



Women sleep on Venus; men sleep on Mars

Dr Ketema Paul is an Associate Professor at UCLA with a background in neurobiology, sleep and circadian rhythms. His current research focuses on sleep disorders and the interactive effects of sex chromosomes on our ability to recover from sleep loss.

Q&A

Your current research examines the effects of sex chromosomes on our ability to recover from chronic sleep deprivation. What is chronic sleep deprivation and what effects can it have?

Chronic sleep deprivation is when you're able to sleep on a daily basis but are not getting the sufficient amount of sleep you need. If you sleep substantially less than you need, you build up a sleep debt which can then accumulate. This accumulation negatively affects your brain's cognitive function – your ability to think properly and remember things.

Can you talk me through the phases of sleep and wake that we normally experience as humans?

First of all, I'd like to dispel the myth of 'normal' sleep – there really is no such thing. Sleep-wake architecture really represents

the different vigilance states you're in – everyday wake, REM sleep, non-REM sleep – and that is dependent on several things. Age, location and artificial light can all affect this but my research focuses on the effect gender has on sleep. Not only do men and women sleep differently, but women sleep a lot more dynamically during their lifespan. How a woman sleeps is dependent on her reproductive cycle, pregnancy, postpartum recovery, and menopause, so sleep-wake architecture depends on these variables.

It can be different for some people – some people need less sleep, some people need more, but that's for each individual person and their healthcare provider to figure out. Some people use naps and for some naps are healthy, so it really is about having the self-awareness to recognise the signs of sleep deprivation.

So, gender affects your everyday sleep as well as your response to sleep deprivation?

Gender is a complicated variable – it incorporates psycho-social, cultural, and a lot of different factors. What we wanted to do was isolate the biology of gender, which is sex, to see whether gender differences when sleeping can be traced to biological sex differences. When I was a post-doc we looked at sexual reproductive hormones and found that these had limited effects on what we call sleep homeostasis – the ability to recover from sleep loss. In our rodent models, we found that when you removed the sexual reproductive hormones, there were still sexual differences in the ability to recover from sleep loss. These differences were only subtle but, like I mentioned earlier, sleep debt is cumulative so over time it ►

would cause much larger differences to health and well-being.

When we first saw these differences, we began to ask questions and we found that sex chromosomes do in fact affect the ability to recover from sleep loss. Perhaps more importantly though, we also found that during the mid-active phase, the time when we normally get sleepy, mice with a Y chromosome tended to favour sleeping more during this siesta time. That effect came to be increased by sleep deprivation – the less sleep the mice with Y chromosomes had, the more likely they were to sleep during the siesta time. So, we think that we have found, and we are still working on it right now, a unique sleep regulatory mechanism that promotes sleep loss recovery using a kind of pressure switch that occurs during the mid-afternoon – it's biological and seems to be related to genes that lie on sex chromosomes.

A large part of your research uses mouse models. How similar are sleep patterns between mice and humans? What are the differences?

Mice sleep differently to humans. Humans have more of a biphasic sleep pattern, where we're awake throughout the day and we're asleep at night, whereas mice have a more fragmented sleep pattern. They are still biphasic but they display more wakefulness during the rest phase, which for them is during the day time. However, what we're really interested in is the genes and the molecules that regulate sleep, and those are pretty well conserved between mice and humans. We know that mice and humans share the same molecular regulatory elements and areas of the brain that regulate sleep so, as researchers, we think that mice are a really effective model to ask these kinds of questions.

One study has shown that major depressive disorders (MDD) affect the homeostatic desire for sleep in a similar way to sleep loss. What relevance do you think your research might have to mental health?

That is what led us to these studies in the first place. I was interested in looking at the impact stress has on sleep as it can dysregulate sleeping patterns and contribute to mood disorders such as post-traumatic stress syndrome. If you could target the sleep though, you might be able to improve outcomes for people with these disorders. We need to find a way to look at how people

respond to stress and the effect this has on sleep quality and, in turn, sleep deprivation. This sleep deprivation is one of the ways that stress acts to dysregulate sleep so we're trying to figure out how this influences the ability of stress to affect sleep. We think if we can do that then we can better understand how sleep homeostasis works, and perhaps can even use sleep as a target to treat major depressive disorders. We already do that behaviourally, as sleep deprivation is used as a therapeutic treatment for mood disorders, but what we would like to do is make those treatments more effective by understanding how sleep deprivation influences the brain and body.

