



## Conscious Life presents

### Balancing Neurobiological Pathways to Heal Trauma

**Guest: Dr Austin Perlmutter**

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#### **[00:00:09] Alex Howard**

Welcome everyone to this interview where I'm talking with Dr Austin Perlmutter. We're talking about neurobiological pathways and how they relate to trauma and mental health. We're talking a lot about neuroplasticity. If you've wondered how trauma can shape us, but also how we can work to reshape that, and how to ultimately set ourselves up for optimum health and well-being, I think this is going to be a really good interview for you.

To give a little bit of Austin's background. Dr Austin Perlmutter is a board certified internal medicine physician, New York Times bestselling author, published researcher, and international educator.

His mission is to help people improve their health by targeting the biological basis of stuckness in our brains and bodies. His writings, presentations, podcasts, and online educational programs explore how environmental factors influence our cognitive and mental state, and have reached millions.

Dr Perlmutter currently serves as the Managing Director at Big Bold Health, a food as medicine company, focused on helping people rejuvenate health through better immune function. He is running a first of its kind study exploring the effects of plant nutrients on human aging through epigenetics. So firstly, Austin, welcome and thank you for joining me again.

#### **Dr Austin Perlmutter**

Alex I'm so happy to be back here with you.

#### **Alex Howard**

Why don't we start giving a little bit of shape and context to where we're going to go in this conversation, which are laying out some of the major neurobiological pathways that are involved in mental and brain disorders.

## **[00:02:06] Dr Austin Perlmutter**

Let's be clear, mental and brain disorders are the most important thing in the world. The reason I say that is because if you trace back all the things that we care about, our ability to enjoy life, our ability to participate in life, these things are a direct manifestation of our brain state, which tells us how we think and how we feel.

There's still a strange setup where we look at our feelings, at our thoughts, as somehow separate from what is happening in our brain. But I believe that there is so much power in understanding the pathways involved in our brain that drive our mood, that drive our thoughts, because then we can act on them. Then we can understand how our modern world is programming our brains for the better, or for the worse.

So what are those pathways? There are many. A couple to be aware of include neuroplasticity. So the idea that our brain is constantly changing the strength and number of the connections between the neurons.

Another one is the immune system. We think about the immune system as something that gets activated or deactivated when we get sick. Well, it turns out that around 15% of the cells in our brains are immune cells. They have a huge role to play in mood disorders, in cognitive issues. So the immune system is big.

We're also learning the role of metabolic health on our brains. You think about the brain is only a couple of pounds, but it uses up around 20% of all of the energy in our body. The reason is because our neurons use a ton of energy to reset and transmit signals. So when there are issues with that energy, there are big problems that can develop in our brains.

Other things to consider would be neurotransmitters. We've heard of molecules like serotonin and dopamine. There are a number of them. Many like GABA, Glutamate, and these are molecules that transfer signals between neurons, and also fine tune the way that data is transferred between neurons.

And then one more that I'll just throw out, which I think is really important is the endocrine system, it overlaps with metabolic health. But the endocrine system is basically a system of hormones. And by definition, a hormone is a molecule produced in one place that has effects somewhere else.

So many viewers know about the HPA axis and hormones like cortisol. But we know that there are a wide range of hormones involved in endocrine signaling in the brain. Things like insulin, as well as ghrelin, and leptin, and a number of other hormones that are produced in our gut that may have effects on our brain. I think that's the playing field as it relates to some of the key pathways involved in our brains.

## **Alex Howard**

I think often we tend to get focused on the symptoms of these pathways not being optimized, as opposed to taking this step back and looking at what's actually going on here. Maybe you want to say a few words about some of those mental and brain disorders, which are a product of these pathways not working effectively, just to really land that in people's understanding.

**[00:05:05] Dr Austin Perlmutter**

Sure. I would say all brain issues are a product of our pathways not working effectively. It's not like there's some extra data that we're missing out on here. How we think, how we act, how we feel is a direct manifestation of basically our brain structure and function. I think there's a ton of value in understanding psychology.

