Brain Stories Ep 6

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**SPEAKERS**

Sanjay Sisodiya, Caswell Barry, Selina Wray

**Caswell Barry** 00:02

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

**Selina Wray** 00:06

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

**Caswell Barry** 00:18

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

**Selina Wray** 00:28

And today, we're really excited to be joined by Professor Sanjay Sisodia. Sanjay is a Professor of Neurology at the UCL Queen Square Institute of neurology, and an Honorary Consultant neurologist at the National Hospital for neurology and neurosurgery and the epilepsy society. Sanjay studied medicine at the University of Cambridge and guy's hospital, before training in neurology at Oxford and the National Hospital for neurology and neurosurgery. He was awarded his PhD for working in brain magnetic resonance imaging in epilepsy. And his key interests are epilepsy, difficult to treat epilepsy, epilepsy, genetics and treatment, response genetics and translational neurology. He runs several epilepsy and specialist epilepsy genomics clinics and is the chief investigator of several international projects. Recently, Professor Sisodia was appointed as the Institute of neurology is Deputy Director for sustainability and climate change. And His research interests also include the impact of climate change on neurological disorders. Sanjay, thank you for joining us, and welcome to brain stories.

**Sanjay Sisodiya** 01:40

Thank you very much for inviting me.

**Selina Wray** 01:41

So maybe we can start by hearing directly kind of from you a little bit about your research interests and what your your work is on at the moment.

**Sanjay Sisodiya** 01:51

Well, my research is driven by my clinical work. And in my clinical work, which is a very specialised practice, I see people with difficult to treat epilepsies. Now, you may know that epilepsy is not one condition, but a whole group of conditions with a range of different causes and different features. But about one in three of the epilepsies are difficult to treat, which means that with all the medications that we have available, with other treatment options, like ketogenic diets, or even surgery, seizures continue to happen. And in association with this, there are a range of additional difficulties called comorbidities. So my practice is almost entirely now composed of seeing people who have these difficult to treat epilepsies. And that's what drives my research to try to understand why people have these difficult to treat epilepsies what's going on in the brain? And how that understanding can help us improve the treatment options that might be

**Selina Wray** 03:04

available. And these can obviously be really debilitating conditions. Are you at these difficult to treat epilepsy is generally things that start in childhood, or can they, you know, kind of span the whole lifespan of an individual.

**Sanjay Sisodiya** 03:19

So both so many of the difficult to treat epilepsies that I see did start in childhood. Many of them have a genetic cause. But not only that, some can also start later in life in adulthood, and still be difficult to treat.

**Caswell Barry** 03:36

Are these difficult to treat epilepsy? Are they a sort of specific set on their own? Or is this just the end of a continuum? Are they are they like normal epilepsies? But worse, or do they sort of are they actually a distinct group?

**Sanjay Sisodiya** 03:50

Well, it's good question. I'm not sure that we have the real answer to that yet. But certainly, there can be a type of epilepsy within which there are people who have that type of epilepsy and respond well to drugs, and other people who appear to have the same epilepsy and don't respond to medication. But there are also a group of epilepsies, where it seems like most of the people who have that condition, have seizures that are very difficult to control with medication.

**Selina Wray** 04:18

You mentioned the genetics underlying these diseases. Now, what has that told us about the kind of mechanisms of these difficult to treat epilepsy as Have they given insights into kind of biological pathways that we can then target?

**Sanjay Sisodiya** 04:36

Yes, they have. They have it's been a very interesting journey in epilepsy genetics over the last 10, maybe 20 years. And what we're seeing is that many of the clinical pictures that we recognised as practising clinicians what we call syndromes, are now turning out to have a genetic cause. So we first saw a group For people who thought had the same thing, we didn't know what the cause was. But with genetic technologies available to us today, we can work out what the genetic cause is, by studying a group of people with the same condition and finding hopefully that they have a change in the same gene. The range of genes involved in the epilepsies, especially the severe epilepsies, that we're talking about is really broad. And many, many different types of gene with different types of processes, different pathways within which they reside, have been shown to be involved. So for example, there are so many epilepsies, which arise as a result of genetic alterations in genes that encode ion channels. And that sort of stands to reason because Epilepsy is a disorder of brain excitability and brain excitability depends on ion channels. And so that sort of makes good sense. But there are also a whole range of other genetic epilepsies, which don't directly involve alterations in ion channel genes. Essentially, there's a huge range. And we're learning a lot about the biology of the epilepsies, generally, from this gene driven perspective.

