31| Biomarkers of Accelerated Aging in Severe Mental Illness – With Dr. Lisa Eyler

November 1, 2019

NAVIGATING NEUROPSYCHOLOGY

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Speakers: Lisa Eyler, Ryan Van Patten, John Bellone

Intro Music 00:00

Ryan Van Patten 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior. I'm Ryan Van Patten...

John Bellone 00:24

...and I'm John Bellone. Today we're bringing you our conversation with Dr. Lisa Eyler about inflammatory and functional neuroimaging biomarkers of accelerated aging in severe mental illness. That is quite a mouthful. [laughs]

Ryan Van Patten 00:36

Yeah, say that three times fast.

John Bellone 00:39

[laughs] We promise it won't be as complex as it sounds.

Ryan Van Patten 00:42

Lisa is a professor in the Department of Psychiatry at UCSD. She's had a very productive career and contributed significantly to the literature on accelerated aging in severe mental illness. We think this is just a fascinating and really important topic for neuropsychologists. In our conversation with her, Lisa gives great definitions of all the relevant concepts and terms so we won't muddy the waters with that here.

John Bellone 01:07

We're going to cover a lot of ground today, and as the title alludes to, there's going to be quite a few topics that we're going to be covering. So the recording time was a little bit longer than we had anticipated, and as a result, we're going to split this episode and bring you Part 2 in just a couple weeks. But for now, we give you Part 1 with Lisa Eyler.

Transition Music 01:27

Ryan Van Patten 01:36

Okay, we're here with Lisa. Thanks so much for coming on NavNeuro today. Appreciate it.

Lisa Eyler 01:41

It's my pleasure to be here.

Ryan Van Patten 01:42

So I think we'll start off by just asking you to briefly describe your research program to us and our listeners. If you were giving an elevator pitch about what you do, how would you describe it?

Lisa Eyler 01:53

Yeah. I'm really interested in what happens to people with serious mental illness as they get older. And specifically with this idea that there might be an accelerated process whereby they're getting older faster than they should be. In looking at that, some of the ways that I examined that have to do with looking at brain function and brain structure as well as the role of inflammation and how those things work together to lead to this process of accelerated aging. And then, of course, with the eventual goal of trying to figure out what can we do to decelerate that and have people live longer and higher quality lives.

Ryan Van Patten 02:32

Yeah, that's really helpful to get us started. I think that the next step that we'll take, because we'll be talking about SMI quite a bit, is to ask you to define serious or severe, whatever word we want to use, mental illness - SMI for our listeners. How do you think about this construct?

Lisa Eyler 02:49

Basically, the "severe" or the "serious" refers to how much functional impairment there is for a given individual. So there's lots of severity levels of mental illness, things like depression, bipolar disorder, schizophrenia. Some people are only mildly affected and others have more moderate to severe impacts of those disorders on their day to day lives. So when we're talking about severe or serious mental illness, we're talking about folks who have very severe functional limitations or impairments that come from the mental disorders.

Ryan Van Patten 03:21

Could there be other mental illnesses that are not mood disorders or psychotic disorders that have severe functional impairment? Would we call those SMI? Or would you say it's really reserved for psychotic and mood disorders?

Lisa Eyler 03:33

I think there are some anxiety disorders that could be called SMI. You know, again, it really has to do more with functional impairment than the exact nature of the symptoms.

John Bellone 03:44

That's a good distinction. So in what way do mood disorders, like depression or bipolar disorder for example, and psychotic disorders overlap? You know, schizophrenia versus depression? How do they overlap in this area?

Lisa Eyler 03:57

They overlap in a lot of different ways. I mean, to some extent, there's actually symptom overlap, right? So people with bipolar disorder or depression can also have psychotic features, for example - they can have delusions, hallucinations, etc, just like people with schizophrenia would have. But they also overlap, as we just talked about, in the level of functional impairment. So in all these disorders, you can have people who have problems with employment, with social functioning. But more specific to my area of research, they also overlap in that they tend to have these potential for high levels of comorbidity with other physical illnesses in a way that is accelerated in terms of when these comorbidities show up across the lifespan. We'll talk later, I think, about the idea of inflammation and how the inflammation is involved in all of these severe mental illnesses.

John Bellone 04:53

That overlap is really interesting because I think people have the tendency to think of these as completely separate entities. Depression is separate from schizophrenia. But people don't understand the overlap there is pretty substantial, potentially.

Ryan Van Patten 05:05

And genetic risk as well, right? So if I have schizophrenia, my brother is at more risk for not just schizophrenia but bipolar.

Lisa Eyler 05:12

That's right. So the genetic risk profiles tend to overlap in terms of just heritability. But also when you start looking at the genome-wide association studies, there's a lot of actual genes that overlap that are similarly found to be associated with each of these disorders. Interestingly, a lot of those have to do with the immune system, which is one other reason why I'm interested in inflammation.

Ryan Van Patten 05:37

Yeah, it's fascinating. I wouldn't guess on the front end if I didn't know that the genes involved would be immune-related. So given this overlap we're talking about

now, what are your thoughts on the DSM diagnostic system versus newer models? Like the RDoC, the Research Domain Criteria?

Lisa Eyler 05:55
I guess my thoughts depend on what we're talking about. If we're talking about [it] as a research tool, as a clinical tool, or kind of just, philosophically, as a way of labeling people. I think when we're talking clinically, what's most important are the symptoms that people are experiencing and treating those symptoms. So in some ways, although most people who have these disorders, but not all, feel like it's important to have a diagnostic label so that they can sort of say, "This is what I have and this is how I'm going to address it." In fact, I think day to day most clinicians are dealing with symptoms. So if you have been diagnosed with schizophrenia but you're having a lot of depressive mood, you may be treated pretty much the same as somebody who is bipolar with depressive mood or major depression with depressive mood. It's important that people focus more on the symptoms in a clinical context, I believe.

