UsAgainstAlzheimer's

Alzheimer's Talks
with Dr. Jeffrey Iliff
August 16, 2016

Welcome to Alzheimer's Talks. This is a monthly teleconference series presented by UsAgainstAlzheimer's where we connect you to the leaders in the field who are working to stop Alzheimer's, to better understand the disease, and to better understand how to reduce the risk of getting the disease.

My name is George Vradenburg, I'm Chairman and Co-Founder of UsAgainstAlzheimer's which is an innovative and disruptive enterprise, transforming the fight against Alzheimer's. Please join us at www.UsAgainstAlzheimers.org.

We are so honored today to have Dr. Jeffrey Iliff join us to speak about his important research, which I'll describe in just a second. But just as a reminder for those of you who may be new to these calls: If you have a question during the call, please press *3 on your phone. By pressing *3 you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff, or if you are listening to us online, you can type your question in the box, and we will get to as many questions, either on the phone or online, as we can after the opening presentation. Please note that Dr. Iliff—as with all of our speakers—is not able to answer personal medical questions.

Dr. Iliff is an Assistant Professor in the Department of Anesthesiology and Perioperative Medicine at Oregon Health & Science University. He was part of a team that discovered a critical brain-cleansing system. He is going to talk about his groundbreaking research on how sleep helps clear waste from the brain and about new studies that are being conducted to figure out the role that this may play in the development of Alzheimer's disease.

I find this topic of particular interest because for all of us who may have this subjective memory concern, forgetting names and addresses and telephone numbers and words in the normal course of our lives, we always ask ourselves, what is it that we can do today to reduce the risk of getting Alzheimer's disease or getting at least the symptoms of Alzheimer's disease or deferring them, and so sleep is one of those things that is fascinating because all of us do it, and all of us can probably do it better. I know there has been great interest in this topic, beyond myself, so thank you Dr. Iliff for joining us today. We look forward to your remarks.

Dr. Iliff: Thank you, George, and thanks to UsAgainstAlzheimer's for this wonderful opportunity to speak to everyone who is on the line today. To me, it's actually a great honor as a pretty young investigator to get to address this group which, from my opinion, is doing really critical advocacy work to drive the public conversation about Alzheimer's and to mobilize the fight against this terrible disease.

This afternoon, I'm going to be talking about how sleep and neurodegenerative diseases like Alzheimer's might be connected. This is a subject, as George mentioned, that there's a great deal of interest in right now. I think that's partly because of clinical and basic science research that has come out over just the last couple of years, that has begun to link sleep and Alzheimer's in some provocative and, I think, somewhat unexpected ways. And partly, I think, because sleep is simply a subject that everyone can understand and we can grab onto at a very intuitive level.

Everyone here on the line today with me, we all sleep. It's something that I think intuitively we all know is very important to our general health. We know how our bodies feel when we've had a good night's sleep; how our minds are sharp and agile; we know what it's like when we don't get the sleep that we need. I know for me—I have three kids and so I remember when we had crying infants, we didn't sleep very well, or when our kids were sick. A lot of us have jobs that keep us up late at night working, and I know as many people get older, people find that they just don't sleep the way they used to be able to, or as well as they used to be able to.

Yet we all know that when we are short on sleep, our minds become fuzzy, we can't concentrate, we make more mistakes, our memories slip—these are all short-term immediate effects of not getting enough sleep. So the question then is, what is it that's so important about sleep? Why do all these things happen to you when you don't get the sleep that you need?

It's pretty interesting. When I talk to folks, I hear a lot of things. I think a lot of people believe that when you're asleep, your brain is sort of shut down and resting, and that nothing very much is going on. It turns out that that really isn't true at all. When you're asleep your brain is actually incredibly active; it's doing many, many different things, just a different set of things than it's doing when it's awake. So when you're asleep, your brain is shifting between a couple of different modes, different kinds of sleep. One of these that I think most people have heard about is REM sleep, which stands for rapid eye movement sleep. During REM sleep, your brain is actually very active, it's in fact pretty much just as active as it is when you're awake, but you're unconscious and your body can't move, but otherwise if you look at brain activity in REM sleep versus when you're awake, it's almost indistinguishable.

But your brain also spends a big part of the night of sleep in a kind of non-REM sleep called slow-wave sleep. In slow-wave sleep, your brain is constantly oscillating, about once every second or so, between a state of being all on and then all off. So your brain is basically going on and then off, and then on and off, and on and off, about once every second. Now, through the course of the night, you pass into and out of these different sleep phases a few times. First you pass through slow-wave sleep, and then to REM sleep, and then back up to slow-wave sleep, and then back down to REM sleep. And you do this maybe four times through the course of the night. And it's thought, by sleep scientists, that these different phases of sleep accomplish different things for your brain.

