, it's introducing probiotics and bacteria. I don't know if there's any systematic study yet, but it can't be a bad thing. Put it that way.

John Bellone 58:05
It also seems like the interaction between our body and our microbiome and the high number of metabolites from our food and medications, it's so complex. It just seems like, given the complexity, it's naive right now to think that we're at the point where we can have a causal relationship between these probiotics and health outcomes. I'm optimistic that there will be progress.

Tanya Nguyen 58:34
Yeah, I agree. I think that we're far from developing specific interventions using probiotics at this point. But I also want to say that it's probably not a bad thing. I mean, it probably positively influences health. It's not as if we see a high blood pressure reading [and say,] "Oh, give this statin." We're far from being able to prescribe these interventions for specific disorders. This one to one treatment.

Ryan Van Patten 59:03
Right. Along those lines, one finding that I read in the literature that seems like it could be a recommendation, like a broad strokes diet-based recommendation, is that - so we're looking for more diversity in our microbiome all else being equal. The finding is that people who eat or report eating more different kinds of vegetables, as

a proxy for variability in their diet - so these are fresh vegetables and it's not just, like, only eat a million carrots to have a lot of diversity in your diet - that predicted microbiome diversity. So maybe we could take to heart and one step we can take, maybe even talk to our patients about is, diversifying your fruit and vegetable diet. Maybe we can say that's accurate.

Tanya Nguyen 59:55

Exactly. The findings that you're talking about are coming from what we call the American Gut Project which is the largest crowdsource citizen science project that is actually coordinated here at UCSD. [It's] kind of a funny side note, there are a lot of people who call themselves vegans. You know, there's vegans who eat plant based foods, and then there's vegans who eat primarily Doritos. So calling oneself a vegan doesn't necessarily mean that you're going to have a more diverse microbiome. So really, it's how many different types of plants that you eat that drives the microbiome, even if a person also eats meat as well.

John Bellone 1:00:36

Maybe going back to the probiotic discussion, from what I've heard there aren't too many species or taxa in those probiotics. You might be getting more of a certain type of bacteria, but it's not the diversity that we get from just eating a healthy diet. A healthy, varied diet in general.

Tanya Nguyen 1:01:01

Right, exactly. And then depending on the strain of probiotic, some are just one specific species, others have more diverse species. So I guess if you are to choose a probiotic, choose the ones that have different strains, or taxa, so to speak.

Ryan Van Patten 1:01:01

Taking this into account, everything we just said about recommendations, to what extent do you bring this up with your neuropsych patients if you have a feedback [session]? We often talk about exercise and other brain health sort of topics. One would be nutrition. Are there things you're learning about the microbiome, such as diverse plant species that you incorporate into your feedback? Or do you feel like we're not there yet, and it just doesn't quite make sense?

Tanya Nguyen 1:01:48

I personally haven't done it in my neuropsych feedbacks. But if I were to do so, I would definitely encourage eating more fiber, more whole foods, less packaged, less processed, limit red meat consumptions, and abide generally by these

Mediterranean style diet principles, so increase healthy fats, lean proteins, like fish. We all know and have heard that consumption of red meat is linked to atherosclerosis and cardiovascular risk. But not many people actually know that the mechanism by which this occurs is actually through intermediate compounds that are produced by the gut microbiome. So the gut actually produces trimethylamine from choline, which then increases atherosclerosis in our blood vessels. On the other hand, Mediterranean style diets have been shown to beneficially impact the gut microbiota through increasing short chain fatty acids, which I mentioned earlier, are a part of probiotics.

Ryan Van Patten 1:02:48

Right. So we've talked about a lot of different things today. I appreciate all the info, Tanya. I think, in terms of what our listeners are looking for maybe one big picture or takeaway question that I would be interested in you pontificating on is, I know that the literature is in its infancy, the data are sparse, so we can't say for sure, but based on what you know, and feel free to have rein here to speculate, what do you think, what is the relationship between microbiome and cognition? Where are we likely going from here?

