110 | Aging, Cerebrovascular Risk, & Digital Cognitive Biomarkers – with Dr. Rhoda Au

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Rhoda Au, Ryan Van Patten, John Bellone

Intro Music 00:00

John Bellone 00:17

Welcome, everyone to navigating neuropsychology, the voyage into the depths of the brain and behavior brought to you by INS. I'm John Bellone...

Ryan Van Patten 00:26

... and I'm Ryan Van Patten, and we are board certified neuropsychologists. Today we talk to Dr. Rhoda Au about multiple intersecting topics related to aging, cerebrovascular disease, digital technologies, and

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brain health. Rhoda is a professor at Boston University and the director of neuropsychology at the Framingham Heart Study. So now we give you our conversation with Rhoda.

Transition Music 00:51

John Bellone 01:00

Dr. Au, thank you so much for coming on NavNeuro! We are so excited to have you here.

Rhoda Au 01:04

Oh, thank you for having me!

John Bellone 01:05

Of course. So, your research program in aging adults: It's diverse... it's extremely interesting to both Ryan and me. A few big themes are the Boston Process approach, digital technologies and cognitive assessment, the Framingham Heart Study, midlife cerebrovascular risk factors, or late life cognitive decline, Alzheimer's disease... I want to at least touch on each of these topics, at some point today, with a strong focus on the cardiovascular and technology pieces, but can you give us a brief elevator pitch about your research portfolio?

Rhoda Au 01:40

Yeah, I think that... Well, I would say that I would describe my current unifying theme around a couple of things. So one is around precision brain health, which I think we can talk a little bit about how that's different from precision medicine, for instance, and then I think the other piece is really focused on this concept of inclusivity... and what does that mean? ...and what and how does that translate? How do you operationalize when you decide to make being inclusive, a central focus of your work. And, and I probably should mention that the two are actually related. So you know, the concept of precision is because you care about every individual, right? And then what you want to do is you want to generate solutions that are relevant for every individual, wherever they are.

Ryan Van Patten 02:27

Yeah, that's a really nice, broad framework that we can use as we move forward and into some of the specific areas. So I'd like to start with Framingham a little bit and give some background on that. I think

many people have heard of the Framingham Heart Study, or FHS, but may not fully appreciate the impressive scope of the study, and really the huge impact it's had on the neuropsychological community, particularly the understanding of risk for late-life cognitive decline, based on early- and mid-life cardiovascular disease. So, FHS is made up of community-based multi-generational observational cohorts of 1000s of people in Framingham, Massachusetts. It began in 1948, and it's been going on for over 70 years. Very impressive. So give us a brief overview of FHS, including the various cohorts.

 Rhoda Au 03:22

Sure. So as you indicated, it started in 1948 with the original cohort, which at that time was a 2/3 sample of the town of Framingham. Believe it or not, there's still one original cohort alive today. But then in 1971, they brought in the children of the original cohort, as well as their spouses, and that makes up our offspring/or our Gen2 cohort. In 2002, they brought in the third generation, which is our Gen3, and, obviously, the grandchildren of the original cohort and the children of the offspring cohort. In addition, because the racial/ethnic demographics of the town and the surrounding areas were starting to shift, in 1991, they brought in the Omni-generation one cohort, which is a more racially/ethnically diverse population. It represents about a 10% sample of the original, relative to the original or actually the Gen2 cohort, and then at the same time that they recruited the Gen3 cohort, they also brought in the Omni-Gen2, which includes again, offspring of Gen1/Omni-Gen1 cohort, but also new participants who are unrelated to the Omni-Gen1 cohort, and that also is about a 10% representation of the Gen3 cohort. So that in total... Oh, and then there's actually one more cohort, and that's the New Offspring/Spouses. Because of Framingham increasing interest in genetics, we have lots of family structures because at the time of original recruitment, in 1948, we were bringing in not just husbands and wives, but brothers, sisters, aunts, uncles, etc. So we have some really rich family trees embedded across our multiple generations. So when we brought in the Gen3 cohort, we actually at the time of recruitment, got oversubscribed. There were more people who responded positively, that they wanted to be part of this new cohort, then we were actually funded to do.

 Ryan Van Patten 05:32

[laughing] That's rare, rare in research - right - that an investigator gets that problem.

 Rhoda Au 05:37

Yeah. And so and so what happened was, is they decided to preferentially bring in people around these family trees. And so the New Offspring/Spouses, it's just a much smaller cohort of, as it says, you know, the spouses of the Gen2 that weren't part of that original Gen2 recruitment. And so that's a smaller subset just to help, you know, build out those family trees a little more effectively.

 John Bellone 06:04
Then could the newer cohorts be from outside of Framingham if they lived outside? Or is everybody recruited from the city?

 Rhoda Au 06:12
So they can currently be residing out of Framingham, but their family roots tie back to the original cohort, or in this case, the Omni-Gen1, the Omni-Gen2, which were, then they're the only ones that weren't, that are unrelated to the original cohort.

 John Bellone 06:28
Gotcha. And as we move forward with the FHS, I'd like to talk about the measurement of cognitive functioning in the study, including the Boston process approach, and then maybe circle back and highlight some of the findings related to vascular issues and Alzheimer's disease. So cognition has been measured in the Framingham Heart Study since the mid- to late-70s, I believe. Can you just tell us broadly speaking, what cognitive assessment looks like in this study?

 Rhoda Au 06:56
Sure. So in 1976, when they first started doing cognitive testing, in Framingham, it was actually part of one of the health exam cycles, which is when we bring people back in periodically for a general health exam. At that time, we didn't have any studies related to cognitive aging and dementia; they just had decided to do that. It was just a brief cognitive assessment was only about 15-20 minutes long. But it really helped to establish sort of the baseline of cognitive status for the original cohort. In 1981, they actually introduced the use of the Mini Mental, as a cognitive screening tool to continue to track for changes in cognition. The formal, I guess, the informal, really the informal studies related to dementia at Framingham started in the early '80s. So at that time, it was an unfunded initiative, and it was using sort of this baseline of testing that happened in '76, along with continued administration of the Mini Mental starting in 1981, on a every two years cycle for the original cohort, and they started to track people who are showing cognitive changes.

It actually became formally funded, as a study, in 1989 by the NIA. That was the very first epidemiology of dementia study. At that time, they were really focused on continuing just to follow people that they thought were showing incident changes in cognition. And so, if triggered by some changes in Mini Mental performance, they would be then flagged and brought in for a more extensive cognitive

assessment, which took the original protocol from 1976-78 and expanded it into what we would consider a more comprehensive assessment.

It actually wasn't until 1999 that Framingham's cognitive aging and dementia studies became what I would say "cohort-wide". So in 1999, you have the Gen2 cohort, along with the OmniGen1, now reaching the approximate age that the original cohort was in '76. So at that time, we expanded, again, you know, now just to more contemporary standards... that original protocol, you know, is probably about 45 minutes long at the time, maybe 50 minutes long, but it was more comprehensive of more cognitive domains than we had done previously. And then we were administering them regardless of whether you had shown signs of cognitive change or not, across these cognitive screening tests. So this is really where we establish the baseline measure of cognitive status, the way we had done in their parents we were now doing in their children and their children's spouses. And we also because you know, we're there are now advances in technology, we also added brain imaging at that time.

Then we had another change in our cognitive assessment protocol in 2005, which was the second round. So we went from 1999 to about 2004/2005 with this initial baseline testing. But during that time, you know, that was when the concept of mild cognitive impairment was really emerging. And what I was really struck by is how insensitive our cognitive assessment, at that time, was going to be to pick up more subtle changes. And, you know, as any neuropsychologist or anybody who does testing knows, is that when you administer a neuropsych protocol, you know, there's the responses that you're expecting... the correct responses, for instance, but it turns out that you get a whole host of responses, other kinds of responses, other incorrect responses, and... we're in Boston, so we're in the land of Edith Kaplan, who really championed the whole concept of the Boston Process approach, and really taught us to think that "wow, not every zero, right, not every incorrect response is the same level of incorrectness". And so when we were testing our participants across, you know, all these different levels of what I would call "normal", we were getting lots and lots of responses that we weren't coding. And now suddenly, we've moved the field where we're trying to detect some sort of change in cognitive status earlier, and we just weren't going to do that with our current tools, you know, our current, what I consider a little bit blunt instrument tools, of just using a total score, and losing the richness of all these additional responses.

