It's also there's two things that are noteworthy about this as well, I believe you're our first guest who isn't actually at UCL. Now, it's something we always meant to do, but you are a branch leading outside. There's also another connection, I don't know whether you remember this. So Kate was my PhD supervisor. But actually, while I was a PhD students, Steve did a rotation in your lab. And I tried to convince him that he wanted to work on grid cells and things like that, and evidently didn't do very well. So we've got the full, we've got the the full family tree here.

Steve Flemming 01:59
Like it's a it's like a family reunion in some ways.

Kate Jeffery 02:04
Yeah, I remember that I consider that one of my great failures is not to be able to persuade you to come work on placing grids hills. For you, I thought

Caswell Barry 02:11
you're about to say having mean.

Steve Flemming 02:16
I was just saying to Cosmo, before we started recording that we might be starting a foray into rodent work in the lab. So it perhaps is coming full circle. And finally, it's taken fantastic teen years, but maybe I'm now becoming convinced. We'll see. Anyway, it's not about me today.

Caswell Barry 02:30
We play the long game. No, don't worry. So Kate, we should we should focus on you. So maybe a good place to start is if you could just tell us about what you're working on the moment or what you think is interesting this field and what you know, what the questions are that you are focused on?

Kate Jeffery 02:46
So yeah, there are there are so many questions. So began with place cells. Because when I was starting to do my PhD, I started learning about play cells. And I got very, very interested in this idea that these are kind of a kind of represent the assembling of a thought in the brain of the rat. And therefore, you know, it seemed to me if we could understand them, and understand how they create their representation that we would understand how thoughts are made, you know, or at least one type of thinking.

Steve Flemming 03:20
Perhaps we could just start to just by defining, giving, giving the listener a brief definition of a place or what, what does,

Kate Jeffery 03:30
sure, so play cells, single cells in the brains of rats that become active when the rat goes to a place. And so when I discovered that these things existed, and they exist in hippocampus, which has been very interesting for a long time, because it's of its involvement and memory, and they were discovered by John OKeefe. So, so I actually when I was a PhD student went to visit O'Keeffe's lab, and he

showed me a play cell for the first time and I thought, wow, this is amazing. So like, how does that cell know whether at is type of thing? So then the question became how how does the cell know? And that's really the question that's that's driven me and a lot of other people will ever since and, and there's sort of two levels to the question. One is just the kind of anatomical physiological one of where does the information flow through the brain on its way to the play cells? And then there's the more psychological question of what is the nature of the information that was telling pay cells were to fire? And so I've been kind of working on both of those levels, both the kind of the physiological and the psychological level. And for me, that that kind of interplay between physiology and psychology is is just a really interesting place to be in. It's where I've stayed ever since.

Caswell Barry 04:49
And, practically, what do we know about what makes these things fire where they do? I mean, I guess, would it be fair to say this is sort of the this is the cell level representation of you knowing where You are in the world are indeed rattling where it is in the world, or is there? Was there more to it?

Kate Jeffery 05:06
Well, that's one of the big unsolved questions. Is there more? Or is that how you know where you are? Or is there some other part of the brain? That's, that's really where you know where you are? Or even, is that a sensible question to ask? Is there anywhere in the brain that knows for sure. So sorry, I've forgotten the question.

Caswell Barry 05:26
What what do we know about the things that actually tell the cells where to fire?

Kate Jeffery 05:32
So there's lots of also levels to the answer to that question. So we know what the inputs are to the hippocampus. And we know where they come from in the brain. So a lot of the inputs come from primary sensory areas of the brain. So we know that the cells are using vision, and olfaction. and to a lesser extent, they can use sound and touch. And so they're using all the senses. So once it's we can say, well, the play cells know where they're at is because the sense organs tell it where it is. But that's not really a full answer to the question. But the question really is, how is that sensory information turned into spatial, spatial representation. And the thing that's important about space, that makes it different from other kinds of, of information is that there's, you kind of go through space, like you move through space. So you translate, and you rotate, and you translate and rotate by certain amounts, quantities that we call distances and directions. So that's kind of quite an abstract conceptual idea. So so the question for the brain is, how do you represent distances and directions in the brain? So turn this war kind of pattern of pixels that are coming into the eyes and so on? How do you turn that into something special, that's got distance and direction. So we, we know that the play cells do get information about the distance that the rat has travelled and the direction in which it's travelled a lot of work, some of it from a keeps lab and colleagues, many colleagues at UCL, including you, and me, and many others, and lots of people, all over the world, really, it's been a very big enterprise, to try and pull all of this apart. We know that the boundaries, certainly in rats and mice, the boundaries of the environment are really important for helping to anchor play cells. So in other words, it looks like a particular cell will get some type of information about how far the animal is away from the east wall of its environment, let's