**Caswell Barry** 06:14

And this might be quite a naive question. I'm more of a sort of systems neuroscientist, but he you sort of described these as genetic epilepsies? What are the sorts of epilepsies? Are they? Are they not all genetic in nature or

**Sanjay Sisodiya** 06:26

so my own view is that it's likely that people's genetic makeup has some influence on their epilepsy. So sometimes there may be a change in their genetic makeup that is so drastic, if you like. That, by itself, it's enough to cause that person to have seizures and associated features. But I think that there's probably also a contribution from less drastic changes in many other people who have epilepsy. So small changes, common variation in lots of different genes adding up to contribute to the chances of that person having seizures. And so it could be, for example, that somebody has seizures, ostensibly because they had head injury. We know for example, soldiers who suffer head injuries in conflict, may go on to develop epilepsy. But I think there's still a question about how much the genetic background contributes to that risk. It may be that actually, if you have a genetic background, favouring the development of seizures, you're more likely to have seizures as a result of another insult whether that's a head injury or a tumour or some other cause. That's not proven yet. That's a hypothesis.

**Selina Wray** 07:46

And so by, I guess, this is kind of a similar question or a follow on question, as well as knowing that some genes are causative, can there be within a specific group of their did the numbers of patients exists, for example, to do things like genome wide association studies to look for disease? modifiers? So coming back to the earlier question, if there are people with a type of epilepsy, if we can call it that, but we might understand what changes someone's severity of their condition?

**Sanjay Sisodiya** 08:18

So really good question. And it's really interesting that you've hit upon what we are looking on looking at exactly. Now. So this is a really important question, I think, because I think there are clues here potentially, to new understanding and new treatments. So exactly as you say, even though many of these genetic epilepsies are rare. There are still sufficient numbers for some of them to develop an understanding of the spectrum of severity and the spectrum of clinical presentations that people might have. So if we take one particular condition, that's a paradigmatic epilepsy if you like an archetypal epilepsy, genetic epilepsy, it's called Dravet Syndrome, after the French paediatric neurologists to first described it, Charlotte Dravo. And this is a really important and intriguing condition. In most individuals who have this condition, it is due to a new alteration or de novo mutation in that person in the gene encoding one of the neuronal sodium channels the gene is called SC n one a. There's a very recognisable core clinical phenotype. And that's of course, how the syndrome was first described because there is a recognisable set of features that people with this condition have. As clinical diagnosis, you don't have to have a mutation SCR one A for the diagnosis to be made, although that's what you usually find. But even people who got very characteristic core phenotype You can still see a really wide phenotypic spectrum. So, I see just because of my interest, I see quite a few people with this condition. And although many have epilepsy, it's difficult to treat associated with intellectual disability, and physical disabilities, such as difficulty walking or difficulty swallowing, for example, you can still see some people who, despite the fact they have the same colour phenotype, are still able to walk and talk and eat normally, and can hold a conversation. And there must be something that explains that phenotypic spectrum. It's not just because of the different types of mutation SCN one a that people have, there must be something more. So taking your point up, we've been we started to look at the rest of the genetic variation in the background, if you like, in a group of people who have this condition, taking advantage of the fact that in the sense, you've you fixed or control the main genetic variation causing the condition?

**Selina Wray** 11:07

Are those genome wide association studies, I assume are ongoing at the moment.

**Sanjay Sisodiya** 11:12

They are they are

**Selina Wray** 11:15

so very much watching this space.

