19| Redefining Alzheimer's Disease: Does Cognition Matter? – With Dr. Adam Brickman

May 1, 2019

NAVIGATING NEUROPSYCHOLOGY

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Speakers: Adam Brickman, 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 wanted to say a couple things before we introduce today's topic. We mentioned at the end of the last episode that we are doing this little side project where we're asking neuropsychologists to visit our website, navneuro.com/mystory, to tell your story about what drew you to the field of neuropsychology. What were the main reasons why you chose to pursue this career and the path that you took to get there? Really there's no avenue, there's no one place that has collected stories from neuropsychologists and we think that it would be really, really cool for students who are potentially interested in pursuing this career to go to the website and see all of the reasons from neuropsychologists about why they are passionate about this field and what initially attracted them to this field. So again, the link is navneuro.com/mystory.

And now, for today's episode, we're talking with Dr. Adam Brickman who is an Associate Professor of Neuropsychology in the Department of Neurology at Columbia University. He's an expert in Alzheimer's disease, which is the topic of conversation today. Specifically, [we're] talking with him about what he thinks of [the] new proposed diagnostic criteria for Alzheimer's disease.

So, Ryan, why don't you give our listeners a little bit of an overview of what the potential controversy is here?

Ryan Van Patten 01:50

Sure, thanks. This is a really interesting topic and issue. To bring people up to speed in terms of how I'm thinking about this at least: So, the topic at hand is Alzheimer's disease, which we've all heard of. And we would think, we've been studying this for over a century now, we think that by now we would know exactly what it is, right? But I don't know about you, John, I still learn new things frequently about Alzheimer's disease. There's a lot of new interesting research coming out. For example, today, our conversation with Adam is around this idea, as John said, of a biological definition of Alzheimer's disease. So the crux here is, in the past, we've talked about several different facets of Alzheimer's disease. There's the biology, which is what is going on in the brain. These abnormal proteins that are pathological, amyloid and tau. And that has been how some people really think about Alzheimer's disease. Then there's also memory loss and the associated clinical syndrome of Alzheimer's disease. That's obviously incredibly important because it's impactful on people's daily lives. We know from movies, potentially from family members, from stories in the news about what happens when someone has Alzheimer's disease and they lose their memory. They don't recognize family members and friends. That's very, very sad. What I'm getting at here is there's

these two different ways of thinking about the disease - the biological way, what's under the hood, the brain pathology that I mentioned, and also the clinical syndrome, the outward appearance of symptoms like memory loss and behavior changes. And what we talked to Adam about today is this proposal for a new biological definition of AD that would decouple the brain pathology from the clinical syndrome and would diagnose AD strictly from the brain disease without needing memory loss or other symptoms that we can observe. Those would not be necessary for a diagnosis of AD. So, as you can imagine, it's a potentially controversial issue. People have different opinions on both sides. Adam certainly has his opinions. And so we dive into that, and John and I ask him a whole whole range of questions to try to really get at the heart of this issue and educate ourselves and everyone else.

John Bellone 04:20

We try to step out of our shoes as neuropsychologists and hopefully we present the other side of the argument from Cliff Jack and other proponents of this new criteria. Hopefully, we have done them justice and their argument justice and presented the reasons why because there are problems with how we're doing things now in terms of the diagnostic criteria and this new set of criteria would potentially solve some of those problems.

Ryan Van Patten 04:50

Yeah. Let's not put the cart before the horse. But I definitely think this is an interesting and impactful topic. I know I spend a lot of time thinking about it. I don't think that there's an answer that we have quite yet on one side or the other. I really like what John said about trying to step outside our shoes and our biases. So John and I are both neuropsychologists. Adam Brickman is a neuropsychologist. And there are people who are trained differently from us. Cliff Jack that John mentioned, is a neurologist physician who has complementary but different training from us. We're trying to be agnostic and neutral as much as possible and just get at the truth. We're all interested in the truth of the matter here. So we hope that today's conversation with Adam gets us closer to that ultimate truth and provides you, our listeners, with a little bit of knowledge that you didn't have yesterday. I know it was the case for me just going through this conversation. It was really fun and enlightening. So without further ado, we give you Adam Brickman.

Transition Music 05:52

John Bellone 06:01
All right, Adam. Thanks so much for joining us here on NavNeuro. We're really excited to have you.

Adam Brickman 06:04
I'm excited to be here. Thanks for having me.

John Bellone 06:06
Yeah. So we wanted to talk to you about this biological definition of AD. And the reason why I was so excited to talk to you about this is because I saw there was a talk or a debate that happened in DC at INS 2018. A lot of people were there, I know the room was absolutely packed. You guys went over time. I mean, everyone was so interested in this topic. And it was between you and Jen Manly, Mark Bondi arguing for cognition to remain in the diagnostic criteria for AD versus Cliff Jack, a physician who had championed this biomarker only criteria, which has been referred to as the ATN model. So, we will have already provided listeners with a broad overview of the differing viewpoints on AD as a biological entity. But I want to turn the floor over to you to see what you think of these issues. What are your thoughts about this broadly?

Adam Brickman 07:08
Yeah, it's a very hot topic, obviously. I mean, I think that - well, just to summarize what the new diagnostic criteria are saying. The new diagnostic criteria are asking the question, "Can we use biological information to determine whether a person has amyloid in the brain?" If they don't, [then] they don't meet criteria for Alzheimer's disease. If they do, then we use a different biomarker to determine whether they have tau pathology in their brain. If they do, then they meet criteria for Alzheimer's disease according to the new scheme. So, as you mentioned, that doesn't at all take into account any aspect of behavior. Once someone does meet these criteria for Alzheimer's disease, then we could ask the question, "Well, how impaired [are they]? Or [are] they impaired at all?"

So that's a big, big, big shift in one way from how we've thought about Alzheimer's disease historically or how we've diagnosed Alzheimer's disease historically, which has been a diagnosis of exclusion. We characterize people based on a clinical syndrome, typically an amnestic disorder that changes over time or declines over time that ultimately affects their ability to take care of themselves. And once we've ruled out other potential causes of this syndrome, we would assign the diagnosis of probable Alzheimer's disease. So, in that way, it differs dramatically. So we've gone

from a diagnosis of exclusion to a diagnosis of inclusion. However, it hasn't changed that much because, historically, the diagnosis of definite Alzheimer's disease has always been based on whether someone has plaques and tangles in their brain and that previously could only be done at post-mortem, or with the biopsy, which very few people volunteer for. So it doesn't vary dramatically from that conceptualization. Now what we could only do definitively in the past, we can do definitively with biomarkers. So I have mixed feelings about the whole thing.

