BrainStories Ep 3

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**SPEAKERS**

Andrew McCaskill, Caswell Barry, Selina Wray

**Selina Wray** 00:01

Hello and welcome to brain stories. I'm Celina Ray, and I'm here today with my co host Caswell Berry. On brain

**Caswell Barry** 00:07

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.

**Selina Wray** 00:16

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

**Caswell Barry** 00:28

Today, we're joined by Dr. Andrew McCaskill. Andrew is a Wellcome Trust. So Henry Dale fellow interested in hippocampus and its role in value based decision making. He's previously worked on the striatum as a Henry welcome postdoctoral fellow when he was at New York University. And he did his PhD with Joe kidder UCL before that he was an undergrad at Cambridge University. Andrew, welcome to brain stories. Thanks very much for having me. It's very nice to be here. Oh, Sandra, can you tell us a bit about who you are? And what your what your research is about?

**Andrew McCaskill** 01:00

Yeah. So I guess I Glaswegian neuroscientist, and I guess we I've recently in the last few years, set up my own lab really interested in it, the mechanisms of how we learn things, and how we use that, that that learning the memories of that learning to kind of guide guide decisions, to get what we need and what we want. And I'm particularly interested, I guess, in Firstly, how that these kind of processes can go wrong in disease. And there's a lot of evidence that, increasingly, that these are the kind of processes that go wrong, and almost almost all mental health disorders, for example, such as anxiety, depression, these these kind of things. But then also, I'm interested really in the mechanistic details, not because like I mentioned, the star, I'm originally a biochemist. And so I'm very much interested both at how the learning actually happens in the kind of fool animal, but also really like the molecular and cellular process for like, how, how is this actually being done by the brain? And with the hope is that we can use information to kind of get at with what's gone wrong, when it goes wrong in disease.

**Caswell Barry** 02:09

And so when you when you say the brain, are you interested in specific regions? What are the you know, for the sorts of tasks, you're interested in animals learning things? What are the what are the relevant brain regions? And why do you think those are so interesting?

**Andrew McCaskill** 02:23

I guess, really, the fundamental thing that that I'm really fascinated by is the fact that we are really, really good at understanding relatively simple learning processes. So everyone has this idea of like Pavlov's dog, right? We've probably most people have heard about this, right? You should ring a bell and then give a dog a bone, it will, it will eventually learn that the bell predicts the bone and will start to salivate to the bell before you even give it the bone, right, this kind of classic classic learning. And so after all that discussed, I'm actually not particularly interested in that kind of learning. But right and because we know a lot about it, what I'm actually interested in is when this kind of learning becomes a bit more complicated, again, so for example, when what happens if the bell suddenly means something else, and you have to update your learning, right about about about that. So for example, the bell suddenly means a cat instead, right? That you have to change your entire learning process. And so for these kinds of things that brain regions are involved in that are kind of more complicated. And so they're in their region, such as the hippocampus, which goes I mentioned before, the prefrontal cortex, and how they interact with the kind of classic learning circuitry that's involved in learning such as the basal ganglia, such as the striatum and the ventral tegmental area. So what I find really fascinating is that all of these kind of high order places like the hippocampus and prefrontal cortex, are actually mainly thought to be involved in kind of spatial type type tasks. Whereas what we're really interested in is how they're actually utilised to learn and to learn flexibly, what I mean by flexibly is the ability to kind of update what you've learned, and understand that you need to constantly be updating your your, your strategies, and of what you're learning about and how you're using it to kind of optimally behave, I guess. So as a result of that my lab is kind of focused on mainly the hippocampal circuits and how to interact with the kind of classical learning circuitry in the striatum and the ventral tegmental area.

**Selina Wray** 04:26

And so I assume that you are testing this in kind of rodent models as your experimental system. Would that be correct?

