

## Wake-up call: How a lack of sleep can cause Alzheimer's by Matthew Walker *New Scientist* # 3147, 14 October 2017

*Even a single night of poor sleep can cause changes in the brain implicated in Alzheimer's. Are you getting enough shut-eye, asks sleep scientist Matthew Walker*

I DON'T mean to pry, but how much sleep did you get last night? What about over the past week? I ask because the answer could have serious consequences for your future mental health.

More than 44 million people worldwide currently have Alzheimer's disease, including members of my own family. The health, economic and personal impact is staggering. There has been a marked acceleration in the number being diagnosed with the disease as the human lifespan has increased, but importantly, as total sleep time has decreased.



As a sleep scientist, I became interested in this connection some years ago. What I have found is striking. Not only does sleep disruption play a role in the declining mental abilities that typify Alzheimer's disease, but getting enough sleep is one of the most important factors determining whether you will develop the condition in the future.

The implications are huge. We are quickly filling in missing pieces of the Alzheimer's puzzle, and now we also recognise that sleep offers a route for diagnosis, therapy and even prevention.

As we age, our sleep gets worse. This is especially true for the quality of our deep, non-rapid eye movement (NREM) sleep (see chart). Unfortunately, this is the very type of sleep that we now know helps fix new memories into the architecture of the brain, preventing you from forgetting.

But if you assess a patient with Alzheimer's disease, the disruption of deep sleep is exaggerated. More telling, perhaps, is the fact that sleep disturbance precedes the onset of Alzheimer's by several years, suggesting that it is an early warning sign of the condition – or even a contributor. After diagnosis, the magnitude of sleep disruption progresses in lockstep with the severity of the symptoms, further suggesting a link between the two.

However, it was only recently that we realised this relationship is more than just a correlation. While much remains to be understood, we now recognise that sleep disruption and Alzheimer's interact in a cycle that can initiate and accelerate the condition.

Alzheimer's disease is associated with the build-up of a toxic form of protein called beta-amyloid, which aggregates in sticky clumps, or plaques, within the brain. Amyloid plaques are poisonous to brain cells, impairing their function and ultimately killing them. What is strange, however, is that amyloid only attacks some parts of the brain and not others, the reasons for which remain unclear.

What struck me about this very selective pattern is the location in the brain where amyloid plaques accumulate early in the course of Alzheimer's disease, and most severely in the late stages: the middle part of the frontal lobe. If you place your finger on the bridge of your nose, then move it up about 5 centimetres, you are pointing directly at it. This was relevant to my research: this brain region is essential for the electrical generation of deep NREM sleep.

Back in 2007, I wondered whether the reason Alzheimer’s patients have such impaired deep NREM sleep was, in part, because the disease erodes the very region of the brain that normally generates this key stage of slumber. At my sleep research centre at the University of California, Berkeley, we set about testing this idea.

## “Could sleep be used to spot people at risk of Alzheimer’s decades in advance?”

A decade later, having assessed the sleep of hundreds of people between 65 and 90 years of age with varying degrees of amyloid build-up in the brain, we have arrived at the answer: the more amyloid deposits there are in the middle regions of the frontal lobe, the more impaired that person’s deep-sleep quality. Importantly, the link with amyloid plaques was not simply a general loss of deep NREM sleep – the latter being common as we get older. Instead, the disease was robbing these people of the very deepest slow brainwaves of NREM sleep.

This highly selective loss of deep slumber meant that the sleep impairment caused by toxic amyloid build-up in the brain was more than just “normal ageing”. It was unique.

With that in mind, part of my research is now focused on diagnostics. In particular, we want to know if that specific “dent” in sleeping brainwave activity can be used to spot those people at greatest risk of developing Alzheimer’s years or even decades in advance. If sleep does prove to be an early warning sign – especially one that can be spotted relatively cheaply, non-invasively and for large numbers of people, unlike with brain scans – then early intervention becomes possible.

Building on these findings, we began to look at another missing piece in the puzzle of Alzheimer’s disease: how does the build-up of toxic plaques contribute to memory loss?

We know that the amyloid deposits only accumulate in some parts of the brain. Mysteriously, the hippocampi – key memory reservoirs in the brain – are largely unaffected. So how can the toxic amyloid deposits cause memory loss in Alzheimer’s disease when they do not affect these memory areas? This question has so far baffled scientists.

