62| Multiple Sclerosis: Cognitive and Emotional Sequelae – With Dr. Peter Arnett

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Peter Arnett, 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, brought to you by INS. I'm John Bellone...

Ryan Van Patten 00:25
...and I'm Ryan Van Patten. Happy New Year everyone. Today we have a few brief housekeeping items before introducing our topic and guests. First of all, I want to congratulate you, John, for achieving ABPP board certification in clinical neuropsychology. I know it's a long process and you spent a lot of time studying and preparing, so this is well deserved.

John Bellone 00:47
Thank you for saying that. I'm glad you brought it up because I wanted to thank you as well for helping me prepare. I think you were integral in my studying process and my passing. At really every stage you helped me. So that's a sincere thank you to you. I also have a couple other people that I have to thank who helped me along the way. A couple of people wrote me letters. In order to submit your application for the credential review, you have to have a couple of letter writers. So I wanted to thank a couple of my mentors, Steve Correia and Tim Belliveau, for those. Then I had lots of other people who helped me prepare for the process. Brett Parmenter was my mentor throughout the ABPP process. Robb Mapou helped me through the oral exam preparation. And then I had a colleague who was going through the process together with me, my study partner for this Ronak Patel. So both a thank you to him for helping me prepare and congratulations to him for also passing the ABPP process. But, you know, Ryan, the main reason I did this was just to have more letters after my name than you, right? [laughs]

Ryan Van Patten 01:59
[laughs] Whatever you can do to feed your narcissism and feel more accomplished than me.

John Bellone 02:05
When you get boarded, I'll have to get another certification or go back to school for something else.

Ryan Van Patten 02:09
Go back for an MD or something. [laughs]

John Bellone 02:14
[laughs]

Ryan Van Patten 02:14
Well, in all seriousness, this is a big accomplishment. So nicely done. I'm sure it's good to have it behind you.

John Bellone 02:19
Yeah, very much so.

Ryan Van Patten 02:21
One other agenda item we have today, we are introducing a new system that we will be piloting relating to our episodes being released for CE credits through INS. So, from now on, for most episodes, we will be embedding two to three code words at random places during the interview. What will happen is we will pause from the interview for a few seconds, give you one of the words, and then resume the conversation. Listeners who need CEs can record or just remember the words and then select them from a drop down menu when they're registering for their CE credits at navneuro.com/ins. Today we will debut the system in this episode, so be on the lookout for those words.

John Bellone 03:08
This new system will only apply to this episode, episode 62, and the new episodes going forward if the system works. For any of the previous content, so pre-episode 62, we will still be using the old multiple choice quiz method. And if you don't need CEs, then this whole process will only take a few seconds of your time. It'll be far less disruptive than even a single ad, which we've been doing our best to avoid. But still, if you have suggestions or questions for us about this process or anything else related to NavNeuro, please email us at feedback@navneuro.com.

For today's episode, we speak with Dr. Peter Arnett about cognitive and emotional symptoms of multiple sclerosis, or MS. Pete is a neuropsychologist and a professor of psychology at Penn State University. He is the current President of the National Academy of Neuropsychology, NAN, and he has a long impressive scientific track record including decades of experience in MS. As we like to do for episodes like this one, we will provide a brief overview before moving into our conversation with Pete. Ryan, do you want to start with the MS overview?

Ryan Van Patten 04:27
Sure. MS is an autoimmune disease, meaning that the body is being attacked by its own immune system. In this case, the central nervous system, consisting of the brain and spinal cord, is the target of the attack. MS is also a demyelinating

condition, meaning that the myelin sheath is damaged. Myelin sheath, or white matter, is the protective covering for axons in the brain that allows for rapid communication between neurons. You can think of it as similar to the insulation surrounding electrical wires in your home. Gray matter, or neuronal cell bodies, can also be involved but typically to a lesser degree than the white matter. MS is a heterogeneous disease, meaning that it can present very differently in different people. However, symptoms often impact movement, including numbness or weakness in the extremities, muscle stiffness or spasticity, poor coordination and unsteady gait, poor vision, dizziness, fatigue, slurred speech, pain and/or tingling sensations, and sexual, bowel, and bladder dysfunction. Finally, cognitive and emotional symptoms are common in MS and this is where we spend the majority of our time with Pete.

John Bellone 05:47

MS can occur at any age, but the typical age of onset for MS is in early- to mid-adulthood, broadly speaking, somewhere between the late teens and mid-50s. White women, especially those growing up further from the equator, are at the greatest risk for the disease. Genetic and environmental factors contribute to the susceptibility to MS but much of the details still need to be worked out here.

Ryan Van Patten 06:15

Diagnosis of MS by an expert clinician includes the evaluation of clinical symptoms and history, MRI of the brain and spinal cord looking for lesions separated in time and space, laboratory tests, and sometimes a spinal tap looking for oligoclonal bands in CSF, cerebrospinal fluid. Importantly, other neurological conditions must also be excluded as explanations for physiological and clinical findings. If you're interested in more information about diagnosis, you can find info regarding the McDonald criteria in our show notes at navneuro.com/62. Finally, severity can vary dramatically from mild fleeting symptoms to very debilitating symptoms. There are four MS disease courses, which we discuss with Pete. These are the clinically isolated syndrome, relapsing-remitting, secondary progressive, and primary progressive. One other term that we want to prime here is the radiologically isolated syndrome, where there is evidence of white matter lesions on imaging, but there's no known clinical history of symptoms.

John Bellone 07:32

There are a large number of treatments for MS. We're going to touch on those in the conversation as well. So keep in mind that MS is a complex disease with a wide variety of potential symptoms, presentations, and treatments As Ryan had alluded

to earlier, this episode will not be an exhaustive review of the entirety of the disease. Instead we're going to cherry pick aspects of the condition that are very relevant to neuropsychologists and hang on to those threads. And, without further ado, we give you our conversation with Dr. Peter Arnett.

Transition Music 08:08

John Bellone 08:17
Pete, welcome to NavNeuro. We're really excited to have you.

Peter Arnett 08:20
Glad to be here. Thanks for the invite.

John Bellone 08:22
So we will have already provided some info in our introduction to this episode, but can you give us a brief overview of the neuropathology and risk factors, clinical syndrome, and diagnostic criteria for multiple sclerosis?

Peter Arnett 08:36
Yes, sure thing. As far as the neuropathology, the central feature is really demyelination that's caused by multiple discrete plaques that are thought to be caused by some autoimmune process - could be something like a delayed reaction to a common virus, so not clear in terms of the exact causal factor at work there, but those are some of the possibilities. As the plaques build up, they can interfere with neurotransmission as you might imagine. In terms of where the focus of the demyelination is, it tends to be around the periventricular region of the brain initially - so that anterior part of the brain right around the ventricles - and especially not surprisingly in those regions that have a lot of white matter. Relatedly, the frontal lobes, the optic tract, the corpus callosum, areas like that that are very large white matter tracts of the brain are typically affected. Plaques can occur in the brain and spinal cord. Their distribution is pretty variable among patients and then that tends to lead to variability in the kinds of symptoms that people have. Gray matter can be affected too, even early on in the disease process. Typical regions affected are things like the thalamus, the cingulate, hypothalamus and so forth. So that's a little bit of an overview of the neuropathy.

As far as risk factors, I think you and others may be aware, being female is probably the biggest risk factor of all. MS tends to affect females at about a two to three to one ratio versus males. Other factors that are important risk factors growing up, the first 15 years of one's life, in a region of the world that is far from the equator. Genetic factors also likely play a role. If you look at twins, identical twins, there's about a 30 to 40% concordance rate. But if you look at fraternal twins, it is more like 1 to 13%. The onset usually occurs between about the age of 20 and 40. About 70% of cases occurred during that time, although there are some cases that have their onset during the childhood years and also some cases that occur in later adulthood, past the age of 40.