**Andrew McCaskill** 04:34

We are Yes, yes. So again, yeah, but my my massive focus is because I'm a biochemist is because everyone understand the cells and the molecules underlying this, but as a kind of first step, we always need to be able to explore the behaviour itself. And so we need to have this kind of halfway house. It's where we're a system where we can actually get animals to do these kind of complicated type behaviours, and the kind of not trivial, right even even like Google's fancy AI that can beat People that chess really struggles with these kinds of cognitive, cognitive flexibility type tasks, as well might, what nice thing is that mice can do these kind of tasks. But also we can use mice to really image in real time and record in real time from individual neurons in these brain regions. While they're doing the task, we can use lots of fancy kind of manipulations such as things like optogenetics, chemo, genetics, and other kind of tools to activate or activate in particular patterns, the different neurons to look at the causality of their activity. And then also something that my lab is very much focused on, is we can actually use similar tools to look at how the different brain regions actually connect with each other, and what information they're actually sending to each other that allows them to, together as a kind of whole support these kind of behaviours, let's see, how does that balance between being able to look at selves, and but also be able to look at those cells in an animal that's actually doing a task that's that's fundamentally complicated, and has direct relevance to disease and mental health?

**Selina Wray** 06:02

It's fascinating. So could you give us an example? And you know, if I'm trying to visualise this, what is what sort of tasks do you ask these animals to do to kind of test this adaptive learning?

**Andrew McCaskill** 06:13

Yeah, yeah. So there's multiple ones, I guess. But the simplest one, I guess, is, is what's called probabilistic reversal learning, right? And this is an awful name, right? It sounds so mathy. And there's like, everyone's like, Oh, no. So it's not that bad, don't worry. I mean, essentially, it's the idea. It's basically slot machines, right. And so we all have this idea. If you go into like Las Vegas, and you have a big roll of slot machines, there's like 100 of them, right? The game there is to try and work out which one is going to is going to pay you out with the highest likelihood. Okay, and the most people won't go in there and just randomly pull levers, right, they'll they'll even if you know that it's the last cause, you're probably going to try and strategize about which one's going to win and which ones losing a particular way. And so forth. The key with these kind of bandit tasks, or these kind of reversal learning tasks is that they're constantly changing to avoid you being able to work out right, it would not be a very good casino, if one machine was the one that paid you out 70% of the time, always right, and it just stayed like that, then everyone would know whenever they would lose money. So the way you learn this is to, you have to quickly work out which one's the best, but then constantly be looking out for it not being the best anymore, and looking for other options to try. So you can imagine that kind of classic learning like Pavlov's dog would be the situation where only one of the slot machines was the best one, right, you can very nicely learn, right? If I press the lever of this particular machine, it will, it will reward me and I can start to salivate other prospects of money coming out the machine, every time I press the lever, right, but what I can interest in is kind of flexible behaviour is the ability to realise that at this particular time, this machine is the one that's given the right the best money, but also when it stops being the ability to switch my behaviour to start pressing another lever that I've now inferred as the one that's that's the best lever.

**Caswell Barry** 08:17

So as you're describing this, it sounds like you're sitting at a really interesting intersection. because on one hand, you were saying how you're interested in sort of effectively the biochemistry of learning sort of what's happening the level of individual neurons, and another level, you're sort of dealing with the whole animal. So you're looking at sort of networks, and what's happening, you know, a population of neurons. But actually, it sounds that we've described me as sort of quite highly theory driven as well. So there are, it sounds like this sort of task is exactly the sort of thing that can be described quite simply with theory, and you seem to be set at the sort of the intersection of those things, or sounds very exciting. I mean, is that, would you say that's a fair assessment of the situation? Yeah, well,

