

## Transcript of [Cerebrum Podcast](#): The Sleeping Brain

Guest: **Chiara Cirelli**, M.D., Ph.D., is a professor in the Department of Psychiatry at the University of Wisconsin–Madison. She received her medical degree and Ph.D. in neuroscience from the University of Pisa, Italy, where she began her investigation of the molecular correlates of sleep and wakefulness and the role of the noradrenergic system in sleep regulation. She continued this work at the Neuroscience Institute in San Diego as a fellow in experimental neuroscience, and subsequently at the University of Wisconsin. Cirelli’s research is aimed at investigating the fundamental mechanisms of sleep regulation by using a combination of molecular and genetic approaches.

Host: **Bill Glovin** serves as editor of [Cerebrum](#) and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Hi, and welcome to the *Cerebrum* Podcast.

One of the great mysteries of human behavior is sleep. What happens inside our brains when we sleep? How much sleep do we need? Why do we dream? How do we compare with other species when it comes to sleep?

Joining us on the phone today from the University of Wisconsin in Madison is Chiara Cirelli, a professor in the Department of Psychiatry at the University of Wisconsin–Madison. Dr. Cirelli, who is both an M.D. and a Ph.D., is the author of our most recent *Cerebrum* article, [“The Sleeping Brain.”](#) You can find the article at the Dana Foundation's homepage at [dana.org](http://dana.org).

Dr. Cirelli wrote the article with her colleague, Giulio Tononi, who is also a Professor of Psychiatry at the University of Wisconsin, as well as the director of the Wisconsin Institute for Sleep and Consciousness. Their research is aimed at investigating the fundamental mechanisms of sleep regulation by using a combination of molecular and genetic approaches.

Welcome, Dr. Cirelli. Can we begin with what inspired you to study sleep, and maybe a little about your background?

Chiara Cirelli: Yes. I studied medicine in Italy in Pisa. I've always wanted to study the brain, and I wanted to do research. I never wanted to be a doctor. In Italy, I think the best way still, if you want to study the brain, is to go through medicine, so I

don't regret that at all. But really, from the very beginning, I started working in a lab, a sleep lab in Pisa and the Department of Physiology, where Giuseppe Moruzzi and Ottavio Pompeiano were my mentors. There was, since the 50s, a very strong background and tradition in sleep research, so it was very easy for me. I started going into the lab in my first year of medicine and never left, basically.

I always knew, from the very beginning, that I wanted to study sleep, and I was specifically interested in the function; not in the mechanism of regulation of sleep. I started there and I never changed my mind. In that sense, I think I was very lucky. I see many students and I mentor many students, of course, and they ask me many things. I see them struggling to find what they really want; that big question. I felt like I knew my big question from very, very early on. In that sense, I think I was very lucky.

I finished my Ph.D. in neuroscience in Italy, and then I moved immediately after that to the United States. First, in San Diego, then in Wisconsin in Madison. Always doing basic sleep research.

Bill Glovin: You write that experiments have shown that cognitive impairments can be reversed by sleep, but not by the same period of quiet wakefulness.

Chiara Cirelli: Yes.

Bill Glovin: I take that to mean that resting, or laying but not falling asleep, is not nearly as useful as sleep itself.

Chiara Cirelli: Yes. That's one of the strongest evidence that we have, although admittedly, there are still very few experiments directly testing that, but that's one of the strongest evidence we have. That, indeed, resting, meaning, again, being immobile, closing your eyes, doesn't do it. You really need to be disconnected, so you really needed to go into sleep to recover whatever is the fatigue that was caused in the brain by being awake.

In tasks in which people visual and attention tasks, usually, you are tested across the day, and then in the middle of the day, for instance, you can have the opportunity to either just close your eyes for one hour, rest, or take a nap. You can see that people, if they just were resting but they were awake, the fatigue when they are tested after the resting period is still there. Instead, with the nap, these deficits in performance go away.

