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Speaker 1

0:00

Hello, it's Ritika, Katie and Neddy and you're listening to the cortex cast. My name is Neddy. And in this episode of Cortex cast, I'll be interviewing Dr. Julia Harris, whose research focuses on one of biology's biggest mysteries, which is why do brains need to sleep? Dr. Harris is an Oxford University Alumni having completed her PhD in Neuroscience at UCL, and recently opened her new lab at the Salisbury Wellcome Center in London, where she'll be investigating how the energetic and computational requirements of the brain are balanced during sleep to allow us to wake up each morning with brains that are increasingly optimized for our environment. So I wanted to actually say congratulations for starting, I mean opening up you new lab (oh thankyou!!). What can we look forward to from Harris's lab?

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Speaker 2

0:57

In the near future, I hope that we'll be able to predict what an individual neuron is going to do during sleep from knowing what it did during wake.

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Speaker 1

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Today, I was fortunate enough to have a quick tour of the lab and I saw really cool experimental setups. And it seems like there's a lot of creative aspects in terms of building the experiment, do you mind just going into brief detail of what you're currently researching?

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Speaker 2

1:26

So this is something that is such a great aspect of Neurophysiology that I can tell in our tour that you were excited by it as well, which is, yeah, there's there's a really like, creative almost arts and crafts aspect to this type of neuroscience. And that comes with really like the worlds that we want to build for our animals. So you could be creating, like a virtual visual environment or a virtual auditory environment, or at the moment where I've been creating is like a virtual olfactory environment. And you are always trying to interrogate behavior in a new way, which means thinking really, really carefully about the experimental setup and design. And almost always creating something new, like a maze with an interesting new aspect, you have to be really thoughtful as well, because you cannot instruct your animals to do what you want to have to like, actually think really carefully. Like, I want this to be this behavior, but how am I going to get my mouse to a place where that's what the mouse will do to really reveal something. So that's, that's a really big and creative part of it and involves a lot of hands on building from electronics to software and programming to actually, you know, super glueing stuff together. So what I have been working on recently, which I have started in Andres Shaffer's lab in the Crick, which is where I am now and we'll be continuing and expanding on in my new lab is looking at how specific populations of neurons change as a function of sleep. So, for instance, at the moment in collaboration with Mihai Kahlo and Andres, this lab, we created an olfactory stimulus set. And we are recording from neurons in the Piriform cortex, which is like the primary visual cortex of smell. So it's, it's one of the first places that odors are processed in the brain. And we use a cutting edge neurophysiology technique called neuro pixels, which allows us to extracellularly record from hundreds of neurons at once. So we're recording from hundreds of neurons in the peripheral cortex, as the animals smell new odors. And then we can track those same neurons into a period of sleep and then into a subsequent period of wake and get an understanding of on a neuron by neuron basis what each neuron is doing in these different arousal states. And can we predict what type of sleep activity one neuron will have based on its weak activity? And then given what type of sleep activity that you're on participated in? What does that mean for that neurons activity, when the mouse wakes up again, and sees the same stimuli or smells the same stimuli? We can look at this on a single neuron level or on a population level. And this is going to allow us to get some questions that were not easily accessible before we can track many individual neurons at once.

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Speaker 1

4:37

I guess when you are looking at neuronal activity and sleep and wake state, some neurons differ in that they are excitatory and inhibitory. Do you mind just giving a brief overview?

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Speaker 2

4:51

Well, I mean, this is a great question. So of course, yeah, there are lots of different types neurons in their brain excitatory At the main class of those being glutamatergic neurons, and also main class of inhibitory neurons GABAergic, these tend to be intermingled within the same area. And then you have other areas of the brain that have high proportions of different types of neurons. So like dopaminergic neurons, serotonergic neurons, for instance, we're increasingly starting to understand as a field that these different populations might be behaving quite differently in waking sleep. So, for instance, one thing that I found recently is that dopamine neurons in the VTA, the ventral tegmental area actually become quite quiet during non REM sleep, and then they become quite active during REM sleep, it was a little bit surprising that the GABAergic neurons in the same area behave similarly. So they also became quite quiet during non REM sleep and active during REM sleep, this is almost not what you would expect, because during wake, we know that this GABA ergic population normally inhibit the dopaminergic population. But you could also think it's exactly what you would expect, because at the level of one increases, the level of the other should compensate. The technique that we were using to study this is called in vivo photometry. And it only allowed us to look at the activity of the whole dopaminergic or GABAergic population, you would need a higher temporal specificity and ideally, to be able to look at both groups of neurons within the same mass to know whether they were antagonizing each other in a similar way during wake. But I kind of leads towards your point of yes, what what are these different populations of neurons doing during the sleep versus wake? And do they tend to behave similarly? There is a lot to explore there. So first, maybe we just want to map out like all of the different classes of neurons that we know expressing different types of transmitters in different brain regions. What are their have rich activities across different stages that we can sleep? But more specifically, can we understand whether the way they interact with each other is different during wake versus sleep?

