37| Neuropsychology 3.0: Phenomics and Cognitive Ontologies – With Dr. Bob Bilder

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Bob Bilder, 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 00:23

...and I'm Ryan Van Patten. Today we have Part 3, our final part of our conversation with Robert Bilder. Today we talk with Dr. Bilder about two topics primarily, one of which is phenomics, and one of which is cognitive ontologies. If you're not familiar with these terms, that's okay, Bob will explain more about what they are. Before we get into that, I'll throw out a few quick definitions just to prime you. Phenomics is defined as the systematic study of phenotypes on a genome wide scale.

John Bellone 01:00

If listeners have listened to our episode with Meg Collier on genetics and Alzheimer's disease, we talk a little bit about this. The genome is the compilation of all of the genes that make up our DNA and our phenotype is the outward expression of those genes - so height or eye color, hair color, things like that. Those are the outward expression, what people can see, the results of those genes.

Ryan Van Patten 01:28

Phenotypes that we study in psychology and neuropsychology tend to be things like depressive mood or anger or behavioral traits that we can observe and experience and see.

John Bellone 01:42

Right. They're ultimately the results of our genes and the environment. But phenomics is somewhat similar to - what the genome is to genes, phenomics is to our phenotype. It's the compilation of those phenotypes.

Ryan Van Patten 01:56

Right. Phenomics builds on the fact that we have now mapped the human genome. But we can stop there in terms of phenomics, because…

John Bellone 02:03

We're going to talk a lot about it.

Ryan Van Patten 02:04

Yeah, Bob, he's the expert, he'll give a better discussion. The other area that we focus on is cognitive ontologies. As Bob mentions, there are two different ways of defining the word ontology. As we are discussing it today, just to be clear, we are discussing ontologies as defined in informatics. The definition here is that an ontology specifies identities and properties of entities within a given domain and

defines the relationships among those entities. This is from Bob's 2013 paper in Abnormal Psychology that we will link to. So it might sound like...

John Bellone 02:49
If there are any philosophy majors out there, it's going to be different from the typical ontology study of being and existence. That's not what we're talking about here. [laughs]

Ryan Van Patten 02:57
Right. The definition that I gave may sound like a jumble of words that don't really make sense together. I think about ontology as a mathematical framework. You might think of a structural equation model, where you have constructs, things, and then you specify the relationships between them in a hierarchy or some other complex system. That's essentially what we mean by ontology. As neuropsychologists, we're interested in cognitive ontologies. We'll let Bob go into more detail about some of the interesting and exciting work that's going on there.

John Bellone 03:33
We think this is integral to the whole Neuropsychology 3.0 framework. If we're going to progress in our fields, we think that this is one way we're going to do that. Not just with computerized adaptive testing and item response theory, but also with these cognitive ontologies and genomics.

Ryan Van Patten 03:51
Yes, that's a good tie in. So, again, this will be our last episode with Bob Bilder.

John Bellone 03:56
You don't have to have listened to the previous ones to benefit from this discussion. It's a separate discussion.

Ryan Van Patten 04:02
But listen to them.

John Bellone 04:03
Listen to them. I mean, we really enjoyed our time with Bob and Part 1 was a general overview of Neuropsychology 3.0, the future of neuropsychology, and then we did a commentary on it afterwards.

Ryan Van Patten 04:16
But you already know that because you've listened to them.

John Bellone 04:18
You've listened to it so we'll just give you this one.

Ryan Van Patten 04:19
Yeah, so no need to explain it. [laughs] Without further ado, here is Bob Bilder.

Transition Music 04:24

John Bellone 04:33
Bob, thanks for coming back on NavNeuro. We are really excited to have you again.

Bob Bilder 04:37
That's nice. Nice to be here.

Ryan Van Patten 04:40
[laughs]

John Bellone 04:40
[laughs]

Bob Bilder 04:40
So much has changed since we last spoke.

John Bellone 04:43
[laughs] That's true.

Ryan Van Patten 04:44
[laughs] I like that you tried.

John Bellone 04:45
[laughs]

Ryan Van Patten 04:47
Our last episode was five minutes ago.

Bob Bilder 04:49
[laughs]

John Bellone 04:49
I tried to make it seem like… [laughs]

Bob Bilder 04:53
The field has really moved on.

