20| The Interplay Between Cerebrovascular Disease and Alzheimer's Disease – With Dr. Adam Brickman

May 15, 2019

NAVIGATING NEUROPSYCHOLOGY

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Speakers: Adam Brickman, 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 a returning guest on NavNeuro. This is Adam Brickman, a neuropsychologist at Columbia University who has done extensive research and some clinical work in Alzheimer's disease, vascular dementia, and neuroimaging. We had him on the podcast previously to talk about ideas around a biological definition of Alzheimer's disease. We both thoroughly enjoyed that conversation. Today, we're talking about a different but related topic. Part of Adam's research has been around white matter hyperintensities, cerebrovascular disease, and Alzheimer's disease - these three constructs and entities, how they're related and different, how they impact cognition - which is of interest to neuropsychologists. John, if you don't mind, tell us what these things are and how we've conventionally thought about them.

John Bellone 01:23

Yeah, it'll be relevant for today's discussion. So white matter hyperintensities, which actually, we went over quite a bit with Dr. Steve Correia in episodes 3 and 4, where we talked about neuroimaging. I think listeners might want to go back and listen to that one, if you're not as familiar with white matter hyperintensities. But basically, they're white spots on MRI - bright spots that come up, when you take these images. They're indicative of underlying pathology, underlying problems with blood vessels that feed the brain. There are different medical conditions that can result in this type of problem - for example, diabetes, or atherosclerosis, a buildup of cholesterol in our arteries. Basically, anything that affects the blood flow through our arteries and causes a hardening of the arteries. Age is one of the biggest factors here. That causes this damage over time that we end up seeing as these white spots on MRI. So that's white matter hyperintensities. Those underlying problems, due to the medical conditions, we can collectively refer to those as cardiovascular or cerebrovascular disease, CVD.

In contrast to cerebrovascular disease, or white matter hyperintensities, Alzheimer's disease is thought to be a completely separate process, which is defined by amyloid beta, colloquially referred to as plaques, and tangles, or tau pathology. This is the traditional view of Alzheimer's disease. Ryan, maybe it'd be helpful if you want to let our listeners who are not familiar know about the dogma that is being challenged here in terms of the difference between Alzheimer's disease and vascular disease and the clinical manifestation of those.

Ryan Van Patten 03:20
Sure, yeah. So this is all going to be simply in a nutshell, of course. I'm going to leave a lot of depth here, but just briefly, there is neuropsych convention around what someone with Alzheimer's disease, what their cognitive profile might look like compared to someone who has cerebrovascular disease. This is really infused into our training from early on. The idea here is that someone with Alzheimer's disease has an amnestic profile, the term "rapid forgetting" is often used. This looks a particular way on memory tests, where a person might have some trouble learning some initial information. But what we really see is that even what they've learned is not recalled even 15, 20, 25 minutes later. They can't recall it and then they don't even recognize it - the information did not get into their brain.

In contrast, the vascular profile, as we think about it, tends to be more dysexecutive, they have trouble with executive functions. They have more trouble with attention and processing speed. But the idea is that people with vascular neurocognitive problems do not have that amnestic profile. They may have some trouble learning information, even retrieving it, but the information is in there. They can recognize it if it's provided to them. Again this is a general rule of thumb that we use as neuropsychologists interpreting cognitive data.

Adam has interesting thoughts about this and his thoughts are backed by years and years of research. So I think it's great for us to listen and contemplate this. Just generally, I always like the idea of my strongly held beliefs being challenged, so that I am forced to question my underlying assumptions. I think that's a really important intellectual endeavor that we all can benefit from in all areas of life, in particular our areas of expertise. So I hope this brief intro has been helpful for everyone again.

Just so you know, this was on the tail end of our prior recording with Adam. So there's no introductions or small talk. We're just going to jump right into this with him and we hope you enjoy it as much as we did. So now we give you Adam Brickman.

Transition Music 05:39

Ryan Van Patten 05:49

Okay, Adam, we'd like you to, if you don't mind, give us and our listeners a brief overview of white matter hyperintensities, cerebrovascular disease, and cognition. And then how these constructs interact with one another.

Adam Brickman 06:01

Yeah. So my lab has been focused a lot on white matter hyperintensities, which are these areas of increased signal that we see on T2 weighted MRI scans or FLAIR MRI scans, which is a type of T2 weighted MRI scan. We think that white matter hyperintensities, mostly in the context of aging, reflect the overall burden of small vessel, typically occlusive or ischemic, disease that's "silent". So we've been quantifying white matter hyperintensities in older adults and asking the questions, “What is the contribution of small vessel disease to cognitive aging? How does it interact with Alzheimer's disease? Is it a part of Alzheimer's disease? What's its relevance in the context of Alzheimer's disease?” So again, we use these white matter hyperintensities as an operational definition, or a biomarker if you will, for small vessel ischemic disease.

Ryan Van Patten 07:05

For listeners who may be a little less familiar with neuroimaging and some of the idiosyncrasies with a few of these concepts, why do white matter hyperintensities reflect ischemic and not hemorrhagic disease?