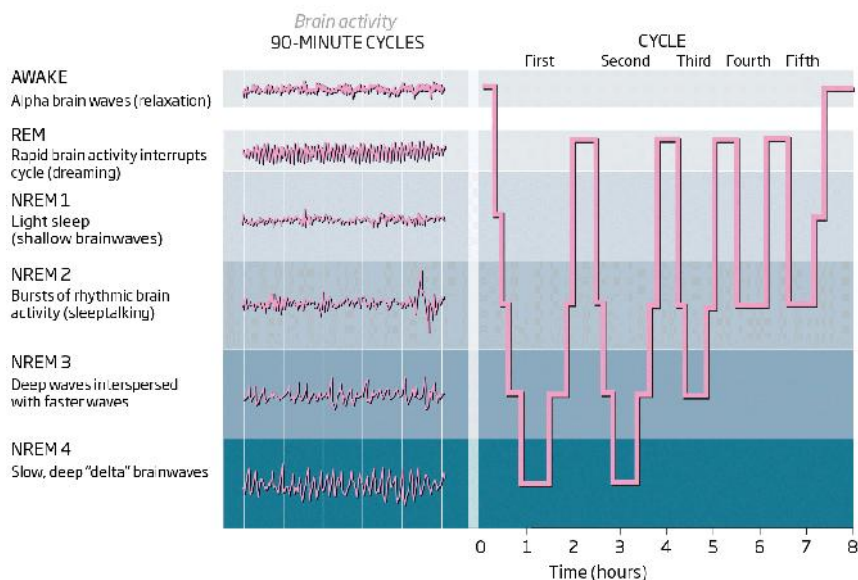
It seemed plausible to me that sleep disruption was a missing link. We already knew that in young healthy adults, the slow brainwaves of deep NREM sleep effectively hit the “save” button on new memories, helping us retain what we have recently learned. Sleep also helps us access and thus remember past experiences.

If amyloid was blocking deep NREM sleep in Alzheimer’s disease, then perhaps this loss of youthful deep sleep prevents older adults from being able to save new memories and hold on to experiences past?

To test this idea, we had elderly Alzheimer’s patients with varying levels of amyloid in their brains learn a list of new facts in the evening. The next morning, after we had recorded their sleep in the

### Sleep cycles

Sleep comes in five distinct stages. A typical night involves several periods in the deeper stages, which are most restorative



lab during the night, we tested the individuals to see how effective their sleep had been at cementing and thus holding on to those new memories.

We found that those with the highest levels of amyloid deposits in the middle frontal regions of the brain had the most severe loss of deep sleep and, as a consequence, failed to successfully “save” those new memories. Overnight forgetting, rather than remembering, had taken place. The disruption of deep NREM sleep is therefore a hidden middleman brokering the bad deal between amyloid and memory impairment associated with Alzheimer’s disease.

However, this was only half of the story – and admittedly the less important half. Our work had shown that the amyloid plaques of Alzheimer’s disease may be associated with the loss of deep sleep, but can a lack of sleep actually cause amyloid to build up in your brain? If this were true, we would all have to accept a sobering fact: failing to get enough sleep, night after night, year after year, would increase the build-up of amyloid in your brain, and directly increase your risk of developing Alzheimer’s disease.

Around the time that we were conducting our studies, Maiken Nedergaard at the University of Rochester, New York, made one of the most spectacular discoveries in the field of sleep research in recent decades. Working with mice, Nedergaard found that a kind of waste network called the glymphatic system exists within the brain, composed of glial cells that position themselves around the neurons that generate electrical impulses. Just as the lymphatic system drains contaminants from your body, the glymphatic system uses cerebrospinal fluid to collect and break down harmful metabolic debris generated by the hard work of your neurons.



### How much sleep is enough?

glial cells were shrinking in size by an astonishing 60 per cent. That created greater space for the cerebrospinal fluid to clean out the metabolic refuse. You can liken it to the buildings of a large metropolis magically shrinking in size at night. The municipal cleaning crews then have easier access to remove the day’s rubbish, followed by a good pressure-jet treatment of every nook and cranny.

What does this have to do with Alzheimer’s disease? Nedergaard showed that one piece of toxic debris washed away by the glymphatic system during sleep is amyloid protein – the very damaging element associated with Alzheimer’s disease. That finding fitted with another remarkable discovery. David Holtzman at the University of Washington in St Louis and his team prevented mice from getting deep NREM sleep, keeping them awake instead. They saw an immediate increase in the amount of amyloid in the rodents’ brains.