What are the next steps for your research?

Our ability to understand the dynamics of sleep homeostasis has been sort of limited by the tools we have to measure it, so what we've been doing is trying to develop more elaborate tools that measure the ability to recover from sleep loss – like a kind of biomarker. In our mouse models, we've been trying to design more effective ways to measure sleep homeostasis so we can map out the dynamics of sleep loss. Over time we know that sleep debt accumulates but what does that look like? Which times of the day is sleep debt likely to be higher or lower, and which times of the day is sleep debt accumulation likely to have a more negative effect on your cognitive abilities? And what are the impacts of sex on those differences? These are the questions we are asking right now. To answer these, we are actively doing experiments on stress and sleep, particularly looking at social stress in our mouse models. We're modelling what we call a 'social defeat', caused by a confrontational encounter, to study how sleep deprivation affects resilience and susceptibility to social stress. I think by improving the understanding of the dynamics of sleep loss, we can truly determine whether sleep can be used as a target to build resilience to social stress.

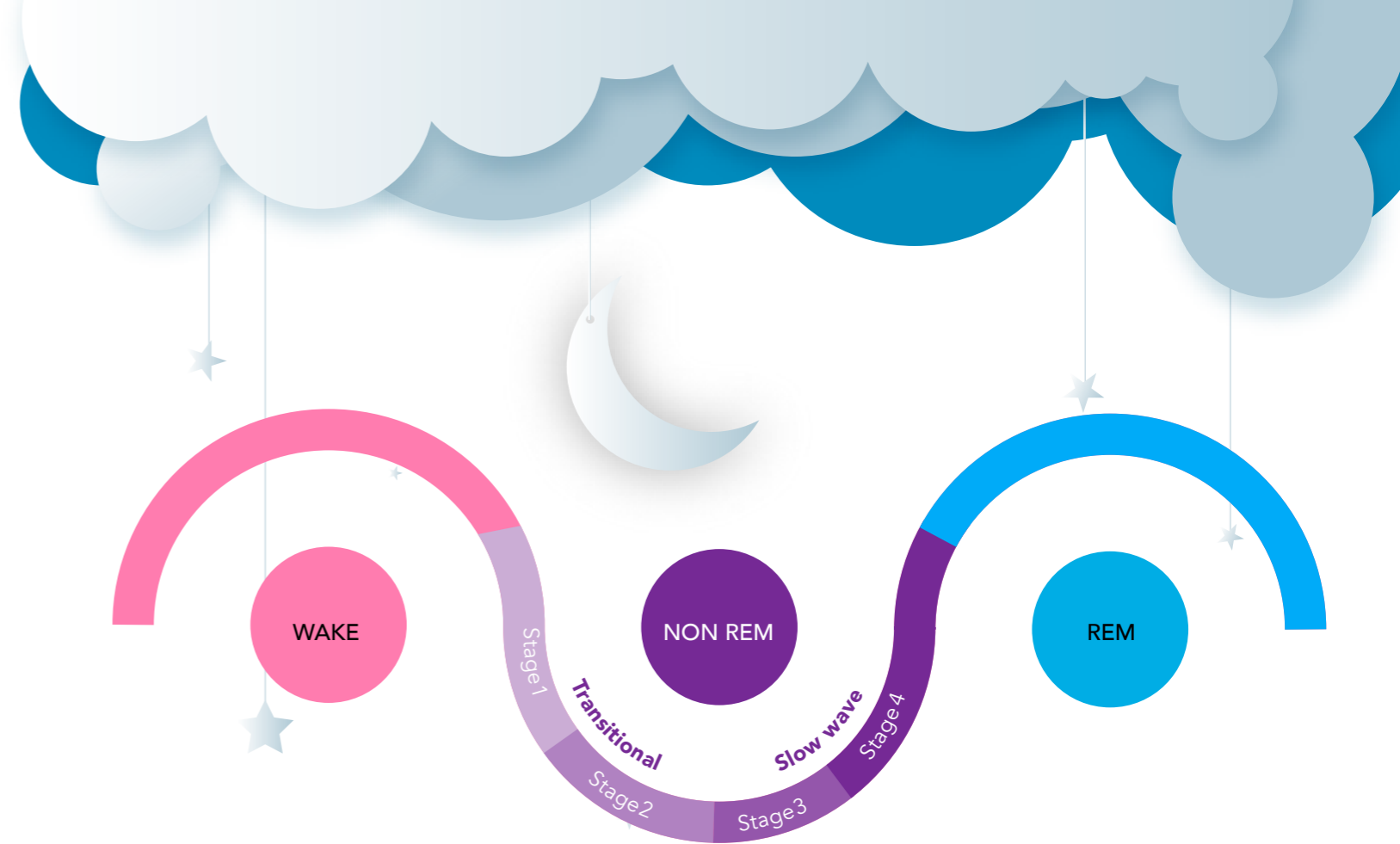
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What influence are you hoping your research will have?