**Andrew McCaskill** 08:53

that's really no good. I think that is exactly what we're aiming for. Yeah. So I obviously find that very exciting, as well. So I'm pleased that you did as well as, yeah, so a lot of, basically, our aim is, and I think we may be an issue with what we've been struggling with in the past is that we've essentially been focusing on recording from neurons or doing can omit patients in tasks that are really historically good for probing that region of the brain, in a most, for example, see, and so what we run the risk of there then is like, potentially inferring the function of that, that neuron or that brain region, solely in terms of the task that we're doing, right. And so what we really, really want to get at is, well, if we do a task that we can kind of mathematically understand, okay, I know that's super boring, but like it's actually really exciting. For me, at least it's so like, the nice thing about these kinds of tasks is you can actually create a computational model that will solve this task, and you can match how the model behaves to match the behaviour of the Most within the trial, what that means is, instead of being like this neuron fires when the most presses the the right lever that was high and then get the reward, you can be like this neuron fires, when the most thinks that there's like a 67% chance that the roads going to be, the leader is going to be rewarded. Whereas this lever fires when it's pretty sure that the other lever is going to be rewarded. But it's just testing out the wrong lever just in case something's changed. And so with this kind of like, framework, it actually although it seems ridiculous to try and go from cells through theory to full behaviour, I think the adding in the theory actually provides that link, because it provides a kind of hypothesis for what we think the individual elements of the circuit, which in our cases the cells should be doing, in order to carry out the task. And so actually gives us what we're what we're looking for, rather than experimentally looking at things are experimentally defined, we look at things that are actually defined by the calculation the most is having to do in real time.

**Caswell Barry** 11:05

So it also I guess, to develop what I said before, is what it sounds, essentially what you're describing is form of reinforcement learning, which I guess is more commonly associated exactly the things that you said before, like DeepMind, DeepMind, agents that are being trained to like beat each other at chess or something like that. Is that true? Am I right in saying, essentially, what you're looking at is a biological simple biological analogue of reinforcement learning? And do you think there are actually points of contact between sort of what essentially is become a successful theory and machine learning world and how the brain solves these problems?

**Andrew McCaskill** 11:40

Yeah. And so that's, I think that's something that's super fascinating, right? And so I need to be wary of my own knowledge boundaries, right. So I'm obviously somebody who's very much interested in the biology of it. And so I don't want to, you know, massively offend people who know much more than I do in the reinforcement field. But I guess the way we look at it is listed that kind of cat, their original kind of RL reinforcement learning type type theories are about a lot of people use, especially in the relevant fields are essentially going back to what I was talking about, kind of Pavlov's dog, right. And so it's like, they are really, really good at learning. One thing really, really well with a lot of training, and actually struggle in a number of ways to be flexible and to update, right. bandit tasks are potentially not the best example for that. But if you make it slightly more complicated, or make it slightly more need for for kind of changes in your behaviour. Classic RL does not actually work that well, right. And that's one of the stumbling blocks a lot, a lot of research, I think in in the field is looking at how you can make reinforcement learning algorithms and AI much better at being as flexible as we know we are. And also, as I'm showing with our behaviour, that minds really are as well. And so, again, I think it's a two way street, right? We're very much focused in this kind of reinforcement learning framework. But also, we're talking a lot to people who are actually at the forefront of these kind of algorithms to try and work out well. We know these don't work. So what, what, what does work and what does fit our behaviour better? And then it's a two way street, right? They can then be like, Oh, cool. of animals, if it looks like animals actually use this, and this is probably quite a good way to do it. Right? And we can be like, Oh, thanks, cool. You've helped describe our behaviour. Let's go and look for neurons and see if they do this. If they include these these variables that you're finding

**Caswell Barry** 13:28

all the fields sufficiently close that you could talk with someone who's like the straight up machine learning RL person, is there, is there a common language? Can you actually do we live the dream where the two worlds interact? And sort of, you know, we suggest they suggest experiments, we can see those sorts of things in the neural data. Are we just too far apart?

