MINDFUL
IN MAY

Dr. Elise Bialylew, founder of Mindful in May (mindfulinmay.org) and The Mind Life Project (www.mindlifeproject.com) and author of The Happiness Plan, interviews Zoltan Sarnyai

Zoltan Sarnyai

Prof Zoltán Sarnyai *is a medically-trained PhD neuroscientist with an active research program in the neurobiological mechanisms of stress and psychiatric disorders, including drug addiction, schizophrenia and depression. Zoltán's particular focus is on determining how environment shapes the brain through hormones, immune and metabolic factors during the course of the development of brain disorders. Zoltán also has a strong interest in the emerging field of nutritional psychiatry and has a number of research projects on dietary factors and mental health.*

What you will learn in this interview:

- What is the gut microbiome?
- What is the relationship between stress and our microbiome?
- How does the gut microbiome effect our mood?
- How can we measure chronic stress?
- What is the role of microbiome gene testing - is it helpful?

Elise Bialylew: Zoltan, welcome to the program. It's a delight to have you here. Now before we jump into things, I wanted to contextualize for the listeners why I've invited you to come on in. One, thrilled you're here because this is a program about mindfulness and meditation and although that's not your exact area of expertise-

Zoltan Sarnyai: Not at all in fact.

Elise Bialylew: I think we're understanding more and more that the mind is not just located in our head, and that actually the mind is a distributed thing and that the split between mind and body is a lot less than we have been led to believe. And so, you and I met briefly at the Lifestyle Medicine Conference in Brisbane where I was quiet illuminated by your talk. And so I'm really looking forward to sharing some of what you have shared there around your area of expertise, which we'll get into. So for those people who haven't met you, I'd love it if

you could share something about your background of expertise, how you ended up being there, and what you get really excited about in this area.

Zoltan Sarnyai: Sure. It's a pleasure to be here. Really. And yes, I don't do anything with my influence directly, but I think lots of the things that I'm doing might be related to mindfulness. So, I'm very happy to belong. So, I'm a medically trained neuroscientist. I've never really practiced, which is, I think in retrospect it's a mistake. But, nevertheless, that's what I've decided because I very early became interested in research and while I was at medical school, I started doing research on the brain basically, neuropeptides and behaviours. So that's how my scientific interests first started.

Zoltan Sarnyai: And after medical school, I was trained at Harvard Medical School, so I was at McLean Hospital, which is psychiatric teaching hospital of Harvard Medical School where I worked on projects related to stress and drug addiction. And then later on I moved to the Rockefeller University in New York, where I had the great privilege of working with Bruce McEwen, who is one of the leaders of, sort of, second half of the 20th century stress research. Really. And this is really where my interest about stress further increased and open from the area of addictive disorders to add other areas including depression, anxiety, and then more recently, schizophrenia as well. And then before I came to Australia, I about seven years ago now, I was, for eight years, on the Faculty of University of Cambridge, and I was teaching pharmacology and did research on neuropharmacology/neuroscience there. So that's my story so far.

Elise Bialylew: Yeah. Wonderful. So I'm just going to jump into a statement that you made in your talk at the Lifestyle Medicine Conference that just really kind of came out at me in fluorescent lights, which was, please correct me if I'm wrong, "There's no health without mental health and there's no mental health without gut health."

Zoltan Sarnyai: Yes. So, exactly. So, I was basically paraphrasing the sentence by some leading researcher in global medicine/psychiatry who coined this sentence, "There is no health without mental health." And published that in Lancet some years ago. And I thought: This is such a powerful statement, which we can make just as well about the relationship between our gastrointestinal functions, especially gut microbiome and brain function. So that's the whole background of that. I think is just to emphasize in a very simple way that our brain function depends on a wide variety of things happening in our body. But among other things. Our gut microbiota and gastrointestinal functions all together.

Elise Bialylew: Okay. So just bringing together this idea that you spend a lot of time specializing in the area of stress – but you also do speak a lot about the microbiota. So perhaps we could just start for those who are newer to this whole area of the microbiota or microbiome… could you just explain what we're talking about here? What this microbiota is, and then perhaps, I guess if you wanted to move into something around what you learned in the field of stress and relationship between the two of those, that would be great as well.

Zoltan Sarnyai: Yeah. So, when we talk about gut microbiota, what we mean basically are trillions, literally trillions of bacteria living in our gastrointestinal tract. And that's pretty much anything and everything between our stomach and large intestine, up to the rectum. And some parts of our GI (gastrointestinal tract) are full of bacteria, especially the ones that are close to the end, like the rectal and large intestines and others such as the stomach, are much less because the environment is not very hospitable for living creatures, having very high acidity. Having said that, it's a major Australian medical discovery, Helicobacter pylori – one of the major goals of the factors of gastric cancer – they live happily ever after in the stomach. So, even under a very inhospitable conditions, these bacteria can live, and they populate our whole gastrointestinal system basically.

