Notes from conversation with

Dr Stuart Peirson

Associate Professor and

Deputy Director of the

Sir Jules Thorn Sleep and Neuroscience Institution at Oxford University

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Introduction

SP is Associate Professor and Deputy Director of the Sir Jules Thorn Sleep and Circadian Neuroscience Institution (SCNi). He completed a PhD in Neuroscience on visual pigments and circadian biology at University College London in 2001. During his subsequent work at Imperial College, he contributed to the identification of the melanopsin pRGC system in humans as well as the characterisation of melanopsin signalling pathways. He was appointed as a Lecturer at Imperial College in 2005 before moving to the University of Oxford in 2006. His work has continued to focus upon characterising the signalling pathways mediating the effects of light on physiology and behaviour, with the aim of understanding mechanisms underlying sleep and circadian rhythm disruption. In this interview he explains how the circadian and homeostatic cycles work together to create our sleep-wake cycle, the impact of ageing and the need for science and the lighting industry to work more closely together to deliver evidence-based solutions.

SJ: How did you become interested in this field?

SP: It's a long story. My PhD was supposed to be on the vision and the ultraviolet in different animal species, but I ended up working on photoreceptors in the pineal organ and circadian rhythms. So my background is very much in light sensitive pigments and how visual pigments are adapted to the light environment.

So it was really a transition from that into how photo pigments are adapted to regulate circadian biology. So it's a bit of a sideways step, but at the same time, it's been a circadian focus really over the last 20 years.

I was incredibly lucky because melanopsin was discovered during my PhD and most of the molecular circadian clock was discovered during my PhD as well. So literally every week, you could go to the library - when we physically used to go to the library - and there was another paper coming out that completely changed how you understood the field. So it was a great time to do a PhD.

SJ - The body clock seems to have become such a common thing to talk about now that it's very hard to imagine a time before we knew about it. But speaking to you, I realize that most of us don't know very much at all. Could you begin by talking about the sleep wake cycle in the normal healthy person?

SP: Sleep is not a simple output of our circadian clock, unlike many other processes that occur throughout our body.

Sleep is regulated by this circadian clock, but it's also regulated by a homeostatic process, which is a complicated way of saying the longer you're awake, the more you need to sleep.

So you wake up in the morning and as you go through the day, you build up the need for sleep. That's why, typically in mid to late

afternoon, you often start feeling tired if you got a high sleep pressure - if you haven't slept well the night before for example. That is typically before your circadian clock has kicked in and started to help keep you awake. That circadian clock helps keep you awake into the evening when your sleep pressure is high.

Then, when that circadian drive for waking drops away, that creates a window in which you can optimally sleep.

That also explains, for example, when you think, 'oh, I'll have an early night', you go to bed two hours early and lie there wide awake as you can't get to sleep because your circadian clock is thinking 'well, it's time you should be awake'. And so it's still keeping you awake despite the fact that you want to have an early night.

Effectively. the two should be working in harmony. What we have a tendency of doing as humans in the modern society is ignoring that and trying to sleep when we think it's convenient with our lifestyles.

If we have a regular cycle of sleep and wake and we have regular patterns, the system works really well. And it means that we can sleep and we sleep around the same time each day. So when we start trying to move our sleeping times, effectively you're trying to sleep when you're not in that window optimal sleep, which means it's a lot more difficult.

And the other thing to bear in mind is that however strong your circadian drive to keep you awake is, if you're really tired, you will still be able to sleep because the homeostatic pressure will overcome that So the two should be working in harmony. What we have a tendency of doing is living lives that don't allow them to do that.

SJ: So that's the ideal- we've been awake long enough, and the circadian drive is also falling away, so it all comes together. We've got our pyjamas on and off to bed. Unless we disrupt that with exposure to light at the wrong time, correct? What are the main reasons we disrupt them?

SP: Typically it will be insufficient sleep, which means that our sleep drive is higher, so we feel tired even though our circadian clock is keeping us awake.

The other thing to bear in mind is that circadian clock is not just keeping us awake at certain times, it promotes sleep the other times as well. So as it falls away during the night it facilitates sleep. So other ways, as you mentioned, a light on an evening, particularly increases alertness and arousal, and that will actually also delay our clock. So then that peak for wakefulness occurs at a later time. So many of the different environmental factors that disrupt our clocks potentially can affect the circadian clock and have direct effect on sleep.

The other thing to bear in mind is that our circadian clock period changes throughout life. So our period is typically slightly longer than 24 hours, but when we're teenagers, it's longer still, and then it declines again as we get older.

