SUMMARY KEYWORDS

cells, work, neuroscience, lab, hippocampus, movement, visual cortex, cortex, animal, motor cortex, started, postdoc, study, motor, basal ganglia, interested, area, behavior, techniques, science

Hello, it's Ritika, Katy and Neddy, and you're listening to the Cortex Cast.

Katy

Today we are in conversation with Dr. Andrew Peters, who is a new Sir Henry Dale fellow working as a principal investigator in the Department of Physiology, Anatomy and Genetics. He's particularly interested in movement, with a focus on the circuit between three different brain areas - the cortex, the basal ganglia, and the thalamus. Each of these areas have been implicated in slightly different aspects of movement, and often studied in isolation. One of the greatest strengths of Andy's work is how he has managed to apply multiple modern techniques to target different parts of the circuit simultaneously.
Perfect - so thank you so much for agreeing to talk to us today. Can we start at the beginning so to think - can you tell us a bit about how your career has taken you to Oxford?

Andy

So I started out my undergrad at Rochester Institute of Technology, which is in upstate New York, and I was an undeclared science major, which means that I was interested in science, but I had no idea what I wanted to do with it. And I didn't know at that point, which I think is probably relatively common, that you can get paid to do research – that was like, you know, a novel concept for me. So I kind of learned that in the first year I was in school. And I also got interested in neuroscience, kind of because it combines a lot of disciplines. So I didn't know if I wanted to do chemistry, or biology or physics - and neuroscience is something that you can do everything in. And that combined with the fact that there's so much we don't know about it, I think really drew me in. From there - I became interested in pursuing neuroscience. So then I transferred to Emory University, which is in Atlanta, Georgia, and a neuroscience degree there. And I started out with humans, and then I switched to rodents working on amygdala-related things. That's where I figured out that recording spikes and neuronal activity is the thing that really drives my interest. From there, I did a year as a tech at the National Institutes of Health. So they have this program where you spend a year - it's slightly more than a tech but less than a kind of PhD student. You become involved in a project, and so I worked there with David Leopold for a year working with monkeys, on vision. And then I went to grad school at University of California, San Diego. I did my PhD there with Takaki Komiyama, working on motor cortex and motor learning. Then I moved to the UK where I did my postdoc with Matteo Carandini and Kenneth Harris, working on basal ganglia and cortex interactions. And then I applied for fellowships and came here.

Katy

Brilliant. It's such an exciting journey, and I'm so impressed by the fact that you've worked on vision, then on motor, and then you've got a paper in review at the moment – and that's got prefrontal cortex.

Andy

Yeah, that's right. I've essentially been across the board, because when I started working in the amygdala, it's very much neither motor nor sensory, right, it's affective - the signals there are harder to interpret than either end of the spectrum. So then when I went to vision, it's nice, because you have all these great questions about how does the brain encode the visual world – (and then we) can kind of get at these things more mechanistically than things like affective neuroscience. So when I moved to San Diego, I was pretty open. Actually, I didn't exactly know what I wanted to do. But I knew I wanted to do a systems level neuroscience. In the program I was involved, as most programs are in the US, you do rotations where you spend three months in three different labs to decide what you want to do. Since I had just come from a vision lab, I would potentially have been open to doing vision. But the labs I ended up rotating in were - one that did hippocampus work and one that did cerebellum work, and then when the motor cortex work, so it was two motor and one hippocampus. Okay, so the hippocampus one, I think, is a good example where it's nice to try something out, and then just see what speaks to you essentially. So when it comes to the hippocampus, there's the remarkable phenomenon of grid and place cells that you have this really strong place encoding in the hippocampus, but then there is memory – and we don't know how those two things go together. And at the end of the day, when you see activity in the hippocampus, it's so far removed from what the animal is actually doing with that information that it's kind of hard to know, like, what is the spike contributing to in terms of driving a muscle to execute behavior. So that's kind of how I got interested in the output of the system where I said, what I think I care about is how these spikes turn into movement. It's getting closer to behavior that I'm interested in. So that was kind of why I veered in the cerebellum, motor cortex direction and the motor cortex just ended up taking more of my interest. It was looking at cross learning, I was doing some of the first two photon experiments so it was just kind of a totally new frontier.

