**CFBT Showcase Seminar 2021 Day 2 Tim Brown introduction, automated transcript 13-Jul-2021**

So, thanks Julie for that general introduction. So it's a real pleasure to be able to tell you a little bit about this aspect of the research that's going on in the Centre for Biological Timing related to brain behaviour and environmental response.

Now, obviously, this is something that is in some way relevant to pretty much everyone that works in the centre but there's a number of us that for which this is of specific interest, myself, David Bechtold, Andrew Loudon, Robert Lucas and also a number of our current fellows in the department, including Annette Allen, Riccardo Storchi who have just started their Welcome trust Henry Dale fellowships and Nina who you heard about, who will be talking immediately after this, I think. So, hopefully, I don't need to go to too much effort to convince you why brain behaviour in environmental responses is an important element of a clock centre. Obviously, we live on a highly rhythmic planet, the rotation of the earth in places, start daily changes in the environment, the rotation of the earth around the Sun, imposes significant seasonal changes. So, availability of light, food, temperature, Etc. And these are important for animal survival, and obviously then animals need mechanisms to sense those changes in the external world and respond appropriately. And obviously, that's why we have biological timekeepers in the most part, it's a way of predicting these changes.

So the kind of questions we are interested in the centre are obviously long standing questions in the field. How do animals sense these changes in the environment? What are the neural and molecular mechanisms that allow them to predict, respond to those variations? And of course how can we use our understanding of those mechanisms to benefit human and animal health? And in that respect, I think it's fair to say that in terms of the primary focus of what we do in the sense, we're coming much more from a basic discovery neuroscience starting point, but at the same time there's a really strong interest and drive towards turning these basic research findings into translational applications that I will touch on briefly in a moment. But in keeping with that, in terms of the kind of approaches we use, obviously we make extensive use of the powerful genetic tools are available in mice, but we also like to extend our studies into into diurnal species with this guy you can see here rhabdomys pumilio which is a close cousin of the mouse but strongly diurnal and of course studies in sheep which are really important for as a model for seasonal timing. And indeed more recently, taking things all the way up into humans and similarly in terms of the actual kind of approaches we use this balance the scales, the detailed analysis of molecular mechanisms, electrophysiological recordings, looking at network properties, opto key mode genetics to manipulate the circuits all the way up to detailed analysis of behaviour and physiology. And so, over the next few minutes what I want to do is just give you some examples of the kinds of current research that's been going on in the centre that kind of draws on some of these things. And so going back to the point I made about translation actually. I think a really nice example of how we've been able to take things from basic animal research through to humans relates to this, this activity that's been going in the centre for a long time now, in terms of developing new metrics for non-visual effects of light, so effects of light on the circadian system, Etc. So as you'll know, one of the big discoveries in the circadian fields this century was the realisation that there was a special class of photoreceptor the melanopsin expressing intrinsically, photosensitive, retinal ganglion cells. That's particularly important for setting the clock and obviously, our centre director Rob Lucas was heavily involved in some of the initial work, characterising this system and through some of that work, it became immediately apparent that this involvement of melanopsin has very important practical implications for how we measure and use light in the world around us, because obviously, the way we normally measure light using things like lux or candelas is based on the sensitivity of the cone base visual system achievements. And that's weighted towards much longer wavelengths than those that activate melanopsin. So Rob started a programme of work which a number of us in the centre were involved with, of developing and validating a new spectral weighting function that was appropriate for describing effects of light on melonopsin and building on some of this early work in animal models and cell-based assays of human melanopsin Rob then organised this scientific consensus meeting of a lot of experts in the field but proposed a new framework for light measurement that's relevant to the IpRCG and that in turn led to this new international standard. From the international writing regulator, the CIE for measuring IpRGC for influence responses to light. So this is really important development because now we have a way of appropriately quantifying light for humans, in terms of how it's going to activate melanopsin, and of course, subsequent work in the sense then was able to show that you can use that new melonopsin based measure to predict humans reading responses to, light and indeed to design new types of visual stimuli and visual displays that allow you to modulate effects of melatonin, for example on, sorry, melanopsin or melatonin secretion without affecting visual appearance.

So, real practical, real-world consequences, and indeed building on this most recently, we've now been up to organise another scientific consensus, which has put some recommendations, healthy daily patterns of light exposure expressed in this new appropriate unit of light measure. So hopefully this is something that's going to have quite significant real world benefits.

Now, as I mentioned, obviously, this is all very exciting stuff, but at our core we're discovery neuro scientists. And in parallel, with all this, we've also been doing lots of work looking at new aspects of century control of the circadian system. So just a couple of examples here. A while back now Josh was looking at century coding within the assay on itself you found this really interesting property.

