Katharina Schmack on schizophrenia and why we all hallucinat...

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**SPEAKERS**

Caswell Barry

**Caswell Barry** 00:01

Hello, and welcome to brain stories, I'm Caswell Berry. I'm here with my co host, Steve Fleming.

00:07

On brain stories, we aim to provide a behind the scenes profile of the latest and greatest work in neuroscience, analysing the stories and the scientists who are making this field tick.

**Caswell Barry** 00:17

We don't just ask about the science, we asked how the scientists got to where they are today, and where they think their field is going in the future.

00:26

And today, we're very excited to be joined by Katrina smack. So welcome, Katrina. Thanks for Thanks for joining us. Out there, no, it's great. So we haven't done one of these for a while. So we're excited to be back in action here at base stories. So Katarina is medical training in in Berlin, she got her MD PhD from the charity. And then she completed postdoctoral training and a psychiatry specialisation in Berlin before moving to do a postdoc in Adam calyxes group called Spring harbour laboratory. So working on mouse models of decision making and competence. And her research focuses on psychosis and the changes in the brain that occur when we hallucinate. And I think it's really exciting work that Catherine is doing as well, as we'll find out because she's taking this cost species approach to applying models of psychosis that we can study both in humans and mice to really study the neural circuits and immune processes that give rise to hallucinations and other psychotics. So, we're really excited to have you here, Katerina. And I'm sure you can give our listeners a more accurate and in depth introduction to your research. So I was wondering if you could just kick us off with a couple of minutes on what you what you do in your lab.

02:00

Yes, thanks. So yeah, as you already said, we are interested in psychosis. And as most people might know, psychosis is this state that is characterised by delusions and hallucinations, which basically are unfounded perceptions and beliefs. And that's what kind of got me into this field. And what I find fascinating about this, and we try to understand the biological mechanisms that govern these unfounded perceptions. And we are doing this by adopting this cross species approach. So our idea is that we can model these processes in a way using behavioural tasks and computational models, that allows us to both relate them to subjective experiences and humans. But on the other hand, also to then dig into the biological mechanisms in rodent models. Yeah, I'm very excited. We just started our lab. And we are working both in humans and in mice, model mouse models to understand both the neural circuit mechanisms that govern, let's say, hallucination, like perceptions. And also we have become very interested in the idea that aberrant immune responses might trigger some of these unfounded perceptions.

03:21

So yeah, I should have said sorry that you have just started your your life at the Crick Institute, which is an amazing building, I came to visit Catherine's lab a few months ago, and really incredible place to be starting up your science. So I was just wondering if you could give us a flavour of one of the recent findings that have come out of those experiments on on hallucinations and delusions?

03:49

Yeah, so I mean, the most recent finding that is kind of established is from my postdoctoral work together with Adam cabbage at Cold Spring harbour laboratory. So what we set out to do there is to understand the long standing question of how dopamine relates to psychosis. So it has been know for a long time that too much dopamine is somehow related to psychosis characterised by hallucinations and delusions. But what has not been was not clear was how does too much dopamine actually lead to these apparent perceptions to unfounded perceptions. And that is because the role of dopamine has been well characterised in the fields of decision making, or in learning so and of cognition or movement, but there hasn't been a good understanding of why they have the role of dopamine in perception. And so we wondered, okay, maybe we can address this in with a cross species approach because the big challenge that we're facing in psychiatry research and in neuroscience in general is that on the one hand, we have subjective experiences that are really hard to capture objectively because they are subjective by definition I'm and on the other hand, we have, yeah, biological mechanisms that we can study only when if we have an objective measure, and we can study them, especially well in rodent models, where we now have all these amazing tools of system neuroscience. And so to bridge to to address this challenge, we started thinking, okay, how can we measure healthy nations or something processes related to healthy nations in a way that both allows us to then go into humans and relate them to their actual experience healthy nations, but also to measure them in mice in that case? And we started out with thinking about, okay, what is a hallucination and when we look at what a hallucination is, it's basically a perception that is not triggered by an external stimulus or an unfounded perception. But one another important aspect is that it is also perceived with high confidence, or high certainty. And we thought that this is something that we can actually capture in a behavioural task. And the behavioural tasks we came up with is basically a task where we play tones. And then humans or mice are trained to tell us whether they hear the tone, or whether they don't hear a tone. And then we ask them how confident they are. Humans just press a position the cursor on a sliding scale to tell us how confident they are. And mice, we train them to wait to invest time to wait for a certain interval of time. And the idea here is that if they are very confident that they actually did hear a tone, then they will wait for longer times, they will invest more time. And now what that gives us is a way to, to measure something that we call hallucinations, perceptions, which is defined as instances where we do not play any tone, but nevertheless, the human participant or the mouse reports hearing a tone, and they do so with high confidence or high certainty. And so that kind of allowed us to first go into humans and look okay, do people with hallucinations that experience hallucinations in their daily lives? Do they have more of these objectively captured hallucination like perceptions, and we found a correlation between these two suggesting that our task might engage some of the processes that might be relevant for these subjective experiences. And that then allowed us to go into mice. And we could also do some manipulations that we know are related to psycho.