**Andrew McCaskill** 13:47

Yeah, well, I I'm definitely I would love to be and I basically spent a lot of my time trying to understand other clever people stuff. And I think, I don't know, I think I think that's definitely something that I like to do, though. So I'm constantly outside your comfort zone, feeling like a bit of an idiot. But it's kind of interesting, because you're always learning stuff. But I think the there's definitely enough that there is starting to be a lot of interaction. And yes, that I've noticed even like, whereas maybe five years ago, there was essentially none more, maybe one or two labs really, really kind of looking at it. Now. It's become much, much more common. And so I think it's definitely interesting for the future that we'd we're really going to see a kind of, like extension of this kind of stuff. Especially with more people becoming more computer literate. I think, I think maybe also bizarrely, although for us the pandemics been kind of really bad for it has done for us. It's allowed us to take some time to sit back and really get on top of the theory. And so we've been doing a lot of kind of linear algebra. tragedy, not a good thing or bad Yeah, like, you know, I, I remember when I was young doing maths right. And I did not remember doing linear algebra at all. I remember life into calculus all the time. And I didn't. Maybe I was just so appalled by it that I just I locked out. But yeah, it's really helpful though, I would recommend if anyone listening who's thinking about doing maths, you should definitely do linear algebra. It's amazing. Now that I remember what it is,

**Selina Wray** 15:27

there we go, a recommendation for is all going forward. maths is helpful. So maybe I could ask a more general question may be a slightly naive question, because this is quite different to my own work. But right at the very beginning, one of the things that you mentioned that I picked up on was the way we adapt our learning to get what we need and what we want. And I think that's quite an interesting distinction. Is the process the same because obviously, in the slot machine analogy, I might want more money, but I don't necessarily need it in the same way that I need food to survive. Are these processes the same? Or are there kind of subtle distinctions between how we learn those things?

**Andrew McCaskill** 16:09

Yeah, no, certainly not. That is a great question. Because it's really fascinating, right? Because you'd, and it kind of gets at that idea of instead of the, what the neurons are doing be defined by the task, looking at like, well, how can you define the actual thing that needs to be done? Right? And so it can't I didn't plan this today, this is you actually asked that question. Right. So you know, we actually are looking we actually are looking at the exact same problem. But from a from a hunger perspective. Right. And so you'd imagine that if you, you know, exactly, if you're playing slot machines, you're just you know, playing around getting money, right? mice, they do it to get sugary water, because should be waters, mice tend not to like playing for money. They don't really like it very much. And so fans of shopping Yeah, exactly. Yeah. They don't know how to work. They don't know how to work eBay, right? Chocolate money.

**Caswell Barry** 17:02

That's what you need.

**Andrew McCaskill** 17:05

Yes, we're actually the key in terms of hunger? Because actually, if you think about it in a kind of abstract way, actually, all it is, is the same problem. Right? It's being able to tell that the correct response right now, in terms of like, what I should do is dependent on whether I'm hungry or whether I'm not hungry. Okay, and that's kind of the equivalent of I should press this bandit task. No, because it is currently the one that skews versus I should post this and this. I keep calling bandit tasks already there. That's the jargon. They are slot machines, right? We should actually press this slot machine if the if it because this one is high now. And it you can kind of abstract it into the same, same problem. Okay, and so for what's graduated in my lab has been doing is is asking that exact question, how does the brain know that it's good to go and press a lever for some food when you're hungry? But then it's better to do something else if you're not hungry? And what's really interesting is we've been, we've actually found is the same circuits that that do both things. Right. And so you have this idea where you have, instead of it being the hunger circuit, which would if we'd only done the hunger stuff we would have been tempted to call it it's No, actually just the, I guess, the context circuits or the, you know, the ability to, to know that that particular time doing the same thing is different from, from from, from another time

**Caswell Barry** 18:33

I think this is so what you said there is so interesting, as you were talking and you mentioned hippocampus, which I'm obviously familiar with, was just so struck by how the interpretation of the same brain region can be so different from different perspectives based on what task you're doing. I mean, you've said it exactly there. In the context of your own lab with you do a Hunger Task or value task or reward task. It seems that's one of I feel like that's one of our big problems in neuroscience, right, is that we've, as neuroscientists, we've expanded we've covered pretty much all areas of the brain, but different people just working on the same bit, just see it as a different thing. I guess it's like that old? Or is it the story of the blind people feeling different bits of the elephant and one of them saying, you know, it's a snake or it's got, it's essentially where we are the same. We're just stumbling around in the dark, and I'm trying to understand different sections of the brain that's unduly negative. I'm not sure why I did that. But I was just struck by exactly that. As you were speaking.