One of the critical things that is pretty well established in the neuroscience community, is that during sleep one of the important things that's happening is something called memory consolidation. This is the process by which your brain converts short-term memories into long-term memories. So, the sleep researchers believe that in slow-wave sleep, memories are being transferred from your short-term memory bank into the long-term memory bank, while, in REM sleep, those long-term memories are being sort of packed down nice and tight so that they stay in long-term memory storage.

As you might imagine, one of the things that happens, if you don't get the sleep you need, is that you just, on a very short-term basis, you have trouble remembering things or learning things. But in just the last couple of years, in part through work that I did when I was a postdoctoral fellow at the University of Rochester in upstate New York, and am now continuing here at Oregon Health & Science University, we found another function that sleep seems to have, that's very basic to how the brain operates. And that is during sleep, the brain appears to be shifting into a kind of cleaning mode. So, the brain is surrounded by a layer of fluid called cerebral spinal fluid. It's very clean and clear fluid; it looks just like water and it has very little protein in it, it just has a bunch of salt in it. And in neuroscience, it has long been presumed that that fluid, that sits on the outside of the brain, it floats the brain and it serves

as a kind of sink, and that wastes from inside the brain kind of make their way out to that fluid that's outside the brain. And as that fluid slowly turns over, that's one of the ways that waste gets out of the brain.

But one of the things that we observed, and this was back in 2012, we observed that that fluid that was sitting on the outside of the brain isn't just staying out there, but rather, it's being actively pumped back into and through the brain tissue, washing through the spaces between the brain cells and that as that fluid washed through the brain tissue, it was clearing away waste that accumulated in the brain tissue.

That waste clearance system, which is called the glymphatic system— it's like lymphatic but with a g- at the beginning—the glymphatic system, it appears to be an important part of how the brain clears away wastes that are produced by the brain cells through the regular process of its activity. So that was, to us, an interesting scientific finding, but what ended up being more surprising was that this cleaning activity, when we observed it in animals that were either awake or asleep, appeared to only be active when animals were asleep. So if you took an animal that was awake, and you looked at this washing activity, you would see that almost nothing was happening. But then if you took that animal and you put it to sleep either with anesthesia or you allowed it to go to sleep naturally, you would see that the brain would sort of turn on this brain cleaning system, which suggested that, in addition to functions like memory consolidation, one of the important functions of sleep is to clear away these wastes, to essentially wash fluids through the brain tissue, to sweep out the debris that accumulates through the course of the day.

In studies that we published in the following years, we observed that this cleaning system, this glymphatic system, appears to slow with age. So the young brain has a pretty efficient way of doing this process, but as the brain ages, as it moves on toward middle age and into sort of later old age, that process seems to slow, which is, if you think about it, it's actually a little bit of a double whammy. Sleep disruption is something that's known to be a very common occurrence with age, so it's well known that beginning in middle age and advancing into the later years, people, in general, sleep less. So this is something that healthy people observe, is that the time that people spend asleep declines, and then there's a disproportionate decline in the amount of time that people spend in slow-wave sleep. So, as the brain ages, not only does it seem to be spending less time asleep, but the time that it's asleep, a smaller proportion of it is spent in this critical stage of slow-wave sleep and even when it is asleep, it appears that this cleaning process that it undergoes during slow-wave activity seems to also be declining.

So the question then is, what does this have to do with Alzheimer's disease? Does it have anything to do with these neurodegenerative conditions? And the place to begin that conversation is to recognize that first, sleep disruption is well-known to be associated with Alzheimer's disease. I think people who are caregivers to patients who are suffering from the disease are well familiar with the kinds of sleep disruptions that they undergo particularly as the disease progresses. So, obstructive sleep apnea and insomnia are very, very common among the populations of people with Alzheimer's. It's long been thought that that association was because, as the degenerative processes within the brain progressed, sleep centers within the brain that control sleep and regulate sleep became dysfunctional and that's why people suffering from Alzheimer's disease would have disrupted sleep. But more recently, data coming out of research labs and out of clinical studies suggest that that relationship may actually run the other way, that sleep disruption may not be the result of Alzheimer's disease but rather sleep disruption may contribute to the development of Alzheimer's disease.

So looking at the brain clearance system, which is called the glymphatic system, the first thing that we observed was that amyloid beta, which is the protein that builds up as amyloid

plaques in the brains of people suffering from Alzheimer's disease, it appears to be cleared along this glymphatic pathway, and that if you measure the rate of amyloid beta clearance in the brain of animals when they're awake versus when they're asleep, you can see that the rate of amyloid beta clearance during sleep is much more rapid than from the waking brain.

