80| Cognitive Reserve – With Dr. Yaakov Stern

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Speakers: Yaakov Stern, John Bellone, Ryan Van Patten

Intro Music 00:00

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

Ryan Van Patten 00:26
...and I'm Ryan Van Patten. As a quick reminder, over 30 NavNeuro episodes are currently available for CE credits through our partners at INS. You can visit navneuro.com/ins to check out the selection.

John Bellone 00:41
Today we speak to Dr. Yaakov Stern about cognitive reserve. Yaakov is the Florence Irving Professor of Neuropsychology in the Departments of Neurology, Psychiatry, and Psychology, and the Taub Institute for the Research on Alzheimer's Disease and the Aging Brain. He is also chief of the Cognitive Neuroscience Division in the Department of Neurology at Columbia University.

Transition Music 01:15

Ryan Van Patten 01:25
Dr. Stern, thanks so much for making the time.

Yaakov Stern 01:27
My pleasure to be here.

Ryan Van Patten 01:29

So, to start, the term "cognitive reserve" is popular in neuropsychology, but there's a lot of nuance in this area, as you know best, that can make it hard for non-experts to develop a deep understanding of reserve and the related constructs. So, let's start with the basics. Define and differentiate brain reserve, cognitive reserve, brain maintenance, and resilience for us.

Yaakov Stern 01:51
Okay. So, here's how I separate all of those terms. For me, "resilience" is a generic, overarching term for all of those different concepts that have to do with how some people age better than others, or how some people cope with disease-related pathology better than others. So, I would call that "resilience".


Then there's the three terms that you mentioned. Let's start with "brain maintenance". It's really the most recent term, but it's maybe a good place to start. The idea behind brain maintenance was put forward mainly for cognitive aging - not for dementia or pathologies underlying dementia - but it applies to both. The idea of brain maintenance is that some people maintain their brains better than others. What do we mean by that? That they don't show as much atrophy of their brain over time. Very structurally, their brain remains more intact during all the kinds of age-related changes that occur to the brain - there's atrophy and the cortex gets thinner; diffusivity, white matter track diffusivity gets worse, and so on. Some people

seem to preserve their brains better than others, maintain them. And, because of that, the cognitive mechanisms or networks in their brain also are maintained and that accounts for some people doing better with aging than others. That's the concept of brain maintenance. That's really the most recent concept to be put forward. It was originally put forward, I believe, for age-related types of changes, but it has been applied also to something like Alzheimer's disease, where it's possible that some people just don't develop these pathologies as readily as others. And, as we'll get into, there might be sets of life experiences or exposures or genetics that are associated with better brain maintenance. So that's brain maintenance.

The earliest concept was this concept of “brain reserve”. This was put forth first by Katzman, who studied Alzheimer's disease. Katzman was central in identifying the fact that older people had amyloid in their brain, and that caused dementia. And that dementia was very similar to the dementia that Alzheimer described. The dementia that Alzheimer described was really an early onset Alzheimer's. In the old days, people called what we call Alzheimer's now a “hardening of the arteries” or something like that - they didn't call it Alzheimer's. Anyway, Katzman had a big study in the Bronx where he was following elderly people and getting their brains. He was very instrumental in showing that the amount of plaques in the brain correlated with the amount of cognitive loss that these people had. He wrote this paper where he described 10 women who had a lot of amyloid in their brain, but were cognitively normal during life. And he wondered about that. He said, "Well, they had much larger brains than average. Most likely they had higher brain reserve." And, by “brain reserve”, I think he meant they had more neurons or synapses to lose. As a matter of fact, the other instrumental people in Alzheimer's disease - Blessed, Tomlinson, and Roth, who also showed Alzheimer's pathology correlating with cognition - made a similar observation, but they didn't call it brain reserve. So, what does "brain reserve" mean? The reason I put it second, as you imagine, some people maintain their brains better than others. So, at any point in time, the status of the brain is their brain reserve. And let's say that, from that point on, they don't maintain their brain. They have a place where their brain is, and those who have more brain material - larger brains, more synapses, more neurons - might be able to tolerate more changes subsequently, and still look better. There's a very recent paper that just came out in PNAS by Lars Nyberg, who really put forward this concept where they show that they have people with different levels of status of the brain, more intact and less intact. They follow them over time and they show that the people who started higher declined, and the people who started lower declined - they declined in a parallel way. But, because the people who started higher had more brain reserve, they do a little better over time. So that's the

concept of brain maintenance. Both of those - brain maintenance and brain reserve - have to do with the "hardware", you might call it. That's just a convenient term. It's not really an accurate term, but it has to do with the brain itself and the status of the brain.

Then the concept of “cognitive reserve” is different. The concept of cognitive reserve is focused on: given the amount of brain changes that people have - either age-related or disease-related - some people do better than others. So, some people can cope with those brain changes better than others. That's a cognitive process. It's an active process, and we could talk more about that. And because the term brain reserve existed, we called it cognitive reserve to differentiate the two. If the concept of brain reserve wasn't there, we might have called it something very different. But that's how the term cognitive reserve came about. The idea is that some people really cope better with these brain changes, be they age-related or disease-related. Some people cope better than others.

Ryan Van Patten 07:44
Great. Yeah, that's a wonderful overview. Thank you. I'm glad you touched on the Katzman work and the early development of reserve. I wanted to check in with you - most of the figures I've seen suggest that about a quarter to a third of people with neuropathology, like AD pathology at autopsy, were cognitively healthy during their lives. And you spoke to this a bit in your last answer. Is that figure about right?

Yaakov Stern 08:07
I think that figure is about right. We now have many studies that are doing amyloid and tau PET. So, for example, in our studies, we're finding about a third of the people over age 60, who've been screened to come into our studies to be cognitively normal - not even MCI, just cognitively normal - have significant amyloid. That might mean that these people have better cognitive reserve, or it might mean that they have amyloid but they don't have other things that are important for Alzheimer's disease. What's been clearer now is that the amount of tau, as measured by tau PET or post-mortem, is much more directly related to cognition than amyloid. But still, yeah, about a third do, and we could get into it, but there is nice evidence that people who meet certain touchstones for the kinds of things that might impart reserve do better in the face of the amyloid or tau pathology.

Ryan Van Patten 09:07
Right.

John Bellone 09:08
Gotcha. That Katzman study, that was the 1989 article?

Yaakov Stern 09:13
Yeah. I could get you the exact date... [laughs]

John Bellone 09:17
That's okay. [laughs] Just so listeners have an idea of when this field started to emerge.

Yaakov Stern 09:22
Right. I mean, Katzman was really revolutionary. I never appreciated this. But, as I said, he and Terry wrote this very influential editorial saying, "Hey, all of these older people that are developing these cognitive changes have plaques." I don't think they focused on the tangles yet. But, they said, "That's Alzheimer's disease. It's the same thing that Alzheimer described." Before that, the study of Alzheimer's dementia was a backwater. Pathologists weren't interested in it because it was so rare. And, after that, that sparked the whole interest in studying Alzheimer's disease. I was caught up in that. So, for example, the National Institute on Aging started to create Alzheimer's centers. We at Columbia tried to apply for one and there was no pathologist here at Columbia that was interested in working with us. They said, "That's just not an important or interesting disease". It's hard to imagine now, but that's what was happening.

John Bellone 10:30
Quite a lot has changed. Yeah.