So it means if our clock's shorter than 24 hours, we will typically get up earlier, go to bed earlier. Whereas if our clock is much than normal circadian period, then we will go to bed later and get up later. So that explains the variation you see in the population that some people prefer to be up early on a morning and go to bed earlier. And others actually operate better getting up later and going to bed later.

SJ: Which brings me neatly onto the next part of the conversation, which is about the impact of ageing on that sleep-wake cycle. Because as I understand it sleep disruption is a major factor in cognitive decline in other kinds of neurodegenerative disorders. Is it a cause or an effect?

SP: It's very hard to say whether it's a cause or effect. Certainly I would say that people shouldn't be worried if you sleep badly: it's not likely to be causing things like neurodegenerative disease, which I think has been suggested before. In fact sleep disturbances are common in many other disorders.

And this is one of the reasons why a lot of the time, medically, this is seen as a symptom rather than anything related to cause. But certainly it seems that in many other conditions that improving sleep can actually improve both quality of life and help ameliorate some of the other symptoms.

Clearly sleeping badly on top of any cognitive decline is not going to make it better. You will exacerbate the effects and make any ability to concentrate and pay attention even worse. So if you can improve sleep, it can help some of the symptoms of cognitive decline with ageing.

SJ: As I understand it, the part of the brain that is processing that circadian signal from light is changing over time as we get older. Can you tell me more about that?

SP: Most of our work on this really comes from animal models, we can't study easily the SCN in humans. But what typically happens is that the strength of that circadian rhythm declines with age. And we're not sure whether that's because of reduced coupling between the neurons and they're not providing us a coherent robust output.

But it seems that the strength of the rhythms can get slightly weaker with age, and that therefore means that this circadian drive, which helps interact with the homeostatic drive to sleep will be affected. So effectively our drive to keep us awake will not be as strong.

And if that central master circadian clock and the SCN is not providing a strong output, then rhythms throughout the whole body will be weaker. And so we end up with a situation where rather than having a very strong time signal in the hypothalamus of our brain, which regulates rhythms throughout the rest of our body, we just have a slightly weaker signal. And that means that as that signal gets weaker, our robust rhythmicity, that is normally important for health robustly orientated in time as we should be.

SJ: So that signalling system is changing and getting less robust. But does that mean that we need more light? Because I also know that eyes are changing over time.

SP: There are couple of factors. One of course, is as we get older, we may spend a lot less time outdoors. We're also maybe engaging in less exercise and we know that light exposure outdoors can be 10, 100 even 1,000 times brighter than indoor lighting. So it's a much stronger time cue.

So we sound like a grandparent telling people 'get outside and get some sunlight', but effectively sunlight is so much brighter and exposure to a reliable, strong environmental time cue is also important in synchronizing our clock to the environment. So setting our clock is important, and robustly setting our clock actually can help strengthen our circadian rhythm. So getting a strong time cue from the light-dark cycle is something that can counter the effects of that weakening clock with age.

But typically of course, people for example, in a nursing home or housebound, may not be able to get out and spend as much time outside. So there's a negative feedback loop that occurs.

In addition, there are changes with the eye that occur with age. A lot has been made out of the fact that as we get older, our lens becomes more yellow, transmits less blue light. Now the change in transmission of the

eye effectively will slightly reduce the amount of light that is available to the blue light sensitive ganglion cells in the retina.

However, those effects are relatively small. One of the other factors that may be important, and again, lots of studies have been done on this, but as we get older our pupil size on average gets smaller - it's called 'age related meiosis'. So as we get a smaller pupil, simply less light is getting into the eye. So simple measures by which you can increase light exposure may actually have quite robust effects on the ageing clock.

SJ: What about the spectrum of the light?

SP: one thing that is often completely overlooked in the discussions about changing the lighting environment is that the melanopsin pigment in these circadian photo receptors in the retina is most sensitive to light around 480 nanometers, which is a blue cyan part of the spectrum.

But actually it has a broad absorption curve. So it can absorb light across quite a range of different colours - effectively it's a classic bell shape, a normal distribution. So melanopsin can absorb light if it's red, it just doesn't do it quite as well. Even if you cut out all the light below 500 nanometer using blue blocking glasses and blue blocking filters, you may reduce the light available to melanopsin by about three-fold.

The circadian responses to a light occur over 10-fold or even 100-fold changes. On that scale, a three-fold reduction is actually quite small. If you've got quite bright light, three-fold reductions won't make any difference. If you've got quite dim light and it's not going to have an effect on your circadian clock anyway, filtering won't have an impact.

Only if you're right in the correct part of the dose response curve, would you have an effect.

So just increasing blue light or just decreasing blue light will have an effect, but actually the factor that probably has a much bigger effect is the light intensity itself.