Tanya Nguyen 1:03:27

So as you've mentioned, we don't really know a lot about the microbiome and cognition at this point. It's kind of an unsatisfying answer. But the evidence from the studies that have been published is very strongly suggestive of this connection with cognition, at least by proxy. It's well established that inflammation has cognitive and neurological effects, and there's a clear relationship between the microbiome and inflammation. We might deduce that the microbiome, at least via inflammation, might have an effect on the brain and cognition. So that's the mechanism that I'm most invested in and interested in, and I think the one that likely has the most support behind it at this point.

Ryan Van Patten 1:04:10

Yeah, that's a good elevator pitch for people to keep in mind if we're justifying or talking out why and where we think the link is and why this is interesting for neuropsychologists.

John Bellone 1:04:20

It sounds like there are several different mechanisms that need to be really hashed out, or possibilities. Do you see any other limitations in the literature here of microbiome and emotional and cognitive disorders?

Tanya Nguyen 1:04:34

I think one of the limitations right now, at least across disorders, is that there's not much consensus around specific relevant bacteria and mental and cognitive health. I think a lot of the studies have been conflicting. Some say the specific taxas increase, while another study may say it's decreased or specific taxa that are increased in inflammatory bowel disease happen to be decreased in schizophrenia. It's really hard to make sense of the data. One alternative approach to pursuing microbiome research [is] from the perspective of functionality. So how does the microbiome function as opposed to just what is the microbiome by classifying specific bacteria. A way we can do this is through metabolomics and metagenomics, and I mentioned both of these really early on. But through metabolomics, we can understand the metabolites and then therefore the downstream effects of these bacteria on function, immune system, so on and so forth. And then metagenomics can give us the genetic potential of these taxa, or these organisms within our gut, and how that could impact the human genome or just human functioning overall. And this might be a lot more useful than just purely delineating taxonomic differences.

Ryan Van Patten 1:05:56

I'm really glad you said that. That informs our earlier discussion about microbial diversity. So we're not just looking for bacteria A is good and so we want to increase that and that makes a person better, and bacteria B is bad, we want to decrease that. Like you said, the literature is so mixed there that that argues and maybe explains why we're looking at these measures of alpha and beta diversity rather than targeting specific taxa.

Tanya Nguyen 1:06:20

Right, right.

Ryan Van Patten 1:06:22

So, Tanya, in case we have any listeners who are also interested in pursuing this line of research, microbiome and cognition and pairing those together, do you have any recommendations for approaches people might take if they're looking to write grants or pursue a research career in this?

Tanya Nguyen 1:06:39

One potential area of research as we start to understand more about the microbiome is looking at longitudinal studies, which can capture both within subject as well as between subject variability and it can give us a better understanding of

the temporal variation of the microbiome composition. So, for example, sampling during different mood states in bipolar disorder, like during manic versus depressive versus euthymic states or during some different symptoms, like during active psychosis versus remission. So this can help us understand a little bit better about whether the microbiome is more related to traits or to states and can also help us measure changes in interventions, as I mentioned before. There has been one study that looked at the impact of Risperidone treatment in drug naive patients with first episode psychosis. You do see this microbiome shift and think that maybe it's in the metabolic side effects of these antipsychotic medications that could be contributing to changes in the gut microbiome potentially.

Ryan Van Patten 1:07:49
So that's where most interviews would end. But we'd like to ask you two follow up bonus questions, Tanya. These are broad about neuropsychology and not specific to the microbiome. So number one, if there's one thing you can improve about the field of neuropsychology, what would it be? No pressure. [laughs]

Tanya Nguyen 1:08:08
[laughs] I think, for me, that would be innovation. Innovation in terms of how we assess people, how we measure change, and understand brain behavior relationships. I attended the APA conference, back in, I think, August, and there was a talk there that was particularly stimulating. It's funny, you walk into a waiting room and you see your patients, they're all on their iPhones and tablets, and then you walk into a room and you hand them a piece of paper and a pencil and ask them to connect these numbers. [laughs] So I think, of course, there's my older adult population, they would prefer to work with a pencil and a piece of paper, but trying to become more innovative and utilize more technology in neuropsychology and understanding brain behavior relationships, I think, is an important direction that we need to move into especially as technology is being integrated in other medical fields. If we don't go there, someone else might step in, because we're using antiquated methods when the rest of medicine is advancing.