**Caswell Barry** 11:17

Yes. What sort of tools do you use to do that? So as you were talking, I can help thinking this sounds like the sort of thing where, you know, they might expect sort of fancy machine learning approaches to sort of come in to sort of both cluster symptoms to try and identify sort of under low lying groups, but also maybe even to ultimately relate, you know, specific genetic mutations to expected function, maybe even via protein folding. Who knows?

**Sanjay Sisodiya** 11:45

Who knows exactly. And there's so many exciting ways to look at complicated data these days. The key, of course, exactly, as you both said, I think is is the numbers. And we have got a sufficiently sized group of individuals who've got this condition with known mutations in SEM money, that I think we can begin to start exploring that there's not 1000s and 1000s, that would be very hard to do, but sufficient that we can begin to use these sorts of methods. So we can look comprehensively at genetic variation, we can bring in brain imaging data, we can bring in EEG data, as well as the clinical data, and then start to use other tools to try to make sense of those data and see where this variation might arise. So machine learning will be one way to do that. Category wise association studies another way to do that another tool to use this really will depend on the on the depth and quality of the information that we're able to secure for each of these individuals in the study.

**Caswell Barry** 12:47

And, and how's this? How's the work so far in sort of isolating these different groups? Is it does that does that translate into new treatments yet? Are we still waiting to take that step are we sort of building the background understanding still or have had the last sort of 510 years resulted in different approaches to actually control epilepsy.

**Sanjay Sisodiya** 13:08

So if we go back to thinking about single gene causes, and if we if we stay with that model, where we think that a single gene is having the most important effect, and the pathways that are disrupted are the most important in that individual's epilepsy, then certainly for some of these epilepsies, better understanding has led to more specific treatment options or a better understanding of the available treatment options, and which drugs for example to use and which ones to avoid? And that's certainly the case. And there are some outstanding examples of what you might call this precision medicine approach involving genetic data. I think it is important to say, though, when we're talking about precision medicine, that, at least I hope, that's what we've always been doing. Actually, we've always been using all the available information to provide each individual with the best available treatment. What's what's changed, I think, is that we have much more personalised information from that individual's genome, which empowers the precision medicine approach, but it's not really that the approach is new. The approach is something that we've always tried to do, we just haven't been. We haven't had access to as much information as we do. Now. With regard to modifiers, I think that's much further behind, if you like, and we're not at the point yet, where an understanding of the modifiers has, has come into clinical practice in terms of how you change treatment.

**Selina Wray** 14:37

I wonder if I could follow up on something that you kind of mentioned about really, it seems that what is essential to our work is having this real kind of depth of phenotyping of the patient's experience and the patient's kind of symptoms. And I guess if for anyone listening who's not part of the Institute of neurology, they may not be aware of that. There's kind of a purpose built clinic for this where I think you spend, this is where most of your clinics are based, is that correct? For the child font centre?

**Sanjay Sisodiya** 15:08

Yes. So, so we started an epilepsy genomic clinic some years ago now. And that's where we try to bring all of these different strands together. And there are lots of good bits to a week, obviously. But it does tend to be one of the highlights of the week, when you can bring your understanding and the research that's being done to life if you like, and take it back to people who've got these conditions, and help people understand what's going on. And that helps you in turn, because people have these rare conditions and their families understand them really, really well. They've often spent years looking after their grown up children, for example, and have a really detailed understanding, they may not have the vocabulary, and sometimes we will find it difficult to describe what's going on. But their understanding can really guide and inform the research and send you down the important directions and make sure you don't go down. You know, pointless alleyways

**Selina Wray** 16:13

must be really quite empowering for them to to really feel that they're feeding into that process and CO developing almost the research directions.

**Sanjay Sisodiya** 16:24

Absolutely. Absolutely. It's it's definitely it is a very rewarding process for everybody who's involved, actually, because I think you're exactly right, that people feel they're contributing, and hopefully preventing the problems their children have had from happening to other people. And we feel, I think, and especially, you know, members of the team who maybe spend most of their time behind a screen or in the lab, actually taking that back to somebody who's got the problem really gives it a different dimension, and I think really motivates their work. So it's a win win.