On the other hand, I think even clinically these diagnostic categorizations may be important. For example, there's a lot of evidence to suggest that the treatments for depressed mood are less effective in people who have bipolar depression versus major depression. So knowing that somebody has had manic or hypomanic episodes when you're trying to decide how to treat their depression may be important because there may actually be less efficacy and or different medications that would be better. We need more research to actually find good medications for bipolar depression. But, for research, I think it's still important to have these categories because there are, clearly, some clinical distinctions between, say a person with psychotic bipolar disorder versus somebody who has schizophrenia and maybe has some bipolar affect because it's a different ratio of symptoms. And particularly somebody who's schizophrenic, but does not have any bipolar symptoms. You know, bipolarity is a very interesting and very different thing. To switch from the poles of being very depressed to manic and back again, that switching doesn't happen in other disorders. It doesn't happen in major depression. It doesn't happen in schizophrenia, generally, unless you're schizoaffective bipolar, which may be just...

John Bellone 08:10
Too much.

Ryan Van Patten 08:11
[laughs]

Lisa Eyler 08:12
Too similar to bipolar disorder. But in any case, I think some aspects of the clinical diagnostic groupings are important for research. On the other hand, I think it is important that we look cross-diagnostically, particularly at things like motivation, things like accelerated aging, and try to understand are there some common underlying processes as well? And can we use that to help people live better lives if we can address those common things?

John Bellone 08:21
I like that. Really balancing both of those things - the labels, but also just the symptom presentation. I like that.

Ryan Van Patten 08:46
Yeah, they're not mutually exclusive. What's your take on the RDoC moving forward? Do you think that's a good research framework for us to use in order to eventually advance how we understand mental illness? Are there alternatives that you prefer?

Lisa Eyler 09:01
Yeah, I think it's always been a good idea to, again, look at underlying constructs and try to see how they overlap. I really like the cross diagnostic focus of RDoC. I think any kind of scheme that only focuses on that and doesn't focus on some other things may be a little bit lacking. For example, in my reading of all the RDoC documents that have come out, there's really not a lot about this switching between highs and lows of mania and depression. There's nothing that really captures that because there are the positive sides and there's the negative side, but nothing about that transition between the two. I feel like that's a really unique part of bipolar disorder that's not being captured by the RDoC approach.

Ryan Van Patten 09:47
Yeah, I've heard that RDoC described - a benefit, an advancement of it relative to the DSM is that it helps us break out of the, "epistemic prison" of the DSM. But we wouldn't want to be then confined to a different epistemic prison cell, the RDoC, right? Hopefully it's flexible and can allow for other constructs, like you mentioned.

Lisa Eyler 10:08

Exactly. I've heard people say that it's great to try different systems and see how they work. But I think it remains to be seen if this system works a lot better than the traditional system for understanding things that will help people live better lives.

Ryan Van Patten 10:24

Yeah.

John Bellone 10:25

And for our listeners, again, the research domain criteria, RDoC, that we've been referring to is a different classification system, or a different way of defining mental illness. Versus the categories of the DSM, we look more at the underlying symptoms and the transdiagnostic values - so what's similar among different mental illnesses, just as one example of that.

Ryan Van Patten 10:44

Yeah, that's helpful. So let's move forward in our conversation, if that's okay, to accelerated aging as you've referenced a couple times. My understanding is that accelerated aging in people with SMI is what it sounds like - the typical age-associated diseases that impact older adults such as cardiovascular disease, cancer, metabolic disorders tend to occur earlier, like sooner in the lifespan of people with SMI leading to early mortality. I believe, often, 10 to 20 years before the general population on average. So people with SMI die more often from natural causes. They also have higher suicide rates, but death by natural causes is a much higher proportion. Why do we think that accelerated aging occurs in SMI?

Lisa Eyler 11:31

That's a great question. I think the big question in this field is "Why?" I think that we've now gotten to a point where we've pretty well demonstrated that this happens as a whole, although I think there's still a question about how much variability is there in this. So is everyone aging at a more rapid pace? Or only some people? And to me, that's the crucial question. Because if we can figure out if there are some people that don't seem to be demonstrating accelerated aging, maybe that'll give us a clue as to what are the causes. There's a lot of different ways to look at this. I think one of the reasons why this has not been looked at a lot in the past is that people just sort of said, "Well, the reason that they're dying sooner is because of suicide or other things associated with their disorders." And that has been shown, as you said, to not be the only reason why they're dying sooner. But then people were saying, "Well, it's the reason they're getting these other disorders,

because there are side effects of the medications that they're taking, and/or side effects of having a serious mental illness and the things that come along with that", which might include housing insecurity, food insecurity, just general stress, and wear and tear from the effects of the disorder. So I think a lot of people have seen these physical comorbidities and actually called them "comorbidities" because they thought of them as things that sort of come along with the mental disorder, with a mental disorder being primary.

But more recently, people have started looking farther and farther back in the lifespan, including near the age of onset of these disorders, and noticing that there are sort of already signs of premature aging so to speak. So for example, in teens with bipolar disorder, they have a lot of cardiovascular risk factors that other teens do not have. These are folks who haven't been on medication for a very long time, if at all. They've only been dealing with bipolar disorder for some years and they're still in supportive family environments, generally, etc. So the idea is that it's also possible that accelerated aging or these comorbidities, at the very least, are part and parcel of the pathophysiology of the disorders. And this gets back a little bit to what we were talking about, about the overlap genetically and how those are in this immune system. Genes are often found in the overlap between these disorders.

