Jarred Younger, PhD | How Brain Inflammation Causes ME/CFS

https://www.youtube.com/watch?v=8XrdSlpUQTE&index=14&list=PLl4AfLZNZEQPxjqF4ojAO3wdCFMeriNBK

Raeka Aiyar: Our next speaker is is going to be Jarred Younger, who's with us here from the University of Alabama, Birmingham. He's going to present some of the really interesting work he's been doing with longitudinal studies of CFS patients and looking at the neurology a little bit more closely.

Ronald Davis: I invited Jared here because he works on examining the brain and clearly the brain's involved in this. The stuff he does is way too complicated for me, (all laugh) so I'm really glad that he's come here and will explain this stuff. Thank you very much, Jarred.

Jarred Younger: Thanks Ron. Despite the fact my first slide has a really big glowing brain on it, I am going to start by talking about a finger, just briefly. What is the function of a finger? A finger bends, right? And it gives us some information about the environment. It can tell us if something's hot or cold or if it's sharp or dull.

Now what happens to the finger if it gets inflamed? If you have arthritis or tendinitis or you get a bad splinter in it or you get a snakebite and it all swells up, what happens to the finger? The finger becomes hard to bend, right? And it really stops giving you good information about what's going on around you because the pain starts to overwhelm all the other messages. So inflammation in the finger disrupts the function of the finger and that's true pretty much anywhere in the body we look.

If you look at your knee, inflammation of your knee makes it hard to bend. If you have inflammation of the gums, then your gums stop keeping out bacteria from your bloodstream. And if you get inflammation in your heart your heart stops beating blood as effectively. Inflammation in the body disrupts that part of the body, especially if it's chronic.

What is the function of the brain? A brain is our mood. It's our personality. It's our cognition. It's our energy, our motivation. It's our sensations. It's our perceptions. It's everything. If inflammation occurs in the brain and it disrupts the function of the brain it can affect anything and everything about us.

I'm going to do something that I actually told myself I was not going to do for my scientific career. I didn't promise anyone else, just myself, but I'm going to ask for a show of hands for a couple of things (audience laughs) in the talk, because I have two questions and I've never asked these before.

The first one is how many of you have ever gone to a physician or a clinician and you got a diagnosis of inflammation in your body. Tendinitis, arthritis, gingivitis, conjunctivitis, bronchitis, any kind of itis or any kind of inflammation at some point in your life. It's almost everybody, right? I see virtually every hand.

Now how many of you have gone to a clinician at any point of your life and you've gotten a diagnosis of brain inflammation, maybe meningitis or encephalitis?

Audience member: Does (inaudible) count?

(All laugh)

Jarred: That's a good question. I saw about five or six. We're having all this inflammation in the body, but so few diagnoses of inflammation, common or chronic, in the brain. How is that the case? How is it true that we can have so much inflammation in the body, but somehow our brain is safe from this? It's preserved from this. The answer is it's not. We do have brain inflammation. A lot of people do have brain inflammation. It's just that your clinician can't diagnose you with it and your clinician can't diagnose you with it because they don't have the tools to diagnose brain inflammation and they don't have the tools because the scientists and the engineers haven't provided those tools. So people with brain inflammation go undiagnosed and they go misdiagnosed and they continue to suffer.

That's the problem that I'm trying to solve. How can we measure brain inflammation in a way that it can be a routine screening so we can say yes, you have this, or yes, you don't, and indicate a specific treatment? That was a long introduction.

I am going to present some preliminary data that has not been discussed before. This is still in review for publication. I hope it comes out later this year. I will not go into extreme detail on it, because it's still in that review process, but I'll give you some some kind of general overview story of that. That was funded by Solve ME/CFS Initiative, one of the Ramsay Awards, and it allowed me to test 15 women with ME/CFS and 15 healthy controls. I'll show you some of that information.

I'm trying to come up with a way to measure inflammation in the living human brain. That is really hard to do. Now technically yes, you could take a needle, you could puncture the skull, you could siphon out some cells and siphon out some fluid and you could know if someone has a neuroinflammatory process. The problem, obviously, is that's not ethical, it's not safe, it's not something we could do with routine screening.