Adam Brickman 07:20

That's a good question. I think mostly what we see are things like atherosclerosis and arteriosclerosis as strong postmortem correlates of white matter hyperintensities. So the assumption is - and hypertension is one of the biggest risk factors, and other classical vascular risk factors like diabetes, and all the risk factors and the pathological correlates point more to occlusive disease as opposed to hemorrhagic lesions. Typically, when we think about hemorrhagic stroke, we're thinking about larger vessels and big bleeds. There is this possibility that some of the white matter disease that we see in the context of aging might reflect cerebral microbleeds due to amyloid angiopathy. So there could be a hemorrhagic component at the capillary, or arteriolar, level as well. So it's not exclusively ischemic or occlusive. It could have a hemorrhagic component to it as well.

Ryan Van Patten 08:25

Okay.

John Bellone 08:26

Just for our listeners who maybe are not as familiar. So atherosclerosis is simply the buildup of plaque in the arteries. It blocks the blood flow and can cause a stroke of its own if it ruptures. And hemorrhagic refers to excess blood versus occlusive, which is something blocking the blood flow and stopping the perfusion, or stopping

the blood from reaching those areas. Some listeners might be wondering, “What's the difference between something like cerebrovascular disease, atherosclerosis, and stroke?” Like, what's the difference between those? Do you mind delineating those for the audience?

Adam Brickman 09:05

So there is overlap among those ideas. As you mentioned, anthro and arteriosclerosis involve hardening of the vessel walls typically due to cholesterol accumulation or plaque accumulation on the inside of the vessel walls. Supravascular disease, I would say, is a blanket term that encompasses small vessel disease, mini strokes, white matter disease, microbleeds, microinfarcts. Some people would lump athero and arteriosclerosis under the umbrella of supravascular disease. Stroke typically refers to the clinical syndrome associated with a bleed or hypoperfusion in the brain. So a stroke would require radiological evidence of either a hemorrhage or an infarct, temporally coupled with onset of signs or symptoms.

John Bellone 10:00

These all show up on MRI typically, which is why we pick them up in addition to the clinical syndromes. When we refer to the white matter hyperintensities, we're talking about the effects of some of these disease processes that we end up picking up on MRI.

Adam Brickman 10:18

Right.

Ryan Van Patten 10:19

Age is the number one and strongest risk factor for supravascular disease. After age, it would be elevated blood pressure as the next strongest risk factor. Can you talk about a few of the pathways through which elevated blood pressure leads to CVD and white matter hyperintensities?

Adam Brickman 10:38

I think the thinking there is that with elevated blood pressure, your heart's working harder, that increases sort of friction, if you will, on the walls of the arteries, and that allows cholesterol to get stuck or trapped on the walls of the vessels. Those are the plaques that you mentioned before. That slowly occludes the arteries or the vessels. Then that eventually causes the vessels to narrow and stiffen and break.

So we think that a lot of the white matter hyperintensities that we're seeing are the end organ result of that accumulation of athero and arteriosclerosis in the white matter. The vessels that perfused the white matter are very, very small and very, very delicate and a lot of where we see the white matter disease is in these watershed areas. So it also makes sense that some of the vessels that are tiny are going to be the most vulnerable to injury due to sclerotic changes.

John Bellone 11:44
And the brain just consumes way more blood and oxygen than other parts.

Adam Brickman 11:49
Massive amounts. Yeah.

John Bellone 11:51
Which is why it's adversely affected.

Ryan Van Patten 11:53

A few other biological risk factors for cerebrovascular disease would be obesity, diabetes, hyperlipidemia, high lipids, heart disease, sedentary lifestyle. Let me know if I missed any. You can be brief, but can you talk about a few of the mechanisms involved in some of these other risk factors?

Adam Brickman 12:14

I think they all converge on a lot of things. They tend to be comorbid and they tend to - I think the final common pathway is going to be the athero and arteriosclerosis that is going to lead to some of the small vessel disease. Obesity typically goes hand in hand with hypertension, and oftentimes with diabetes. So there's a convergence, sort of end organ convergence of all these different risk factors. There are likely other mechanisms that lead to white matter hyperintensities, particularly in the context of Alzheimer's disease. But I guess we'll get to that.

John Bellone 12:52
[laughs] Yep.

Ryan Van Patten 12:53

This is a quick two-parter: Can you first define autoregulation in the brain, and then talk about how fluctuating levels of blood pressure put older adults at risk for cerebral hypoperfusion and associated cognitive decline?