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Speaker 1

7:13

How did you go about planning some of the experiments that you're currently working on?

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Speaker 2

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Iterative refinement. So, you know, I started with a question, actually, the first way I was thinking about trying to address this idea, do different neurons that are active during different aspects of awake behavior, participate in different aspects of sleep activity? My idea was to in-vivo patch, clamp those neurons. Which that was my hope, I feel that would be really great thing to do, because then you will be able to see a sub threshold. So before you get to the output spike of the neuron, you would then be clearly able to see whether their synaptic inputs to that neuron changed as a function of which pattern of see but in vivo catch clamping is really difficult, low yield, and it's hard to code for myself for long enough to do this kind of experiment. I think it will still be really instructive in the future when we have a better idea of what we're looking for And we can target the patching better. But yes, then I was near Andres Schaefer's lab at the time and started talking to him and his lab and Mihai, for instance. And we talked about this new newer technology that Mihai and others in the lab had been developing a way of recording extracellularly from hundreds or 1000s of neurons at once. And this basically created a new avenue for how to address these questions. So no, we can't look at the sub-thresholds, synaptic input activity of individual neurons. But if we can look at hundreds of neurons at once, then we're much more likely to be able to understand what different populations are doing from wake to sleep. So kind of moved in to this new way of addressing this question. And I joined Andres Shaffers lab, then you start to think, okay, so what brain areas we do this and because I work in the olfactory system now, this is a system that Andrea Schaefers Lab works in, but it's not really because I joined Andres lab, but I work in the olfactory system, it's because the olfactory system is very accessible and has lots of advantages for my particular question that I work in the system. Similarly for Andreas, he's interested in information coding, it's a system that provides a lot of advantages. So yeah, then you think okay, which part of the olfactory system and therefore which type of olfactory stimuli do we need to use? And how exactly Shall we design the stimuli? And how long should each odor pulse be? And how should we present it to a mouse? And what kind of training and habituation should each mouse go through Before we do the actual experiment? And you see, you just slowly build up, you start for me, like, start with a big question. And then slowly narrow down, like, what's the technique? What's the best part of the brain? Maybe you start with, like a part of the brain you're interested in, but not for me. For me, I think that sleep is doing different interesting things throughout the brain. So we may as well start somewhere where we think we understand the circuitry, we think we understand the inputs, we think we understand how to control the environment. Any principles that we discover in the olfactory system can see if they are upheld in other sensory regions. But when we move on to look at another part of the brain will go through a similar process? What's the right behavior to study here? What what exactly do expect to be changing in the neural network here? How can we design a task that is likely to create the kinds of changes that we will be able to pick up with our technique, and you just kind of hone-in and hone-in until you are sure that you have the right experiment for your question.

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Speaker 1

11:14

In your experimental design process, I'm assuming that you worked with also engineers and you know, people from different fields kind of like help you move forward in a sense, when did you know Oh, okay, maybe I should approach this person who might have different insight and help me to like make this design better.

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Speaker 2

11:31

So we depend hugely on the amazing teams at the crick right now. And then the FWC where my lab is starting to have similar teams that work with mechanical engineering. So with in collaboration with them, you can design, like the physical aspects of the setup that you need. So for us, it was an effort to create a way of delivering odors that wasn't leaky, that didn't contaminate each other. And this involves, like, a lot of tweaking, making different holders, testing them, choosing the way that each odor vessel is closed and releases its odor. And then also we worked with the more computer engineering group, to once we designed the electrical circuits that we needed, they helped us design more efficient electrical circuits and print them so that we weren't having to solve everything, ourselves. And with the help of these teams, like without the help of these teams, we would we would not be where we are.

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Speaker 1

12:49

Yeah. That's amazing. So did you have any eureka moments in this in your career path?