**Selina Wray** 17:03

So I wonder if I could change slightly the kind of subject we've asked you a lot about the kind of genetic epilepsies and the genetic basis for epilepsy. But one of the things that I know you've been working on recently is the kind of environmental modifiers of people's epilepsy. And I was fascinated to find out that climate change may actually be a disease modifying it. Could you tell us a little bit about what we know about that, please?

**Sanjay Sisodiya** 17:31

This is, I think, a really interesting and important development of what we've been doing. The whole area of genetic epilepsies became interesting to me, when I first saw somebody as an adult, who turned out to have a genetic epilepsy, he was in his 50s. And at that time, I wasn't really thinking about genetic causes of epilepsy so much. But at some point, in his care, the penny dropped. And it became clear that he did have a genetic epilepsy actually, he had Dravet Syndrome. And at that time, the condition had been known as severe myoclonic epilepsy of infancy. And so most adult neurologists weren't thinking about it, because it was of infancy. So why should it concern us, it doesn't obviously happen in adults, but this person that had had seizures for their whole life. And in fact, when you went back to the very first records, which we actually had more than 50 years old, you could see that he had a free typical history for Dravet Syndrome. So we made the diagnosis, and got genetic confirmation, because at that time, we weren't thinking that people of this age could have that condition. But he did have a variant of that gene changes treatment, and significantly improved the control of his seizures. But actually, it was it was studying and looking after people with Dravet syndrome that then brought in the whole environmental aspect, because it was families of people with Dravet Syndrome, who started saying that their grown up child is an adult who has had seizures that were worse during the hot weather, especially during the heatwave that we've all experienced in the UK and in Europe over the last decade or so, there had more seizures, and other features such as lethargy, or worse during this time. And then the penny finally dropped, again, linking my own sort of personal concerns and interest in climate environment with my professional work. I hadn't really put together before, but it became sort of obvious that the climate must potentially have a role and must impact severity, frequency of seizures, all sorts of features in people with epilepsy, because we know for example, that some of these epilepsies have fever sensitive seizures. And so it makes sense that if the environment changes, then actually the epilepsy might change too. So that was sort of next time point really in thinking about actually what is going on in these epilepsies? And what impact is that of the environment?

**Selina Wray** 20:05

And are there now data starting to emerge around this? Because as you've just described it, the awareness came from people saying, well, look, this is what's happening with with my child's condition. But there is the data kind of emerging on kind of how susceptible people are to these temperature induced kind of worsening of their condition, if I'm making sense, rather than kind of the individual and anecdotes is a worldwide view emerging from this.

**Sanjay Sisodiya** 20:35

Yes. So I think thinking in this area is really developing rapidly. So when I first started thinking about this, I contacted a few colleagues around the world, tentatively, because I had no idea what the response would be I kind of I suppose I was a little anxious that they would think this was a totally mad idea, and that I should get back to my day job. But in fact, that's not what happened. And they too, I think, had a moment of connection. And thought, actually, what might happen, you know, if if everything changes or not, if when everything changes. And so we then began to get together and think about this more and try and get more data together, we formed a group called epilepsy, climate change, which is just a loose affiliation of people who are concerned about this around the world. And we're trying to get data together. So I think we're still in that stage between anecdotal and sizable large scale studies. But we are getting data together, we are getting signals from a variety of different sources, ranging from larger scale collection of seizure data from individuals to nation wide data sets, in some countries where they have excellent records of both climate and, and epilepsy. Admissions, for example.