The inflammatory things are there to measure, it's just it's too dangerous to get to it. I have to find a way to do this non-invasively. Even if we could get to the brain how do you get to the deeper parts of the brain? Even if we get through that skull a lot of this inflammation will be occurring in the center of the brain, so this is a really big problem.

You can't sample it like you sample blood. We have to come up with something different. That's gonna be a neuroimaging technique.

Before I can tell you about the neuroimaging technique, let me tell you what we need to measure. What does that mean when we say there's neuroinflammation?

These are microglia cells. You're familiar with the inflammatory response in your body. In your brain it's kind of similar, but it involves different cells and different pathways. In the brain you have these microglia and these cells are usually ... you can kind of see in the top-left, they're usually in this patrolling state. They're looking around for problems, viruses or bacteria. When they find a problem they pull in those arms, those processes, and they take that state you see on the bottom right. That's a hyperactive, hypermobile, pro-inflammatory state.

When they're in that state they pump out a bunch of pro-inflammatory chemicals: interleukin-6, tumor necrosis factor alpha, interleukin-1 beta, you've heard these things elsewhere. These chemicals make the central nervous system adopt an attack state so it takes care of the problem, but those cytokines that are released do something else. They also change the way your brain functions and it causes something called a sickness response.

You might recognize these. You might recognize these with a lot of chronic illness and if you don't have a chronic illness, if you've ever had a severe flu, you will recognize these symptoms. This is kind of echoing some things you've heard before. These cytokines change the way the neurons function in a way to make you feel horrible. That's the design of it, as you heard just a little while ago.

It'll cause body aches and pains, severe fatigue. It'll make it hard to think, hard to concentrate, hard to memorize things. It may cause a little bit of anxiety. It'll slow you down, psychomotor slowing. It'll make you not want to be around people and it will lower your motivation and make things not as enjoyable. It'll just make you feel bad. Malaise. That's the function of cytokines released within the brain and the reason why that exists, as you heard, is to get you in bed so your body will fight off that infection and so you don't spread it.

There's a lot of different areas where these cytokines work. I'm not gonna go through the neuroanatomy.

The subgenual ACC controls a lot of the mood stuff. Amygdala, insula, these are regions you've probably heard of before, but we're not gonna go in those in-depth. I'll show you a few in a little bit, but there are several known regions that mediate these sickness responses when they're inflamed.

That's how these cells are supposed to work. They're supposed to detect a problem, they take that hyperactive state, they fight off the problem and they go back to normal. The

problem is, as we now know, that those microglia can adopt a primed state, a hypersensitive state, and then they look more like the upper-right. They're like angry microglia cells and they're hypersensitive and it takes very little to set them off. There's quite a few things that can push them into that state.

Once they're hypersensitive you may take a walk for two minutes and the cortisol you produce or the beta endorphins you produce might be enough to cause those now primed microglia to go into they're fully activated state, pump out those pro-inflammatory cytokines and make you feel horrible. Someone may get sick multiple times a day, because they can move in and out of this state within a few seconds. You have these triggers that should not normally make you feel sick that, because the central immune system is primed, it's reacting as if you just had a severe infection and all you did was take a walk. That's what we think is happening.

How do we pick that up? What I would love to do would be able to measure the cytokines directly, the interleukin-6, the TNF alpha. If we could measure those in the brain non-invasively, that would be incredible. The problem is we have no idea how to do that. They're too small and they're not made up of different enough stuff for us to pick it up with any of the known scanning techniques we have. If anyone has any ideas how to do that you can talk to me at any time. I would love to hear that.

In lieu of doing that, in the meantime, there are some things we can pick up with MRI scanners. This is a technique called magnetic resonance spectroscopy. It allows us to get things, like lactate. These are things that are associated with neuroinflammation. Lactate is something that in a healthy brain you should not see any of it and it's because you really only see a buildup of lactate when that area of the brain is not receiving enough oxygen and enough glucose to feed the metabolic requests. That means that something is going on that's so significant that the normal blood supply can't meet that demand and so it converts over to an alternative energy source and you get lactate production. We consider lactate, if we find it in the brain, to be indicative of neuroinflammation.

