

Alzheimer's and the Importance of Sleep:

An Interview With Jeffrey Iliff, PhD



Jeffrey Iliff, PhD

BY MICHAEL DREGNI

Recent research has found that sleep is one of the key weapons our bodies use to ward off Alzheimer's disease. Sleep plays two roles, explains Jeffrey Iliff, PhD, assistant professor in the department of anesthesiology and perioperative medicine at Oregon Health & Science University.

When you're in deep, slow-wave sleep, your brain produces less amyloid beta protein, a protein that triggers the disease by strangling brain nerve cells.

In addition, research done by Iliff finds that during deep sleep

your brain also cleans out amyloid produced during the day, as well as other inflammatory "brain debris."

As people age, however, their ability to reach deep sleep falters — for unknown reasons, Iliff says. In addition, those with Alzheimer's often find it difficult to sleep, too, creating a vicious cycle.

He is now doing MRI-based imaging to detect the clearing away of waste from the sleeping human brain, funded by a \$1.4-million grant from the Paul G. Allen Family Foundation.

Iliff explains sleep's role in combating Alzheimer's.

Q&A

Experience Life | Can you explain the relationship between sleep and Alzheimer's disease?

Jeffrey Iliff | The way the brain clears away the waste from between its cells hasn't really been very deeply explored. It's something we know a lot about from the rest of the body — it's what the lymphatic system does in the rest of the body. But the brain seems to need to do that in a different way, partly because of the way it's designed and the way it functions and the ways it's different from the rest of the body; it's kind of this super-duper, high-performance

machine. So the biology that we are focusing on answers the question of how does the brain clear away waste from the spaces between its cells.

There's a second question that was thought to be an unrelated question, but it turns out that it may not be so, and this is regarding sleep: Why is sleep refreshing to your mind? Everyone knows from your own experience when you don't sleep well at night, your brain just doesn't function as well the next day. So why does sleep have that refreshing function? It hasn't really been well understood. The biology that we've been working

on for the last couple of years ends up possibly answering those two questions.

There are two basic findings that were published. One was published in 2012, the other in 2013. The first was an answer to that first question: It looks like what the brain does is it takes the fluid that's on the outside of the brain that the brain floats in, which is called cerebral spinal fluid [CSF]. Most people think of it as like a cushion, which is one of the things that it does. But it turns out that it's also something that the brain uses to clean itself. It's actually being recirculated back through

the brain tissue itself. And as it recirculates through the brain tissue, it's sweeping away proteins and waste and things like that that are being produced in the brain through the process of its activity.

The second finding was publishing in *Science* in 2013 and got lots of media attention. It was the observation that that process of the washing of fluid through the brain tissue was happening during sleep — but not during waking. So it appears to be a feature of the sleeping brain. So at least one of the functions of sleep — not the *only* — appears to be that the brain is doing its housekeeping that it needs to do during sleep, instead of when it's awake, and doing all the other things it needs to do.

[It wasn't] explicitly answered in that study, but we found some evidence that it occurs during deep, slow-wave sleep rather than REM sleep, but actually parsing out the piece of sleep that is specifically responsible for that function hasn't yet conclusively been done.

How this connects to Alzheimer's disease is that both of those studies showed that one of the wastes that's cleared along this pathway during sleep is amyloid beta [or beta-amyloid], the protein that aggregates in the spaces between the brain's cells and forms the plaques.

EL | Does this process break down as people age or in people with Alzheimer's?

J|| There are a couple of parallel lines of evidence that we didn't do that came up contemporary with this that helped to sew the story together. A lot of it was done out of Washington University in St. Louis by Drs. David Holtzman and Randy Bateman. There were two

key findings that helped put some of the puzzle's pieces together. These were studies that were carried out on mice and in humans. They showed that amyloid-beta levels — in the brain tissues in mice and in the CSF in humans — go up during the day and go down when you sleep. And if you're sleep deprived, that drop that's supposed to happen at night doesn't.

So people as they get older have slower rates of amyloid-beta clearance, and people with Alzheimer's disease have slower rates of amyloid-beta clearance.