The idea that the immune system may be playing a role very early in these disorders, which might be leading to kind of both things happening - both neurodevelopment that goes awry and leads to a mental disorder, as well as aberrant development of the innate immune system so that you get inflammation and more susceptibility to these diseases at an earlier age. So I think the trick is to distinguish between these possibilities, which I don't think are mutually exclusive. But in a given individual, is this something that's kind of been there from the beginning so that they've kind of been aging more rapidly all along? Or is it something that once the onset of the disorder happens, then the lifestyle things that go along with that and/or the medications etc, are promoting a faster aging?

Ryan Van Patten 14:58
Fascinating.

John Bellone 14:58
Yeah, really fascinating. They don't have to be mutually exclusive, like you mentioned. You can have some limitations because of all the side effects, the medications, and the functional impairments, but you can also have potentially this underlying cause that's responsible for both the physical problems and mental

health issues. Yeah, that's really fascinating. You mentioned inflammation, and this is one of your areas of research, right? Inflammatory process in mental illness and accelerated aging. Can you talk a little bit more about that? Maybe just give us kind of a high level explanation of the inflammatory process in general, for our listeners who might not be as familiar.

Lisa Eyler 15:34
Sure. So the immune system can be broadly divided into the innate immune system and the adaptive immune system. Most people might be more familiar actually with the adaptive immune system. This is the T cells and the B cells where you have an antigen that's recognizing an antibody. It's the thing that's taken advantage of in vaccines, right? Where you put a little bit of whatever it is you're trying to fight off in there inactivated, then your body sort of mounts a response to that and is ready and waiting with a memory of that next time you get that. But the innate immune system is kind of the advanced guard - I love all the war-like analogies that we have. [laughs]

Ryan Van Patten 16:14
[laughs]

Lisa Eyler 16:14
But they're kind of like the scouts or the advanced guard. So when there's an injury of some sort, whether it be a bruise or a cut or initial infection in some way, the proteins of the innate immune system - so that would include cytokines and chemokines, things like interleukin 6, interleukin 10, TNF alpha, C-reactive protein - these sort of things go to the site of injury and they start the healing response. In fact, they call to the adaptive immune system and signal to the adaptive immune system to say, "Hey, come over here and take a look and see if there's anything you want to recognize and remember" while they're doing things. So the reason it's called inflammation is it involves things like basically redness, heat, fever - that initial response to any kind of an injury that you would get. And then, in the ideal situation, what happens is that once the adaptive immune system has been called, then anti-inflammatory proteins will come in and kind of dampen down that response. It'll be like, "All clear, we're good now" and then go back to normal in waiting for a new injury. Unfortunately, what happens as you get older, is that you tend to have a prolongation of the pro-inflammatory response. So that there's a relative ratio of more pro- than anti-inflammatory proteins there and so you're in a chronic state of mild inflammation. And that seems to get worse as we get older. And that's for everybody, not just in SMI. But in some of these mental illnesses, we

also see that there's inflammation that's greater than you would expect for somebody's age - this kind of pro-inflammatory state.

John Bellone 17:23
And sometimes this is referred to as "inflammaging", kind of a portmanteau of inflammation and aging, right?

Lisa Eyler 18:12
Exactly.

John Bellone 18:13
Can you talk about inflammation in respect to age-related cognitive decline?

Lisa Eyler 18:18
Yeah, so people have been wondering whether there's a relationship to one of the main things that we see with aging - what neuropsychologists are very interested in, what happens to cognition as we get older? It seems to be that there are cognitive changes, regardless of if you have a disorder like Alzheimer's disease or other dementia, right? So people have wondered if there was a connection there between this pro-inflammatory response and cognitive decline. There have been quite a few studies now, even longitudinal studies, that have shown that people with a higher level of circulating pro-inflammatory cytokines at Time 1 have greater cognitive decline at a later time in a follow up period. So there does seem to be a link there in research studies. But we know a little bit less exactly how that happens biologically.

John Bellone 19:12
I know you said that we don't know too much about that, but I am curious about the potential mechanisms underlying that relationship between inflammation and cognitive decline. I've heard of maybe synaptic damage from some of this inflammation. Can you talk about some potential mechanisms?

Lisa Eyler 19:29
Yeah. So this brings us into this idea of neuroinflammation because most of what I've been talking about and most of the research is looking at inflammation in the periphery - so just measuring these cytokines and chemokines in the blood and trying to see how those are related to brain outcomes, whether it be cognitive decline or brain function or whatnot. So the question is how do these peripheral cytokines get into the brain and then what do they do there and is there

neuroinflammation that results. There is mounting evidence that although people used to think that the brain was somehow special, in terms of being isolated from the immune system, there's actually been, in the last 10 years, discoveries about much more two-way communication between the periphery and the brain. Of course, there's the blood brain barrier and you can, in some conditions, have more permeability of the blood brain barrier that would allow things to come and go a little bit more. And in the brain, there are also responses to injury as most people may be familiar - like the role, for example, of microglia. They're kind of like the vacuum cleaners of the brain. When there's neuronal damage or decay of different parts of the brain, microglia change forms and come in to basically suck it up and get rid of all this stuff. [laughs] And microglia are activated by cytokines. So if there's neuroinflammation, you get more of the microglia in an activated state. Which, again, just like peripheral inflammation, it's a good thing, in general, you want to have these vacuum cleaners cleaning things up. But if you have too much inflammation, then you have them overactivated and they themselves can actually then be destructive instead of just cleaning up destruction.