So in 2005, when we started our second round of testing, we implemented the Boston Process approach into our scoring system, so that we were scoring all participants responses, not just the correct ones. And that's really is actually, and we're going to discuss this later, also laid the foundation for why our digital component became very important. Because here's the thing, when you decide that you want to now score everything a person says during cognitive assessment, you can't write fast enough to keep up with them. So the only way I could figure out how to capture everything people were saying during cognitive assessment, was to record it, so that we could go back and capture it. And because it's

Framingham, I worried about well, we have to save things for all times. So I was I didn't want to have at that time, you know, you have like tape recorders, and I didn't want a bunch of cassette tapes.

 Ryan Van Patten 12:46
[laughing]

 Rhoda Au 12:47
So I decided we should digitally record them, because that would be much easier to save. That's actually why we started digital recordings at Framingham; it was because of this Boston Process approach. And my, you know, really my desire to make sure that we accurately scored all responses, not some responses.

 Ryan Van Patten 13:10
Yeah. And that decision, back then, has led to so much power now in ability to use these digital responses in various ways that we'll talk about. So very glad you made that decision in the foresight you had. [laughing]

 Rhoda Au 13:25
Yeah

 Ryan Van Patten 13:26
And then just stepping back, you know, Framingham, the large amount of cognitive data we have on such a large group of people for such a long period of time, is really impressive, and we'll talk about some of the findings that have come from the cohorts. I also appreciate your intro to the Boston process approach; I'd like to you to talk a little bit more about that. Before we go there, though, describe the reasoning behind maintaining the same tests and/or the same versions of tests - like the WAIS - over many decades in Framingham, for the sake of continuity.

 Rhoda Au 14:02
Yeah, I always say, you know, the great thing about Framingham is its longitudinal nature, right? So if the reason we give the same test repeatedly is so that we can do comparative analysis and go back in time. And I do think that that's probably the greatest value of Framingham is that we've maintained some of

our protocols. Now, as you mentioned, though, I mean, we're, we're using tests where today they're like version 4 or 5, etc., nd we're still adhering to the original task. And I think that it's sort of the use of bringing in things like the Boston Process approach, and then now obviously, capturing things digitally, that allow us to actually do both, which is to maintain the longitudinal integrity of the original tasks, but now extract from that much more out of it, that is much that is more reflective of what we're trying to do today as we tried to detect, I guess even more now, even at asymptomatic, so it's hard to even say that you're detecting disease at this point. All you're trying to do now is just detect changes. And, um, so I think that it's this marrying of both the old and maintaining that longevity, along with embedding some of these new methods along the way, that I think that it's actually that convergence that has made the Framingham dataset of some value.

Ryan Van Patten 15:35

Right. It's great, very important to measure cognition in asymptomatic or presymptomatic people, as we're learning with the anti-amyloid trials. We can't just wait until people already have MCI or significant cognitive impairment to start measuring it and trying to intervene. So it's great that the Framingham study does that. And to circle back around to the Boston Process approach, as you mentioned, championed by Edith Kaplan, at VA Boston. And a focus here is on cognitive functioning as being comprised of different components, which can be assessed by paying attention to the process of how a test is completed, like the how, when, and why of a particular error or a test failure, as opposed to relying more exclusively on a quantitative composite score... the historical example being the Halsted Impairment Index. So talk a little bit more about how Framingham has used the Boston Process approach and what the process approach gives us that we wouldn't otherwise get from looking at a an overall score.

Rhoda Au 16:39

Sure. So I think one of the things that we do in at least in research, that's inappropriate, in terms of neuropsych testing, is we presume that every task measures a single domain. And it's not true. Every single neuropsychological task actually requires multiple domains in order to understand and complete. And so what you're doing with the Boston Process approach in capturing all these ex-, you know, extraneous or additional responses, is you're actually trying, you're trying to tease out what are all the different cognitive processes that are being used in order to deliver that final response. So what we've been able to do within the Boston process, using the Boston process approach within every single one of our tests, is we can start to tease that out. We can tease out from a memory test, executive function errors. So for instance, we code perseverations, you know, which is just repeating a response over and over again... we have preservative responses recorded across all our tests. And we can actually now come up with a perseverative score. That's not just within a test, but across tests, and that's actually

really important, too. Why? Because as most neuropsychologists, all neuropsychologists, really, know, you can never interpret anything from a single test; it's about the pattern of responses, and so the fact that you perseverate within one test, versus whether you perseverate across all tests, that's a very interpret... different interpretation, and certainly, for someone who's highly preserv... uh, perseverative, I'm going to worry about much more executive function, frontal-mediated, right, pathways, compared to if they just did it once or twice, here or there. So I think that we need to start being much more critical about our misuse of neuropsych testing, particularly in research, and the Boston process approach is a way to help minimize that misuse.

John Bellone 19:01

And like you said, um, it's, there's so much data that's getting lost, we're just throwing away each time we give these neuropsychological evaluations, but like you had said, it's just too much data to process by hand and you know, for a human, and so you really need the computerized assessment and digital approaches to really gather and use that data, which we'll get into a little more later. Can you talk about the importance of FHS as a community-based cohort compared to a research done at Alzheimer's Disease Centers, for example, and the advantages of that approach?

Rhoda Au 19:40

Yeah, I think this is the case with all community based cohorts, right, is that you're really getting a snapshot, uh, within the general population. What happens when you have, uh, disease based centers is you get really bias participants. They usually have some sort of connection, personal connection, to the disease. So what you'll do is you get a disproportion of people who are probably have some genetic risk, because it's in their family, you know, etc. And the other thing is you're going to get a disproportionate picture of what the prevalence of that disease is in your community, because, again, it's people self-identifying themselves to come forward. Whereas in a community based sample, you're just... it's an observational study, and you're finding out how this disease naturally occurs in the general population. And that's why community based, uh, studies are so important, because they really give you a much bigger picture of what's happening in the community in an unbiased way that you have a hard time avoiding when you do center based research, disease center based research.

Ryan Van Patten 20:54

Makes sense. So let's get into some of the findings from FHS and how they're impacting neuropsychology today. One of the biggest themes I've noticed coming from the study is knowledge about the impact of early and mid life, cardiovascular, and other health factors on late life, cognitive decline. So for example, I've seen papers on blood pressure, lipid and glucose levels, coronary artery

disease, BMI, Afib, metabolic syndrome, sleep hypoxia, and other examples. There are a ton of papers coming from this study, not surprisingly. So can you just summarize for us what we know, in general about the associations between these health factors, especially their cardiovascular piece in midlife? And then cognitive decline in late life?

Rhoda Au 21:44

Yeah, I mean, I would say in doing sort of a deep dive, I still think it's a little bit mixed in terms of what our knowledge is. Certainly, I would say blood pressure, we see some consistency that, you know, managing your blood pressure levels, your glucose levels, those are probably the two most most prominent kinds of results, if I look across different studies, that suggest have a much more robust impact on later life. It's a little hard now to look at things like smoking because we've done such a good job from a public health perspective, in terms of the impact of smoking. But one of the things that I actually would like to point out is, you know, in my early days, yeah, people used to ask me, "What's the major message out of Framingham?" And I would say, "Midlife health matters", just in the way that you describe. But what I realized is that we say midlife health matters, because we were missing early life data. And so we have not just from Framingham, but in general, within the research literature, this belief that it's midlife, and I actually wonder if it's earlier life, and that's why, you know, I've taken on sort of this more lifespan approach. I think it's, it's... we happen to be measuring data at midlife and are able to look forward and be able to say, "Oh, what your cardiovascular risk was at when you were in your younger years is having an impact on your later years". It'll be interesting to see how that plays out with the Gen3 cohort, as they get closer to the age of risk for cognitive impairment, because we started to collect data on them even earlier. There actually is another study, the Bogalusa Heart Study, that's a 50 year study that started following people at the at childhood. So this is from kindergarten, through grade school, and they're starting to move into that age of risk. So I would agree that Framingham has played a significant role in contributing to the literature, and I think it's... I think where we've been able to show the most impact is around blood pressure and glucose. I think the other area is to understand that it's not any one risk factor its actually multiple risk factors. I think we've shown that multiple times. So you need to be monitoring all your cardiovascular risk factors, not just one or two, because there is some synergy across them. And, and sometimes it's a different mix. So I, for instance, my colleague, Philip Wong, who's one of our postdocs, he's been looking at some of the midlife risk factors within Framingham. And it just seems that any combination of two or more is going to put you at higher risk rather than any particular one. So I think that those are important messages. But I do think that there's more to come where we're going to just discover as we collect data further and further down the age continuum, that it turns out, whatever is bad for your heart, is bad for your brain, and that's going to be across your entire lifetime.