I think I've been criticized a little bit for being anti-biology and that's certainly not the case. I think that the brain controls behavior and when something goes wrong with behavior, it's because something has gone wrong in the brain typically. But I think that my overall problem with the whole model is that it embraces the amyloid hypothesis as the only pathogenic way to get what we have always called clinical Alzheimer's disease. That there's amyloid processing abnormalities that cause tau in some way, which causes neurodegeneration, which causes dementia. And I think that it's premature to make those causal inferences at this point in history. And I think that a lot of the literature and a lot of the experiments that are coming out now are speaking against the amyloid hypothesis. So I have a big problem with that.

Ryan Van Patten 10:04
The framework you refer to, the new definition, is that the 2016 Cliff Jack ATN framework?

Adam Brickman 10:12
The 2016 paper is when Cliff and colleagues introduced this idea of ATN. The diagnostic criteria, I think, were published just in 2018. It was a diagnostic framework published on behalf of the Alzheimer's Association and the National Institute on Aging in Alzheimer's and Dementia. I think Cliff put out the ATN framework in this Neurology paper in 2016.

Ryan Van Patten 10:35
Right. The 2016 [paper] was laying the groundwork for the 2018 [criteria], the actual formal definition. So, in looking over those papers, I actually hadn't come away with the idea that they were so focused on the amyloid hypothesis exclusively. I thought, “Oh, this ATN model is helpful in terms of saying: Amyloid? Yes/no. Tau? Yes/no. Neurodegeneration? Yes/no.” But there may not be a temporal ordering that is implied by the ATN model. It sounds like your interpretation is that it's really tied to the amyloid hypothesis. Like, amyloid is the first step.

Adam Brickman 11:12

I think it's definitely tied to the amyloid hypothesis. And I get that they're being agnostic to temporal ordering because the data haven't necessarily supported the temporal ordering of the amyloid hypothesis. But if then we just reduce it to a diagnostic scheme that says, "Okay, these factors, which might or might not be related to each other causally are necessary for a diagnosis of Alzheimer's disease", why stop at those three elements? In my mind, it's arbitrary. If you're not embracing a causal - amyloid leads to tau - but you just have to have some combination of these things, that to me is arbitrary. There are myriad pathologies that affect the aging brain. Many of them are associated with cognitive problems, and many of them co-occur with amyloid and tau. So why not throw them in the mix as well? As long as we're already defining this as a mixed dementia, which is amyloid and tau, two different pathologies not causally related to each other necessarily, let's open it up and include other pathological features. So with that sort of framework, what's my alternative? What I still prefer is that we think about the Alzheimer's syndrome, which I think clinically is very comfortable for most people, right? And then we start thinking about these different pathologies in the aging brain as their own diseases. So rather than requiring amyloid and tau to define Alzheimer's disease, I'm in favor of saying someone has amyloidosis and tauopathy. How do those things interact to induce - or do they interact to induce this clinical syndrome that we've been defining as the Alzheimer's clinical syndrome? So it's more of a hypothesis-generating way to think about Alzheimer's disease, because I think there's a lot of hubris right now in terms of what it is and what it isn't and we're not ready quite yet to embrace this definition.

John Bellone 13:22

Just for our listeners, when we refer to temporal ordering, we're talking about what comes first. Is it the amyloid that then causes tau and then neurodegeneration? Just so everyone knows, that's what we're referring to. So I'm trying to play the devil's advocate, I'm going to try to be a proponent of the ATN.

Ryan Van Patten 13:42

You're going to be Cliff Jack for a moment.

John Bellone 13:43

Yeah I'll be Cliff Jack.

Ryan Van Patten 13:44

You wish.

John Bellone 13:45

Yeah, I do. [laughs] But so I think what he would say, what proponents of his model would say, is that we're calling Alzheimer's disease, the plaques and tangles. Let's be clear, let's clean up the language here a little bit. We'll just call it this, it's much simpler. We can target it for research. And then all the other syndromes, the other diseases, vascular disease and everything else that falls under that syndrome, we would just call something else and treat it differently.

Adam Brickman 14:18

Right. Yeah, I get that argument. It's very confusing for people who are our patients. It's very confusing for practitioners. And it doesn't really represent reality. It's a definition of a disease that doesn't exist. The definition exists, but the disease doesn't exist as it's defined. Alzheimer's disease, pure Alzheimer's disease as defined, is only really present in asymptomatic people. In other words, once you have symptoms, the pathological landscape is much more heterogeneous. So I get exactly that argument. That we need to all be on the same page when we're talking about X, Y, and Z. It helps inform research studies, it helps us design appropriate clinical trials. But I would argue that if we embrace the definitional aspects of the actual pathological features, as I just suggested, calling things amyloidosis, calling things tauopathy, calling things TDP-43opathy, calling things supravascular disease - we have all these different disease conditions that seem to co-occur [in] the aging brain, and then we can still do all the science that Cliff is worried we're not going to be able to do if we if we don't embrace his definition. In other words, if you think that amyloidosis is a cause or definitional aspect of the Alzheimer's syndrome, then let's design a clinical trial that treats amyloidosis and see if it affects the outcome, which is clinical Alzheimer's disease or clinical Alzheimer's syndrome. You can still do all those things that we're concerned about if you're a little bit more precise in your definitions by calling each element that you're concerned with by its proper name. As opposed to just simply arbitrarily or quasi-arbitrarily putting together these two pathologies that seemed to co-exist in a lot of people and saying that's the disease, everything else is either comorbidity or something else that happens in other people.

Ryan Van Patten 16:30

Yeah.

Adam Brickman 16:30

I don't know if that helps explain that viewpoint. I think, on the one hand, clarifying and making sure that we're all using the same language is very, very important. On

the other hand, it's really, really making the view of Alzheimer's dementia much more myopic. And, right now, in terms of treatment, therapy and prevention, we need to be thinking out of the box, not in the box.