Where actually, whereas people might have originally thought that what SEO neurons were doing was just measuring ambient light intensity, he actually finds there are some cells there in the clock that are optimised to detect spatial patterns. So they have this kind of centre-surround receptive field structure almost like what you would find in more conventional visual parts of the brain. So it's much more sophisticated, what's going on in the SCN than just measuring ambient light intensity and indeed along the same lines later on Josh was able to show that actually colour signals coming from cones are also an important control in the circadian system and so they act to modulate responses to brightness and that's a neat way that animals can adjust the sensitivity of their clock to deal with weather-related variations in the world which make brightness an ambiguous signal of time of day. And then most recently, a really nice study from Bano-Otalora looking at these guys Rhabdomys that I mentioned a while ago, so the really neat thing about these studies in diurnal rodents is that they allow you to address some aspects of circadian function that are quite hard to study in nocturnal rodents, for example, the effects of daytime light. And here she was able to show this really neat effect where increasing daytime light intensity increases the amplitude of circadian rhythm and importantly, that's maintained. Even if you take the SCN out of the animal, they still have much higher daily variations in firing compared to animals, kept in dim light. So this is a potentially useful new way we can think about protecting our clocks against disruptive effects of evening light. Of course, there's also plenty of interest in the centre, in understanding clock output pathways. So how do signals from the central clock, the SCN, control physiology and I'm going to be talking about some of this later today. So I won't say any more on that and simply I think David Bechtold is going to be talking about some of his really neat stuff tomorrow.

So I encourage you to see that. Moving on from the circadian system though. Certainly, our research isn't just limited to circadian things. So as you'll know, Andrew Loudon has a long-standing interest in seasonal timing mechanisms. And as an example of that most recently, his group was able to identify the origin of the mammalian circadian coincidence timer. So this is obviously a sort of hypothetical mechanism. That's long been considered to be important for seasonal timing in all organisms. Andrews's groups found this in mammals and involves this circadian transcription factor, BMAL2, and its interaction with repressor DEC1. We also, there's interest in the centre in things that are much faster than circadian rhythms as well. So the other end of the scale for example, But from the clinic thought, you know, this is has focused on looking at kind of forced oscillations in the brain, which are known to be important, but kind of sexual finding type features in the visual system and dwelled among lots of the modulating nodes. And also, in terms of understanding better the acute responses of animals to unexpected events in your eye, so things that you can't predict and time and Andrew has developed this really neat automated detailed animal tracking approach now. Which allows you to produce really fine grains information about mouse responses, and allows you to dissociate, particular different, kinds of behavioural responses to different sorts of sensory events in the environment. So, for example, sudden sounds or approaching spots or flashes of light, which is a really neat tool for the future in terms of studies that will then probe the neural circuitry that's controlling these responses.

And finally, I guess sticking with the theme of things that are quite fast. It's is worth noting here that although melanopsin was originally discovered as a kind of circadian photoreceptor significant work over the years has revealed, that it isn't just limited to that, it also plays a role in vision and that there's been a lot of interest in that aspect within the centre for example.

What's happened to my presentation? Can people still see it? Because I can't. No it's disappeared. Let me see if I can bring it back again. Yeah, it's back again. Okay.

Apologies for that. So anyway, so there's been plenty of interest in this idea of melanopsin contributions to vision and Annette Allen, Ricardo Storchi and Nina have all produced really nice papers, on different aspects of that in recent years, in so far as it relates to mice. But really what I wanted to highlight here was as part of that work, they've been developing tools for creating new types of visual display that allow one to independently modulated signals for melanopsin in conventional photoreceptors, and therefore, present patterns that are only visible to melanopsin, for example. And using this approach, which obviously, it works in mice, but you can also do it in humans, and Allen has done that, she's taken these new display technologies into humans and she's been able to show for the first time how melanopsin actually contributes to vision in people. So, things that are only visible to melanopsinn support a kind of low, spatial temporal acuity form of vision. But most interestingly what she was able to show is that if you manipulate the melanopsin in contrast with conventional images, you can make them appear more lifelike and distinct. So, you know, potentially, this is a really neat approach that can be used in future. On one hand, you can make visual displays a more lifelike and realistic. On the other hand, you can modulate melanopsin signals and adjust their impact on your circadian system, I kind of touched on that briefly, at the beginning of my talk. So maybe we'll see this sort of technology appearing in TVs and things in the future, who knows? But hopefully that gives you a flavour then of the kind of breadth of activity across the centre and the kind of interesting things we're doing. I won't say anymore. Thanks for listening to this brief overview.