**Andrew McCaskill** 19:28

Yeah. No, I think that's where I think that's kind of exciting, though, right? Because it's not as if the the blind man feeling the elephants task was not correct. And a description, right. And so we're literally we, we have this amazing situation where like, although the kind of unsaid thing right is I'm the awful person who studies the hippocampus, but doesn't study space, right, which is the fourth what the hippocampus is really famous for encoding. Right? And so, yeah, the outcast says and this is exactly why everybody thinks I'm an idiot, right? And so I'm you know, I'm fine with that, you know, it's okay. But so the the fact that people have parked study space that actually the only reason my lab exists and can exist is because there's such a beautiful set of data and understanding of how it works in a spatial context or a spatial task. And so we're out what we're doing is we're actually applying all that knowledge to these other kind of tasks. Right. And so we're just generalising what's already known. And I think I hope that's helpful to the field. And I think I think it is, but I think it's just that we would not be in that position if if all this work hadn't been done before. And so although there was a kind of his negative, that we are all kind of stumbling around in the dark, I think, is each, we will eventually join altogether. And that's gonna be very, very exciting.

**Caswell Barry** 20:46

I think actually, the other thing that strikes me is how it's rare for me, especially for colleges to hear your point of view, because we're not very good at talking to people outside your immediate spheres. And even even exercise like this, it's quite useful hearing different take on a brain region that you think you're familiar with. And that I guess that problem is maybe not problem. It's just that we need to be sort of cognizant of and sort of get our comfort zones, like you said, and talk to some other people. Exactly.

**Andrew McCaskill** 21:12

So I've increasingly been giving these like, excruciating talks, where I'm trying to trying to talk about something that I'm completely outside my comfort zone with, but like, you know, the acute, the acute awfulness is amazing in hindsight, because it exposes you to ideas and other people to use ideas, and you'll get towards the end goal, I guess, right? Which is actually to understand, I really do think the the computational side of things is going to be huge, because it again, if across tasks, but the same calculations is is how it's how it's gonna be. We're gonna work out what's actually going on, I think.

**Selina Wray** 21:48

So I think that segues quite nicely into what the kind of other half of this podcast is about, which is to find a little bit more about you, and how you ended up working in this this area. So maybe you could tell us a little bit about how your journey your journey kind of started out. And how you ended up doing what you did you spend a lot of time in slot machine.

**Andrew McCaskill** 22:12

is not everyone's as everyone in science is meant to study the thing that they're absolutely awful at right. So am I really bad at gambling? Mme? Who knows? Terrible? I also when I was in America studied addiction, so hopefully not bad addiction, which means I'm fine. You know, it's kind of Yeah, so I guess yeah, so I don't know, I've had this like really weird trajectory. I guess everyone has a really rich trajectory, that must be the thing that everyone on your show will see. Right? I thought it's really unique.

**Selina Wray** 22:35

But that's good. We want to hear that kind of diversity of journey. So the weirder, the better.