Yaakov Stern 10:32
Just a little. [laughs]

John Bellone 10:35
I wanted to highlight something else you had said in your first answer about larger brains and how that might be important. I know this might be surprising to some listeners, but head circumference can act as a rough proxy for brain reserve and potentially protect against dementia. Can you tell us about that?

Yaakov Stern 10:54

Yeah, people were very interested in that. We had a very early study where we had a fellow from Australia who was visiting and he got very interested in this idea of brain reserve. We had this study in North Manhattan, this Washington Heights study, following elders in the area, and he convinced the research assistants to just take a tape measure along and measure head circumference. And, basically, he found that the larger the head, the lower the prevalence of the disease. Sounds a little simplistic, but there were several studies like that - some using head circumference, some actually measuring brain volume. And epidemiologists were very, very interested and sold on this idea. It sounds simplistic, but, I mean, it sort of makes sense in a mechanistic way. There was a neuropsychologist called Paul Satz - he was quite the influential guy in his time. Paul wrote this paper where talked about thresholds. And, basically, his concept, I think, was a brain reserve concept. He said: What happens is, people show changes in their brain, and at some point they hit a threshold, where now they start to show functional problems. And people who have more brain reserve have less farther to go until they show these cognitive problems. So, yeah, head size and head circumference - there are a lot of papers out there like that.

John Bellone 12:34

Yeah. My understanding is that a larger brain indicates likely more neurons and more synapses, and so you have more that you can lose before you hit that threshold.

Yaakov Stern 12:45

Correct.

John Bellone 12:46

That's my understanding.

Yaakov Stern 12:47

You know, it's really hard. I've worked with people and worked with consensus groups on definitions, and it gets complicated because everything is in the brain, right? We're talking about all of the cognitive networks in the brain, and then sort of the structure of the brain - and that's all brain. I think the people who think about brain maintenance or brain reserve have it easier, because they don't have to separate those, right? The whole brain is preserved or is larger, that means that there's more neurons or more synapses, so the cognitive apparatus is preserved. When we get to cognitive reserve, we're trying to make some kind of a

differentiation of two kinds of things that happen in the brain. One is these brain changes that we know happen - atrophy and all the things I listed before. And the other is the brain's attempt to cope with those changes, which comes down to what I would say are cognitive networks of some sort - but they're in the brain, too!

John Bellone 13:55
[laughs]

Yaakov Stern 13:56
So, I think it's really important to get these definitions very clear, so that they're understandable. So, I think, if we want to jump to... Well, let's finish. You have more questions about brain reserve?

John Bellone 14:11
Well, I think it's funny. We talked with Bob Bilder a while back about how the further you get from the underlying physiology, the more difficult it is to actually pin down different constructs. It sounds like that was what you were referring to. I also think it's interesting that head size has anything to do with it. I mean, it's imperfect, but it does hold up in a lot of studies. I guess the phrenologists would have gotten something right there. [laughs]

Yaakov Stern 14:38
[laughs] Well, they were looking for bumps and stuff.

John Bellone 14:41
They got a lot wrong, too. [laughs]

Ryan Van Patten 14:43
Not quite that. [laughs]

John Bellone 14:46
Yeah, I did want to also solidify the difference between brain reserve and cognitive reserve. You had alluded to the difference between "hardware" and "software". I think you also said "active" versus "passive". Can we linger there for a second more?

Yaakov Stern 15:03
Sure. I think I'm trying to say the same things with both terms. So let's talk about active versus passive. So these are - it's hard for me to demonstrate figures, but Paul Satz did write this paper on thresholds. And, basically, he had a figure where one person had a bigger brain and one person had a smaller brain, but there was a common threshold under which, once you reach that level of depletion, you started to show cognitive change. You can think about it with Parkinson's disease where you have to lose X percent of the cells in the pars compacta...

John Bellone 15:41
80-something percent.

Yaakov Stern 15:42
80-something percent. Right, thank you for helping me with that. [laughs] So people with larger pars compacta might have to lose more in order to develop Parkinson's. That's a threshold approach. It's not taking into account the brain actively trying to cope with the change, so I call that a passive approach. The cognitive reserve concept is that - look, some people can cope with these brain changes better. Even if they lose a significant amount of the brain reserve, the brain substructure, they can still cope because they're actively dealing with these brain changes. So that's active versus passive. And then what was the other...?

John Bellone 16:33
The hardware / software?

Yaakov Stern 16:36
Yeah, so the hardware / software - people don't like that. [laughs] You know, but yeah, it's the same thing. So, in the brain maintenance or brain reserve, you're sort of lumping all that hardware and software together. But, in the cognitive reserve concept, you're saying, "Look how people do tasks" - we'll get into it more as we go along. Some people, even though they've lost more hardware, can have better software that allows them to cope and maintain normal functioning.

John Bellone 17:10
Yeah, it's like a structure / function dichotomy to throw in another analogy.

Yaakov Stern 17:15
Exactly.

John Bellone 17:16
I think these concepts can be really difficult to conceptually parse out. So I wanted to dive a little deeper into those things.

Yaakov Stern 17:23
Sure.

Ryan Van Patten 17:23
I think it's pretty intuitive for people. We use the analogy of a computer to explain the brain often. The idea of software as being analogous to our cognitive processes, whereas hardware is the underlying substrate upon which that occurs, you know, the computer itself.

John Bellone 17:39
Right.

Ryan Van Patten 17:40
I think that that works in a broad, gross sort of manner.

Yaakov Stern 17:43
So think of the 2001 Space Odyssey. They're pulling out in ships from Hal's brain.

Ryan Van Patten 17:48
[laughs] Exactly. Later, we'll ask you more about functional neuroimaging.

Yaakov Stern 17:56
Right.

Ryan Van Patten 17:56
But, for now, just give us a broad overview of how, as technology progresses and science moves forward, we'll have a more in depth understanding of neural underpinnings and brain microstructure and we can take brain reserve and cognitive reserve and sort of move them closer together. The distinction might ultimately be artificial. Right?

Yaakov Stern 18:17
Right. I think that our ability to image the brain has really helped us understand these things. Let's just back up for one second, though, because I want to make a very important point that I think will help people understand the basic concept of cognitive reserve a little better. I always say this: In order to study cognitive reserve, you need three things. You need some brain change that you're interested in, the cognitive consequences of that brain change, and then what cognitive reserve is positing is some form of a moderator - something that influences the impact of that brain change on cognitive change. So that's a very important thing to keep in mind. I don't know how many papers I've reviewed, where they say, "Oh, IQ is cognitive reserve. I found this other test that correlates with IQ, so that's cognitive reserve." Cognitive reserve is not a measure. It's not IQ, it's not education. Cognitive reserve is a process that allows people to cope better with brain change.

The very first paper that I wrote about cognitive reserve, and I didn't even call it cognitive reserve then, took advantage of imaging in its early stages. We first thought about cognitive reserve in the context of Alzheimer's disease. So, imagine two people with Alzheimer's disease - and, their Mini Mentals, their cognitive status, and their functional status are equivalent - but one person had way more education than the other during their lifetime. The cognitive reserve concept might say that, well, the person with higher education could cope with the pathology better over time. Even though these people look the same clinically, if you could look at these people's brains and count plaques and tangles, you would see that the person with higher education had more advanced disease, more plaques and tangles. Our very first paper did that with a measure of cerebral blood flow, which captures what we now call neurodegeneration. Sort of the final common path after amyloid and tau is this neurodegeneration that affects blood flow and volume. And we were able to show that, matching people for their severity of Alzheimer's disease, there was greater neurodegeneration in the people with higher education. So that's like a very early use of imaging. This was before we had a lot of pathology studies, where they followed people over time, but later on people did that with measures of the brain as well. Yeah, so I think it's important to keep that in mind.