Adam Brickman 13:09

So autoregulation is this phenomenon that blood flow to the brain remains relatively constant even in the face of varying blood pressure. You can imagine when you're exercising, or even when you're standing up and sitting down, your blood pressure is bouncing all over the place, yet the blood flow to your brain remains relatively stable. So the problem is - so you have to sort of envision what we call the autoregulatory curve that has very, very low levels of blood pressure, blood flow to the brain is reduced, so there's hypoperfusion. At very, very, very high blood pressure, blood flow to the brain increases, so there's hyperperfusion. But in between those very low and very high stages, there's this plateau phase where you can have variability in your blood pressure, but the blood flow to your brain remains relatively constant. So when there's a failure of autoregulation, or when autoregulation is really challenged in the face of injury or possibly age, we're not sure, those boundaries of the plateau phase can shift such that there can be hypoperfusion deficit at relatively higher levels of blood pressure and there can be hyperperfusion deficit of relatively lower areas of blood pressure. So what happens is, if those boundaries of the plateau phase are shifted, then the risk for hypo or hypertensive injury increases. I don't know if that answered it. If I could show your listeners the picture, it would be pretty simple. [laughs]

John Bellone 14:52

We can include a link to that in our show notes. Yeah.

Ryan Van Patten 14:56

Autoregulation sounds a little bit like homeostasis. Like a homeostatic mechanism.

Adam Brickman 14:59

A very similar concept, right. That something has to be maintained constant in the face of changing something else.

John Bellone 15:08

The brain is unique in that way. Not every organ autoregulates their blood pressure.

Adam Brickman 15:13

That's right. Yeah. I think kidneys do, maybe. I think I wrote in a paper that the brain is the only organ that does it and then someone pulled me aside and said, "No, this other organ does it, too." I can't remember which one it is.

Ryan Van Patten 15:28
Importantly, though, to this conversation, high blood pressure is bad for the brain, generally speaking, and can lead to supravascular disease. In addition, fluctuations in blood pressure are bad for the brain. So it's important for us to know that variability. Like, if we go to the doctor's office and we have our blood pressure taken, and if it's high, that's bad. We might do things to reduce it. But we also want to keep in mind that variability, a lot of changes up and down, that's also bad. So it's another piece, I think a nuance that people sometimes miss.

Adam Brickman 16:06
I think that that's really important. And I think that the standard for blood pressure measurement, in general, is shifting from just a one time blood pressure in the doctor's office, which could falsely elevate blood pressure due to this white coat syndrome and doesn't necessarily capture all the things that happen throughout a 24-hour period. And so 24-hour blood pressure monitoring is quickly becoming a standard for evaluation of blood pressure.

John Bellone 16:33
As our mentor, Steve Correia, would say, the fluctuations in blood pressure are "bad juju."

Ryan Van Patten 16:39
[laughs] Juju.

Adam Brickman 16:41
That sounds like Steve, yeah. [laughs]

Ryan Van Patten 16:44
In terms of specific cognitive abilities that are impacted, cerebrovascular disease and white matter hyperintensities tend to be associated with a dysexecutive profile - with executive functions, processing speed, attention, and new learning differentially impacted due to this preponderance of pathology in the prefrontal cortex and the associated cortical subcortical circuits. Do we know why these abilities are differentially impacted?

Adam Brickman 17:12
It's a good question and one that I'll take a little bit of issue with. I think that our classical neuropsychological conceptualization of a supravascular versus an

Alzheimer's profile is a little bit less clear than how it was when I was trained. Yes, the white matter, because it connects parts of the brain relevant for things like executive functioning and new learning, when it's damaged, it's not surprising that it affects those cognitive abilities. But I would say, in community versus clinic based samples, white matter disease certainly reliably predicts memory dysfunction as well, declarative memory dysfunction not just executive dysfunction. So it's not as clean, I think, as it might be suggested in textbooks. We can talk about some of the research that went into why we have this “vascular is dysexecutive” and “Alzheimer's is amnestic”. I think a lot of that was self-fulfilling or compounding in research design early on. I was taught that we see memory difficulties in people with pure cerebrovascular disease purely because it affects learning. You know, there's an executive component to learning new information.

Ryan Van Patten 18:28
And retrieval.

John Bellone 18:30
And retrieval, right. That's also executive. But recognition is spared and the information is there. It's just the patient has a difficult time pulling it up.

Adam Brickman 18:41
Again, I would argue that that's textbook. And yeah, like a lot of things in textbooks, there's a truthiness to it for sure. But I think it's not that clean. We certainly, for example, see classic retention difficulties. The proportion of information retained over time is related to the degree of white matter hyperintensity in the brain. So it's not it's not a pure dissociation. Although, again, I'd argue that it's sort of true, but also sort of not true.

John Bellone 19:20
So, clinically, when I'm trying to figure out - if I've got this patient who performs poorly on learning tests, let's say, or other measures of executive dysfunction and I'm trying to figure out the etiology. What's the cause of these problems? Do you have any guidance here if it's not as clear of a profile? I mean, I hate saying, "Well, it's unclear. The etiology is unclear.” I say that all the time. [laughs] It could be this, it could be that...

Ryan Van Patten 19:46
Do you know anything, John? [laughs]

John Bellone 19:49
[laughs] Yeah, right? I don't know if you have any guidance for me here.

Adam Brickman 19:51
So tell me a little bit more about this patient. It's a 75 year old patient, who has had some cognitive changes. They haven't had a frank stroke, but they have a lot of white matter disease. They have dysexecutive syndrome. They might also, if you believe me, have some amnestic type symptoms or retention type problems. What's their diagnosis? So what would you see if you cut open their brain and did some histology? What would you see?