Ryan Van Patten 16:53

Right. Part of what you're saying that really resonates with me is that I've worried that, in clinical trials, if we are defining AD as amyloid and tau, then we could "cure AD" by eliminating amyloid regardless of whether or not someone ultimately develops dementia. An older adult doesn't care if they have amyloid or not. They care if their memory is impaired or not. So the target of a clinical trial shouldn't be only amyloid, and then amyloid is reduced and you're "cured". If the person then goes on to develop memory loss and dementia, then the amyloid point is moot to them, essentially.

Adam Brickman 17:35

That's exactly right. You can do this with all sorts of thought experiments. So let's say, for example, I have a compound that treats inflammation. And I show that in people with or without amyloidosis, if I treat them with my new magical compound, none of them go on to get dementia of the Alzheimer's type, what we've always called Alzheimer's dementia. But it has no effect on amyloid, zero effect on amyloid - it just changes neuroinflammation. Amyloid keeps accumulating, no effect on amyloid at all. According to the new criteria, and possibly by FDA adaptation of this framework, that's not a treatment for Alzheimer's disease.

Ryan Van Patten 18:19

Right.

Adam Brickman 18:19

We haven't treated the disease. We've prevented the dementia that we've called Alzheimer's dementia, but we haven't treated the disease. So that would not get FDA approval in this thought experiment for a treatment for Alzheimer's disease, yet it might totally prevent the syndrome associated with Alzheimer's disease.

John Bellone 18:34

But wouldn't it be a treatment for what we're calling dementia then? I think in their model they're arguing to separate it - separate the biology from the clinical presentation. And so if it does reduce cognitive decline, then it could be FDA approved under this other name, maybe “dementia”.

Adam Brickman 18:55
But what would your other name be? Dementia?

John Bellone 18:57
Maybe. I mean, that's what we use now, right? Everyone asks...

Adam Brickman 19:02
[crosstalk]

John Bellone 19:02
Sorry.

Adam Brickman 19:03
Sorry, I'm cutting you off.

John Bellone 19:08
Like you said, it's so confusing. Every patient asks me, "Okay, so what's the difference between dementia and Alzheimer's disease?" And, it's confusing. I have to say, "Well, there [are] still some questions that we have even as professionals." And that's not comforting to them. So I guess embedded with my question is, to what extent is this just semantics and we're calling one thing, one thing, and another thing something else?

Adam Brickman 19:33
Right. I think that's a big part of it. It's not just semantics. It's also a guild issue. So we're all neuropsychologists, like, how dare you take away our ability to diagnose Alzheimer's disease? That's what we do! We're neuropsychologists! So that's a guild issue, but it's also an emotional issue. A radiologist is going to tell me how to diagnose my patients? I don't think so. So there is that element of non-science semantics, guild issues, personal biases, skin in the game, emotionality, all that stuff. I totally acknowledge that. But I think that there's something bigger than that. I'll illustrate it with the point. Have you heard about the recent failure of the amyloidosis trials, the Biogen trial? Did you guys hear about that?

John Bellone 20:30
Yeah, it was the aducanumab or something like that.

Adam Brickman 20:34
I can never pronounce it. It was just recently announced that Biogen did an interim analysis and there was no outcome whatsoever. It was an anti-amyloid trial. Big news, all over the newspapers, another failed trial for Alzheimer's disease. Did you guys hear about the SPRINT MIND trial?

John Bellone 20:54
No.

Adam Brickman 20:55
The blood pressure trial? Did you hear about that?

Ryan Van Patten 20:57
No, me neither.

John Bellone 20:58
Oh, yeah. I did. Yeah, it was for MCI, right? Yeah, it helped for MCI but not for dementia. Lowering blood pressure, right?

Adam Brickman 21:08
Right. So was that as big news as the Biogen failed trial?

John Bellone 21:12
No.

Adam Brickman 21:12
No.

Ryan Van Patten 21:13
Right.

Adam Brickman 21:13
Right. So what the SPRINT MIND folks found was that an aggressive reduction of blood pressure reduced the incidence of mild cognitive impairment. It also reduced the incidence of dementia, the effect sizes were similar to mild cognitive impairment. Although the p-value wasn't significant, the effect size was quite similar. So there is very, very encouraging news about this trial that reduced blood

pressure reduced the incidence of mild cognitive impairment and the incidence of dementia. So, yeah, it got some news, but had the title of that trial been "lowering blood pressure reduces Alzheimer's disease risk", what kind of news do you think it would have gotten? It would have been huge. And not only would it have been huge, the publication of that paper itself and the publicity around that paper, had it had the word “Alzheimer's disease” in the title would have in itself been a public health intervention. People would have been like, "What is this news about blood pressure?" They would have gone to their doctor, they would have asked about blood pressure. People would be more aware of blood pressure as a reasonable target to lower the risk of Alzheimer's disease. People are terrified of developing Alzheimer's disease. So when we make it the esoteric, myopic definition based on pathology, it somehow diffuses or robs the public health impact of the actual syndrome as it manifests in society.

Now, if you look at that SPRINT MIND paper, their definition of dementia was pretty good. It was pretty close to how we've historically diagnosed clinical Alzheimer's disease. They didn't have biomarkers, so they couldn't really say, "Oh, these people did or did not have Alzheimer's disease." But it's similar to, for example, all the genetic studies that have identified risk genes for Alzheimer's disease. Those studies tend to use these clinical definitions of Alzheimer's disease, and they call it Alzheimer's disease because they need hundreds of thousands of people to find genes. But now with this biomarker age, there's a hesitancy to refer to things that we've historically called Alzheimer's disease and it's diffusing or reducing the potential public health impact of things that are actually working.

Ryan Van Patten 23:40

Right. There's a power to the term Alzheimer's disease that even dwarfs dementia. A lot of people know about dementia, but to get publicity for public health purposes, using AD will elevate that finding way above everything else.

Adam Brickman 23:56

Absolutely. And my point there is really that it is semantic, but it's much more than semantic. It is a real public health thing. And it's very, very confusing to talk to the public and say, "Oh, yeah, you can have Alzheimer's disease without symptoms. Or you can have dementia without Alzheimer's disease." People get very confused by that.

Ryan Van Patten 24:18

Right.

John Bellone 24:18

I think that's a great point. To move into clinical trials, let's say, a lot of times what we call dementia, dementia due to Alzheimer's disease or probably due to Alzheimer's disease, when we later autopsy them or we give them an amyloid PET scan, we find that a lot of them didn't actually have the amyloid, or didn't cross the threshold of amyloid. So if we're leaving it as is within the syndrome, are our interventions not going to be as targeted in some of those clinical trials? Meaning that, let's say, 30% of the people in those trials that we're calling probable Alzheimer's disease won't actually have the same underlying pathology as the other patients in this study.