Of course, there are some significant differences between mice and humans. Is the same really true if we skimp on our sleep? Alarmingly, in July, Holtzman showed this to be so. His team deprived otherwise healthy adults of their deep NREM sleep, but kept total sleep time the same. To do this, they waited until the subjects entered this phase of sleep and then played sub-awakening sounds that

Although the glymphatic system is somewhat active during the day, Nedergaard and her team discovered that it is during deep NREM sleep that this sanitisation system kicks into high gear. With the pulsing rhythm of deep NREM sleep, the brain expels 10 or 20 times more effluent. Consider it a night-time power cleanse of sorts.

If that were not remarkable enough, Nedergaard made a second discovery that explained why cerebrospinal fluid is so effective in flushing out metabolic debris at night. During deep NREM sleep, the brain’s

would lift the brain out of deep sleep, but not wake them up. The next day, they measured the amount of amyloid within the volunteers' spinal fluid. Without the cleansing benefit of deep NREM sleep, they found a significant escalation of Alzheimer's-related amyloid.

It was damning evidence that a lack of deep sleep will cause a direct and immediate increase of amyloid in the human brain. Simply put, sleep is our neurological salvation – or, perhaps, sanitation.

These findings proved that inadequate sleep and the pathology of Alzheimer's disease causally interact in a vicious cycle. Without enough sleep, amyloid builds up in the brain, especially in deep-sleep-generating regions. The ensuing loss of deep NREM sleep further prevents the removal of amyloid from the brain at night, resulting in greater amyloid accumulation. More amyloid, less deep sleep; less deep sleep, more amyloid, and so on.

## **Universal truth**

This all leads to a concerning prognosis: getting too little sleep across your lifespan will significantly raise your risk of developing Alzheimer's disease. This is true regardless of whether you are already predisposed to getting it. Unfortunately for the under-slept masses, precisely this relationship has now been reported in numerous epidemiological studies. You are at even higher risk if you have an untreated sleep disorder such as insomnia or sleep apnea.

Invert these findings, however, and a radically hopeful prediction emerges. By improving someone's sleep, we should be able to reduce their risk of developing Alzheimer's disease – or at least delay it.

Early support for this idea has emerged from clinical studies with middle-aged and older adults who have sleep disorders, but have not yet transitioned into Alzheimer's disease. When their sleep problems were successfully treated, their rate of cognitive decline slowed, delaying the onset of Alzheimer's by up to 10 years.

So improving sleep quantity and quality helps battle back the approaching onslaught of the disease. For those who are healthy without sleep issues, this means carving out more time to sleep – ideally a solid 8-hour opportunity each night (see “How much is enough?”).

But what about those individuals for whom sleep is difficult, or due to ageing and dementia, physiologically not possible? Medication does not appear to be the answer. Current sleeping pills do not produce naturalistic sleep, and are associated with higher rates of mortality and cancer.

My research group is now trying to develop a number of electrical brain-stimulating methods for amplifying deep NREM sleep in older adults and those with dementia. Like a support choir to a flagging lead vocalist, we are trying to electrically “sing” in time with weakened sleep brainwaves, artificially boosting their size. We hope that by restoring some deep sleep, we can salvage aspects of learning and memory that have failed in older individuals and those with dementia.

That is treatment, but my goal is prevention. If we are successful in our smaller trials, I aim to develop a method that is cost-effective and can be scaled up to population level for repeat use. The ideal would be to begin supplementing the declining deep sleep of vulnerable individuals during mid-life, many decades before the tipping point where Alzheimer's is inevitable. I admit it is a lofty ambition – even a foolhardy one – but when one sees family members dealing with the disease, it becomes an imperative.

To be clear, insufficient sleep is only one of several risk factors associated with Alzheimer's disease. Sleep alone will not be the magic bullet that eradicates dementia. Nevertheless, prioritising sleep – however old you are – is a clear way of lowering your risk of developing Alzheimer's disease. That's a fact well worth waking up to.

### **How much is enough?**

Getting enough sleep could play a crucial role in protecting your brain from Alzheimer's disease. But how much do you need?

Most adults need a recommended 7 to 9 hours a night, according to the US National Sleep Foundation. But as we age, the amount of sleep we need does change. An 18-year-old, for instance, might need anywhere between 6 and 11 hours. Older adults appear to need as much sleep as younger adults, but struggle to get it.

As a general rule, you shouldn't need to set an alarm to wake up in the morning. If you do, you probably aren't getting as much sleep as you need. What's more, time in bed doesn't equal time asleep. Try aiming for 8 hours in bed for a good night's rest.