And then for some clinical symptoms, some of the early symptoms are things like muscle weakness, paresthesias, which are things like numbness, tingling of the hands and feet, the face. Gait and balance problems are also common. Visual disturbances like double vision, blurry vision, or the absence of vision in a particular part of the visual field. And I'm sure of great interest to neuropsychologists, cognitive problems are also very common. Fatigue, depression, those are very common in MS. With cognitive problems, about 50% of people with MS have significant cognitive problems, if you do a cross sectional study or something like that. Depression has about the same prevalence in terms of lifetime prevalence, it's about 50% of people with MS will have clinical depression at some point during their lives. That's much elevated above the population, which is more like 10 to 15% in the general population. As far as fatigue, almost everybody who has MS will have problems with fatigue at one time or another. About 80 to 90% of people with MS complain of fairly severe fatigue. I'll talk a little bit more about that later, when we get into our discussion of fatigue.

As far as the types of cognitive problems that people typically experience, memory acquisition problems are probably the most common cognitive difficulty, along with complex attention and processing speed. Those are things that you will typically see in many people with MS. And, yeah, that's what I had in terms of the overview. I can talk about the criteria for MS too, if you want, but I don't know if you have any questions about those factors thus far.

John Bellone 12:44

Excellent. Yeah, that was an excellent overview. We'll break down each piece throughout the course of the discussion, but you had mentioned that it's more common in women. That's one of the biggest risk factors, just being female. And then also, the further you live from the equator, the more likely your risk is. Do we have any thoughts about why either of those might be risk factors?

Peter Arnett 13:09

In terms of the risks associated with sex, one of the important factors involved here is - well, first of all, it's unclear. But there's some suggestion that testosterone in males can have a protective effect against the autoimmune process. So it's one of the reasons females may be more susceptible because they don't have that protective factor. Related to this, there have been a couple of recent successful phase one and phase two treatment trials in male MS patients that show this protective effect of getting more testosterone. In terms of other factors, in terms of why females may be more susceptible, there's some evidence to suggest that there's some autoimmunity from a sex chromosome linked gene or genes. As to the specifics of that, that's still being kind of worked out. But those are some of the factors that might account for why it's more common in females. In general, if you look at females, for any autoimmune disorder, they're more likely to be at risk for those kinds of things, whether it's multiple sclerosis or rheumatoid arthritis or what have you. Typically, females have stronger adaptive immune responses and it results in better control of infections compared to males. But, also, it's going to be more likely that if there is an autoimmune response, it may get out of control because females have a much more adaptive and active immune response.

John Bellone 14:52

And then in terms of moving away from the equator, I've heard that maybe vitamin D has something to do with that. Can you give us any kind of insights there?

Peter Arnett 15:01

Yeah, that is one of the factors that has come to light in recent years - that vitamin D could be a factor. Vitamin D seems to be important in the immune process in general, and given that people who live far away from the equator get less sunshine, they get less vitamin D and that somehow leads to an increase of getting MS. Possibly because of some mechanism that's associated with vitamin D and in the immune system.

Ryan Van Patten 15:28

So if we fortify foods or milk with vitamin D for people who live further from the equator, might that reduce incidence and prevalence?

Peter Arnett 15:37

I think so. I know in talking with some of my colleagues in the medical community, they're pretty big fans of people getting higher doses of vitamin D like that. I think the minimum daily requirement is like 400 milligrams or something. But it's not

uncommon for people to suggest that patients or people who might be at risk to get much higher doses, in the thousands per day, just to raise the level. People can get their vitamin D levels checked fairly easily. I did this myself several years ago, I was surprised to find that, like, if this was a neuropsychological test, I'd be in the severely impaired range. I think it was below the 1st percentile, was my vitamin D level. So, at that point, I started taking mega doses of vitamin D. I was working with my primary care person, she gave me like 10,000 milligrams a day for like a week. I continued to take it since then, like 2000 or 3000 milligrams a day, and it eventually got my vitamin D level into the normal range. Things like that could be done. Yeah, people should have checked for sure, especially if they might have some risk.

Ryan Van Patten 16:47
You had mentioned that you'd be open to talking about the criteria. I think you're referring to McDonald criteria for MS.

Peter Arnett 16:55
Yeah, sure. This is something that has really evolved over the last 10 or 15 years. I know one of the questions that y'all had before we had set up this meeting was just to talk a little bit about progressive-relapsing MS, that's no longer really a category. The way things are set up now there's been a recent revision of the McDonald criteria in 2017. And there is a clinically isolated syndrome, or a CIS subtype, that involves a discrete clinical episode with patient reported symptoms and also objective findings that might reflect a focal or multifocal inflammatory demyelinating event in the CNS. So it can either be acute or subacute, but has to last at least 24 hours. It can occur either with or without recovery, but has to be in the absence of a fever and infection as well. The key to this particular subtype of MS, the CIS or clinically isolated syndrome, is that it occurs in someone who's not known to have MS. So it's an attack that looks a lot like an MS attack, but it's a single event, so it doesn't meet the criteria for MS where the person has to have evidence for lesions that are disseminated in both space and time. So given that it's only a single event, it's not disseminated in time. And given that it's typically a single onset and indicative of a single symptom, then it typically is not disseminated in space. Although it could be, technically, because a person could have several symptoms that occur with this attack that indicate the involvement of more than one part of the brain. But, technically, to get a formal diagnosis of Multiple Sclerosis there has to be evidence for dissemination of lesions in space and time.

John Bellone 18:55

So that would be like you going to see your doctor and you have a symptom, you have blurred vision, let's say, they give you an MRI, they see a lesion on imaging. Okay, that's a clinically isolated syndrome potentially. Then maybe they repeat the MRI a month later and see somewhere else in the brain that there's another lesion and maybe another symptom associated with that - that kind of distinction.

Peter Arnett 19:18

Yeah, exactly. That's a pretty good example. That's a good way to think about it.

Ryan Van Patten 19:21

My understanding from the update of the 2017 McDonald criteria is that now MS can be diagnosed if someone has a clinically isolated syndrome and the MRI suggests a lesion that occurred previously and elsewhere.

Peter Arnett 19:39

Yeah, like an older lesion. So a non-acute lesion or something like that. That's right.

Ryan Van Patten 19:43

So important to diagnose MS, as we've been talking about, would be history, clinical interview by a neurologist, MRI and then CSF, the oligoclonal bands, are also important. Can you speak to those briefly?

Peter Arnett 20:01

Yeah, sure. If you don't mind, I'm going to continue to talk a little bit about the different types, course types, and then I'll come back to that.

Ryan Van Patten 20:09

Sure.

Peter Arnett 20:10

So there is a progressive course, as I think you know, that's characterized by steadily increasing neurological disability that occurs independent of relapses. There can be fluctuations, or periods of stability, and then relapses can occur, but right from the start, there's this progressive course that occurs. There are really two types of the progressive course. There's the primary progressive course that occurs right from the disease onset. And then secondary progressive always follows

relapsing-remitting. So we can't just get secondary progressive, that has to have been preceded by relapsing-remitting.

John Bellone 20:50
Meaning that you have a flare up of symptoms, and then they go away, and then a flare up, and they go away. There's a period of time in between where you don't have the symptoms.