And as I said earlier, one of the big factors that is different between our artificial light environment and the natural light environment is that our artificial light environment in a typical room may be from 100 to 300 lux.

If you go outside, even on a dim winter's day, it could be a 1,000 lux or more.

On a bright summers day, you can have light intensities of up to a 100,000 lux. So the difference between daylight and artificial light is enormous in terms of intensity. People have started to get more obsessed with the spectrum or the colour of the light and forgotten about the intensity.

But the intensity is more likely to have a big effect. On a perfect world what you can do is shift the spectrum and change the intensity in a way that will effectively maximise the effects.

But just wearing, for example, blue blocking glasses is not likely to protect you from effects of light on a blue light in an evening because if you've just got lots of light anyway, it's actually going to delay your curve.

SJ: So it sounds as though f we can increase the light level and increase stimulation, then the circadian system and the homeostatic system will work in a more harmonious fashion

SP: And good routines. So getting up and going to bed around the same time. And one thing related to that is, yes, bright light during the day, but also darkness in the night. But also ideally in the evening, we want to be reducing light levels.

But one of the things that is a bit more tricky about optimizing light in our environment is there will always be effectively a conflict between our visual need and our circadian need.

Our circadian system loves bright light during the day and complete darkness all night. But nobody really wants to sit in the living room in complete darkness before they go to bed. And similarly, with an elderly population, you don't want to have very dim light in the night for example, if you're trying to get up to go to the bathroom and tripping over falling hazards are also an issue. So I think that's where we are at moment, is trying to find that sweet spot balance between the two of what, are our visual requirements of light on an evening and can we get those low enough so it won't have an effect on our circadian clock.

And I think that's why it's a little bit more complicated than just simply saying 'well, just blue filter things, yeah, everything will be okay.'

SJ: It sounds as though we've done a lot of work in animal models. Where would you say, in just a sentence or two, what the future holds for this area of research? Particularly when we're thinking about in hospitals or elderly residential care?

SP: So the lighting industry has become very interested in the non visual effects of light, because it's also important for health and wellbeing. But there's sometimes a rush to translate that before we know what are the important features that we need to translate.

So we find it quite surprising as scientists who work in this area that people in the lighting industry have moved into this and it's been applied to building design within 25 years of the new receptor being identified.

And the fact that the man on the street now knows about the effects of blue light, sleep and circadian rhythms. So that uptake in the public understanding of this has moved very quickly. I think sometimes the translation of this has run ahead of the science.

There's a tendency of lighting products being pushed into market making claims that are not necessarily supported by evidence or effectively, we don't know the basic science on which they're trying to

design the product. So I think, better work between the lighting industry and academia in terms of the basic research would be important in terms of making sure that the products that have been developed are based upon the proper science.

We see a lot of things, we just think *'That will never work! That's just nonsense!*' And vice versa. Scientists need better understanding of the lighting industry requirements and the building industry requirements. Because it's all very well for us to do experiments under laboratory conditions or to look at animal models.

But the reason we do this is to translate it to humans. And we should be providing better guidance as to what is being done. So I think a better integration of work between the end application and the basic science is probably a good thing.

And in addition, what are the key factors that we still don't understand?

One thing that I think will change the field quite a bit is better personalised light measurements. Because our environment is filled with artificial sources of light. What we don't know is actually what people are really exposed to on a day-to-day basis. And the only way of really doing that is to measure someone's light exposure. And we've done that before in a small example, and it's amazing.

It could be potentially very complicated. It seems like actually, if you've measured the exposure of people to a whole range of light sources that they see day to day, it could be seemingly almost infinitely complex.

However, there are lots of real regularity. If you think about your day to day, the light sources you're going to be exposed to. It will be in your home on a morning maybe outdoors and public transport or whatever on the journey to work, and then your work environments.

And then in reverse back home again. So actually there are a lot of regularities in our light exposure day to day.

One of the biggest sources of variability is that early evening. We particularly notice this time of year as it starts to get darker where we get home and we start turning lights on, because our home can be filled with such a variety of artificial light sources.

Although the light levels are lower, we're just exposed to a real mixture of different light levels. We can be exposed to light as the sun is going down. We start turning on lights, we've got screens, TVs, we've got fluorescent lighting and LED lighting all over the place.

So it's a real mixture of different light sources and that can add a lot of noise to what the signal that our circadian system is trying to get.

SJ: It's a very young field, but it's clearly getting lots and lots of interest and excitement as we move into the LED age and trying to work out which ones we should be buying and developing and using.

And a really interesting conclusion that I really wasn't expecting, which is to do with translation, building better bridges between the lighting sector and the scientists and the built environment.

So thank you very much, indeed!