 John Bellone 24:56
Yeah. You've written about Alzheimer's disease and other forms of dementia as lifespan conditions. I know which, you know, might seem surprising to some of our listeners, given that we typically talk about the diseases, you know, as those of older age. But that's excellent that you're looking at more of the early life risk factors. I mean, I'd be so interested if you know what factors in someone's 20s or 30s really make a difference for their cognitive functioning at age 60, 70, 80, it would be so fascinating. So I'm glad you're highlighting those.

 Rhoda Au 25:30
Well, I would also argue that aging isn't something we do at toward the end of life. Aging is something we do across our entire life, and we do it from conception to death. I really do think we need to rethink what we mean, when we say the word "aging", and understand it actually is something that's a lifespan process. And that, with respect to brain aging, we're just continuing to develop we're just in different data stages of development. I think it's just, it's a subtle change, but I think it would, it would really, if we operationalize that it would really significantly challenge I think, what we think we know,

 John Bellone 26:11
Excellent.

 Ryan Van Patten 26:11
Yeah, there's public health advocacy that's very relevant here, right? Like, we can know this as clinicians and scientists, but then it's about getting that information out into the public so that people start to make the connection in their 20s and 30s, that what they do now will matter for the rest of their life. And you can't just wait until you're 50 or 60, to start worrying about your own health.

 John Bellone 26:33
So many, many of your studies on cardio risk factors and late life cognitive decline. They examine a potential moderating effect of APOE status on cognitive outcomes. What can you say about the interplay between those cardiovascular risk factors and APOE status on cognitive decline?

 Rhoda Au 26:33

Yeah, so I think that, you know, obviously, APOE always provides additional genetic risks. Actually, one of our earliest studies, looking at midlife showed that people with diabetes, it was actually those, once you remove sort of the genetic risks, that was when then diabetes sort of stepped in as an additional risk factor. So APOE itself is pretty powerful risk factor. And so I thought that was really interesting that it was sort of once you remove the genetic risk that it was having cardiovascular risk, and in this case, diabetes, then conveyed additional risk above and beyond that. So I think that it's not that simple, right? It's not simply that, oh, among people who are APOE4 positive, if they have cardiovascular risk, you know that that means that that will enhance the risk. I think that it's more complicated than that. And so I think that I like to point out that finding, because it's a little bit counterintuitive, from what you would expect. And so certainly, you can find where having increased cardiovascular risk, along with increased genetic risk is going to increase your overall risk. But I do like to point out that that interaction between genes, you know, and next bones is a little bit more complicated. I don't think I'm the expert on that. I would say people like Eric Ryman, who's done a lot more extensive work around that is probably better suited. But that would just be my sort of cautionary interpretation as we as we go forward. And think about sort of APOE relative to cardiovascular.

Ryan Van Patten 28:38

Perfect segue, I'd like to hear you talk about the differential diagnosis of Alzheimer's disease and cerebrovascular disease and neuro psychology. So this comes up frequently in geriatric neuropsych practice. You know, we have our conventional cortical/memory and subcortical/executive profiles that we map on to cognitive test performance. You talked about how the Boston process approach can be relevant there to try and to identify more executive versus episodic memory issues. But it's also the case that AD and cerebrovascular disease are really highly comorbid. There's even some speculation that the ultimate upstream cause of AD which may not be amyloid, could be microvascular in nature, and we don't have to, we can't answer all those questions today. But given what we know right now, how do you recommend that neuropsychologists in a clinical evaluation try to think about disentangling Alzheimer's disease and vascular etiologies?

Rhoda Au 29:36

Yeah, I think it's really important not to put things in dichotomous buckets. So I really think that we have to think about this as more of a continuum of you know, from AD pathology and vascular pathology, and as you said, the fact that there's actually a lot of mixed pathology, right. So my colleague, David Libon, and has long championed this idea that it's spectrum. It's a spectrum disorder from between AD to cardiovascular, and that we should really be thinking as neuropsychologists, where along that spectrum do you follow, you know, and can we tease out then those that are much more sort of on the AD side of that spectrum, versus when we see them more, equally comorbid versus when they're much more

driven by vascular? I think one of the things we have to remember is that for both vascular and AD, there are multiple etiologies. There isn't one pathway. And so I think that it's not useful to think of them as separate. And I think that we have to be much more flexible in understanding and the role of the neuropsychologist is to try to figure out what are all the multiple etiologies that might be operating, rather than any single one? So I hope that helps.

 John Bellone 31:01
Yeah, Ryan and I are in full agreement on that.

 Rhoda Au 31:04
And I think that's where the field is going. I don't even think that, you know, I think when David was talking about this, you know, maybe two decades ago, when no one was listening to him, that was more compelling than it is today, because you know, we have all the work, for instance, the great work that comes out of the Rush group, right, and, and Julie Schneider's team, along with Patricia Boyle that, you know, just shows that "Oh, wow", you know, I think they looked and identify 256 different patterns of combinations of pathologies. Yeah.. and so, you know, so from a neuroscience perspective, then what's your job there? And you know, what, to tease out the fact that there's all these different combinations.

 John Bellone 31:47
And then we've touched on this a little bit throughout the conversation already, but I wanted to focus a little more time on lifestyle factors and brain health behavior change. You've written that a goal of the field should be to, "optimize brain health wherever a person aligns on a normal to disease continuum," rather than focusing our research dollars exclusively on disease states, like Alzheimer's disease. So how can we best optimize brain health and research and in our clinical work with patients?

 Rhoda Au 32:02
Sure. So even with all our biased data, we have lots of biased data, but even within our biased data, we've been able to demonstrate that probably at least about 40% of a person's risk for dementia is mod... is not inevitable. Right. So and I suspect it's probably even more but at least with the data we have, and we certainly have the Finger Study, you know, the Worldwide Finger Studies, as well as the US based Pointer Studies, that's really now addressing this idea and demonstrating that you can do these prevention kinds of strategies through behaviors that we actually can control ourselves. And so I think that that's, um.... But for me, I think of the fact that we're talking about an insidious onset process, and again, we mentioned that it's multiple etiologies. So I think rather than focusing on disease, we should

really be just focusing on our brain health generally, and this fits into that general picture that aging is something we do from conception to death. And so regardless of whatever our current cognitive status is, we should be trying to optimize that, and we should be trying to monitor and as we see shifts and changes that are suggesting that there's a little bit of decline or impairment going on... we should be trying to intervene, then, you know, it's "Oh, do we are we making sure we're getting enough sleep? Are we getting enough physical activity? Are we eating the right foods? And how can we address that on an ongoing basis to keep our brain functioning at its most optimal level?" And it turns out that if we actually focus on our brain health, just like we focus on our heart health... You know, you go in for a physical exam, they're worried about "is your liver functioning; is your ... are your lungs functioning? Is your heart functioning? Are you seeing? Are you hearing?". But we don't do these brain checks to make sure if your brain operating at its most optimal level? And, and just like all these ways in which we monitor our other organs and intervene in order to prevent some delayed, you know, disease outcome, further down the track, we should be thinking about that for our brain. And if we do that, we actually sow the seeds of prevention right up front. Right, the brain is not the organ to neglect, not that any of them are but it's probably the last one that I would want to a neglect in terms of long term health.