If your person is feeling stuck and they're feeling like they're just keeping on looping over those same pathways time and time again, a psychologist, or a therapist, or even just in conversation, you can understand how that may not be adaptive, and how it's important to think about things in another way.

I think the biology here, which is really what we're describing neurobiology, is another really important part of the process. So as an example, certain people get stuck in loops of rumination where they're worried about the past, and other people get stuck in loops of anxiety about the future.

We know that, for example, the default mode network is a series of interconnected hubs within the brain that has something to do with self-referential thinking. And certain molecules, in this case I'm referring to psychedelics, in the right set and setting, have been shown to quiet down this network, and in doing so may have an effect on us not ruminating as much, and not having so much ego.

Now, I think there's some really interesting work being done around things like inflammation and neuroplasticity. Research shows that by and large, people with certain mental health conditions may have perturbations in their immune system that tend towards inflammation. Some good examples would be major depression, PTSD, and even schizophrenia.

Now, that's important because if we look at therapeutics that can basically lower inflammation in the body, and quiet down the brain's immune system, those may have more efficacy in people who have higher levels of inflammation to start with. It helps to explain why certain diets, for example, a Mediterranean pattern diet, have been linked to lower levels of depression, because we know that that is a diet that tends to bring the immune system closer to balance.

As it relates to neuroplasticity the idea that our brains are constantly being rewired, that neurons are forming, shaping connections between themselves and in networks, we know that certain therapeutics may act on neuroplasticity. For example, Ketamine, which has now been used in many clinics around the United States, is thought to work in part by increasing neuroplasticity.

But we also know that exercise is an amazing thing for neuroplasticity. We know that exercise increases a molecule called brain derived neurotrophic factor, which is critical to neuroplasticity. And this might help explain why exercise has been shown to be effective in large scale data, and having antidepressant effects in certain populations.

I think it's really helpful to think about what are the things all of us can do today to get our brains into a better state of health. But as we start looking at where things go significantly wrong, it's really relevant to ask what pathways might be at play here? Because that will help at some point. I don't think this is being applied in clinics just yet, but it'll help us at some point to understand what are the interventions that make the most sense for a person, based on what we expect and at some point can measure, is happening in that person's brain as it relates to these pathways.

**[00:08:17] Alex Howard**

What really comes to my mind as you're talking is that to be really effective in terms of intervention, we have to diagnose what's happening. So often the interventions are treating symptoms rather than treating what's really going on that's causing those symptoms. So it makes a lot of sense what you're saying, that we need to make sense of, and have a map of, these pathways to address that, and then the symptoms are going to take care of themselves.

**Dr Austin Perlmutter**

That's right. Let me say one thing, I live in a world of science where I want to know about each pathway, exactly how it's being perturbed. I'm involved in research where we measure really nuanced levels of some of these pathways, including the immune system. But I will say, as an overarching theme, the immune system in particular is an important place to start. And the reason for that is, if you look at the top causes of death and disability around the world, they're all really related to the immune system, to imbalances in the immune system.

We know chronic inflammation in the body, linked to heart disease, linked to cancer, linked to diabetes, linked to obesity, and so on and so forth. But chronic inflammation in the brain is now being recognized to be a driver of a number of issues with the brain, including decreasing neuroplasticity, which might explain why it's linked to worse mental health states.

I think everyone should be involved with taking steps to bring their immune system back into balance. Whether or not you get lab testing or go in and see a doctor, each day we are making changes to our immune system with the decisions we make.

So getting some exercise is a vote for a more balanced immune system. Eating real food as opposed to processed food is a vote for a more balanced immune system. Engaging in stress mitigation techniques, same thing. Getting good sleep, same thing.

I think that while it really does make sense for people who are at the extreme end, meaning that they're having such significant symptoms that they need to see a provider to get a more nuanced approach to these things. I think everybody needs to be paying attention to, what am I doing today that is helping to bring my brain to a state of better balance? I think the immune system is a great place to get involved in that conversation.

**Alex Howard**

You mentioned the immune system, you also mentioned one of the interventions being exercise. But let's talk a bit more about, what are some of the lifestyle factors which ultimately influence our neurobiology?