There's some other ones as well. I'm just gonna pick another one, myo-inositol, is something that you see in microglia, but not in neurons. If you see a lot of myo-inositol somewhere in the brain where there's supposed to be neurons, that suggests that the microglia have kind of crowded out the neurons and they're aggregating there.

We can use this scan to quantify a lot of things that indicate neuroinflammation and it allows us to get maps like this. I'm gonna switch over to the other side, so I don't ignore this side of the room. We can get 3D maps of the entire brain and this is really cool. This gives us the potential ability to take a patient, put them in the scanner, scan them for 20 minutes and be able to read that data as it comes out and say hey, there's something wrong here. There is a spot in your brain that has elevated lactate. There might be something going on here. A lot of potential with this.

It allows us to do patient versus control. This is on the right you see healthy a individual, on the left you see someone with ME/CFS. This is an increase of the neuroinflammatory markers. This is choline. We can look throughout the brain and say look, you have widespread neuroinflammatory markers.

Let me tell you some of the results. They look pretty good. For this talk I'm gonna focus mostly on lactate. You saw there were other things, but we don't have time to go through all of them. Just looking at lactate, lactate we found in our 15 versus 15 was elevated throughout the brain, in many, many regions of the ME/CFS brain, which is what we would have hypothesized, and it was in the direction that we thought it would be. You can see here on the left is an average of the ME/CFS brain. I don't know if you can kind of tell the orientation. We're looking down from the side and the brain's kind of top-half's cut off. That's what we're looking at.

You can see those red areas. Those are areas where the lactate is about four times higher than normal than what we see in the healthy brain. On the left side you see a normal brain where you do not see that elevated lactate in the middle. You do see on that outside edge, I have to mention that little red strip, that's an artifact of the skull. That's not real lactate. That's just some technical stuff we have to work out as we improve the scan, but you can see the elevated lactate.

Another shot where you can just see that throughout the ME/CFS brain, on average, there is elevated lactate.

What's interesting is these regions are regions that we know mediate the sickness response. These are not just random regions. It's not the visual stuff. It's not how you smell. These are regions that mediate sickness response. We see elevated lactate in the cingulate. This is where the malaise comes from, the suffering component and the fatigue. The hippocampus has elevated lactate in ME/CFS, which would suggest there may be problems with memory formation. The thalamus is the switchboard for the entire brain, all of the sensory information is coming through there. We see elevations in the cerebellum, which could suggest there's psychomotor slowing and general motor impairment. Then we see elevations of lactate in the insula and this controls a lot of how you feel in your body and also anxiety. These key sickness response regions, we're seeing elevated lactate in them, which is exactly what would happen if ME/CFS is a neuroinflammatory disorder.

There's something else cool we can do with this MRI scan and that is we can get brain temperature with it too. With the same sequence, 20 minutes. I'm not gonna tell you how. It's a pretty cool technique. It's a little trick that you measure distance between a couple of peaks and it has to do with the water shift with temperature, but we can reliably get absolute brain temperature from this sequence. What you're looking at is behind someone's head, their brain's kind of cut out, and we can get 3D temperature and we can

see your cool spots and your warm spots. We can see if your whole brain is hot or if there's certain spots that are hot.

Now, why would we look at temperature? Just like the lactate, if you have a temperature buildup in your brain that suggests that the metabolic activity is so great that the circulating blood can't cool it off. That should only happen if you have a neuroinflammatory response, because you can't think hard enough to have your brain go that high.

(Audience laughs)

What we're seeing is the ME/CFS brain is hot. It's hotter than a healthy control brain. These red spots you see on the left, these are about one degree Fahrenheit warmer on average than the control. Some of the patients have much warmer than that. On average it's about one degree Fahrenheit difference. That may not sound like a lot. In the brain that is a lot. That is enough to make you feel sick. If you go from a normal, like 99 Fahrenheit to 100, that's when you would start to feel symptoms. The brain is supposed to be very, very narrowly controlled with temperature, so this is enough to create the symptoms.