John Bellone 21:20

What's the best way that we are able to assess the degree of inflammation? I know we have blood tests, obviously - you mentioned IL-6, IL-10, TNF alpha - is that the only way? Or we can also look at CSF, right, cerebrospinal fluid? I'm also interested if there are any imaging techniques that look at inflammation.

Lisa Eyler 21:40

That's a great question. So most people that are doing this work right now are looking at peripheral levels of cytokines but there's some limitations to that, as you can imagine. One is that it's pretty far away from the organ of the brain. If you're interested in what's going on in the brain, it's sort of a shadow of what's going on in the brain potentially. The other problem is that there are a lot of acute things that can influence your level of peripheral inflammation - like how much you exercise that morning, or how much coffee you drank, or whether you smoked a cigarette, or whether you have really bad allergies this morning, etc - that may or may not be having a similar effect on the brain. So people are very interested in looking at either CSF measures of inflammation or looking directly at inflammation in the brain. So there have been some Positron Emission Tomography, or PET, scan ligands that have been developed that are supposedly looking at the levels of activated microglia. There's some promising studies using PET. Unfortunately, compared to something like MRI, PET is a lot more invasive because you have to inject this radioactive labeled tracer which not everybody wants to do. Also, there's

some issues with some of the ligands that have been used where there are polymorphisms in certain genes that affect how much binding you get. We have to do a genetic test first and then exclude those people because you won't be able to see the binding in those people. So it gets really kind of complicated and you can't use it. And then there's also apparently age-related differences in the binding of the ligand, which may or may not relate to age-related differences in microglia. And so, people were like, "Oh, you have to control for age", when I went to a talk about this. And I was like, "Well, I want to look at the effect of age..." [laughs]

Ryan Van Patten 23:35
[laughs]

Lisa Eyler 23:35
I don't really want to control for age and get rid of that effect. So there's some PET methods. And then more recently people have been interested in looking at some diffusion tensor imaging MRI methods. There are some relationships between peripheral inflammation and traditional measures that you get out of DTI, or diffusion tensor imaging, including you can look at the relationship with things like fractional anisotropy, which is a very common measure of the integrity of neuronal tracts in the brain measured with DTI. But there also are other measures you can use that look more at free water diffusion. And the idea is, in the case of there being edema or neuroinflammation, that there might be an effect on the free water diffusion. So there's protocols that you can use that are sensitive to that, that you can use for analysis of MRI data. People have started to look at that and how it's related to the peripheral cytokine levels. I have a study right now where we've used DTI and we're doing analyses trying to look at neuroinflammation in people with schizophrenia and people without schizophrenia on whom we have peripheral cytokine measures to see what the association might be.

John Bellone 24:51
Yeah, lots of ways. You mentioned how coffee and exercise could potentially increase inflammation. People are going to be worried now. [laughs] So this is just a short-term, temporary increase in inflammation that's adaptive. That's not harmful. Right?

Lisa Eyler 25:06
That's right.

John Bellone 25:07
Okay.

Ryan Van Patten 25:09
Good clarification.

John Bellone 25:09
Yeah. Don't stop exercising. [laughs]

Lisa Eyler 25:11
It's an interesting thing about exercise, though. And maybe we'll get to this later because there's this idea that part of what's going on with this pro-inflammatory response as you get older is kind of that there's the stressors of life that are, you know, leading you to get this short term thing. And then that short term response keeps on going, it doesn't resolve. But it's kind of counterintuitive, because we know that exercise increases inflammation in the short term. But exercise is really good for you and good for cognition in the long term as far as most of the studies show. So it's kind of a question of there must be a sweet spot there, right? So a little bit of stress, or a little bit of perturbation, is probably good for you. But too much, maybe not.

John Bellone 25:58
Yeah, kind of like a vaccine type of scenario. Hormesis is a technical term for this. You introduce a little bit of something harmful and that actually leads you to mount a bigger response later or to prepare those cells later, like the vaccine.

Lisa Eyler 26:13
Exactly.

John Bellone 26:14
I'm not sure if that's actually the case for exercise, or to what degree that's the mechanism, but it's a possibility.

Lisa Eyler 26:21
That's right.

Ryan Van Patten 26:21

This is a great discussion, really diving into inflammation here. So to reiterate and clarify, I want to talk about inflammation as it relates to SMI and then move into a few other conditions. Based on what you said before, my understanding is that one idea, maybe the best idea right now, is that the way that inflammation and SMI are related are through a shared genetic underpinning, right? There's shared genes in different types of severe mental illness that relate to the immune system. So that genetic risk likely contributes to inflammation and to the development of psychiatric disorders as we know it. Is that generally right?

Lisa Eyler 27:01

I think that's definitely one of the strong contenders. But I also think that we haven't ruled out that, for some people, or even for all people to some extent, the inflammation is a result of the stress and challenges and sort of insults of the psychiatric disorder itself.

Ryan Van Patten 27:20

That's helpful. Good clarification. So I have also seen neuro-inflammation as a potential mediator for cognitive decline in a multitude of disorders to the extent where I've joked with people that like, "It just seems like a black box that we can throw at the wall." Like, disorder X leads to cognitive decline and we ask why, "Oh, neuro-inflammation." [laughs] Without really knowing what that means, or what's truly going on. So maybe take a disorder or two like Alzheimer's disease, or HIV, or one that you're familiar with, or just the literature in general, and talk about how the similar mechanism may be functioning across all these different neurological conditions.