build up a picture of the space that the rat is walking around. And you would just know that cell A was sometimes active, and then Selbyville, sometimes active in cell C, but sometimes active and so on. And it's not until you've listened to the cells for a very, very long, long time that maybe you discover that when cell a is active, often B is active shortly afterwards, and that C is active shortly after that. And so you starting to understand that these places are connected, so they have a relationship to each other. So I think the you know, the picture that's kind of emerging, is that the maybe the function of the hippocampus is to understand these relationships between places. And it does that by experiencing the kind of sequences that that the rat walks through, and it's walking through space, and you get sequences of play cells active. So So you know, the picture of the, the internal map is very much one of not just knowing where you are at the moment, but of knowing where are the other places? And how do you what's the best way to get to them from here. And that's where we're still relatively limited in our understanding. So we don't know whether the large scale map is whether it's also in the hippocampus, where the play cells are or whether it's in other parts of the brain and hippocampus kind of teaches those other parts of the brain. We're still trying to answer that question.

Caswell Barry 12:47
I guess I'm using the sort of backbone that you just described, if you think of play cells as things that just sort of associated locations together, I guess that naturally feeds into a lot of the work you've been doing, where you've sort of extended, extending the typical experiment from two dimensions to three dimensions. And you've done I guess, over it's probably over the last 10 years now a whole array of beautiful experiments sort of making rats do increasingly interesting things like I remember seeing you talking about rats that are climbing through a helical staircases, then climbing walls. And then finally, there was a very what actually went fully 3d and sort of, were able to get through or maybe was mice but get through this sort of three dimensional cube. Do you see that sort of thing as just sort of the the natural sort of endpoint of play cells as in, you know, if you can associate places in 2d, then you should definitely be able to do 3d. And I guess more? More importantly, do you think there's a limit on that, like, if we could design a task with animal moves in 4d, whatever that looks like, with this system? Just adapt? Or what would happen? Yeah, it's

Kate Jeffery 13:47
an intriguing question. Yeah. So the so the results that we've got from these explorations into three dimensions have been not completely straightforward to interpret. I think the starting point was, yes, the map, the internal map is probably three dimensional. And three dimensions is a bit like too, but there's more of it type of thing. So and when people I think, weren't really interested in these experimen

rising and following. And so the consequence of that is that you get strikes. So if there's a place in the horizontal space where the cell is supposed to be firing, then it will keep firing, as the rat climbs up the wall at that location. And if there was a place where themselves supposed to be quiet, it continues to be quiet. So the consequences as the rats walking over this wall, there are all of these vertical stripes. So it looks very much as though the grid cells were interested in the distance that the rat walks on the horizontal plane, but not in the vertical plane. So So then we started thinking, does this mean that the map is not really three dimensional? That actually, it doesn't have a good representation of height above ground? But then how do you explain how the play cells know what to do? And just, it was just all very confusing and puzzling. So then we thought, well, maybe there's something about the way that the rats are climbing on the wall that's restraining the ability of the cells to track distances, because the rats were standing on little footholds. Very much like a rock climb aboard. So so they were holding on to these footholds and because rats are quite small, they were actually able to stand so that the body was horizontal. So not not flat against the wall like a human would be, but actually horizontal. And we thought maybe, maybe that's affecting how the cells are able to track the vertical distance and it messes them up so so then we change the environment, and put chicken wire over the wall so that now the rats could climb very much more like a human rock climb aboard with their body flat against the wall and all four limbs on the wall. And suddenly, we got the blobby pattern back, so they were no longer stripes, we now got blobs again, so that was cool. But the regular polka dot pattern wasn't discernible. And the size of the blobs was far too big, relative to horizontal. So it sort of looked like the system was trying to track distances, but its scale was kind of messed up. So that was also quite puzzling. And then finally, we thought, okay, let's really put this to the test and create a situation where the rat can really fully explore the three dimensional space. And it took a long time to get that set up, we needed to have a way of tracking the rats in three dimensions, we needed to have an apparatus that they could move through in three dimensions, which was, you know, turned out to be this big kind of jungle gym kind of apparatus like, like those used to get in children's playgrounds. And before they decided it was too dangerous, you know, sort of criss crossing bars. And so the rats could climb through these. And we also developed wireless tracking, so that we could record sorry, wireless recording so that we could record the the neurons. So now the rats could climb through this space. And they weren't encumbered by recording cables and, and the camera could see them and all of that kind of stuff. So when we recorded in this space, we weren't really sure what we were going to find. So we thought we might see a nice, regular packed lattice of these nice round kind of firing fields is locations where the cell is active, we might see strikes, like we saw in one version of the of the wall, we might see big blobs, like we saw on the other version of the wall might just see a huge mess. And what we actually found was, we saw blobs, so these focal regions of space where a cell would be be active surrounded by a region where it wouldn't be so. So it kind of looks like the cells are very much trying to identify locations in the space where they should be active. And then they want us around that by locations just beyond that, where they're not active, it sort of looks like the system was trying to do that. But there was no regularity to the pattern that we could discern. And there's quite a lot of variability in the size of the blobs. And a pretty similar finding came out from the bat lab, as we call it. So loskis team in Israel who was studying bats, they also found that the grid cells in the bats even though the bats can fly smoothly through the space, also produced irregular blobs, they actually found a slight difference, which was that the distance between the blobs was not completely random, it was it was more uniform, than you would expect, the chances of the system was trying to preserve those distances, but it was pretty irregular, and ours was just as far as we can tell, completely irregular. So that made us do a lot of rethinking about what the