Everything we do influences our neurobiology. And the reason I'd say this is, if you think about what's going on inside your brain right now, I guess your brain Alex, everyone's brain has somewhere around, let's say, 80 billion neurons, which is a lot of neurons.

And it also has an equal number of what are called glial cells, which were once seen as support cells, but really are playing an active role in how our brains work. That's where these brain immune cells are called microglia participate, they're glial cells. But let's say somewhere in the

neighborhood of around 160,000,000,000 cells in your brain, probably a bit more, and then connections by trillions of synapses.

**[00:11:2]**

Our brains are really, really good at trying to keep us alive, not necessarily good at keeping us happy, not necessarily great at making us make healthy decisions. But in order for us to stay alive, our brains have become super skilled at taking in data from the outside world, and then changing themselves to increase the odds that we deal with whatever threats are available.

That could be something as straightforward as saying, you watch stressful news on TV, so the brain is going to activate the HP axis, going to activate stress hormones, and it's going to put you in a state of high alert because your brain perceives danger.

Now, food also impacts our brain function, not only because food actually becomes the actual building block of the brain, but because it sends data from the outside world, as far as what's going on. And some of that is direct from nutrients that come from our food, and some of that is coming actually from the microbiome, which is influenced by our food.

In addition, we know that, for example, exercise sends data to the brain in the form of these molecules called myokines. And if you're going to say, where are we going with the future of mental and brain health? Myokines is definitely one of the places I would say to look for. Because it's long been taught that you exercise and something, something happens, you just feel better because you're moving your body. Well, it turns out that when you exercise, you produce these molecules out of your muscles that get into your bloodstream and speak to your brain, and modulate things like neuroplasticity.

### **Dr Austin Perlmutter**

They have interesting names like irisin. But the point being here that our moving through life, the motions we actually make, what we consume through our mouths, what we take in through our eyes and our ears, the air that we breathe, all program our brains for the better or for the worse. And that's just the way our bodies and brains are set up, because the brain has to be aware of what's happening in our environment to keep us alive.

That can be a little bit daunting. We say, well, everything I'm doing is impacting my brain. But I think that's an incredible opportunity because it means that everything you do is a chance to wire your brain for better health. Every food that you eat, every piece of content you consume, every conversation you have, every decision to either sit on the couch or go for a walk, is actually a reprogramming vote for your brain. There's nothing that isn't participating here. And that, again, can be scary, but I think it's opportunity.

### **Alex Howard**

You mentioned food. Food is one that often people will connect with digestion, maybe they'll connect a little bit with mood. But as you've already touched on, food is impacting so much more than that, particularly in terms of what's happening in our brains. Maybe you can start speaking a little bit to that piece.

## **[00:14:11] Dr Austin Perlmutter**

I think people have always known that food has a major impact on our health, including our brain health. There's a movement right now for Food is Medicine which is the government, some academic institutions, some commercial institutions, in essence finding that food can help to reverse disease and prevent disease.

But people for thousands of years have recognized that food has a role in our health. Ancient Egyptians gave prescriptions for food in order to reverse things like night blindness. We've all intrinsically known that food does something to our health.

In the last 100 or so years, the dominant theme has been that food is calories, and that food helps to prevent deficiencies. We don't want to get scurvy, we don't want to get beriberi. We need to make sure that we have enough vitamin C, enough vitamin B and of course we need enough calories so we don't starve to death.

But the reality is that each bite of minimally processed food, and this is important, real food is comprised of thousands of different molecules. And if we only are thinking of calories, or only thinking about even vitamins and minerals, we're really missing the majority of the conversation.

For example, if we eat a plant, that plant contains some group of these thousands of nutrients called phytochemicals that are used by the plant to defend itself against its environment. But we know that these phytochemicals with names like rutin and quercetin may have an impact on our health.

Think about food not as calories, think about food not even as macros, or vitamins, or minerals, but as a ton of data that is programming our bodies. How does it do that? Well, the first stage is that it has differential effects based on how it gets incorporated into our cells. For example, if you ate a diet rich in omega 3 fats you might put more omega 3s into your neurons, as opposed to omega 6s, and that seems to be of benefit to neuronal health.