Adam Brickman 25:13

It's a great question. My response to that is if you think that your clinical trial that you're designing requires there to be amyloidosis, then make that an inclusion criterion. That's not complicated. We do it with all sorts of things. If you don't want people with a history of stroke in your Alzheimer's trial, exclude people who have a history of stroke and you can still test your medication. So I agree that, yeah, if we just use a clinical definition to define Alzheimer's disease, that if we run clinical trials based on only the clinical definition of Alzheimer's disease, then we're including more heterogeneous populations or samples into our clinical trials. However, we have control over the science that we do. So like in my example of inflammation, if I think that inflammation is a target - and I'm just using this as an example, I don't have some secret inflammatory drug that I'm testing. But [if] I think that it operates on something that's independent of amyloid, I might include people who have clinical AD or at risk for clinical AD into my study, irrespective of their amyloidosis status, and test to see if my anti-inflammatory drug improves their outcomes. Or if I have a tau drug, I might require people to have evidence of tauopathy outside of their entorhinal cortex in order to be my trial, based on my inclusion criteria. It's not threatening how we define or not define Alzheimer's disease. We can still design the experiments we're running, the clinical trials, which are experiments based on the inclusion and exclusion criteria and test the hypothesis.

Ryan Van Patten 26:58

Yeah. I have a couple of follow up questions.

John Bellone 27:02

Before you go there. Sorry. I guess you could potentially argue it the other way, though, right? Cliff Jack could say, "Well, it doesn't affect your trials that you want to run by calling Alzheimer's disease the biological definition because you would just

have a separate word for dementia. Or you can include people with Alzheimer's disease, people with vascular disease, you can still run the same trials." I guess, potentially, right?

Adam Brickman 27:30
I think I follow what you're saying. Yeah. I mean, I think, yes. To me, it just really depends on what mechanism you're testing. Because I think that, ultimately, if there's one thing that the amyloid trials have taught us is that simply removing amyloid plaques from the brain is not so far a reasonable approach to treating this.

John Bellone 27:58
I guess they would counter that they're trying to administer the intervention earlier and there have been some of those drugs that are different from others.

Adam Brickman 28:09
Yeah. All testable hypotheses, right? So show me. Show, with some clinically meaningful outcome, that treating amyloidosis earlier or as early as possible will have some later effect. These are all hypotheses. These are all hypotheses that have been generated by failed trials because they're always post-hoc, right? They're always like, "Oh, why didn't that work?"

Ryan Van Patten 28:34
Right.

Adam Brickman 28:35
"Maybe it's because of this, let's test that." And I'm in favor of that. At some point, the field is going to have to make a decision about whether or not we and the pharmaceutical companies are going to dump literally hundreds of millions of dollars into these trials because we keep hearing the press releases and the thought leaders saying, "Oh, well, we wouldn't have expected that trial to be successful because it was too late in the disease." Well, why did we run it in the first place? When are we going to say that we're early enough? I think the A4 trial is going to teach us a lot. I think the trials in autosomal dominant forms of Alzheimer's disease are going to teach us a lot. But, at some point, the field is going to have to make a decision about whether we're barking up the wrong tree or whether we're really onto something that's going to help people.

John Bellone 29:26
Yeah, they keep moving the goalposts when they don't score.

Adam Brickman 29:30
No one's ever questioning the hypothesis. It's always "Oh, the experiment we designed to test the hypothesis was wrong." You know, at some point, we have to start believing our experiments.

John Bellone 29:41
It seems like maybe we would get more funding for Alzheimer's disease research versus funding for -you know, to your point that the name really matters. It makes a difference. It potentially could impact funding, too.

Adam Brickman 29:58
I think so. I think from NIH's perspective, they take a more broad view. The buzzword is Alzheimer's disease and related disorders. I think given what we know about Alzheimer's disease and aging and neurodegeneration, most other things that you can think of are somehow related.

Ryan Van Patten 30:17
"Other" is doing a lot of work there.

Adam Brickman 30:19
Even the Alzheimer's Association isn't myopically focused on Alzheimer's, per se. They also take this "Alzheimer's and related disorders" sort of viewpoint. I think funding wise, the good news is folks like the Alzheimer's Association have really done a phenomenal job getting congress to agree to fund more aging research. That's really been a change. I've been in the field long enough to see or to remember when we were getting grants scored very, very, very well that just weren't funded because the money wasn't there. Now grants that are scoring well, maybe not as well as in the past, are getting funded. So it's really been a changing landscape. I think access to funding has only improved with these debates and these arguments. But I think that there's still this public health, guild, semantics issue that's not trivial.

Ryan Van Patten 31:18
It's important to recognize that we are all part of groups, professional groups, guilds and that impacts how we think about things as neuropsychologists. We are only

naturally going to value cognition and what we do from a personal defense perspective. I'd like to back up for any of our listeners who didn't quite catch a few things that were implicit earlier. So we talked about temporal ordering of AD, the traditional model of how Alzheimer's disease works. These are some of Cliff Jack's older papers, the temporal dynamics of the biomarkers. The idea has been that, in the amyloid hypothesis, amyloid develops first [and] this can happen 15 to 20 years before clinical syndrome. Then there's some impact of amyloid causing tau to develop, especially in the medial temporal lobe, which leads to neurodegeneration and then a clinical syndrome. My question, Adam, is, what, if any, evidence is there for a relationship between amyloid and tau? It's always been implicit that amyloid accumulates more so than in healthy older adults, and then that, in this temporal ordering, is leading to or even causing tau to increase in the medial temporal lobe. But your proposal of separating those, amyloidosis and tauopathy, and studying them separately, I think you're suggesting that amyloid does not have an impact on tau. Is that correct?