Ryan Van Patten 20:23
Mixed.

Adam Brickman 20:24
You'd see mixed. Right? Most people who have cognitive impairment - these older adults who have some degree of white matter hyperintensity also have evidence of Alzheimer's disease. And most people who we think have Alzheimer's disease also have evidence of cerebrovascular disease. So it's difficult to say what bin you should put them in because there's no bin. It's like a gommish.

John Bellone 20:54
[laughs]

Ryan Van Patten 20:54
[laughs]

Adam Brickman 20:58
It's a mixed profile. Which isn't to say that we can't play the neuropsychology game and say, "Okay, well, I think that a lot of what we're seeing here is driven by vascular dysfunction. So let's try to get that under control and see if we can do something about it." But, in most cases, I would argue what you're seeing clinically is a mixed profile.

Ryan Van Patten 21:22
That goes into a question that's come up for me a number of times. I've read some of your work for a while and I've wondered, you know, we spend all this time on a

differential diagnosis of AD versus vascular dementia. It takes up a lot of space in our reports and our brains as we're thinking through this, but recommendations tend to be similar. You know, if it's "pure AD", if we think it's pure AD or pure vascular, we still give the same brain health recommendations and functional recommendations. And it tends to be mixed more often than not, so...

Adam Brickman 21:53
Right.

Ryan Van Patten 21:54
Is it clinically useful for us to try to engage in this differential? Do you think so?

Adam Brickman 21:58
Maybe I'll propose something, or argue something sort of radical. I think that vascular dementia almost never exists. So I would only diagnose vascular dementia if someone is fine today - they're running their company or functionally fine, they're doing everything as they've always done, and then they have a stroke tonight, and then they come and see me tomorrow or a month or two months from now and they have dementia and there's a clear evidence of a stroke on imaging. That's the only scenario, personally, where I would diagnose vascular dementia. I always tend to favor this mixed dementia profile. You're right, the recommendations are similar. And the reality is that the contribution to their cognitive profile is most likely mixed. Again, we can always argue - we can put beta weights on the different pathologies that we think are relevant in every individual person. We can say, "Okay, this is a mixed profile. We think a lot of this is also is due to Alzheimer's disease, but a fair bit of it might also be due to vascular disease." Or someone might be more, "vasculopathic" and you might say that they have more of a vascular profile of dementia or cognitive impairment, but we also think that Alzheimer's disease is present and contributing.

Ryan Van Patten 22:10
It's a continuum.

Adam Brickman 23:17
Yeah, it's a continuum. It's a pie chart with different pathologies represented in different sized pieces.

John Bellone 23:25

I'm going to send all the neurologist's questions to you when I get them. [laughs] That's primarily who refers to me and often they want to know, "Should I start them on an acetylcholinesterase inhibitor?" Or "What should we do for this patient?" They want it to inform their treatment, the etiology.

Adam Brickman 23:45

Yeah, no, I get that. Yeah.

John Bellone 23:47

But, I mean, the other service, obviously, is the diagnosis of yes or no, is this MCI? Is this dementia? That's also very important to the neurologist. So it's not just the etiology. But, yeah, fascinating. But all white matter disease is not equally distributed in the brain, right? So cortically, white matter hyperintensities are usually found in the frontal lobes but also the parietal lobes. Can you expand on this and kind of talk about the prevalence of white matter hyperintensities elsewhere in the brain and its relationship to different cognitive abilities? Does it matter if it's frontal hyperintensities? Do we see more dysexecutive symptoms compared to parietal hyperintensities?

Adam Brickman 24:30

That's a great question. Just a couple points of clarification. We see most of the volume of white matter hyperintensities in the frontal lobe and the parietal lobes, as you said. The frontal lobes are bigger than the temporal and occipital lobes, so part of it is just real estate. There's more tissue to be affected. But even in our analysis, I don't know if I've ever published this but I've looked several times. When we look at relative volume - the relative amount of white matter hyperintensity, for example, the amount of white matter hyperintensity to the total volume of each lobe - it's still the case that there's relatively more white matter disease in frontal and parietal lobes. And those tend to be where the ventricles hang out mostly. So a lot of what we're seeing are in these periventricular areas, sort of growing out from the walls of the lateral ventricles. That's where the watershed areas are. So we certainly see a lot of white matter disease in frontal and parietal areas. In our data, it does appear that frontal white matter hyperintensities do seem to track a little bit more of a general cognitive aging, and are characterized mostly by speed and executive dysfunction. Whereas if you do it dichotomously, or categorically, if someone has cognitive impairment and they're older, they tend to have elevated white matter hyperintensities in the frontal lobes. But we've seen this dissociation where a more

posterior - more parietal, specifically - distribution of white matter hyperintensity seems to track more along with risk for clinical Alzheimer's disease and more of this amnestic syndrome that's associated typically with Alzheimer's disease. So there's a dissociation in our data, and other people have seen it as well, that posterior seems to go along with Alzheimer's disease. And anterior seems to capture the individual differences in cognitive aging, which best reflects or manifests as executive dysfunction - attention and those types of abilities.