 Ryan Van Patten 35:04

Yeah, this is great, Rhoda. Thanks. One more question before moving on to the digital tech piece, you had mentioned the Omni cohorts as part of Framingham. And I'd like to just talk a little bit more about the efforts to recruit ethnically and racially diverse participants into FHS. I know the original cohorts were less or more homogeneous, I should say. So from the FHS data and the research how well does it generalize to diverse groups of people?

 Rhoda Au 35:34

Yeah, I would say that's the biggest limitation of Framingham is that we actually don't even though we have our Omni Gen1 and Omni Gen2 cohorts, and that was sort of our attempt to try to reflect the increasing diversity, racial/ethnic diversity, in the surrounding area. I think our numbers are just too low. And I think that there's certainly a great movement within the US and with support from the NIA to really change that narrative, and make sure so. You know, Framingham is closed cohort. So we don't recruit new participants. There's been rumors about a Gen4 cohort, and that might actually open up, because even if you think about it genetically, and now with much more racially mixed marriages, etc, I suspect we'll get a more genetically enriched population, even from the Framingham cohorts, if we go down to that fourth generation. But that's still to come. I'm optimistic that it will come. I know, Gen4 who asks, already, if there was a Gen, you know, if there could be a Gen4 cohort, so I suspect that there's probably discussions that I don't know about, that are going on. But I don't think that Framingham is, is really the ultimate solution on that front. I think Framingham is a model of how to do

multi generational and we need to carry that into our more racially/ethnic diverse populations, which for some are much more family structured as well. So for instance, I know that within the Hispanic-Latino, Latinx community, you know, healthcare is really much more a family affair across generations. And so I think that, that example, right to make sure that it's not about just focusing on one age group, but thinking about that multi generational component. And bringing that and actually understanding that that's how some of these other communities may be better engaged.

 Ryan Van Patten 37:42

Great, thank you. So let's now move on to digital technology and cognitive assessment. You've done a lot of work and different specific areas within digital assessment. So voice biomarkers, machine learning, the digital clock, digital trails, the internet of things, and others. Let's just start with what is a digital biomarker? And why are they important?

 Rhoda Au 38:05

So, so that's an interesting question, because there's what I would call the mainstream definition of what a digital biomarker is today versus what I would want a digital biomarker to be. So what do we generally refer to when we talk about a digital biomarker, which I think is a little bit of a misnomer, is that we are probably just using some digital technologies to measure some health outcome of interest. And it tends to be a health outcome of interest that we're already familiar with. So one of my concerns, actually, is that we are moving the digital biomarker field toward just doing a better version of what we already do. And I don't think that that is where we should stop. It's a good starting point. So I'm not you know, and we have to start somewhere. So that is what I would say is the current most common use of digital biomarkers.

 Ryan Van Patten 39:03

Can you give me an example of that?

 Rhoda Au 39:05

Sure. We do that all the time right now... even what I've been doing. So if we say for instance, digital voice recordings, digital pen recordings, that's just from standardized neuropsychological tests. And what people you know, right now, "oh, let's do the let's do the cognitive assessment on a computer. Let's do it on an iPad, let's do it on a smartphone. And we're going to call that a digital cognitive, you know, biomarker"... It's just a digital version of what we're already doing, and that's not what I would like to see. Right? I mean, we talk about in other fields, you know, it's oh, let's measure glucose, let's

measure heart, you know, atrial fibrillation, let's measure hypertension, you know, it doesn't really matter. You can take pick whatever you want. We're using lots of digital health technologies to just measure what we've always been measuring digitally and calling it a digital biomarker. And I think we can do better than that. I I think that, you know, I mentioned that the whole reason that I started to do voice recordings is because I wanted to promote the Boston Process Approach and thinking, within our study to capture information that we're missing. And I look at digital, at least, you know, my conceptualization of why do digital, at least in the cognitive self assessment realm, is that's just doing the Boston Process Approach on steroids. Like the basis for why we do digital is already we've been the it all it does is make it easy to do the Boston Process Approach, and that's what we should really be doing. And so we're now capturing behaviors, and far better granularity than I was even able to code off of listening to the recordings, right. So that's really the difference of what we're trying to do. So in digital voice, you know, speaking is a such a cognitively complex task. So independent of whether you're giving a response correctly or incorrectly, there's so much other richness that we can pull out of that audio recording. And so I think that that's really what the directions that we need to be pushing ourselves on. And I, the other thing that I think we have to understand is, if we're capturing these complex, heterogeneous behaviors, at such a granular level, we should not expect out of this that a digital biomarker of that is going to be a single measure, or a single response. We don't do that clinically. I mean, if you think about, for instance, how do we first determine when someone has a cognitive impairment? We don't do it by going around testing someone, we actually do it by asking the person, "When did you start noticing symptoms?", and we ask the family members the same thing. And I like to point out, the person isn't going around testing themselves, nor is their family members. But here's what they do, they start to give you different patterns of behavior. They'll start, they'll tell you, "Oh, you know, I forgot to turn off the stove, I forgot to pay that bill, I got lost driving to someplace I always go to", and you ask a family member, they'll give you a different set of examples. You ask a different family member, they'll give you yet a different set of examples. And here's the thing, those examples, they're not static. The person doesn't always forget to turn off the stove, they don't always forget to pay their bills, they don't always get lost. And so what we're trying to do with, whether it's digital or paper and pencil, we're trying to capture really dynamic behaviors with a single measure. It's not going to work. And that's the beauty of digital digital will actually allow us to capture this whole richness of changing dynamic behaviors, and allow us to put it together in a way that truly reflects, "oh, they have a memory impairment." That's what I think digital biomarkers is gonna have to be.

John Bellone 43:07

I hope we have a little bit of time at the end to talk about some ambient technologies, so to speak, you know, the internet of things that maybe we get a little closer to what you're talking about. I want to ask you, though, I want to spend a bit of time on the digital clock soon, in just a minute, also, because I'm curious if that is assessing, is gathering some of that digital biomarker data that you that you're referring

to. But can we just touch on machine learning? So generally speaking, can you tell us what machine learning is and how we might use it to detect cognitive decline? What has been done so far in this area?

 Rhoda Au 43:42

Sure. So machine learning is going to be computer-based, because the one thing that computers can do that our minds cannot do, is that they can pull together and search through vast amounts of information, and look for embedded patterns. And they can learn over time. And so and they can do it across multiple dimensions that our brains can't do. So that's really what machine learning, what you're doing is you're taking sort of a complex set of data that probably has lots and lots and lots of embedded relationships that we just can't figure out or see on our own. And they're there, they're detecting them across really, really messy, what you call messy data, right? And then what you do is you develop a model with a subset of the data. And then you learn, right, you create a new model, and then you do it again, with a different subset. So that that's the learning component, right? It's now taking whatever it first generated and go into the next step and the next step so that over time, it's getting better and better and better. So and usually what you're doing is you're setting some sort of threshold of accuracy, that you're trying to do. So in case for instance, like a differential diagnosis, someone who's cognitively impaired versus not. So you keep feeding them different combinations of the data. So that you know, and that's, you know, these test runs right that they do. We call it bootstrapping, you've got whatever you want. But it's always sort of taking, you know, you take your baseline model your test, and then you have your confirmatory data sets, which could be just different mixes of what your total data set is. But it's always a unique mix, and your training and training, and then the models to get better and better and better. And that's really what the machine learning approaches, and our brains just don't operate that way. Current, you know, biostats epistats, it just doesn't do that... that kind of work. And at the end of the day, you know, when we just talked about sort of the whole heterogeneity of the disease, that's what it can do, it can pick out all these different, ever-shifting patterns, and nonetheless, get to that predictive model.

 Ryan Van Patten 46:06

Yeah, it can be a black box for us. We won't look at the pattern of data and all of its richness and complexity and be able to see A leads to B leads to C in a very straightforward diagram that we're used to looking at. So it won't be clear to us both because we're missing all that complexity and those relationships.

 Rhoda Au 46:25

Yeah.