Peter Arnett 20:59
Yeah, exactly. This varies a lot from person to person, but it could be that there's a flare up, and then that kind of resolves, and then the person shows some improvement back to their baseline, but may not get all the way back to where they were before. So there may be a new plateau, a little bit lower than the level before. Another relapse occurs, there may be some recovery again, the plateau may be a little bit lower than before. So it does tend to be this decline of functioning over time that can occur with the secondary progressive. Eventually, for people who then go from relapsing-remitting to secondary progressive, it'll just sort of become progressive over time.

John Bellone 21:05
The vast majority of cases initially present as relapsing-remitting. I think 85% is what I've seen.

Peter Arnett 21:46
Yeah.

John Bellone 21:47
Especially the younger folks tend to have that. Older adults, I've seen, maybe have a more progressive course than younger [adults].

Peter Arnett 21:57
Yeah, you're much more likely to see that primary progressive course in people who are diagnosed past the age of 40. Interestingly, we talked a little bit earlier about the sex distribution, for the primary progressive course it's about even between males and females, you don't see the same kind of discrepancy in terms of the ratio there.

Ryan Van Patten 22:17

And obviously progressive is worse, right? Relapsing-remitting is that stair step method, there can be some recovery of function in between steps and the person may not be declining rapidly. But when it's progressive, primary or secondary, the outlook or the prognosis is worse.

Peter Arnett 22:35

Yeah, I think there are a couple reasons for that. One is that they're just two different course types, they tend to have a different time course to them. But the other factor that's become really important in, say, probably the last 15 or 20 years or even a little bit longer, is that most of the drugs that have been developed that really are effective in treating MS work with people who have relapsing-remitting MS. There really hasn't been a lot of headway in terms of treating primary progressive, although there have been trials and some headway there. But the vast majority of medications that have been developed have targeted relapsing-remitting. The goal is to keep the person at that level as long as possible. So you want to prevent the person from going from the relapsing-remitting to the secondary progressive phase. You're not necessarily going to reverse the disease process, but the goal with a lot of these disease modifying treatments is to stop the disease in its course and keep people at this level where there's no evidence for disease activity. That's really become the new standard for treatment. Not just slowing the progression, but showing that there's no evidence for disease activity with the use of the disease modifying drugs.

John Bellone 23:51

Just to hang on to that thread for a second, my understanding is that, if the relapsing-remitting is treated, people are less likely to develop into the secondary progressive phase.

Peter Arnett 24:01

Yeah, that's right.

Ryan Van Patten 24:11

Thanks for outlining the different subtypes or courses. That's helpful. Can we now circle back around to polish off the diagnostic part of MS? Can you talk about oligoclonal bands briefly?

Peter Arnett 24:25

Yeah, it's not really an area of my expertise in terms of that underlying pathology but those are used in diagnosis. There's really no pathognomonic sign, which I think you know, and many of the listeners may know as well, but it's more or less trying to use as many diagnostic markers as possible to ultimately make the diagnosis and oligoclonal bands are just one of those factors that are determined through a spinal tap or something along those lines.

Ryan Van Patten 24:55

Makes sense. So there is no single pathognomonic feature, as you just mentioned. My understanding is that there is a bit of risk for misdiagnosis of MS. MS has a wide variety of different symptoms, you mentioned some of them. So someone could be diagnosed with neuromyelitis or some other condition. Can you talk about the risk for misdiagnosis and how that can be reduced?

Peter Arnett 25:22

Yeah, that's been one of the primary motivators of continually updating these criteria, so that there's less risk for that misdiagnosis. I think it's important for clinicians and researchers to be aware of these evolving criteria, which keep getting more and more refined. There was a big improvement in terms of diagnosis once the McDonald criteria were developed because they began to incorporate MRI parameters, which typically were not formally included in the diagnostic criteria prior to that. So I think including those kinds of factors is really important, and also is going to reduce the risk for misdiagnosis. But it is important that clinicians who are making these diagnoses stay up to date on these criteria and actually apply them to reduce the possibility of misdiagnosis. MS is one of those disorders that was chronically misdiagnosed, especially 20 or 30 years ago, because a lot of the symptoms are very nonspecific and they could reflect a lot of different things. People would often be labeled as somaticizers or something along those lines because a lot of the symptoms are very vague. They would complain about things like fatigue, dizziness, depression, paraesthesias that might happen intermittently. I think having these new criteria are really going to reduce the likelihood of misdiagnosis or at least make that less likely. I think that one of the key risks of misdiagnosis is that if somebody is misdiagnosed as having MS, but they actually have something else, then the person is started on some disease modifying treatment. There could be some pretty negative side effects that the person would experience and the drug will not necessarily help them with whatever they were misdiagnosed with.

John Bellone 27:18

To go back to the treatments, you had mentioned some approaches. I know that in 2019, there were several drugs that were approved by the FDA. In 2020, I think in March, there was a new drug. So these are starting to come out. Like you had said, they're more for the relapsing-remitting course. Other approaches to treatments, my understanding, are by symptom. Depending on the symptom presentation, there might be a difference in what gets treated. I don't know if you want to say anything else about the treatment.

Peter Arnett 27:53

Yeah, sure thing. As far as the things we've talked about so far, in terms of things you just mentioned, the disease modifying drugs are like Avonex, betaseron, and Copaxone. Tysabri is a more recently developed one. Those are really designed to slow the disease progression and are used over a long period of time. In terms of dealing with more acute kinds of events - so if a person has an attack of the disease, one of the most common treatments has been to give the person IV steroids. So if a person has an acute attack, that can often be really effective in reducing inflammation and mitigating the attack. So that's something that is often used to treat those discrete attacks, at least for the immediate symptomatology.

John Bellone 28:41

Also, maybe for individuals where steroids aren't effective, I've heard of plasmapheresis or IVIG, the intravenous immunoglobulin. So there are other potential interventions. Interferon, potentially, is another one I've heard.

Ryan Van Patten 29:02

Of course, for our listeners, in terms of symptomatic treatment, psychologists can get in this game as well. Psychotherapy for depression, cognitive training for issues with memory and attention. We're focusing on medical treatments right now, but of course, an interdisciplinary approach would be ideal.

Peter Arnett 29:20

Yeah, absolutely. Do you want to talk a little bit about depression and treatments that are available for that? It might be a good segue to talk about some of those things.

Ryan Van Patten 29:30

Yeah, you beat me to it. Definitely talk about depression. So I'll transition to that by referencing your 2008 review paper in JINS. You laid out a theoretical model of

depression in MS. If you don't mind, give us an overview of your model in terms of disease factors, common MS sequelae, possible moderators of the relationship between MS and depression.

Peter Arnett 29:57
Yeah, sure thing. The goal of this model is just to try to integrate all the different factors that have emerged in the literature that might be associated with depression and MS. So the way we set up the model is that we had these distal factors that were associated with the onset of MS. So the changes that occur physiologically, the changes that occur in the brain that could represent distal contributing factors to depression in MS. Then there are a lot of common sequelae in MS like fatigue, cognitive problems, physical disability, pain, all of which had at least some support in the literature in terms of them being associated with depression. Obviously, the causal direction could go both directions. So, in other words, it could be that cognitive dysfunction leads to depression, but also depression could lead to cognitive dysfunction. So we acknowledge that, but for the purpose of trying to articulate this model, we have depression as the centerpiece and everything feeding into that.

As far as the common sequelae, fatigue is something where there have been a number of studies that have looked at the association between fatigue and depression. That is something that you almost always see in the literature. When people look at fatigue and depression, there's typically a pretty high correlation. It's not surprising at some level because fatigue is a symptom of depression. So partly, this is a confounded relationship because if you're using a measure of fatigue and depression that have overlapping symptoms, you're stacking the deck in your favor so to speak. But there have been other studies that have looked at the association between fatigue and depression that have removed the fatigue items from the depression scale and still found that the two are pretty highly associated. So I don't think it's just an overlapping or confounded relationship in terms of item overlap.