Ryan Van Patten 26:31
Right.

John Bellone 26:31

It's really interesting that we think of Alzheimer's disease as medial temporal damage, but now we also have this posterior pathology that is also causing… You know, we're looking at the temporal relationship here. Does that happen after the medial temporal lobe is affected?

Adam Brickman 26:56

Yeah, we think clinically of a medial temporal lobe syndrome in Alzheimer's disease. But if you believe the ATNR, the amyloid tau degeneration framework of Alzheimer's disease, amyloid doesn't deposit earliest in the temporal lobe. Tau pathology certainly is restricted primarily to the entorhinal cortex. So the spatial relationship between where the Alzheimer's pathology is and where the symptoms of Alzheimer's disease are doesn't always map on. So you have to either question the symptoms or question the biology. With respect to your question about parietal lobe white matter hyperintensities, it definitely seems to be the case that increased parietal lobe white matter hyperintensities predicts later incidents of Alzheimer's disease. So we see it before the symptoms of clinical AD emerge. And that seems to be in some of our analyses independent of the medial temporal lobe atrophy that I think you're referring to. So we see both independent effects of hippocampal atrophy, for example, and posterior white matter hyperintensities on later risk for developing clinical Alzheimer's disease.

John Bellone 28:15

That's fascinating. Do you think that affects the clinical presentation? Do we see some visual spatial deficits because of the parietal white matter hyperintensities? What does that look like clinically?

Adam Brickman 28:28

To me, it gets at the temporal parietal memory systems more than visual spatial or attention, but that's where we tend to see relationships.

John Bellone 28:41

Clinically, radiologists don't usually - or rarely, I guess, they say the location of the hyperintensities. I almost never see "Oh, that's primarily frontal lobe white matter." It's usually just, "Oh, there are scattered foci of hyperintensities." So, I don't know. Is there a way of knowing? There's no way for us to know if they just say "Oh, there are white matter changes."

Adam Brickman 29:06

I think radiology is an interesting discipline. Because two radiologists will look at the same scan and one will say, "White matter changes expected for age", one might - or three radiologists - one might not even comment on it, a third will say, "Massive evidence of small vessel disease". So, I think there's already a subjectivity to clinical radiological reads. They can certainly comment on things regionally. Sometimes the scattered foci might point to more incomplete infarcts than to these continuous lesions that I typically talk about. But one thing that I think is important to emphasize is that even though we see a relationship between posterior parietal lobe white matter hyperintensities and risk for Alzheimer's disease, I'm certainly not advocating that it's a biomarker for Alzheimer's disease or diagnostic in any way. I use radiology to help point to biological systems that might be involved in understanding the disease or the syndrome, not really in the classic diagnostic biomarker sort of way. So that's not something I would advocate. I've given talks where people have come up to me and said, "Oh, I got an MRI scan. I have white matter hyperintensities. Does that mean that I've Alzheimer's disease?" And I'm like, “No, no. It's not a biomarker for AD.” It's something that's helping us to understand what are some of the contributors, biologically, to the disease or the syndrome.

Ryan Van Patten 30:38

I've seen claims - I think you're a part of a 2016 paper and Annals of Neurology that used DIAN, the dominantly inherited Alzheimer network, data who were studying autosomal dominant AD to learn about sporadic AD. The claim that white matter hyperintensities are a core feature of AD, that's a big claim. It's not too surprising going off of the current conversation we're having. But can you talk through the findings of that paper and the reasoning here?

Adam Brickman 31:10

I was deliberately being provocative in the title of that paper. If you look at the authorship list, you can imagine there's a little bit of pushback from my colleagues about titling the paper that, but the concept was quite simple. I published a lot of papers implicating white matter hyperintensities as a marker for cerebrovascular disease in late onset Alzheimer's disease. The typical review that I get is, "Well, that's not so surprising because these people are from the community. They have mixed dementia. The more garbage you have in the brain, the worse off you are." So this is just an added pathology that's very much in line with, say, the, as we've talked about previously, the Cliff Jack models of AD. No one is saying that multiple pathologies can't exist and can't contribute, but there is an argument about what's a primary feature of the disease and what's not. So the argument that I was trying to make is like, “Look, vascular disease is part of Alzheimer's disease. When we talk about Alzheimer's disease, we have to incorporate vascular disease.” The best way that I could think about, in humans, convincing people is taking the "purest form of Alzheimer's disease" I could get my hands on. And that's these autosomal dominant forms of the disease. So what does that mean? That means that if you