**Caswell Barry** 07:19

So actually, I'm really, really curious about this interesting definition of psychosis you have, so it captures more than I would have imagined psychosis as someone who doesn't work in this in this bit of the field at all. And I guess there's a question that comes out of it, which is, is psychosis are sort of these sorts of hallucinations always pathological? Or is this actually just something that happens part of everyday life, especially thinking of your tone task? I often think I've heard like the doorbell go or something like this, this seems like a normal continuum of of effects.

07:50

Yeah, that's exactly right. That's how we view hallucinations and psychotic experiences in general. And I think that's also why we study them, because for me, hallucinations are kind of an extreme expression of our normal perception. So understanding what's going on in hallucination will actually inform us about what is how perception works in general. And so indeed, there are we all have, we are all on a spectrum, and we move on the spectrum. As we sleep more or less, we move more towards the psychotic spectrum. For instance, if we don't sleep a lot, or if we take it there, like all these, this is the exactly like the right description. And as you said, we most of us know this kind of experiences, we have the feeling that our phone vibrates, but then it didn't vibrate, or another experience that many young parents have that they hear the baby crying, and then they go there to check on the baby. And it's perfectly asleep. And that happens, especially when parents are tired. But also when there is a background noise, let's say the AC is running in the in the states a very common thing so that there's this background, white noise, and then we start to hear things. And I think it is basically a reflection of our basic perceptual machinery. I think that's basically what we do in our life. When we perceive things, we always impose our expectations on the sensory input. And s as the sensory sensory input gets the like, the weaker the sensory input is, the more we have to do that. So if there is like a white background noise, we need to impose more structure on that to actually make out what is going on. And that might lead to the to the effect that we might hear something that we're just expecting to hear, such as our baby crying. So

09:34

I'm wondering if I don't want to take you too far off topic, but when you mentioned the issue of sleep. I mean, the main time in my life that I've experienced, strong, tactile hallucinations was when I was you know, just after we had our son. I used to wake up thinking he was still sleeping on me. It's kind of panic that I have fallen asleep and I could just feel him on me. And I'm just wondering, do we know about the mechanisms behind how sleep deprivation might lead to greater hallucinatory perception.

10:09

And I think it's not well understood. It's a very interesting topic. And I think, yeah, we now have the tools to address the questions. There are some findings that sleep deprivation does this, that it kind of shifts the perceptual thresholds. But there's not really a good understanding why this happens. I mean, my first guess now would be dopamine. And there are people working on the role of dopamine during sleep. And there are some really interesting, there's some really interesting work on the role of dopamine during REM sleep and how this impacts also future learning. So I think, yeah, there's much to be discovered. And we don't understand yet. But we have all the tools now to address this question.

**Caswell Barry** 10:51

I really love this, by the way, this example you gave of parents hearing things. So it times is a personal experience. A few years ago, we used to have a joke in the lab when my children were young, against the background noise of a shower, so like white noise that you said, I would hear them crying. And so the joke was that I have a crying prior because I guess we're all Basie and I suppose there's a serious message in here, which I think is what you're saying, basically, this is, am I right in thinking then that you sort of view these forms of hallucinations as essentially an inappropriate trade off between your internal model of the world and sort of the incoming external sensory stimuli? Does that without getting too detailed? Do you think there's a role for dopamine in sort of arbitrating between between the model and the incoming data? Because that sounds quite an interesting idea.

