How Dopamine and Methylation Shape Attention and Neurodevelopment Transcript

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MAPS Webinar Introduction

The default mode network has a ton of different functions, but it's involved in, for example, the sense of self and the idea that somehow you have internal representation of the world.

This default-mode network operates at gamma frequency when you're not attending to something else. But if something else catches your attention, then you have to turn off the gamma frequency of the default mode network so the other information can dominate your consciousness.

Turns out in autism, kids with autism don't turn of their default-mode network. Hi, welcome to the MAPS Webinar Series. Healing Tomorrow's Future. We are thrilled to be bringing you this series packed with valuable information and education within our community.

My name is Honey Rinusella and I am the Executive Director of MAPS, the Medical Academy of Pediatrics and Special Needs. Within these webinars, we're able to empower clinicians on the knowledge and tools to support patients facing a variety of health challenges.

For more information on MAPS or to register for a conference, please visit us at www.medmaps.org. Thanks for joining us on this journey towards a brighter, healthier future.

Dr. Deethu2019s Background and Dopamine Research

Hey everybody, welcome to the MAPS Healing Tomorrow's Future podcast. I'm Dr. Neu, president of the Medical Academy of Pediatrics and Special Needs. And my guest today is Dr Richard Deeth.

He's a PhD and gave us a fantastic presentation yesterday on some kind of mind blowing stuff. Now I got to warn you. Before we go too much farther, we're going to geek out on some biochemistry in this interview.

And this is what I love about this man. I learned more bio chemistry listening to him for 45 minutes than I did in my entire career in college and medical school.

So Dr. Deeth, welcome to the podcast. If you want to introduce yourself to our viewers. Well, thank you for that. And thanks for asking me to chat here and otherwise talk about what I love doing and being a part of.

That's the research that we're doing about autism and developmental disorders, what is really about the brain across the lifespan of our lives. by way of background, who I am and so forth.

I got a PhD in pharmacology from University of Miami. Go Hurricanes. They're playing, I guess, Virginia tonight. And after I get my PhD, in 1970, went to Belgium for a year, had a postdoc, came back.

and took a position at Northeastern University in Boston, where I was for 38 years. And that's really where i developed my interest, which was really understanding things at the molecular and even sub-molecular level.

I enjoy knowing exactly how nature does things and why they happen. How enzymes work, how receptors work and so forth. And while I was at Northeastern University, I took an interest in applying that interest, that molecular perspective to dopamine receptors and how did they work.

When they bind dopamine, how do they activate? How do the signal? And as I was understanding those events at the molecular level, I stumbled across, literally, a new signaling activity of dopamine receptors, but only one

dopamine receptor, the D4 dopamine and that receptor has a methionine residue that actually moves when dopamine activates the receptor.

It's usually hidden, it's occluded, but when Dopamine activates a receptor a movement, a few angstroms, ends up exposing it and then allows that methianine to donate its methyl group, its carbon atom, to the phospholipid molecules that are surrounding it in the membrane of the neural cell.

And so this was never known before. It's called phospholypid methylation, and dopamine-stimulated phospho-lipin methylation. And so we discovered that in about 1998 while I was at Northeastern University.

Didn't know exactly what it meant. When you discover a new signaling pathway, you have to ask what's the role of that. But it wasn't too long before we connected it to attention because that D4 dopamine receptor, which is the only one with the methionine that can do that, is linked to ADHD.

It's one of the most, if not the, most important risk factor for ADHD, so I began to explore the possibility that that methylation process, phospholipid methylation, might play a role in attention.

And now we've been doing that for 20 years or something more, 25 years. And what we now understand is that the phospholipid methylation that's stimulated by dopamine here influences the synapse.

The other proteins that are clustered around the D4 receptor feel that. They feel the change in their membrane methylation and as a result they modulate their activity a little bit.

It includes things like NMDA receptors and channels and pumps and so forth. And that changes the firing frequency of the neuron that the D4 receptor is embedded in.

These happen to be GABAergic interneurons, and they, when they're affected by dopamine, they increase the firing rate of their neural networks that they are a part of.

And that increase ends up bringing the fire ring into the gamma frequency range, which is 30 to 80 hertz. And that's pretty fast. And the fast firing in the gamma range brings the information in that particular neural network into your consciousness at a higher level.

When it's happening every 40 times a second or something like that, it becomes the dominant information.

Attention, Gamma Activity, and Autism

That's what you're noticing and attending to and so forth. So you're actually creating a molecular network for attention itself? This is a Molecular Explanation for Attention, and that was pretty much the title of the book that I wrote in 2003, now 23 years ago.