These findings mesh very well with findings that have come out of some other research labs. In particular, there's a well-known Alzheimer's group at Washington University in St. Louis led by David Holtzman who observed, around 2009, that amyloid beta levels in the brain during the course of waking and sleeping, they go up and they go down. So if we measure amyloid beta levels in the brain throughout the day, you see that the levels go up and with the onset of sleep, they come down again. And so through day and night, they cycle through going up and then going down, going up and then going down, which suggests that something's happening during the night that's causing these amyloid beta levels to go down.

Those studies also demonstrated that if you disrupt sleep, if you keep either animals or people from sleeping, that drop in amyloid beta that's supposed to happen during the night doesn't happen. They also demonstrated that if you take animals and you disrupt sleep for a long period of time, you can actually accelerate the process of amyloid plaque formation suggesting that there's a close association between how the brain handles amyloid beta both in the short term and in the long term, and the integrity of the sleep process.

What appears to be the case is that as sleep disruption progresses with age, either because of having less sleep or because the sleep that you have is less effective, it appears that that may be promoting the development of amyloid plaques.

Now, consistent with that idea are findings coming out of clinical studies that show that even among people who don't yet have Alzheimer's disease, so these are cognitively intact people, people with no apparent memory impairments, if you look for markers of Alzheimer's disease, using amyloid PET and measuring amyloid burden within the brain or looking at levels of amyloid beta or CSF [cerebrospinal fluid] or tao in the CSF, it's observed that among people who have shorter sleep durations or worsening sleep quality, both of those appear to be associated with greater amyloid burden which suggests that there does seem to be an association between either worsening sleep quality or reduced sleep duration and the development of Alzheimer's pathology.

The findings that have come out of our studies on the glymphatic system suggest that perhaps one of the ways in which those two things are related, is that this process, which in the healthy brain is involved in the clearance of amyloid beta, becomes dysfunctional either because there's less sleep that's happening as the brain ages, or because the sleep that the aging brain has is less efficient. That may contribute to the development of, to the deposition of amyloid in the form of plaques as the brain ages.

Data suggest that the association between sleep disruption with amyloid pathology and the development of Alzheimer's disease, runs in one direction, that sleep disruption may promote Alzheimer's pathology. But it turns out that things aren't quite so simple, which I guess maybe isn't very surprising.

Some fairly recent work suggests a basis for that association running the other way as well. Work coming out of some clinical populations, in just the last year or so, have shown that amyloid deposition itself may disrupt sleep architecture, which would suggest the presence of a sort of vicious cycle, in which sleep disruption with age may promote amyloid deposition and neurodegenerative processes, while amyloid deposition and those neurodegenerative processes may in turn further disrupt sleep efficiency and sleep architecture. You put those

two things together and you can see the beginnings of what may be a very vicious cycle, where sleep disruption and amyloid deposition feed back upon each other into this sort of circle of pathology that may be contributing to the development of Alzheimer's pathology.

One of the reasons why I think this is really important, is because we want to understand the underpinnings of Alzheimer's disease so that perhaps we can prevent it, perhaps we can treat it. But one of the reasons why I think it's so important for the public to understand this right now and for this to be emerging within the Alzheimer's field within just the last couple of years is the fact that sleep may be a modifiable risk factor. So when we think about risk factors for Alzheimer's disease, we think about the APOE-4 allele, which is a genetic risk factor that confers vulnerability to Alzheimer's disease. But your genetics are something that you can't do much about; you can become informed about them, you can be tested about whether you carry that genetic variant or not, and you can make life decisions based on that, but at the end of the day you can't change that. In contrast, sleep may be something that you actually do have some control over.

More recent clinical data coming out of especially amyloid PET imaging studies suggests that the process of amyloid deposition appears to be at work in the brain perhaps decades before the onset of obvious memory impairment. So people appear to be depositing amyloid as early as their forties or even earlier. Now whether or not those people will eventually develop mild cognitive impairment or Alzheimer's disease, we don't really know, but I think many people in the Alzheimer's field believe that this is a process that's beginning many, many, many years before the development of what we recognize now as Alzheimer's. So the question then is, if this is a process that's starting so early, where can we find leverage to bend that curve that's already beginning to take shape in midlife? It's already fairly clear in the Alzheimer's field that cardiovascular risk is the place where you can do that. It's become clear through many, many studies, that the same risk factors that confer vulnerability to heart disease also confer vulnerability to Alzheimer's disease. And that your cardiovascular risk profile in middle age, your hypertension and your hyperlipidemia, and your control of those factors, are ways that you can modify your risk of Alzheimer's disease later in life.