Ryan Van Patten 46:26

Rhoda, you had commented earlier on the richness of speech and language in our lives and how we function. So you've done some work and voice recognition and natural language processing for detecting early cognitive change. I know FHS has 10s of 1000s of audio recordings, you had mentioned earlier, from 1000s of different participants. So you have this database to work from. What's the general approach to detecting subtle cognitive decline in this area? What do we know based off the the language literature?

Rhoda Au 46:59

So I think that I think we've been developing methods on how to do it. I think that it's some combination of audio and linguistics. But what that combination is, is going to shift and change. So it's kind of what we were talking before. You know, this is a very dynamic, heterogeneous, and also insidious, shifting process. Right. So I think one of the things that we have to understand is that as we're analyzing our digital voice recordings over time, what that distribution of audio linguistic features is going to change over time. And so I think what I've been learning is that I need to remain agnostic in order to find the right solution for the right person at the right time. And this is still very much an emerging area. So that's the other piece of it. So some are more audio-based, some are more linguistics-based. I think the other thing that's limiting sort of what we know today so far, is the number of samples we have. So you mentioned we have a bunch of Framingham, we have about 10,000, actually, over time that we've collected longitudinally, and that's great. But I've also talked about how biased the Framingham dataset is because we're largely a Caucasian population. So one of the things we have to get to on digital voice, and I would say this for almost digital, anything digital, we need to become test-agnostic. We need to be able to find the same kinds of patterns, the same kinds of features, but be able to extract it, regardless of what your language is. So I'm always very leery to say we know anything right now. In this realm, because this is such a, an emerging area, there are methodologies and there's software processing solutions that didn't exist two, three years ago. I used when I first started, I thought the only way you could do this is you had to manually transcribe all these recordings, which I can't even tell you what a labor intensive process that is. It takes about 10 to 15 hours to transcribe one hour recording accurately, just to let you know. So more recently, my colleagues from the data science AI side have said just give me the raw recordings and let me process them. And even using automated transcriptions, which aren't as accurate as manual. But again, because we're using machine learning, they can in this sort of even more inaccurate data transcripted data, they can still pull enough of the patterns out that they can produce results that are equivalent to manually transcribed. So that It's kind of where we are in terms of the state of the art, and I think that digital voice is just one piece. The reason I'm so interested, though, in digital voice, is because most people speak. So I'm very interested in this concept of making sure that

we're developing solutions that are applied to all people, not just some. And voice is very powerful in that way.

 Ryan Van Patten 50:22

If you look into the future, and feel free to go out on a limb here, you know, decades in the future, as this, the technology improves, and we get good research methods for using the digital voice and natural language processing... I'm wondering how this might be used in people's everyday lives. Like, are we going to be talking on cell phones, or Alexa is listening to us, and picking up on speech latencies and the use of filler words or mitigated speech to detect the very earliest changes associated with neurodegenerative disease? Or what might this look like?

 Rhoda Au 50:58

Yeah, I think looking in the future, and I think we touched upon this in terms of passive technologies, which is that we're monitoring through multi-sensors, it's not just going to be voice, it's going to be other, you know, GPS, accelerometer, you know, etc. So it's going to be multisensor inputs that are coming in, that are going to be dynamically changing. So it's not going to again, be any one pattern, it's going to be a flow of different patterns of behaviors... that's going to start to pick up that something might be amiss. And again, if we can focus this more on brain health, rather than on disease, I think we can turn this into, you know, we're just trying to optimize where you're at at that moment. And I think that that would make it more palatable to this idea that you're trying to keep your brain functioning at its maximum capacity at all times. And here's the input. You know, it's no different than right now, when people were physical activity monitors, right, and counting the number of steps that they have, and then realizing that, "oh, maybe I've been a little bit low, maybe, maybe when I go grocery shopping, I'll park further down on the parking lot, just to make myself walk a little more". You know, it's those kinds of little incremental micro, right, right, micro interventions, I think that we can do, that won't be so much, you know, big brother monitoring, but more that these are assistive technologies to help you live an overall healthier lifestyle that's going to ultimately help you, you know, function.

 John Bellone 52:32

That's excellent. We're gonna have to run the NavNeuro audio through your AI so that I can pick up on all of Ryan's linguistic idiosyncrasies, and everything.

 Ryan Van Patten 52:41

You're supposed to take those out in the editing process.

John Bellone 52:45

I do my best. I also wanted to say congrats on a recent paper I saw last week. You had a paper published in the Alzheimer's and Dementia Journal, I believe, on looking at voice recording as a way to differentiate between normal and MCI, normal and dementia, MCI and dementia, I believe in it did pretty well.

Rhoda Au 53:07

Yeah, I mean, that's really to the credit of my data science AI colleagues. So Ioannis Paschalidis led that along with his graduate students. So I think that it's... I get the privilege of sharing these voice recordings that I have with these people. And then they they're actually the brilliance behind anything like that. We just had actually another paper published, I think it was today, out of the Journal of Alzheimer's... Prevention of Alzheimer's Disease...? JPAD, you know? Sure. And it's the same idea, you know. And this is with <?evidation> health. And in that case is this, it's just again, showing that there's a lot of automated tools now out there that wasn't there, like just a few years ago, that's allowing us to process it. And they did it differently. You know, that's the the other message, right? They did it differently than my colleagues at the College of Engineering did. And yet we're coming out with, you know, fairly similar kinds of results. So that's why I'm a little bit leery about sort of saying, "Oh, this is the right way are this is the right way". And again, you know, just reminding, this is a very dynamic behavior that we're trying to track. And it's sort of probably well, when you capture this one point of time over this one point in time, they're equally valid.

Ryan Van Patten 54:31

So let's move on now and talk about the digital clock in some detail. The paper pencil clock drawing test is a classic neuropsych paradigm that fits in very well with the Boston Process Approach, as we talked about earlier, because the clock has high task impurity, meaning that it's measuring multiple cognitive constructs in one test. Edith Kaplan liked this test so much that she famously said once that if she had only time to administer a single test, it would be clock drawing. So that's saying something, right.

Rhoda Au 55:03

Yeah.

Ryan Van Patten 55:03

But paper/pencil administration and scoring misses a lot of nuance in the clock drawing. And there's issues with interrater reliability, as I know, you know. So tell us about the rationale and the mechanics behind a digital clock drawing test.

Rhoda Au 55:18

Sure, so the way we implement this digital clock drawing test, and this is really technology that was developed out of MIT Lahey Clinic, you know, it was Randy Davis, Dana Penny. And that along with David Libon, and Rod Swenson, as you know, the neuropsychologist... Both David and Rod had trained under Edith. So they are Edith disciples. And so they worked with Randy and Dana, actually, to develop this technology. And it was really about using a digital pen, which actually had been developed commercially for artists in order to draw. And so it has this specialized paper, which is basically these little tiny dots that are printed. And those are, what the pen tracks is these timestamped, as you're moving the pen across this paper, it's picking up how long it's taking you to move that pen from one dot to the next, to the next, to the next, right? And then it's aggregating all of that. And so it's from that.. and so Randy, who's at MIT, he's really obviously the one who did the programing did behind this... in order to then translate all these timestamps features into strokes, and then be able to then combine them and aggregate them to pick up... and as you're drawing the clock, you have the face of the clock, you have the numbers, you have the hands, and then you have all the time that it takes you to each do one of those, right. And so we're able to now suddenly detect, not just how long it took you to, let's say, to draw the face of a clock, which is generally a circle, but then how long it took you to decide what to do next. Alright, so we call, we have a number of what we call the sort of decision making latencies. So there's sort of the post clock latency, because you've now just very routinely drawn the circle. Now you have to think, what's my next step? And there's that pause. And how long was that? Before you start to and normally, it's drawing the numbers, right? And then there's a pause, as you think about what's the next step. And it turns out that some of those latencies, and the length of those latencies are very reflective, because of your cognitive processing. Right. So that's what I think really, you know, this, I started using it in 2011. They believe it or not started developing this, I think, around 2004. Before that, when they brought me in, when it was a more mature technology to apply at Framingham. And we had, with Edith, had developed our own manual scoring system for our clock drawing test. And so when I saw this, I was like, "Oh, wow, we have to do this at Framingham". And this just takes what we've been doing by hand, and blowing it out of the water, and letting us expand it, you know that much more so. So it turns out from the, you know, all these timestamped features, there's over 1000 different ways in which you can combine them. And so through the work that Randy has done, and others, particularly on the machine learning side, they've been able to figure out different combinations of these different timestamp features that come together to create more discrete measures that we think of as processing speed, for instance. And so that's how we've been utilizing the digital clock.