And I linked it to the Full Weight Pathway because that activity, the methylation, depends upon methionine synthase, a folate-dependent enzyme that's highly sensitive to oxidative stress, and that helps explain why attention can be oxidated stress sensitive.

Also, it can help explain in supporting this activity there. So in that case, that launched an interest in attention and I got invited to a Dan meeting, Defeat Autism Now meeting.

I think it was 2001 maybe, something like that, maybe 2002. And from then I was able to see the relevance to autism and things took off from there One of the things you spoke of yesterday was this concept of default mode network and how that develops and dysfunction in that might be linked with autism.

Maybe you can explain a little bit of that. Before you do, I just want to point out to all my psychiatrist friends that behavior really is neurologic.

It's all based on these molecular pathways and what you were talking about with all of us know we're going to use a dopamine agent, a drug to simulate dopamine receptors, but how does that actually get us to focus and attention.

And that's a great explanation there. Well, that what I wanted to do now and yesterday, my talk was to take this sort of biochemistry, if you will, and even the network activation and try to move it along toward things that we actually see in autism, which are really behavioral outcomes.

And you have the triad, repetitive behaviors, socialization, and language deficits, these things. So looking into that, as it turns out, of course, they derive from the firing rates of neural networks here.

And I started to think about and otherwise investigate the role of gamma activity and attention in building the networks from which behavior arises. So when we look into that, when you're born, the dopamine attention mechanism is not functional.

When kids are born or we're all born if you will, the neurons where the D4 dopamine receptor resides have not yet developed. Nature holds back on those neurons until prostnatal development.

And during that time networks develop and they develop in response to attention. So, in other words, if Kid A experiences something having to do with, let's say, the color red or something like that, then he'll start to incorporate that into his attention and to his networks and his brain experiences.

Whereas somebody else experiencing color red, not red but color green instead, might have different experiences. So in any case, the experiences start to build your networks as memory and so forth is developed.

And this ends up creating networks that can operate at the gamma frequency, as I mentioned. And it turns out that the networks that develop earliest include the default mode network.

Default mode has a ton of different functions, but it's involved in, for example, these. a sense of self, and the idea that somehow you have internal representation of the world, also that other people have an internal self.

And this default mode network operates at gamma frequency when you're not attending to something else. But if something catches your attention, then you have to turn off the gamma-frequency of the default-mode network so the other information can dominate your consciousness.

So it's like internally-derived consciousness versus externally- derived consciousness And it turns out in autism, kids with autism don't turn off their default mode network.

And so their ability to take in and respond to the external environment is impaired in that regard. They're really driven behavioral-wise by their internal default-mode network being on all the time and not turned off.

Oxidative Stress, Aluminum, and Inflammation

You had spoken in your presentation about how environmental toxins and particularly some of the toxins in the vaccines can impact the function of that default mode network and things in general.

You want to explain that a little bit in terms of how those things can affect behavior. Thanks for asking that because once we have a picture of the molecular events and we translate them up to that behavioral level, you have to ask a question about what is it that goes wrong when that doesn't work out right.

and when you have a developmental disorder like autism in particular. And we know that autism has biochemical features, it has oxidative stress, has impaired methylation.

They fit right in, because the enzyme, B12 enzyme methionine synthase that supports that methyllation activity, is built by nature to be sensitive to oxidation.

So it's going to be turned off when there's oxidative stress, so implying right away that attention might not be normal, especially external attention under conditions of oxidated stress.

So we could see how that would happen. And then the question becomes, what causes that oxidate stress? And if we're thinking of early development, which we are, what kind of things that could be generally widespread exposures that would occur within the first couple of years?

There are things, pesticides, herbicides, BPA from plastic lining and stuff like that, but really aluminum and the immunization itself come to mind. because it's been something that's certainly been linked to autism for years, and so we currently actually are looking in more detail about that, but it is well known that aluminum causes oxidative stress.

Everybody in the medical world would agree to that. So even the oxidative stress of aluminum is enough to say that could be a factor in causing default mode network problems and so forth.

But there is also things that aren't adequately known about aluminum as is adjuvant in vaccines. There's always been uncertainty, there still is uncertainty among experts.

as what exactly it is that's causing its adjuvant activity and so forth. And we've been studying inflammation, studying the NLRP3 inflammasome. So we are currently, and over the last few months, I would say, been looking at the effects of aluminum on that process, because the nLLP3-inflammasome is activated by oxidative stress.

So there's an obvious link right there. But during my talk here, I also brought up something novel, which I think is exciting and worthy of our investigation, but others too, that aluminum interferes with what are called iron sulfur clusters.