inherit one of these genes, the presenilin 1, presenilin 2, or APP mutations from your parent, you have a 100% chance of getting Alzheimer's disease. It's autosomal dominant. If you have a parent who has the disease, you have a 50% chance of inheriting that gene. So this is the closest we can get to a randomized experiment of Alzheimer's disease in human people. So basically, everyone involved in the study, the DIAN study, has an equal chance of inheriting the gene by virtue of having a parent with the gene - that 50% chance of inheriting the gene. If they inherit the gene, they have a 100% likelihood of developing Alzheimer's disease, more or less. So I reasoned that if I think that white matter hyperintensities as a marker of small vessel supravascular disease is a core feature of Alzheimer's disease in these autosomal dominant forms of AD, where they have early onset, and they're "pure", without all the vascular risk factors, and they're randomized into whether or not they get Alzheimer's disease, essentially, those who are randomized into the Alzheimer's group will have increased white matter hyperintensities. And that's what we found. We found that in the posterior areas and parietal and occipital lobes in this case, up to 20 years before estimated onset of symptoms, they had increased white matter hyperintensities in the mutation carriers compared to their non-mutation carrier, but equally at risk for inheriting the mutation, counterparts.

Ryan Van Patten 34:08

Right. That's very clear to me and makes a lot of sense.

John Bellone 34:11
Yeah, that's pretty convincing.

Adam Brickman 34:13
So I can tell you - I don't know if we want to get into this, but the argument there is, “Well, are these white matter hyperintensities we're seeing in the context of early onset Alzheimer's disease, are those really vascular in origin?” And that's a whole other question. That maybe what we're seeing is the result of having neurodegeneration and Wallerian type degeneration. So, in stroke, you have a stroke and all the fibers and all the axons and stuff that are attached or connecting to that area, there's dieback. There's been some argument that what we're actually seeing are the results of neurodegeneration, not vascular lesions driving potentially the neurodegeneration. I think there's a lot to be argued there, as well. So there's a lot to work out still.

John Bellone 34:59
There's also cerebral amyloid angiopathy, right?

Adam Brickman 35:02
Right.

John Bellone 35:03
Could be related to that. Can you talk a little bit about that?

Adam Brickman 35:06
We tried to get it. So cerebral amyloid angiopathy is the circulating amyloidosis in the vessels. People with Alzheimer's disease and certainly people with autosomal dominant forms of Alzheimer's disease have increased amyloid not only in their parenchyma as plaques, but also in soluble forms in their vessels. So amyloid angiography causes cerebral microbleeds. These are tiny hemorrhagic lesions that we see on gradient echo MRI or susceptibility weighted MRI. We use those microbleeds to operationally define whether or not someone has evidence of amyloid angiography. So we did a follow up paper to that 2016 Annals paper, and we showed that it doesn't seem to be the case that the increased white matter hyperintensities in people with autosomal dominant mutations for Alzheimer's disease is mediated or is attributable to whether or not someone has amyloid angiopathy or evidence of amyloid angiopathy.

John Bellone 36:14
The amyloid that builds up in the blood vessels, is that different from the extracellular amyloid?

Adam Brickman 36:23
Yeah, so typically what we see in the blood vessels is a-beta 1-40 length. The a-beta 1-42 length of protein is the stickier form that forms the plaques. So it's the same protein, it's just the different lengths.

Ryan Van Patten 36:40
Yeah, the extracellular amyloid is what is traditionally associated with AD.

Adam Brickman 36:44
Exactly.

John Bellone 36:46
I saw in one of your papers that you refer to the white matter hyperintensities as a "second hit" to a brain that already had some Alzheimer's pathology.

Adam Brickman 36:56
Yeah.

John Bellone 36:57
I know it's very difficult to pin down the temporal relationship between the hyperintensities and amyloid, but if you want to talk more about that...

Adam Brickman 37:07
Those findings are interesting. This is a paper - I can't remember what year we published that, 2014 maybe - where we took the ADNII data set, that's the Alzheimer's disease neuroimaging initiative, and that's a consortium of sites that that study people with Alzheimer's disease and at risk for Alzheimer's disease with standardized neuroimaging and neuropsychological and, in some cases, cerebrospinal fluid protocols. We identified people in that sample that had evidence of amyloid in their brain. Some of those people, as we know and expect, had Alzheimer's dementia. So they were demented, they had dementia. Some of the people had amyloid, but did not have dementia, but they still had enough amyloid in the brain to meet criteria for at least preclinical Alzheimer's disease. What we found

was that the people who had dementia, but we're amyloid positive, had increased white matter hyperintensities. We could dissociate the two clinically diagnostic groups pretty well based on how much white matter hyperintensity they had in their brain. We concluded, again, sort of provocatively, I guess, that maybe white matter disease, the cerebrovascular disease that it represents, is necessary for people to manifest symptoms of Alzheimer's disease in the context of amyloidosis. We're following up some of that stuff now. We haven't published it yet, but we're working on a paper. I've started doing more animal modeling and we can, of course, have genetic mutations for Alzheimer's disease, the same mutations we see in humans, APP, for example, and PS1, and you can take an amyloid mouse, and they won't have tau pathology. But we have what we think is a good model for white matter hyperintensities. We can hyperfuse the MCA of the mouse transiently and cause widespread white matter damage that we think sort of approximates white matter hyperintensities. And in the APP mice, they don't have tau pathology unless we hypoprofuse them. They don't naturally get tau pathology, but when we hypoprofuse them, they do get tau pathology. So again, they have amyloidosis but they don't seem to get some of the neurodegenerative type lesions until we give them a vascular insult.

