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Keynote presentation

The enigmatic brain: from synapses to neural networks

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Thank you for that introduction and lovely talk. It is a great honour to be here. It's wonderful: the brain is a great passion of mine, and, as George said, for me neuroscience started with a lecture at university where I heard about jellyfish and their not-quite brain but somewhat brain-like features. Yes, I was sucked into the world of neuroscience and trying to understand how the brain works.

Today I'll be talking about the mysteries of the brain: what makes up the brain and why it is so mysterious. Even though we know a lot about the brain, we're really getting down to the nitty-gritty. George has been instrumental in our understanding of the connectivity of the brain. It's almost the case that the more we know about the brain, the more we realise we have yet to learn. We have many more questions than we have answers for at the moment, so it will keep us busy for a long time to come.

The brain is a complex biological organ

"The brain is a complex biological organ of great computational capability that constructs our sensory experiences, regulates our thoughts and emotions, and controls our actions" (Kandel, 2007). The different parts of the brain control different aspects of what makes us who we are. As I move my hand, the top is the part of the brain that's involved in controlling motion. Our visual system is right at the back of the brain. But this is what makes us who we are. And, actually, as you listen to me talk, you'll probably realise that your entire brain is communicating all within itself in order for you to really understand what I say.

The brain in its whole is one complete, large organ that has to bring together all information from our sensory environment, our world around us. If those coming in and out don't quite line up, then it's really distracting. You know when you watch those movies and the audio is just slightly out of sync with what you see, I personally then totally lose track of what's being said and it's really distracting. So the brain does this on every moment-to-moment basis and is such a finely tuned structure that we're just starting to find out about.

This all comes down to the interconnectivity of the brain. The brain has to communicate with one another either directly or indirectly. And we're just starting to delve into the different functions of the brain and what parts of the brain all come together to create this holistic picture of the world that we live in.

Understanding the brain and the fundamental aspects of the brain and how it

1 This is an edited transcript of the address [Ed.]

works as a complete and complex organ is really vital for understanding what goes wrong in cases of disease. Alzheimer's disease, amnesia, dementia are diseases that are associated with learning and memory, which is what my lab largely focuses on. We focus on trying to understand the fundamental capabilities of the brain and how we form memories and how we learn things. Only by understanding the fundamentals of how the brain works can we really understand the mechanisms as to what goes wrong in cases of disease.

The brain comes in all shapes and sizes

As George said, the brain comes in all shapes and sizes and it's actually quite a remarkable organ. A lot of work is done on tiny brains — the mouse brain — and that's because they're a great model of the mammalian brain. If you plot brain weight against body weight across mammal species, you can see there's a linear correlation between the size of the brain and the size of the animal. Basically, the bigger animals have bigger brains, and smaller animals have smaller brains. So if we ask what makes us human, then it's most probably not literally the size of the brain that counts: it's probably what's within the brain and the communications that occur.[2]

The cortex is evolutionarily conserved

Something that I find fascinating is that the cortex — what some people refer to as the helmet of the brain, the part of the brain that enables us to make sense of our environment — is evolutionarily conserved. If we look at our common ancestor, and if we just look at our primary senses — the visual sense, the auditory sense, the other senses — then mammalian species are able to compute these senses. But depending on our needs, we alter the amount of the brain dedicated to these regions. If we focus on the auditory area — in humans we don't really use our ears too much, we've got a limited range of hearing compared to other animals (and I'm personally half-deaf so I particularly have a smaller auditory region in my brain) — but if we look at things like the ghost bat, their auditory cortex has really expanded, and that's because they use echolocation in order to find their food. The message here is that the brain is evolutionarily conserved but has adapted to the needs of each of the animals.[3]

The computational capacity of the brain is immense

I think that its secret is actually what makes up the brain. It has 33 billion neurons. If we take just one of these neurons, it has all these different projections which receive information from synaptically coupled other neurons. The cortical neuron has 17,000 different inputs. This is called the synapse where information is transferred between brain cells. Our brain has a thousand trillion synapses, so the computational capability that the brain has is really immense.[4]

Neurons act as a computational unit

The complexity of the brain doesn't just change with the morphology: it's also what different neurons do with this information.

2 Roth & Dicke (2005)

3 Krubitzer & Seelke (2012)

4 Loomba et al. (2022)

Neurons don't necessarily just receive one bit of information and then spit it out to the next neuron. The communication of the brain is something that's called an action potential, which is a 100-millivolt signal. But they're able to actually take information and actually make it larger than the sum of its parts. The computational capability of the brain is not just in the sheer numbers of the neurons, but it's also in how the neurons take the information that they receive and transform it into something that is meaningful for us.[5]

Neurons come in all shapes and sizes

The complexity doesn't stop with numbers: neurons come in all shapes and sizes, and this is largely what we believe due to basically the needs of each individual neuron according to the brain region that they're in and what information they receive and how they have to transform this information to cause an output. If you ask me, the most beautiful part of the brain is actually our cerebellum that has Purkinje cells associated with movement. The range of different shapes of neurons from humans and also all different animal species is quite immense. Basically, the brain is this immense organ that has so much complexity and diversity within it that enables us to be who we are and enables animals to survive in this ever-changing environment.[6]

Neurons are the building blocks of behaviour

Neurons are the building blocks of behaviour, but we don't really know how they control behaviour. We don't really know why we think the way we are, why we have free will. There's a large area of research that will no doubt continue for a long time.

How do we record from such tiny structures?