Ryan Van Patten 04:57
[laughs]

John Bellone 04:57
[laughs] We're using computerized testing.

Bob Bilder 04:58
It's Neuropsychology 7.0. [laughs]

Ryan Van Patten 05:00
[laughs] That's great. He's not going to try to do that again with any of our guests...

John Bellone 05:08
No, no, that's perfect. [laughs]

Ryan Van Patten 05:09
…after being shamed. [laughs] The next two topics that we'd like to talk to you about are phenomics and cognitive ontologies, both of which are also very related to the Neuropsychology 3.0 2011 paper. Other good descriptions of these constructs and concepts, in case people are interested, are your 2008 paper in Biological Psychiatry and 2013 paper in Abnormal Psychology. We'll link to these. To start, what's the Human Phenome Project? And, relatedly, what is phenomics? How might this line of inquiry impact neuropsychology?

Bob Bilder 05:41
I'm almost embarrassed to highlight the -omics anymore, because I just saw somebody using the term Gestalt-omics and then I realized that we had jumped the shark, so to speak, on the -omics thing. I mean, it's been a joke for all. I guess the -omics may have gone too far. [laughs]

But the idea came out of genomics - it's a systematic study of genotypes across the entire genome. When I first came to UCLA, back in 2002, I met Nelson Freimer, who is a well known behavioral genetics expert, and who together with Chiara Sabatti, a statistical geneticist, wrote a paper about the Human Phenome Project. The basic idea was that, with the human genome already being characterized and sequenced at the time, it's big 3 billion base pairs, a lot of base pairs, but it's a one dimensional sequence and you only got four nucleotides. So this is a tractable problem. It was actually completed, the sequencing of the human genome. So, now, we don't know what it all means. Like, what happens once you start translating the genome? A lot goes on. There's a lot of messy biology between that and the phenotypes.

But what Freimer and Sabatti highlighted is that the real work is not in genomics, but in phenomics and figuring out what the genome does. The idea of phenomics in a nutshell was to study phenotypes on a genome wide scale. Now that creates basically an impossible scenario where you could imagine trying to study all human phenotypes, all of the manifestations of genetic action throughout biological processes. Behavior is an infinite set of things that has no bounds on it, really. What we did in order to try to gain traction was we said, "Well, it can't characterize the entire human phenome." What you can do is rather than, say, there's one disease phenotype, which is most genetics up to that point, up to the turn of the millennium, most genetic studies have been done between cases and controls.

In fact, when we started a project for the Consortium for Neuropsychiatric Phenomics in 2008, we talked to the people at the genetics repository, and they said, "Well, when are you going to deposit your phenotype data?" We had somewhere between 20 or 30 thousand phenotypes that we were collecting, depending how you count them. I said, "Well, we really need to talk about the structure of the phenotype data we want to submit, because we got 20,000 variables." They said, "Oh, no. We just want to know if they're cases or controls." That's why all genetics that had gone on was basically to find out, "Oh, this group has schizophrenia, this group doesn't have schizophrenia. We'll do 3 billion *t*-tests, and see whether or not there's differences between the groups." That's the way most genetics are gone on. What we argued is that it will be valuable to look at the

actual configurations of diverse phenotypes and the patterns of phenotypes, and preferably to look at phenotypes across different levels of analysis in order to figure out where the genetic signal was really arising.

So, at that time, it was very popular to talk about endophenotypes. The idea of the endophenotype is that there's something that is not the disease phenotype, like not schizophrenia, but something closer to the level of gene action that we could detect. Some people thought cognitive phenotypes might comprise exactly that kind of an intermediate phenotype. Like, rather than looking at schizophrenia as a phenotype, what if we looked at prepulse inhibition or working memory deficits or Wisconsin Card Sorting Test deficits or failure to activate prefrontal cortex when you're doing the Wisconsin Card Sorting Test? Maybe that would be a better phenotype. That would get us closer to understanding the action of certain genetic polymorphisms like a genetic polymorphism in the gene for catechol-O-methyltransferase. That's where the field was at the time.