It may be similarly true that sleep is another similarly modifiable risk factor. The interesting thing about sleep is that it's not necessarily predetermined. Genetics does play an important role in some elements of sleep but a big part of whether you sleep or not and how much you sleep or not and how good your sleep is, is determined by your habits. It's determined by your environment, it's determined by your job, it's determined by your health, and many of those things are places where you have some degree of control over, so you can modify your environment, you can modify your habits, you can undergo clinical interventions like cognitive behavioral therapy or potentially even through the use of certain medications to change the way in which you engage with sleep, over the long term.

By intervening potentially early in life, in something that's potentially changeable, like sleep, it may be possible to change the trajectory of the development of Alzheimer's pathology and Alzheimer's disease. Now, where are we at in that process now? I think it's pretty early. There's a lot of interest but there's a lot of things we don't know. There's a clear association between sleep disruption and Alzheimer's pathology. We don't yet know whether that's a causal relationship; we don't know if sleep disruption causes Alzheimer's pathology or promotes it. And conversely, we don't necessarily know that Alzheimer's pathology causes sleep disruption. We're still trying to get to the bottom of that.

In the basic science and the neuroscience side, we think we've identified at least one way in which sleep and Alzheimer's may be related and that's through the activity of this glymphatic system during sleep. Currently, there is not any way to evaluate glymphatic function in the human brain. The science at this point is just too new. But in just the past year, the Paul G.

Allen Family Foundation, which is Paul Allen, who's one of the founders of Microsoft, his foundation, funded our group here at Oregon Health & Science University, to develop new approaches to imaging this process in the human brain using MRI. Our hope is that this is going to allow us to measure in people whether this cleaning function is impaired as they age, and whether that function can be modified.

But in the end, it's not yet clear if by modifying the amount of sleep that you get or the quality of sleep that you get, whether you can modify the development of Alzheimer's pathology. But what I think the data does show and what I think is sort of the take home lesson for the folks on the line today, is that there's at least a suggestion that it may be. I think most of us in our day to day lives, we think of sleep and sleep debt as being kind of like a short term loan. It's like a pay day loan almost, where I take out a loan for not sleeping tonight and I'll pay it back just over the next couple of days, right? It's sort of this very small short term economy. But I think the implications of this emerging work suggest that sleep may be much more like a bond, a thirty-year bond or a mortgage or something like that, where there may be long-term consequences for your present sleep habits and that, particularly long periods of a lifestyle or medical conditions that are associated with either short periods of sleep or poor quality of sleep, they may be involved and they may potentially modify the risk for developing chronic diseases like Alzheimer's in the future. That may be a possible place for lifestyle-based interventions, beyond just thinking about developing a new drug. So to me that's an important take-home message and one of the reasons why I think it's such an exciting time to be in the Alzheimer's research field and to be studying specifically the possible interactions between sleep and Alzheimer's disease.

George Vradenburg: Thank you for a very, very clear, very, very interesting presentation, one that's accessible to us laypeople out here.

To your last point: What work is going on to try to understand the causal relationships here? What further work is going on to try to understand the causal relationships?

Dr. Iliff: So, that ends up being a little bit difficult because a lot of the work associating sleep disruption and Alzheimer's disease is coming out of these longitudinal cohort studies, like the ADNI study or we have a longitudinal aging cohort study here at Oregon Health & Science University and typically sleep is being assessed primarily by self reports, so, among many many, many questions that a study participant would be asked are: How much do you sleep? What is the quality of your sleep? Do you have insomnia? Do you have trouble going to sleep? Do you have trouble staying asleep? And those kinds of questions, while they are somewhat useful in evaluating general patterns of sleep, they're pretty subjective, and they can sometimes lead to somewhat weak correlations. And so, a lot of those studies have begun to show associations between these two features, but it's hard to get at causality with that kind of an experiment.

What's going to be necessary is an interventional experiment where we try to intervene in a population of people who are susceptible to Alzheimer's disease, so either a group of patients with the APOE-4 allele who we know are at a higher risk of the disease, or a group of people with MCI, or a group of people who are identified as being amyloid positive on PET scan. Can we identify them, try to intervene with sleep therapy like cognitive behavior therapy which can modify sleep behavior; can you then detect a change in the trajectory of the disease. I think the place where we see that the most clearly at this point is in the sleep apnea field, where there's a very clear treatment for sleep apnea, that's positive airway ventilation, the CPAP machines that many people use, and the initial data coming out of those studies suggest that treatment of obstructive sleep apnea does appear to delay the onset of particularly mild cognitive impairments, and may delay the progression of certain memory symptoms. That's at least, I think, a taste of the kind of studies that will be necessary to show that causality.

George Vradenburg: Do you know, one way or the other, whether sleep questions or sleep measurement is included in the prevention trials in the familial mutation trials or in the homozygote trial that's being done out of Banner?