Adam Brickman 32:47

So, yes and no. There is a lot of evidence. I mean, when you study histopathologically people who have Alzheimer's dementia, the vast majority have both tau and amyloid pathology in their brain. And the vast majority of people who have tau pathology in the Braak stages, the pathological staging, spatial staging for tau pathology, the vast majority of them outside of the Braak stage 1 and 2 have amyloid pathology. So these things co-occur a lot. We can certainly find more people who have amyloid pathology without widespread cortical tau pathology, but people who look clinically like Alzheimer's disease have tau throughout the cortex [and] are more likely than not to have amyloid pathology. So they definitely co-occur. They definitely co occur a lot. And you can look at all the early amyloid hypothesis papers, the arrow is always that amyloid causes tau pathology. And I think that's where the question has arisen recently. That there doesn't seem to be a known link between amyloid causing there to be tau hyperphosphorylation or anything like that. Rather, it does seem to be that once amyloid is present that tau, which is typically, in aging, restricted to the medial temporal lobe, specifically the entorhinal cortex - the hypothesis is that amyloid is somehow releasing, potentiating propagating tau pathology outside of the medial temporal lobe into lateral temporal lobe, parietal lobe, and frontal lobe throughout the cortex. So there definitely does seem to be this co-occurrence. There definitely does seem to be at least the possibility that amyloid is contributing to the propagation of tau pathology. And that tau pathology is much more closely linked to cognitive outcomes. But this causation, I think, is still under much debate.

Ryan Van Patten 34:58
Yeah, that's helpful. So then moving forward, I'd like to propose or put forth a few additional models that I've seen and get your opinions on them - models of AD, broadly. So one idea would be, going back to the Jack ATN model, obviously ATN - amyloid tau neurodegeneration - does not take into account cognition, which is a big piece of the AD picture. [It's] what we've been talking about. So could we take ATN and then add a C for cognition? Or is that still off?

Adam Brickman 35:35
Yeah, I think it all helps. Do I think that cognition... - Yeah, I think we have to question the overall framework. You can add C, and you can add V, and you can add the other T, TDP. And then you can have like, you know, an 18 dimensional space...

Ryan Van Patten 35:57
[laughs]

John Bellone 35:57
[laughs]

Adam Brickman 35:57
You know, where someone is in one of those boxes, right? I don't want to come across as being overly critical of ATN or overly critical about frameworks. I think they've done a tremendous job in focusing the questions and forcing us to think about, "Well, what's relevant here?" But I think that the idea of just having a grid and putting a checkmark in this grid and saying, "Okay, you have Alzheimer's disease based on one of these three dimensional space grids here" is a little bit simplistic, where the biology is much more complicated.

Ryan Van Patten 36:40
Yeah. What if we used that model but dissociated it from Alzheimer's disease? That sounded similar to what you were suggesting earlier. You could take a patient, even clinically potentially one day, and say, A positive, T negative, N positive, C positive - that sort of thing, without saying you do or don't have AD. And maybe that could be clinically helpful.

Adam Brickman 36:59

Yeah, that I'm super jazzed about. I mean, particularly as we're getting better biomarkers. And particularly as we're learning, for example, from Julie Schneider's work at Rush about all the heterogeneity about what happens in the aging brain. Ultimately, we're going to want to characterize the different pathologies that we can measure. But we still have to test the hypothesis that what we're seeing pathological is causally related to the syndrome that we're seeing. Alzheimer himself didn't do that. I mean, he had a patient with dementia syndrome and he saw some sticky stuff in her brain and made the causal link, but it was just correlational. We can only do correlation at that level. So I'm in favor of biomarkers and characterizing the brain in detailed fashion, both on the pathological histopathological side, but also on the neuropsychological side as well.

Ryan Van Patten 38:04

Right. One other model that I've come across that I'll propose and I'm curious [about] your thoughts. I originally saw it in 2011, NIA Alzheimer's Association paper, Reisa Sperling and others, who were taking AD and breaking it down to ADP for AD-pathological and ADC for AD-clinical, which felt like it was giving equal weight to both biology under the hood in the brain and the clinical syndrome that we're seeing. Then potentially using that model, we could say that the SPRINT trial that helped in terms of the clinical syndrome, the MCI dementia, that's treating AD-C, which is Alzheimer's disease, but then biomarkers antemortem are measuring AD-P. What do you think about that?

Adam Brickman 38:55

I think that's a little bit closer to how I probably think about the whole thing. That was from the 2011 criteria for the MCI due to Alzheimer's disease, right? Oh, no, a preclinical Alzheimer's disease. I think that that resonates a little bit more to me as a clinician and as a clinical scientist. I think that that's actually closer to where we should go. Although, in that model, you still have to categorically accept that we know what pathological AD is.

Ryan Van Patten 39:35

[laughs] Right.

Adam Brickman 39:36

I think that that, to me, is where the hubris is a little bit in our field. "Oh, like, we've already established that tau is the whole story."

John Bellone 39:47
[laughs]

Adam Brickman 39:47
"So, like, what else is there?" And that, to me, is what's scary as we're facing time and time again failed clinical trials. Maybe we should be questioning the fundamental assumptions of our field, which is [that] amyloid and tau are causing the syndrome that we're seeing.

John Bellone 40:08
Yeah. You could also have the AD clinical without any of the pathology and that also could cause some problems. One other argument that a lot of proponents of this Cliff Jack model pose is that, since the pathology begins - let's say it is the amyloid hypothesis, let's say that's correct. The pathology begins long before cognitive impairment shows up. So by the time the symptoms appear, it's way past the ideal intervention period. One analogy that I can think of that they would use is that it's like the difference between hypertension and stroke-related cognitive impairment. So, wouldn't calling the AD pathology and the clinical symptoms the same term be like calling hypertension and stroke the same thing? I understand we haven't established the cause of Alzheimer's disease, and maybe that's the argument against this.

Adam Brickman 41:10
Yeah. I mean, exactly, right? So we know that if you reduce hypertension, you reduce the risk of stroke. Do we know that if we reduce amyloidosis, we reduce the risk of clinical Alzheimer's? We don't know that yet. It's a hypothesis. This idea that we're not treating early enough? I'll just say it again, it's a hypothesis. It's a reasonable hypothesis, but it's a hypothesis. I would say that even in someone who has stroke with cognitive impairment, if they're still hypertensive, if you treat their hypertension, you'll reduce the risk of another stroke, right? So in people with Alzheimer's disease with amyloidosis, if you reduce amyloid, it doesn't do anything clinically. So that part doesn't fit with the stroke and hypertension analogy. Cliff is very, very good at drawing lots and lots of analogies. And they're very convincing, I think. You know, prostate cancer is an interesting one, because we've over treated prostate cancer, I would argue, and caused a lot more harm in many cases than good. But certainly, there are other analogies that fit in with the ATN model. I always like to think of analogies to counter the other analogies.