Zoltan Sarnyai: They don't just live there. They live there in a symbiotic relationship with us human beings. Actually some people in the field turns it around and they say that it's not the bacteria living in us, but we live around the bacteria. May not be a big exaggeration really, if you considered their number. And if you consider how many genes they contain, which are many waters of magnitudes more than our 20 something thousand genes we have in our bodies us humans. So, it's the symbiotic relationship between the whole of our physiology, and this large number of bacteria cells in our gastrointestinal system. So that's the gut microbiota we just usually call the gut microbiome. So-

Elise Bialylew: And-

Zoltan Sarnyai: Go ahead.

Elise Bialylew: No. So, I mean I want to dig deep into this – the different areas that you spoke about. What do we know... Well, actually, first of all, can you speak about the relationship between the gut and the brain?

Zoltan Sarnyai: Yeah. So of course some aspects of relationship have long been known in medicine. So, for example, when I went to medical school, which is a long time ago, when we talked about gastric ulcer, the sort of general wisdom at that time was, it's caused by stress.

Elise Bialylew: Sorry, the gastric ulcer?

Zoltan Sarnyai: Yeah. So it's caused by stress, stress has a big impact, then flares up and individually is under a stressful situation. And also again, when I was at medical school, we'd spend a lot of time in the gastroanthropology department of our teaching hospital, and they had a special unit for individuals with irritable bowel syndrome. So then the physicians there said, "Oh, they all have some psychiatric issues. They're all, you know…' So, there's a sort of known that it has to do with the brain. And it was also known that it's a bidirectionally interaction.

Zoltan Sarnyai: So the gastrointestinal system obviously communicates to the brain. So now, at beginning of 21st century, they have a much more detailed understanding

of that relationship. And we know that the brain talks to the gut and the gut talks to the brain. And that communication occurs through many different channels. So that includes hormones coming from the brain and the hypothalamus and the pituitary gland. It also occurs to direct nervous collections like the vagus nerve. That's the main conduit of information from the brain to the gastrointestinal system. And it also occurs to metabolites that are being produced in the gastrointestinal tract. Then they get into the systemic circulation, and they reach the brain through the systemic circulation.

Zoltan Sarnyai: And similarly, vagus nerve is not just a unidirectional route. It also carries information from the GI tract. Yes, intestinal tract up to the brain. And some of these, the materials that are now carrying the information are metabolites produced by the bacteria that are living in the gastrointestinal tract. So it's really a true bidirectional interaction.

Elise Bialylew: So let me just clarify this for the listeners. So, in what you're saying there, particularly the direction from the gut to the brain, you're saying that the bacteria that live in our gut, which essentially eat and live off the food that we eat, mostly – when they digest and break down that food in different ways, I imagine, depending on maybe what bacteria they are, then the metabolites – which are the breakdown products – send off different signals that go back up.

Zoltan Sarnyai: Yes. So, this is more or less true. So, the bacteria living in our gastrointestinal tract, they eat exactly the same food as we eat, because that's what they get. That's the whole essence of this symbiotic relationship. Different kinds of bacteria eat different things. For example, the only reason we can digest certain long chain carbohydrates like cellulose and related long chain carbohydrates, is that we have bacteria living in our guts that do that for us.

Zoltan Sarnyai: So these low carbohydrate molecules, are actually not digestible for us human beings, we can't absorb it, we can't digest it, but the bacteria living in our gastrointestinal system can, and they produce what's called the short-chain fatty acids as the metabolite – the breakdown product of these long chain carbohydrates – and these are biologically active molecules. They have effects on our neurotransmission. They have epigenetic effects as well. So they modified the enzymes that fix the structure of the chromosome. So they really have hardcore biological effects.

Elise Bialylew: It's just… it's quite amazing. I mean, you don't learn this at school, do you? You learn-

Zoltan Sarnyai: We have more knowledge, which we didn't have before.

Elise Bialylew: Yeah. But I think that's why I got so excited about having this conversation with you, because I think that this knowledge – is still, it's emerging, but it's not, I don't think it's 100% mainstream that most people would know this. So, and I think it also reminds me we got taught in school, "You are what you eat", but actually: You are what you eat and which kind of bacteria you have in your gut… kind of thing.

Zoltan Sarnyai: That's right.

Elise Bialylew: Yeah. Okay. So, can you say something, because I found it very interesting, the topic of sort of neurotransmitters. So, serotonin and that connection to the gut microbiota, and then the relationship there with mental health.