What I think that we've learned between then and now is that that was really still over simplistic. Indeed, it's now pretty clear that as you go across different levels of analysis, you go from the genome - think about well, what's the next step up to the proteome? Well, already, just from the level of genetic structure to the coding and the construction of three dimensional proteins following that process of translation, you've already lost a lot. In fact, just the correlation between genetic structure and the level of the amount of transcript, this is before even coding for a protein, you're only sharing about 20% of the variance. So if you've lost 80% of the variance before even getting to the protein, then you can think about how many levels you're going to traverse. You've got to get up to level the proteins, proteins have got to get incorporated into cells, a lot goes on there. You've got to go from cells to neural systems. And, anyhow, we had a - somebody referred to it as a burrito, because it looks sort of like a layer. Anyhow, it's a bit of a stretch.

John Bellone 10:33
[laughs] No chance.

Bob Bilder 10:49

Anyhow, a seven layer thing that you can prove, basically, if you're losing 80% of the variance as you go across levels, by the time you get up seven levels, you can basically prove that it's scientifically intractable. That you can't get there from here. But still, I think that it is important. What we think is still true is that it's critical for people to be able to specify the hypotheses that will get you from one level to the

next. And that it's only by specifying those hypotheses that we're going to begin to extract out the mechanisms through which some of this gene action takes place.

We now know that probably for syndromes as complicated as schizophrenia, out of the 30,000 or 25,000 genes in the human genome, there's probably about 8,000 of them that contribute to the known risk. But then we have to tease apart - okay, well, what networks of genes are doing what? And what kind of functional differences are they contributing to? But the likelihood is that the level of action that we can attribute to these biological processes is very unlikely to relate to any of the currently defined neuropsychological domains that were derived largely from studying people with focal brain lesions following normal development. It just doesn't make any sense that we would expect executive functions or language functions to be dependent on any specific subset of genes or gene networks, per se.

John Bellone 10:52
[laughs]

Ryan Van Patten 10:52
[laughs]

John Bellone 11:30
We're just too far from that level to expect that.

Bob Bilder 12:25
That's right. That's right. I think that, instead, what we need to do is identify those genes that are probably going to confer risk for certain kinds of vulnerabilities in development. That then would subsequently lead to disarray of certain role systems owner of developmental basis, or interacting with development and environmental exposures with certain other disease processes that unfold and lead to the disorganization of neural systems. I think that's why the circuit level is still probably a great place for neuropsychologists to route their basic science. And then to try to understand, well, what are the genetic contributions to variations in the vulnerability and risk for dysfunction at the network level?

Ryan Van Patten 13:09
Yeah. We recently spoke with Lisa Eyler, from UCSD and she was talking about genes that encode for particular immune profiles that potentially confer risk both for psychopathology and also for…

John Bellone 13:25
Neurodegeneration.

Ryan Van Patten 13:26
…and physical health problems that lead people with mental illness, severe mental illness in particular, to die, accelerated aging, and die much earlier. Is that sort of what you're talking about when you say genetic risk for vulnerabilities to later cognitive or psychiatric problems?

Bob Bilder 13:41
Yeah, I think that's exactly right. Because the level of gene action is actually on a whole host of immunologic functions or vulnerability to certain inflammatory processes gone awry. It's that that is the culprit that's messing with certain neural architectures in a way that we can then discern as neuropsychologists and that's the link ultimately to dysfunction. Whereas the way that we do it, or there's a conceptual model, I think, that neuropsychology often has is, “Oh, we take these tests, we lump them into domains that were based on people being shot in the head, and then we try to apply them to disorders have nothing to do with being shot in the head.” It doesn't make any sense. Sorry to be stark about stating it this way, but there's a virtue in that.

John Bellone 14:31
Do you think the main applications in neuropsychology then is to help improve our diagnostic power?

Bob Bilder 14:37
Well, I think that currently there's really not that many of the disorders that we confront that are just genetic disorders, per se. I mean, there's a handful of relatively rare monogenic causes of intellectual disabilities.

John Bellone 14:54
Huntington's disease.

Bob Bilder 14:54
I mean, there's a few. In fact, one of my favorite papers at any International Neuropsychological Society was Igor Grant highlighting the number of abstracts in the INS program relative to the prevalence of the disease. It was really amazing that you focused on Huntington's disease. There's like 50 papers on Huntington's disease relative to the percentage of the population that actually [has] Huntington's disease.

John Bellone 15:19
It's very rare.

Bob Bilder 15:20
Yeah. As opposed to how many papers were there on cardiovascular illness and what it causes in terms of neurocognitive morbidity.