Bill Glovin: Does resting have any significant benefit on the brain?

Chiara Cirelli: For what we know now—again, there aren't many studies, it looks like resting can have a very immediate, very short-term advantage for a few minutes, but then the fatigue comes about very quickly. It's not a long-term recovery function. That's what we can say from the evidence that we have now.

Bill Glovin: Do dreams have any ability to help our brains recover from what you call the fatigue of being awake?

Chiara Cirelli: I don't think we know that directly. Meaning, I'm not aware of studies in which the two conditions, let's say, sleep without dreaming and with dreaming, were compared, so I can't really answer that question. It's important to stress the fact that now we know that dreaming is very common during sleep. It's not happening only during REM (Rapid Eye Movement) sleep, as it was thought early on; it's very frequent, also, during non-REM sleep.

When you talk about dreaming, dreaming is actually a feature that is quite common during the entire sleep period, so it would be even more difficult, let's say, to piece apart the dreaming part relative to the normal dreaming part.

Bill Glovin: Why is sleep so inconsistent? Some nights, you might experience uninterrupted sleep, while the next night you wake-up during the night three or four times?

Chiara Cirelli: Well, sleep is a very delicate state, so anything in the environment. Again, because yes, there is this partial sense of a disconnection, but it's very partial, so anything that happens is poised to disturb your sleep. We are really a slave of the environment of anything, in terms of the quality of our sleep.

In fact, when you test subjects in a protected environment, like in a lab, and you ask people to come several nights in a row, the result is the opposite. The people are extremely consistent in their pattern of sleep. They may vary very much from one individual to the other, but not within the same individual. That's one of the reasons why we think there is also a trait, a genetic basis for sleep, because there is the inconsistency once you, again, correct and take care of all the possible variants due to the environment.

Bill Glovin: Microbiota and the brain have been, obviously, connected in a huge way in recent years. How about microbiota—or nutrition and sleep? Has there been much work done in that area?

Chiara Cirelli: No, I think it's just starting. It will come out, I think, soon, but I think, for now, we certainly have evidence that there are effects on the circadian system, in general, but whether or not it effects sleep per se, I think the evidence is still a missing thing. But I know people are actively working in this area.

Bill Glovin: Why do people have more trouble with sleep as they age?

Chiara Cirelli: It's a difficult question to answer. Again, sleep is disturbed by everything. You age and there are many reasons. You are sick. You are in pain. All these conditions will affect sleep. The question is more whether, is even extremely perfect—if there is anything like that—perfect aging, healthy aging. Is it really associated with fragmentation or poor sleep? I'm not sure we really know that. It's very difficult to control for all the factors that in aging could affect sleep.

In the few studies that have been done with very healthy elderly, in general they are more resistant to the effects of sleep deprivation. It seems that the need for sleep is less. Therefore, if you do sleep deprivation studies, it's actually much easier to enforce wakefulness in old people than in very young students.

Does that mean that they need less sleep? Maybe. That's an interesting question. Based on our studies, I would say, well, that may be. If you don't use enough of your brain, if you don't push your brain to learn many things, you will need less sleep. That could be an explanation. A very easy and perhaps too naïve explanation.

But in healthy elderly, in general, the total amount of sleep tends to decrease. The deepest phase of sleep, which is the deepest phase of slow-wave sleep, is gone. And that's true not in very old age; it starts early on, by age 40, it's basically gone, but I'm not sure we can say that, really, the quality of sleep in very healthy people is affected, if you control for all the other aspects.

One other thing that we know is that very healthy aging is associated, usually, to more resistance to sleep deprivation and they tended to—if you sleep deprive them and then you allow them to sleep, what we call the sleep rebound—the ability of them to recover some of the sleep is less blunted. Perhaps, that, again, is an indication that they need less sleep, but again, this is a very open area of research. I think we, as a field, feel this is still a very controversial area.