**Andrew McCaskill** 22:41

Because I went to university convinced I was going to study chemistry. And I think to be honest, it was mainly because at my school, there was the the good teacher in the school was the chemistry teacher, right. And so it's like amazing how that kind of rubs off. But within about three or four lectures, I realised that that was way out of my league, until I decided to switch to biochemistry instead, which is, which is actually much more interesting. But as part of my degree, I actually focused on Plant Sciences. And so I was doing a lot of like ARV adopters. And kind of the composition of organelles and membranes. The dat for my, for a lot of my stuff. And so I got really into kind of molecular makeup and trafficking and how, how the cell forms, essentially, and how it functions at the kind of very molecular level. That had a little segue in my last year where I happened to do kind of this trafficking stuff, but in turn, but just happened to be in a neuroscience model. With I was working with Rick Lindsay at the time, but I think I just moved to UCL, I think, right, but and yeah, and so that led to my introduction to neuroscience was because I wanted to study something else and the model system that happened to be studying it and was a neuron. I found it super fascinating, right? It's like, it's the complexity of the nervous system is just amazing. And so that basically shot me off in this direction. And it's basically been an uphill like movement. Ever since I went then I went to UCLA to do a PhD. But again, I did it in trafficking of mitochondria. So mitochondria are like the batteries of the cell. And the reason that I wanted to do in neurons is because obviously, neurons have this beautiful architecture, right? And so you have these huge dendrites that span and axons that can span metres and metres in humans. And you need to kind of push these little batteries all around this complex architecture, right. So it's in a neuron. This is a super fascinating problem. Just to clarify, when

**Caswell Barry** 24:41

you say trafficking, you mean, you don't mean sort of international drugs trade, you mean moving things around inside cells? And I do. Yes. Yes. Sorry.

**Andrew McCaskill** 24:50

Yeah. So yeah, so they basically these, these are little like little buses and they have little roads that are made up of microtubules and they use the motor proteins to kind of one mate, push them around. Then pull them around the the entire architecture the neuron. And so my entire PhD was basically spent looking down a microscope at these like beautiful mitochondria moving through the dendrites of neurons. And so then when it sounds silly, but like, literally, I just went with whatever happened to be interesting at the time. So then I went from my postdoc, I then was like, oh, wow, neurons are really pretty funny. And they're really big. And I wonder if like, synapses at one part of the neurons might be different from synapses, or the other parts of the neurons. And so I got really into kind of dendritic dendritic integration, essentially. And so my postdoc, I went to New York to kind of build and use a fancy microscope that would allow me to look at the properties of different connections along the kind of big complicated architecture of the, of the neurons. Yeah, and then, again, once they pop, it was like, well, then I'm interested in neurons and their connections are totally different, I found across the length. And so I wonder what that does to me.

**Selina Wray** 25:59

And then to different scale each time.

**Andrew McCaskill** 26:02

So I'm pretty sure my next card is going to be in humans or something, right, that's the only way that you'll know that it's gonna. So there's really, it's basically, because it had kind of quite a lot of experience at all of these different levels is kind of where my interests come in, right? It's like, I really, actually, I'm interested in them, the trafficking of the molecular, or in positioning of molecules in synapses that have formed the circuits that are going to carry out these complicated calculations during behaviour. And, and I think, fortunately, fasting about that is that if you think about what goes wrong in disease, and almost all diseases, right, it's almost always at the level of molecules, genes, you know, sitting on top of these, which just means stuff going wrong at synapses. And so I think being able to have that understanding of the synaptic connections, as well as the kind of overarching goal, I think, is really cool. So that's kind of that's basic working from C all the way from chemistry to, I guess what, computational systems neuroscience?

**Caswell Barry** 27:03

That is very diverse, I've got to say, I know you were I know, you were conjecturing that everyone has a sort of a unique and interesting story. But that that is quite an interesting, you diverse story that you've got to write there. Do you think that that, would you say the breadth of experience trades off against sort of the the ability to sort of specialise? I mean, some people might just work on the same, you know, the same model, the same brain region 1520 years, whereas you've sort of hopped around a bit? Yeah. Do you feel disadvantaged? Or do you think that actually is a positive benefit? Yeah, no,

**Andrew McCaskill** 27:35

it's that I've obviously, I worry about that a lot, actually. Right? Because I'm constantly the idiot in the room who's just entered the field, right? And so I think I feel like now, I think maybe I'm at a stage where I feel like I can ask the questions I want to answer. And so I think if anything, I'll probably start going back towards more molecular stuff, because you know, kind of right, to call it square, the circle rendus enemy. You know what I mean? Going back and starting to go into more depth for the same thing. But yeah, definitely over the course of, especially my postdoc, and starting the lab, I kind of moved from, essentially cell culture to in vivo, for the position. And then from my post from a postdoc to my, my running my own lab, I literally switched from basal ganglia, and essentially, Pavlovian learning, to hippocampus and all this complicated adaptive, flexible behaviour and updating and all this kind of stuff. And so I'm, I'm kind of learning I'm learning as the guys in my lab are learning, right? I think that I personally, that's what I find. I just find joy, right? But it definitely comes with a big pinch of kind of imposter syndrome constantly. Right?