Ryan Van Patten 1:09:19
You're preaching to the choir. Yeah, computerized testing, ecological momentary assessment, capitalizing on iPhones and people can be taking cognitive tests at home, we can collect huge amounts of data easily and quickly. So I agree.

John Bellone 1:09:34
I'm going to rein you guys in a little bit, though. [laughs]

Tanya Nguyen 1:09:37
[laughs]

John Bellone 1:09:37
I think, absolutely, we need to continue advancing and continue, especially with the younger folks, like you mentioned. Maybe older adults prefer this type of paper and pencil kinds of testing. But, yes, I think we need to advance for the younger population. But I don't want to throw the baby out with the bathwater. I think we should hold on to the tests that do continue to distinguish between different neurological neuropathologies, and not throw paper and pencil types of testing out altogether, but maybe incorporate it into the new.

Tanya Nguyen 1:10:16
Yeah, I agree completely. I think these tests have been around for this long because they have such great utility in distinguishing brain disorders and understanding domains of function. But how can we also advance and utilize technology a little bit more, at least in some settings.

Ryan Van Patten 1:10:36
Right, we certainly shouldn't use a computerized test just [to] use a computerized test so that we feel like we're in the 21st century. We should only use it - I think there are advantages, like precision and scoring, and reaction time measures, advantages of these computerized test tests which we could capitalize on that could increase the sensitivity and hopefully, ideally, add more discriminatory power and utility above and beyond what we already have. But we shouldn't blindly make the switch either.

John Bellone 1:11:03
Yeah, we need a whole discussion on this.

Ryan Van Patten 1:11:07
Debate.

John Bellone 1:11:07
A debate. Yeah, Ryan and I.

Ryan Van Patten 1:11:08
Point, counterpoint.

John Bellone 1:11:10
Tanya, the last bonus question is, what is one bit of advice that you might give to someone in training or that you wish you were given that would really have made a difference? Just an actionable step that trainees can take that might help their training and performance overall.

Tanya Nguyen 1:11:32
That's a great question. There's so much advice that I've been given. But I think the one that really stuck out to me the most is, especially for graduate students about to go on internship, interns about to go to fellowship, and then fellows about to try to take that leap into the next step, those trainees at these critical transition points - I was advised when I was an intern trying to decide on a fellowship to pick the option that leaves the most doors open for you. It doesn't have to leave all the doors open, but it gives you enough opportunities in all the different areas that you might be potentially interested in, to then at least have some experience and some opportunities to, if not fully pursue that area, at least take a good look at it and make a decision at a later point whether or not that's something or a road that you might want to travel down or not. That's probably been the most helpful and the most fruitful advice that I've been given. In every decision that I make, I try to make sure that I'm not closing any doors unless I'm ready for it. And then choosing an option that leaves more doors open.

John Bellone 1:12:46
Yeah, I love that answer.

Ryan Van Patten 1:12:47
Yeah, me too.

John Bellone 1:12:48
So, Tanya, thanks so much. This has been really great.

Tanya Nguyen 1:12:52
Well, thank you guys for giving me this opportunity. Appreciate it.

Ryan Van Patten 1:12:54
Yeah, no problem.

John Bellone 1:12:56

Well, that does it for a conversation with Tanya. If you found today's episode interesting and engaging, Feel free to share your thoughts and/or questions on our website's forum at navneuro.com/11. We also wanted to update everyone very quickly on a change to our book raffle. We've decided to shift to a model where we raffle off a book every 10th entry rather than once per month. So if you leave us a review at iTunes and email us with your username, you will have a one in 10 chance to win an AACN Oxford Workshop series book of your choice.

Well, that's it for today. Thanks so much for listening, and join us next time as we continue to navigate the brain and behavior.

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