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Speaker 2

12:55

Not in terms of discovery; I hope that I will. But maybe in terms of my thinking, my PhD, although I told you in the beginning that I have always been interested in studying sleep. And that that kind of question actually got me into neuroscience in the first place. But when I started my PhD, there were very few labs in the UK studying sleep, and certainly not studying sleep on a kind of Neurophysiology level, so not able to look, you know, there was more cognitive research looking at humans, and I did know that I wanted to look more at single cells and networks of cells. So I just kind of like changed my, you know, I just forgot about sleep a little bit and followed what I was interested in and I got really interested in how energy is used by neurons and whether the design of neurons and neural networks is prioritizing information transfer versus energy use, or just how is the brain organized such that it can do these very, very complex tasks that we know the human brain can do using much, much, much, much, much less energy than your typical computer. So the brain is obviously a very efficient computational device and I when I got interested in the biology of how this works, and then, towards the end of my PhD, I became aware of something called the Shy hypothesis, which is a synaptic homeostasis hypothesis of sleep. Giulio Tononi, his lab in the States was providing or producing some evidence that neurons tend to downscale their synaptic strength during sleep. And in my PhD I've done a lot of work looking at how much energy synapses used and it's a lot it's the most energy consuming process in that Brain. And it's also like a computational unit of the brain like, it's how neurons up-regulate or down-regulate their communication with other neurons in the network. So if all of these synapses are downscale during sleep, then this is a great energy saving for the brain. But at the time, the formulation of that hypothesis was that they would all be downscaled by the same amount. And so relative strengths would be maintained. And so you would only forget things that you know, had very low synaptic representation, weak signups in the first place. But I started to wonder, could sleep be managing both the energy use of the brain's neurons and components at the same time as effectively managing its information processing so like the more traditional way that we think about sleep consolidating memory, and if it was doing both it will probably be happening at the level of the synapse? You know, memories are altered at the level of the synapses. Classically, the biological substrate for memory, energy is used in the brain primarily at the synapse. So let's look at sleep's effect on synapses and connections between neurons. And for me, I suppose that was a bit of a not a Eureka, but that's, that's how I now think about sleep as an opportunity to reorganize brain networks. But my question is, how is it doing this in in a strategic way, because our feeling when we wake up in the morning, is, is really that we're like, more prepared for the environment than we were the day before. And this happens progressively and iteratively throughout everybody's life, so that every single day that you wake up, you should be a bit more prepared for the environment than the night before, but also like much more prepared than last weekend. So sleep, I think, can really be part of this process. Yes, we learned during the day, but also what changes during the night to make sure our brains will remain and increase their efficiency at interacting with the world.

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Speaker 1

17:13

That’s brilliant, and really fascinating. So my next question is very different, almost a change of topic. And that is, what is the day in your life look like as a neuroscientist.

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Speaker 2

17:26

So I have a three year old and a six year old. So my mornings start quite early, quite chaotic. Then after I get them off, I'll get into the lab, have a cup of coffee, check my emails, try to keep up with any recent literature that's relevant to my research. And at the moment, I'm still doing all of my own experiments. So there'll be some lab work to do. You might be like soldering my own electrodes for the EEG and Ecog for the mice, or during the day of surgeries, or doing preparation for the experimental days, like habituating my mice, or doing the actual experiment. And then usually, there'll be lab meetings or a seminar to go to and maybe some following up with some old papers like, I don't know, today, I had some revisions back that I'm working on. And yeah, then going home,

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Speaker 1

18:33

what would you consider to be like the best way to get into science?

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Speaker 2

18:38

Increasingly in the in the field of neuroscience that I am in, and the type of data that we are able to collect now from hundreds of neurons 1000s of neurons at once over long timescales with really high temporal resolution. This is big data. And the way that neuroscience is moving or Systems Neuroscience, the kind of neuroscience that I'm interested in really, really good skill to have some advanced mathematical and programming abilities. So if you start off with these concepts already familiar to you, because in your undergrad you've studied physics or maths and really good at coding, then that puts you at a great advantage. Of course, the biology is still important.

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Speaker 3

19:34

In today's episode, Julia has talked about some of her previous work, and her future ambition to understand what individual neurons do during sleep after experiences during wakefulness. She has discussed how she creatively plans and sets of experiments through iterative refinement to hone in on the most interesting questions, and how she employs some of the latest techniques to observe neural activity in a relatively easy access brain Region, the Piriform cortex, while mice interact with the olfactory environment. We wish her all the best with setting up her new lab in the Sainsbury welcome center this year, and in studying how the brain better prepares us for the world with each and every sleep. Thanks for listening in on our conversation today. We hope you enjoyed it as much as we did. Please keep an eye on our social media to find our next one.