11:43

Yeah, so actually, that's kind of our that's what our findings suggest. So what we could do in mice, we could actually measure dopamine during this task. And what we found was that first more dopamine and especially more to baseline dopamine, so baseline high baseline levels of dopamine, they preceded these hallucination, like perceptions. And they also, also, if we stimulated dopamine, they induced these hallucination like perceptions. And then and that's the answer to your question, when we looked, when we use the model, and we looked, we try to model the the agent as some as an agent who learns a model of the world. And we do this in a very simple way, we just assume that if you hear a stimulus, you, you're more likely to expect hearing a stimulus on the next trial. So a very basic, simple model. And we found indeed, the dopamine scaled with with the strength of these expectations. So it was really a linear relationship. So it looked very similar to this expectation of hearing a tone as modelled by our model. So yeah, I think dopamine might encode these predictions of what we are expecting to perceive. And this is kind of reminiscent of reinforcement learning where we also think that dopamine encodes, I mean, maybe we don't call it a prediction, but it encodes responses to a cue, which in a way is a prediction of an upcoming reward. And so I think we probably still need to kind of bring together these two aspects of dopamine in a coherent model. But I think there is really, there's reason to believe that dopamine might be important for constantly encoding at prediction about about the world about whether there will be something relevant coming up or not.

**Caswell Barry** 13:25

That's really cool. It feels like very close to having sort of both a really complete model ways of attacking it and animal models and understanding of what's happening in humans. That seems quite exciting in the world of neuroscience more more exciting than my world Navy. It is the implication that then in in people who are suffering from psychosis, that there are pathologies of the dopamine system, is that is that something that's already known? Or is that a hypothesis or?

14:00

Yeah, so that's one of the leading hypothesis of psychosis, the dopamine hypothesis, it's grounded in the observation that antipsychotics that were discovered by serendipity that these antipsychotics all blocked dopamine transmission at the D two receptor. And also not only do they block the dopamine transmission, but there's also a linear relationship between the dose that is needed of an antipsychotic to generate a clinical response and the affinity of the of the substance to the receptor. And so that's why people have formulated this hypothesis a long time ago. And this has been recently backed up by some imaging studies, where they find that increased dopamine uptake in the striatum actually is observed in people with psychosis, but also people who have pre psychosis who have a very high risk for psychosis. So yeah, this is the evidence that we have for increased dopamine transmission in the striatum in psychosis.

15:06

Picking up on something you said just before about the the role of dopamine in reinforcement learning and updating the values of the things we act on the role of dopamine you've discovered in perception, and I'm wondering how you think about those, I guess dual roles, do you think there's two distinct roles? Do you think there's a kind of common framework within which we can understand what dopamine is doing there.

15:35

So I think there is a common framework to understand dopamine. And what I have not told you yet is that we actually also find these value signals, but we find them in a different region of the striatum. So we find that dopamine and Coates, more of these value based expectations and the ventral striatum, which is kind of an expected finding, it's where were we what processing is start to happen. But then if we look at the tail of the stranden, which is a region that receives more input from sensory areas, especially auditory cortex, but also visual cortex, we find the dopamine encodes more of these perceptual expectations. And so what I think I think dopamine probably doesn't have any content, like it doesn't encode what we will perceive or what we will what we are expecting. And because there are just a few dopamine, a few 1000 dopamine neurons, it's impossible to encode all the possible contents that we will ever perceive. So what I think is happening is that dopamine is part of these loops of the corticostriatal thalamic loops. And it has a probably a role in kind of tuning these loops towards relying more on the cortical inputs or relying more on the thalamic inputs. And dependent on where in the striatum we are, dopamine has these different roles, because it kind of has the same computational role, but for different loops that carry different kinds of information. And so the idea that we have is that maybe dopamine leads to a state where the striatal transmission starts to rely more on the cortical inputs that might convey these internal models of the world, rather than on the thalamic inputs that might convey these more sensory inputs. But that's just a hypothesis right now. And that might explain why when there is, when there is more dopamine, why we start to expect something that is in line with a more our model of the world, this might be a perceptual model, this might be like about what we are going to proceed, but it might also be a kind of reward encoding model, what what what we enforce that we're going to encounter. So that's my current view on that. But there's lots to be there lots of hypotheses to be tested to actually approved or established this this framework.

**Caswell Barry** 17:47

How far do you think that model extends? I mean, we're talking about it in terms of sort of perception. But do you think the same sort of framework sort of applies to things like people's beliefs? I guess I'm thinking like, you know, one of the topics or does your is your how polarised the world is on social media, and people only look for information about you know, their own worldview? Isn't the same same logic and neural systems apply to that?