**Caswell Barry** 28:46

That's pretty cool. I think that's, I think that's, it's a way to stay really interested and engaged and things. I think it's, I imagine, imagine you're not in danger of feeling overly jaded by like what you're doing this day. It sounds quite an exciting mix of different things.

**Andrew McCaskill** 29:03

Yeah, instead of feeling overly jaded, I feel that I might just be doing something that's completely wrong.

**Selina Wray** 29:09

But I think it's good as a way to have people see old problems with fresh eyes in a way I mean, I think one of the biggest risks sometimes in science is that things get so dogmatic and you know, there are ways and concepts of thinking that it's really difficult to challenge when you're kind of in that field for a long time and coming in with a different skill set different range of expertise just lets you see things slightly differently. So I think it's it's probably quite powerful should be encouraged hopefully we saw we shall see in a few years I guess.

**Caswell Barry** 29:44

Was it straight through for you I gather I know that you've done other things as well as being a scientist

**Andrew McCaskill** 29:50

I had a brief a brief time outside science in between. It wasn't to say science the road cuz it was directly after my undergraduate degree. I was in that kind of awful, you know what you're like, when you're 21, you're like, I don't know what I want to do, I really don't, I had no idea. And I was like, don't wanna do science, I don't know, might be cooler to be in a band. And so over the course, when I was undergrad, I was in a band. And we were kind of playing lots of gigs and stuff. And I basically, after undergrad decided that I wanted to do music for a bit, very, very briefly, like matters of months, I got a position at EMI, which is like one of the major labels, and I just failed miserably at it. It was one of those, you know, when you guys got this dream, I was like, I'm going to join, I'm going to be an a&r person for a record label that is going to be that's like ticks every single box for me. And then I went in, and it was like, well, it's you really, every job is the same, right? Especially when you're a massive major label. It's like, I was just filling in Excel spreadsheets with numbers and arranging meetings. And I think a lot of my time was spent putting, deciding who to send record samples to, and posting them. It was just said, Yeah, so yeah, so I had a, I had a kind of brief sojourn with with with the music industry, but then after that, I decided to do a PhD at UCL. But cynically kept on being quite serious with the band that was in at the time. To the extent that I have this very specific memory of my boss, do my PhD, at this time, because there's actually another person in his lab, at the same time that had there was also super into music, and was kind of teetering on the edge of, of switching to music. And my boss sat us both down and had a proper chat with us. And he was like, You must decide, right now, you can either, you know, start applying yourselves. And, you know, then you might have a chance to do something decent with your scientific career, or you can just was about to swear there. But just remember that I'm not allowed to. Yeah, and so both of us, both of us got schooled by our boss at the time. And both of us say, stick with science. And both of us have our own lab. So it was obviously good. It was obviously a good device at the time. So

**Selina Wray** 32:27

I mean, it's pretty amazing because I think music and science have got to be two of the most difficult career trajectories to try and pursue. So to crank up both, I think deserves a lot of credit and to be very successful in the one that you chose.

**Andrew McCaskill** 32:42

Also, the tragedy of the music thing was I was so into music, and I thought I was going to do all that stuff. But then really actually, what happened was my brother You know, I just happened to be super successful at music A few years after I failed miserably. Exactly. So my brother is like, played the main stage or the, the permanent stage of Glastonbury and always played on Jools Holland and all this kind of stuff. You know, he is he's much better, much better than I was. It's very sad,

**Caswell Barry** 33:12

are you? Do you think you'll be one of these, you come across these sort of great neuroscientists who like it turns out have a totally extra sort of string to their bow and like, they're an artist, whatever Do you think that might? Do you think that's the route This is gonna take, you'll be like, collecting your Nobel Prize, and then you'll play your guitar afterwards.