John Bellone 39:28
That's fascinating. But we're not there in humans yet to know that the tau is caused by hypoperfusion?

Adam Brickman 39:35
Right.

John Bellone 39:36
We can't say that.

Adam Brickman 39:37

I think we're moving in that direction. We're starting to see some very interesting, at least correlational, data between white matter disease and vascular risk factors and tau pathology, if not amyloid pathology.

John Bellone 39:55

Okay, and for our listeners, we'll link to all of Dr. Brickman's studies. The one that I was referring to about the second hit was actually I think your 2013 JAMA neurology paper. But you have many, so people can read more about that.

Ryan Van Patten 40:06
So we're talking about brain insults, supravascular disease, white matter hyperintensities, what's going on in the brain, but we're also talking about the associated cognitive effects. I'd like to move into getting in between those two things - talking about moderators of the impact of cerebrovascular disease on cognition.

Adam Brickman 40:29
Sure.

Ryan Van Patten 40:30
One in particular that we talk a lot about in neuropsychology would be cognitive or brain reserve, the Yaakov Stern concept. These are related constructs referring to the ability of the neural system to withstand insult without showing measurable functional changes. People with healthier brains as a result of physical exercise, life experiences, cognitive stimulation, and social stimulation may be better able to enter some degree of neuropathology, like white matter hyperintensities, without showing cognitive decline. Reserve as the buffer or moderator. There are multiple ways to measure this cognitive or brain reserve. Can you talk about this in the context of white matter hyperintensities and cerebrovascular disease?

Adam Brickman 41:14
Sure, I could try. So Yaakov is certainly an expert on it. He's down the hall from me. The way that I think about reserve is as a relationship. You sort of need three ingredients in this relationship. You need some sort of a pathology, and you need some sort of an outcome, and then you need some sort of a proxy measure for reserve. If you have those three ingredients, it could form a prediction. And so the prediction is, if you have reserve, which is still, I think, pretty loosely defined, but if you have, let's say, let's use education as a proxy for reserve. If you hold constant two people's cognitive abilities, so you set their cognitive abilities at the same level, those with higher education will have more pathology.

Ryan Van Patten 42:07
Yep.

Adam Brickman 42:08
Right. So suggesting that there's some element associated with education in this example that's buffering the effect of pathology, in our case, white matter

hyperintensities, on cognitive outcomes. That's always a little bit counterintuitive to people, right? Because the prediction is that people with higher reserve actually have more pathology for any given level of cognition. That's a relationship that we've seen with respect to white matter hyperintensities. The question is, “Well, what are the factors that confer that type of reserve?” I think reserve in general can be thought of, as you mentioned, as cognitive reserve and their life experiences that might lead to how the brain is organized or adapting to a pathological insult. Then there's brain reserve, which suggests that there are actual structural changes or elements in the brain that are the results of healthy exposures that buffer the effect of pathology on its outcome. Then there's the direct effect of some of these things that could be conferring reserve on the brain itself, which I'm not sure what Yaakov Stern is calling that these days either. So, for example, aerobic exercise can both have an effect directly on the accumulation of white matter hyperintensity, that's not really a reserve scenario. But it could also potentially buffer the effect of white matter hyperintensities or cerebrovascular disease on cognitive outcomes.

John Bellone 43:42

Gotcha. I've also heard anecdotally that a person can tolerate more amyloid and tau pathology, but if there's also a co-prevalence of white matter hyperintensities, then exhaust some of their reserve. The white matter hyperintensities might exhaust some of that reserve. If we look at a tank of gasoline, it's using up way more gas with this hyperintensities present.

Adam Brickman 44:07

Yeah. So in that model, then you're operationally defining your white matter hyperintensities as your measure of reserve or as your depleter of reserve. I think these are all sort of important conceptual ways, or ways of conceptualizing some of these different changes that happen in the aging brain.

John Bellone 44:29

Age is another potential moderator. You know, where older adults have a greater risk for cognitive impairment, obviously. Are there any other kinds of sociodemographic moderators that are important here?

Adam Brickman 44:43

It's a big, big question for us in our group. As you guys know, I collaborate very, very closely with Jennifer Manly, who's really a champion and one of the world's experts on the social determinants of health and healthy aging.

John Bellone 45:00
We have plans to have her on, hopefully in the future. She's great.

Adam Brickman 45:05
She and I collaborate very, very, very closely. We meet every single day and we have a lot of joint projects together. We have a joint lab meeting as well. A lot of the work that we do collaboratively is addressing this question of racial and ethnic disparities in cognitive aging and dementia. I think a lot of what we're trying to understand is: are there psychosocial or sociodemographic aspects that co-vary with race and ethnicity that are driving some of the disparities that we consistently see across racial and ethnic groups? And, from my perspective, we definitely see "main effect differences" across race and ethnicity in cerebrovascular disease. In my mind, that might be one of the driving forces that might explain some of the disparities we see in cognitive aging and in Alzheimer's disease manifestation. There's certainly a lot of other psychosocial factors that are very, very complicated that probably interact in very, very complicated ways with health and have a direct effect on how we cognitively age that are clearly playing a role as well. You know, I look forward to hearing what Jen has to say about all that.