Ryan Van Patten 42:35
[laughs]

Adam Brickman 42:35
Ridiculous sort of game of logic.

John Bellone 42:39
[laughs]

Adam Brickman 42:40
But you can imagine… - I've discovered a biomarker for depression. And I have two patients, one who's fine and happy and living life, but their biomarker for depression is elevated. I'm going to diagnose them with depression, because they're positive for my biomarker and I'm going to treat them. I'm going to start you on this treatment for depression because you have depression. And that patient may say, "I don't have depression. I feel great, I'm fine." They say, "I'm not depressed. My friend over there is depressed. They're suicidal, they have anhedonia. They can't get up. They're sad." And I say "No, they don't have depression because their biomarker is negative for depression. That's something else, that's not depression. That's something else. You're the one who's depressed. You're the one who has depression because of your biomarker..." So there's an analogy.

You can also think about amyloidosis as gray hair, right? Like, most people with Alzheimer's disease have gray hair, right? Some people with Alzheimer's disease don't have gray hair, is it really Alzheimer's disease? People with gray hair are certainly at greater risk for developing Alzheimer's disease in the future. If we color the gray hair, it's not going to change the outcome very much. You can concoct all sorts of irrelevant analogies.

John Bellone 44:06
Right. So now we're giving amyloid PET scans to preclinical individuals. Individuals who have amyloid but haven't shown the clinical syndrome yet. And now we're scaring them and their families into thinking that they are going to get Alzheimer's disease.

Adam Brickman 44:26
Well, that's dipping your toe into the whole ethical dilemma. There hasn't been too much work on disclosure yet. Jason Karlawish was just starting to really look at this

at Penn. It's a real issue. What do people want to know? So, you say, "Okay, you have amyloid in your brain." So they say, "Okay, well, when am I going to get symptoms?" And what can we tell them? "We don't know. You might not get symptoms if you die before the symptoms manifest. So, hopefully, you'll die." Or, [laughs] like what do you tell them? And, "Okay, well, how much amyloid do I have in my brain?" "Well, it seems to be sort of a bimodal distribution. The dynamic range of amyloid doesn't seem to be as important as whether or not you have amyloid in your brain. And you have amyloid in your brain." "Okay, well, should I quit my job?" "I don't know." You know, we have very little we can tell people because we don't really understand what's going to happen to them and when. Everyone is so enamored by biology, that all we can say is "you have a disease", but we don't necessarily know how or when it's going to manifest.

John Bellone 45:39

I read a recent JAMA article on the idea of a “pre-caregiver”. Someone who knows that they are going to become a caregiver because their partner or spouse has been told that they are amyloid positive.

Adam Brickman 45:55

Yeah, that was Jason and I can't remember...

John Bellone 45:59

I forget the author's name.

Adam Brickman 46:02

…who took the lead on that. But, yeah, it's the same sort of thing. Like this concept of pre caregiver and just the ethics of disclosure and communicating to someone that they have a disease that doesn't have symptoms. It's very, very complicated. There's no consensus yet. It's very tricky.

Ryan Van Patten 46:22

I think we could potentially draw a little bit on the literature on disclosure of APOE status. John and I had a recent episode with Dr. Megan Collier on that topic. You know, there's more work on that. I think genetics and AD-APOE, we could maybe use that to inform PET amyloid positive disclosures.

Adam Brickman 46:42

It's probably similar. If someone has APOE-4, it's probably similar in terms of risk as someone who's asymptomatic and amyloid positive. Someone who's amyloid negative, doesn't mean there's the flip side. You get a PET scan and, "Oh, I don't have Alzheimer's disease. I'm safe." And then who knows what happens in five years. So.

Ryan Van Patten 47:06
Communicating that to patients and participants in research studies can be challenging. It's hard for a lot of folks to understand relative risk. It's complicated.

Adam Brickman 47:15
Oh, yeah, for sure. I think some of the early findings, I don't know if it's been published yet, [but] I heard about it at an Alzheimer's meeting, the A4 trial, which enrolls people who are asymptomatic but amyloid positive, they have it embedded in them. This is the study that Jason Karlawish was just leading. A study that discloses their amyloid results and tests the impact. So this gets at the bias of who's involved with these studies or who's enrolling in these studies. People are enrolling in the studies because they're concerned that they have amyloidosis. So when they disclose that they have amyloid, one of the logical responses would be like, "I suspected, so." No change in my feeling, that's why I'm here. I think I have amyloid in my brain, you just confirmed it. Versus, "Guess what? You don't have it in your brain." And then the reaction there could be tremendous relief and happiness. So some conclusion can be like, "Oh, in this particular population, you tell them that they don't have amyloid in their brain, it increases the mood and the positive affect. But if you tell someone that they do have amyloid, there's no consequence whatsoever to their emotionality." But that's entirely biased by the people who do come in. Now, move that into the community, into different populations where there's more education diversity and more socioeconomic diversity, and it's more of a community-based environment, then try to disclose this type of information to those folks and the reactions, I think, would be much different and much more difficult to handle clinically.

Ryan Van Patten 49:00
Yeah, without a doubt. It's a very interesting discussion. I'd like to follow up on one more thing. We've talked a lot about amyloid and the amyloid hypothesis. I've seen at least a few alternatives to the amyloid hypothesis. One that has stuck with me for a few years is this idea - I don't think there's a lot of support for this, just thinking outside the box - that amyloid is not the upstream cause of AD. It's simply a marker along the way. This alternative proposal was that maybe microvascular changes

are the ultimate upstream cause. I think the author, this is Drachman 2014, was citing the overlap between vascular dementia and AD - similar risk factors, similar processes. That's just one example. I'm curious if you have thoughts about a leading alternative to the amyloid hypothesis, or is that too early?

Adam Brickman 49:51

I think it's too early. You can imagine a scenario where what Drachman was arguing could be the case. So amyloid is a big sticky protein. And, if, let's say there's breakdown of the blood brain barrier or some primary vascular lesion, amyloid could be seeping out from the vasculature into the parenchyma and just accumulating because it's big and sticky. The problem there isn't the amyloid itself, but the vascular impairment or endothelial dysfunction or whatever. You can concoct different biological scenarios that would lead to amyloid accumulation without actually amyloid being an initiator of the cascade of events and really understand why amyloid is deposited. The genetic models are very seductive. In the APP and even in Down syndrome, they seem to overproduce amyloid and then get dementia. So it's very seductive to say, "Okay, well, the genetic models prove unequivocally that this amyloid is really driving this whole thing." But even in those models, you could probably concoct different biological changes that would initiate amyloid deposition even though they're producing amyloid at a greater rate than in other populations.