Ryan Van Patten 15:29
It's a huge burden in society.

Bob Bilder 15:30
Yeah. In terms of there being a growth area for neuropsychology, we focus on where people are sick. Now there's a big focus on dementia, of course, but I think the intersection of other medical illnesses is also critically important.

Ryan Van Patten 15:44
Yeah. My follow up question is around our general discussion we're just having around cognitive phenotypes, which you alluded to. In your 2013 paper, you talked about cognitive phenotypes as potentially being unique and useful and special to us and "phenomics" moving forward. Tell us about that.

Bob Bilder 16:02
I think that the allure of cognitive phenotypes as being endophenotypes is perhaps more of a red herring than people would have hoped years ago. I do think that cognitive phenotypes offer a particularly useful intersection between brain function and ecologically valid real world functions. I think that's the primary virtue. I think the data I was talking about from the Centrax initiative before highlights that and showed that the more precise levels of neural circuitry were less related to real world outcomes and the more complex polyfactorial, neuropsych tests were more related to real world outcomes. I think that we can, if we're very thoughtful about it,

think about exactly what we are validating these tests with respect to. Then we could develop, as we were talking earlier, better measures that are more ecologically valid on the one hand, or more physiologically valid on the other hand, and know why we're doing them. Because we're asking different questions about them rather than using the Trail Making Test to solve all the problems.

Ryan Van Patten 17:06

Another really unique and I find to be helpful construct that you've talked about are cognitive ontologies. Can you first briefly define what you mean? I think a lot of people won't be familiar with ontology in this context and what it meant, and then how this is useful for neuropsychology?

Bob Bilder 17:24

Right, right. Yeah, there's two pretty discreet meanings of the word ontology. One of them is used in philosophy, and I'm not sure exactly what it means in the philosophical context.

Ryan Van Patten 17:34

Whatever it is, Kant doesn't like it because he does deontology. The opposite of whatever it is.

Bob Bilder 17:39

[laughs] That's right. I just have a weak spot in understanding philosophy. But in biomedical informatics and healthcare informatics contexts, ontologies have emerged as the formal specification or definition of a domain of knowledge. In brief, the definition of biological processes benefited from establishing a controlled vocabulary so that everybody is using the same terms to describe the entities that exist within that domain of knowledge. It's really important. Like, gene ontologies is a really good example of an ontology in this context. And that is when a workgroup got together and they said, “Look, we’ve got to stop this Tower of Babel talking past each other because we're just using different names. And we're dealing with 3 billion base pairs and there's a lot of information here. If we want to connect it together, we’ve got to at least agree on the terms.” They got a controlled vocabulary [and] everybody agreed to use the same terms. Then you have to define, well, what does that term mean? And get people to agree on what the term means. So, in terms of making any system that tries to get machines to operate on the knowledge, you have to have agreed upon definitions of those systems. During the Consortium for Neuropsychiatric Phenomics, we worked on developing cognitive ontologies to try to better specify what we meant when we use terms like working

memory or declarative memory. I think that the real learning from that, I mean, we've made some progress. We work with Russ Poldrack on really making a system that I think still you can poke at and see what's there. So you know that that exists as an outcome of that work on cognitive ontologies. But where it's going, I think, is the next step of really getting to the level of the indicators rather than the concepts. Because what we found is that, as we dug in, you could get some agreement on what people defined these constructs as being, like working memory. There's a definition, we had an NIMH workgroup on working memory, and we had a bunch of people crowded into a room in Bethesda, and we'll all agree that "Oh, yeah, we'll call it this." Some people would argue and quibble, but finally they get tired and they say, "Fine."

John Bellone 19:55
[laughs] We want to go to dinner already.

Bob Bilder 19:57
Yeah, when's dinner? [laughs]

Ryan Van Patten 19:59
That's what a work group is, basically. [laughs]

Bob Bilder 20:01
But I think that it's like a metric - we always define these cognitive constructs with respect to the actual measurements that we do. One of my favorite examples, and there's a nice paper that's from Fred Sabb and our colleagues. Fred had a really straightforward question that he wanted to know - what's the heritability of cognitive control? Because, as those people who are into that literature know, cognitive control has become even more exciting than working memory. It's been shooting up like a bullet in the charts on PubMed. So what is the heritability of cognitive control?