This work is very important to women's health. When I first began the research, it wasn't because I was interested in sex difference research or women's health, I was just amazed that there was so much we didn't know about women's sleep – women's sleep is so dynamic and yet we were asking so few questions about it. That really floored me when I was a post doc, so I decided that if I wanted to learn more about sleep, I needed to study it more in females. I felt that one of the reasons we knew so little about the ability to recover from sleep deprivation was because we included so few females in our studies, so I decided to do the opposite. Women, in several ways, have a biology that is more dynamic and that's a great thing – it enables the fitness of the human population.

So, music is your other great passion in addition to science. Can you tell me more about the role it has played in your life? How important is creativity to your scientific career?

I think creativity is critical to good science. The best scientists – the ones who I admire and aspire to be like – come up with the best experiments that answer the most important questions. You need to be really creative to do that. If there's a really pressing question or need in biomedical science you have to be able to expand your creative outreach to come up with the most effective and conclusive experiments. You then have to communicate those results effectively to reach the largest audience and resonate with as many people as possible. That is what draws me to science, as it provides a creative outlet that really allows me to continue to do creatively the things I do with music. And quite frankly coming up with experiments and completing them, writing them up and communicating them is not much different to producing music.



Sleep is essential for human health and the long-term consequences of sleep loss can be different in men and women. Sleep-deprived women have higher rates of affective disorders such as depression. Moreover, the dynamics of sleep recovery in women are more sensitive to reproductive processes. Dr Paul's work, in collaboration with colleagues, focuses on picking apart the underlying biological reasons for these gender disparities in order to understand the differences between men and women's sleep health.

MEN AND WOMEN SLEEP DIFFERENTLY

Sleep is controlled by two systems: the circadian system, which regulates the timing of the sleep-wake cycle and consolidates it into phases; and the homeostatic system, which determines the amount and intensity of sleep based on how long the person was previously awake. Reproductive hormones interact with these systems, and therefore may be responsible for some of the differences in sleep between men and women.

During sleep, the body goes through several sleep cycles, each incorporating three separate stages of vigilance – wake, non-REM and REM. REM sleep and the deeper stages of non-REM sleep are very important, as they provide cognitive repair and restoration which, in turn, improves memory and

prevents disease. As Dr Paul states: 'Non-REM sleep has several stages. Stage one and two are transitional stages while stages three and four are slow-wave sleep. This slow-wave sleep is restorative and helps you to recover your cognitive ability and restore certain peripheral processes, while also acting to prevent disease and keep you healthy. REM sleep, on the other hand, is especially important for consolidating memories and maintaining brain fitness.'

In rodent models, as used in Dr Paul's research, androgens reinforce sleep, whereas oestrogens enhance wakefulness. Female mice are awake for 1.5 hours more per day, but their sleep patterns are more 'consolidated', meaning they are less likely to wake up during sleep, and more likely to stay awake for sustained periods without interruption. Male mice get more non-REM sleep than female mice, as well as more total sleep.

LOSING SLEEP

Our response to sleep deprivation is still quite unclear because the underlying mechanisms have not yet been clearly identified. However, men and women respond differently to sleep deprivation, and the differences between the sexes increase as sleep loss increases.

This suggests that the sleep homeostat is regulated differently in men and women.

The homeostatic drive to sleep, which increases as the period of wakefulness lengthens, is dissipated during sleep. This pressure, or sleep propensity, is typically measured by looking at slow wave activity (SWA) in the brain during non-REM sleep. Women seem to have higher basal sleep pressure and slower age-related reduction in SWA.