Epidemiologic studies as well, just to give you another example. So, in very early papers, many of them show that people with higher education or higher occupational attainment are less likely to develop Alzheimer's disease over a period of time. So what are the three things going on there? What is Alzheimer's pathology? Now, those early epidemiologic studies didn't measure Alzheimer's pathology. But they had an underlying assumption that no matter what your education or IQ was, that the Alzheimer's pathology was probably comparable, in

the high or low. So, that was the Alzheimer's pathology. The outcome was developing dementia and the moderator was education. So, again, there's these three things you always have to keep in mind when you're thinking about cognitive reserve. And I think it's very, very important.

We've taken two steps now at just sort of standardizing the terminology. We went through this PIA, which is these groups that meet surrounding the Alzheimer's Association. And now I also have this INS-supported collaboratory that was designed to get a consensus on definitions across human and non-human investigators - not the non-human investigators, investigators of non-human species - just to be clear on these operational definitions.

John Bellone 22:30

Yeah, there are so many terms thrown out there. I've heard "global reserve" for combining both brain and cognitive reserve. And sometimes people use cognitive reserve to refer to both concepts.

Yaakov Stern 22:41

And there's many different papers that have been written with totally alternate concepts. What happened was: the National Center on Aging, well, they always have these brain summits, aging summits - they haven't had one recently, but they've had quite a few. The last aging summit, I don't know, quite a few years ago now, was about cognitive reserve. And the people at NIA were a little taken aback because of the variability in the approach and the confusion about these terms. You know, some people talk about resistance and resilience. Some people use totally different terms. Some people just talk about compensation or scaffolding. These are all complimentary terms, but with different meanings to different people. So they actually asked for this process. They wrote a grant for this three year process to get a large group of people across the field to come to some consensus. So, if you look, we have this website reserveandresilience.com where we've come up with a consensus framework for these definitions with a lot of the people who wrote the alternate papers. So, there was a big paper from some very influential people - this Montreal paper, Roberto Cabeza was the first author. So I brought in Roberto as one of the executive committee members. There were papers on resistance and resilience. There were papers by this guy, Tom Montine. We got everyone together. And actually, the final meeting will be on the last day of October and the first day of November - that meeting is still open. It'll be both in person and online. So, anyone who is listening is really welcome to join in to that meeting. They can listen in and go to the website to see what the framework is that we developed.

John Bellone 23:52
We'll definitely link to that website in our show notes.

Ryan Van Patten 24:42
Great. Well, let's start focusing on cognitive reserve for this conversation. I like how you've described cognitive reserve as a heuristic in some of your papers before. And that speaks to what you mentioned before that years of education is not the same as cognitive reserve.

Yaakov Stern 24:59
Right.

Ryan Van Patten 25:01
But we can talk about sociobehavioral proxies, or indirect measures of the construct of reserve. Some of these proxies are years of education, also verbal intelligence, occupational complexity, leisure activities, exercise, and others. Education is easy to collect and has a long history of support as a proxy for cognitive reserve. But some of your recent work that I've seen suggests that measures of verbal intelligence, such as the NART single word reading test, might be a more accurate proxy. You've talked about the limitations of years of education, such as the fact that it can hit a ceiling in young adulthood and it doesn't always continue to grow with expanding crystallized knowledge. So, talk us through your thinking about education compared to verbal intelligence, and then anything else you want to say about the other proxies.

Yaakov Stern 25:50
Okay, so what these proxies really are, are experiences that people have undergone that might promote reserve. So, as you're saying, education was an early one that people used because everyone had it in their data. And IQ, leisure activities, job complexity - all of these measures are things that people use. Education turns out to be very interesting. As I said, my first sets of analyses and studies were reserved against Alzheimer's disease. And their education actually still is a very powerful proxy. We had a very early paper with Jen Manly, when she was my postdoc, that looked at education or sort of the quality of education. And we were able to show an age-related cognitive decline, that education seemed to moderate the effects of normal aging, and that people with higher education had a less rapid decline in cognition over time than people with lower education. But many, many papers have come out in normal aging, where they don't find that. There are these very huge studies from the Scandinavian groups where they just

do not find the same. They find that education is associated with the intercept where people start, but not with the slope. In other words, people decline at the same rate. We did it much better, in our study with a North Manhattan population, which is a very large study. Larissa Hodney (sp?), who was a postdoc with us and is now in Michigan, did a very nice analysis and we did find that education moderated normal aging. But, for some reason, it doesn't seem to in many people's studies, whereas it does in Alzheimer's disease.

I mean, really, what we're talking about is something very complex. These are very simple constructs. Any one of them, no matter what you pick - you pick education, well, what is that? What's the quality of education? What were the opportunities? What was, you know, societally what's the nature of that training? You said people went to college? Well, you could be a fine arts graduate, or you could study astrophysics, you know. Of course, you can delve more and more deeply. Same thing with occupational attainment, leisure activities. I think what's really nice is how people are now using very sophisticated epidemiologic approaches - like birth cohorts, people that have been followed since they were born - where all these variables are available.

And then we have to think about genetics, too. So, at this point in time, there are these polygenic risk scores - these aggregations of gene markers that people have associated with IQ and others that they've associated with education. So what's up with those? You know, how much of education is really just fulfilling your genetic gift? And how much of it is what happened in terms of your SES and who your parents were, and all of that? So these things are really very complex.

Ryan Van Patten 29:11
Yeah, clearly. If, generally speaking, I know there's a lot of nuance, but if I had to choose one proxy - I know there are different populations that I could be studying, but my sense is that verbal intelligence, these tests of single word reading, might be the ideal choice, all else being equal. Would you say that?

Yaakov Stern 29:33
I think it's fine. You know, I think we use it a lot because it's easy to collect. What I think, really, is that each of these exposures contributes to cognitive reserve, in its own way, and those are not the same. So Marcus Richards, who's a good friend of mine - he was actually my postdoc a long time ago, but now he's very much involved in running this British birth cohort study. So in the British birth cohort study, they tabulated all of these children who were going to be born right after World War

II, the mothers and the children. They were really interested in fertility, because they were worried about maybe lowered fertility. But that turned out not to be a problem, there was this baby boom, really, after World War II. But, anyway, so they have these people - they know all about their mothers, they know them since they've been born, and they've been following them ever since. And he wrote a very nice early paper, where he looked at childhood IQ, education, occupation. Later he included leisure activities. It was very simple. And then he had cognition at age 50-something. Now they're much older, these people, but this is an early paper. And, you know, you could say, "Oh, look. Kids are born with a higher IQ, they get a better education, they get a better job, it's all sort of one big thing." But what he showed is that there were unique paths to cognition in the 50s, age 50s, from each of those different experiences. Such that each contributed differently, independently, or at least some unique variants to where what people were doing. And I think that's really important to remember. All these experiences probably do something different and unique. So, you're right, I use verbal IQ because it's easy. But, really, it's important to realize that there's probably a whole set of experiences we're not thinking of that make a difference. There's amazing studies on how many words parents use to kids, right? For literacy, I'm sure that makes a difference.