**Caswell Barry** 22:08

This is totally fascinating. It's not something I'd ever, ever thought about. Selena mentioned it this morning, when we were talking about having what we were going to say to you, and I guess it just blew my mind. Have we gone far enough yet to know whether, for example, is it just something like, you know, the mean background temperature is likely to be a factor? Or is it something like maybe temperature spikes? I guess, I'm thinking a little bit like febrile convulsions in in children, I believe, are more about the rapid rate of change rather than sort of sustained body temperature, I wonder if the same might apply to sort of you step out of an air conditioned room into like 40 degrees? Is that it? Do you think I don't, I don't want to make you say things you don't know already. I'm just curious what your thinking is? Well, I

**Sanjay Sisodiya** 22:52

think these are all really interesting points. I think once you get thinking about it, you know, all sorts of potential connections and complications emerge. So anecdotally, the point you make about the rate of change of temperature seems to be key. So that does seem to be important in febrile seizures, but also, in people with Dravet Syndrome. Many of the families, again, anecdotally report that peak temperatures, so hot days can certainly make a difference. But also rapid changes in temperature. So for example, one of the mothers of a child with Dravet Syndrome, very nicely describes how it's very difficult when it's hot for her to take her son out. Because one of the comorbidities is behavioural difficulties, or autism spectrum disorder, a number of things that make it difficult, for example, to persuade somebody with this condition to wear a sun hat. So that makes obviously the problem worse. And then you've seen these fountains that we find in public spaces where people will be cooling themselves off. So of course, the natural thing to do, but in some people, this condition that provokes seizures, that rapid change in temperature seems to provoke seizures. Now, that's still anecdotal, and it's still something that we need to explore. But I think it is something that we need to consider. Because although we are obviously warm blooded creatures, and we do thermo regulate, there are limits to that thermo regulation, and I think we're beginning to see where those limits are and how they can be challenged. So you're right, I think it's not just at the the kind of mean temperature, but also temperature peaks. I think it's going to be both

**Selina Wray** 24:33

it's fascinating and I think again, it kind of this it's hearing this is really powerful to me because it just shows you the the importance of actually listening to what people who are living with these conditions are telling you. And kind of actually noticing the patterns when multiple people are coming and giving you slight variations of the same story then you realise No, actually there's something here that we need to investigate, and I presumed that epilepsy wouldn't be the only condition that could be affected by these changes. Is it known if other neurological syndromes could could be impacted by by this?

**Sanjay Sisodiya** 25:15

Yes, absolutely. So we already know that this is the case for some conditions. So for example, we know that for some people with multiple sclerosis, that symptoms may be aggravated or brought on by high ambient temperatures. So that's so that's, that's been done some time called do tufts phenomenon. But we also know that for some other conditions, there is growing evidence of a link with peak temperatures. And with higher mean temperatures, and some quite good data actually, on rates of increase of incidence of various things like stroke or admissions for things, including stroke, but also for some mental health disorders associated with increased temperature and hot days. So it's actually more and more evidence accumulating to show that, that, that temperature and humidity changes and pollution, of course associated with with global heating, or can have an impact.

**Selina Wray** 26:18

And so it's another reason as if we didn't need more reasons, but another reason that we actually need to listen to the evidence and take action. And so obviously, this conversation is very topical, because we've just had the cop 26. Summit. Was this featured in the discussions anywhere, this kind of impact on neurological syndromes. It should have been right. We should be shouting about it, I think,

**Sanjay Sisodiya** 26:43

yes. Well, given the the disability that neurological diseases cause globally, and the mortality with premature mortality with which they're associated, you would think that this would have been higher up the agenda. I wasn't at COP 26. So I don't know absolutely everything that happened. But it didn't feature highly health did feature more than it has done in the past, which is an excellent outcome, but not specifically neurological diseases, to any great extent,

**Selina Wray** 27:14

seems like it will be something at least that will gain a lot of momentum in the coming years as people as as you say, is the data and the evidence really starts to emerge. I think it's, you know, another reason that we need to get our act together. And quickly, I think

**Caswell Barry** 27:29

I'm curious more on this sort of climate change related neurologic questions. Is there any direct link through co2 concentrations by chance? Is that is there? Should we worry about that on top of just the change in sort of background temperature, we also going to see sort of a direct mode of action, do you think?