Beyond this though, we know that food programs the microbiome, and the microbiome itself creates a whole host of molecules that are absorbed by our bodies and can influence overall and brain health. Including, for example, short chain fatty acids. I'd say that's the best example of what we know about, as it relates to the microbiome and how it programs our brains and our bodies.

We know that food programs the immune system, specifically the gut immune system, but also the immune system throughout the body. A Western pattern diet which is rich in ultra processed foods, added sugars, preservatives, is one that leads to an immune system that's out of balance, chronically inflamed and that, as we've already discussed, is a risk for overall, as well as brain health.

Consuming more of a Mediterranean pattern diet rich in plants, nuts, seeds, minimally processed foods in general, more fish and poultry than red meat, is one that is associated with a better microbiome health, with a better state of immune state, as well as lower rates of mental health issues, and potentially lower rates of Alzheimer's disease.

Why is that the case? Well, the Mediterranean Diet again, programs the immune system, programs the microbiome, and may create molecules that help to generally keep all the pathways that we've discussed in the brain in a state of relative balance.

**[00:17:26]**

I think there's something to be said here as far as, wow, that's really interesting, Austin. I didn't know all this, but what does it mean to me? And it really comes down to the basics here as far as saying, we've been recommending, and doctors and other health people have been recommending, that people eat a more balanced diet, that they get exercise, that they eat fiber and plants.

And the reasons for that tend to be, well, people have better health when they do these things. But if you really want to get excited about this, I think you can say, well, this is a vote for a healthier microbiome. This is a vote for a better balanced immune system. And when you layer that into what we discussed at the start of this interview, as far as what are these pathways doing in the brain? You see how it's all connected and how the small things we do each day compound to get us better health outcomes.

### **Alex Howard**

Well, I think that's an interesting point because I think people often think about it in, well, I eat that and I feel fine. There are certain people that may have food allergies or intolerances, and they simply can't eat certain foods. Other people may not have an immediate obvious negative impact. And so it potentially becomes death by 1000 cuts, as opposed to one single thing which is a major issue. I think that can sometimes make it trickier for people to recognize these impacts, but also it can make it harder to engage with doing something to change them. Because they're like, I feel fine.

### **Dr Austin Perlmutter**

That's absolutely true. And it's one of the reasons why we see so many young people basically engaging in unhealthy diets, engaging in unhealthy habits because they haven't reached the point of inflection where something's gone wrong enough that they say, I need to pay attention to this.

Everyone has their moment where they realize their body is not the same as it was when they were in their twenties and thirties and appreciate that. They're getting injured more easily, or they're upset because they're gaining more weight, or they're upset because they have less energy, or maybe their mood isn't as good as it used to be.

But many of these things, I'd say most of these things, and for most people it's the slow build. And that slow build matches what we would expect to see because what is happening under the surface is progressive metabolic dysfunction. It's insulin resistance, it's trouble managing our blood sugar, it's chronic inflammation. It's throwing these hormonal pathways out of whack. And it may not mean that you wake up one morning and say, oh, my goodness, things are really wrong and they were fine yesterday. Because what we're talking about here is the compounding effect of decades of unhealthy choices on our bodies.

But what I would say is anybody who's watching this cares enough to learn more. Cares enough to say I'm curious. And I think really curiosity is the first step in this process. Now you can get curious because you're in pain and you say, well I'm curious about what I can do to get rid of this pain. You can get curious because people in your life are in pain, or you can just be curious about science. But I think that's really where this whole thing starts.

**[00:20:26]**

Because as much as it's fun to wait until things go wrong and then try to see your doctor, or try to find the fix that's going to get rid of every ounce of fat that you've accumulated in the last few decades. That's the standard mentality I would say growing in the world, especially over here in the United States is, do nothing, live for the moment, and then things are going to go really wrong at some point, and then you'll seek care. But to fix health care, to fix our own health, and our mental health, we've got to be preventive with it.