Sleep disorders also exhibit sex differences: for instance, insomnia is more common in women, but obstructive sleep apnoea is more common in men. Disorders like depression can affect the homeostatic sleep drive in a way similar to sleep deprivation (making people with depression want to sleep more often), and affect women and men differently.

SLEEPING IT OFF

The reduced ability to recover from sleep loss of women compared to men may explain the dissimilarity in the adverse health effects experienced by men and women. Dr Paul's team has shown that reproductive hormones, which differ between males and females, are responsible for some of the sex differences in daily sleep amount. However, the ability to recover from sleep loss appears to be relatively insensitive to reproductive hormones, therefore Dr Paul and colleagues have hypothesised that sex

chromosomes directly affect recovery from sleep deprivation.

In some rodent studies, there were no differences in the male vs. female response to six hours of sleep deprivation, but the difference in SWA between male and female mice in the first two hours of non-REM recovery sleep was heightened, as in humans. Results also showed no differences in the absolute amount of recovery sleep following deprivation, but that females regained more non-REM sleep than males, while males regained considerably more REM sleep. Results from fruit fly studies also suggest differences in the recovery from sleep deprivation between sexes.

HORMONAL VS. GENETIC EFFECTS

Dr Paul's team has been working with the four core genotype (FCG) mouse model, which offers some exciting and promising insight. The sex chromosome complement (XX, XY) of mice in this model is independent of their phenotype (male or female), allowing scientists to determine whether differences observed between males and females is genetic, or to do with other sex-specific characteristics such as hormones. The FCG model in mice shows that genetic sex does not determine the difference in baseline sleep propensity. This supports the notion that it is reproductive hormones that affect the differences. However, it also suggests that sex differences in recovery from sleep loss are dependent on something else.

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The effects of hormones can be organisational or activational. Organisational effects are relatively permanent effects on the structure and function of the body, often established during critical moments in development, such as during foetal development or puberty. Activational effects are immediate (and temporary), and depend on the momentary presence or absence of the hormone.

Rodent studies have shown that female gonadal hormones inhibit sleep amount and that these hormones have an organisational effect on sleep architecture. Multiple studies have demonstrated that the female hormone oestrogen reduces the amount of REM sleep or non-REM sleep, or both. Reproductive hormones also influence the ability of circadian rhythms to adapt to light–dark cycles.

OF MICE AND (WOMEN)

Models like the FCG mouse model are instrumental in advancing research on sleep loss and recovery and, although they may not be directly comparable, the genes responsible for sleep regulation are 'well preserved' between the two species. As Dr Paul explains: 'We know that mice and humans share the same molecular regulatory elements and areas of the brain that regulate sleep so, as researchers, we think that mice are a really effective model to ask these kinds of questions.'

Dr Paul's team hopes to use these models, alongside improved techniques to measure SWA in active animals, to increase their understanding of the mechanisms underlying the differences in sleep regulation and recovery between the sexes – but especially in women. Throughout his research, Dr Paul has become an advocate for women's health and his team now hope to further develop their understanding of how sleep deprivation affects diseases more commonly suffered by women. As he says: 'I think it's imperative we understand the things that could increase disease risk, and particularly diseases that are more prevalent in women. I've kind of reversed that in my own research since I first started and, because of the work I've done, I am now a very large advocate for women's health.'

Detail



RESEARCH OBJECTIVES

Dr Paul's research is helping to determine how sex chromosomes impact on the ability to recover from sleep loss. His work increases our understanding of sex-based differences in sleep deprivation and the mechanisms underlying these differences in sleep control.

FUNDING

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COLLABORATORS

- Karyn Esser, University of Florida
- Gianluca Tosini, Morehouse School of Medicine
- Chris Ehlen, Morehouse School of Medicine
- Jason DeBruyne, Morehouse School of Medicine

BIO

After receiving his bachelor's degree in biology from Howard University, Dr Paul went on to study neurobiology and circadian biology at Georgia State University in Atlanta, Georgia where he received his doctorate. Dr Paul completed a postdoctoral fellowship at Northwestern University in Evanston, Illinois in 2006 at the Center for Sleep and Circadian Biology, after which he accepted a faculty position at the MSM. Dr Paul is currently an Associate Professor at UCLA.

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