Lisa Eyler 28:00

Right. I think we need more cross disorder studies because most of the studies have been done in one disorder or another and there haven't been enough where we've looked at it across different things. So one nice thing about the work that I'm currently doing is that we have parallel studies going on in schizophrenia and in bipolar disorder where we're measuring the same peripheral inflammatory markers that we can eventually combine those data and see, are there any differences in inflammation? In what it's related to or what kinds of symptoms or sort of moderators, demographic moderators - are there any differences in schizophrenia versus bipolar disorder? Or is it all working in the same way? And similarly, if we use more of a technique where it can look at exactly what's happening in the brain. I think, again, having cross disorder studies because I think you're right. Right now,

it's kind of like, "Yeah, inflammation might be an issue in all of these different things."

Ryan Van Patten 28:55
[laughs]

Lisa Eyler 28:55
And I really don't think we have good evidence yet to say, "Well, sure, inflammation is working in all these, but it's working in this way in this disorder, and it's working in that way in this disorder. And that way..." We don't really know, yet, how they're different. I think we're still in that phase of excitement about like, "Well, let's take a look at inflammation in this disorder. Maybe it's there, too." We've found all this, but now our challenge is to figure that out. One of the things that I think is important is looking at different inflammatory cytokines because a lot of times a study will focus just on one, or there might have two or three, or they might have a whole panel and people haven't really done a lot of work in terms of figuring out are there real differences between those inflammatory cytokines. Could some of them be biomarkers in one condition versus another? And then relating that to what's going on in the brain. I think that's going to be really a key thing. But I think for serious mental illness, the thing that I think is important is that we start thinking about these as not just brain disorders because the evidence is there that there's stuff going on in the whole body. I think that framework, of thinking of SMI as a whole body disorder, is actually helpful clinically. It may actually be helpful in terms of decreasing stigma. So I think the inflammation piece actually is helpful to remind people that this disorder is not just from the neck up.

Ryan Van Patten 30:25
Yeah, I like that a lot.

John Bellone 30:27
Is there anything that's being done in the larger healthcare system to address accelerated aging in people with SMI?

Lisa Eyler 30:34
We published a paper recently where we showed that, unfortunately, people with schizophrenia don't seem to be benefiting from the extra longevity that the general population is seeing. So I would have to say, not enough, no, is being done. Because while other people are living longer people with schizophrenia don't seem

to be living longer. So that suggests to me that there's not enough awareness of the possibility for accelerated aging. Even doing the same things that we're trying to do in people without mental illness to extend their lives - getting them on statins, for example, or preventative things like exercise or encouraging these things - I don't think they're being done with SMI in mind. I think a lot more could be done. Now, there has been a move in recent decades to this idea of integrated primary care and mental health care and I think that has the potential to address this issue. Because if you're having the same team, the same doctors, the same medical record that's addressing both the physical issues and the mental health issues, there's more of a possibility that people will see the synergy there and will think about ways to treat both at the same time. So I think that move is a good one. But I don't know that we've seen the benefits of it quite yet.

Ryan Van Patten 32:03

Yeah, it's really helpful. You were the co-author of a case study that examined an especially high functioning woman with schizophrenia. The idea was to identify factors that might protect against accelerated aging in SMI. I'm curious if you could briefly talk about that model, generally, the conclusions of the study, and what we might learn from it.

Lisa Eyler 32:25

Yeah, this study was a really unique one. But the general model is very consistent with what I've been talking about, which is to try to understand individual differences in the rates of aging among people with the same disorders or the same collection of disorders. Because I think most of what we've done in research historically has been like, "Okay, we're gonna put you guys in this box. And then we have this healthy box. And then we can see, on average, how are the people in this box different from the people in this box." There's clearly such heterogeneity within "healthy people" as well as within people who are suffering from some kind of mental disorder. So we need to understand why people are different. And if we can understand why they're innately different, or just naturally different, then we could maybe take lessons from that and apply that in terms of helping everybody get to a more ideal state. So we've done that in studies of just normal aging in terms of looking at successful agers. But we've also done this in the context of severe mental illness and trying to identify some people who are functioning quite well despite their very severe symptoms, at times, and try to see if there is anything about those folks that we can learn to help us understand the process. It was fascinating that with this index person that compared to other women her age that didn't have mental illness, and other women who had schizophrenia, she was doing

better in a lot of different realms, despite the fact that she had kind of equally severe symptom history and symptom course. There were some brain regions that she was more active than even the people without schizophrenia, as well as some of her levels of these inflammatory cytokines were sort of healthier, less pro-inflammatory than the comparison women that didn't have mental illness, as well as those that did. Suggesting that maybe there were some protective factors that she had that were keeping her from having accelerated aging, and if anything, maybe even decelerated aging.

Ryan Van Patten 34:39

Wow. I love this idea of wellness within illness, right? Just because someone is afflicted with even something as severe as SMI doesn't mean they can't function well. And we want to look for resilience factors. This reminds me of Elyn Saks' book, "The Center Cannot Hold," which I had read and really, really enjoyed. She's a Professor of Law and Psychology at USC. I'd recommend her book to anyone who's listening. So Lisa, do you think that this model, the case study, is a good way or the ideal way to go about examining individual differences better than group comparisons? Are there other research designs that would better capture the heterogeneity?

Lisa Eyler 35:19

I think the case study is maybe a little underrated. It was difficult for us to figure out exactly how to get that published, because most people were like "Oh, n of 1".

Ryan Van Patten 35:29

Right.