In terms of cognitive dysfunction and depression, that has been very mixed in the literature over time. I would say since we published this paper, though, many more studies have come out that have more consistently shown a relationship between depression and cognitive dysfunction in MS. Whereas prior to that, I would say that literature is much more mixed. So I'd say that you don't see studies even now that don't show that relationship. But I would say that there have been - one of the questions that you had posed prior to our meeting today is, what's happened since this particular paper? I think one thing that's happened because there have been a

lot of studies that have supported this relationship between cognitive dysfunction and depression.

As far as physical disability and depression, that has been more mixed, or at least it was at the time that we published this paper. It seemed like almost exactly half of the studies showed that disability was associated with depression, the other half did not show that. I'm not quite sure why. I don't have a great answer for that. It could have to do with maybe a limited range of disability and some of the studies that didn't find the relationship. But there certainly are a decent number of studies now that have shown that people who have more physical neurological disability are also more likely to be depressed.

And then finally, with pain and depression, a more limited set of studies, but there is at least some evidence that those two things might be related. So in terms of these common sequela of MS, there seems to be at least a decent amount of evidence in the research literature to support those relationships.

Then as far as the possible moderators, this is an area where it's maybe not as clearly delineated. I'm just going to give you one example just so it can illustrate what we're trying to get at here with the possible moderator. Coping is something that has been widely examined in MS. Just about every study that has looked at coping and depression in MS has found that coping is associated with depression. Typically, people who use more adaptive coping, like active coping, more planful kinds of coping, as opposed to avoidant and more emotion focused coping typically do better. So that relationship is very clearly established.

I'll come back to that in just a second. But to at least touch on the other moderators. Social support is also something that very consistently has been shown to be associated with depression in MS. People with higher social support or greater levels of social support are less likely to be depressed. Same with stress. People who report higher levels of stress typically have more depression in MS. Then conceptions of the self and illness, people who have more negative conception of the self and the illness will typically be more likely to be depressed. So it's kind of getting at that negative cognitive schema that tends to go along with depression but also can be associated with a negative attribution made to one's disease.

Coming back to coping for a second. One of the ways that we looked at this is to parse out coping into active and avoidant coping, and then look at the interaction of that and cognitive functioning. One of the things we found in a couple of studies now - we found this in a cross sectional study we also found in a longitudinal study -

is that when you look at the interaction of these things, people who use adaptive coping but who also may have cognitive problems, will be much less likely to be depressed than people who use more maladaptive coping, more of the avoidant style coping, who also have cognitive problems will be much more likely to be depressed. Now people whose cognitive functioning is good tend not to be depressed when they have MS. So really, coping comes in as a moderator in those cases where people are experiencing cognitive problems. If you pair poor coping, or maladaptive coping, with greater levels of cognitive dysfunction then that person is going to be very much at greater risk for depression.

John Bellone 35:48

Sounds like that understanding might inform treatment quite a bit. We can maybe get people to lean towards that active form of coping and teach them how to do that and help them through that.

Peter Arnett 35:58

Yeah, absolutely. I'm glad you brought that up because that's, I think, one of the great appeals to coping is that we know it is something that we can change. So it's something that we're pretty good at with therapy in terms of helping people to develop more adaptive coping strategies. I think that is a good target for intervention in terms of treatments.

Ryan Van Patten 36:21

So, Pete, you had mentioned the overlap between symptoms of MS and symptoms of depression, with fatigue being the most salient [and] notable. The symptom overlap creates challenges when we're attempting to measure depression in MS because both conditions share common symptoms. So tell us about the measurement of depression in MS, including the MS specific BDI that you talked about in the 2015 JCEN paper.

Peter Arnett 36:52

Yeah, this has been a real conundrum. This issue has been around for 30 or 40 years in terms of people being aware of this overlap between MS symptoms and neurovegetative symptoms of depression, like fatigue, sexual dysfunction, sleep problems, concentration, difficulties, and so forth. So an easy way to get around this would be to just get rid of the neurovegetative symptoms. That's effectively what's being done now I would say. The most typical way of screening for depression in MS right now is to use the BDI FastScreen, the Beck Depression Inventory FastScreen, which is a 7-item measure that really consists only of mood

and negative evaluative symptoms. So it doesn't include any neurovegetative symptoms. The BDI FastScreen was initially developed for use in medical populations in general because of this same issue that you see with medical populations, where somebody who has a medical condition may have a lot of those neurovegetative symptoms of depression as part of their medical condition but they may have nothing to do with depression. The same goes for MS. So that was the appeal of just applying the BDI FastScreen in MS because, again, it avoids all those neurovegetative symptoms and it seems to work pretty well. There have been several studies now with the BDI FastScreen to show that, using a cutoff of 4 or more, it has pretty good sensitivity and specificity in terms of screening for depression in MS. So that's probably the easiest and most efficient way to go in terms of screening for depression.

Now, the thought that we had, this is an article that Lauren Strober and I published in 2015 in JCEN, we decided to approach things in a slightly different way. Realizing that an easy way to diagnose or screen for depression in MS would be just get rid of these ambiguous symptoms that overlap with MS symptoms and focus on the mood and the negative evaluative symptoms that are clearly tied to depression - that's one way of doing it. But another way, we want to make sure that we're not throwing out something important by just throwing out all of the neurovegetative symptoms. So that was the motivation of this trunk and branch work where we wanted to try to determine whether there were certain neurovegetative symptoms of depression that were more severe in depressed people with MS. And so that's where we developed this MS-BDI.

So we looked at the trunk symptoms of MS and, basically, these are symptoms that you might consider as depression symptoms that are different between an MS group and a healthy control group, but they're shared by both depressed and non-depressed people with MS. Now, in terms of identifying those branch symptoms, that is typically done - the way we achieved this with this particular study is to look at the difference between depressed MS and non-depressed people with MS. Those symptoms that were higher or reported at a greater degree of severity by the people with depression and MS compared to those with MS who didn't have depression were clearly considered branch symptoms and clearly indicative of depression since they distinguish the depressed and non-depressed MS. Finally, in terms of parsing out those neurovegetative symptoms that we typically might dismiss or just get rid of, we wanted to see whether there were certain neurovegetative symptoms that were more likely to be endorsed at a higher level of severity in depressed people with MS compared to non-depressed people with MS. There were some of those symptoms that we ultimately included in this

MS-BDI that we developed, which consists of 12 different depression symptoms some of which are neurovegetative symptoms that, again, distinguish those who are depressed with MS and those who are not depressed with MS.

Ryan Van Patten 40:57

I like the logic of a trunk and branch system a lot. Before we move on from treatment of depression in MS, you had spoken about increasing more healthy problem-focused coping. Anything else you'd like to say about psychological treatments for depression in MS? Is it CBT? Or anything else?

Peter Arnett 41:20

CBT has been shown to work really well. There have been a number of clinical trials now that have shown that CBT works very well in MS. That's definitely my go-to treatment if I'm going to recommend treatment for somebody with MS who's experiencing depression because there's a lot of evidence to suggest that it works really well. The neat thing about this, too, is that when these initial clinical trials started to emerge that were designed to treat depression and MS using CBT and other kinds of psychological treatments, people started doing telephone based therapy. The reason, the motivation for that is that for anybody who's going to try to go see a therapist, it's a major inconvenience, right? You have to take an hour out of your day if you're working. It's going to be challenging to make sure you can carve out that hour to get there and get back.