Zoltan Sarnyai: Yes. So, serotonin received a lot of attention, of course, in this particular relationship, because it's all there, it's sort of the common knowledge that serotonin has to do with regulation of mood and depression. And we know that all clinically effective antidepressants, they basically elevate serotonin levels in the brain. So, therefore, if you find that certain bacteria produce serotonin, then you make the connection, "Oh, that's great that these bacteria influence brain function through that serotonin." But I think it's not that simple, really. Because yes, the bacteria that live in our gastrointestinal system, they pretty much produce all the main neurotransmitters that are already in all the brain, not just serotonin. Acetylcholine, dopamine, noradrenaline – they produce all sorts of neurotransmitters.

Zoltan Sarnyai: The problem is, how do neurotransmitters actually get into the brain? And I don't think that we really do know the answer. And probably a lot of those never get into the brain, which again doesn't mean that these neurotransmitters are not functionally important in the gut-brain communication, because what is more likely, I think, that these locally produced transmitters – which includes, again, GABA, which is the main inhibitory neurotransmitters, all anxiolytics drugs increase GABAergic tone in the brain. So then if you see GABA being higher in bifidobacteria, then, oh, great. Then just some difficult bacteria and then you don't have to take-

Elise Bialylew: Valium.

Zoltan Sarnyai: But it's not that simple. I think these transmitters can't just pass freely from our guts to our brain. They first would have to go through the liver and then they would be metabolized mostly there already. And even if they don't, they would have to pass the blood brain barrier, and then they would have to be taken up by neurons. So I think it's a lot to ask from neurotransmitters locally produced in the gastric. But what is likely, that these locally produced transmitter talk to the nerve endings that are there locally, and these nerve endings are the nerve endings of the vagus nerve, and then all your nerves that will have projections up to the brain. So I think that's fairly possible.

Zoltan Sarnyai: We know that some neuron transmitters like dopamine, it does not cross the blood brain barrier otherwise patients with Parkinson's disease will get dopamine instead of L-dopa but dopamine doesn't get into the brain. But again, it doesn't mean that dopamine produced by certain bacteria could not have an impact on brain functioning. It could by other means, like indirectly modulating the activity of the neurons that project from the gut up to the brain.

Elise Bialylew: Okay. Thank you for clarifying that. So, what… I mean, through the various research in this field of gut and mental health. Is there anything that you can think of to share that we do know, that he's kind of relevant to this

conversation around either diet or… anything… research that we do know, that has an impact between the gut and the brain or mental health conditions?

Zoltan Sarnyai: Yes. So this is an emerging field as you have just mentioned. There is a whole lot of work going on in this area and there's lots of excitement. And a little bit of hype is about, and I'm just trying to be a little bit careful and make sure that what we are talking about here, are all properly supported by published scientific data. Because, yeah, you can make assumptions and conjectures and that all sounds good and logical. But that doesn't necessarily make it true, unless we have a hard scientific data to back it off.

Zoltan Sarnyai: So we have a lot of information about the relationship between gut bacteria and brain in experimental levels, in mice and rats. And the evidence is very strong that the presence or the absence of a neuronal microbiota, have a great impact on brain function. Just to give you an example, if we have germ free mice, and these are mice, which are brought to life by caesarean section and kept under sterile conditions – so they do not have their own microbiota within their guts. Their behaviour is completely different from the ones that are delivered normally. And that means they are more anxious, they are more sensitive to stress and all of that. If we inoculate these animals with normal gut bacteria, and those gut bacteria actually get hold there and proliferate, then their behaviour becomes known.

Zoltan Sarnyai: So that is a strong indication that the brain does require the presence of a normal microbiota in order to function properly. We have even stronger evidence that the gut microbiota seems to be mediating behaviours. For example, in behavioural neuroscience, in experimental animals, we have mouse strains, which are very, very similar to one another within a particular strain. They are inbred, they are almost genetically identical. So one strain is very anxious and other strain, not anxious at all. It's relaxed, can't be bothered.

Zoltan Sarnyai: So if we transferred the microbiota of an anxious train to a non-anxious, we can make them anxious and vice versa. I think that's a very strong demonstration that whatever happens, whatever these gut microbiota produce, they have an impact on brain function that has behavioural outcome. We know that and we have, by now, hundreds of papers from experimental models to support that. Then the question is, "What's the relevance of that to us humans?"

Zoltan Sarnyai: I think it's highly likely that we would find similar relationships in humans as well. There are other areas of human medicine outside psychiatry, that takes advantage of the emerging knowledge of the gut microbiota. For example, faecal microbiota transfer is being used in the management of a number of inflammatory GI conditions. There is a huge interest in using faecal microbiota transfer to manage obesity as well, helping weight loss.