How do we record from the brain? George showed some methods of recording from the entire brain. As I was saying, there's a lot of complexity within the brain with respect to these individual neurons, so my lab has been interested in recording from individual neurons to see how they compute information. A technique that essentially won a Nobel Prize for Bert Sakmann and Erwin Neher in 1991 is called "patch clamp electrophysiology." This is where we're able to record from individual neurons within an intact brain or outside of a brain.

There is something called a pipette, and this is a really small thin slither of glass, with a one-micron tip, that we're able to go in and poke into a neuron. Then we're able to record the neural activity in response. Action potentials are generated by putting input into neurons and recorded. We are able to look at individual neurons, see how they take this information, and then how they transform it, and look at what's important.

In my lab, we do these electrical recordings from mouse models but also from human neurons. A lot of research has been done especially at the cellular level, looking at mice and rodents, and they're a wonderful study of the mammalian brain. However, I must admit that, riding to work one day, I did wonder how much of this is translatable into the human condition. Really interest-

5 Stuyt, Godenzini, Palmer (2021)

6 Mel (1994)

ing learning about memory, and we studied in mice, and mice are amazing little critters. But is it reflective of how we learn and how we form memories?

We now receive human tissue from patients across the road at the Royal Melbourne Hospital and then we're able to record from living human tissue. Human neurons are really similar to the mouse brain, so we can record from a human neuron. If you showed me the traces of electrical activity of recording from a mouse neuron and a human neuron, I actually wouldn't be able to tell you which is mouse and which is human. I find that really quite remarkable because we are very different. But there's only one cell type that is different between mice and humans; everything else is essentially the same. I think it comes down to connectivity and numbers.

How do you record from such tiny structures?

There are other modes of recording from individual neurons — more so populations of neurons. This is a technique that has really revolutionised neuroscience lately. You record calcium. Within individual neurons, calcium is a great proxy for activity within neurons, so you're able to put a calcium indicator into the brain. And then we're able just to put a little window on the brain and then we can see how the brain is active when it's active and in particular what this means to certain types of behaviour. We can see flashing lights which is essentially a great way of looking into when certain brain cells are active — how they're active and what essentially makes them tick.

Calcium Imaging is a really powerful tool that no doubt will also win a Nobel Prize at some point because we've learned a lot about the brain and its capabilities from using this technique. You're able to hone in on an individual neuron and an individual input onto a neuron. (These little spines — there 17,000 of them) and then you can record the activity of this particular brain region over time. Here you're we're looking at this particular input pattern on day one, and then we typically look into how memories are formed, and then we can look at the activity pattern of this exact same neuron two weeks later: we can really see what changes in the brain and associate it with changes in the neuron in the mouse behaviour.[7]

How does the brain change through learning?

I've been talking about the complexity of the brain, but something that is absolutely remarkable about the brain is that it's really dynamic. It has to change its activity, its encoding of our environment, according to the challenges that we receive day in day out. If we think about learning — say learning to ride a bike — a quote from Albert Einstein which really rings true to me is that "Learning is experience and everything else is just information." If we're thinking about learning how to ride a bike — and I was just teaching my daughter this the other day — I was telling her, "Okay, you've got the seat, you sit on the seat, you turn the pedals, the wheels will go around, that's great, you'll be off, you'll be riding." She's like, "Great, that's wonderful." She got on the seat, tried to put her feet up on the pedals, and fell over straight away. Even though she had all of the

7 Chen et al. (2013)

information about how to ride a bike, she certainly couldn't ride a bike, and I think it'll be a while before she does.

Something that's actually really important is that just because you have the information about how something would work, you have to learn through experience. That's something that's really important to look at in the brain, and there are different levels of investigation that you can do this. So, as George was alluding to, you can look at the entire brain and how different parts of the brain are active. Something that my lab more so looks at are the individual neurons and how they change their activity as we learn how to do something or as we remember something.

Something that I think is absolutely fascinating is that memory essentially defines us. It is who we are. However, we don't really know how memories are formed. We know kind of where they're formed but now we're starting to realise that they're formed in more regions. There's a lot for us to discover. But we do know that changes do occur in the brain, and also importantly, they change but they also have to really adapt day-to-day. How we can look at this is by training mice on a simple task and then we're able to look at their brain activity on a day-to-day basis and then see how the different activity levels change throughout learning.

We can train mice just to associate between two different auditory tones —it can take about three weeks — and then we're able to look to see and correlate neural activity with the changes and the learning. I won't go into any detail, but we're able to record from the brain and we're able to look at the different times of learning. So as mice are passive and how they just essentially encode new information and then as they're starting to learn. I think that the take-home message is if we put all the stages of learning all up next to each other we could see that this is just an example of an individual neuron and we see it at the population level too that it's dynamic. As the animal's learning and as we're learning things, the brain is changing, and in how neurons encode information is changing over time. That is absolutely crucial for this whole process.

The brain is enigmatic

I hope I've convinced you that the brain is really mysterious. It has to receive information from our sensory environment. All of this information has to come in and that's fine. I think that we've got a good handle on how our sensory world is encoded by the brain and how the brain actually receives all this information, but something that we really don't know is how this information is combined within the brain, and how it changes from day-to-day. This is a great area of research that will probably be never-ending and beyond me. With that, I definitely have to thank my lab in Melbourne, and if you're ever down in Melbourne, come and drop in and talk about the brain and how wonderful it is for a long time to come. So thank you.

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