Ryan Van Patten 46:23
[laughs]

John Bellone 46:24
Don't steal her thunder here. [laughs]

Adam Brickman 46:25
I won't and I couldn't.

Ryan Van Patten 46:26
[laughs]

John Bellone 46:26
[laughs]

Adam Brickman 46:28
But certainly one of the big problems with Alzheimer's research is the lack of diversity of our participants. And certainly a lot of what we know in humans about

disease risk and biomarkers and the relationship between biomarkers and outcomes and pathology. All these different things have been informed primarily by white and well-educated populations and have not included diverse participants. Even the studies that have included more diverse participants suggest that there are differences in the relationships among variables that put people at risk for dementia and cognitive aging, as a function of race and ethnicity, for example.

Ryan Van Patten 47:16

Yeah, that's helpful. We've been talking primarily about white matter with respect to neuropathology and you did touch earlier on white matter changes in healthy aging, so to speak. But I wonder if you could expand on that a little bit. Specifically, what happens to our white matter in healthy aging in the absence of AD or vascular disease. How do these changes impact age expected cognitive decline across the lifespan?

Adam Brickman 47:43

Okay, so there does seem to be evidence that there are microstructural changes in the brain's white matter with age, even in the absence or even in the presence of very little vascular risk. The microstructure of white matter changes seem to fall on this anterior to posterior course, where frontal systems seem to be more vulnerable to white matter changes than posterior regions. That seems to go along with the subtle changes we see in executive functioning with normal aging. That's been in the literature for a while now. And sometimes it falls under the umbrella of the frontal aging hypothesis, which was very popular, I think, in the 90s. But I think there's some veracity to that. Also with something called the retrogenesis hypothesis, which is sort of the last fibers to myelinate seem to be the first ones vulnerable to injury in normal aging. George Bartzokis, who died very young unfortunately, was a big champion of that hypothesis. So there seems to be some evidence of white matter change with normal aging that seems to have a predilection for the frontal lobes more than posterior areas, and that seems to predict some of the dysexecutive changes and some of the psychomotor speed changes we see with normal aging.

John Bellone 49:13

It's pretty ubiquitous among older adults, some burden?

Adam Brickman 49:18
I think, like everything we measure, there's variability. Even in normal adults, we see an increase in variability in just about everything we measure whether it's cognition - except in Salthouse's work, he doesn't seem to see increased variability with age.

Ryan Van Patten 49:38
[laughs]

Adam Brickman 49:38
But a lot of other people do. When we use diffusion tensor imaging, for example, to look at white matter microstructural changes with age, we certainly see increased variability in older adults compared to younger adults.

John Bellone 49:52
Just to wrap things up. We're going to talk a lot more in the future about how lifestyle factors contribute to healthy aging and cognition but we should at least mention here that behaviors like exercising, eating healthy reduce risk for white matter hyperintensities.

Adam Brickman 50:09
Yeah.

John Bellone 50:10
I don't know if you want to say anything about these other potential interventions.

Adam Brickman 50:13

I mean, I think it's almost cliche to say now, but “healthy heart, healthy mind” or whatever. I think that there’s more and more evidence, particularly with respect to exercise. The diet literature is a little bit messier, but I think we're starting to see some convergence there as well - that healthy diets and healthy lifestyles lead to, or maximize, healthy brain aging. Like I said, it's almost cliche to say now, but 15, 20 years ago, it was still - you know, we thought of the brain and the rest of the body as sort of separate entities. But they're clearly part of the same thing.

Ryan Van Patten 50:52
Well, this has been really great, Adam. Thank you so much for taking all this time. It's been about two hours of your time [laughs] for two episodes.

John Bellone 51:01
We're so appreciative.

Ryan Van Patten 51:03
Yeah, really helpful for us and our listeners. Thank you so much.

Adam Brickman 51:07
It's been a lot of fun. Thank you guys. I really appreciate it. And I look forward to listening to all the other folks you guys are interviewing. As I mentioned, a great service to the field to bring people together and to have conversations about neuropsychology.

Ryan Van Patten 51:22
Yeah, we appreciate it.

John Bellone 51:23
Thanks for saying that.

Ryan Van Patten 51:24
Yeah.

John Bellone 51:24
Take care.

Adam Brickman 51:25
All right guys. Take care. Be well.

John Bellone 51:28
Well, that's it for our conversation with Dr. Adam Brickman. If you've been enjoying these episodes, we ask that you take one minute to leave us a rating, hopefully five stars, or a review on iTunes or on any other device that you might be listening to this on. It helps other people find the podcast by moving us up in the rankings. So

we would greatly appreciate it. And I hope that you'll join us next time as we continue to navigate the brain and behavior.

Exit Music 51:54

John Bellone 52:18

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Ryan Van Patten 52:29

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