John Bellone 51:23

Or they could be different. There could be something different about the familial versus the sporadic Alzheimer's disease as well.

Adam Brickman 51:29

Yeah, for sure.

Ryan Van Patten 51:31

This is a fascinating discussion without a doubt. I'm really glad we've touched on this.

John Bellone 51:35

I have a few other things, just so we don't exclude other potential alternatives. We should probably save this for a longer conversation another time, but there's the energy shortage due to mitochondrial damage [hypothesis]. That's another one that I've heard of. There's also an infectious hypothesis where an infection, herpes let's

say, leads to amyloid increase. And so it's a byproduct or even a protective response to neuroinflammation. Which [is] kind of chicken and egg because amyloid causes inflammation. So there are a number of other hypotheses.

I wanted to ask you a couple of questions before we finish. One is that I want to hear how you define the difference between Alzheimer's disease and dementia. Do you have a canned response that you give to patients when they ask you this?

Adam Brickman 52:28
I know that I like to ruffle feathers, but clinically I'm pretty conservative. I tend to give the same spiel that we've always given. “Dementia is a syndrome that manifests as memory or cognitive decline, and ultimately affects their ability to take care of themselves. But it's a category. And there are lots of different causes of dementia. Alzheimer's disease is one of the causes of dementia. There are other causes of dementia, too. I think that you have Alzheimer's disease.” That kind of thing. I tried this out for the first time actually, I gave a community talk two or three weeks ago, and I tried to start explaining.

John Bellone 53:14
[laughs] Good luck.

Adam Brickman 53:14
I usually ask the audience, "Tell me what the difference is among dementia, Alzheimer's disease, and senility or being senile." I'm just curious about what they say. And, you guys know, like, you get all sorts of different stuff. "I only have Alzheimer's disease, I don't have dementia." Or, "My mom has Alzheimer's disease but not dementia." There's still a lot of confusion, [even though] we've worked very hard over the last several years. Then I tried to introduce this idea that today scientists think that you can have Alzheimer's disease without having any symptoms. And everyone was like, "Oh. No."

Ryan Van Patten 53:59
[laughs]

Adam Brickman 54:01
"When you can't find your way around your neighborhood or you can't remember your grandchildren's names, that's Alzheimer's disease." And I'm like, "No, some people think that you can have Alzheimer's disease and be completely totally fine."

And they're like, "Doctor, you're crazy." I got, like, payback. That was, you know, a community talk in Washington Heights, which is a neighborhood in northern Manhattan where I work. At a YMCA, like a community center. So people who were interested in learning about cognitive aging and memory, so [they were] motivated. But still there's a lot of nuance to what we're doing and what we're arguing and how that's interpreted by the community.

Ryan Van Patten 54:50
You're listening to your constituency. You're asking the people. [laughs]

John Bellone 54:56
Yeah, colloquially, you're right. It's very intertwined, Alzheimer's and dementia. So, for us neuropsychologists, do you have any suggestions of what we might do if we feel particularly strongly about this new nosology? It seems like it's already been established or the physicians have already - I don't want to do neuropsychology versus physicians, but it seems like the field is progressing as if Alzheimer's disease is a biological disease. Or at least the new papers that I see coming out, especially with all the new biomarkers.

Adam Brickman 55:32
Yeah.

John Bellone 55:33
Those are going to continue to come out. Do you have suggestions of what we might do?

Adam Brickman 55:37
I don't think it's bad. I think it's good that all these papers are coming out that embrace a biological orientation. I just want to reiterate that I'm not anti defining things biologically. Again, the brain controls behavior. Something's wrong with behavior, something's wrong with the brain. Let's figure it out. I think that there are a lot of very, very influential thought leaders or knowledge leaders, however you want to think about them, that are very much defining the conversation, but that doesn't necessarily reflect what the whole world thinks. In fact, I give these talks at different institutions and you end up that when you're talking to the front end, front line clinicians they're like, "Oh, yeah, it's not just plaques and tangles. My patients are medically very, very complicated." And I think that, while the thought leaders in the field are very much hardlining this idea, there's actually a lot more - I don't know if

it's skepticism or understanding that what we're dealing with is a lot more complicated than these hyper-simplified models. My approach in my research, with respect to these new definitional changes in Alzheimer's disease, is to test things empirically. If I think something else is important, or more important, or interacts in some way, let's test it scientifically. I'm not so rigid or dogmatic that I'm not willing to at least test hypotheses that incorporate amyloid and tau into cognitive aging and dementia. So my advice or recommendation would be to do some science and test these things out and see what pans out and what doesn't pan out. I think a lot of what we argue about is in academia. But what's happening clinically, I'm still a little bit traditional in terms of embracing some of our traditional or historical ways of conceptualizing Alzheimer's disease clinically.

John Bellone 57:56

Awesome. Well, thanks for this discussion. This has been really fascinating and a good discussion. I'm glad it didn't derail into a shouting match. [laughs] But, no, I largely agree with you. I just wanted to play the devil's advocate for some of these questions.

So we have some bonus questions for you that we ask all of our guests. These don't have to be specific to Alzheimer's disease. The first one is what is one thing that you would improve about the field of neuropsychology?

Adam Brickman 58:28

That's a great question. I think one of the things that I've been a little bit disappointed about with the field is this - and I understand why it happens - this emphasis on board certification in clinical neuropsychology, which I think is potentially or has potential to diffuse the rigor of our science because it takes a lot of training, particularly at the post-doctoral level, to become an independent scientific thinker. The concern that I have is that because people who enter the field of neuropsychology often feel obligated to become board certified, they're not going to be able to engage in this much science at the postdoctoral training level. We're going to be missing out on innovation in the science of neuropsychology even though we're amplifying the legitimacy or the standardization of the practice of neuropsychology.

Ryan Van Patten 59:24

Yeah, that resonates with me. I'm a research postdoc right now doing neuropsych research and I also do want to get boarded. So it's clear how much clinical work must be done. I love clinical work. It's important. But, looking at Houston

Conference guidelines and ABCN, I often find myself wishing that we would also include the importance of neuropsych research, the clinical science, within the boarding process. Maybe emphasize that a bit more.