For any audience, this might be a challenge. It's not an everyday topic. That's why I didn't know about it much until I took the time to look into it.

So iron and sulfur clusters, you got maybe four irons and four sulfurs that form a cluster. And these things have been around since the beginning of life.

and they form a fundamental functions in certain enzymes and in a certain situations like mitochondria, the complex one of the mitochondrial electron transport chain, it's got eight iron sulfur clusters to it, carrying electrons along.

And so does the enzyme known as aconitase, it's part of the Krebs cycle for providing energy in the form of NADH that the mitochondria use to make ATP.

So, in any case, I looked into, and we're looking into now, this aconitase enzyme as a potential target for aluminum because it's in the literature. There's papers saying that, oh, aluminum, because its plus three, it interferes with iron-sulfur clusters because the iron is plus 3 as well.

And as result, if interfered with acotase activity, And actually Dr. Jill James, whose work has been fundamental in autism, she published a paper a number of years ago looking at the brain aconitase activity in Autism and found that it was low and in proportion to the oxidative stress level.

And so I'm thinking these days that we need to learn more about aluminum's effects because that aconitase enzyme helps produce a shortcut in the Krebs cycle called the itaconate shunt.

And the itaconate molecule that's produced during inflammation depends upon the aconitase activity to produce that shunt. And if aluminum blocks that, then maybe with less of a shun you don't have the effects of the Itaconates that normally occur here.

This is a challenge, it's a new area I didn't know about, but hopefully your audience will maybe start to think about Itaconate and think that it may have some role to play, because in macrophages in particular, It rewires the

macophages, changes them in terms of their gene expression, their activity, and usually the Itaconate inhibits inflammation.

And if you don't form it, maybe aluminum blocks that, then the lack of it will allow inflammation to be overexpressed and to not go away, not be turned off when it shouldn't get turned on.

Yeah, you could certainly see that. And by the way, never heard of a taconate priority yesterday, so don' worry about it. That's a new thing. All right.

So you have the situation where on the one hand, you're stimulating inflammation through NLRP3, that's going to create problems. And then you had this secondary pathway with the tachinate where you are not creating something that can lower the inflammation.

Am I getting that right? Yeah, the attackinate normally actually inhibits the NLRP3 itself. One of the things that makes this attackinate fascinating is its chemical properties allow it to bind to sulfur groups, to thiols.

Itaconate, Immune Regulation, and Closing Remarks

And if there's a sulfur group either floating around free, like homocysteine, for example, and form a new chemical compound, but on the NLRP3, there's these sulfur groups, the attackinate can bind to that, and so it inhibits, turns off your inflammation, what if you don't have enough attackinate?

Inflammation is going to keep going. That's great. The nice thing about listening to you, and why I love listening, is you're giving us these pathways for how these compounds can actually create these behaviors that we're seeing over here.

Yeah, it's a personal pleasure to be able to at least verbalize these things, bring them out and communicate them to the scientific and the public community, medical community here.

But they're all subject to scientific verification, because even though I have confidence in these things, in order to be really respected and to acted on, then they have to have general scientific validation, if you will.

So the taconate story is relatively new. It was only appreciated for this macrophage immune activity about six years ago, eight years or something like that.

So it's relatively knew. And people have shown some amazing things that it does. Like it seems to be involved in aging and slowing down protein synthesis as you get older like me.

You don't make proteins every day. Don't turn them over like when you were five years old or And it looks like the attackinates effects are associated with that with, you could think of it as like graded inflammation across the lifespan and so forth.

So we'll have to wait and see. I think it's going to play out over time as more people investigate that. Awesome. Well, how can people get a hold of you?

Oh well, I'm available, generally speaking, and I have to say we need funding for our work, but otherwise I am at Nova Southeastern University in Fort Lauderdale, Florida now.

have a lab there with enough people to keep things going and so forth. I'm at rdeth at nova.edu, that's n-o-v-a dot edu. And you can contact me there.

I'm sure if they contact you, you'll pass along my contact information as well. But I am certainly open to interacting with whomever, especially to advance some of these ideas and see how they fit into the autism explanations.

Well, thank you so much for taking the time today. I really appreciate all the work you're doing. You really have

made a huge difference for the autism community.

Well it's great to hear anybody say that, but to here you say it in particular means a lot to me. So thanks for that. Alright. Thanks so much for joining us today.

I'm Honey Rinusella, and this is MAPS. As we heal tomorrow's future, we appreciate you joining on the journey. We'll see you next time.