Lisa Eyler 35:29

Like, well, but there was a large comparison group, two large comparison groups. So but I think, in general, it's just a matter of, again, taking an individual difference approach. So instead of just doing group differences, looking at correlations, looking at moderators of any group effects that you do see. And then, of course, with my interest in aging, I think it's just crucial that we do more longitudinal studies. They're hard to do. It's difficult to get people to follow up. In my area of neuro-imaging work, it's really hard because the equipment keeps changing and the state of the technology is different. But following the same people over time, and then looking at individual trajectories and how some people's trajectories may be particularly healthy, and others may be falling off more rapidly and trying to understand what are the baseline predictors of that is really the way to go. It's very

similar to the approach that people are taking in Alzheimer's disease, where they're trying to find early markers of those that will eventually decline to Alzheimer's disease versus those that maintain a good level of cognition or only have normal age-related cognitive decline. Or the approach that other people are taking, where they're looking at super agers or successful agers and those that are not even showing that typical level of cognitive decline. What are those features that we can identify early on that seem to predict who goes where? And if those are modifiable, then applying those to people as a therapy.

Ryan Van Patten 35:31
Yeah, I love it.

John Bellone 36:59

Before we move forward, there's another biomarker that we want to focus on a little bit because it has been a large part of your research program, functional neuroimaging, specifically, functional MRI. This might feel like a little bit of a tangent with respect to inflammation, but it's really relevant to accelerated aging. So can you just give us a little bit of an overview of how fMRI works and how we might use it to investigate neural processes?

Lisa Eyler 37:25
Sure. So fMRI is a great technique for looking at the function of the brain because of the fact that MRI is pretty non-invasive. So I've mentioned before that we can use Positron Emission Tomography with different tracers. I can get into and look at oxygen consumption and can look at the functioning of different neurotransmitters as well as glucose consumption, etc. So those are all really good, but they are pretty invasive and not everybody wants to do it. And they're hard to repeat. If you're talking about longitudinal studies, you don't want to expose people to too much radioactivity. So MRI, had this great promise that maybe we could use it to look at some of the same types of functioning of the brain that it would be a lot more repeatable and less invasive. People have been using it for a long time to look at the structure of the brain and look at the amount of gray matter, white matter, etc. And they're still using it for that. I mentioned diffusion tensor imaging, also an important technique.

But functional MRI is looking at the BOLD signal, which is the blood oxygenation level dependent signal. And it's taking advantage of some naturally occurring things in biology to be able to image where the brain is using the most oxygen. So the first thing that it's taking advantage of is the fact that hemoglobin is the protein that

carries oxygen in the blood. Hemoglobin contains an iron group in the middle. And when you have oxygen on the hemoglobin, that iron group is hidden inside. And when it doesn't have oxygen on it its conformation is slightly different, so the iron is more exposed. So what that means is that since, as we know, metal disrupts a magnetic signal, we can tune the MRIs to be very sensitive to these little disruptions in the field due to the iron. So that's the first fact - is that the iron is hidden when an oxygen is on there and is more obvious when there's no oxygen there.

The second fact is that when the body delivers oxygen to a site where the neurons are working hard, it actually delivers more oxygen than is needed for the functioning of the neurons. So there's this pool of excess oxygen in the vessels surrounding the neurons that are working the hardest. And in that pool, most of the hemoglobin has oxygen on it and less of it doesn't have oxygen because it's being sent there to feed the neurons. So in the areas where the neurons are working the hardest the vessels around them have more oxygenated than deoxygenated hemoglobin, and therefore their signal on MRI is a little bit better. So what we do with fMRI is we try to have tasks in which you have them do something and then not do something and then do something and then not do something and you look for these minute changes in this BOLD signal when they're doing something versus not. Or you can actually also measure minute changes in the BOLD signal when people are not doing anything in particular, just at rest. And there, it turns out that, at rest, that BOLD signal kind of idles together. Regions idle together that have similar functions when they are active. So for example, the left and right motor cortex tend to have a BOLD signal that even when you're not moving, actually goes up and down across time together. And we don't really know why that is. But the idea is that it's ready and waiting for a stimulus that then can be coordinated because it's in tune functionally. And that's what people talk about, called functional connectivity. It's just a correlation across time of the BOLD signal between different regions.

John Bellone 41:09
It's really amazing that number one, it works like that, and number two, that we figured it out.

Ryan Van Patten 41:13
Yeah.

John Bellone 41:14
And can see it.

Ryan Van Patten 41:14

Yeah. This explanation is great. Thanks. Yeah, as John said, for our listeners, it may seem like we're taking a sidestep, but I'd like to stay and talk about the method of fMRI for just a few more minutes before we will then connect it to inflammation and accelerated aging. So, I know that a big potential issue in the field of fMRI work in the general public is that the results are prone to misinterpretation. Sometimes we're mesmerized by pretty pictures, DTI, etc., and which area of the brain lit up. And so what does that mean? It's easy for us to over simplify and draw one to one relationships. Do you have any advice that you can package in our conversation today for how to account for the complexity and just be more accurate? What does it take to accurately interpret fMRI data in a sort of rigorous way?

Lisa Eyler 42:09

Well, there's a lot of different factors that go into it. Part of it is that there's a lot of decisions that have to be made at many different points in the processing. So what we get out of the MR machine are these signals that are time varying. And, again, what you're ultimately trying to do is see which parts of the brain have a signal that varies at the same frequency, or in pattern with the stimulus that you put in. Or in the case of resting state functional connectivity, how do they vary together with other regions of the brain? But there's a lot of decisions that you have to make in the processing of the data from the moment it comes off the scanner to where you make that pretty colored picture of what lit up, so to speak, right? So one of the things that you have to decide is what are you going to contrast with what? Because the BOLD signal is a relative signal. It doesn't have something where it's, like, milligrams of this per unit time or anything like that, unlike some other neuroimaging methods. So you have to know that it's always in contrast to whatever the non-experimental condition was. So one thing that's important in interpreting fMRI results from a task-based thing is to really understand what are they comparing it to. So this lit up relative to what? And do you believe that that's a good comparison? And, psychologically, it's not even really clear whether you can do that. It's a cognitive subtraction. Basically what you're doing, you're saying this area of the brain lit up more when I was moving my fingers than when I wasn't moving my fingers or it lit up more when I was moving my fingers in a pattern than when I was just moving my fingers randomly. And there's been a lot of work in psychology to suggest that that kind of subtraction doesn't necessarily work very well. Because there's so many interacting things that happen and and ways in which if you think you're just adding one cognitive process on top of another, you may actually be adding four or five different cognitive processes. So that is important for interpretation of fMRI. Another thing that's important is the multiple comparisons problem. We usually have somewhere tens of thousands of little parts

of the brain that we call voxels, that we're painting a color based on their correlation. And as you can imagine, that's tens of thousands of univariate statistical tests that you're doing. We all know that lots of those things can be significant by chance alone.