So what Fred discovered pretty rapidly is that no one had studied the heritability of cognitive control because the concept of cognitive control only emerged more recently. So he used literature mining to find out, okay, well, what are the contexts and the other concepts that people had used in association with cognitive control? He found there was a series of four or five other constructs. There's working memory, response inhibition, response selection, task switching, and something else. Anyhow, what he found is that, yes, you could actually define heritability if you looked at the measures that were used to measure each of those other concepts. But then there was the most astonishing finding. That when you looked at the papers on cognitive control, not a single paper had studied any measure of

cognitive control that wasn't already studied in the context of one of those other concepts. So basically, all we've done is put lipstick on the pig and try to call it something else. But that measurement that we have is exactly the same. It was still Digit Span from Ebbinghaus in 1880.

Ryan Van Patten 21:40
[laughs] The theme of our conversation.

John Bellone 21:43
[laughs]

Bob Bilder 21:43
[laughs] We've got to give Ebbinghaus some credit. So anyhow, what I realized is that when we're trying to understand how to make progress, talking about these constructs is almost worthless. We don't need to say somebody has a problem [with] working memory, because that could mean various different things. This person can't do Digital Span, that's actually different from a person who can't do Arithmetic. They both load on the working memory factor on the WAIS. That's a well done factor analysis. We can actually support that, well, yeah, they do have something to do with working memory as defined in that way. Yet, still, it's probably the differences between somebody's digit span and arithmetic performance that may be more important to their functioning than other questions about their working memory, per se. So why don't we just stick with the tests? People routinely are drawing conclusions about the domains when I think that the permission to talk about the domain is not justified by the data. Then we have trainees coming in all the time. They say, "Well, this patient has inconsistent performance within the domain."

John Bellone 22:42
[laughs] So surprising.

Ryan Van Patten 22:43
[laughs] What domain?

Bob Bilder 22:44
What does that tell you? It tells you the domain is terrible. This is not a real domain, right?

Ryan Van Patten 22:49
Executive functions are the worst.

John Bellone 22:50
I was going to say don't even get him started on executive functions. [laughs]

Bob Bilder 22:53

Yeah. If people call them frontal lobe functions, then we get really upset, right? Trying to attribute any particular function to a particular bit of the brain or trying to attribute or trying to discern what these domain values are, I think, is not as valuable at all. Just look at the test performance and think about what it means.

John Bellone 23:16
And, yet, that's what we as neuropsychologists are tasked with doing or that's the task that we think we're doing [or] we should be doing. How do you balance those?

Bob Bilder 23:25

I think we can get past it. I mean, maybe my trainees just ignore me and are polite because I'm a supervisor, so they try to be nice. They say, "Don't listen to Bob." [laughs] Okay, you could just get the report done.

John Bellone 23:40
Just say, executive functioning is impaired. That's it. [laughs]

Ryan Van Patten 23:40
[laughs]

Bob Bilder 23:43

I think that we made progress. Even though they still group things in the summary tables, I think one things we explicitly focus on is how to get past the idea that what we're doing is trying to extract values of these domains, and instead look at the individual test scores, see if they hang together to answer some kind of a differential diagnostic question. Or if they play out somehow in recommendations that we can make to the person and their family or their doctors. What else is important? There's nothing else. It's not helping the patient to tell them, "Oh, you have an executive functioning deficit." But it does help them if we can enable differential diagnosis of different kinds of brain diseases that helps them and their

doctors. Or it makes a difference if we can give them specific recommendations that, "You could benefit from this kind of training."

John Bellone 24:32
Based on this test.

Bob Bilder 24:34
That's right. That's what this test does. Now sometimes talking about functions can be helpful. Like talking about attention and talking about the mechanisms of attention, how that relates to detecting mismatch, how it disrupts your ongoing behavior. These are the kinds of things that can be valuable.

Ryan Van Patten 24:52
Some of our cognitive domains may have more utility than others, with executive functioning having the least because it's so heterogeneous. But it seems like visual spatial, visual constructional tests seem more similar. I'm not pulling any data to mind right now in terms of a factor analysis, but that they seem to hang together better. Certain measures of language - well, language is heterogeneous, but less so than executive functions. Do you have that same prior that some domains seem to be more meaningful than others? Or even with visual spatial skills and receptive language, do you think it's better to stick with individual test scores?