The other thing I would say is that, from my point of view, it's important to keep these various proxies a little separate. People use these cognitive reserve scales - there's various sets of scales that query all of these things we're talking about and try to come up with a cognitive reserve score. But by doing so you might be losing something. And Rich Jones, who's a very, very good epidemiologist - I don't know if you call him an epidemiologist or a statistician - he wrote a very nice paper about this. I'll see if I can capture the concept. As neuropsychologists, we're used to this idea of latent variables, right? So you have seven different memory scores and you can create a latent variable, which is sort of the real memory ability. It's reflected by all of these scores. So it's called a "reflective variable". So let's say you do that with cognitive reserve. You've got education, occupation, leisure activities, and you get that latent variable in the same way. What you're getting is sort of what's common to all of those different activities. It's chopping off what's unique about them. So what he said is, you really have to create what's called a "formative summary variable". A formative summary variable is different. It's really each of these different experiences that are contributing unique variants to the summary measure. There are ways of creating these formative variables, but it's much more complicated. Obviously we're talking about a very complex, lifelong process.

John Bellone 33:40

Yeah, that's interesting to hear you talk about the different variants potentially with different variables. I've also heard that bilingualism and multilingualism can be potentially a proxy. There's so many possibilities like you alluded to. And, yeah, I had heard of the cognitive reserve index questionnaire and the fact that there are some statistical methods for lumping proxies together. So, again, it's interesting to hear you talk about it.

Yaakov Stern 34:02

Yeah, the questionnaires are fine. I think it's about what you do with them, and how you summarize them.

John Bellone 34:09

Yeah. And, again, just to make the concept of cognitive reserve extra clear for our listeners - it's not that something like education is protecting against Alzheimer's disease pathology, the pathology is accumulating regardless. It's just that the symptoms of AD pathology, the clinical manifestation, is either absent or less pronounced or just pushed off. That's cognitive reserve.

Yaakov Stern 34:33

Exactly. You're coping with it better, for longer. And, I mean, one of the things we found early that sort of makes that point very clear is that what really happens to people with higher reserve, if they do develop Alzheimer's disease, by the time they develop it, the disease is much more advanced, the pathology is much more advanced. And, really, what happens is they decline very quickly at that point - they sort of drop off a cliff and they die sooner. So, it's protective in a good way and that may be they had more years of non-demented life. But, if the disease is going to win, it's going to win no matter how brilliant you are.

Ryan Van Patten 35:14

Right. Yeah. I know, for myself, I would rather have that scenario where I am intact for longer, and then I quickly fall off a cliff and die soon afterwards. As opposed to a long protracted period of disability, where you're slowly declining. I think most people would probably feel that way.

Yaakov Stern 35:31

Yeah, I think the aging people call that "compression of morbidity". Right? So the bad stuff is compressed into a smaller period of time. When we first published this paper on how education was associated with lower risk of getting Alzheimer's, a

woman wrote me a letter. She said, "You know, my husband was a Nobel Prize winner and he had Alzheimer's disease. What kind of idiot are you?" [laughs] Yeah. She was very angry. The disease is bad. If it's virulent enough, it's probably going to win.

John Bellone 36:07

Some of your recent work suggests that cognitive reserve may confer differential protection for some cognitive abilities more so than others, from what I've read. Can you summarize these data briefly for us?

Yaakov Stern 36:18

Yeah, I mean, this is pretty new. There are not enough good longitudinal studies, where we're really following people over time and looking at change over time. I think we really do need longitudinal studies to look at these issues effectively. We have a paper that's being revised for publication in a regular journal. So we have a five year follow up study of people aged 20 through 80. And we've been looking for what Tim Salthouse calls "reference abilities". These are four key latent variables that he's picked out that are important in aging. One is vocabulary, which really gets better over time, so we leave that out. And then we have episodic memory, reasoning, and processing speed. Where's executive function? Tim feels that, really, that's a messy term. He's written brilliant papers showing that most executive tasks could really be accounted for by reasoning and speed. But, anyway, let's leave that aside. So, we've looked at IQ as a potential moderator of change over time, a five year change. And it does moderate change in memory. It does moderate change in reasoning. But, so far, and it's only five year data, it's not moderating change in processing speed. So, yeah, I think we have to be very attuned to the different cognitive processes, different exposures, etc.

John Bellone 37:55

Yeah. And, I guess, different proxies could differentially impact different cognitive domains, too. It's just early days.

Yaakov Stern 38:02

Really makes sense. I mean, you know, now we could take occupational attainment and really dissect people's jobs. There's this thing called the O*NET - if people are not familiar with it you just go to the website. It's a very instructional website. They take every occupation, and they have a whole database. And the part that we use is 240 different descriptors of the demands of any occupation. Some of them are cognitive demand, some are physical demand, social demands, reasoning. So you

can really get very, very granular about what these occupations are and what kind of reserve they might help generate.

Ryan Van Patten 38:52
Right. That's a way of quantifying occupational attainment, which isn't as easy as quantifying years of education.

Yaakov Stern 38:58
Exactly.

Ryan Van Patten 38:58
It's important work.

Yaakov Stern 38:59

Exactly. That's what's so beautiful about research, of course. Whatever thing you're interested in, even if it's just occupation, you can really sink in there very, very deep. So you really, always have to decide, "Okay, what am I interested in?" We didn't get the functional imaging, so I'm going to keep some of my proxy simple. Or you can just focus on occupational attainment for your whole career, you know.

Ryan Van Patten 39:29
Right.

Yaakov Stern 39:29
That's what makes it fun.

Ryan Van Patten 39:31
Yep.

Ryan Van Patten 39:40

I wanted to go back briefly to this potential for differential effects of cognitive reserve on some abilities more than others. The paper that you referenced where you showed that reasoning and episodic memory may be protected by reserve, but processing speed may not. In the discussion, I liked how you speculated, or theorized, about why that might be. That is, you know, reasoning and memory being higher level abilities - requiring more high level networks - whereas

processing speed might rely more on simple like perceptual and motor abilities. And, so, maybe cognitive reserve doesn't. Is that the general thinking right now?

Yaakov Stern 40:19
Yeah, I mean, that's a sort of facile. It's our first. I never had really seen it before. I don't know if anyone else has published something like that yet. And again, it's not cognitive reserve, it's just IQ. So maybe there's other exposures that might be protective against processing speed.

Ryan Van Patten 40:37
Right.

John Bellone 40:40
So, let's transition into some clinical populations. We've talked about Alzheimer's disease, and much of the research on cognitive reserve has been with older adults with neurodegenerative conditions. But there's also work in other clinical populations. Before we get to those other populations, though, can we just touch on the idea of cognitive reserve explaining differences in healthy older adult populations? So what utility does the construct have with healthy brains?

Yaakov Stern 41:06
Right. So that was a transition for me, because the original observations were really on AD and Alzheimer's. But, I think normal aging is real. It's a process. Cognitive aging - normal cognitive aging, as we call it - normal cognitive aging is real. It's a process that starts early.