John Bellone 44:48
The more tests you give, the more likely you are to find a significant finding.

Lisa Eyler 44:51
Exactly, exactly. So there's things that the field has done to try and reduce the chance of false positives, but there was a lot of concern about that - the things that we've been doing were maybe not rigorous enough, and therefore, that there might have been more false positives out there than we thought. So people have tried to come up with some more ways to make better inferences about the results from fMRI. But, it's an ongoing thing. I think, just like with any kind of science, you also need to have replication across studies, not just control of that within a study. So I think it's important for people to take each finding with a grain of salt. But if you see a pattern across studies - for example, if there's a meta analysis and you see that in 20 or 30 different studies, then you can be a little bit more sure that that's kind of there. But then you get into, again, this idea of interacting regions. So, the interpretation that sometimes people have of fMRI is this area lit up therefore that area is involved in process X. So first you have to think about process X relative to process “what?”. Because, again, the control condition is important but also, clearly, that's not how the brain works. I mean, we know there's been a whole debate about localization versus a distributed processing. I think we pretty much have decided that there's probably not very many places in the brain that just do one thing and do that one thing only. And fMRI needs to be interpreted in that way, as well. So, you know, we see this part lit up, but that part didn't. Also what things were going into that that maybe didn't quite cross our threshold for significance. And so just because they're not a pretty blob on the brain, they might have been involved. And, you know, there's this whole thing about necessary versus sufficient, right? So I think it's really important for us to combine traditional neuropsychological studies that are based on lesions, for example in strokes, with what we see. Or localized damage from things like hypoxia and things like that with what we see with fMRI. Because just because something lights up, on average, in college undergraduates doing a task doesn't mean that that area must be involved, it just means that it was in that case. We really can't know whether it must be involved unless getting rid of it loses that function, you get a loss of function.

John Bellone 45:25
Yeah, we could do a whole episode on this. Functional neuroimaging.

Ryan Van Patten 47:27
But this is great. I have one more MRI-specific question before we bring ourselves back into the fold. If I allow you free rein to speculate and predict the future, when do you think or do you even think that fMRI will be useful clinically in terms of measuring cognition? Like, will future clinical neuropsychologists be able to put people in a scanner and use it in that way? Or will it remain a research tool for a long time?

Lisa Eyler 47:56
I think we're definitely not there yet. And I would caution anybody listening that if you hear of somebody that you're going to have to pay a lot of money to get an fMRI scan to help you diagnose your condition, or to figure out about treatment, I would be very, very skeptical of that.

Ryan Van Patten 48:13
Which is different from a structural MRI scan, which can be used clinically now.

Lisa Eyler 48:16
Yes, definitely. But there are people in our hometown here of San Diego, that are advertising the use of fMRI as clinical tools.

Ryan Van Patten 48:25
Oh wow.

Lisa Eyler 48:25
And with really not much evidence that I can see behind that, except for anecdotal. So I think there's a couple of problems with the current state of using fMRI clinically. That was certainly, I think, the promise that everybody thought was. So here's MRI, which is less expensive than PET and it has a really nice temporal resolution, so maybe we could find things about individual people that would help predict treatment response or be used for diagnosis, and that might be more sensitive than traditional neuropsychological testing because of the fact that it's like you're looking directly in at the brain. But I don't think that that promise has been borne out yet. I think one of the problems is reliability. There have been some studies out there about this. But, again, there are a lot of things that can affect acutely kind of what

somebody's BOLD response looks like to a task and there are fluctuations from day to day. If the task is not reliable, just like in neuropsychology, then using it to predict something it's going to inherently not be able to predict as well if it's not very reliable.

The other problem is a lack of norms. So obviously, in neuropsychology, we benefit from the fact that we've had a lot of people take the exact same tests. We have age and demographically normed tests. And for fMRI, we don't really have that because different tasks are used, different scanners are used, different processing is used. So there's nothing so far where you can kind of send your fMRI results out and then have somebody say, "Oh, your hippocampal activation is 1.5 standard deviations below the norm for your age group." So in the absence of that, it's really hard to say how that could be clinically useful at the individual level. One exception that I understand is going on in many centers is using fMRI as a substitute for the Wada test. If people aren't familiar, this is the test where you basically put one half of the brain to sleep in order to see, prior to epilepsy surgery, whether somebody has, you know, which side their language function is localized to etc. And fMRI has been shown to be equally sensitive to testing which sides are dominant for language as the Wada, and so it's a lot less invasive. So that's one clinical use for fMRI.