Dr. Iliff: I don't know if those are included in those particular studies. My understanding is that as this subject, this is sort of, it's not what I would call a fad, in the Alzheimer's field, but it is something that has fairly recently emerged into the awareness and consciousness in the Alzheimer's research field. So I know that many different groups that are running these longitudinal aging studies have begun to put sleep questionnaires into their process, but whether it's permeated through those larger studies, I don't know.

George Vradenburg: This is a strange question, but, what is sleep? If your brain is as active in a conscious state as in an unconscious state, why sleep? Is the brain doing different things even though it is equally active? What is unconscious? I mean, this is a strange question to ask, it's more like a philosophical question than a clinical question, but why do we sleep?

Dr. Iliff: It's actually, I think, a really interesting question from a biological perspective, because if you think about sleep in an evolutionary context, sleep is maybe the worst decision that evolution has ever made, right? We're going take animals in a very competitive violent and brutal environment, and we're going to have them be completely defenseless and senseless and immobile for, in the case of humans, eight hours at a time, which, when you think about things from a competitive advantage perspective, that's an enormous cost, just in terms of the lack of safety that's present there. And if you look throughout the animal kingdom, sleep is present all the way down the phylogenetic tree so it isn't a recent thing, it's not a new thing. In fact, there's a study published in *Science* just this last year, where a group took Australian lizards and hooked them up to EEG machines, and they found that Australian lizards, which are in this very primitive arm of the reptile family, they have a strikingly similar sleep architecture to what we have, which means that that sleep architecture of REM sleep, non-REM sleep, cycling in and out, is very, very ,very old. So for something to come about that is so costly from a perspective of safety, it must be super important.

So, my take on it, and this is sort of, a little bit of editorializing, is that you can optimize the function of your waking brain, in a way, with sleep, with what we think of as maybe a dormant period, much better than if you were just awake the whole time. So what the brain is doing is, it's taking a set of activities, and I mentioned memory consolidation, that's one, waste clearance appears to be another, and there may be many others, and it's taken a bunch of these activities and it's sort of packaged them together and put them into this place. It's kind of like how, in our working lives, I put my lab work and a lot of my work life into Monday through Friday. And on the weekends, that's when I put chores, hiking, sailing, hanging out with my kids, and doing those sorts of things. And there's some optimization it has from sequestering one set of activities and behaviors into sort of the waking, active phase, and a whole different set of behaviors during this other phase. And it's not that I'm inactive on the weekends, I'm just doing other things, so that come Monday morning, I'm ready to roll. I'm ready to go to work because my house is clean, my relationships are good, we've had some fun, we've relaxed, we've unwound, and we've done those things. So I think it's like that.

George Vradenburg: A couple of questions have come in, one from Arthur Hartz and one from Diane Nowicki, about whether naps count as sleep or how do they affect the analysis here?

Dr. Iliff: I certainly hope naps count as sleep because I'm a big fan of them. I think it's to the great detriment of our society that napping at work is regarded as something you're not supposed to do. I'm a neuroscientist by training, not a clinician so I come at things from a basic science perspective—but when I talk to sleep physicians and we talk about naps, the

rule on naps is that you're supposed to nap for either twenty minutes or ninety minutes, because in twenty minutes, you don't go all the way into deep sleep, you just sort of rest a little bit. But ninety minutes is enough time for you to go through a whole sleep cycle. So it's a whole period of non-REM sleep, REM sleep, and then out. So it's actually enough time for you to complete an entire cycle and if you're napping for ninety minutes and you're actually engaging in slow-wave activity and REM sleep, we think it's the slow-wave non-REM sleep that is where this cleaning is happening. If that's true, then presumably a good-sized nap that doesn't stretch out for two, three, four hours, ought to be of some benefit.

George Vradenburg: But if you normally thought that eight hours sleep was useful and healthy, could you take a ninety-minute nap and only have a six-hour at-night sleep time and get the same effect? Or do you need also that longer cycle of evening sleep?

Dr. Iliff: We don't really have the answer to that yet. One of the things that we do know, though, as the brain goes through those cycles, the slow wave to REM cycles, it goes through about four in a night, the composition actually changes. So, the first cycle of the night has a lot of slow-wave activity and only a little bit of REM sleep, whereas the last cycle of the night has very little slow-wave activity and a lot of REM sleep. That's one of the reasons why you are believed to remember more of your dreams from later in the evening. So, if you're, you can imagine that if you are skewing your sleep patterns one way or the other, you might be getting more of that slow-wave activity by doing a nap or you might be getting less of it. So thinking about how those two things are balanced through the course of a night and which piece you're cutting off is something you need to think about, but we don't yet have the answer to that.