Zoltan Sarnyai: So if immune functions, if systemic metabolism, or amiable for gut microbiota interventions, we have no reason to believe that the brain would be different. In the area of psychiatric disorders, we are not quite there yet in humans. But we know that in certain conditions – depression, in particular –

there are changes in the gut microbiota. We know that if we modify, if we sort of normalize that these BIOSIS, the abnormal constitution of gut microbiota, by, let's say, using certain probiotics, we can improve the symptoms of depression.

Zoltan Sarnyai: We also know that if you use certain dietary modifications that has an impact on depression, and I'm talking about a Mediterranean diet in particular and there is a strong emerging and repeated independently confirmed evidence that Mediterranean diet is linked to decreased depression, and it's even therapeutically beneficial in mild to moderate depression. Okay, so-

Elise Bialylew: In contrast to what diet? So is that sort of like the Medit-

Zoltan Sarnyai: In contrast to what you would consider a normal diet. If the question is actually quite good, because if you compare it to what's called at the Western life which is a high fat, high carbohydrate diet, the difference is even bigger.

Elise Bialylew: But sorry, between the Mediterranean and which diet?

Zoltan Sarnyai: What we would call a Western diet: high fat, high carbohydrate diet. The detrimental effect of such diet on brain function has been demonstrated both in experimental animals and insurance. But if a dietary intervention has a beneficial effect on a psychiatric condition, you can ask the question, "Is it because of the contribution of the gut microbiota?" And I think we're just at the beginning of really understanding the link between diet changes in microbiome and beneficial effects on the brain.

Elise Bialylew: Yes. Because when you just said then that there is an association between depression and dysbiosis, when … sort of, when the microbiomes are a bit not in balance, you saying we don't really know what came first?

Zoltan Sarnyai: We don't really know what came first. Just because there's an association, it does not necessarily mean causation of cause. It could be rigorous causality on one hand or they could be completely independent, happened to be occurring at the same time in the same individual. And it's really hard to do such studies in humans. It's easy to do it in experimental models, but for obvious ethical reasons, we can't try doing the same in humans.

Elise Bialylew: So I really appreciate your clear message around the fact that it's an emerging field, and it's easy to get excited about these things, and people can get a bit over excited. But I really appreciate that you're sharing what we definitely know, and what is kind of on the edge and emerging. That's really helpful. On that note, I think at the conference I said to you there were a lot of tests – the microbiome tests– that you pay about $500 for. I don't know if, on record, you could speak about that, but what are these tests actually telling us or not telling us? Like who should have these tests, if anyone?

Zoltan Sarnyai: So, I think I would start at a slightly different point. If you want to have a diagnostic test, let's say, if you really establish that an individual has Type 2 diabetes or dysregulation of glucose metabolism that you measure blood

glucose, you measure a fasting glucose level. And you can measure that because you are fairly confident that beyond a certain level of fasting blood glucose, there is a very high likelihood that this individual cannot respond properly for the endogenous insulin production. So likely to have – or becoming to have – Type 2 diabetes. Okay. So do we know such things with the gut microbiome? Do you know what an optimal microbiota is? We don't know. It's not unlikely that there are tremendous individual differences between one person to the next.

Zoltan Sarnyai: Some bacteria have their labels, such as good bacteria and bad bacteria. It's sort of common knowledge that Lactobacillus a good bacterium. So what would you measure? Would you measure the amount of Lactobacillus, the amount of something that we know it's bad? Like Staphylococcus? They are talking about trillions of bacteria, more than a thousand different families living there. And they live there in a complex symbiotic system. So they live together with us, and they live together with each other as well. So there are bacteria that use the breakdown products made by other bacteria, and I think we just don't have the complex understanding in order to be able to sell a diagnostic product really, or even something that would suggest that if you have such a composition of gut microbiota, then you'll likely have this and that condition. I don't think we are there.

Zoltan Sarnyai: I'm not saying that you're not going to get there. There's tremendous research going into that particular area. But I don't think they are there at the moment, even in our own scientific projects. I think we just really have to be very careful. So I'm looking at the gut microbiota in mice, in response to certain dietary intervention in the schizophrenia model. And yes, we see these bacteria up other bacteria down, and we can look into that in the literature those bacteria are considered to be beneficial sort of dampening the immune response or beneficial in the sense of increasing insulin sensitivity.

Zoltan Sarnyai: So we can do that, but really, these are focusing on individual bacteria. But in reality there's a huge complex system – and so these bacteria living together. So I think we are very far from fully understanding the complexity. We are definitely making headways in our understanding. But, yeah. And if you consider that the reason why gut microbiome has become a major focus of research and also public excitement, is technology. So now we have a technology that allows us to determine the presence of bacteria, which we cannot culture.

Elise Bialylew: I see.