Bill Glovin: Well, connected to that idea is the idea that some people function very well on five hours of sleep, while others seem to need a full eight hours to function well. I guess that's sort of the same; going down the same road.

Chiara Cirelli: It's very clear now that there is a huge inter-individual variability. Just looking at sleep duration is not very helpful. That's why, also, one has to be careful. I'm always asked, "Well, how many hours should I sleep?" Well, I don't know. You should know, because you should know when you wake up. If you feel fully restored, that's how much you needed to sleep. But people vary a lot. That's also, now, we know, true, not just for adults, et cetera, but even in infancy, newborns, in adolescent people.

The variability is very high, so one has to be very careful, because then, some people feel that they need to sleep eight hours, and maybe they don't, and then they get concerned because they are not sleeping enough when, in fact, this is not the case.

Why sleep duration is not crucial? That's probably because what really counts is not so much the quantity of sleep but the quality. Again, in general, at least half of our sleep is a superficial, shallow sleep that, perhaps, is not as important as the deepest slow-wave sleep, or even REM sleep, that we have.

One evidence for that is that, if you are sleep deprived, again, in the next night, finally you go to sleep. Would you recover? Of course, we can never recover all the sleep that we lost. We recover a few hours, and those hours usually are of this deepest sleep, suggesting that's really what counts. The other part, we can probably get to read with less consequences, if not any consequences at all.

Bill Glovin: Well, that also leads to the idea of why some people are able to nap while others can't. But I commonly hear in older people who say that, let's say, after lunch, I guess, because your system is processing digestion that it leads to sleepiness and, then, perhaps, maybe a nap. Then, some people, they take a little power nap, maybe for 10 minutes, and then they wake up and they're feeling much better and are able to function at a much higher level for the rest of the day.

Chiara Cirelli: Yes. These people are very lucky. Again, we don't know. Some people are very good nappers. Others are not; are unable to nap, to go to sleep, or they do nap, but they say that when they wake up, they have this phenomenon that is common in most of us of sleep inertia. They feel very groggy for a long time after the nap, and actually, they feel that the restorative power, then, is gone because they are really slow for a long time.

We don't know why some people are more able than others. The napping, the feeling sleepy after lunch, is actually very much due to the circadian; the timing regulation of sleep. The circadian system, that is the one that helps us to stay awake more or less continuously for the entire waking day; for 16 hours or so, for most of us. Because that system is not super powerful around, let's say, 1 or 2 p.m., that's why we have an increase in sleepiness.

It's not so much related to the fact that we ate lunch. You still have this dip in performance, in attention, even if you skip lunch. The lunch may help or give you the sense that, well, yes, it's digestion, but actually, it's independent of that. The strength of this system of the clock of the circadian system to keep you awake, varies among individuals. Probably, one of the reasons is that, in some people, this drop that allows you to nap is stronger. That's one possibility, but you're right.

There are studies, for instance, that tested if you are sleep deprived. You've been in a car driving all night, and then should you take a nap? Can you recover through a nap, or by taking caffeine? Well, the result is that you can try both and both work. It depends on whether you can do the nap or not. Some people, again, really, they cannot.

Bill Glovin: Well, on the other side of the coin, over-the-counter drugs and supplements, like melatonin, are used by a vast amount of people. I'm wondering, in your research, is that something that you take into account? Or do you try to, when you do research on human beings. I know you do a lot of mice work, but if you were doing something on a human being, do you factor in the idea that they could be taking some over-the-counter drug?

Chiara Cirelli: Yes. We screen for them. Either we don't use those subjects, or we ask them to refrain from anything, including caffeine, for instance, or drinks, et cetera, for several days before they go into the study. For instance, if we do sleep deprivation studies, et cetera. Yes, because it's very, as you say, common.

Bill Glovin: Can you explain what led you to develop the synaptic homeostasis hypotheses? And maybe you can explain a little about what it is.