George Vradenburg: A question here from Jeton Kellogg from San Antonio, Texas, Could you please ask your question of Dr. Iliff?

Caller: If you're taking sleep medication, or Xanax or something like that, to sleep, is your brain working the same cleaning process, as if you're not taking anything?

Dr. Iliff: This is a question that we get a lot, because actually a lot of people are on medications to aid with sleep. I have two answers to this. One is sort of a scientist's hedge, which is that we don't yet know what is the effect of sleep aid drugs like Xanax on this process. So whatever I say from here on out, is sort of what we think based on what we've done in animal studies, and what we know about the effect of these drugs on sleep architecture. What we know is that the different sleep aids, while they promote sleep, they don't necessarily promote slow-wave sleep. In fact, they tend not to promote slow-wave sleep. And that's true of most of the hypnotic drugs that are on the market for the treatment of insomnia. And so, I think one of the concerns that we have, is that if this cleaning function of sleep is a feature of slow-wave activity, then many of the drugs that are currently in use for the treatment of things like insomnia may not be promoting that. So while you may be getting more sleep, you may not necessarily be getting the right balance of sleep that you need. And so this is something the sleep field is in the process of starting to think through. Do the drugs that we have promote the right balance of sleep, and if not, how do we fix that? How do we develop new medications that promote slow-wave sleep and REM sleep in the proper proportion, because currently, most of the drugs that are available by prescription or over the counter don't.

George Vradenburg: Another question here from James Boland, if you'd ask your question, I'd appreciate it.

Caller: Have you done any testing of the concentrations of melatonin as a function of sleep time? We all know that it tends to promote when you go to sleep and if it cycles properly, you

have a normal sleep cycle. If it doesn't, you don't. Any work being done on measuring melatonin levels?

Dr. Iliff: So, melatonin is a molecule that is produced and driven by your circadian cycle, so your sleep behavior is determined by kind of two different influences. One influence is your circadian clock, which is your brain's natural day-to-day timing of activity and it's influenced, sort of regulated, by sunlight. That's the part of your clock that gets messed up if you fly to the East Coast or fly to the West Coast or fly to Europe or something like that, your body's natural day-to-day rhythm of activity changes. And so that circadian rhythm tends to make you want to wake up in the morning and go to bed at night. And melatonin is one of the key cues to that; its levels rise sharply and help to time the onset of sleep normally.

The other big controller of sleep is what's called the homeostatic sleep drive, and so it sits on top of this cycling clock, and that's the one that basically says, *hey, I've been up for a really long time, I'm really tired*, and those two things sort of fight with each other to determine whether you're awake, whether you're sleepy or whether you're wide awake. The work that's been done on this brain cleaning system has focused primarily on that second piece, not necessarily on the circadian rhythm. So whether either jet lag, or things like shift work, which is sort of this constant work-induced form of jet lag, impairs the function of this system, we don't yet know. We think that it might. We think there are some reasons why we think that it should, and whether melatonin, which is one of the potential ways to begin to re-entrain your natural sleep clock, this circadian clock, whether that can improve this process or not, we don't know yet.

George Vradenburg: We've got one question that has come in online from Laurie Ann Sprague asking, is there such a thing as sleeping too much?

Dr. Iliff: So, different people have different right amounts of sleep. The studies coming out of the sleep field show this. What seems to be the right amount of sleep for adults appears to be between usually seven to nine hours. There are certain genetic mutations that run in families that make certain families appear to require less sleep than normal, and some that appear to make certain families require more sleep than normal. And whether their sleep is fine and whether this cleaning function, for those short sleepers, is just more efficient, or for the long sleepers is just less efficient, we don't really know. But it appears that there's a right amount of sleep for different people and that there's a pretty big range.

There are studies that suggest that long sleep periods are associated with different chronic diseases like cardiovascular disease, depression, including dementia. But the issue there isn't that you're getting too much of a good thing; it's that many things that come along with poor sleep, like depression, also come along with things like dementia. So, depression and dementia are very often what's called comorbid; they often come together. Depression often comes along with problems with sleep. And so people who sleep long periods of time, it may not be the long periods of time of sleep that is the problem, but that just may be a sign of something else that's wrong, that is not a good thing, like depression or other kinds of mood disorders or things like that.

George Vradenburg: There is a question here online from Deena Taylor Rolls. Why do diagnosed Alzheimer's disease patients—and you notice this in nursing homes—sleep so much?

