

Harvard Medical Labcast

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Genetics of Sleep

Tour a lab that studies slumbering fruit flies

Dragana Rogulja

Interviewers: Stephanie Dutchen, David Cameron

[MUSIC PLAYING]

DAVID CAMERON: Hello and welcome to the September 2015 episode of the Harvard Medical Labcast. This podcast is brought to you by Harvard Medical School's Office of Communications in Boston. I'm David Cameron.

STEPHANIE DUTCHEN: And I'm Stephanie Dutchen.

CAMERON: And in this episode, Stephanie tells us about a disturbing new study that shows how the current formula for assessing a hospital's readmission rates may have some unintended consequences.

DUTCHEN: And in today's conversation, David speaks with Dragana Rogulja about what fruit flies have to tell us about the science of sleep. Tell us a little bit more about this, David.

CAMERON: Well, Dragana Rogulja is a professor of neurobiology here at the Medical School and she studies the genetics of sleep, and the animal model that she uses is the fruit fly, as you just mentioned. And she essentially has this gigantic sleep lab for flies.

She has these flies and she genetically manipulates them in all sorts of ways. And they literally have flies there that have insomnia. They have flies there that have trouble falling asleep. Flies that have trouble waking up. And what they're doing is looking for

the genetic components of all that and hoping to find clues into why you and/or I might have these same problems.

DUTCHEN: Who knew?

CAMERON: Yeah, exactly, who knew. It's pretty interesting. A lot of our conversation happened actually in some of these rooms where she has some of these machines and we were walking around the lab. So at times it gets a little noisy and you'll hear some doors open and close and things like that.

DUTCHEN: Ah, science at work.

CAMERON: Yeah, actually it is science at work, so let's take a listen.

[DINGING]

DRAGANA ROGULJA: This is a really important area.

CAMERON: Yes.

ROGULJA: We have our popcorn machine.

CAMERON: You've got your own popcorn. That's awesome. I don't know if I've ever seen one of these in a lab before. I've seen lots of espresso machines.

ROGULJA: Yes, we have a good coffee machine. Very important. I didn't actually offer you guys coffee, but--

CAMERON: That's OK, I'm caffeinated and now I'm--

ROGULJA: OK. And this--

CAMERON: --chocolated.

ROGULJA: OK.

CAMERON: So when I-- oftentimes when I've spoken to people in this department, the Department of Neurobio[logy] here, their particular areas of interest are often incredibly arcane and very specific and just this -- unless you know a lot about molecular biology, you probably wouldn't even understand the problems that they're trying to solve. And yet you're -- here you are and using the same tools and everything, but you're asking questions that are, in a sense, very obvious, very plain, but using such a sophisticated tool to do so. I don't know. Can you talk a little bit about that?

ROGULJA: I like that. I like that. I like asking really simple and plain questions, as you say. Because we can't all understand them and we can intuit that these are important things. And I also think it's fun to study things that you can relate to on a personal level, too. So we all know what not getting enough sleep feels like. Right? We all know that horrible, crappy feeling that follows a night of-- right? Like inadequate sleep.

CAMERON: Some of us do at this very moment.

[LAUGHTER]

ROGULJA: Well I hope not. I hope I'm entertaining you enough not to feel--

CAMERON: No, no. No, right here. Last night was a little off for me.

ROGULJA: Well, so you see it's something that affects us really a lot, right? And you know that there are days when you're just -- all you can think about is just wanting to crawl back into bed. Now we don't know what that feeling is, really, where it comes from, but we've all experienced it. And I think it's something that can really drive you

forward, propel you to look into things further. Because you know that this is something important. You know that there's the real basis, biological basis, for what we're -- or physiological basis -- for what we're studying. And anybody can understand--

CAMERON: What's your--

ROGULJA: --your questions.

CAMERON: Oh, I'm sorry.

ROGULJA: That's OK.

CAMERON: Didn't mean to throw this paper to you. What is your sleep--

ROGULJA: My experience-- I--

CAMERON: --pattern history like? Are you a good--

ROGULJA: Bad.