Zoltan Sarnyai: In the old days, what you did, you took a sample of a certain bodily fluids-

Elise Bialylew: Saliva, you take a swab-

Zoltan Sarnyai: Certain bodily fluids of the individual, spread it on the agar gel and try to culture it on a certain temperature over a certain period of time. And then you look the bacteria under the microscope. And many bacteria can be cultured but probably a lot more cannot because there are just too few. And now, molecular biology techniques allow us to look at their RNA. And there is a

particular RNA that is only present in bacteria. So that's what we do in the lab. We measure what score 16S RRNA. And we know that that type of RNA is only in bacteria, not in our mammalian cells. And there is a fair bit of bioinformatic schools into identifying that this and this and that.

Elise Bialylew: I see. So it is this sort of there's a drug – it's great to make that point – that the technology is allowing us. It's like when we went to the moon as humans, like the capacity to open up new landscapes. And as you're talking about the bacteria, it really like, as you're talking, I think it's like as unknown to us as outer space was before we were–

Zoltan Sarnyai: Or the deep oceans.

Elise Bialylew: Yeah. Fascinating. Very, very fascinating. So what do we know, if anything, about sort of diet and what we feed the gut? I mean...

Zoltan Sarnyai: This is another, sort of, controversial topic because there are so many dietary advisors out there, and I will not venture into that job. Just not. It's not my area of expertise anyway, but it's been known for a very long time. Actually. Even if you think about ancient Greeks, Hippocrates, they already knew that food has an impact on health. "Food be thy medicine." That was, Hippocrates said that two and a half thousands years ago. So that's sort of common knowledge.

Zoltan Sarnyai: But again, exactly what type of diet, in what way, and for which individual, I think it's obviously debatable. You can probably have a common sense approach. A balanced diet is a better diet than any of the extremes. But if I'm looking at different dietary approaches to manage psychiatry conditions or mental health conditions, rather, Mediterranean diet, definitely, emerges as a very promising one. But if you ask me which bit of the Mediterranean Diet that matters, is it omega-3 fatty acids in the olive oil and in the fish, or is it the fibre and then the short chain fatty acids produced by the bacteria using, in all of us, using that fibre? We don't quite know that. Or is it the chemicals in the red wine? We don't know that. We know that resveratrol, the chemical from the red wine, has a number of beneficial effects and extends lifespan in Drosophila, extends lives in mice. But again, we haven't been able to demonstrate the contribution of the individual bits and pieces of the Mediterranean diet. But all together it seems to have a beneficial effect, and it's been replicated across many different groups.

Zoltan Sarnyai: Having said that, it's unlikely that this dietary intervention would replace taking medication for individuals with severe depression. However, for individuals with moderate and mild depression – together with psychotherapy, physical exercise, mindfulness, and all that – it's a very important addition and probably makes the pharmacological interventions less necessary.

Elise Bialylew: Thank you. I think that it's still, even though it's emerging and it does get very complex… diet, want to eat what not to eat… I think the fact that we can just be mindful and consider that this area is so important to our overall

health is significant. I want to move on to stress. So this is really what you spent a lot of time as you said… what was his name? Bruce Mc…

Zoltan Sarnyai: Bruce McEwen.

Elise Bialylew: Yes.

Zoltan Sarnyai: Bruce McEwen was the first scientist, who in 1968, demonstrated that the brain contains receptors binding proteins for cortisol, and that was the first actual guided demonstration that the circulating hormone in our body may have effect on the brain, because there is a physical basis for this effect. And his contribution to the field was very, very significant.

Elise Bialylew: So I wondered if we could just start for the listeners who – I think it's in pop culture, this fight or flight response. Most people have heard that, but I think what people don't really understand is how a deadline at work can turn your whole physiology into a completely different state. Do you want to just share a little bit about that? And perhaps also the significance around chronic stress versus acute stress?

Zoltan Sarnyai: Yes. So I think this is a very, very important question as just like anything else in biology, it doesn't make sense without, making sense from an evolutionary point of view. And really have to keep in mind that the life we're living now in the modern 21st century is a very different life, to the ones lived by our human and other mammalian ancestors, millions and millions of years ago. So the biological stress response, which you described as the fight or flight response, is a highly evolutionary conserved response. So even lower species, they also has similar steering hormones like we have cortisol, and they respond to an increased production of these stress hormones in response to environmental stresses. And it's not necessarily have to be a deadline. It can be a changing environment or temperature. If you are, let's say, a gecko or a snake, that's a stress because it's a threat to the environment, from the environment to the individual.

Zoltan Sarnyai: So it's highly evolutionary conserved. And it's really important to understand that this evolutionarily conserved stress-response, if you'd like to, designed for, or developed for, how being the individual to survive. And as a result of that, it's using biologically tremendously powerful modules. So let's just single out two: adrenalin – and in the popular culture we all know about the adrenalin rush, so we know what adrenaline is – and the other one is cortisol. So these are the main circulating biological stress molecules. Adrenalin goes up within milliseconds after a stressful stimulus, because it gets released from the adrenal glands and cortisol takes another 10, 15 minutes, then gradually rise and reach each top levels after a stressful stimulus. And they are there to help the organism to maximize the chances of survival.