The beauty of telephone-based therapy is the person can do it from the comfort of their own home. The neat thing that occurred with these early studies that looked at telephone-based CBT is that it worked just as well as in-person therapy. Then that led to a refinement of that by using CBT online. So having people go through a number of modules that they would typically do if they were to do a systematic, CBT-based approach if they saw a therapist, but they do it online. So a person would go to a website, they would click in and go through a module each week, and then over the course of, say, 10 or 12 weeks they would show a big improvement in depression. The nice thing about those studies, the phase one and phase two clinical trials for the CBT done online work really well as well. Now our group at Penn State along with a group at University of Missouri, Kansas City, Cedar Sinai in LA, and also two sites in Germany, just completed a phase three clinical trial looking at online CBT in a group of 300 plus people with MS across these five different sites to see whether it would work with this phase three clinical trial. We just completed that study over the last couple months, and we haven't looked at the

data yet, but it was an RCT looking at that and we're hoping that this phase three trial works.

I think if it does, then this type of treatment can be made much more widely available to people with MS who are suffering from depression, who may not have the resources or may have transportation issues or what have you that may prevent them from getting in to see a therapist. They could do this in the comfort of their own home and it would work just as well. So that's pretty exciting. I think that's some of the most exciting work to emerge in recent years because depression is such a common problem in MS, and it's often untreated. So if this is a way to provide more people with access to treatment, it would be a really great thing, just given the negative effects that chronic depression can have on people's functioning.

John Bellone 44:24
Those remote delivery systems are even more valuable now in the post-COVID-19 era. [laughs]

Peter Arnett 44:29
Yeah, absolutely. It's a treatment that's found its moment, I think, for sure. [laughs]

John Bellone 44:35
Is there anything else you wanted to say about other types of psychopathology in MS? Anxiety, anything like that?

Peter Arnett 44:41
Yeah, sure. I wanted to just say one other thing about treatment, though. And that is that there's something that's really exciting that also has emerged since our 2008 review paper. There have been a number of studies now that have looked at exercise in depression treatment. And that seems to work pretty well. In fact, the effect size seems to be just about at the level of what you see when you do a treatment of depression for psychotherapy or medication. So aerobic exercise is something that can actually treat depression in MS pretty effectively. It's another type of treatment that people should be aware of. Exercise, in general, has been shown to have a lot of positive effects for people with MS not only in terms of treating depression, but also in terms of having positive effects on people's cognitive functioning. Rob Motl and his colleagues at University of Alabama, Birmingham, have done a lot of nice work in that area.

John Bellone 45:45
And then in terms of other psychopathology?

Peter Arnett 45:48
Oh, yeah. In terms of anxiety, that's also something that is definitely very important. For some reason, it's just been way under-studied relative to depression in MS even though, as you all probably know, and a lot of listeners probably know, anxiety and depression are very commonly comorbid. Anxiety has been far less studied in MS [and] when it has been looked at, it seems to be just about as prevalent as depression in MS. But there haven't been a lot of good comorbidity studies, so I think that's definitely an area where we need to do a lot more work.

One of the reasons I think is so important is that when you're trying to treat somebody with depression who also has comorbid anxiety, you might approach things somewhat differently. When you're trying to treat depression, you're - typically with any kind of a treatment, you're only going to be successful with about 50% of people. So if we do psychotherapy with a large group of people with MS, about 50% of people are going to benefit. That's true with anybody. That would be even true for just a general group of people who are experiencing depression in the general population. For the other 50% that aren't responding to treatment, it could be due to something like comorbid anxiety that hasn't been appreciated or assessed adequately and that's contributing to the persistence of the depression. There could be other aspects of psychopathology that could be important as well, like personality disorders, for example, or personality factors. There really hasn't been a lot of work there - like Ralph Benedict and his colleagues have done some work on personality in MS, but there has not been a lot of work there. I think, especially in terms of looking at things like personality disorders, that could be a potentially productive area to explore further. To see whether there may be, again, a comorbid personality disorder that is undiagnosed that is contributing to a person's chronic depression when it doesn't respond to the usual treatments like medication or CBT and so forth.

Ryan Van Patten 47:48


A set of symptoms that goes along with both depression and anxiety in MS that we haven't touched on in depth yet would be sleep problems. You're welcome to speak to that if you want. I just want to make sure that was said in this conversation.

Peter Arnett 48:01

Yeah, I think that's a great point, Ryan. I'm glad you brought that up because sleep is a problem in MS and for a variety of reasons. There are things like restless leg syndrome that can get people up a lot in the night. Urinary problems, having to go frequently. Things like worry, that keep people up. Problems with sleep, not surprisingly, also contribute to fatigue that people might experience during the day. So that is definitely something that should be assessed systematically. Any neuropsychologist who's seeing a person with MS should assess their sleep and get a detailed account of that.

The other important thing about sleep, since we were talking about depression, is that there have been studies, I don't know if there's been anything specific in MS, but in the depression literature more generally, there have been clinical trials that have been conducted that have just targeted sleep problems in people who are depressed. When their sleep problems are addressed, they typically show as great an improvement in their depression as somebody who's just going through, say, a CBT or a medication trial or something like that. So being able to characterize sleep in a systematic way in a person with MS is very important, not only for addressing potentially problems with fatigue, but also depression.

John Bellone 49:23

Great. Why don't we transition and talk a little more about the cognitive symptoms of MS. There are multiple standard neuropsych batteries that are developed specifically for MS. There's the Minimal Assessment of Cognitive Functions in MS. There's the Brief Repeatable Battery of Neuropsych Tests for MS, the MS-COG, among others. A lot of overlap in the tests that are used in these batteries. What cognitive tests would you recommend for MS clinicians? Do you have a preference in terms of the battery?

Peter Arnett 49:52

Oh, you know, I think the things that I tend to favor - originally, I mean, I think the BRB is still a pretty good measure. That was the initial battery that was developed by Steve Rao and his colleagues in the early 1990s. Those tests are still very sensitive to cognitive impairment in MS. They essentially consist of a selective reminding test, the was first the 724, then later the 1036, spatial recall, the PASAT, symbol digit modalities, and the COWAT. And all this together only takes about a half hour to administer and they are very sensitive to cognitive problems in MS. So you could use that. The MACFIMS, or the minimal assessment, that you

mentioned, I think, it says “minimal”, but only a neuropsychologist would consider this minimal.

John Bellone 50:41
[laughs]

Ryan Van Patten 50:41
[laughs]

Peter Arnett 50:41
Because it takes about an hour and a half to two hours if you include all self report measures and so forth. But that's a pretty decent comprehensive measure. I mean, in terms of the things I prefer, I like to get at memory. So a lot of the things that are suggested with the MACFIMS, like the CVLT, the BVMT-R to get it memory. Also, I don't think this is part of the the MACFIMS, I think a story type test like Logical Memory, or the story memory tests from the from the WRAML-2, things like that could be - that would be a pretty good assessment of memory, if you use those three kinds of tests.

As far as getting at processing speed, the symbol digit modalities tests have become the go-to test for screening for processing speed problems. The PASAT has also been used. In fact, that was part of the typical cognitive screening test that was used for clinical trials for a number of years. The reason people didn't like the PASAT, though, is that it's very anxiety provoking. And so because it requires, as you may know, people to add numbers presented three seconds at a time on the first trial, and then two seconds apart add each number to the immediately preceding number, and the numbers just kind of keep coming at you. And so it's pretty stressful. But that is very sensitive to cognitive impairment in MS. People have gravitated more toward the symbol digit in recent years because it doesn't tend to generate that kind of anxiety because it's self paced. The person has to go as quickly as they can, but it's not like they have stimuli coming at them at a rapid pace. That combined with the fact that people have to do mental math is pretty anxiety provoking. So symbol digit and PASAT can be good for getting at processing speed.