Katy

That’s brilliant, I think being able to measure behavior is such an interesting way into the complexity of the brain. And I really want to also be near that behavior. Well, you've also talked already about how your previous experiences are now driving what you want to do in your own lab, can you talk a little bit more about how you've made all of these decisions? Because it's a little bit different, isn't it from working as a PhD and postdoc where someone's always telling you what to do? Or at least giving you lots of guidance? Now you can suddenly do whatever you want?

Andy

Yeah, I think probably for the better, I actually have had a lot of freedom and both my PhD and postdoc projects. So in both labs, I could just walk in and the PIs say, you know, here are the themes of what we want to study, you just pick something you're interested in, do a project on that. So as a PhD student, my advisor, Takaki Komiyama invented, or was one of the co-inventors of doing head fixed behavior with longitudinal two photon calcium imaging. So this was a brand new thing we can have animals learn and behave while tracking the activity of single cells over the course of learning. So there were a few kinds of just easy - not easy, but there was some kind of obvious next steps to take. So for example, how does a particular cell

respond as the animal learns to make a new movement? So there was kind of a relatively clear next step from what he started to what I could do, but it wasn't like I came in and he was like, here's your project, you know. So I think that that was really nice. And as all projects do, it evolved over the course of time, you know, that I started out doing one thing, and then it kind of veered into something else. And then when it came to my postdoc, it was even more so. So Matteo Carandini has a lot of visual neuroscience experience, and Kenneth Harris does a lot of computational work – he started out mostly in the hippocampus. So I come in, and I say, I'm interested in the basal ganglia. And they say, okay, sure, you can say the basal ganglia. So I started recording from the basal ganglia, when that hadn't been done in the lab before, having that experience was nice, because it meant that I had this thing that I could do that no one else was working on in the lab. And then when I started my own lab, I could kind of just keep branching that out. So ultimately, my goals are to keep working on this cortex – basal ganglia interaction, but also to get back onto the motor side, because that's kind of where my original original heart was that

Katy

Because you're going to say brain-wide, and you're targeting these multiple areas and lots of your experiments, I think the techniques that you're using have only been developed relatively recently. And it's really interesting to see how you use say, in your recent Nature, paper, the neuro pixels in the striatum and the calcium imaging in the cortex. How do you decide which of these brilliant techniques we now have available to us, to use in any single experiment?

Andy

Yeah, so largely, in part because of the labs, I've joined. It's nothing to do with me, they have been at the forefront of using new technologies. And then I, very fortunately, being able to just step in and try them out. In the Komiyama lab, as I was saying, it was the early days of two photon calcium imaging, especially longitudinal with behavior. In that case, the techniques actually open avenues for questions we hadn't been able to ask before. So it's not that I had the question first, I actually went a little bit backwards to say we have this amazing new technology, we can look at what single cells do over time, and then you say – okay, with this new thing, what kinds of questions can we ask that we couldn't ask before. So that had this really powerful thing of tracking defined single cells over the course of time. And then as a postdoc, again, I just walked into this amazing situation. So the Carandini and Harris lab had gotten these Neuropixels probes in the alpha stage available to four people on the planet, and our lab was one of them – which meant every time you broke a probe, you felt extra horrible, it was a totally remarkable thing, because in my experience is electrophysiology before you get a handful of cells, and you have to spend a huge amount of time post processing them so that you can identify which cells are which, and with this technology combined with some software, so Mario's patch target, for example, Marius Pachitariu came up with this spike sorting algorithm called kilosort, which is currently still the best there is, it's almost magic, you just throw your data at it, it throws you a bunch of neurons. So again, this technology was available, also, wide field calcium imaging and started to become a thing where you could look not at individual cells, but at the entire dorsal surface of the cortex. So again, it was it was slightly backwards. I knew I was interested in the basal ganglia, but we had these two technologies –

wide field calcium imaging and the Neuropixels. So we could say with this new stuff, what kinds of questions can we ask that we haven't asked before? And in this case, it was how does the cortex talk to the striatum, which we can do with these dual recordings? It's very nice to be question focused, but in my case, I think in both situations, I little bit went backwards from the technology. So I think my luck in that sense is run out a little bit because there's no amazing new thing that's just been developed. I'm just going to have to work with the tools that I already know how to work with but hopefully I'll have enough traction to get things.