18:08

Yes, I definitely think that beliefs and perceptions are more or less the same thing. And, obviously, they're not the same thing. But they are governed by the same inferential processes of the brain. So it's always about inferring the state of the external world. Sometimes we do this on a very sensory level, where we infer what objects are present in our physical proximity. But sometimes we do it on a more intellectual level or more belief than where we kind of believe, what are the rules that govern the world? What are the connections that govern the world, and this what we call beliefs, but I think it's always about predicting, predicting, predicting the, what is what will happen next in the world, that might be relevant to us. And so I completely believe that beliefs and perceptions or delusions and hallucinations are the same, are governed by the same inferential mechanisms. And that's also why we observe them so often occurring together and psychosis, I mean, delusions and hallucinations, there is a reason there must be a reason for why these two phenomena called cluster together. And yeah, it's a very interesting question. And I think it also, yeah, it's very interesting to, to think about these. Yeah, conspiracy theories are observed why, especially now, during the pandemic, we have seen this that there has been this shift towards conspiracy theories are this. They have searched and they're really studies showing that people have started to believe more in conspiracy theories. And also we know that people differ in their tendency towards kind of, or their susceptibility towards this kind of conspiracy. Yeah, frameworks. Yeah, and I think it's the same. It's on the on the, on the same spectrum as psychosis. And yeah, lots to be discovered.

19:57

There is absolutely fascinating, very exciting time. recovered research. So I'm just wondering, What first got you interested in this area? So we mentioned before you did psychiatry training? What was the point at which you realise you could create this bridge between animal and human work on psychosis?

20:18

Well, there were like several steps. It wasn't a one first one step where this happened. So it all evolved over my career, I think. So I don't know, it depends how much you want, how far you want me to go back. But if I can, maybe do it retrospectively, all the way? Okay, perfect, because I think so. So I obviously, I studied medicine, which is not directly neuroscience, and I was not particularly interested in psychiatry, or neuroscience or anything. But it was not really fulfilled by medicine, because it takes away a lot of your time, because you have to study a lot. But I didn't really feel like let's say intellectually stimulated because it's a lot of memorising, you need to just know your facts. And so I was left with this kind of feeling of Yeah, I'm not sure whether this is right. For me, I was not really happy with my career in medicine in the early years of, of med school. And then I had the seminar on fMRI in psychiatry. And that completely spoke to me like I was blown away by this, because I learned about this technique that allows you to visualise brain activity, while people are having emotions and thoughts. And then I thought really opened up like, a whole new way from your thinking about how you can actually understand why what makes us human, and what what the substance of our substrate of our subjective experiences. So I was very excited by that. And that kind of got me in touch with the psychiatry department, where I then did my thesis on fMRI. And in my thesis, one project was concerned with the so my thesis wasn't dopamine, again, dopamine in the context of working memory, and reward processing, and one finding we had was that genetic variant in a in an enzyme that encodes for differences in dopamine, catabolism, and the competent, what's actually related to responses to reward and brain responses to reward. And I thought that this was extremely fascinating, because it directly provided this bridge between really hardwired biological factors a base pair, basically, and this subjective response to something such as like, how much do we value, the same amount of reward, and that kind of got got me into this? Yeah, fascination of how biology relates to this. Very few that are hard to capture subjective experience. And so as I went along, I did my specialisation, and I kind of this biological interest was reinforced by encountering some patients. So one of the first patients I ever treated was a person who happened to have like, typical symptoms of psychosis paranoia, she thought that there were cameras in her bedroom that were broadcasting on the internet on the internet. And it turned out that this person had multiple sclerosis, it was the first manifestation of multiple sclerosis something more or less defined, like a very defined biological process, an autoimmune attack against some proteins in the brain. And this kind of experience really got me into this. Yeah, okay, that this is this is interesting, like how can something so defined on a biological level lead to these very strange symptoms of psychosis? And as I went along, obviously, in many patients, we do not know the biological causes, we are unable to find the biological causes. But I, yeah, thought that these are the symptoms, they, although they are hard to grasp, they occur in these patterns that lead psychiatrists to basically come up with diagnosis. So there is something that kind of, yeah, that allows us to group them together into diagnosis. And although we know that this pattern, this has limitations, but still two psychiatrists see our patients and they might agree on a diagnosis for this patient. And so yeah, I really became more and more fascinated in this, why why do these symptoms occur? And especially these psychotic symptoms? Yeah, in this delusions and hallucinations, especially because they can be triggered by biological processes. And at that time, I then read a paper that was very influential for me, it's a review by Paul Fletcher and Chris breath. Perceiving is believing. It's, I think, a classic by now, but the main idea put forward in this paper is that basically what we talked about earlier today Is that beliefs and perceptions are grounded in the same inferential process of the brain. And we can understand these apparent beliefs and apparent perceptions as the same alteration of how we integrate incoming sensory information with our predictions derived from our internal model in the world. And psychosis in this case can be viewed as a state where our predictions from our model overwrite the sensory input too much in a way that is dysfunctional or maladaptive, let's say. And so that kind of got me started in this opened up like a new framework for really now generating testable hypothesis about psychosis about psychotic symptoms. And I was very lucky to be able to join and Phillip status lab who was a clinician scientist at MIT, and he had just started his lab there. And together, we could now test this hypothesis and test whether psychosis is really associated with an over reliance on these prior expectations. And we did a series of studies and we found some very interesting results. It was, in a nutshell, we found that indeed, people with psychotic experiences are related to an over reliance on these prior expectations. But not always, there are also some other kinds of expectations where that are actually weakened. And I think our working model now is that psychosis, there might be kind of some kind of very automatic predictions of psychosis might become weakened. And that leads to an unstable sensory processing unstable sensory representations. And now in response to that these more higher level or more cognitive priors, more conscious priors, they take over. And in an attempt to restructure this very unstable sensory representation,