way, I have a lot of sympathy with this view that you're having about grid cells saying that, you know, we've all been potentially been slightly misled by the fact that spatial experiments typically done in these totally bare 80 centimetre square boxes. And as a result, we have this view of what things look like. And you know, for many good reasons, because we want to sort of, you know, reduce things to their core components and do the experiments in a pure way we've done these things, but as a result, we've come so far away from the sort of ethologically, naturally valid environments. But some of the things we've all become obsessed with might just be terrible artefacts of the wave of Denise has happened. I guess it's

Steve Flemming 27:55
Yeah, I mean, there's a slight

and various places and working in different countries. What you know, what were the defining steps along the way to being where you are now?

Kate Jeffery 34:17
Yes, I did. I did start out in a slightly slightly different direction. I started out in medicine, because I knew I was intensely interested in science, particularly biology, but I was growing up in New Zealand, which has a bar at least back then it had a very small scientific community didn't really know that one could be a scientist. As a career, I just thought of new as interested in science. So I studied medicine. And while I was a medical student, I got introduced to the to the discipline of behavioural science. And in fact, part of that introduction was that I was able to do an elective in my first year where I could choose anything I wanted to do and I just chose psychology just kind of randomly And I just had never heard of psychology didn't really know that one could study thinking. And when I discovered that one could do this, I thought, wow, this is kind of cool, you know. And so as I was carrying on through my training, I became more and more interested in the science behind thinking and, you know, how does the brain generate thoughts and consciousness and so on. And I decided at the end of my training, that I wanted to research that and not treat sick people, but to actually dig around and find out how the brain works. So I, I visited the local neuroscience community in the place where I did my training in Geneva and New Zealand. And they were, they had a group of very, very active neuroscientists studying this thing called the hippocampus. And I'd never heard of it, vaguely knew it had something to do with Alzheimer's disease. But they said, come and work with us. So I went to work with them and found myself studying what we now call synaptic plasticity. So the the ability of neurons in the hippocampus and elsewhere to change the strength of their connections between them to form memories. And I thought this was pretty cool. And, you know, memories are the building blocks of, of thoughts and thinking, and so at the end of my master's degree, I decided I wanted to carry on doing that. And so I tried to find a PhD position. And I saw an advertisement in one of the science journals by Richard Morris saying he was looking for a researcher to come and work with him. And that person was supposed to have a PhD, and I didn't have a PhD, I only had a master's degree, but I also had a medical degree. And so I thought maybe that will do. So I wrote to him from the other side of the world and said, You know, I think what you do is really cool, can I come work with you? And And amazingly, he said, Yes, you know, he said, Come on over. So I went over to work with him. And he, he was also working on hippocampus, but he was relating it to behaviour. So, he had invented this very famous test of hippocampal function called the Morris water maze. And he was trying to understand how synaptic plasticity underlies the learning that goes on in the waterways. And so, I learned how to record from freely moving animals in, in challenging situations, serum water and so on, and to study their behaviour. And, and it was while I was there that I encountered John OKeefe and the play cells and decided that after my PhD, I really wanted to, to kind of come and study the play cells and I had actually visited. I keeps lab a couple of times by then, and I mean, I must have been a strange sight the first time I met him because I was on a kind of a gap year that I had a kind of a year I was just doing locums in London and I had it was kind of the post punk era and I had spiky blond hair. And this really quite aggressive looking don't materialise, that I want to find out how the brain works. But he remembered me a few years later when I was in Richards lab. And so when I, you know, got talking with him, and he had space for a postdoc, and so I went to work with him. And yeah, this sort of took off from there.

Caswell Barry 38:06

they just don't understand they're not able to build a mental map of a space that makes them feel

different from what you first built it before? I guess. But that's, I think that's cool. My other my life's goal and favourite factors that, that dolphins sleep with one half of their brain at a time. And I think quite a lot of constantly mobile animals do. And I think that's amazing. And what what was the experience of the dolphin be like, and how does that happen? I think that's, that's a cool, interesting fact as well.

Caswell Barry 48:59
That's fantastic. I imagine it feels like me before I had my coffee in the morning is what?

Steve Flemming 49:09
Yeah, we need to check whether Caswell sleeping with it.