I think prevention really starts with finding the thing that you care about, and that you're curious about doing something about. I don't tell people you have to do everything. You don't have to fix your diet, exercise, start sleeping better, meditate for 30 minutes a day. All of these things are great.

But realize that the default option for most people is going to be basically being unhealthy until things go so wrong that you get put on medication, that you're told you need to be doing something now that's extremely aggressive for the rest of your life. And any opportunity we want to live healthy and meaningful lives necessitates that we do something different from what the average person is doing.

So again, there are a lot of ways into this, but I think curiosity is the first step. And curiosity can come from pain. That's the most common way that I see it. But it can also come because of a sense of things could be better. And I know that it's meaningful for me and for the people around me. And if you're coming in at that point too, I think it's fantastic. The goal here is just to find something that you care about enough to start making a change.

### **Alex Howard**

One of the impacts of trauma obviously is on these pathways. But another impact of trauma is the coping strategies that we develop to try and manage that nervous system dysregulation, and that emotional pain and so on. It strikes me that the relationship with trauma here is really twofold, it's one, the way that it impacts these pathways. But number two, it is the lifestyle changes that we may make to try to manage those feelings, that actually perpetuate the very problem cycles that you're speaking to.

### **Dr Austin Perlmutter**

Yeah, I think what makes brain health so unique, complicated, and also a place of opportunity is it's really hard to study the thing that is, basically it's hard to look at the thing that you're looking at, or that's looking, I should say. So we could talk about my knee is painful and I see the knee, I can point to the knee, I can tell you about the pain, and I can make a change there.

But when it's our brains, and it's literally our brain reprogramming that is the issue, it's hard to see it with any level of objectivity because the person who's doing the seeing, is also the one who's having the experience of these brain pathways being rewired.

I talk a lot about this idea of getting stuck, getting stuck in our biology, getting stuck in our psychology, and I think around the brain that's really the best example of this. Because the more we do something, the more we think a certain way, feel a certain way, the more likely we are to



continue to do something a certain way, think a certain way, because of the fact that we are rewiring our brains.

**[00:23:49]**

I've heard a lot of analogies, but I really like the snow analogy which is you start out clean snow, white snow and as you walk between A and B you forge a little path. As you keep doing that, you basically pack down the snow. And it is the most likely thing that at any given time you're going to take that same path, because it's where you're used to walking.

I think there are certain aspects of this that everyone is able to make changes around. And that's why I'm such a big fan of the neuroplasticity piece, because there are things we can do to help enhance neuroplasticity. It's also one of the reasons I highly suggest people seek professional help when they're having significant issues with this, because it can be really hard to do this mental surgery on yourself, when you're not able to get good perspective on the things that need change.

This is just my general appeal to this, which is if you're somebody who's really struggling with these types of things. I'm all for lifestyle modification, all for exercise, diet, so on and so forth. But there are some people for whom it's not about knowing those things are helpful.

I've been in this situation many times where I've told people, hey, really what you need to do is change your diet. Or really what you need to do is start exercising. You need to start meditating, working on your stress, so on and so forth. But they can't do it.

And in part they can't do it because their brain isn't set up in a way that allows them to do it. So that's a really important point. I think it's something that really benefits from people having somebody else on their team, that's able to support them through some of those changes.

Because it's really hard to change the thing that when you are the person that's trying to change yourself specifically around your brain, there's not a lot of distance between the person who wants the change, and the thing that needs to be changed. And sometimes that gets all conflated and it's really hard to break that up.

I think your point is well stated, and I think this is the scenario in which it's really helpful to get some outside assistance, sometimes when this stuckness gets too significant.

### **Alex Howard**

I want to talk a bit more about how we can rewire our brain, how we can leverage the power of neuroplasticity. I really appreciate what you said a little bit earlier about the importance of curiosity, like that first step, really getting curious about what's happening.

As that curiosity allows us to have some clarity and to start to see the beginnings. Like a lot of these things, I imagine for many people, it reveals itself as they go down the path and you can't always see all the pieces at the start, but what's often some of the next steps beyond that initial understanding and curiosity, what can we start to do to start to create change?