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if you can very, I was interested in what you said, at the start of the journey was essentially, you were not sure at that stage, whether medicine was kind of sitting in medicine, the way the way you see, it was fulfilling enough. I'm just wondering, I'm thinking of listeners who might be at the stage of thinking about how to get into neuroscience. And I guess there's these two potential routes, you could go down the clinician science route, but you need to invest in your medical training early on, and it feels like now you've kind of come out the other side of that, and are in a really amazing and exciting place where you can combine the patient work and the and the neuroscience, but I'm wondering, what would you say to your former self? Who was struggling with the or not struggling necessarily, but sitting there Learning the facts about? What would you say to them? About what's

**Caswell Barry** 27:49

in there? Good advice to us.

27:56

I mean, it's, um, I think there's no what unique route to anything anywhere in the world anymore. I mean, obviously, if you want to be a doctor and see patients, you need to study medicine, I think that's a really good thing. But I mean, I'm, I came out on the other side, quite happy about being a physician scientist. And because I think I mean, I'm, obviously would recommend everyone to become a physician scientist. But no, I think what it gives me is, first of all, I mean, on a personal level, it's, it's very satisfying, it's very easy for me to just go back, like if we know and research like, it's can be very tedious at times, that can be long periods of where nothing happens. And where we, it's easy to get to lose track of the of the big picture. And then it's very easy for me to just go back into clinical work. And it's a very different way of working, although it has some commonalities, but it's very easy to find my motivation and just be satisfied by this clinical work. So on a, on a very personal level, it's, I feel really privileged to have this possibility to just go back and see patients. And yet, remember what got me into research, again, and again. So I think that's, that's a very good thing. But then also, like for the research side, I think, and that doesn't mean that people have to do translational science. And I think having a clinical background just gives you a different kind of way of thinking about problems. And I think this is just a perspective that is very important in science. I mean, we need diverse perspectives to solve the difficult problems we're trying to solve. But I think the perspective of clinicians is really valuable. And that doesn't mean that it has to be applied to a clinical problem, but it means just how you think of even about basic science problems is influenced by this clinical perspective. And so yeah, I really feel fortunate that I went through all this because I feel it has informed my science and it keeps it's definitely a continuous source of inspiration for me.

**Caswell Barry** 29:59

I'm I'm really struck by how how motivating it must be to be able to sort of it feels like you're almost back to close the loop. And that you can potentially be seeing in the relatively near future some sort of actual tangible outcome that can be applied to people in the clinic. I mean, do you think that's now that we've got this sort of pretty good model of, you know, the cause of the hallucinations? Do you think that suggests a route through to a treatment profile? Or is that is that actually quite a big step to take?