As far as executive functioning, the D-KEFS sorting test is a pretty good measure for that. In terms of getting motor kinds of things the grooved pegboard test, finger tapping test, things like that. As far as other domains, the one tricky thing about a lot of this stuff, especially when you're getting at processing speed - this is

something we've written about as well in a 2008 paper, and we actually are working on a paper more recently we'll probably submit within the next few weeks or so - but, basically, one of the problems with things like the symbol digit, the PASAT, even the COWAT is that they require people to make a rapid oral motor response. You have to have some method for getting a response. And so you could have people write something out, but a lot of those types of tasks, like the written symbol digit or the trail making test, have been eliminated from MS batteries because people with MS often have motor writing problems. So you don't want to have somebody who has motor writing problems do a cognitive test that requires them to do a lot of motor writing, because you can see that they have a lot of deficit but that may just be because of their motor writing problems.

So largely things that can MACFIMS, the Brief Repeatable Battery, the MS-COG have gotten rid of these kinds of tests that require motor writing. The problem that remains, though, is that the person still has to make a rapid response. People with MS often have problems with articulatory speed, have a lot of problems with dysarthria, and that can impact a person's performance on a task like a symbol digit, where they have to say these numbers as quickly as they can, or they have to add up and make a rapid verbal response, say with the PASAT, or they have to generate a lot of words that begin with a particular letter for the COWAT or for animal naming something along those lines. So that's an area, I think, that is underappreciated. But I think it's important that people need to keep in mind that even when you eliminate the motor writing component to it, the person still has to say something. So because of that, people who have dysarthria, who have articulatory speed problems that have nothing to do with cognitive impairment, could look really impaired on something like the symbol digit or the PASAT the COWAT because of that. So we need to be able to actually factor that in in some ways.

One of the tests that's included in the MACFIMS is this MRR task. It basically involves people just saying phonemes as quickly as they can. So they say "pah, pah, pah, pah, pah, pah, pah", do that phoneme. "Tah, tah, tah, tah", and then "kah kah kah". So yes, it's different parts of the vocal apparatus. And then the "pah-tah-kah" is the last part of that where the person just has to say "pah-tah-kah" as quickly as they can, in one good breath, and you're basically looking to see the number of syllables per second. Not surprisingly, people with MS, if we take a large community-based sample of people with MS, they produce fewer syllables per second compared with just a healthy control group. In fact, typically, at least in the studies that we've done, we've found that people with MS produce about one syllable less per second, compared to healthy controls. That may not seem like a

big deal, but over the course of a minute, you're talking about 60 fewer syllables. Multiply that by an hour, by days, by weeks, that's potentially producing a lot less speech. And so, again, that's just something I think is important to keep in mind, especially trying to get it a person's cognitive processing speed because there can be that confound there of oral articulatory speed problems.

Ryan Van Patten 56:25
So even the oral STMT, which removes the motor components, still have that articulation component. You referenced a research paper that you'll be submitting soon. Are you attempting to get around that issue? And, if so, how do we measure processing speed without incorporating oral motor responses?

Peter Arnett 56:42
It's very difficult. It's kind of hard to do that, at least with the clinical tests that we currently have that are available. But the purpose of this paper that we're working on now is just to look at all the factors that might contribute to symbol digit performance. So it could be comorbidities like depression, fatigue, anxiety, but also motor problems like articulatory speed problems. So you just want to throw all of those things into the equation. Then after you've accounted for all that variance, you look at the difference between MS and a control group, there's still a difference. There's still a significant difference in the variance accounted for in the STMT. But it's much smaller than before accounting for those comorbidities and the oral articulatory speed seems to be one of the heavy hitters in terms of the amount of variance in symbol digit performance that's accounted for. So I think we just had to be careful. Like, I don't think there's anything wrong with using the symbol digit as a screening tool. What we want for a screening tool is for something to identify anybody who might have a cognitive problem as having a cognitive problem and then we can work to further refine that with a more detailed battery once we've screened a person out. But, again, one of those factors that needs to be taken into consideration is that oral articulatory speed could compromise the person's performance in the symbol digit, and make them look like they have processing speed problems, when in fact, the problems are due to dysarthria or slow oral motor speed.

John Bellone 58:13
Yeah, and that's why the STMT is so sensitive to symptoms in MS. I guess you can make the argument that these measures are ecologically maybe more valid, the ones that do include the oral articulatory speed issues or the motor writing impairment, this is what the patient is dealing with on an everyday basis.

Peter Arnett 58:33
Yeah, that's true. That's a good point.

John Bellone 58:34
I see the utility in separating those, but I think we should also maybe keep that in mind. That they're dealing with these issues in their everyday life.

Peter Arnett 58:42
Yeah, absolutely. I think that's a great point, John. And I think, speaking to the ecological validity issue, I think it is really important. I mean, if we parse things down to these micro-cognitive processes, we're gradually getting to the point where we're not really looking at something that realistically happens in the real world. I mean, it's important, theoretically, to try to understand what the mechanisms are, but, you're right, in terms of really trying to understand what goes on with people as they're trying to function in the real world, then I think using some of these clinical tests that we've often use can be a good way to go.

Ryan Van Patten 59:18
Yeah, just so our listeners are aware that there's been a lot of research on the STMT. In particular, you referenced several times that the STMT is thought to be a sensitive and psychometrically supported screener for MS. I believe Ralph Benedict has done a lot of work in this area. Anything else you want to say about STMT and/or the centrality of processing speed to MS in general? Other deficits and other cognitive abilities like memory and executive functions sometimes are due to slow processing speed in MS, right?

Peter Arnett 59:52
Yeah, I think they could be and I think there's some evidence for that. Just to give a real world example, let's say that you read somebody a story and you ask them to tell that back to you. If their processing speed is slow, the time it's taking them to tell you that story, if they're doing it very slowly, then they're going to be losing aspects of that memory as they're trying to say that back to you. The same could be said for a word list [test]. If you read a word list to somebody and then they're trying to say that back to you, if their processing speed is very slow, they might initially have remembered a lot of words, but as they're going through and slowly giving you that list back, it could be they're losing those memory traces of the list as they're going through it. So I think, in that way, processing speed could impact things like memory. The longer it takes a person to say what it is they're trying to remember, they're going to lose parts of that memory trace they as they go through that.

Ryan Van Patten 1:01:03

Okay, Pete, let's transition now and talk about fatigue for a few minutes. As you've mentioned, this is a very common symptom in MS and one that you've studied in the past. So give us an overview of prevalence, symptomatology, and the problems that fatigue causes in the lives of people with MS.

Peter Arnett 1:01:21

Sure thing. Well, the prevalence is about 80 or 90%, as I mentioned previously. If you ask people with MS what their most debilitating symptom is, by far, the most common thing you'll hear people say is that fatigue is their most debilitating symptom more than any other symptom. It often leads to people having to leave their jobs because they can no longer function. It can also impact things like social relationships because people feel like they don't have the energy to engage with people socially that they had in the past. It's a big production just to get out of the house and go meet somebody for a cup of coffee or grab lunch or something along those lines.

As far as the different types of fatigue, one of the types that are obviously of great interest and important to neuropsychologists is cognitive fatigue. That typically involves having the following kinds of problems because of fatigue: feeling less alert, having difficulty paying attention for long periods of time, having trouble thinking clearly, being forgetful, having trouble finishing tasks that require thinking. A lot of these kinds of cognitive fatigue measures are operationalized in a measure known as the Modified Fatigue Impact Scale, which you may be familiar with. So it gets at cognitive fatigue, physical fatigue, and then social fatigue. So there's a scale that includes a lot of those aspects of the impact on cognitive function that I just mentioned, that gets at cognitive fatigue. So you can operationalize that pretty well. But fatigue is certainly something that should be measured in any neuropsych evaluation with people who have MS and the Modified Fatigue Impact Scale would be a pretty good way to go.

