Sleep deprivation is a risk factor for Alzheimer's, say scientists who turned to animal models to find out why

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Scientists have long explored the link between disturbances in sleep patterns and neurodegenerative diseases. Powerful evidence has emerged

in recent years linking disrupted sleep to Parkinson's, and a massive body of research has explored the serious sleep disturbances associated with chronic traumatic encephalopathy—CTE—a condition linked with repeated head injuries, such as the trauma sustained in boxing, football and other aggressive sports.

Of equal concern has been sleep impairments associated with Alzheimer's disease, a condition that is increasing globally as the world's population inexorably ages. According to data from the Mayo Clinic, an estimated 25% of people with mild to moderate forms of the disorder have disturbed sleep and 50% are estimated to have sleep problems when the condition is deemed severe.

Now, scientists at Washington University School of Medicine in St. Louis, Missouri, have posed a series of provocative questions about the impact of poor sleep and the development of Alzheimer's disease. Chronic sleep disturbances, these scientists say, are an inescapable Alzheimer's risk factor.

The St. Louis scientists have also demonstrated in a series of experiments that sleep deprivation prevents immune cells known as microglia from properly cleaning up deposits of amyloid protein during the sleep cycle, a finding that helps explain the long-observed connection between sleep loss and neurodegeneration. Amyloid proteins are the building blocks of gooey amyloid plaques, a key hallmark of Alzheimer's disease.

In their research, which is reported in *Science Translational Medicine*, the team turned to multiple mouse models to show how disrupted sleep patterns allow deposits of amyloid to accumulate. Sleep is biologically beneficial to the brain because that's when an elaborate network flushes away excess amyloid as well as cellular and metabolic debris. Without that daily clean-up cycle, the brain can pay an enormous price.

"Sleep loss is associated with cognitive decline in the aging population and is a risk factor for Alzheimer's disease," Dr. Samira Parhizkar of Washington University's Hope Center for Neurological Disorders, Knight Alzheimer's Disease Research Center asserted in Science Translational Medicine.

"Considering the crucial role of immunomodulating genes, such as those encoding the triggering receptor expressed on myeloid cells type 2 in removing pathogenic amyloid-β plaques and regulating neurodegeneration in the brain, our aim was to investigate whether and how sleep loss influences microglial function."

"We chronically sleep-deprived wild-type mice and the 5xFAD mouse model of cerebral amyloidosis," Parhizhar wrote, describing the basics of the study, which led the team to make new discoveries about how a lack of sleep can contribute to cognitive decline in Alzheimer's disease.

The 5xFAD humanized mouse model, the team explained, expressed either the human gene variant known as TREM2 common variant, which stands for triggering receptor expressed on myeloid cells type 2, or the animal models expressed another gene variant. For instance, one mouse model had the R47H AD-associated risk variant without TREM2 expression. Sleep deprivation enhanced TREM2-dependent amyloid-β plaque accumulation compared with mice with normal sleep cycles, the scientists found.

"Sleep deprivation not only enhanced TREM2-dependent amyloid-β plaque deposition compared with 5xFAD mice with normal sleeping patterns, but also induced microglial reactivity that was independent of the presence of parenchymal amyloid-β plaques," Parhizhar and colleagues emphasized in the journal report.

The research adds to the growing catalog of data on the importance of

sleep and underlines its role in neurodegeneration. By leveraging different genetic mouse models, the team was able to assess the effects of sleep loss on the brain.

"Our findings highlight that sleep deprivation directly affects microglial reactivity, for which TREM2 is required, by altering the metabolic ability to cope with the energy demands of prolonged wakefulness, leading to further amyloid-β deposition, and underlines the importance of sleep modulation as a promising future therapeutic approach," Parhizhar and colleagues concluded.

More information: Samira Parhizkar et al, Sleep deprivation exacerbates microglial reactivity and Aβ deposition in a TREM2 -dependent manner in mice, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.ade6285