Dr. Iliff: I think one of the things that's noticed is they sleep a lot during the day, and so this is something that's very common among people who have sleep disruption, so if the normal sleep architecture which is supposed to happen during the night isn't providing them with what they need, a lot of times what will happen is sleep will begin to intrude into the daytime

hours. And so daytime sleepiness and daytime sleeping is often accompanied by nighttime sleep fragmentation, so that's where your normal sleep architecture, which is sort of a continuous time of sleep, becomes discontinuous and it's interrupted by waking and moving around and getting up and wandering around which ends up actually being one of the parts of Alzheimer's disease that is often one of the reasons why people have to leave care in the home and move into institutions, because of the activity at night that is very, very difficult to manage, that is associated with sleep during the day.

George Vradenburg: Is there any relationship between sleep deprivation and hypometabolism? That is, lesser energies in the brain? And is there, therefore, some association of some kind between hypometabolism in the brain, a lack of glucose, and sleep deprivation and confounding of Alzheimer's?

Dr. Iliff: That's a really interesting question and that's one where, the people who are thinking about sleep and Alzheimer's disease right now are thinking about that question very directly right now. So, if it's true that sleep disruption is associated with amyloid aggregation, and that sleep is associated with dropping amyloid beta levels, it could be because either the clearance of amyloid beta is supposed to be happening during sleep and it isn't happening; an alternative explanation—and this is the explanation that's proposed by David Holtzman's group at Washington University in St Louis—is that during slow-wave activity, because your brain is actually oscillating between periods of activity and quiet, right?, it's actually, because it's spending a pretty big fraction of its time not active, its metabolic demand is actually lower during that period of time. During that period of lower activity, it's producing less amyloid beta, because amyloid beta is produced by active neurons, and it is actually less metabolically demanding. So it's sort of, the sort of metabolic cost of the brain during slow-wave activity is maybe forty percent lower than it is during other periods of sleep.

So particularly as you age, slow-wave sleep drops away. In fact, elderly people over seventy-five have a shockingly small amount of slow-wave activity compared to what you have when you're young. So you can imagine if slow-wave activity is a time of relative energetic conservation, because you're less energetically active, then spending more time either waking and not in that conservative state, you can imagine that that could be associated with more metabolic stress and more of a metabolic disruption, so that's actually one of the things that's thought might be driving this association between sleep disruption and Alzheimer's pathology and Alzheimer's disease.

George Vradenburg: A number of questions here relating to clinical trials; I'll just ask it generally. Where are clinical trials going on, and what is the nature of the studies that are associated with clinical trials in this area—clinical trials or studies?

Dr. Iliff: Many different groups are investigating the interrelationship between sleep and Alzheimer's disease. Many of the national Alzheimer's centers are beginning to look at this question just as part of their longitudinal aging studies that they have going on. I know that the group at Washington University is pretty active in this; there's a group at UC Berkeley that's doing a lot of work in this space. When we look at the very specific question of whether this cleaning pathway is involved or deficient in the aging human brain, currently there are no clinical trials looking at that question and that's because the clinical tools are not available to evaluate that. The ability to detect early amyloid deposition came about because the technology involved with amyloid detection in the CSF and detecting amyloid with positron emission tomography, which is an imaging approach, enabled those questions to be asked.

There are groups right now, including our own, trying to develop imaging approaches that can detect this cleaning system so that once we can do that, then it will be possible to go into some of these cohorts like the one here, or the one at NYU, or the one in St. Louis, or in all

these different aging cohorts, and begin to evaluate this sleep wake behavior and this waste clearance pathway to find out: Is this deficient in people as they age? Is that associated with Alzheimer's pathology? And are there interventions that can be done to improve that function and to improve that process?

George Vradenburg: So if a person on this line were interested in whether there's a study, they should call their local Alzheimer's Disease Research Center—there are about thirty or so across the country—and ask them. Or their local major university or medical center, and ask them whether they have a set of memory studies or longitudinal aging studies, and whether they're doing sleep studies.

Dr. Iliff: Absolutely.

George Vradenburg: Do you know—this is Dirk Walter asking a question—if one could participate in a sleep study if one was already involved in A4, for example?

Dr. Iliff: I think that something you'd have to talk about with your A4 coordinators and I think one of the questions is, this went to the question that you, George, asked earlier, in the conversation, was whether some of these studies have a sleep component or not. I actually don't know, off the top of my head, whether A4 does or not.

George Vradenburg: We've got a question again here from Laurie Ann Sprague, who seems to be a prolific question asker, thank you, Laurie Ann: I have recently read that acid reflux medication may be a risk factor for Alzheimer's disease by preventing nutrients to the brain.

Dr. Iliff: I've not heard that myself. There's a lot of thinking, that sort of overall health—like when you think about diet and nutrition, cardiovascular health—may influence the development of vascular pathology or the development of these kinds of degenerative or inflammatory processes. Whether acid reflux medication in particular is involved in that, I've not heard that myself, so I don't know what the basis of that might be.