John Bellone 1:01:32

Given that fatigue is an issue, what would you determine as the upper limit of our cognitive batteries? I know we talked about some of the brief batteries being anywhere from 40 minutes to up to an hour and a half or so. Would you say that that's maybe the ceiling in terms of length?

Peter Arnett 1:03:19

Probably. I mean, I think most people can tolerate like an hour and a half battery. The MACFIMS may take a little bit less than that, it may take a little bit more depending on the person but I think most people can tolerate that. Like if a person is severely fatigued, though, you could certainly do something like the BRB, BRNB, whatever you want to call it, or a reduced battery that might take more like a half hour. But fatigue is definitely something that has to be considered because if you're trying to test somebody for four or five hours, like somebody might do with a comprehensive neuropsych battery, that's probably too long and it's probably going to ultimately end up impacting the person's performance.

It depends on what your purpose for the evaluation is. If you're getting somebody who is, let's say somebody who's in their 20s, who's recently been diagnosed with MS, doesn't necessarily have a lot of cognitive complaints, I think that's a good opportunity to do a pretty comprehensive neuropsych battery just to establish a good baseline. And, of course, you want to evaluate fatigue as part of that evaluation. I think doing something like the MACFIMS would be reasonable, I think it's tolerable for most people at that stage. Now somebody who's further along, has very severe problems with fatigue, maybe other comorbidities that could interfere with cognitive testing, and you can be a little more careful. I'm not sure what the upper limit is. I think it really depends on the person who's being tested.

Ryan Van Patten 1:04:49

But, importantly, that's something neuropsychologists should be aware of when they're testing people with MS. Even more so than some other conditions, is how central fatigue is and that you really want to limit the length of your battery.

Peter Arnett 1:05:00

Yeah, absolutely. I should mention, as an aside, I think we were going to maybe talk about this in terms of the cognitive variability stuff, the reaction time variability. But there have been a lot of studies in MS that have looked at self reported fatigue and looked at association with cognitive functioning, and the vast majority of studies for decades have not found anything, which is very surprising, right? Because you've got this problem that 80 to 90% of people experience. I think we can all appreciate [the effects] in our daily lives of real fatigue, we're not going to be able to think as well. We feel like we can't remember things as well, we can't process information as well, we can't pay attention to things as well. So it's very surprising when you've got this group of people in MS for whom fatigue is a central problem, [and] you've got study after study after study after study where people basically are not finding that

fatigue is associated with cognitive functioning. At least if you're looking at the mean kinds of levels of function that people typically look at.

John Bellone 1:05:36
And that's where...

Ryan Van Patten 1:05:49

You've done work with response time variability, within person variability, do you find differences? Do you find correlations between that and fatigue? Or you didn't with means?

Peter Arnett 1:06:05
We did, yeah. Because this was something that was a real conundrum and something that we talked a lot about in my lab before we published this paper, I think it was in 2010 in Neuropsychology, looking at response to variability with Jared Bruce is the first author of that paper. But we were really struck by - and I think this is a good illustration about how a lot of our ideas about research come out of our clinical work. One of the things we're really struck by is that just about everybody with MS we talked to said that they have good days and bad days. And typically, the bad days for cognitive function were those where they're very fatigued. They felt like they couldn't remember things as well, they couldn't concentrate on things as well, they couldn't process things as quickly on those days when they're feeling really fatigued. And yet, we go back to the research literature, and again, we find study after study after study after study finding nothing. No association between cognitive difficulties and fatigue in MS.

So we decided to take a little bit of a different tack on this. This also evolved out of our clinical work by people saying that, again, sometimes they have good days and bad days, or sometimes toward the beginning of the day they'll be doing well, but then it'll be variable over time. So we decided to look at this at a micro level by looking at reaction time variability within the context of a reaction time test, a complex reaction time test in this study. Our reasoning was that maybe we're not capturing what's really going on by just looking at correlations with mean performance. And that, really, what we need to look at is some measure of cognitive variability that might be more likely to be associated with fatigue. So we quantified variability in terms of reaction time with this task and we looked at the relationship with fatigue. We found these very nice effect sizes, where the higher a person's self reported fatigue, the greater their variability in reaction time. And so that was a real eye opener. It suggested that the way we've been looking at fatigue

and cognitive functioning, we may have been looking at it in the wrong way. Assuming that we would just find these correlations between mean levels of fatigue and mean levels of cognitive function when, in fact, the real action was occurring in variability. So that was a very exciting finding to see that that came out so clearly.

Now, we did a recent study - and this is something that's not published yet - but we actually did present this at INS in the golden days of February, when everybody was able to do everything in person. [laughs] It might be the last INS conference in person for a little while. But, anyway, we want to try to capture this variability in a little bit different way. Essentially, what we did with this study that we presented at INS, it was presented by a grad student of mine, Kaitlin Riegler is the first author on it, and we wanted to look at variability across a test battery. So we'd already looked at it within the context of this one task, but we wanted to see how variability in cognitive performance across a longer battery of tests, say a two or three hour battery, might be related to fatigue. Because that would seem to capture the ecological validity of what's really going on in people's day to day lives where they may become fatigued over time, and then there may be some variability in their ability to pay attention, to remember, to focus, and so on. So we looked at this by putting all of the tests that we use in our battery, things like the CVLT, the STMT, the BVMT, the standard tests that we typically use clinically in MS and some other things as well, and we put them all in a standard score metric, then calculated measures of variability across the test battery. We found some really nice effects with fatigue showing that, again, people who self-reported higher levels of fatigue showed much more variability in their performance across the neuropsych battery compared to people with lower levels of fatigue. So, to me, that was very exciting. And that's something that we could do more work on to try to quantify that in some way.

So you could, say, do another study, looking at the MACFIMS across a group of people with MS and just calculate the variability across the test battery across all the tests of use of the MACFIMS, then compare it to a control group. So you could establish norms, essentially, to show what is typical. What is the typical amount of variability across this battery in a healthy control group? And how is that different in a group of people with MS? And so I think more work could be done there. But I think that our understanding of how fatigue might impact cognitive functioning is still in its infancy. But I do think that looking at variability across the battery, also looking at variability within tests, like we've done previously, I think might be a promising way to go. I would like to see us get to a point where we could quantify that variability and use it in a normative way, just like we do our mean scores for individual tests.

John Bellone 1:11:23
Yeah. Excellent. Once we move to a fully computerized battery, it would be even easier to measure something like that.

Peter Arnett 1:11:29
Yeah, that's true. That's a great point.

John Bellone 1:11:31
I guess you can do it with paper and pencil [tests]. You can maybe give the same measure repeatedly across time, within the same day, but, yeah, it'd be harder. Are you advocating for maybe giving a CPT in addition to the normal MACFIMS?

Peter Arnett 1:11:46
Perhaps, yeah, that would be a good way to look at variability. You could quantify the reaction. But I guess what I was getting at with the variability across the battery is that these were all different tests that we use in our study. So they would be the CVLT, the STMT, the BVMT, the COWAT animal naming, and so forth. And then we converted all of those to standard scores and quantified measures of variability across the battery. So, it's not like we were looking at the STMT, like the beginning, the middle, and the end or something like that.

John Bellone 1:12:18
I see.