Katy
It's amazing how close you've been to one of these really cool techniques. It's just such an exciting field to be in I'm sure a new technology will appear that we can all use.

Andy
Yeah, although I'm not against stopping. It's so much troubleshooting. It's nice to just have something work once in a while.

Katy
You touched the idea of single cells, encoding things, also populations, especially when you're looking at such global circuits – I sort of want to ask the horrible question of like, which bits do you think actually encodes the information? Do you think we should be looking at the population level more than the single cell? Well, is it just going to be a mixture of both the whole way?

Andy
Yeah, well, that's that is one of the key questions in modern Systems Neuroscience, I think it very much remains to be answered. And I think that there's answers in both directions. So, we certainly do care about whether single cells change their activity over time. And maybe that really does contribute to behavior, or maybe like you said, it's that a population encodes it somehow and together, and then it doesn't matter what an individual cell does. So we have studies on the one hand, where you can stimulate a very small amount of cells like two to three cells, and an animal can sense that and make decisions on it. On the other hand, some work that I've done and what other people have done, show that there's a huge amount of drift in terms of what cells care about over time. So, at some level, I think it kind of has to be population based. But there are some cells that seem to care about something for a long time. But even in, in my case, I looked at cells in the motor cortex that project directly to the spinal cord. So it's almost as close as you can get to movement. And those cells have a shifting relationship with movement just on a regular daily basis. So something about the system is constantly changing. It's unclear why or what that gives the animal. So yeah, I think it's I think it's a mixture of both. And certainly, that's one of the big challenges we're addressing.

Katy
I think I always find that everything is changing all the time in the brain on multiple timescales. And I noticed that one of the things you have studied a lot of is changes with learning over time studying single cells, most recently with the sort of looking at the projection to the medial

prefrontal encoding information differently once you've learned to task. So there's this debate where some representations have to be stable so that we can continue to remember things, whereas others need to be adaptable to learn. Which sort of cortical pathways do you think are going to be most effective by learning is everything up for grabs in every moment?

Andy
I don't know. So when I was a PhD student, that was one of the things I was trying to address. So in the motor cortex, I was looking at layer two and three cells. And what I found was that they changed their relationship to movement over the course of learning. So the long story short, is that it kind of looks like there's a group of cells that develop some novel pattern of activity, that then becomes robust as the animal learns. So it's almost like a specialized circuit to produce this movement that the animals learned. So after that study, I said, you know, the cells that are deeper, that project directly to the spinal cord, surely, they're stable, because that would be a beautiful story. In the superficial parts of the cortex, you have this circuit, which is constantly shifting to accommodate learning, but then that plugs into a system which is stable. So it's, you know, at some point, at the end of the day, when you press a key, you've got to have a defined response. So that was why I did that study, actually, to look at cortical spinal cells. And even though I had a huge shift over days and over learning - so yeah, the question about is everything up for grabs, I think, to some degree, yeah, because that was an example where I was like, if anything's going to be stable, surely it's this. And I mean, even going down to the spinal cord, this is something which has been super difficult to study up until even currently, because you can't do the same techniques in the brain as you can in the spinal cord. But it turns out, the spinal cord also has a fair amount of changes. And we don't know even how cells in the spinal cord relate to movement. I would say at this at this point in time, almost everything is up for grabs in terms of changing.

Katy
And I think that's another area that I'm always really interested in is how visual is a visual area compared to how motors and motor area. And when you're looking at these big circuits, as well, you see similar activities representing similar variables in multiple areas and seemingly quite a lot of redundancy, especially in these kinds of studies. Why do you think this happens?

Andy
There's this there's this idea that's been popular within the last five years, that movement is represented everywhere. And this is something which is kind of funny, because coming from a motor background, I said, you know, yeah, like, of course, movement is very important. And it's all over the place. Whereas you had all these visual neuroscientists being like – why are there mixed representations between movement and vision? So, some of us were surprised and some of us weren't that surprised. I think it depends on the area. So, the primary visual cortex is one of those places where once we started seeing effects of movement, we started thinking, Oh, no, there was something we really don't understand here. So I remember, for example, when I was in grad school, there was one of these kind of early seminal papers that came out from Chris Neill's lab. And the idea was that you have changes in visual encoding in the visual cortex, depending on whether the animal is running or not. And it was one of these moments