Bob Bilder 25:32
I think that if - and I guess that's what I was alluding to before in talking about attention - that it's worth it when it makes sense with respect to the underlying brain mechanisms to talk to people about the brain mechanisms. I think if you've got people with a specific language disorder, then it actually is very valuable to talk to them about the distinctions between expressive and receptive language functions, although we wouldn't just talk about "Oh, your language system is a problem." We would actually be more nuanced about that. We tell them, "Oh, your repetition is bad, but your comprehension and all these other things are okay." That's a good way to explain those kinds of things. It involves more refined ways to get at how to give people a brain explanation of the problem. I've talked to patients about having difficulties in the subiculum accumbens projection. In effect, it's giving them something physiological to hang their hats on and something objective that we could talk about, and it can be used to explain the mechanism that might be responsible for the kind of problems they're having. But always relating it from the brain back to the actual things they're experiencing in day to day life, rather than trying to talk about, "Well, that's your language function or executive function."

Ryan Van Patten 26:40

Yeah. To step back to a theoretical level with cognitive ontologies, in some of your work, you talk about, again, theoretically, how we might move to a place where we better understand these constructs - working memory, executive functioning, or if we want to break it down to inhibitory control, more granular level. I know some of your work before, maybe it was work with Russell Poldrack, was around creating an online repository where we have these models that are theoretically tested, we can create hypotheses that are testable with our neuropsych measures, and then move forward in our understanding of how cognition is truly organized in the brain and how it manifests. That theoretical work, do you think there's progress to be made in cognitive neuroscience and neuropsychology there? Or not so much?

Bob Bilder 27:30

No, I think there is. I think that, and I guess the best I've stated it was in that journal of Abnormal Psychology paper. In talking about what is really the missing link, and that is at the level of neural circuits we lack a description framework that enables us to specify things at the circuit level and then attach ideas or literature or data to those circuits. For example, I blurted out something about the subiculum accumbens projection, which I believe is important in certain kinds of attentional regulation processes. But I just if we think about the different functions of the hippocampal formation or the amygdala, enough is known about the circuitry of these bits of the brain - what they're connected to, what are the relevant networks - that we could begin to relate actual evidence to the hypotheses about those circuits. And, that way, if we can actually specify the hypotheses we have formally, then we could begin to put evidence on those hypotheses and see if the evidence supports them or rejects them. I think that that's a potential way forward.

Currently, we lack a very coherent neural circuit description framework and I think that it will take time before that will happen. It may be that it will only really happen when we have other automated text mining tools. In the effort that we did, our guys in computer science were really into doing text mining and found it to be impossible at the time because the field is not well enough organized and there isn't enough following of conventions and rules. But I think, ultimately, as we move forward the future of scientific publishing and literature may be that we deposit data according to certain rules, and then machines can discern the structure from looking at those data. That may tell us more about neural circuits than we do in a top down way.

Ryan Van Patten 29:33

Right. Machine learning, AI, these really powerful tools.

Bob Bilder 29:36
Yep. And they're getting smarter. [laughs]

Ryan Van Patten 29:38
Yeah. [laughs]

John Bellone 29:40
This conversation, just from reviewing your papers and your work, really demonstrates the breadth and the depth of knowledge that you have across a number of different areas.

Bob Bilder 29:50
More breadth than depth.

John Bellone 29:52
[laughs] Fair enough. But I think that allows you and others who have that similar breath to approach problems in a different way. I was wondering if you can say anything about that. How can that be replicated? Or do you agree that breath is very important for us, as neuropsychologists, rather than the tendency nowadays to just get very narrow and very niche? I think that's a detriment sometimes. What do you think?

Bob Bilder 30:20
I think both are critically important. I was really impressed when I met the guy, the head of the Nature Publishing Group, and he seemed really smart. I couldn't believe all the stuff this guy knew. He says, "Oh, yes. I have very broad knowledge." But it's [unintelligible] and I admire that. [laughs] But that's me. I'm not that good at - I have a short attention span. I really like big ideas and stuff like that. So, for me, breadth is more fun and more exciting. But I think that scientific progress really demands people who will stick with a single problem. If you look through the list of Nobel laureates it's not people who are glossing over a bunch of areas, usually. Although being able to span different domains, I think, is the advantage of breadth. Being able to see examples from one discipline that may apply to another, that kind of interdisciplinary scope, I think, is critically important. But if it weren't for people doing in depth explorations and really digging down to the bottom of certain key areas, I think we would lack progress.