Adam Brickman 59:53

I agree. I've almost fantasized about board certification in research neuropsychology. Or just one board certification for neuropsychology, clinical track versus research track or something like that. Because the reality is [that] I do almost no clinical work now. I have no incentive at all to be boarded. But I know that there's a contingency of neuropsychologists who would say that I'm not really a neuropsychologist unless I'm boarded. So I'd be dismissed by my guild because I don't I don't have ABPP after my name.

John Bellone 1:00:28

Yeah, I can see both sides of the argument. Being clinically focused, I think, like you said, it's overall a huge positive for the field that people get boarded. It's an easy way to spot someone who is a bonafide neuropsychologist versus someone who's calling themselves a neuropsychologist when really they don't have the training to do that. But then you might lose some other scientists that are actually neuropsychologists. I like your idea of maybe a separate board certification or separate track or something. I think there needs to be some way to distinguish bonafide trained neuropsychologists from non-neuropsychologists.

Adam Brickman 1:01:12

I agree.

John Bellone 1:01:13

That's a whole other discussion.

Ryan Van Patten 1:01:17

Adam, what's one bit of advice that you wish someone had told you when you were in your training, or that someone did tell you that really made a difference? We're looking for an actionable step that we could give to trainees who are listening.

Adam Brickman 1:01:28

I saw this question before and I had trouble thinking of one thing. I think one thing that I've learned is that I have to often step back and think about what are the things that I'm doing in my career that I really enjoy, and amplify those things. If it's

research, if it's stats, if it's reading, if it's interacting with students, if it's whatever. I think that we, as academic researchers in my neck of the woods, so much of our lives are wrapped up in our work that I wish I had been given permission, if you will, to focus on the things that I love doing the most and maybe diminishing the things that I don't love doing as much. So that's one piece of advice. The other big piece of advice I give people is to go to meetings and talk to people. Science is social. Idea exchange is critical and [so is] interacting with people. Everyone has different personalities and shyness and everything like that. I think it's important to try to interact with other people in our field in an academic/social way. Because I think a lot of innovation happens there.

Ryan Van Patten 1:02:46
Yeah, that's great. I know John and I get a great dose of that just through conversations like this today. It's super helpful.

Adam Brickman 1:02:52
You guys are doing a great service to our field. It's very exciting.

Ryan Van Patten 1:02:55
Thanks. Now that we've covered advice for trainees, we want to add in a question about advice for early career professionals. So the context of this question is the changing healthcare landscape. Of course, we as neuropsychologists, want to remain relevant and useful. So once we're established as neuropsychologists at the early career level, what steps can we take to ensure that we're providing cutting edge scientific and clinical services for the next 10, 20, 30 years?

Adam Brickman 1:03:23
Wow, um, I don't have a good answer for this. Apart from not being afraid to innovate, I think a lot of neuropsychologists are very quick to criticize approaches that are outside of neuropsychology without taking the lead on innovating those. For example, there's a lot of implementation of computerized neuropsychological evaluation right now, and certainly a lot of criticism and very, very legitimate criticism of those approaches. But I think that our field could use a little bit of innovation, and we shouldn't be afraid of taking the lead on introducing innovative approaches to our field. Adapting. We have to adapt. I think the first neuropsych reports I wrote were 12 pages long. Nobody reads those. [laughs] I think we can be a lot more efficient in our practice of neuropsychology as well. I also think we all have an obligation to stay on top of the literature and on developments in our fields,

not just through CE credits. By the way, New York state doesn't have a CE requirement for psychology at all.

John Bellone 1:04:39
Really? We have 36 hours here in California. [laughs]

Adam Brickman 1:04:43
I think that there's some utility to that [laughs], because I see a lot of old ideas sort of in perpetuity continuing.

Ryan Van Patten 1:04:54
Well, this has been a great discussion, Adam, we appreciate it.

Adam Brickman 1:04:57
Thanks. I've enjoyed talking to you guys.

John Bellone 1:05:00
Well, that's it for our conversation with Adam Brickman. I hope you guys enjoyed it as much as we did. I thought that that was such a good back and forth conversation and a lot of good arguments on both sides to be made. I don't think we have definitively answered this question of what criteria is best to use, but I hope that all of you out there got something useful out of the conversation. It's going to be seen how we are going to end up specifying the Alzheimer's disease criteria. So these conversations, I think, are really helpful in this matter.

Ryan Van Patten 1:05:33
If you'd like to participate in the conversation NavNeuro now has a Twitter account, so feel free to tweet at us.

John Bellone 1:05:42
Tweet at us, Ryan?

Ryan Van Patten 1:05:43
That's right, right? [laughs]

John Bellone 1:05:46
I can say I'm a very big Twitter user with my zero tweets so far, but I'm pretty sure it's not tweet at us.

Ryan Van Patten 1:05:53
No? Okay. Well, how about we... twit? Twit at us? Is that what you're asking?

John Bellone 1:06:01
Tweet it with the hashtag @navneuro?

Ryan Van Patten 1:06:04
Okay.

John Bellone 1:06:04
I think? I don't know.

Ryan Van Patten 1:06:05
Well, I think I'm right.

John Bellone 1:06:06
That's going to be the first thing that [people] comment on.

Ryan Van Patten 1:06:09
Clearly John and I do not run NavNeuro's Twitter account. We can thank Leslie Gaynor for that.

John Bellone 1:06:14
Yeah, big thanks to Leslie.

Ryan Van Patten 1:06:16
For handling that and maybe Leslie or someone else who's actually knowledgeable about social media, which is not John or me, could set us straight.

John Bellone 1:06:24
Well, that will be the first thing they tweet about is what is the proper way.

Ryan Van Patten 1:06:27
They'll tweet at us about how to tweet. [laughs]

John Bellone 1:06:32
In all seriousness, though, I'm sure there's going to be a lot of questions that come up that we didn't get a chance to talk with Adam about on both sides of the argument. So we would love to get a discussion going on Twitter. Please tweet in our direction? [laughs]

Ryan Van Patten 1:06:49
Whatever the correct terminology is, you know better than us. [laughs] Yeah. And so thank you all for listening. And, as always, join us next time as we continue to navigate the brain and behavior.

Exit Music 1:07:01

John Bellone 1:07:25
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Ryan Van Patten 1:07:37
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