Elise Bialylew: Thank you. I think, as I said, I think that the fight/flight is pop culture and people kind of understand that real distinction between the acute adaptive response and the chronic toxicity of it.

Zoltan Sarnyai: Fight or flight is a good thing and stress is not necessarily a bad thing. The all experience, especially you mentioned deadlines. So if there are people who actually function very well under the pressure of deadlines because they have just enough stimulus from the stress of an upcoming deadline that their concentration, attention, cognitive functions, really increase and their general arousal goes up. They do not get sleepy and they can get through the night to finish the work. That's okay. But if that happens to [inaudible 00:37:51] for two years, that's not good.

Elise Bialylew: Yeah. Have you had much, sort of, investigation around this… We hear the term "burnout".

Zoltan Sarnyai: Yeah.

Elise Bialylew: It's kind of a layman term, but do you have anything to say about the, sort of, very real physiological state of "burnout"?

Zoltan Sarnyai: Yeah.

Elise Bialylew: So just to kind of extend that a bit. Like, because what I'm thinking is, people know when they're under pressure chronically, but I was wondering, are there tests, medical tests that we can do to actually measure, like, our level of chronically raised cortisol – or it doesn't really work like that? And also, yeah, I guess just to explain to people that when you say "burnout", I think from my perspective it is actually a physiological thing. It's not just: I'm feeling really tired. So, yeah. If you could speak to that a little bit.

Zoltan Sarnyai: Yes. I think you're absolutely right. It's physiological, and it's well beyond feeling a little bit tired or feeling very tired. in fact. If we just continue that line of thinking, what happens if our body – which means our physiology – is continuously and relentlessly subjected to the fact of these highly powerful molecules. And that includes adrenalin, includes cortisol, and the number of immune molecules as well that are called proinflammatory cytokines.

Zoltan Sarnyai: So these are molecules that are also becoming active as a result of this chronic stress. And there is a catch 22 here as well because then these elevated proinflammatory cytokines, they will stimulate our cortisol as well. So it's a vicious cycle here. And especially if we consider this chronic nagging non-disappearing nature of the stress we're under in our 21st century existence. It's not like the major traumas that occur after a physical or sexual violence or experiencing something really, really terrible at a certain point of our life, which is a major stressful event. These are continuous, chronic nagging aspects of our life we are not able to deal with.

Zoltan Sarnyai: And that's another important point here, which I would like to add for us humans. But even for rats and mice, controllability is really important. So whether we can control the situation, it's not that how much difficulties we have to deal with it. It's whether we can control those difficulties or we can't. I think that makes a huge difference. Even in rats. If we administer some mild electric food shock to rats, it's not good for them, and it stresses them out but,

if they are able to switch the electric food shock on and off, and they can control, even if they are getting exactly the same amount of electric shock, if it's coming in a controllable fashion, they are fine. They are fine. And that tells us, a teaches us a big lesson to humans because it seems to be the case for us humans as well.

Zoltan Sarnyai: So, the controllability, the chronicity of these stressful stimuli are very important. So, and all adds up, which we probably call that as burn out, which is a combination of a continuous sort of low grade inflammation in the body that is at least we start to understand, seems to be an underlying factor for metabolic syndrome and obesity and even depression as well. So there is this continuous immune activation on metabolic issues. And of course all the psychological aspect, due to the fact that these molecules that are circulating in our body in response to chronic stress, they get into the brain, and they have actual biological effect on the brain. So this is not necessarily imagined, not imagined at all. Stress is a real thing. It's a physical thing on the body. And these chemicals, so let's say proinflammatory cytokines, they induce something that's called sickness behaviour.

Zoltan Sarnyai: I think sickness behaviour is very similar to what you would describe as burnout. You feel fatigue, you do not feel motivated, and you feel sort of sad, and you don't really see the point. It's a little bit like depression, but it isn't. It wouldn't fit DSM-5 diagnostic categories of depression, but might be actually a little bit similar to what score the sickness behaviour, which is in use by systemic immune function having an impact on the brain. So that's an answer to the first part of the question. Second part was about how to measure stress. Can we objectively measure stress? Because I think one of the big problems of the field, is that up to now, the way to assess stress was to using questionnaires. So how stressed do you feel and then you tick box. And of course that's very subjective, and we know that perceived stress and the actual biological stress, they do not necessarily overlap 100%. So that's very important.