Every day, your amyloid-beta levels are going up and they're going down; part of one of the things that that rhythm is driven by is the sleep-awake cycle. That washing process gives one potential explanation for why that is.

A second series of studies was done in humans by Randy Bateman and they showed that if you compared between Alzheimer's subjects and age-matched controls, or if you look at people across age, in cognitively intact people as they get older, it is the rate of clearance of amyloid beta that is lost. So it's actually not that amyloid beta is made more in the brains of old people with

Alzheimer's disease; it's the clearance that seems to be defective. So people as they get older have slower rates of amyloid-beta clearance, and people with Alzheimer's disease have slower rates of amyloid-beta clearance.

So then the question is why — why does amyloid-beta clearance fail as you age?

The next study that forms the core of the narrative of what we're talking about shows that when we look in the brains of aging animals, we see that this washing process fails, and this is associated with a slowing of the clearance of amyloid beta. So this suggests that this process that is occurring during sleep is less efficient as the brain ages, and that may underlie the overall slowing of amyloid-beta clearance, and *that* may underlie the development of amyloid plaques and whatever roles they play in the development of Alzheimer's disease.

EL | So, can you say that lack of sleep is one cause of Alzheimer's, or even that it accelerates the disease?

J|| There's corollary evidence linking changes in sleep and amyloid deposition, which is related to Alzheimer's disease, but there is not yet an established causal link: We don't yet know that worsening sleep *causes* Alzheimer's disease; we can't say that. People are actively looking at that question: Does worsening sleep promote amyloid deposition or does amyloid deposition promote worsening sleep. We'll know more about that in the coming years. The two seem to be linked in some way, and many of us think it's an important way, but the definitive proof isn't yet there.

EL | Many of the current studies on sleep and Alzheimer's you reference were done on mice, correct? So what's next to move the research forward?

J| Everything we've done is in mice and rats — except the CFS study and the measuring of amyloid-beta clearance, which were in humans. But all the washing biology was done in rodents. We have to now find out whether this biology is actually happening in humans, and to do that we need to be able to see this process; the technical approaches we took to see this in mice are not applicable in humans. So we need to be able to develop imaging processes that allow us to see this in humans while they're awake and asleep without being invasive or harming them in any way.

That's where the Paul G. Allen Family Foundation comes in. They put out a call 18 months ago for high-risk, game-changing ideas in Alzheimer's, big ideas that are maybe too risky for the federal government to try to fund. And so we proposed to them that we wanted to take all of this work we've done in rodents and explore and define this biology in humans for the first time.

We were funded to do that with a large grant from them to develop new MRI-based imaging approaches to see this process in human subjects, potentially for the first time. We will define that biology first in young, healthy people. The goal is then to extend it into aged subjects and subjects who are developing Alzheimer's disease to determine whether this is a process that fails in the aging human brain: Is it a process that precedes the development of Alzheimer's disease?

We need to be able to develop imaging processes that allow us to see this in humans while they're awake and asleep without being invasive or harming them in any way.

EL | Is the breakdown of the amyloid-clearing process gradual or sudden?

J| When we look in rodents, the deterioration process seems to be at least somewhat gradual. If we look at a mouse that's "collecting social security," we see a profound impairment. If we look in a middle-aged mouse, we see an impairment that's in between a really old and young mouse. So it looks to be a graded slowing.

But there's an interesting interplay here. The biological pathway, the pipes of the system, can degrade. But then the amount of time that is spent cleaning can also change — and those are two separate things and both of them have impacts.

So what we've observed in the aging brain is that the pipes — the overall pathways — seem to be impaired. But there's also some evidence that suggests that sleep itself is disrupted in aging people and in people with Alzheimer's disease — that is well known — but that actually the impairment of sleep is associated maybe with more rapid amyloid-plaque deposition. So not only is the system that's clearing away amyloid beta degrading, but actually your opportunities even to use the system may be declining as well.

EL | Are there ways to rebuild that system?

J| On the sleep side, we don't know why aged subjects have worse sleep. There's some evidence that suggests amyloid deposition itself can impair certain parts of sleep, so maybe there's a vicious cycle at work there. It's long been thought that the neurodegenerative processes hurt the parts of the brain that govern sleep, so maybe that's why. But the data suggests that patterns of sleeping change throughout life: It's obvious between an infant and a kid and a teenager, on to a 30-year-old adult.