## **[00:26:38] Dr Austin Perlmutter**

There's something that I say sometimes which is, change isn't optional as it relates to the brain, but directing that change is. And what I mean by that is, there's no way to opt out of neuroplasticity, or to opt out of brain change, that is intrinsic to how our brains work. So every day, whether you like it or not, you're changing your brain. You Alex are a different person today than you were yesterday, because your brain is set up in a different way than it was yesterday.

And most people, most of the time, I feel like just allow that programming to happen based on whatever's available around them. If we're spending 4 hours a day, in the United States at least, watching TV, that means we're allowing 4 hours of our brain's rewiring to be driven by whatever we're taking in through the television.

If we're spending 2 hours, 2 and a half hours in the United States now, on social media each day, that means we're allowing social media to do the brain rewiring for two plus hours a day. And so the first point I would make is, you don't get to opt out of neuroplasticity, but you do get to opt into directing that change.

So that means that literally anything that you do in a given day that is pushing that change towards a more positive state. And we'll go over some of the reasons why that may be the case, is a significant benefit to your brain health.

I think there's this idea that we all have to have these transformational experiences, our hero's journey, and it's a great thing, I'm not basically taking away from that. But realize that at any given moment you're having the opportunity here to direct your neuroplasticity. It doesn't have to be this incredible moment where all of a sudden switch goes off and you have this life changing realization.

These changes, these life changing changes, are happening at a very nuanced level between your 80 billion neurons each day. And so recognizing that even the little things matter a lot is really important to that.

Now as we think about how do you direct that change for the better? And this is important I would say, too. Neuroplasticity is an agnostic term. It doesn't mean it's for the better. Neuroplasticity just means your brain is rewiring itself. So if you are taking in a full day of stressful news, neuroplasticity is working against you. You're wiring your brain for stress. So you're going to feel stress that night. The next day you're going to wake up and still carry over some of that because you've changed your brain wiring.

So the goal is to wire it for your own health, for your betterment. And to this end, I would say you need to open up neuroplasticity. And the way you can do that is just by doing new things, basically having new experiences, learning new information.

Exercise also enhances neuroplasticity by increasing BDNF. And then you say, well, what is it that I want to put into this? So if you think about neuroplasticity as like a shopping bag that you would fill at the grocery store, and you realize if you're not paying attention the grocery people will just fill it for you with junk food, that you actually have to be the person in the grocery store putting in the healthy food.

**[00:29:51]**

So what are the signals that you want to tell your brain? You want to wire it for positivity. You want to wire it for meaningful connection. You want to wire it for generally better health. And that's where we really start to talk about the fundamental meaningful things in human life.

Are you filling your shopping bag with junk food? Because why not? Or are you filling it with things that really are going to enhance your health? So some examples of this would be, we find meaning in our connections with other people. Having meaningful interactions with other people is wiring your brain for better connection and better health. So calling up a friend, or a loved one each day is wiring, using neuroplasticity to build a better brain.

Similarly, learning something new is an amazing way to enhance neuroplasticity and wire your brain for more resilience. So trying something that scares you a little bit, for example, public speaking, learning a new language, playing an instrument, these are really great ways to enhance your neuroplasticity, and build some cognitive reserve.

I think that there's certainly something to be said for, you want to harness neuroplasticity with exercise and diet, and basically stress mitigation, time in nature. These all seem to be things that give it good signals. But at the end of the day, as much as there's science to support this and there's nuance to it, it's really finding the things that make life meaningful, and that connect us with other people, and ourselves, that enables our brain to be programmed for a good life.

There's no easy way around it, and it's also not that complicated. It's about the day to day things we do that bring us meaning. And that can be through work, that can be through volunteerism. But this is core to the human experience. You can perfectly set up a diet. You can perfectly set up an exercise routine. You can get 8 to 9 hours of sleep a night.

But the reason that we're here, as much as there could be a reason, I would say, is to have a full life experience, have meaning, have connections with other people. And if that is the case, you have to actually find ways to bring that into your life.