30:33

Well, I hope it's not that big. But I think, and I'm really a strong advocate of basic science, I think that's what I'm interested in. And so I think we really need to understand the mechanisms to then generate new treatments. So I think we should not jump too early into kind of trying to find new treatments, although this is a goal of our of our outcome, but there won't be good treatments without understanding the mechanisms. And in psychiatry, in particular, that's a huge challenge that we know so little about how the medications we have even work. That's true for antipsychotics. But even antidepressant lithium a very, very effective track is we have no idea how it actually works. So that means we cannot really improve on them, right? Because if we don't know how they work, we don't really know what the next steps will be. So we all we can do is control serendipity, basically what people call it. So we can just try and try and try and see whether we find something and there have been some advances using this approach. But it's not really doesn't seem like the fastest way to get to breakthrough. And that's why I think we really need strong basic neuroscience. And it's not always clear what exactly the outcome of this will be. And I hope that our research will definitely try some new treatments and psychosis. And I'm very confident that it will but it's not exactly like it's not clear to me, it's not clear right now, what exactly these treatments will look like and what exactly it will be. So, yeah, this is just my pitch for basic science.

32:06

I want to make sure that along along those lines, that we get a chance to ask you about your new line of work on immune processes, which I think is you're getting off the ground at the moment. So I'm wondering if you could just give us a few lines on what the what the key focuses there.

32:24

Yeah, so I mean, so I got started on that, because I was really unsatisfied with the causal models we have for psychosis enrolled. And so we now have, I think we now have a way to measure hallucinations, but we still don't have a good way to induce hallucinations. And so I thought that maybe the immune system might be a good way to try to come up with a with a with ideas, how to actually induce hallucinations in a way that is more similar to what happens in people who are experiencing hallucinations. And the evidence for this is. So there is quite a few lines of evidence that suggests that psychosis can be triggered by aberrant immune responses that probably target the brain. And so for instance, we know from epidemiological studies that people with autoimmune disorders, such as lupus, or other classic autoimmune disorders, they have an increased risk for psychotic episodes and the other way around as well. So if you have a psychotic disorder, you are have a higher risk for getting a diagnosis of an autoimmune disorder later on. And if you have an autoimmune disorder, you have a higher risk for getting a diagnosis of psychotic disorder, like later on. So that suggests that there might be some shared process here. We also know that sometimes

33:39

the case for acute infections early in life, someone has a acute infection. Does that change?

33:48

as well? Yes. So in fact, previous infections, both prenatal that also postnatally early in life, but also later in life in general infections in the in the previous history, they also increase the risk for psychosis. And there have been some fascinating case reports, even with COVID, where people have had I mean, it's rare, it's very rare, but it happens, just to illustrate that might be something to it, that people have had COVID, acute COVID And then a few weeks later, they start having really classic acute psychotic episodes. It's something that has been known for other viral infections as well, there is something called post viral psychosis. So that's another line of evidence. The other line of evidence is comes from genetic studies. So there is a there jiwa studies that show that the the some of the genetic risk that is associated that predisposes for psychosis is located in immune related gene regions. The strong set of the jivas was on chromosome six that encodes for the HLA, which is kind of one of the most important immune regulatory regions in the genome. And there are some fascinating case reports, although they are case reports but it's still interesting to to, to know them So, there are case reports of people who had stem cell transplants. a stem cell transplant basically replaces your immune system with the immune system of another person to simplify things. And so there's one case report from a person who had schizophrenia. so upset, treatment resistant, severe psychosis. And, and this person needed a stem cell transplant for another reason, and after receiving the stem cell transplant, so after receiving a new immune system, this person got much better for his treatment resistant schizophrenia. And this is even more intriguing when considered with another case report, which is kind of the opposite of that. So this is a person who did not have any mental health problems, but needed a stem cell transplant. And this person got a stem cell transplant from his brother, who was the only available donor, but his brother happened to have schizophrenia. And so after receiving the stem cell transplant, this person developed symptoms that were consistent with schizophrenia. So, again, these are case reports. So it's always important, it's not a systematic study. So it's important to be cautious when interpreting them. But still, together with all the other evidence, I think it speaks to the possibility that psychosis might be caused by an autoimmune process targeting the brain. And there's more evidence, we also know that people with psychosis have increased inflammatory cytokines in their blood. We also know that some autoimmune disorders really manifest as psychosis. So there's auto immune encephalitis that targets NMDA receptors. And these patients, typically at the very early stages of the disease, they they have psychosis, they have symptoms that they look, as someone with early schizophrenia, it's then evolves further on, and they get more severe symptoms. But still, this just shows that this process in theory, or in principle, can trigger psychotic symptoms. So that's what we're trying to now understand and follow up in the lab and use our mouse model to really get at the mechanisms and understand how what exactly needs to be targeted in the brain to, to trigger these, these experiences to trigger hallucination, like perceptions.