John Bellone 58:54

I love the richness of those parameters, the think time versus ink time, you know, for example, and you know, it's excellent. I'm curious how the digital clock compares to other digital cognitive tests that are performed on computers and tablets, smartphones, just some advantages versus disadvantages compared to other technologies.

Rhoda Au 59:14

I don't necessarily think I mean, as we've already discussed, you know, drawing the clock is a cognitively complex task. That's multidomain. Right. And I think that you could say the same thing for the Digit Symbol, you know, you could probably say the same thing for almost any drawn test. I think what's happened is, is that we have a richness of history with the with the clock drawing test, I think that clinically, particularly those who have sort of that Boston process, approach mindset. I think that they've been doing this clinically with the clock for a while and now this operationalizes it in a much more objective way. I think that's really important. So we can take, you know, neurologists, it's not just neuropsychologists, neurologists, geriatricians, you know, they've all been giving the digital the clock drawing test. And now suddenly, we're giving them a tool to take something that they're already familiar with that they've already probably worked into their clinical practice. And we're giving them a much easier way to do it. And so I think that that's its advantage, I don't think is a test necessarily, I think it's the history of the test that brings that. But I think as we move forward, one, as we know, is we now have moved from analog clocks into digital clocks, I think the relevance of the digital clock drawing test is going to start to fade off because not as many people are familiar with analog clocks. But I think that the lessons that we're learning out of the digital clock drawing test will continue on, even as they're being transferred to other digital tasks. And so I mentioned that if we're capturing, you know, digital data streams, and more or less the same way, and we understand that all cognitive tests are actually multidomain. In their execution, we should be able to find the same types of features from the digital clock and transfer them to other digital tasks is just that there'll be, there'll be the those features will be extracted from different components. We're actually trying to do that right now at Framingham, because we've been using the digital pen, not just for the digital clock drawing test, but for all participant drawn tasks, since 2013. So we're trying to figure out is there a set of digital pen measures that we see are consistent regardless of what the tests are? So like these decision making latencies, there's always points in any test where you're making a decision, right? That think time, we should be able to pull out think time from any test, not just the clock drawing test. But I do think that the clock drawing test helped lay the framework for how to go forward.

Ryan Van Patten 1:02:02

Right. Within the digital clock landscape, there are a lot of different varieties of clocks, there's, there's a fully automated DCT clock that's commercially available. One thing I'd like you to hone in on is some of the other aspects of technology, like you've been talking about the pen, and how that works on the paper. I've also seen that some of the pens have Bluetooth compatibility so that the data collected by the pen are automatically sent to a processor and everything is automatically scored. So it's very low burden in terms of human time and effort. So can you talk about just a one or a few of the different clocks available? And what what you prefer to use?

 Rhoda Au 1:02:44

Yeah, I mean, we started with the digital pen. And I will tell you that right now, in terms of the the fidelity of the recording, the best is still from the digital pen, with the paper. But having said that, over the last few years, what you can do on tablets has been becoming increasingly better. So it's not quite yet at the level of what you get from the digital paper, you know, the pen, the pen with the paper, but it's getting close. And I do think that that's where we need to move toward, we need to move toward where we're doing much more screen based, because that's what we use. So whether it's tablets initially with a stylus, and eventually, where you really want to get to, you really want to get this on a smartphone with your fingertip. That's actually where you really need to head. So we're not there yet. But that I'm looking into that, right? I'm looking into and what's the trade off? Because as you move toward, you know, more scalable ways in which to do it, you're we're still losing some of that very fine granular detail that we're getting out of that digital pen. So we're kind of I think we're in the middle of that journey right now. But I do think that that's where we're headed. And that's where we should be thinking about heading. So that as you're interacting, because at the end of the day, the digital pen is all about gesture movement. And so if we can now suddenly translate that into gesture movement that we do in our natural environment, then I think we will have really come up with the solution that we need for the long term.

 John Bellone 1:04:32

So excellent. In addition to picking up on more rich data, you're also potentially increasing the ecological validity of some of these measures. And if you're doing it on your smartphone with your finger, that's more real life adjacent. So I'm curious about the literature about psychometrics and clinical utility of digital clocks in clinical populations.

 Rhoda Au 1:04:56

Yeah, I mean, I think well, first of all, if we talk about today A I think that the clinical, the digital clock test is actually really useful from that standpoint, you know, it's already part of the standard of care, for

instance, at the Lahey clinic. I mean, that's not particularly surprising since Dana Penny was one of the creators of this, but she has been able to bring that in. Also, you know, Kate price and her colleagues down at University of Florida, Gainesville, they've been able to pull it in and use it to, for surgical patients, right. And so they've been able to bring it in into the EHR records, I think that that's what's really important is that one, you have a task that's highly familiar to the clinicians themselves, right, so I've mentioned neurologist, geriatricians, etc. Two, it's very, very quick to give, it can even be self administered. And three, it's now able to move into these EHR, you know, work streams. So I think that even though I do think that they'll need to be some transition to other kinds of technologies, today, the digital clock drawing test does have extremely great utility in the clinical setting.

 John Bellone 1:06:12

So if clinicians listening to this now are completely convinced about using a digital clock, is it possible for them to acquire and use the tests clinically? I'm wondering, you know, about the digital pen and the type of paper you mentioned? I mean, can clinicians use this now?

 Rhoda Au 1:06:30

Yeah, so I think you mentioned that it's commercially available. And so that is sort of the route at this point, at least that, you know, I believe they have the license on that the patent on it, the license on it, from a commercial standpoint, and that is with the digital pen and paper, but there's other, you know, emerging solutions as well on the tablet. And I think that that will continue to move forward. I think I'm probably not supposed to endorse like, a company. So I can I could say, Yes, it is commercially available, it has been FDA cleared, you know, etc. But there are other options besides just using the digital pen and paper.

 John Bellone 1:07:12

Yeah. And you co-authored a paper providing some norms for several indices on the digital clock. So we'll link to that in our show notes as well.

 Ryan Van Patten 1:07:21

Stepping back, much has been said and written about the chasm between cutting edge 21st century digital technologies, things we're talking about on the one hand, and paper pencil and neuropsych assessment on the other. This is also a big focus of the upcoming Minnesota update conference in neuro psychology. So generally speaking, what are your thoughts on the chasm?

Rhoda Au 1:07:44

Yeah, I think that, you know, in general, we like to do what we know. And that's probably the biggest problem, because I mentioned that, you know, right now, our, our way of doing digital cognitive assessments is just to take what we've already done and do them digitally. And that, I think, is under utilizing the promise of digital. And then because we're underutilized, and we're using it that way, the natural question is, what am I doing that I've not already doing? So we're not making that leap forward that you really need to convince people to take this on and move in a different direction, right? So the other problem we have, at least from a research standpoint, is that it's the it's actually the strength of research. And then it turns out to be the weakness of research, which is our peer review system. So in order to get anything published, or in order to get anything funded, you have to go through a peer review system, you have to have people determine whether what you have done is appropriate, has been done, you know, done with the right methods, right analytic methods, etc, you've interpreted it correctly, etc, right? But what happens when you're trying to do something that hasn't been done before. So that's what real innovation and cutting edge is supposed to be. Right? You're not cutting edge if you're just doing things that everybody's already been doing. So but if you're doing something that's really cutting edge that truly meets the definition of innovation, we overuse the word innovation, but in fact, we don't do many things that are innovative. And if we actually do something that's innovative, that means it's not been done before. So what do you do when you don't have peers to do the reviews that you need to move it forward? In a peer review system? That's a big barrier to moving forward between what I've described as the promise of digital versus what we're doing with digital.