CAMERON: --sleeper? Oh, a bad sleeper.

ROGULJA: No, I'm not a good sleeper. It sucks. I mean it's really -- it's horrible. It's just something that my mom's side of the family is like that. They have trouble sleeping and I'm the same way. So I can fall asleep but then I just can't stay asleep. I just wake up and I continue--

CAMERON: After just a couple hours?

ROGULJA: After maybe like an hour and a half, two hours. So I would say probably--

CAMERON: Then are you up for the rest of the night?

ROGULJA: No, I go back to sleep, but I stay awake a little bit and then I go back, sleep again. I think I go probably through a cycle of sleep, non-REM, REM, and then I wake up and then I go back to sleep. So what's interesting is we can see this in humans and we can see this in flies that some people like me, or some flies like me, have trouble staying asleep. Other animals can stay asleep, as I said, once they fall asleep, right?

And so what's exciting to us is that we can genetically really separate these mechanisms and we know that -- so, in other words, some of us have problems with one process or the other and we can find genes that affect either initiation of sleep or maintenance of sleep. And so this is important because, first of all, when we're intellectually curious and we want to know how you separate these. But second, they're really -- a lot of us do have sleep problems and there's a lot a need for finding better sleep medications.

CAMERON: Right.

ROGULJA: And the sleep medications that we have now -- I'm not going to say too much bad about it because they've helped me, they've helped me in the past.

CAMERON: They've helped me.

ROGULJA: Yes, they're great, but at the same time there's really a lot of side effects that are associated with this because you're affecting many general processes in the brain. So we don't have things that would really very specifically target sleep, let alone initiation of sleep versus maintenance of sleep.

CAMERON: So is that sort of a long term -- I know you're doing very basic, fundamental discovery here, but do you sort of have this sort of a vision of maybe your work one day being applied to more targeted therapies for different kinds of sleep?

ROGULJA: Sure, I mean, I would love that. I would say on a day-to-day basis, it's not something that really shapes our day-to-day experiments, but we're always keeping this in our minds as long-term, long-term solution. Because if you can combine things that are exciting and fun and intellectually stimulating with something that can be actually useful in the long run and help people, of course we would love that.

So we do think about this. The fact is that there's a huge market for this and there are the solutions that we have right now--

CAMERON: Yeah.

ROGULJA: --are very unsophisticated. So you've heard about all the side effects that are associated with taking some of these medications and so on because you're affecting a lot of the processes in the brain.

CAMERON: Sure. They're kind of messy.

ROGULJA: Yeah, they're pretty messy. We usually say here it's like a sledgehammer approach. You affect the whole brain. So it's just weird stuff. But at the same time sleep is quite complicated and so I don't think that there's going to be a really simple solution coming soon to fixing all of these problems. But in the long run, definitely.

So our goal is to find, for instance, genes that act in smaller populations of cells or find smaller clusters of neurons that regulate sleep. And so if you could manipulate the function of those as opposed to something in the entire brain then you could, maybe, achieve more specific sleep.

[WHIRRING]

ROGULJA: So this is -- we're now getting into the room where we're looking at different arousal states of the fly, arousal threshold experiments.

[DOOR SHUTS]

ROGULJA: So come on in. So this is -- one other question that we're very interested in is understanding -- actually, I would say that this is kind of the reason why I got into sleep research originally, is thinking about awareness. Really what awareness is. What consciousness is. What awareness is. What does it mean? What does it mean to really be alive and perceive the world around you?

So there's this really big difference between what goes on in your head when you're asleep and when you're awake. So I thought that studying sleep and waking could be a good way to get to what perception is. What it means to be aware of something.

So we thought that it would be really good to study arousal threshold during sleep. In other words, the fact--

CAMERON: Arousal threshold?

ROGULJA: Arousal threshold.

CAMERON: OK.

ROGULJA: Meaning that what will arouse you from sleep, the stimulus that would arouse you when you're sleeping, needs to be stronger than a stimulus that would elicit a response when you're awake.

CAMERON: OK.