**Andrew McCaskill** 33:33

Like, nightmare visions of like, the dad rock band, I'm gonna be annoying. I'm like, 50. You know, like, I'll have like a big bold patch on long here. Right, then decide on I'll play Pink Floyd covers as more or less more what is going to be like, right, that's not going to be I think I think they should probably should be avoided. Right?

**Selina Wray** 33:50

Well, we had to me before he was famous. Yeah.

**Caswell Barry** 33:55

So, so Andrew, what would you say? Is the sort of the big question in your field? Or what's the future? What do you expect to happen in the next 10 years in terms of things being sold from technologies coming to bear that can make a big difference?

**Andrew McCaskill** 34:09

Yeah, it's, I guess we kind of touched on it already. Right. But I think I really, I'm very excited at the kind of the linking between all the kind of fantastic computational modelling, and, and real kind of cellular systems neuroscience, and it's really it's, it's linking up those those blind men trying to work out what the elephant is. And obviously, like, the main goal is to try and work out what the brain is right. But I think for me personally, the next big question I really think is important for us to focus on is, is understanding the brain to an extent that we can actually understand what is going wrong in disease. And I think a lot of our efforts are we just simply don't know enough about how the brain works in order to understand what's going wrong in my in my opinion. And so I think it's, I would really like to get to the stage where instead of being like, this model of of depression, doesn't press the lever as much to being like this model of depression has a has a problem with this synaptic connection. And that results in it being unable to encode value properly. Right. And I think once we get to those kind of specific quantitative, like understanding of these problems, we can then target our interventions much more effectively. I think I think there was amazing quote, by, by I think it was David Anderson, he's like a very famous California and you're a scientist. And he was like, the current stage you're at now with with kind of interventions with for neuroscience is that when your car runs out of oil, what you do is you just pour all the oil over all the whole car, and hope for some of it goes in the right place. And obviously, when you do that, something's going to go in the wrong place in the heart of the card just as just as much as not having oil in there. That's what we're trying to understand is understand, like, how, where does oil have to go? Right? Because then we can just put it straight in, and we'll fix it, we'll fix that much better. So I think that's really where I think and I really think this kind of link between computation and the kind of wetland cellular understanding is going to provide that that kind of link. That's a

**Caswell Barry** 36:18

great analogy. Yeah. Interesting. So the final question, we ask everybody, back to us, to you to what is your favourite or maybe most unusual facts about the brain? Yeah,

**Andrew McCaskill** 36:32

so my fear is, it's maybe not as kind of quirky or unusual. But my, my favourite fact about the brain definitely is this idea that aren't, we are getting really good understanding, like, how to learn things like how the brain might learn things, how we carry out all these complicated computations, especially with all these models we've been talking about so far. But what I find fascinating, right, is that, because I come from this molecular synaptic background, what we currently envisage the brain being is lots of neurons that are connected to each other to perform a calculation. But we also know that every single neuron actually has about 10,000, sometimes more different synaptic connections on it. And so this is to the extent that an individual neuron in terms of computational power can probably just by itself, perform almost every algorithm that we can think of, and currently model an entire brain region doing. And so I just, I just find that absolutely fascinating, right? So like, we, our brains are insane. They're they're just so complex and have so much computational power, and are amazing models that can do so many things, are actually an order of magnitudes simpler, at the very best approximation to what's actually going on. And so I think, just imagine the manner of things that can happen when you have this enormous increase in these capacities. So synapses, remember about synapses, and how fascinating and wonderful we actually are a

**Selina Wray** 38:01

great way to end. Thank you so much for joining us for that fascinating discussion. Thank you for inviting me.

**Caswell Barry** 38:11

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