where I think I've kind of gone back and forth about this, I have these moments sometimes where I think the brain is so complicated, and there's so many neurons that we can only record from so little bit at a time, but they'll never understand it – totally hopeless. And this is one of those moments where you think, you know, okay, this is visual cortex, and this is motor cortex. And then they say, no visual cortex also has movement stuff, and you think, Ah, geez there's this, you know, we'll never get it. I actually, I go back and forth. Sometimes I think we're doing a pretty good job. And sometimes I think we don't know what we're talking about. But yeah, so that was surprising. But then after that finding movement signals all over the brain is something that I wasn't hugely surprised by, because it's just a lot goes on too when the animal moves, you have changes in arousal, and the animal starts moving all over the place. So their vision changes, you know, they start sniffing, and there's a lot of sensory stuff that goes along with movement. So I think that's part of it is all these signals look like they're mixed, because a lot of stuff happens when animals move. Again, that's another fundamental question in Systems Neuroscience at the moment – is how mixed these areas are, and whether they really encode the things we think they're encoding. I mean, another example to counter that everything is everywhere, and there's actually a paper on BioRxiv, which is titled, I think – not everything, not everywhere, not all at the same time. So one of the papers that just came out from the Carandini and Harris lab, it was led by Célian Bimbard was looking at auditory responses in the visual cortex. So this is something that people said that they might have seen before, that you have this area of the visual cortex maybe has responses, but certainly, it's just visual. And then some people said, actually, it gets input from the auditory cortex, you have auditory responses in the visual cortex. So he did this nice study, which whether it was almost an accident that they kind of got into this, but I think it's one of these important things in science to clarify this particular issue. So it turns out that when you play a sound to an animal, it has a characteristic behavior. So let's say you play a sound that goes like ‘ba ba ba’ , you'll have the animal do ‘ba ba ba’ – three little twitches, and those twitches cause a motor response in the visual cortex. And it's not an auditory response. And you can figure that out by doing these particular manipulations. So at least in that particular case, it's not that everything is everywhere, he doesn't see at least for what it's worth, auditory responses, in the visual cortex.

Katy

I'm glad you've ended up with some sort of hope, or definitely made some progress in this field. I think one of the other things I'd love to ask is now you're building your own team. Now you've given everybody hope that there is hope through neuroscience, what sort of thing do you look for in young scientists and people joining labs and your team members? What do you think it takes to be successful and publish two Nature papers and get…

Andy

What it takes to publish two major papers is a huge amount of luck seriously. I think anybody that's been through the wringer knows that so much of what you find is just luck, from what techniques you happen to walk into till how reviewer 3 cares about your paper… So honestly, that's a huge amount of luck. Yeah, I mean, I think the most important thing, for me, at least has been just interest and excitement about science, that there's going to be a lot of times when things are difficult, and you're going to really have to slog through things to get it

working. But as long as you can keep coming back to this fundamental interest in science, then you'll always be motivated, I think, as long as you always are interested in how the world and nature functions, and that that's some driving force, it's just this really deep thing that you can latch on to. So I think that that's probably one of the ideal things to have when going in to science. And that's not to say that you necessarily have to bear in sight like, you know, research scientist, where you when you finish, like you could go in industry, there's a million things you can do with a PhD. So it's not that you necessarily definitely want to be a professor and do research, right? I don't think that that's part of it. It's just that you're very interested in science, and you want to contribute to learning how things work. And then everything else, you can learn all the skills and stuff. I mean, you build up the knowledge by going to talks and you build the skills by doing things. As long as you have that foundation of interest. I think that's probably one of the most important things in sustaining staining you through your career.

Katy
Fabulous! It's really nice because I think that's one of my favorite things about science is the community, is that everyone does have that deep interest in how the world works and yeah, sense of its beauty almost.
So thank you so much for agreeing to talk to us today!

Neddy
It was such a lovely experience working with Andy, a dedicated and hardworking P\principal investigator yet so down to earth and humble.

Ritika
If you are looking for a lab to join and are interested in Andy's work, please head to his labs website where you can find links to all his recent papers. He is also still in the process of establishing a new team in Oxford. So definitely get in touch as soon as you can.

Katy
Thanks for listening in on our conversation today. We hope you enjoyed it as much as we did.