I think that there is this potential that we could develop biomarkers for early detection of cognitive decline in Alzheimer's disease, but we're not quite there yet. But that would be the other thing. Because, right now, I would say if somebody already has a disorder, good cognitive testing is probably much better than fMRI. Because you can do all the things that good clinical neuropsychologists do, right? Testing limits, you understand the context, you can do a retest really easily, you can understand how this has changed from premorbid baseline. And this is just hard to do with an expensive, really weird situation where the person's in the scanner and is looking through a mirror down at something at their feet. And it has even worse ecological validity than your laboratory neuropsychological test would. So I would say in most situations, you'd be much better off just doing a really well done clinical neuropsychological battery than fMRI. However, there may be some things that you could see prior to overt cognitive behavioral changes, that you could start to see in terms of how the brain is responding to these stimuli that could give an advantage to fMRI. But again, we're going to have to do a lot more longitudinal studies, and we're going to have to do a lot more norming to really understand what kind of pattern at Time 1 really predicts what's going to happen later on.

John Bellone 52:34
It made me think of another tangent. Ryan had a tangent, so I'm going to take a quick tangent too. [laughs]

Ryan Van Patten 52:38
Make it fast. 30 seconds.

John Bellone 52:40
Lisa, you mentioned that there are some clinics in San Diego - I think I know who you're talking about, remain nameless - practitioners who are using fMRI clinically. I've seen some clinics, maybe it's the same ones, that are using PET for diagnosing mental illness - bipolar, for example. I'm curious your thoughts about using other types of functional imaging, like PET, for clinically diagnosing mental illness.

Lisa Eyler 53:09
Yeah, I just haven't - I mean, show me the research. I just haven't seen the research to suggest that it has good sensitivity and specificity. And, honestly, although I'm sort of upset with people who try and sell things that don't have an evidence base, really, actually, I do think that us in the field have missed a little bit of an opportunity because we've been so interested in using these as research tools to compare groups of individuals, or even to look at correlations in individual differences within groups, that a lot of time we don't take that extra step of trying to compare our techniques to existing techniques and see whether they actually have improved sensitivity and specificity. I don't think people have been thinking about these techniques enough in terms of individualized medicine. Or undertaking projects to do norming. I mean, the problem is that norming is an expensive endeavor, right? And unless you're going to be selling a product that is supported by that, like PAR or something like that, where you put the money into it so that your product is more attractive. Unless somebody is going to somehow bottle a particular fMRI task and decide to see if they can sell it to consumers, there won't be this push to do the norming that's needed.

John Bellone 54:30
Maybe this is a business opportunity for someone out there to work on the norming of PET, let's say, in different diagnoses, mental health diagnoses.

Ryan Van Patten 54:41

Yeah. To your original question, John, when I think about the idea of using PET or any biomarker to diagnose mental illness, specifically, at a basic level, that seems off, right? If someone has depression, the best way to understand their disability is their subjective experience, right? So we're also in this episode tying psychiatric emotional illness and disturbance to physical changes, which is very important. But at a basic level that's why psychotherapy tends to be the best treatment for mental illness, right? So if someone wonders if you have depression, anxiety, or something like that, clearly in a more straightforward way, understanding their phenotype and their subjective experience, to me, is at least the best first step before biomarkers.

Lisa Eyler 55:34

Yeah, I agree. I think where biomarkers can be useful is in the circumstances where we could find some that basically precede people's own awareness of, or our ability to behaviorally test it - if we can find something earlier on. So in some of the work that I've been doing with young toddlers with autism, we're actually testing people that we're not sure yet whether they have autism because we can't really test it yet - maybe they're not even speaking yet, right? But if we can look at how their brain is responding to language stimulus and see that it turns out that that predicts who is going to have language problems, then maybe we can get them to treatment sooner. And in the realm of serious mental illness with bipolar disorder, I was actually talking to somebody recently that wanted to use the microbiome. It's a whole other topic [laughs]

Ryan Van Patten 56:32

[laughs]

John Bellone 56:32

We've already covered it.

Lisa Eyler 56:33

Have you? Okay, good. So they asked me, like, "What kind of study should we do to diagnose bipolar disorder using the microbiome?" Like, we could probably come up with a combination of microbiome things that would help with sensitivity and specificity decide who has bipolar and who doesn't. And I said, "I think that's totally uninteresting and unhelpful." Because you can just ask people what their symptoms are and we can decide whether they have our definition of bipolar disorder or not. I said, what could be helpful in bipolar disorder is that with bipolar, oftentimes, the first presentation is of a depressive episode. And in some people who start off with

depression - most people, if you come in and you say, “I'm depressed”, they'll give you a traditional antidepressant medication or they'll start you in therapy that's specific for major depression. But then some of those people will go on to actually manifest bipolar disorder and to have the swings into mania. And, as I mentioned before, the treatments that work for major depression don't always work for bipolar depression. So you may delay them getting the right kind of treatment for their depression. And in fact, it might make things worse. Some people say that if you have bipolar disorder and you're treated with a typical treatment for depression, that it can actually swing you into a bipolar episode.

Ryan Van Patten 57:58
The pharmacological treatment?

Lisa Eyler 57:59

Yes, that's pharmacological treatments. So if you had a biomarker, whatever it might be - neuroimaging, microbiome, whatever - that when the person first comes in, that you can tell the difference between somebody who's eventually going to actually have bipolar disorder versus somebody that's going to have major depression and never have a bipolar episode, that would be really helpful.

Ryan Van Patten 58:19
Yeah, perfect. I love that argument. I'm fully on board.

Transition Music 58:27

Ryan Van Patten 58:27

Well, that does it for Part 1 of our conversation with Lisa. Be sure to tune in again about two weeks from today when we release Part 2. Part 2 will conclude our conversation with her and then once we wrap that up, John and I will come on at the end and provide a little bit of commentary. Some of our thoughts about some of the interesting stuff we talked about with her. As always, join us next time as we continue to navigate the brain and behavior.

Exit Music 58:53

John Bellone 59:17

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Ryan Van Patten 59:29

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