George Vradenburg: We've asked you whether sleep medications, Ambient or Xanax or others, may have a positive or negative effect; don't know. Do you have any recommendations on how to enhance your regular sleep cycles including slow-wave sleep cycles?

Dr. Iliff: So the recommendations are surprisingly common sense. A shocking number of them are things that your grandmother would have told you when you were young. One of the important things is, you have a natural sleep clock, that a part of your brain is always driving, and it trains to the day and night cycle, and one of the ways that you can optimize the connection of that clock to your normal sleep cycle and your body's and your activity is to maintain a constant waking and bed time. So one of the things that we have is what's called social jet lag, where Monday through Friday, you go to bed at a reasonable hour, which is maybe 10 p.m or 11 p.m., and you wake up at a reasonable hour which is maybe 6 or 7 a.m. And you do that for five days. And then on the weekend, particularly young people, you stay up very late and sleep very late and you spend two out of seven days essentially in a jet lag situation, not because you flew to London but because just for two days you totally shifted your sleep cycle and that desynchronizes your circadian clock from your behavioral clock and that causes your sleep to be less effective. So that's one thing that sleep physicians say, is to maintain a constant, or as constant as possible, bedtime and waking time.

Another important thing is optimizing your sleep environment, making sure that there isn't disruptive noise, making sure that you're not sleeping with the television on. You talk to a lot of people who say, "Oh, yeah, I can sleep just fine with the television on," but this goes back

to that question of while you may be sleeping, you may not be sleeping as well as you need, or getting the right kind of sleep. If the television's going on and some weird infomercial comes on at two in the morning, you may not wake all the way up, but what will happen is, you won't be achieving the deep levels of sleep that you need to be achieving, and you may just be kind of skimming the surface of very shallow sleep all night long and not getting to those levels of sleep is what the problem is, so making sure that your bedroom is quiet, or if you don't live in a quiet place, making sure there's enough white noise that you don't wake up.

Light and screen exposure is really important, so making sure that you fast from screens for at least an hour before bedtime, because one of the things that the light that comes off our devices does, is it sends a signal to your retina, to the back of the eye, which sends a signal to the part of your brain that turns on this cycle to say "hey, it's daylight, not bedtime" and so screen exposure, particularly right before bed, can lead to either a delayed onset of sleep, so you don't fall asleep until late, or a disrupted sleep where you wake up or you sleep shallowly. So making sure that you're not exposing yourself to bright light or particularly screens around bedtime is also an important thing.

George Vradenburg: One last question and then I'm going to wrap up. Someone asks here about the power of meditation. Is meditation a useful way to get a better quality or quantity of sleep?

Dr. Iliff: There's actually I think a couple of different, there's two important answers to the meditation question. One is, whether meditation itself can promote this process directly. So, one of the things that's interesting about meditation is that EEG activity, which is the activity of your brain, actually changes with certain types of meditation and depending on how good of a meditator you are. So it may be possible to engage some of these processes even just through the act of meditation and that's something I think that research in the next couple of years is going to get at. I think more importantly, though, for normal people who aren't monks living on hillsides in Tibet, is the effect that the process of unplugging, and the process of being mindful, and the process of being internally focused in that way, what that does to your stress profile, what that does to the arousal state of your brain and whether it can sort of shut down properly or even when you lay down it's still running at a million miles an hour. So I think the processes of unplugging, including meditation, are potentially beneficial in this space.

George Vradenburg: Well, Dr. Iliff, thank you so very much today for your clear answers, for your research into this important space, and really, actually providing a way to potentially develop a new set of interventions around things that will enhance sleep or the performance of the glymphatic system. Because what it suggests is, if you can create some causal relationships here, you're going to create some targets for potential intervention which will enhance the right kind of sleep in the right way.

I'm sorry I couldn't get to all the questions today. Our next call will be on Monday, September 12, from 2:30 to 3:30 Eastern, with Teepa Snow, a well-respected dementia caregiving expert. If you would like to register for this call, please click here.

If you have not already joined UsAgainstAlzheimer's, please do so at www.UsAgainstAlzheimers.org/. You'll get invitations to future calls, important updates, and a wide variety of ways in which you can take action, to actually affect a faster cure. I hope that you all will join us. Thank you to everyone on the phone or online for participating today. In a couple of weeks, we will have a copy of the recording and a transcript on our website for you to share with friends. As always, please stay on the line if you would like to leave us a

message with a question or comment. We are particularly interested in what you would like to have us discuss on future calls.

Thank you, Dr. Iliff, for attending today, thank you for your research, and thank you for your commitment to this field. Thank you all for joining us today and have a good afternoon.