So again, that can be through a number of different venues. You can join a sports team as an adult. You can have religious interactions. You can have spiritual interactions. But it's that deeper connection with other people and our world, can be with nature, and with ourselves. That, I feel, is the fundamental goal that's going to support this healthy neuroplasticity.

It's a two part thing. You need to open up neuroplasticity. You want to give your brain the right nutrients it needs in order to support healthy neuroplasticity. But to direct it in the way that it's actually advantageous, you've got to actually make some of these deeper connections with our environment, with each other, and with ourselves.

### **Alex Howard**

It's interesting as you were talking, I was thinking, going back to where we were a little bit earlier, that people are often very fixated on symptoms. Be that physical symptoms, be that mental, emotional symptoms and often, I think, people can struggle to see the importance of fundamentals.

**[00:33:12]**

They can think, well, why is exercise, or eating right, or finding purpose in my life, how's that going to impact this symptom that I've been told I need to take this drug to fix? In a way, what I'm hearing and what you're saying is a very empowering message, which is that as much as there may be requirements for more complex diagnostics and intervention, these fundamentals are setting up the landscape within which everything is happening.

And maybe sometimes they're enough on their own, and other times other things may be needed. But we need these fundamentals in place anyway.

### **Dr Austin Perlmutter**

Yeah, I agree with that. There's so many ways to look at the issue of mental health today, and there's so many reasons why things can go wrong, and how things can be supported with various interventions. I think about depression a lot, I think about how we approach it, why do we consider depression to be such a big deal? And by and large, the conventional therapeutics for depression have been around SSRIs.

It's the idea that there's a serotonin issue in the brain and we can support the serotonin with a drug. There's a lot I could say about whether that is or isn't valid. There's some really interesting recent research suggesting that this whole theory isn't as substantial as we thought it would be.

But the issue with a human not having a meaningful life, I can't say is a serotonin issue. There's more to this conversation than simply saying this person, who is isolated from their friends and family, who spends their whole day indoors, their only issue is serotonin. If serotonin was higher, they'd be happy. They don't change anything else about their lives. I think the deeper piece of it all, is this question of what brings meaning and purpose to us.

There are many things that can change in our brains that can take us away from connecting to that deeper sense of meaning and purpose. I don't think that we can resolve meaning and purpose with just saying we're going to boost the level of a neurotransmitter.

It is definitely the case that certain perturbations in our brain lead to challenges in experiencing deeper meaning and happiness. For example, take healthy people inject them with LPS, which is a piece of a bacteria, creates inflammation in their bodies, they will feel more socially isolated and they will feel more depressed, which is really interesting.

But I think that actually gets to a real key mechanism here, which is when we feel disconnected from our environment, from the people around us, that's when things start going significantly wrong. I think there are a number of ways and reasons why that may happen. Many of them may actually be adaptive. If our bodies, if our brains are sensitive to inflammation, when we have inflammation, they say, let's not spend time with other people because we don't want to get them sick. That has an evolutionary mechanism.

But so much of this comes back to the point I made before, which is our brains are not there to keep us happy. That's not their point. That they're not there to provide us lives of meaning. Our brains evolved to keep us alive, to help us to reproduce, to keep the species alive. So we can't have some assumption that if we just navigate through life and let our brains run the show without any sort of reflection, that things are going to go well.

**[00:36:45]**

Because the reason why people get so stuck on social media. There are some primitive loops involving dopamine that make it really hard to put down the phone and stop watching TikTok. TikTok, in my opinion, has almost nothing to do with meaning and purpose in life. But it's a great way to put your brain on autopilot. So recovering that meaning and purpose is bigger than just fixing a neurotransmitter.

But I do think that is part of this because it gives you the opportunity to actually see and engage in the behaviors necessary to find meaning and purpose. And sometimes that's really hard to do if your brain chemistry is out of whack.

### **Alex Howard**

Austin, what do you see as the future? You've mentioned a few things in this interview that I know are emerging areas, like ketamine therapy and psychedelics and so on. I'm curious as to, you imagine 5, 10, 20 years in the future, what are the things that you see emerging now which you're excited by?