John Bellone 31:23
Sure.

Bob Bilder 31:24
I actually have a great idea for a book, and I'll share it with you because I'll never write it but maybe you'll write it. It's called The Other Thing. I wanted to write this book because you can go into any self-help section and you can find all these books about the "one thing" that you need to do to be richer or smarter or thinner or whatever is the desertarata of the moment. But I find that whenever people focus on one thing, it's always leaving out the complementary stuff and all the rest of the universe that's actually equally important to be in balance.

John Bellone 31:58
Yeah.

Bob Bilder 31:59
There's no “one thing”. You have to always think, "Oh, this is complemented by that."

John Bellone 32:04
Right.

Bob Bilder 32:04
Like, with creativity, where we've been looking at the roots of that, the definitions of creativity focus on novelty on the one axis and utility on the other axis. But basically, that involves a process of exploration and then selection. There's an expansion process and then a narrowing process. Those two things have to go on, I think, constantly in order to really generate forward progress. If you never go out and explore stuff that wasn't done before, you're never going to get anything new. But if you do things that are too new and they just fritter off into nothingness, then what's the utility of it? It's finding that balance - on the edge of chaos, that's where great things happen.

Ryan Van Patten 32:50
That's where you're living. [laughs]

Bob Bilder 32:52
Got to be on the edge, but not over it. That's the idea.

Ryan Van Patten 32:56
[laughs] Well, with that, I think we can wrap up our conversation. Bob, thank you so much for your generous offering of your time. This has been great.

Bob Bilder 33:04
Well, thank you guys so much for coming all the way up from San Diego. It's great to see you here.

Ryan Van Patten 33:08
Yeah, no problem. Appreciate it.

Bob Bilder 33:09
Stay as long as you like.

Ryan Van Patten 33:11
[laughs]

John Bellone 33:12
[laughs] Do you have another hour? We can... [laughs]

Ryan Van Patten 33:13
[laughs]

John Bellone 33:15
Thank you again.

Bob Bilder 33:16
Yeah, thank you guys.

Transition Music 33:16

Ryan Van Patten 33:21
Well, that does it for Part 3 of our conversation with Bob. Before ending this episode, I'd like to follow up on one of the threads of our conversation with Bob, around cognitive ontologies and how we define our constructs in neuropsychology

right now. Bob talked about this for a few minutes and he has really interesting perspectives on the issues with some of the labels that we give to our cognitive domains. As a neuropsychologist, we're all familiar with attention, language, visual spatial functioning, memory, executive function. The five really big core constructs that we categorize all of our cognitive tests under. Bob sort of referenced the fact that a big influence on this framework for thinking about cognition comes from lesion studies where, as he said, people are shot in the head and based on their lesion location and the deficits that they showed, we grouped their cognition into these domains. We're not going to summarize all the history of that literature. What I'd like to talk about for just a few minutes is what this means for our everyday practice in clinical neuropsych. Let's take executive functions. This is the easiest victim I think.

John Bellone 34:44
We were tongue-in-cheek making fun of [executive functions] with Bob [and] the fact that what we call executive functions are really a heterogeneous set of abilities. There's not really great footing to link them together. But that's just an umbrella term that we use because we don't really know what else to lump them in.

Ryan Van Patten 35:04
Right. So a practical question - well, let me back up for a second. One of Bob's arguments is that we should tie the constructs that we use to the specific tests that we administer, as opposed to taking a term like cognitive control and applying it to the Stroop task. Where the Stroop task can also be called a measure of attentional control and executive control and inhibitory functioning, we should just select the term that is close to the test, what the test is measuring, and use the tests themselves as really the construct of interest. That makes sense. Certainly, this proliferation of terms does not do us a great service because it's very confusing. One test can measure five different constructs and it's not clear in the literature. When we're writing clinical reports, for example, we can either use a term like executive functions, which is overly simplistic and doesn't capture all the nuance, or we could describe every single test, which is more accurate, but…

John Bellone 36:11
It's cumbersome.