Chiara Cirelli: Well, the starting point was, of course, trying to understand why we need to sleep, because from an evolutionary stem point, it seems that sleep makes little sense, meaning, again, by definition, when we are asleep, we lose the ability to respond to stimuli, and so, potentially, we are in a very dangerous situation. Why would you spend a third of our life, and all animals do that, in a situation, in a condition, that is potentially so dangerous.

There must be a reason, a very good reason, to do that, that counteracts all the possible negative consequences. We reason that that reason must be really related to the feature of sleep that is this disconnection from the environment. The brain is offline when we are asleep, and somehow is able to do the function of sleep only it's offline.

That was our starting point, and we think that this function, this job that the brain can only do very well during sleep, is to re-normalize the top amount of synaptic strength that has increased during wake. By that, I mean, when we are awake, we are always learning something new. It's not just when we go to a class. We are always adapting again to situations, to something unexpected that is happening, and this is learning.

This is the definition of learning, which means, in the brain, the connections among neurons get changed and, overall, get strengthened. The synaptic connections, the synapses that allow neurons to communicate to each other, get potentiated, which is, we know, the way we learn. It's good. But as a long-term consequence, that is not so good, which is ...

First of all, synaptic activity is very expensive. It accounts for a lot of the energy that the brain is using in general, and also, if you keep strengthening synapses, they will, at the end, saturate. No more learning would be possible. That's why we think, and we are not the only ones. Everybody knows that there is a need for the brain, after learning, to re-normalize synaptic strength. The synapses get potentiated because you learn in wake, but then you need to depress.

Now, most people think, "Well, maybe the brain is smart enough." But actually, on this part, online, while you are learning something, you can also actually depress other connections in other parts of the brain that you are not using right now. We think that, overall, that's not possible during wake because the system that I mentioned at the beginning, these groups of neurons, the histaminergic, the cholinergic, there are many of them. All these systems are

very active during wake, exactly because they are helping you to pay attention, to learn, to potentiate.

It's very difficult, in this neuro-modulatory condition, to actually depress the synapses. Instead, when you are asleep and all these systems are off, it's much easier. Also, the principle reason is that, well, when you are awake, let's say, today, you are only listening to me for the entire day. It seems very unfair if you were to now strengthen all the connections that are related to this conversation but then depress everything else because, today, you only listen to me. It makes more sense that when you decide to do this re-normalization, you do it offline during sleep when all neurons are active ...

As I said before, neurons are, more or less, also active, all simultaneously, but they are detached from the environment, and the brain is able to activate all the synapses and decide how to do this re-normalization offline in a much more comprehensive and fair way, which is not possible in wake when, again, you are attending to something, and you are a slave of the here and now of that particular task, and you forget everything else. That's the general idea.

Of course, how exactly does sleep do that? We assume the brain is smart enough in sleep to be able to do this re-normalization in a comprehensive way. Well, it's very difficult to know that exactly in detail, but I think we are getting there. Until now, we have done computer simulations, for instance, to show that one possible way is to assume that all the synapses, all the connections that we have used today, let's say now, listening to me, those are tagged and marked by this learning experience, and when, then, the brain goes to sleep, all your neurons are active. Those tagged synapses are protected because they have a molecular tag. Probably, a protein. Something that was expressed because of the learning. They escape the re-normalization.

Everything else, all the synapses that are not tagged, go down. Because of sleep, they re-normalize, they depress, but the ones that were used stay there; don't potentiate but don't depress either. They stay there, and relatively speaking before, since everybody else went down, they get, relatively speaking, strengthened and protected from the re-normalization. That's what we think what happens.

You can show this in computer simulation. It's much more difficult, of course, to see this, to prove this on an experimental level, but I think the techniques are there that people can really test these and it will happen, I hope, in the next few years.

Bill Glovin: How has advances in imaging helped?