Peter Arnett 1:12:19
But that is a good idea. I hadn't thought of that. But that is a really great idea.

John Bellone 1:12:23
Okay. Well, I'll accept authorship on the next paper. [laughs]

Peter Arnett 1:12:26
[laughs]

John Bellone 1:12:27
No. I'm kidding. [laughs]

Ryan Van Patten 1:12:29
I've heard the variability across battery called cognitive dispersion.

Peter Arnett 1:12:34
Yes.

Ryan Van Patten 1:12:34
There's some research on that in other conditions, Alzheimer's disease, traumatic brain injury. This idea of reaction time variability is of interest to a lot of different researchers. There's a more precise way to get at neuropathology than just mean reaction times.

Peter Arnett 1:12:48
Yeah, absolutely. We found the same thing, actually, in a study we published a few years ago in Neuropsychology looking at variability in sports concussion. We didn't find mean differences in terms of people who are concussed versus non-concussed, but we did find big differences in variability. There was another situation where the mean difference didn't really play out, but we found that there were big differences in terms of variability.

John Bellone 1:13:16
Yeah, maybe an analogy here. It makes sense that concussion would result in a similar profile, I guess. I think maybe ADHD, you know, the person can...

Peter Arnett 1:13:24
Yeah, absolutely.

John Bellone 1:13:25
If they're focused and attentive, and there are not many distractions, they can keep it together in the same way that someone with chronic fatigue might be able to keep it together for a brief period. But, over time, you're going to see ups and downs in terms of attention.

Peter Arnett 1:13:37
Yeah, absolutely. ADHD is a great example. That's something that, like I was mentioning earlier, I do a lot of clinical supervision of the grad students in our doctoral program who do neuropsych evaluations through our clinic. That's definitely one thing we really pay attention to in ADHD referrals is looking at that

variability over the course of the test battery. It's not that people with ADHD can't pay attention. If given the proper motivation, they pay attention just fine. It's just that you see a lot of variability because their motivation tends to wax and wane.

John Bellone 1:14:08
Yeah. Excellent. All right. Well, before we wrap up, I wanted to ask you about social functioning and ADLs. How does MS affect interpersonal relationships? And activities of daily living like driving, working?

Peter Arnett 1:14:22
Yeah, that's a great question. This became a really hot topic. There's going to be a book coming out. The editors of the book are Igor Grant, Tom Marcotte, and then also Maureen Schmitter-Edgecombe. It's an update, the second edition of a book on ecological validity of neuropsych tests just across a bunch of different conditions. We're writing a chapter - or one of my former students, Megan Smith, who's now at the VA in Baltimore, we're writing this chapter together, where we're looking at ecological validity of neuropsych tests in MS. The thing that has really come out very clearly is that our neuropsych tests are pretty good at predicting real world function, like predicting driving ability, predicting working, even predicting things like sexual functioning, other activities of daily living. So that, I think, is pretty exciting to know that even though we're using these abstracted tests in our typical neuropsych battery, they do pretty reliably predict real world functioning.

So if you look at that in a group of people with MS, you find the same kinds of things where people who perform poorly on things like the symbol digit, like the California Verbal Learning Test, the BVMT also have more problems with driving, with maintaining their work status, with their interpersonal relationships, things like that. So we're not just dealing with these things in the abstract. I think it's nice to know that the tests we have traditionally used in our neuropsych batteries do actually predict what's going on with people in the real world in terms of important kinds of functions, like being able to drive, to work, maintain relationships, things like that.

John Bellone 1:16:04
Awesome. Okay, well, before we let you go, we've got a couple of bonus questions.

Peter Arnett 1:16:07
Okay. [laughs]

John Bellone 1:16:09
The first one is, if you can improve one thing about the field of neuropsychology, what would that be?

Peter Arnett 1:16:15
Okay, well, I think the thing that I would improve is to try to find ways of translating work from the research lab into clinical practice more quickly. We don't really have any systematic way in terms of how we're doing that right now. There are a lot of really exciting things that are occurring in the research lab that then just sit there. Then we don't translate the knowledge that we gained from that into clinical use. I'll give you one example. Coping is something that I mentioned earlier, and that's something that's been very intensively studied in MS. There have been dozens and dozens of studies have shown that coping is associated with depression in Ms. So it could be a really good target for intervention, but we don't have any tool for measuring coping that we routinely use in clinical practice. So what's the hold up? Like, why aren't we doing that? I think there are a lot of other examples that I could cite. But, in general, that is a real area in the field of neuropsychology, I think, could be improved upon. To work on developing more systematic ways of translating our work in research to clinical practice.

Ryan Van Patten 1:17:22
Bench to bedside. I love it.

Peter Arnett 1:17:24
Bench to bedside. Yeah, exactly.

Ryan Van Patten 1:17:26
That's not a common answer that we've heard from guests, but I'm on board for sure. Pete, what is one bit of advice you wish someone told you when you were training, or that someone did tell you that really made a difference? We're looking for an actionable step that trainees could take that they might not have thought of to improve their performance.

Peter Arnett 1:17:45
Okay. Well, I think a bit of advice that I would give is to be patient. Okay. It takes a long time to get a PhD with a focus in clinical neuropsychology. Sometimes it seems sort of never ending. I remember that from my own days of training. It's like, you know, you do your doctorate, you have to do your internship, you do a two year

postdoc. It just feels like you're never going to finish, you know. [laughs] I'm sure you guys can relate to that.

John Bellone 1:18:11
[laughs]

Peter Arnett 1:18:12
It does take a long time to become independent, but once you get to that level, there are many ways to keep your career meaningful and exciting for many years to come. I can just tell you that like my work with students, the clinical work that I do and that I supervise, exploring new research questions, that stuff never gets old. If you like neuropsychology and are turned on by the brain and clinical applications of that, as we do in neuropsychology, then this is a field that you can grow into. And even though it does seem to take forever, at times it feels like you're never going to get there, be patient. Your career is going to pay a lot of dividends, or this training is going to pay a lot of dividends as you go throughout your career. And, you know, I wish somebody had told me that early on. I had some great mentors. I don't know if that's one bit of advice that I got, but that's one that I'm often telling the students that I work with. Just be patient. You're going to get there, and you're going to have a great career because it's a great field to go into with a lot of exciting things happening now. It's never gotten old. I've never gotten bored with it. And it's something you really grow into, and it's going to be exciting for many years to come.

Ryan Van Patten 1:19:21
Good advice.

John Bellone 1:19:21

Words of inspiration for sure, to all the trainees out there listening who might feel a little bit disgruntled about the dissertation and how long it's taking and how much effort everything is.

Peter Arnett 1:19:33
Yeah, exactly.

Ryan Van Patten 1:19:34
But it gets better.

John Bellone 1:19:34
It's worth it. Absolutely.

Peter Arnett 1:19:35
Yeah, it does get better. It felt that way to me anyway.

Ryan Van Patten 1:19:39
Well, Pete, this has been wonderful. Certainly cognition and emotion are very important in MS, so thanks for talking through all these questions for us.

Peter Arnett 1:19:48

Yes, sure. Thanks. Thanks for inviting me, Ryan and John. It was really a pleasure to talk with you both and hope you have a great rest of your day. Thanks. I appreciate it.

Ryan Van Patten 1:19:57
Thanks. You too.

Transition Music 1:19:57

Ryan Van Patten 1:20:02

Well, that does it for our conversation with Pete. If you like the show then please consider rating us on Apple podcasts. The five star rating really helps us out. And, as always, join us next time as we continue to navigate the brain and behavior.

Exit Music 1:20:18

John Bellone 1:20:41

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Ryan Van Patten 1:20:53

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