Ryan Van Patten 36:12
It's cumbersome. We're not going to sit there in a feedback with a patient and go through every test that we've administered and what that specific test measures. So

there's this tension, I think, between simplicity and ease and practicality, which does argue for using our five simple domains. That tension is versus precision accuracy. There'll be a lot more complexity if we were to go down that road. So what do you think?

John Bellone 36:40

Right. So rather than saying “executive functioning was impaired overall,” if there was, let's say, there's mixed, we would say “response inhibition was impaired” and we can talk about what that means for everyday functioning. This is the tension and I don't have a good answer. I use the traditional executive functioning to incorporate the umbrella of tests that we think map on to executive functions - higher level kinds of abilities, planning and organizing, and problem solving. When it makes sense to separate them I try to in the report. We're not going to solve this right now, which one's best. I think we need to just maybe split the difference sometimes or take it on a case by case basis. I'm not sure.

Ryan Van Patten 37:23

Some of Bob's work that he referenced, work with Russ Poldrack has been around doing research in this area to move us forward. In other words, defining our constructs in a more precise way. Like, what exactly is working memory? Some people would say Digit Span Backwards is a test of working memory. I know at least some theorists who would say it's not, or it's not always a measure of working memory. We can give a lot of examples like that. We can have these philosophical arguments in an abstract way all day and night. What we really should be doing is coming together with data. So this project, that Cognitive Atlas that they worked on, was an attempt to allow us, as neuropsychologists and neuroscientists, to do research, factor analyses and other approaches, to provide good data on what our tests are measuring. Is it response inhibition, cognitive flexibility, working memory, attentional control, and even weigh in and vote on what terminology is best so that we, like people in the field of genetics, could start to come to a consensus on our terminology, the words we use to describe what our tests are measuring, so that we can get to a better clinical state so that you and I could resolve this discussion and not be like, "Oh, there's no answer."

John Bellone 38:49

Right. I think it also depends on the referral source and the patient and whatever's best for them. It depends on how we're planning on giving feedback to the patient about their difficulties and their family. Or the referring provider, if they understand

the nuance within executive functioning, that there are different abilities. I think it's going to be dependent on those cases.

Ryan Van Patten 39:15

That's a great point. We want to be able to communicate well to the referring provider, and certainly the patient. Then again, there's this tension. We might say executive functions and they understand that and so they're nodding away and it feels good to them. But if it's not accurate or it's not as accurate as something else, it's like to what extent do we feel like we need to go into a little more depth in order to capture the precision of what's really going on in the brain versus presenting this information at a more surface level so that it resonates with the person. Again, there's no answer.

John Bellone 39:51

This problem is not specific to executive functioning. There is, I guess you could call it domain impurity, like task impurity where there are diverse abilities under these umbrellas. So language, right? We have naming, we have expressive and receptive abilities. You can't just say "language is impaired" or "language is average", it doesn't fully answer the question. But it is a shorthand. I mean, all this is just a shorthand for helping people understand their abilities better and their difficulties.

Ryan Van Patten 40:25

I guess the take home, for me, of this conversation is that I love that Bob Bilder has put a lot of thought and effort into this - creating the Cognitive Atlas, writing about it, because it's easy for us in our field to just reify our categories and say, "Oh, yeah, of course, that's executive function. That's what I was trained on. That's easy." I think it's really important, as opposed to cutting corners and going the easy route, that we continue to question our assumptions and do research on it.

John Bellone 40:55

Yep, agreed. And have discussions like this. Please feel free, for all our listeners, to chime in about what your thoughts are here. We'd love to get a discussion going on either on our website navneuro.com, or on Twitter @navneuro. We'd love to hear your thoughts on this issue as well because this is one thing that we need to resolve, I think, as a field.

Ryan Van Patten 41:15
For sure. Yeah. Hopefully Neuropsychology 3.0 completely resolves this problem.

John Bellone 41:20
[laughs] It'll resolve everything.

Ryan Van Patten 41:22
[laughs] Neuropsychology is in a perfect paradise.

John Bellone 41:27
Yeah. So, to be continued.

Ryan Van Patten 41:29
Yep. Well, that wraps it up for today. Thank you so much for listening. And, as always, join us next time as we continue to navigate the brain and behavior.

Exit Music 41:39

John Bellone 42:03

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Ryan Van Patten 42:14

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