37:10

Now, when I hear cases like that I just realised is, there's so much there is still less to understand. It's really quite amazing system. And yeah, you just you just realise that there's, you think you think you understand how system works or partner system works. And then you have a case like an immune transplant leading to schizophrenia. And now it just completely opens up a new line of inquiry, various ICD

**Caswell Barry** 37:36

is mean, how established it is that is there any role yet for using sort of immune system suppressant drugs to treat schizophrenia or other sorts of Yeah, psychosis.

37:48

So, okay, so there are some studies that show that if you give like an anti inflammatory drugs, such as aspirin, as an adjunctive, treatment to antipsychotics, it kind of has additional beneficial effects. But the effects are small. And there are also some clinical trials that try and have tried to use classical immunomodulatory drugs to treat psychosis. And these trials have been not successful so far. But I think one big issue here is I think Schizophrenia is a very heterogeneous disease. So I, it might be the case that only a proportion of patients is only in a proportion of patients, we find really this auto immune Genesis, and let's say it's 20, or 50% of patients who have this, where it is an autoimmune disease. So if we then do a clinical trial, and we treat like all the patients with an immunomodulatory drugs, and we don't even know exactly, because immunomodulatory drugs, they also target different processes in the immune system. So we don't even know whether we're targeting the right the right the right mechanism. It's just it's very likely that this might be not successful, because it might even if there are effects for some patients that might just dilute out in the in the in the in the average, that is important for clinical trials. And that's why I think the way to go is really understand the mechanisms. And then from there, we can then do stratified clinical trials where we see okay, we have identified a mechanism. So let's let's do that look for patients where we find evidence that this mechanism is at play, because they have an elevated cytokine or because we find antibodies against a certain antigen. And then let's treat these patients with a drug that targets that mechanism. So that's kind of my vision here, but there's a long way to go to get there.

**Caswell Barry** 39:36

Is there anything else you want to you want to cover?

39:39

Maybe one thing i i would like because I've imagined there might be some students listening and maybe one kind of message I have for students. We're thinking about their careers and what steps to take and what is the right way. I think in general, it's I really observed that I made a lot of progress. When I was willing to take risks, and with risks, I mean, when I was willing to embark on a journey that I had actually no idea where it would end. And I would just encourage people to, to be open to kind of taking on risk for their careers, because I feel it usually pays off. If you, let's say, try to go into a new discipline, or if you try to go to move to a new country, I think the the beneficial effects just just yet doing these, these moves are really high. So if you have an opportunity to do something that might seem a little anxiety provoking in the beginning, just try to remember that usually, these steps can pay off very well at the end. So that's just my encouragement for people take risks if you can.

**Caswell Barry** 40:45

Okay, fantastic. Thanks, Katrina. So we're almost out of time, and we're going to need to wrap up, but before we do, we'd like to ask each of our guests the same question. So are you ready? What's your favourite fact about the brain?

41:01

Yes, so my favourite fact is actually my kids favourite fact about the brain, which is about brain freeze. I don't know whether you've heard about this phenomenon. So if when you eat something very cold, you get this sharp pain in your forehead, I guess I've never experienced it, my kids experience it. And it actually has a medical name. It is called sphenopalatine ganglion neuralgia. And the phenomenon behind it is quite interesting. So if you eat something very cold, your blood vessels just shut down because they it's too cold. And then when the blood vessels shut down, they usually after that, they just like, open up all the way. And that is what, what leads to this pain. It's like when you have very cold hands, and then they warm up again, it's really painful. So that's the same thing that is happening there. And it happens more frequently in kids, probably because they just eat more ice cream. And like larger amounts of ice cream, so that's why they get no brain freeze.

**Caswell Barry** 41:58

That's amazing.

42:00

I go straight to my three year old.

**Caswell Barry** 42:04

Do you remember the name though? Steve, I'm gonna test you on it. Let's

42:06

not remember the very first episode to get. That was just a fascinating discussion. So thank you, Katerina, for joining us on this episode. Great.

42:16

Thank you. It was a fun discussion. Thanks.

42:19

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