John Bellone 1:09:50

I'm curious if you're aware of the upcoming, at some point in time, D-KEFS 2.0 and what they're, what they're looking to do. There, it's going to be fully digital. And there will be the possibility for stimulate, to appear and disappear and different aspects that we cannot do on paper and pencil measures. I don't know if you're familiar at all with

Rhoda Au 1:10:13

I'm not familiar with that, in particular, but I am familiar with this idea that we're gonna do that we're going to continue to find different ways to administer neuropsychological tasks. And I think we have to get away from testing. If we want to get to accurate assessment of people's cognitive status, we got to get away from the concept of testing. And as long as we continue to test, we're not doing that. And we're not doing it, particularly if we're saying that these tests have to be administered by a trained clinician, if we start to think about this, so in the major cities in the US, you can find neuropsychologists, if you start to go outside of the major cities of the US, you start to have a problem in finding

neuropsychologists. Now think about that, globally. There are parts in the world where there are no neuropsychologists. So what do you do? If we continue to develop tools that depend on doing assessments, which are usually culturally language education biased, and/or we require that they be administered by people who are trained, we're never going to get there.

 John Bellone 1:11:23

I've seen you talk about the difference between testing cognition and inferring cognition. This ties in with the ambient technologies that I had, I had commented on earlier, can you tell us a little bit more about what you meant by that difference between testing and inferring cognition and just the internet of things in general.

 Rhoda Au 1:11:45

So everything we do, we do through our brain, like everything, there's nothing we don't do, that we don't do through our brain. So everything we do, we're always reflecting our cognitive capabilities. So what we have to do is capture what we're doing. And then we have to interpret our cognitive status from there. That's the direction I think we really need to get to. And we just need to understand that, you know this, our cognitive capabilities are changing all the time, we have a good day, a bad day, a good moment, a bad moment. And so right now, when we do this active engagement testing, is just about what did we capture at that moment in time, and, you know, in testing itself, is just, it's such a burdensome unnatural process. So if we go back to my original description of what we do when we first bring in a person who is saying that they have cognitive impairments, we don't make an assessment of when we thought that those cognitive impairments might have started, we weren't there to do it, we did it on the basis of the description that they gave and their family members gave. And that's usually our most accurate way of doing it at this point. Now, in that scenario, where we're relying on their ability to detect these changes within themselves, what we need to do is get to these ambient technologies that can detect it even before we are conscious of it. And that's what I think we're, I think that that's where the future should really be.

 John Bellone 1:13:27

Yeah, and you're just as an example, you know, data coming from your refrigerator, how many times you open it or different driving parameters that come from your car directly, you know, data just gathered from things in your life, right, that's what you're referring to.

 Rhoda Au 1:13:41

Yeah, if you have, if you have food that you use to eat, and replenish on some sort of regular schedule, and suddenly you have more of your food, rotting, you're not replenishing. It's your don't have food in your refrigerator. And you combine that with your physical activity, data that shows that you went from going all you know, going out into your world in many different directions too, restricting it to you know, your sleep pattern. So it's these, right, these all these combinations that are going to tell you wait a minute, something's wrong.

Ryan Van Patten 1:14:25

You've written about a lot of good examples of this different ways that digital technologies, passive technologies can detect changes in our behavior, like, for example, increased repetitive steps to a single location, a decrease in the diversity of locations visited, like somebody's world is getting smaller, they're isolating more, we talked about digital voice patterns. There are uncountable very many different variables we can be using here passively over time early on in cognitive decline to detect it. I wonder Rhoda, if few talk for a few minutes. Really big picture for us. Health care, preventative medicine, etc. Like how can digital biomarkers help us break the cycle, so to speak, of high health care costs?

Rhoda Au 1:15:10

Yeah. So right now about 86% of diseases in this country are chronic diseases and chronic diseases, it's in the name, chronic. So what we're doing right now, using the medical model, is we're tracking different kinds of symptoms. And we're waiting until you hit a certain threshold, before we call it a disease. So blood pressure's a great example. Right? So once you get to hypertensive, it turns out that once you get to hypertensive, once you have diabetes, you know, etc, you're now in a chronic state. We don't cure it, we just treat it. And because we're much we're better and better at detecting and treating chronic diseases, and we live longer and longer. That's why our health care costs are going up. So here's the thing, though. The other thing about all chronic diseases, is their insidious onset, you don't go from being a normal-tensive of one day to hypertensive, the next day, your glucose levels have been going up steadily, your weight has been going up steadily, your cognition has been declining steadily. And so right now, what we do is we're so bought into this medical model that we wait to hit a disease state, and then we start treating it, and then we just treat it forever. That's why we have high health care costs. And that's why we're not getting rid of high health care costs. And that's a problem with most well developed countries today. So now, imagine that you're trying to you, instead of thinking of disease as your focus, you're thinking about health as your focus, so that you're tracking your blood pressure, you're tracking your weight, you're tracking your glucose level, you're tracking your cognition, you're tracking your mental health state. And when you're still well within the realm of normal, you start to see some sort of persistent negative trajectory of change, you know, there's gonna be lots of bouncing around. But over time, you're going to be able to detect, if there's any kind of subtle decline going on,

you know, it's something that's persistent. If you intervene, then then you're going to start to drive down health care costs, because nothing will drive down health care costs faster than avoiding the need for health care. You know, so that's my message of what I think digital can do, ultimately, is that if we start to understand that we can detect while you're still normal, and do something, then then we prevent the need for health care down the road. And that's how you drive down. You drive up health quality, and you drive down costs.

 John Bellone 1:18:19

You think that health insurance companies and you know, the Center for Center for Medicare, you think they would be all over this. I'm surprised that we're not seeing it more emphasized. Just this approach. I don't know if you have thoughts about that.

 Rhoda Au 1:18:34

We're very bad at prevention. We've proven that with COVID. We can know lots of things. We are bought into the medical model, as our business model. There's a lot of interests in keeping that model. And so you have to always understand what are the financial incentives that are driving things right now in the medical care system. We're starting to play around with those possibilities within the healthcare realm. We need to incentivize it, where we are rewarding prevention rather than treatment. And we don't do that right now, for lots and lots of reasons. There's lots of stakeholders in this. And so we have to find a better way to communicate the immediacy of benefit of prevention, because we don't do that.

 John Bellone 1:19:34

Yeah, I fully agree. Looking at identifying cures or methods for intervening for certain diseases. Can you talk about your Open Science Data Challenge and how it might help us discover digital biomarkers and potential interventions?

 Rhoda Au 1:19:51

Yeah, I so I think I mentioned that right now I'm very loath to try to recommend like this is the right way versus this the right way etc. because this is such a new emerging area. And and I also mentioned that I get to benefit off the brilliance of my data science AI colleagues. So I just want to make more of that happen. And the way to make that happen is first, I need to help enable the collecting of the right data. Right? I mentioned one of the problems with Framingham is we don't have enough data on a broad enough swath of people. So number one, we need to collect that data as broadly as possible as inclusively as possible, but then we need to share that data, we need to put it out there. Because here's

the great thing, there are really, really smart people everywhere. And what we need to do is we need to get this data into their hands. Because when I when you put the digital recordings in my hands, all I did was think like, Oh, I gotta manually transcribe, I gotta do this, I gotta analyze it this way, blah, blah, I hand it to my data scientist colleagues and I'm like, just give it to me, I just - and phew! and they'll say, Oh, it'll take me a little bit of time to process this. It'll take me a couple of weeks, I'm sitting there thinking, Alright. I like transcribe one recording in two weeks. So to me, that's the magic of data sharing. And I do think I would encourage my research colleagues to understand that for most of us who are funded by the NIA, or the NIH, that's taxpayer money. So we are taking taxpayer public funding, collecting data from volunteers. And we somehow think this data is ours. This data isn't ours. The only people who own data are the people who gave the data. That's our volunteers. And we as researchers, we have a responsibility we first we have a privilege, we have the privilege that they're allowing us to use their data. But then we have a responsibility to take their gift that they gave us their gift of data, and put it out there and put it in the hands of people who are far smarter, or far more capable than I am. But it doesn't matter how smart you are, it doesn't matter, no one person is going to solve this. And in the concept of precision, where we're trying to find the right solution for the right person at the right time, there is a myriad of different solutions. And if we put it out there and let the best minds work on it all together, we'll get to those solutions faster.