Chiara Cirelli: We took advantage, recently, on advances in electron microscopy. Well, if overall there must be a depression of most synapses, all the ones that were not used today, well, it must be that if you measure molecular markers of the

synapses overall, there should be the total amount of these markers. They should be higher in wake than in sleeping. This is true. This is what we found, and other people have confirmed our findings. That's one possibility.

Imaging should also be true, because there is a very strong correlation between the function and strength of synapses and the size. Stronger synapses are also bigger, and so, you could literally think that, then, a prediction of this hypothesis is that synapses should literally grow in wake and shrink in sleep. Of course, we are talking about very small structures, and these changes that we expect between normal sleep and wake, across 24 hours, are very small. You need electron microscopy to see that. That's what we did recently.

We did it because, finally, there is a method of serial electron microscopy that allows you to collect the stacks of images relatively quickly. It's called serial block-face scanning electron microscopy. It's a new method over the last, maybe, 10 years or less that, now, people are starting to use much more than before because it's much easier now to have these stacks of images. Now, what is not easy, then, once you have acquired, automatically, these images is actually, then, to look at the synapses and segment and measure the size, which you still need to do and we did manually.

It took, actually, a few years to do that, but we did it and we found, indeed, that, overall, the size of most synapses. Not all of them, which is consistent with the idea that I was saying that, well, some synapses, they must escape the depression, but most of them went down and showed this shrinkage with sleep. That's one imaging technique that's been recently very helpful.

Another one certainly is in vivo. That's repeated two-photon imaging. Now, we have animals, transgenic animals, in which some neurons are labeled. They're fluorescent; they're green. Even without opening the skull of the mouse, so in a non-invasive way, we can look at, actually, the synapses. At least, some. The ones that are more superficial; closer to the skull of these mice. We literally can look whether their number, at least, and perhaps also their size, changes between sleep and wake.

This is not electron microscopy, and so the resolution, I think, is not still optimal, but at least you can count the number of synapses. When you will have the ability to do this for many synapses, and we're getting there, we will be able, in vivo, in a live animal, to really see what happens between sleep and wake.

These techniques have only become available in the last, maybe, 10 years or so.

Bill Glovin: Have you been able to establish a relationship between memory and sleep?

Chiara Cirelli: Not directly yet, but we are getting there. Ideally, what we want to do is, for this hypothesis, I mean, is really to see which kind of synapses are engaged, that are strengthened, because of a specific task. And again, doing methods like, as I

mentioned, repeated photon imaging, then follow them in the sleep that follows the learning, and see whether, indeed, it's true that those synapses that are paired by this process of re-normalization and everything else goes down. That would really link the two processes.

Overall, we think there is evidence that sleep brings about re-normalization. There is also a lot of evidence in animals and, especially, in people. Of course, behavioral evidence is that sleep is important for memory consolidation and learning. But the difficult thing is to really understand, why is that? What is the mechanism, which we think is this re-normalization? And can we prove that, again, really at the level of single synapses, which means, can we link single synapses to a specific learning event and then see what happens in the sleep that follows the learning? Again, we're getting there, but the technology is right enough now that we can do these experiments.

Bill Glovin: Well, thank you so much. I think it's been very interesting. I know that I asked you a lot of questions about sleep and behavior, which might not be your specialty, but I think people find it interesting to hear your thoughts about it because it can relate to people's day-to-day lives. How do you sleep, yourself? Are you a good sleeper?

Chiara Cirelli: Yes, I am. I'm fortunately am a good sleeper, but I'm follow what I preach. I really think that sleep is important, so I try to be very protective of my sleep.

Bill Glovin: Okay, great. Well, that's a great place to end. Thank you so much, and-

Chiara Cirelli: Thank you for the opportunity.

Bill Glovin: Okay, folks. That wraps up this month's [Cerebrum Podcast](#). I'm *Cerebrum* Editor Bill Glovin, and once again, you can read all about the mechanisms about what goes on in the brain during sleep in our article, "[The Sleeping Brain](#)," at [dana.org](http://dana.org).

See you next time.