John Bellone 41:27
In our 20's, unfortunately. [laughs]

Yaakov Stern 41:29
The data that we have are showing this cognitive decline from ages 20 to 25. And now we're studying it longitudinally. It was hard because people always showed that cross sectionally. But I'm sure a lot of people have seen these figures of people aged 20 through 90, and they show these cross sectional data, and it's almost like a linear decline.

John Bellone 41:49
That's why we have 18 year old Formula 1 drivers.

Yaakov Stern 41:53

Well, yeah. I mean, when you think of sports, you really understand that, in sports, people are finished early because of that. But, from ages 20 to 25, there's cognitive decline. We really don't understand cognitive aging the way we understand Alzheimer's. We really don't understand Alzheimer's either, but at least we see that there's some key pathologies there. There are more and more people adding to the research. You talked with Adam Brickman who's in our group. So Adam, from the time he was doing his dissertation, was interested in white matter hyperintensities saying, "Hey, you can't ignore these things." There's all these other things that are happening to the brain, but at least there's things that are pretty gross and measurable. The brain changes underlying normal cognitive aging are much more complex to describe. But the concept of cognitive reserve or brain maintenance, all these are equally applicable there. It's just more subtle. I'm telling you about this study where we're following people from ages 20 to 80 with all kinds of imaging. A lot of the reason that I started that study, I called it The Reference Ability Neural Network Study, is really to understand cognitive aging and its neural underpinnings well enough that I could really better apply reserve concepts to it. So it really applies to normal cognitive aging. And then the concept has been applied to many, many other conditions other than Alzheimer's disease. So multiple sclerosis is a very interesting one, because it's a brain disease but it impacts younger people. There's very nice work trying to apply the reserve concept there. Almost any other disease that impacts the brain, people have looked at. I mean, what's really interesting to me is some of these psychiatric conditions - like schizophrenia. The concept has been applied to several psychiatric conditions. It's a very, very broad concept. It's not just aging and dementia.

John Bellone 43:56

Right. And there have been studies - you mentioned multiple sclerosis, but also HIV-related dementia, Parkinson's, schizophrenia, and TBI. Many others.

Yaakov Stern 44:03

Yes, exactly. Exactly. And, you know, each one is a different story. So, TBI, for example, is one where a lot of the literature on TBI is a brain reserve literature. People with bigger brains really do better with TBI - there's many papers like that. But there are some cognitive reserve supporting papers along with that. But, yeah, each one of these different diseases or things that impact the brain is a whole different story.

Ryan Van Patten 44:39

Well, I think this is a good time to move into a little more of a neuroimaging, neural implementation, of cognitive reserve. I know a major focus of your recent work has been on using neuroimaging techniques, such as fMRI, to identify reserve networks that might serve as mechanisms that underlie some of the proxies we discussed earlier such as education and verbal intelligence. First, tell us how a more direct assessment - more direct, even if it's not completely direct - a more direct assessment of cognitive reserve through functional neuroimaging can move us forward. And then describe some of your recent work on a task-invariant cognitive-reserve network in a resting-state BOLD connectome.

Yaakov Stern 45:21

Okay. So, as soon as I was convinced that there was this thing - cognitive reserve - which was quite a while ago already, the next question is, “Well, how does it work? Okay, it's there, how?” And one way to ask that is, “How is it normally implemented?” I have to say, I was very much influenced - it's hard for you guys to maybe appreciate this, you younger people - but it was just the advent of brain imaging. Even before fMRI, there were techniques to image the brain in action. My motivations were really pretty simple. "Oh, can I use brain imaging to understand this neural implementation of cognitive reserve?" Just as a sidebar, you know, as a cognitive psychologist or neuropsychologist, I could easily have said, "Well, can I develop tasks that will help me understand how these cognitive processes differ across people?" And that's something I'm thinking about now. But let's stick with that. So, part of my thinking was really very simple. At that time, there were some early papers introducing the idea of compensation. Typically, what people found is that whatever the more impaired population was, young versus old, the old people very often when given a task activated some areas, utilized some areas, that the young did not. Cheryl Grady was one of the first I believe to study this. She gave some face recognition tasks and the old people activated the prefrontal cortex, while the young people did not. She said, "Maybe they're compensating by recruiting these extra areas." So this idea of compensation was something that I thought about.

John Bellone 47:07

It's kind of like efficiency, right? The younger ones were just more efficient in their use of neural networks.

Yaakov Stern 47:13
Right. So that is efficiency, and capacity was another part. So if they're more efficient, they don't need to compensate, right? So these ideas of efficiency and capacity were another. So there's two terms I put forward: neural reserve and neural compensation. I feel a little badly because I shouldn't have said neural reserve, because it has "reserve" in it and it's just confusing.

Ryan Van Patten 47:36
[laughs]

Yaakov Stern 47:37
But I wrote it in one paper, so I kept using it. Compensation is sort of like you're doing something you don't normally do. You're recruiting some extra network or some extra brain area you don't normally use in order to maintain function, in order to do the task. And some people might be able to compensate better than others. Now, not everyone defines compensation that way - that's my way. Then I thought, as we've been discussing, we see cognitive reserve even in unimpaired individuals, right? So I said, "Well, probably, there's differences in how people do various tasks." Just, you know, some people are more astute at some tasks than others. And depending on the task, you might think of the two concepts: efficiency and capacity.

The idea of efficiency is just that as you make a task harder and harder and harder, if you have some network, some set of brain areas that are activated during the performance of that task, as you make the task harder and harder and harder, you might find that some people don't have to increase activation as much. Their networks are more efficient. And then the other one is capacity. If you really load people up, you make things very, very hard, perhaps some people have a greater capacity to their networks than others. So the ideas of capacity and efficiency were just normal differences that people might have. Then the other concept that I put into the neural reserve bucket was flexibility. I thought, "Well, the idea is that maybe some people have multiple ways of approaching a problem. And so if one gets blocked, very simplistic, they have another way." So efficiency, capacity, flexibility - I call this neural reserve. They're sort of normal, even healthy adults do that. And then "compensation", I tried to reserve for doing something that a healthy person would not do that allows them to still maintain function.

Then we had to think of ways to use imaging, fMRI, to approach those concepts, right? But I think, you know, you tell me that sort of thinking underlying that. And

then later on the sufficiency capacity compensation, it was really very task-dependent, right? Because whatever type of tasks you give, there are sets of brain areas associated with that task. So we could look at efficiency or capacity with regards to this particular task. But then we got certain sets of results in our data which suggested that maybe, let's say people with higher IQ, can do something generically. That's not task-specific, that might allow them to do better. So that's when we said, "Oh, let's look for a task-invariant network. Can we find some brain network that is activated no matter what the task is, that allows some people to do better than others in the face of let's say, volume loss or cortical thickness loss." And we're not the only people who were thinking about that. Other groups were looking at resting BOLD networks like that. That's the idea of the task-invariant networks. It's that maybe looking at test-specific things is one way to go, but another way is just to see are there some general networks. And people have thought of a lot of things. So, Nico Franzheimer (sp?) works with Michael Evers in Berlin. And they've written a lot about the left frontal resting BOLD network that seems to be associated with reserve. And that people who have more connectivity in that network, again, can tolerate more brain change, or more Alzheimer's pathology, and maintain function. Because we're doing fMRI on these four different reference abilities - vocabulary, episodic memory, reasoning, and speed - working with my long-term colleague, Chris Habeck, we said, "Let's find a set of brain areas that's differentially-activated as a function of IQ across all these 12 tasks that we're giving people". We gave three each for each of the four abilities. And Chris was able to identify a task pattern that was ramped up as a function of IQ in all of those 12 tasks. And when we forward apply - when we looked at it in a whole totally different task - we again saw that network, and the expression of that network, was related to IQ. So as I was alluding to the real test that we put it into is, "Okay. In those people, we saw a relationship between cortical thickness and cognitive performance. Does the expression of this network moderate that relationship?" So we did that with an activation network, and that was resting BOLD networks. So that's a quick summary of that.