### **Dr Austin Perlmutter**

I think there are many things I'm excited about, and I'll say psychedelics. I'm very bullish on how they can be used to help people with mental health issues, and people who are just trying to develop more meaning, purpose, and so on in life.

The immune system, I think, is a huge part of this too, and understanding how the brain's immune system works. But the thing that I'm most hopeful for and most excited about, is the idea that we can start to understand who needs specific therapeutics.

And even now, the algorithm for prescribing medications for the majority of mental health disorders is saying, well, we have these classes, we start with this, we'll try this one. Maybe if a person has a family history of response, or not responding to an SSRI, we'll use one or the other. When things don't get better, we'll progress to a more potent one.

But where we started this interview was this conversation around all of these different pathways that we know are critically involved in how we think, and how we act, and how we feel. The brain's immune system, neuroplasticity, brain metabolism, neurotransmitters, all of these play a role, and it's a really nuanced network type effect.

What I would love to see, and where I think we're moving, is the idea of doing diagnostics on an individual to understand where things may be out of alignment. So doing deep immune style testing of what's happening in the body and in the brain, doing metabolic testing to see whether a person has insulin resistance and in some cases, let's say, would benefit from more of a ketogenic diet.

When we go to the immune type of dysregulation, maybe there are certain drugs or lifestyle measures that specifically target immune dysregulation. Maybe a person's issue resides in the microbiome, and the microbiome is sending unhealthy signals to the brain, so they get a targeted probiotic intervention.

**[00:39:47]**

The goal here would be to say we would understand different types of, in essence, brain types, and based on that we would be able to provide the interventions that are necessary to support that person towards getting to a state of overall better quality of life. I think psychedelics fit into that framework very well. We've often thought about psychedelics primarily as sigma, or sorry serotonin 2 A receptors, but we're now learning that they have effects on other receptors like the sigma 1 receptor, which is metabolic and immune.

And so my unified framework here would be to say, let's do an assessment of a person using imaging labs, as well as a whole lot of data from conversation, and then let's use machine learning, and AI to better match them to therapeutics that are going to bring them closer to a state of better brain health.

There's a lot I could say as far as some of the breakthroughs in the field of epigenetics, which we haven't touched on yet, but I think is transforming how we look at things like trauma. As well as things like how various drugs, and or lifestyle measures may reprogram our brains.

There is a recent study published by Candace Lewis, and other researchers, showing that in the case of MDMA that we may be able to use epigenetics to measure who with a history of, for example, trauma, may benefit from psychedelic therapy. And we may see that those benefits are by way of removing, or changing out epigenetic marks.

And that gets to some really interesting question of where does trauma live in the brain and how does it look? Is it network style effects, is it changes in the brain's immune system, is it damage to neurons? Or is it epigenetic? Meaning that it's on top of our DNA, and if it is there, can we change out some of those marks, and in doing so actually reverse or at least get rid of a person's experience, or the negative experience that comes with a prior trauma? So many, many things.

But I'd say the big aggregating theme here is the ability to personalize mental health interventions based on what is actually happening in a person's brain, as opposed to guessing, and hoping, and thinking that we're doing the right thing, simply because this is the best technology or understanding that we have.

### **Alex Howard**

Yeah, I think it's going to get super interesting in the coming years. Austin, people that want to find out more about you and your work, where's the best place to go, and what's some of what they can find?

### **Dr Austin Perlmutter**

[austinperlmutter.com](http://austinperlmutter.com) is my website. I send out a weekly newsletter so that's the best way to keep up with the latest brain research and opportunities for further learning.

I've tried to, in general, just create as much educational content as I can, specifically around lifestyle education for brain health outcomes. So you can see some of my peer reviewed research on there, and I'm really excited about a project that should be coming out soon where we're

looking at how plant nutrients might reprogram immunity by way of epigenetics. So keep an eye out. You'll see that on my website when that's available.

**[00:42:59] Alex Howard**

Awesome. Dr Austin Perlmutter I really appreciate your time.

**Dr Austin Perlmutter**

Thank you Alex.