Ryan Van Patten 1:22:37

Powerful words. Yeah, thank you for saying all of that. I think there's a lot of a lot of different directions we could go based on what you just said, I just want to make a quick comment about the importance of interdisciplinary work. You know, in psychology, psychiatry, neuropsychology, we might not think of computer science, engineering, data science, some of these areas as being our closest colleagues per se. There's a lot of power to these professional relationships. We do things well, you're very humble and talking about your colleagues. But we do add something to the picture. And we are important players, but they have skills and knowledge that we don't. We have to work together.

Rhoda Au 1:23:18

Yeah, I like to point out like, you know, one of the things that's really important research, data security, no question right? Hands down. That's our most important responsibilities as researchers: to protect the confidentiality, privacy of our participants who have given generously. Who does data security, the best? It's not researchers, it's the financial and military. What are they doing? They're moving trillions of dollars around, they're protecting and protecting. I mean, just, you know, protecting countries. We need to know what they're doing. Because whatever they're doing on the security side, we should be doing. That's actually why I have a lot of interest in blockchain. I learned about blockchain from FinTech conference in Hong Kong. By the way, it was one of the very first, because Hong Kong is all about

finance. So I attended, I got to be I had to have been the only certainly the only AD researcher in that crowd. I understood nothing that was being said. But what I did understand is, wow, they have been figuring out how to move all this money securely, and getting it to the end. So the right people at the right time. And I need to understand what this blockchain technology is and apply it to our research data.

 Ryan Van Patten 1:24:38

At the beginning of our conversation, you made a few key points about when you were describing your research portfolio, and the key themes of it like precision brain health inclusivity, these hot hot button terms. Now that we've talked to you for a while about the research you've been doing, can you just quickly map those onto some of what we talked about?

Rhoda Au 1:24:59

Yeah, I think that so I have this phrase that I use, "The path to zero is one." So our goal is to eradicate the disease, and we need to do it one person at a time. So that's what the concept of precision is, right. And the only way we're going to do it is if we are maximally inclusive in our reach. Because if we don't put inclusivity, at the top of our priority list, we won't achieve precision, because we won't have figured out what works for anybody anywhere. And for me, that has really impacted how I think about how to do research, and the power that digital puts in your hand to try to achieve it. So one of the things I've done is revamped a lot of how I think about doing research around what's the technology that's available. So the smartphone has emerged as a really important tool. Because it's the most penetrating technology out there. There's 6.7 billion people with a smartphone. And in the next couple years, it's going to go to about 7.2-7.3 billion. There is no other technology that's more penetrating than that. That doesn't mean that there aren't pockets, but can you name anything else? And that smartphone? It has at least 27 different sensors, if not more. Those are data collection tools, right? And a smartphone, it's a computer in every single person's hands. So we need to leverage that. And the reason I like voice, digital voice, because it turns out, oh, all these smartphones, they all have recorder. It's so easy, and most people talk. And it's a cognitively complex task! So these are kind of the things I do is think about what helps us get down to that individual person no matter where they are, and what do I have to do in order to make that happen? So my latest catchphrase, is I think we need to stop fitting the science into the methods, into our existing methods. And I think we need to start thinking about how our methods are going to fit our science. What's the problem we're trying to solve, and what do we go and find that allows us to solve it? So that's sort of, you know, my reason for embracing technology, it's a solution to the problem. And we have a very big problem.

 John Bellone 1:27:36

I'm glad you talked about the privacy and security piece, because the more digital data that we collect, the more privacy and security are going to be of utmost importance. So thanks for talking about that. We have a couple of bonus questions. Before we let you go. The first one is very applicable to most of what we talked about today. So you can take it however you'd like. But if you could improve one thing about the field of neuropsychology, what would that be?

 Rhoda Au 1:28:02

Yeah, I think it's to have neuropsychologists embrace that what is being done now actually isn't sufficient. I think we need to be much more self-critical. And I want us to think about the idea that we have to find ways to assess cognition, beyond the current sporadic and examiner of monitored methods. I think that we need to understand we have to take it out of our hands, as we are the ones who know what to do, how to do, etc. And I think it's, again, this idea that we need to focus on what's the problem we're trying to solve? And what are the ways in which we might actually be able to solve it? And so that's, I think that's really hard. It's really hard. And I actually did this once in Grand Rounds a few years ago to a bunch of neurology residents. I said, it turns out that probably most of what you're learning today might be obsolete in about 10 years. That's really hard to embrace. I think we have to do it because ultimately, our job isn't to secure what we do on how we do it. Our job is supposed to be to solve the problem. And our problem is how do we assess cognition accurately?

 Ryan Van Patten 1:29:21

Second bonus question, what is one bit of advice that you wish someone told you and you were training? Or maybe somebody did tell you that really made a difference? So here, we're looking for an actionable step that trainees could take to improve their performance.

 Rhoda Au 1:29:34

So I'm actually going to go back to my parents, your parents are always your first teachers in life. And my parents told me that the point of going to school is to learn how to think and I think that that's really important. It's not just to take whatever you're being told, "This is the way to do it. This is what it means. This is what we do. This is convention." I think it's to look at it and think, "Is it really doing what we say it's doing?" Because that's what I did from the very beginning. I'm like, Wow, is this really accomplishing what we think it's accomplishing? Then the other thing, which comes from my mother, is, she told me that the hardest thing to do is to be honest with yourself. And that means not just to be critical about what you're being taught, be critical about what you're doing. And be honest, are you really doing it? Or what you're doing, why you're doing it? Is it real, etc, you got to get rid of whatever anybody else is telling you. And you got to look deep inside you and say, Is it true? Right? So that's, that's sort of what I

would, I do tell people actually, about this idea of being honest with yourself, and how hard that is to do, by the way. The other thing I tell all trainees these days, I even sometimes put it in my reviews. You got to take business classes, and you got to push outside your comfort zone. So again, getting back to what's the problem you're trying to solve, and consider what's it going to take to really solve it, and what kind of knowledge skills or at least language you can understand to do it. So we've talked a lot about multi-disciplinary, interdisciplinary, really multisector if you're not if you don't understand how these other sectors think you'll never embrace and bring them into your world. And I think that this separation that academics tends to have between oh, we're academics, pure science, and what like the rest of the world does, for instance, in private industry, whether it's startup companies, investment companies, pharmaceutical companies, you know, other mature companies. I think that it's very naive of us to think that we're going to solve this really, really difficult problem without embracing them, and we need to know how to talk to them. We need to know how they think. And we need to be able to understand their value proposition and figure how do you bring it together so that we can work together?

 Ryan Van Patten 1:32:24

Rhoda, we've taken up a lot of your time, this has been fascinating. I really appreciate you sharing your wisdom on all these topics. So thank you.

 Rhoda Au 1:32:32

Yeah, thanks for having me. Good luck with all your editing.

 Ryan Van Patten 1:32:35

I don't think there's gonna need to be a whole lot.

 John Bellone 1:32:39

Easy, this is going to be an easy one to edit. It's been fantastic. I've really enjoyed it.

 Rhoda Au 1:32:45

All right!

 John Bellone 1:32:46

Thanks so much.

 Rhoda Au 1:32:46
See you later.

 Ryan Van Patten 1:32:47
Thanks.

 Exit Music 1:33:12

 John Bellone 1:32:53
Well, that does it for our conversation with Rhoda. We hope you enjoyed it as much as we did. If you like what we're doing here, please consider leaving a rating on whatever podcast platform you're listening to this on. As always, thanks so much for listening and join us next time as we continue to navigate the brain and behavior. The Navigating Neuropsychology podcast and all the linked content is intended for general educational purposes only, and does not constitute the practice of psychology or any other professional healthcare advice and services.

 Ryan Van Patten 1:33:47
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