Zoltan Sarnyai: So what would be really, really crucial for the field is to have objective ways of assessing how stressed an individual is. And especially how that changes over a long period of time. And we can do a few things now. So for example, in my lab we were looking into chronic stress biomarkers in humans, and we are measuring cortisol from hair. That is really interesting. If you thinking about measuring cortisol… so from the blood, yeah, you don't necessarily want to stick a needle into everybody. Plus the fact that cortisol changes across the day, it changes tremendously. It changes so much that having a blood cortisol measure is meaningless. Unless the person is suffering from Cushing's disease, or they [inaudible 00:44:41] medication. It's completely meaningless because it changes so much.

Zoltan Sarnyai: We can also measure cortisol from saliva. Again, it follows blood cortisol level very closely. So it's a much better way to assess acute change of cortisol. But, if we will not ask questions about what's happening over time, hair offers a really unique opportunity. So cortisol – the stress hormone – is fat soluble. So it gets into the keratinized tissue of the hair. Hair at most grows about a centimetre a month, and it goes continuously. So if you cut the

hair and take the first three centimetres closest to the skull, roughly your last three months of life, and we can measure cortisol from hair, actually. And we have been doing that in different settings, in treatment-seeking adolescence and in indigenous communities in here in Northern Australia. And it's giving us really, really interesting findings. And it's stable over time, and it gives you the summative amount of cortisol during the last three months.

Zoltan Sarnyai: And now we are getting into measuring cortisol from fingernails. So fingernails... you don't have to remove the whole. You just sculpt the free nail bit. The timing is interesting because it also grows, but when you cut the very end of the fingernail, which you would otherwise cut for yourself on a regular basis, that's, let's say two weeks, three months ago.

Elise Bialylew: Like is there an example you can share, of like what you've gleaned or is it like you do a haircut, test it, then do an intervention then get another piece of hair like six months later or?

Zoltan Sarnyai: So we haven't done any particular intervention in this setting, but what we have been doing, we're working with a few indigenous communities in North Queensland, and as a part of their young person's health, we obtain hair samples and analyse hair cortisol. And the analysed hair cortisol is all levels in relation to their psychological well-being. And what we're seeing is actually quite interesting. There seems to be relationship with in certain aspects of the depressive symptomatology and hair cortisol.

Zoltan Sarnyai: Again, we are at the beginning of a longer research project. So not much more I can say. And we haven't done any intervention as such. In another project that we are collecting hair samples from young people who are seeking treatment for mental health complaints, at their first time of interacting with the healthcare system. What we would love to do all the time, to follow them. What happens later on in response to psychotherapy or pharmacological therapy or perhaps if there was no need for therapy, then how they be able to would track in terms of their mental health complaints, and their chronic biological stress.

Elise Bialylew: Oh, it's very exciting. I didn't know this about the hair. I want to send my hair off to a lab every few months.

Zoltan Sarnyai: Happy to measure.

Elise Bialylew: I'll send you a piece of my hair. Okay. The other point that I wanted to ask you about there is my understanding around the fact that we all develop different sort of, correct me if I'm wrong, but sensitivity to the stress response. So like, we can be more or less, activated by the impact of cortisol. So that's like a variant. And what determines that? Obviously it's genetic, but just something around that topic.

Zoltan Sarnyai: Yes. As you said that there must be genetic components, which we don't necessarily understand fully, but there are individual differences. That's absolutely certain. And some of these individual differences or driven by

environmental events rather than genetic factors. And these environmental factors can be almost anything from in utero foetal life exposure through Mum. We know that maternal stress has an impact on the development of the child. And just because during the time of the pregnancy, Mum was under considerable amount of stress that could through many, many number of different ways, have an impact on the development of the foetus.

Zoltan Sarnyai: If you consider stress, blood vessels constrict and not enough blood gets to the placenta, and the foetus is not getting sufficient oxygen nutrients. Yeah. So you can make many different possible pathways, which might contribute. So we do know that such relationship is present. And we also know that all after birth, during very early development, the interaction between the baby and the environment and I'm being careful, saying the mother and the environment is absolutely crucial. It's very, very important. I'm just trying to build a little bit less potentially controversial.

Zoltan Sarnyai: I would rather use an animal experiment to illustrate. We know that if we remove rat pups from mum for three hours a day during the first week of their lives, but otherwise provide them with warmth, food and all that, except they are removed from the mother for three hours a day for the first week of their lives, they will become a lot more sensitive to stress, biologically and behaviourally they will develop cognitive impairments as they age much earlier. And I could list the number of abnormalities if you'd like that these animals were developed further down the line just, because of the events occurred in the first week of their lives.

Elise Bialylew: It's incredible.

Zoltan Sarnyai: Or I can turn it around a little bit. And there was another real interesting series of experiments when they removed the pups, but not for three hours, just for 15 minutes, remove pup for 15 minutes, reunited with mum. So these little ones, when they grew up, they became resilient. They showed less anxiety-like behaviour and they were cognitively superior to even a normally raised rat pup.