John Bellone 52:51

If and when we do identify a really reliable cognitive reserve network, I'm curious what the benefits of having that knowledge might be. So when you're writing the grant section, the clinical application part of the grant, what do you include there?

Yaakov Stern 53:07

Well, I think there's some interesting things to think about if let's say you really have a network like that. So, first of all, it would be cool to test it now that you've

identified it. There are various techniques now where you could really, I think, go in and mess with that network - use TMS, transcranial magnetic stimulation, and really sort of suppress that, and see whether that really makes a difference. Now you can use this direct-current approach, and perhaps maybe even induce people to use the network more. Can you show an intervention study that that network changes? Or can you actually have people work specifically to upregulate that network and see that it's helpful? I think, on one level, once you have a network, you can test it in various ways to be sure that it really works. And then the other thing is: Okay, yes. How's that going to help people? So it might give us a target. Let's say that you can create some meditational intervention that allows people to upregulate such a network. So, that's some of the promise of that.

Ryan Van Patten 54:25

Yeah. With the idea of interventions, the network, if it is reliable and replicable in neuroimaging work, could be a surrogate endpoint in clinical trials, right? So that we don't have to wait and see. Twenty years from now, is the group with the intervention less likely to develop AD or not? Instead of that, a surrogate endpoint could be looking at upregulation, increased functioning of the network, right? Is that the idea?

Yaakov Stern 54:54

I think so. Especially for these tasks-invariant types of networks. Yes, I think so. You could build them into an intervention study and use them as some sort of a surrogate marker. And, you know, I think that's part of the promise of using imaging. The other side of the imaging story is - okay, we're characterizing these networks that we feel might help underlie the neural implementation of reserve, or at least one piece of it, not all of it, but one piece of it. And at the same time, we have to understand well, what are the brain changes that are affecting cognitive aging? Because really, we want this network to somehow help cope with the key brain changes that are associated with brain functioning.

John Bellone 55:49

Yeah. How do you think about personal characteristics - like gender, or race, or SES - how they might relate to cognitive reserve?

Yaakov Stern 56:01

I think there's two ways to think about it. One is sort of innate differences; and one is opportunity costs. Socioeconomic status is a good example. Just a function of SES really can influence the kind of upbringing children have - the kind of schools

they go to, the kind of stuff their parents do with them. There's loads of stuff there. Not even adding in discrimination and lost opportunities based on discrimination and the like. On the sex side, not a lot of work so far. But clearly, we have to take a look at that. You know, there's just differences there. We throw it in as a variable in analyses, but I think we're just starting to pay a lot more attention to it. I'll give you an example that's not quite a cognitive reserve example. I just recently did an exercise study. So exercise is one of the things that's just unbelievable. You take people who've never exercised, couch potatoes, you get them to exercise and their cognition gets better.

John Bellone 57:15
Magic.

Yaakov Stern 57:16
Yeah. I mean, I was never an exerciser and it convinced me that I really have to do something. [laughs] But we had a study focused on people aged 20 through 60, because a lot of the studies were for participants aged 60 and above. So we did this study, with people aged 20 to 60. It was aerobic exercise versus stretching and toning. We showed that there was a benefit of exercise on cognition. We saw findings particularly for executive function. And the older you were, the more you benefited. Then when we published this paper - it was published in Neurology - and then we said, "Let's step back and look at these data by sex." And it was, I was

embarrassed because what we found is that the men were benefiting much more than the women. And the men were benefiting in domains that the women were not. It was really interesting. I thought that was a much more important finding. So I sent that to Neurology. They didn't even want to review it, so it was published in another journal. So then we said, “Well, what about all these other exercise studies?” And there was someone who had done a meta analysis by sex, but they didn't do it right. They didn't really get the raw data by sex. They just said, "Oh, here's a study that's primarily men, so this must be a male result." That doesn't work. Because, like in our study, we had two thirds women and one third men, but we really saw a greater benefit for the men. So it's a cautionary tale that you need enough data and you really have to look at these things very, very carefully.

John Bellone 58:48
Another variable that I'm curious about is how depressive symptoms or other mental health syndromes might fit in with the cognitive reserve picture.

Yaakov Stern 58:56

Right. So there's two different ways that I think people have looked at this in the literature. One is, you know, there's some nice reviews of various psychiatric diseases, and how reserve might help people escape those the same way they escape something like Alzheimer's or cognitive aging. The other sort of intriguing idea, but there's just not enough data on it, is that maybe there are certain situations where whatever we call cognitive reserve, or at least the variables that we're using to capture it, are more helpful for cognition than, let's say, depression. But there's really not a lot of work done in that area. We had one paper like that that we could talk about if you'd like. But, yeah, I haven't seen a lot of work in that area.

Ryan Van Patten 59:47

Clearly lots to be done in several domains along the cognitive reserve lines.

Yaakov Stern 59:52

Yeah. I mean, Alzheimer's disease is really interesting because I think it's probably the case that depression is an early manifestation of Alzheimer's in many people, right? So there are sets of studies, not many, but one or two suggesting that perhaps cognitive reserve as we know it, the variables that we use, seem to be capturing reserve in terms of the cognitive manifestations, but not the depressive manifestations of the disease. There are early, early studies of this - Miriam Heeling (sp?) published papers, but they were like in 2000, and I don't think anyone's really followed up on that.

Ryan Van Patten 1:00:38

Interesting. For this conversation, I'd like to move into a few questions about clinical neuropsychological assessment, and how we might use all the work you've done and other people have done in cognitive reserve and apply that in our clinical practice.

Yaakov Stern 1:00:52

Right.

Ryan Van Patten 1:00:53

I know I have followed your work since I was in the early years of grad school and I've often wondered about how best to apply the cognitive reserve idea. So I wanted to run one idea by you and get your feedback.

Yaakov Stern 1:01:04
Sure.

Ryan Van Patten 1:01:04
So, given that many people with high cognitive reserve and who also have advancing neuropathology are initially buffered against cognitive decline, but then, as you said earlier, they sort of fall off this cognitive cliff and decline rapidly. I've imagined this from the perspective of a neuropsychologist who evaluates a patient with high cognitive reserve, maybe we have multiple proxies for it. But this patient is also currently cognitively intact, although they may have biomarkers of AD such as CSF, amyloid, and tau. So we're thinking this picture might be somebody who's approaching that cliff. If I were that neuropsychologist, I would consider whether they might be in the early preclinical stages of AD. And I've thought about having them back in for repeat cognitive evaluations sooner rather than later - maybe even in six or nine months - to capture the possibility that they are declining rapidly. I might caution the patient and their family, hopefully, without causing panic, to observe their cognition closely and get in touch with me if they notice any changes. I may or may not explain the cognitive reserve idea to them, depending on the situation, but I'd want to monitor them extra closely because of the work on reserve. So what are your thoughts about this? And do you have any other recommendations for clinical neuropsychologists?