What's interesting is we're seeing the same regions where we see elevated lactate have elevated temperature. The insula and the thalamus and the cerebellum.

Now we're looking at from below. I switched it. The patients on the right. You can see the elevated temperature in the cerebellum. We get convergence of these different types of neuroinflammation centering on the same regions and that gives me a lot of confidence that we're actually measuring neuroinflammation.

Okay. Where are we at now? What are we gonna do with this? I do hope this will be a useful clinical scan, not just a research tool. We have to verify that it is neuroinflammation. I'll keep talking.

(Audience laughs)

The way we do that is there is a positron emission tomography, PET, scan that uses TSPO. We're back to the same slide? That's cool. You can inject it, this TSPO ligand, and it goes to the microglia cells and it specifically has affinity for the cells when they're in their activated inflammatory state.

There's a PET scan that's a marker for microglia activation, which we would say is a proxy for neuroinflammation. This has only been done one time in ME/CFS that's published and that was in 2014. This is the results of their studies.

Their main regions they found where the thalamus, the cingulate, and the hippocampus. Those are regions where there seemed to be abnormal microglia activation. Now, did

those regions sound familiar? They should, 'cause that's the same regions we found with our spectroscopy scan with elevated lactate and that's very promising.

They also found the midbrain and pons, which are lower down and we haven't looked there yet. We have the ability to, but I just haven't analyzed it. We may have matches there.

Those are the brain regions. This scan, this study has to be replicated. The ligand they used was really old and now we have much, much better radioligands to better mark the activated microglia. This needs to be done again. We do not have funding to do this in ME/CFS, though we just received a grant from the American Fibromyalgia Syndrome Association to do this in fibromyalgia, which I think is a related disorder, so that should be informative. Now we have access to fluorine-18, DPA-714, that's a much better marker. I think it's gonna be a tremendously important study to do to say whether or not ME/CFS is a neuroinflammatory disorder.

There's also a group at Stanford, Dr. Michelle James and Dr. Jose Montoya, are gonna be using a very similar compound to look at severely ill ME/CFS patients and so doing very similar things at different locations on different severity levels of ME/CFS. Should be very, very important. Within about a year you'll see some interesting things there.

Last a research slide and then I'll conclude. We just received a grant from ME Research UK, so United Kingdom group, to look at leukocyte infiltration of the brain in ME/CFS. What we think might be happening is T cells and B cells might be penetrating the blood-brain barrier, getting into the brain when they're not supposed to and contributing to this inflammatory response. Hopefully in a year we'll have the results from this and I can tell you whether it's the case. If we are able to find these cells in the brain it's gonna be really, really important to understanding the pathology of ME/CFS.

I was gonna tell you a story about how this tree got into this building. I don't have time, (audience laughs) so I'm gonna skip that. I've got something else I have to say. I have one minute.

I'm gonna conclude with something else. We could talk it with the drinks at five o'clock.

Audience member: You have two minutes.

Jarred: It's a long story. The point that I wanted to make is as you're hearing all these talks and we're all talking about different things. You've heard genetic stuff and metabolic stuff and T cell stuff and you've heard neuroinflammatory stuff and you'll hear more stuff. I hope no one's worried, trying to think which one of these things is right. Which one of these is the answer to ME/CFS, because I think it's becoming very clear, as we learn more about the body and more about ME/CFS, that all of these things are talking to each other and they're all working together. I think the problem with ME/CFS is this kind of ... these systems are holding each other in place in this pathological state and I think that's what

makes it so hard to treat. I believe we're gonna have to hit this from different angles at the same time.

I'm sorry it's taking so long, but over the last few days seeing the scientists work together and seeing the light bulb moments and the stuff from this field of science making someone in this field of science go oh yeah, now this makes sense, in the new collaborations. I know it's gone slow, but I can see it going faster and you'll probably hear that again. I find that really encouraging. It's a good time to be doing research in the field. That's it

(Audience applause)

Thank you to our wonderful volunteer transcribers for transcribing the Symposium.