Zoltan Sarnyai: So what does that tell you? It actually tells you that if you remove the pup for 15 minutes, it's not the removal that was beneficial. It was the excess maternal care they received when they were returned to the mum. Because the mum's reaction was to give excess grooming. So, relatively simple. They fed their offspring's and they groomed their offsprings. This grooming, excessive maternal grooming, was the reason why they turn out to be much more resilient as others.

Elise Bialylew: So the moral of the story could be that you cannot have enough love if you're a rat.

Zoltan Sarnyai: Exactly. And it's fairly common sense, but it's good to see from a scientific point of view that it works the same way in rats and mice because it cannot be a social construct if it works in rats and mice.

Elise Bialylew: Yeah. And I mean, as you say, you've been cautious and talking about rats and mice, but really humans, we're just animals really, we're just highly evolved animals in many ways.

Zoltan Sarnyai: With a little bit less hair.

Elise Bialylew: Yeah. Okay. Just as we round up, I wanted to ask you something I ask all the people I interview, which is, "Have you got a couple of books that have impacted upon your thinking?" Generally probably nonfiction books just that come to mind, thinkers or books that... And it could be in your field. It doesn't have to be mainstream.

Zoltan Sarnyai: Yeah. So I can probably give you three examples. So one I read when I was finishing high school, I think I just started university and that's the autobiographical book by the German physicist Werner Heisenberg. I think the title was *Physics and Beyond*. It was about life in physics at the beginning of 20th century. Basically conversations with Niels Bohr, with Einstein and all the others. And that was extremely important for me at that age, not because of the quantum physics aspects, because that was beyond me, but just the fact that science as an intellectual endeavour, it's something exciting. And I think that really put me on the path that I've been following ever since.

Zoltan Sarnyai: So I think that's a key book in my career. And the two others I'd like to mention, they are probably a little bit more recent. So one is by a stress biologist, currently active stress biologist at Stanford University, Robert Sapolsky. So read Robert Sapolsky. If you want to understand stress, read Sapolsky. If you want to be entertained and learn biology, listen to and watch his YouTube lectures to first year undergraduates at Stanford. So he's amazing. So his book on stress, *Why Zebras Don't Get Ulcers*. I think that's a very important book of getting across the message, which was trying to do not as well as Robert would have done.

Zoltan Sarnyai: The distinction between the beneficial adaptive acute stress as opposed to the chronic toxic stress. As zebras don't get ulcers because they die and they are eaten by the lion if they are not eaten they are not stressed. So I think that's another really important book. And he's a great author to read. His most recent book is called *Behave*. It's a much more sort of weighty tome. It's a really good summary of what we know about brain and behaviour, especially progression and the biological roots of human aggression.

Zoltan Sarnyai: And probably the third one is slightly related to that. This is Steven Pinker's *Blank Slate*, which I think emphasizes what's, I would say blatantly obvious for anyone who has more than one child, that there are in-made biological features in the brain we're born with. And yes, we can make a difference as a parent, but not a lot.

Elise Bialylew: With a three-year-old, that's quite comforting to hear.

Zoltan Sarnyai: Don't stress about it.

Elise Bialylew: Yeah. Unless it's because, actually it's all about the microbiota.

Zoltan Sarnyai: Yeah. It could be.

Elise Bialylew: It's like maybe it's the bacteria that is different and they're creating a behaviour.

Zoltan Sarnyai: I'm sure. Having said that, having the books on your bookshelf probably is not bad. But, you know, clever parents have books. Clever parents have clever genes. So, yeah.

Elise Bialylew: Thank you so much Zoltan. Thank you. It's been a wonderful conversation. I just wanted to offer you space. If there was anything that, you know, you just feel compelled to share about your work or anything fascinating that you've just discovered that we haven't covered. I just wanted to open it up. There may not be, but...

Zoltan Sarnyai: Yeah, so I'm not sure what to emphasize at this point, but what I would like to get across really that, this is an emerging field, both human stress research and gut microbiome and the role of gut microbiome in mental health. It's an emerging field, very exciting field. When you read about it in the media, in the lay press. Go for the evidence. Always, always go for the evidence. If you cannot find a link to the original publication, be very suspicious.

Elise Bialylew: Thank you. Well, thank you so much for your time and your thought provoking shares and I'm wishing you well.

Zoltan Sarnyai: Thank you very much Elise.

Elise Bialylew: May you and your gut microbiota thrive and flourish.

Zoltan Sarnyai: Thank you.

Book Recommendations

Physics and Beyond by Werner Heisenberg

Why Zebras Don't Get Ulcers by Robert Sapolsky

Behave by Robert Sapolsky

Blank Slate by Steven Pinker