Yaakov Stern 1:02:22
Well, I think that's an interesting one. Because I think, clinically, if you've seen enough Alzheimer's patients, and you've seen them over time, you really do see that. I remember the first time I saw just a brilliant guy who we diagnosed with Alzheimer's disease. I guess today we would call him MCI but it was before the concept of MCI. He was really quite functional. And then, you know, boom. Of course, today, it's a different world. All of a sudden we have biomarkers, right? We didn't have those biomarkers before. So yeah, you could really imagine a situation where someone has quantified amyloid beta and tau from CSF or via PET. And that is something that I like to keep in mind. I think when someone's not demented, you really have to broach that very carefully. But I think it's something that could be discussed with people who are really sophisticated enough - you know, you don't want to scare people to death. And we really don't know. We couldn't predict in an individual subject, what their time is. I guess maybe people could pull this data together. I mean, if we had those data, it would be important. I think that's one clinical implication of our utilization of CR.

I think in other areas where I see it being very important and not really implemented is in clinical trials - let's say of Alzheimer's medication. You would hope because all those trials are, you know, they're not curing the disease, right? They're just aiming to slow progression. And here you have a variable that you know is associated with differential progression. So you would think that it would be important to somehow get a handle on reserve and trials. It was quite a few years ago, someone did approach me and it was sort of a baffling question, because he said to me, "How could you do it?" So, let's say word reading, you know, all these trials are international now. So I was a bit stuck on exactly what I could, at that point, what I would recommend to them if they really wanted to include some reserve-related proxies. Now, I think, if someone came back to me again and asked my advice about it, which hasn't happened lately, I think we could think of things. First of all, there's more work being done on harmonizing tasks. I think occupational stuff and certain SES variables could be used. Yeah. So that's another level where I think it could be important clinically.

John Bellone 1:05:06

Yeah. Continuing with the clinical discussion, is there anything else neuropsychologists should be doing? Or, in terms of our assessment of different proxies? You know, we very often give a single word reading tests, like the WTAR or WRAT or TOPF or NART or something like that. There are other measures, like the Lifetime Experiences Questionnaire, there are different proxies. Is there anything you see lacking from our clinical assessment in terms of the CR construct?

Yaakov Stern 1:05:36

It's hard to say. I think neuropsychologists now are sophisticated in, first of all, in norms. So we do correct, in some way, for educational attainment and the like. I think it's important to be aware that if someone is having subtle problems, and they are, let's say, very high IQ and very accomplished, that they might have a more rapid fall. It's just hard for me to translate that into something very practical...

John Bellone 1:06:13

Yeah.

Yaakov Stern 1:06:14

Yeah. You know, and neuropsychology is sophisticated. So, I mean, we do judge people differently. As you know, the first thing we do is ask them about their education and their work and what they did, and we're making judgments of their

problems relative to that, right? But if we don't find a problem, it's hard for us to say, "Oh, yeah, they should have had one." I don't think... - we're just not good enough yet.

John Bellone 1:06:40

No, I agree. And, like you said, there's not an easy answer to any of these problems. It's a delicate line you have to walk because you don't want to make people concerned about - you know, if someone comes into my office and they have their E4 homozygotes and they may be noticing some symptoms, but they're very high baseline intelligence, very high occupational and academic achievement, and they do fine on my tests, I don't want to worry them that they're going to fall off this cliff. And maybe if I say something, it's going to cause them to think more or be more hypersensitive to their symptoms when they shouldn't be.

Yaakov Stern 1:07:16

Yeah.

John Bellone 1:07:17

But, on the other hand, I do want to prepare them for that possibility.

Yaakov Stern 1:07:20

Yeah, well, I think generically, you can talk about what data have shown in a positive way. Another thing that I worry about - this came out, you know, like, various Alzheimer's associations want to say something positive. I remember on our public radio station, they said, "Come to our website and see what you can do to preserve your brain or maintain your brain", which I think is great. I think we just have to be very careful. Because I remember in the cancer world there was some data purportedly showing that people with a better attitude did better in the face of cancer. And what always worries me is some poor person who develops cancer saying, "Oh, I just didn't have the right attitude", right? So I think with the CR, we have to be careful also in how we discuss this. If someone's going to develop Alzheimer's disease, it's probably going to happen no matter how brilliant they are. Let's face it. We're talking about a moderation of time. The last thing we want people to start to think about is, "Wow, I didn't do enough. What if I would just have more leisure activities?" You know, the way people phrase it now, "If I played sudoku every day...". [laughs] So I think we have to be very sensitive about these things.

John Bellone 1:08:41
Yeah, I'm glad you mentioned that because people could have a tendency to blame themselves. The way I approach this with patients is I say, "Look, there are things we can do to decrease our risk for dementia, for cognitive impairment, or push it off. But those aren't foolproof. And sometimes people who are doing everything right still succumb to the symptoms and it's not their fault.

Yaakov Stern 1:09:02
I think it's important to be very careful. When people ask me, I try to say things that are data-based but very cautious. So I'll say "Look, there are things that the data suggests - heart healthy diet, maintaining activities, doing things you like to do, having social contact. All of these things seem to be associated with more successful aging." I would not tell them,"Go learn to juggle", right? But people do this, you know. I had a reporter call me up from a TV station and say, "We want you to go into a restaurant and tell people they should do crossword puzzles", because there was just an article that came out that featured crossword puzzles as an activity. So I think we just have to be very careful about what we say. If we knew a lot more, we could be more specific. But I think we have to be fair. Sometimes I couch it in "everything that your mother told you is right." [laughs] Eat well, stay active, exercise. So that kind of guidance, I think, can be given, and I endorse that. But I shy away from giving people very specific advice. Like, for me, over time I decided I would do some things. I told you I was never an exerciser, so I started. My office is on the 18th floor here at Columbia, so I walk up every day - at least when I was at my office. Today I'm at my office, but usually I'm not. The other thing is I wrote a grant about tai chi. I found that, for normal cognitive aging, the evidence is very convincing - because it's meditative plus exercise, and those are two benefits. So I started to take tai chi. Now, is that the right solution for someone else? No. But that's what works for me.

John Bellone 1:11:01
And even if it doesn't contribute to your cognitive reserve, it could be preventing fall risk or cardiac issues.

Yaakov Stern 1:11:09
Yeah, it's not gonna hurt me. [laughs]

Ryan Van Patten 1:11:12
I like how you mentioned walking up the stairs. I often think about these atomic habits that we build into our daily life - parking a little bit further away from the store,

walking up the stairs rather than the elevator. If we're pressed for time and it's hard to dedicate an hour or two at the gym three times a week, there can be small things that we can do in our daily life with diet, exercise, and social engagement that can really help.

Yaakov Stern 1:11:35

There are some people who love exercise. But for those of us who may not... I remember Skinner was famous for forgetting his umbrella. So what did he do? He hung it on his doorknob, right? A very behavioral approach. So yeah, the more you build these things into your daily habits, the easier it is.

Ryan Van Patten 1:12:00

Well, this is great. We've been wanting to have you on NavNeuro for a long time, so thanks for taking the time. We just have a few more questions. I wanted to ask you about future directions with regard to CR. Like, what are the two or three biggest unanswered questions? Where is the field headed? What do you think?