**Sanjay Sisodiya** 27:50

So? It's, again, a really good question. And we know that humans are very sensitive to carbon dioxide concentrations. But I'm probably not the best person to ask this question. Actually, you really need a human physiologist or a respiratory physiologist to be able to answer the question in terms of the sensitivity, because obviously, we're talking about parts per million change in the environmental concentration. Certainly, if you make percentage changes, you know, I've no 1% changes or something. Those are things that I think most of us would feel, and that would lead to a change in our breathing. But whether that sensitivity is at the level that we're talking about the climate? I don't know, I'm afraid,

**Caswell Barry** 28:33

excellent to find out. Yeah,

**Sanjay Sisodiya** 28:35

yes, absolutely. And

**Selina Wray** 28:36

so I wonder if we could maybe move away from your current research. Talk a little bit about you, Sanjay, and how did you What was the trajectory that kind of brought you into this area? How did you first develop your your, your kind of interest in medicine and your, your interest in epilepsy?

**Sanjay Sisodiya** 28:56

Well, so when I first started, I was really interested in the, in the science. And I found that really fascinating. I have to say, I found being a medical student, not particularly enjoyable. The time that I was doing, I think we were definitely to be placed on the corner and not to be heard. So I actually that wasn't everyone's experience, but I didn't enjoy being a medical student. It was really I think, when I first did neurology, that that excitement of putting the science into practice came back into the work that I was doing. And then I became interested for various reasons in nonlinear dynamics. This was a time when Fractals have become sort of very popular. So I was looking to see if I could somehow wangle that into into medical science and research and an opportunity arose which I thought might allow this to take place. And it happened to be in epilepsy. I didn't know anything about epilepsy at all at the time. And I remember that my, my clinical supervisor at the time said, Do you really want to be doing clinics in epilepsy for the rest of your life? And actually, I do, I have, and I've really, really enjoyed it. It's been amazing. And so that's how I got into epilepsy. And then from there, things just developed as all sorts of opportunities arose. It's just chance, really, as I think many things often are,

**Caswell Barry** 30:34

are there any sort of specific events where you sort of really realised, yeah, this is this is the right one for me, or, or maybe where you actually did get fractals into the clinic, I'm not sure whether that's how easy that would be to do.

**Sanjay Sisodiya** 30:46

I didn't get fractals into the clinic, I definitely got fractals into the science. And that was, that was an exciting time was I think the the excitement of being able to follow your ideas during your PhD and to be given the leeway to do that, actually, I had two excellent supervisors who let me do that. And it was nice to be able to develop ideas and to think about things in a different way. And I guess, since then, there have always been, you know, turning points. So for example, the first patient in whom I made a genetic diagnosis had a huge impact on the way I thought about epilepsy. And in fact, one of the most important things about that was, was the fact that it was never too late, should never give up. Because even at his late stage of his epilepsy, he's in his 50s. With a Lifetime, literally of seizures, it still made a huge difference. And that was a huge lesson. And then I guess, the next turning point in terms of bringing the climate work into it, there have been, I guess, the key turning points.

**Caswell Barry** 31:51

And we were tempted. So you said you sort of started off on medicine, then? And then you branched out and did a PhD? Was it ever in doubt that you'd go back to sort of a mixture of research and clinic? Or were you ever tempted, just stay, stay in research when she'd got there?

**Sanjay Sisodiya** 32:08

I think I was attempted a little bit. But at the end of the day, I think what really interests me is the interface between the two and taking the science back to people who are affected by these conditions. And in thinking what we can do for people who have these conditions and how we can use science to do that. It's that back and forth, which I think really makes. It's what interests me in what I do, and it's what gets me up and keeps me up.

**Selina Wray** 32:40

And what would you say are the things at the moment that you're most excited about it? Not? It can be in your own research, or just in the field more broadly? You know, what are the things that you think, yeah, we need to kind of keep an eye on this.