But from then on, the time that people spend in sleep and the time that people spend in slow-wave sleep, in particular, declines pretty steadily with age — but why that is isn't clear.

So one side of the equation is that we don't really know why time of sleep and sleep quality change with age. If you ask your mother or grandmother, "Why don't you get more sleep?," it's not that their alarm clock is getting them up at 4 or 5 in the morning; it's that the processes that govern sleep in their bodies have changed. Why that is we don't know. And how you would counteract that we don't yet know.

On the other end of it, if you look at the pipes of this process we're describing, it looks as though it is related to cardiovascular function, and it may be related to respiratory function, so you start to think

about things like fitness and diet and heart disease, all of those very standard risk factors — maybe those will have an influence, but we're so early in that research that we just don't know.

EL | What about our microbiome?

J|| It may play a part, too. It's this vast, undiscovered continent of effects, and it seems like it touches everything. It's hard to imagine *how* it would, but given how far reaching its implications seem to be, it's hard to imagine that it wouldn't.

EL | And how might neuroinflammation affect this?

J|| We think that inflammation — peripheral inflammation and brain inflammation — is intimately related to this process of brain cleaning, so to the extent that that's interacting with inflammatory processes, that's a possible touchpoint of interaction. But that's also unexplored.

EL | What's the next step in your new MRI research project?

J|| The study itself has three pieces to it. We are currently finishing up the first piece where we are doing very sophisticated MRI approaches in animals to pioneer the approaches we're going to use in humans — to validate them and optimize them for seeing what we want to see in the best possible way. We're neck-deep in that work right

now. We anticipate starting out our first exploratory studies in humans in probably the next six months.

Once that's all pioneered out, the next piece is to put together a larger cohort study so we can look at the same kind of imaging in a group of initially young people. That's probably six months to a year away before we begin that.

Because this is a biology of the sleeping brain, one of the challenges is how do we get people not just to fall sleep in the scanner but to have long periods of normal sleep. A part of that is making the scans quiet enough that they don't wake up a person, because we have a very powerful magnet and the scans that we do are not your normal scans you would do to check out your knee; the noise they produce can be much different from what you expect from a normal scan. So we need to optimize them so the noise is more in the background.

The goal is to potentially have people sleeping in the magnet for several hours at a time so we can capture multiple sleep cycles. If a sleep cycle is about 90 minutes and if we want to capture two of those in a night, we have to have a person in the magnet for six or seven hours and do overnight scanning. That's not trivial, because the MRI magnets are not the most comfortable place on Earth to spend the night. So we're still figuring out how to make that work.

At the back side, we also have to do EEG

[electroencephalogram] recordings of the subjects while they're in the magnet, so we can confirm that in this period of time, this person was in REM sleep or non-REM sleep. And it turns out that conducting really sensitive electrical recordings in a massive magnet field is not easy. So we have these technical hurdles to get over to perform the EEG in an MRI magnet.

We're not that long from having humans in the magnet doing these studies. If it's hard to see an effect and it's a small effect, yes, you could be talking a couple of years; if it's a massive effect that's obvious with the first subject and everything works out great, it could be much sooner. It's very hard to predict how long it's going to take.

We'll start with young, healthy people. Young people can sleep anywhere and they'll do anything: My students are all very anxious to participate — it sounds like a great time! That's important biology to define what's happening between waking and sleeping.

But the thing that's important to Alzheimer's disease is finding out if that process changes as people get old. So now we need to have 65-year-olds taking part in this study and people with mild cognitive impairment that are at this early stage of pre-Alzheimer's disease. We're going to need to iterate that process in our young people to figure out what's the minimal amount of scanning that's necessary to get the information we need, because when it comes time to do the more elderly subjects, we really want this to be as easy a process as possible to get them through the study without inconveniencing them or hurting them in any way.

We're at an exciting time in Alzheimer's research.

We anticipate starting out our first exploratory studies in humans in probably the next six months.