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ALZHEIMER DISEASE

Sleep alleviates AD-related neuropathological processes

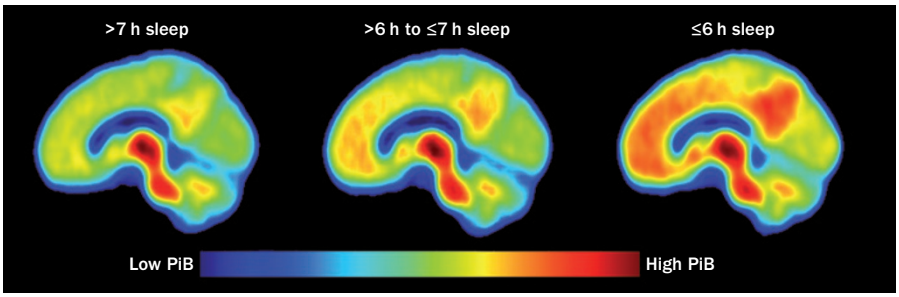
Sleep disturbances have previously been associated with Alzheimer disease (AD) and age-related cognitive decline. Now, three studies have addressed the link between sleep and pathological processes that underlie neurodegeneration and cognitive impairment.

Adam Spira and colleagues found that poor sleep quality in older adults was associated with increased brain levels of amyloid-β (Aβ), a well-known AD biomarker. Andrew Lim and co-workers showed that unfragmented sleep could decrease AD incidence and attenuate AD pathology in individuals with the ε4 allele of apolipoprotein E (*APOE*), which is the best-established genetic risk factor for sporadic AD. Connecting with the findings in humans, Maiken Nedergaard and her team discovered that sleep enhanced clearance of Aβ peptide from the brain interstitial fluid in mice.

Sleep deprivation has been shown to increase Aβ plaque deposition in a mouse model of AD. In humans, Aβ levels in the cerebrospinal fluid (CSF) vary with the sleep–wake cycle. In a study of 70 community-dwelling older adults from the Baltimore Longitudinal Study of Aging (mean age 76 years), Spira *et al.* combined data on Aβ burden, as measured by PET scanning, with the participants' self-reports of sleep duration and quality. The investigators found that individuals who reported shorter sleep duration and poorer sleep quality had higher Aβ burden than participants who reported sleeping well.

The researchers note that their study cannot resolve the causality of the relationship between sleep quality and Aβ accumulation. "We need to conduct prospective studies to examine whether poor sleep comes before or after the increase in amyloid deposition," Spira explains. Furthermore, self-reported sleep quality should be validated against objective measures of sleep.

To investigate whether the increased risk of AD associated with *APOE* ε4 might be influenced by sleep, Lim and colleagues collected *APOE* genotype data, cognitive testing results and actigraphic recordings from 698 community-dwelling older adults (mean age 82 years) for a follow-up period of up to 6 years. In addition, autopsy data that enabled quantification of Aβ and another hallmark of AD—neurofibrillary tangles—were available from 201 members of the cohort.



Shorter sleep duration is associated with higher amyloid-β burden, as measured by PiB-PET. Abbreviation: PiB, Pittsburgh Compound B. Image courtesy of A. P. Spira and the Baltimore Longitudinal Study of Aging.

Lim *et al.* found that unfragmented sleep could reduce the risk of AD and attenuate age-related cognitive decline and development of neurofibrillary tangles in individuals with the *APOE* ε4 genotype. "Even among *APOE* ε4 carriers, there is a subset of individuals with excellent sleep consolidation who may be at a reduced risk of AD, and there is also a subset of individuals with very poor sleep who may be at a particularly high risk of AD," says Lim.

The study in mice by Nedergaard and colleagues represents an important step towards unveiling the neuropathological mechanisms by which sleep disturbances are linked to cognitive impairment.

In both wild-type and AD model mice, levels of Aβ peptide in the brain interstitial fluid correlate with time spent awake and decreases during sleep. Nedergaard's research group had previously described the function of the brain glymphatic system, which clears interstitial proteins through recirculation of CSF, which interchanges with interstitial fluid. The team hypothesized that the energy-consuming transport of fluids and soluble molecules might be affected by the sleep–wake cycle.

Nedergaard's team used fluorescent markers and two-photon imaging in awake, sleeping and anaesthetized mice to follow the transport of brain interstitial fluid and Aβ peptides. To their surprise, they found that the interstitial space in the brain was about 60% larger in sleeping and anaesthetized mice than in awake mice, which increased exchange between CSF and interstitial fluid, thereby enabling more-efficient clearance of neurotoxins from the brain during sleep.

Together, these studies shed light on the mechanisms that link sleep disturbance with AD pathophysiology, and suggest that the importance of sleep might relate to its ability to enhance clearance of metabolic waste products from the brain.

According to Nedergaard, the findings support the idea that neurologists should take sleep disorders seriously and perhaps treat them more aggressively. Both Lim and Spira suggest that future directions should include intervention trials. "If we find evidence that poor sleep precedes or increases the rate of amyloid deposition in humans, we will need prevention trials to investigate whether we can prevent or slow AD by improving sleep or preventing insomnia," Spira concludes.

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Original articles Spira, A. P. *et al.* Self-reported sleep and β-amyloid deposition in community-dwelling older adults. doi:10.1001/jamaneurol.2013.4258 | Lim, A. S. *et al.* Modification of the relationship of the apolipoprotein E ε4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol.* doi:10.1001/jamaneurol.2013.4215 | Xie, L. *et al.* Sleep drives metabolic clearance from the adult brain. *Science* **342**, 373–377 (2013)