Yaakov Stern 1:12:18

Sure. One thing that I think is really important is to get, and it is happening, is research in animals. There are people doing that, but not a lot. That's something that our collaboratory really went out of our way to do. We brought in a lot of very good investigators in mice and in rats. And why? Because I think that they can get to these neural networks and neural processes at a level that imaging can never get to. And they can do interventions in a short period of time. So I think it's important. Something that I've been trying to do is to team up with various people that do that, but to try to make sure that they're approaching it in a way that seems to comport with how I see reserve. I think that's very important. Non-human research is really important.

I think intervention studies are also important. There's a few people who do them. I'll give one example - Sylvie Belleville, from Montreal. She is one of these people who not only does amazing intervention studies, but uses fMRI pre and post to look at a lot of these complex concepts that I've been talking about - like efficiency and capacity - and seeing how they might change. I think we have to do a lot more of that. There's someone else who's doing meditation studies like that. So I think intervention studies paired with imaging. To me, I think that's, first of all, it's important to do intervention studies. And secondly, they can really test some of the concepts that we've developed from imaging studies. So I think that's another area.

Something else I alluded to earlier is to develop cognitive tasks that really get at some of these concepts. Like one of them is flexibility of solution strategy. So there is a bit of literature on creativity. There is someone that does some work on flexibility, mainly in children, but to me, it seems like a very interesting and important area. You know, the way I explain it is: when my daughter was in second or third grade, I was doing homework with her and she was learning seven plus six. And I said, "Oh, you know how I do it? Seven plus three plus three." And she looked at me like I was a little crazy. But I mean, what I was really saying in my "daddy way" was, "Oh, there's multiple ways to approach a problem." And math is sort of easy to show that. If you have multiple ways to do it, you're more likely to be successful. So that's something that I feel is very interesting and I'm pushing. But I think the intervention and the animal studies will be really very helpful. And then these multimodal studies where you not only intervene, but you get the measures.

The other things that are, I think, really cool that are happening is, as I'm sure you've talked maybe with Bob Bilder or other people, is ways to capture cognition in the real world, using cell phones or monitors. So you really get these data in real life, and much more accurately. So, yeah, I think there's a lot of cool directions where these things could go.

John Bellone 1:16:00
Awesome. Well, we have two bonus questions before we let you go that we ask all of our guests. These don't have to pertain to CR but they can. The first question is, if you could improve one thing about the field of neuropsychology, what would that be?

Yaakov Stern 1:16:14
Well, there's different answers. I'll give you one answer. I feel like neuropsychology is great, but I feel like we need new measures for Alzheimer's disease. We need better measures for Alzheimer's disease. I think that's one simple thing. And what's even more scary to me is that the neuropsychologists need to work with the people who do trials. Because if you see what the cognitive outcome measures are in clinical trials, it's a little disturbing. The ADAS COG is really not a very good cognitive instrument. And the CDR Sum of Boxes isn't a cognitive instrument. So, yeah, I think that's one answer to your question.

John Bellone 1:17:04
Any ideas on what a different type of measure might be for AD? What are your thoughts?

Yaakov Stern 1:17:10

Well, there's probably new and different cognitive measures out there. One that I found very intriguing is this binding test - it's a shape color binding test. It's really not nice that I'm forgetting the guy's name, because I've just been emailing with him yesterday. But that's my aging coming in - it'll come back to me in a minute. But this task really seems to be specifically sensitive to AD pathology. That's something that we have to work towards. You know, it's great to demonstrate memory, but it's better to have a task that's specific to AD pathology and not to depression, right? He's shown that with this task. I think neuropsychologists have to be good cognitive psychologists also. I think that's, for some reason, that's just not a popular area of investigation. There's maybe two or three types of tasks that I've seen. Some of them look really promising, somehow sensitive to a deep pathology, let's say, and there's very little work like that that's being done.

John Bellone 1:18:24

It's not Mario Parra?

Yaakov Stern 1:18:25

Mario! Yeah, that's him. Thank you very much.

John Bellone 1:18:28

I just looked it up. [laughs]

Yaakov Stern 1:18:29

You looked it up! [laughs] Yeah. Mario. So yeah, we have some data with Mario that he's writing up. But he's collaborated with these groups, with the early onset populations, and so we have some data. I think he's presented it, but now he's finally going to write the paper. We have a bunch of people that were getting amyloid PET and that we administered his binding task. It's very, very sensitive to the presence or absence of amyloid. It's amazing. And there's a reason why he thought that might be. So yeah, Mario is a very good example. And I think we have to think about that more. The tasks we do are great, but there's probably better stuff out there to do.

Ryan Van Patten 1:19:17

And, finally, what is one bit of advice you wish someone told you when you were training? Or maybe something someone did tell you that really made a difference?

So, with this question, we're looking for an actionable step that trainees could take that they may not have thought of that can improve their training and performance.

Yaakov Stern 1:19:34
Well, it's interesting because I was not very astute about all of this. We could talk about this another time, but I sort of fell into neuropsychology by accident. I just applied to some program and they said, "Oh, we're doing neuropsychology." I'd never heard of it. Actually, they said to me, "You have no idea what our program does." Maybe in those days you could get away with that at a graduate interview.

But, your question was advice. I would say two things. I feel that it's important, from college on, to get involved in research. Maybe people do that automatically now, because they want to get into graduate school. But I think people really need to find what rings the bell for them. And it takes a little time to learn that. You know, I work with a lot of postdocs that are really very smart, and they're teaching them a whole other level. They're all great with statistics and know a lot, but it's more research as a craft, research as a business, research as how frustrating the whole process is. I think people don't see that part - they see a paper and they see the results, but not that it took two years to develop the task. And, you know, the data didn't look quite right for a long time.

The other thing is more of an interpersonal kind of thing. I had a very good advisor and he always said to me, "You know, Yaakov, if you're going to do something, tell people. Always tell them." He said, "They might not believe you. But they can't say later that you didn't tell them." It's more of an honesty and an openness of communication that I think people might be reticent to have. But I think it's something important, you know. I'm not saying to be rash, but really, just to try to be clear on what you're thinking, what you want to do, and be able to express that. And with that people can really help you or tell you why it's not a good idea. But that was just an interesting piece of advice I got a long time ago that I do try to adhere to.

John Bellone 1:21:50
I'm curious now, if you have an example of that. [laughs]

Ryan Van Patten 1:21:54
Don't be too direct with us, you know, if you have some harsh feedback. Feel free to keep it to yourself. [laughs]

Yaakov Stern 1:22:02
I'll stay away from examples because I'll get into trouble. [laughs]

Ryan Van Patten 1:22:08
Well, this has been great. Thank you so much for taking the time. We've wanted to talk about cognitive reserve for quite a while so we can think of no one better. Thank you.

Yaakov Stern 1:22:17
My pleasure.

John Bellone 1:22:17
We really appreciate it.

Yaakov Stern 1:22:19
All right. Take care.

John Bellone 1:22:24
Well, that does it for our conversation with Dr. Yaakov Stern. Be on the lookout for upcoming episodes on behavioral variant FTD, Spanish norms for cognitive tests, culturally-informed neuropsychological evaluations, and many other topics. And, as always, thanks so much for listening and join us next time as we continue to navigate the brain and behavior.

Exit Music 1:22:48

John Bellone 1:23:11
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Ryan Van Patten 1:23:23
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