**Sanjay Sisodiya** 32:54

Cautiously, there are lots of things that really excite exciting, I still think that there's a lot to do in genetics, we're just scratching the surface. Really, I think we've been lucky in a sense in that there are some epilepsies, where single gene defects can produce detectable phenotypes that we can study. But I think there's a lot more there still to do. There's the whole of the rest of the genome, there's the non coding genome. There's the epi genome regulation. And you know, we understand so little about all of this in real practice. So there's huge amount there to do. And that's certainly I think, something that I find really interesting. But also, I think that climate change work, I think is really important, because this is something that's going to happen. Even if we stopped all carbon emissions tomorrow, there's embedded changes that are going to happen. And I think we have to understand what that's going to mean for people with these conditions, and how best we can help people cope and adapt.

**Caswell Barry** 33:55

And just pushing you a bit more what what do you think if I said, next 10 years, what's going to be the sort of the big thing, the big development or the big thing you work on? Will it be? Would it be more sort of feeling out the effects of climate change? Or do you think this link new on the horizon?

**Sanjay Sisodiya** 34:13

It's so difficult to say, Isn't it because of course, something can happen tomorrow that changes your perspective entirely. But I think it's going to be to better understand each individual's epilepsy using all the data that we have available and to put those data together. So it's not just looking at the genetic changes, but also thinking about how imaging is telling us what happens over the course of the epilepsy, a sort of diary, if you like, of changes that have happened over time, and how EEG and the microbiome and all sorts of other areas of variation that we haven't looked at, if you put all of those together, can you better understand each individual's epilepsy, because one of the things that I think has become clear Over the time that I've been doing this, I calculated that I've seen over 10,000 people with epilepsy, I don't think any of those two people are exactly the same except two particular individuals who are not related who have astonishingly similar conditions, which must be genetic. We haven't sorted that out yet. But it must be genetic. But otherwise, I think everyone is different. They fall into certain categories, but they are all different. And we have really fragile understanding of what drives those differences. And yet, in those differences, might like click might like clues to treatment, if someone's got the same condition, but they're much less severely affected. Why is that? And can that help us understand somebody who's much more severely affected and what we can do to help them? It's fascinating,

**Selina Wray** 35:42

and I think about this in my own area of a lot of Alzheimer's disease that we now we have a reasonably good understanding, I would say in Alzheimer's of the genetic basis. But when I try and think about the number of permutations of genes, environments, genetic regulation, you know, diet, lifestyle impact, there are so many different permutations that it makes sense to me exactly what you've just said that no two people will therefore have the same experience. And but as a cell biologist, I think why will we ever will biology ever keep? Would we ever? Will we ever managed to disentangle this. So I'm happy to hear your your kind of optimism around that. Because I think you're right, there are just such opportunities there to to have an understanding the science scientifically interesting, but that will also benefit the patient and their care. So it's kind of nice to hear that optimism.

**Caswell Barry** 36:38

So we're almost out of time, and we're gonna need to wrap up. But before we do, we we like to ask all our guests the same last question. Are you ready? This is it. So what is your favourite fact about the brain?

**Sanjay Sisodiya** 36:49

I hate to disappoint you, I think actually, because I don't know if I have a favourite fact about the brain. But what I always find really amazing, I think is how quickly we can think about things and how quickly, literally, within the course of a sentence, you can link so many different ideas together. So I'm not sure if that's a fact. But but it's certainly fascinating, I think.

**Selina Wray** 37:15

I think it's a perfect point to kind of finish and to go away and ponder on how amazing the brain is. And we've heard a little bit more from a different perspective today. So thank you very much, Professor Sisodia for joining us on this episode of brain stories.

**Sanjay Sisodiya** 37:31

Thank you very much.

**Selina Wray** 37:36

We'd like to thank Matt Wakelin, Maya Sapir and Trevor smart for their roles in taking brain stories from an idea to a fully fledged podcast, Suzie McCarthy for editing and mixing. And please follow us on Twitter at UCL brain stories for updates and information about forthcoming episodes.