ROGULJA: And so the threshold is higher so the stimulus needs to be stronger to get over that threshold. OK? So if I whisper something to you now, you're going to be aware of that, right? If I do the same when you're sleeping, you're not going to be aware of that

unless I say your name in which case you may be more aware, or if it's your kid crying, even softly. Stimulus that's more salient will somehow [get] through. But there's a general change in the way that your brain perceives and processes this information and decides what to do with it.

And so we decided to basically set up a system to look for animals that are much easier or much harder to wake up from sleep than normal. Meaning that their arousal threshold is different. OK? So they still are sleeping but the depth of their sleep is different. And that, we hope, will help us understand how that barrier during sleep is constructed in the brain-

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CAMERON: And what the genetic mechanism part is--

ROGULJA: What the genes are, what the neurons are that are regulating this, and then eventually understanding that barrier can help us understand how, in general, information gets to the brain to generate awareness. So my postdoc, Iris Titos Vivancos, she can start -- so when she came to my lab, we talked about this and then she came up with this system that you see here. OK?

CAMERON: Wow. OK.

ROGULJA: Yeah, to automatically wake flies up. And we can now look--

CAMERON: So just describe what this is. So this is a refrigerator here.

ROGULJA: This is the, yeah, the same incubator that we have.

CAMERON: And we have these little wells or tubes--

ROGULJA: And we have this--

CAMERON: --with how many flies are in each of these?

ROGULJA: So each of these little machines is 32 little monitors. It's 32 flies.

CAMERON: OK.

ROGULJA: And so here you have a lot. There is like 500, 600 flies in there now.

CAMERON: OK.

ROGULJA: And we can automatically produce different stimulation.

CAMERON: Like what?

ROGULJA: So we have a program to produce vibrations of different intensity, either very gentle or very strong, that we can apply to flies during their sleep. And then we can look for animals that are much more responsive, say for -- to a gentle stimulation. So we found -- Iris found some mutants that are -- when you very gently shake them, for instance, normal flies are refractory to that. OK? Because of that elevated arousal threshold, they don't respond. Right? Your brain is kind of guarding itself against these assaults. Right? It happened in your sleep.

But she found animals that are much, much, much easier to wake up.

CAMERON: And did she manipulate them genetically or did she just--

ROGULJA: Even very gentle--

CAMERON: OK.

ROGULJA: Yes. So she-- what she does is she--

CAMERON: Maybe we should step outside for a minute.

ROGULJA: Yeah.

[DOOR SHUTS]

ROGULJA: So what she does is she actually manipulates different genes, so she kind of turns off or dials genes down one by one in the nervous system and then looks for animals that respond in a different way.

CAMERON: OK.

ROGULJA: So the beauty of that is that we can immediately -- we immediately know what the gene is that we've manipulated because we're directly targeting different genes. And there's a lot of ways that you can do that now.

CAMERON: So it still just strikes me from conversations I've had with various people around here at the Medical School that just the fundamental question of why we sleep is still something of a black box.

ROGULJA: Yeah. I would say that's definitely the case. That's something that we don't -- I would say yeah, we really don't know. We have some ideas. There are clearly many processes that are affected if you don't sleep, so there's different--

CAMERON: Well, if you don't sleep, you die, eventually.

ROGULJA: Eventually, yes. So that's the idea. Although the long-term deprivation experiments are a little bit trickier than you would think. But yes, there is that idea.

CAMERON: It does seem sort of funny. I mean, we know why we eat.

ROGULJA: Yeah, exactly.

CAMERON: We know why we breathe.

ROGULJA: I would say that's definitely true. For all the basic animal behaviors, from all the basic behaviors, this is definitely the most mysterious one. It's really not clear.

CAMERON: Why is that?

ROGULJA: Why is it that it's the most--

CAMERON: That it's the most mysterious, yeah.

ROGULJA: Well, it's most mysterious because we don't know what it's doing. But I think that the answer is not going to be -- well, because the answer is not something that's obvious. But I think that there's not going to be a really simple answer to why we need to sleep.

So many things have been proposed. You know they're regulating, for instance, immune system or your body temperature or metabolism. Now there's this idea that you're clearing some toxins from the brain. That the sort of space between cells in the brain is changing--

CAMERON: Oh, really?

ROGULJA: --in mammals between waking and sleeping. They are kind of flushing out toxins. It's almost like drainpipes changing size or shape during sleep.

CAMERON: That's interesting. I've never heard that.

ROGULJA: So there's that idea, but I think that it's not going to be just one thing. I would say that you probably -- so what is clear that we can see in flies that don't sleep well. They do die. They tend to have decreased lifespan. And it's easier, much easier, to do these kind of longevity studies in flies. Right?

We don't know really where the lethality is coming from. Is it that your brain is messed up? Is it your heart? Is it your heart explodes, not literally, but is it something in your circulatory system, whatever. So we could maybe, in the fly -- because we have all these tools to affect functions of different genes in different parts of the body -- we can do some manipulations that would help us kind of pinpoint where changes are happening when you're sleep-deprived.

But like I said, I think that the answer to that is not going to be really a simple one. "This is why we need to sleep." What I like to think about is how do we -- not just how do we get to sleep -- why do we sleep, how do we get to sleep, but how do we get to be awake, really. Because it seems to me that a lot of the -- we think of sort of wakefulness as the kind of primary state that the--

CAMERON: The default.

ROGULJA: The default state and then you go into sleep. But if you think about way, way back in evolution and more primitive organisms, are they more similar to a sleep state or they more similar to a state where you're awake and you have this awareness and these some amazing mental processes. Maybe they're more similar to sleep and then you had to kind of develop this awareness and consciousness and arousal. So I think--

CAMERON: I've never thought of that. That is really interesting.

ROGULJA: Yeah, I think it's really interesting to think how do we get to experience things around us, actually, in a way that then we do when we're awake. To process things. I mean, obviously, that's something that requires a lot of resources. So I think

we're kind of lucky. Right? Because you're like, oh, I get to be in this state that allows me to interact with the world. So we're thinking about it that way, too.

And again, I think these experiments that we're doing with studying arousal threshold, how that changes between wakefulness and sleep will hopefully get to get us closer to understanding.

CAMERON: OK. Well, thank you. This was great.

ROGULJA: Thanks.

CAMERON: Thank you so much, Dragana.

ROGULJA: Thank you, guys.

[DINGING]

CAMERON: And now for this month's abstract.

DUTCHEN: One of the ways Medicare tries to encourage hospitals to improve quality is to penalize hospitals with high rates of patient readmissions. Medicare standard formula adjusts only for patient age, sex and certain diagnoses. Using that formula, the worst-performing hospitals had 4.4 percent more readmissions than the best-performing hospitals.

A new study from Harvard Medical School's Department of Health Care Policy found that the current formula leaves out key social and clinical factors that explain nearly half of the difference in readmission rates and suggests that hospitals that serve disadvantaged communities are being unfairly punished. In other words, a program designed to penalize hospitals for poor quality of care ends up penalizing them for treating sicker patients.

The researchers developed a set of 29 patient characteristics, such as self-reported health, functional status, race and ethnicity, income and education. When they applied the more comprehensive formula, the difference in readmission rates shrank from 4.4 percent to 2.3 percent.

Why does it matter? Last year, Medicare levied readmission penalties of \$428 million across 2,600 hospitals, most of which serve disadvantaged patient populations.

The researchers emphasized that it's possible to reduce readmissions without exacerbating health disparities. The standard formula can be adjusted where each hospital could be incentivized to improve over its own baseline.

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And now for those of you who have actually listened all the way to the end here, we are going to treat you to a really horrible, horrible science joke. So, you ready, Stephanie?

DUTCHEN: Here we go.

CAMERON: OK, here we go. So, Stephanie.

DUTCHEN: Yes, David?

CAMERON: Ever heard of Pavlov?

DUTCHEN: I'm not sure, but I think it rings a bell.

CAMERON: Oh, God, yeah, I know.

DUTCHEN: Groans, groans.

CAMERON: That hurt, that hurt. OK. Bye.

END OF INTERVIEW