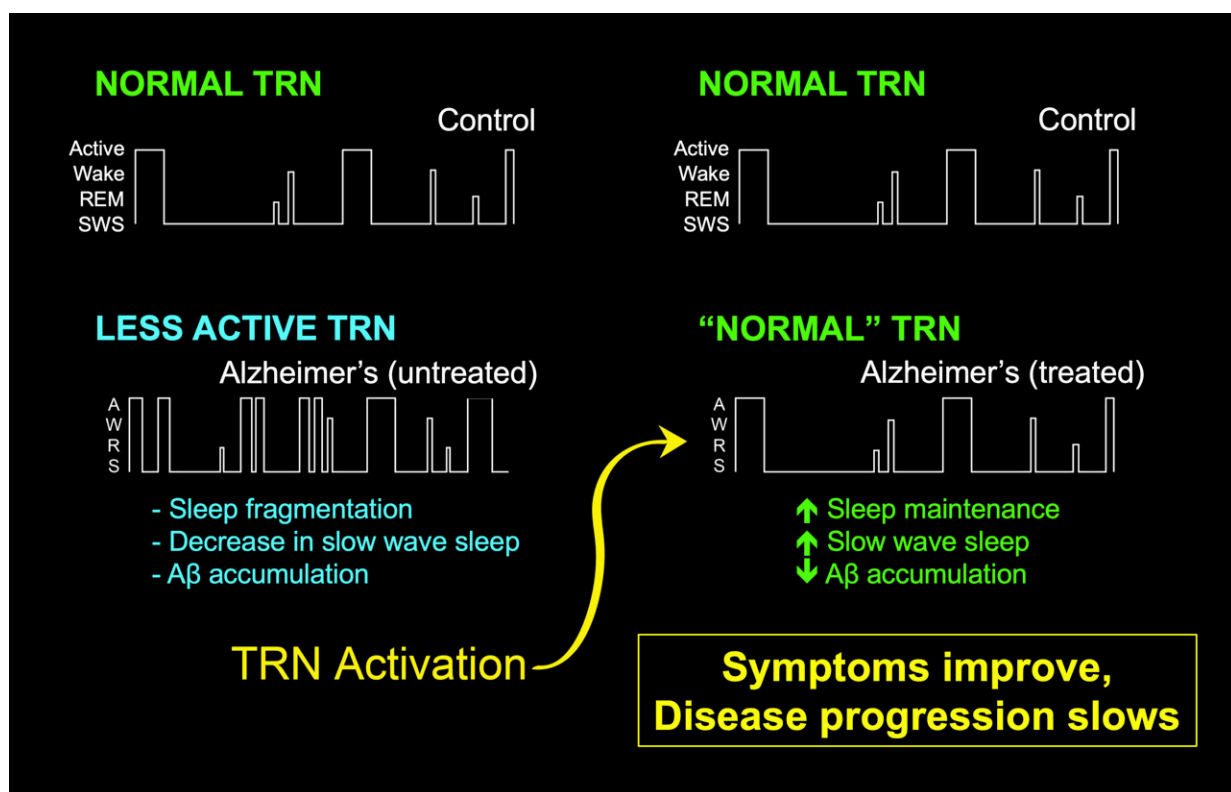# Restoring normal sleep reduces amyloid-beta accumulation in mouse model of Alzheimer's disease

November 3 2021

The white line represents a hypnogram that indicates what state the brain is in during your sleeping time: active wake, quiet wake, rapid eye movement (REM) sleep, or slow wave sleep (SWS). In normal animals (and humans), it is typical to fluctuate between different states over the course of your sleeping time. Activity of the thalamic reticular nucleus (TRN) is critical during sleep, as it helps maintain stable sleep states and promotes the pattern of neuronal activity that underlies SWS. (Bottom left) However, in mice and patients with Alzheimer's

disease (AD), the activity of the TRN is lower than normal. When the TRN is not active, sleep becomes fragmented. In addition, there is less time spent in SWS, the deep restorative sleep during which the brain clears out toxins and metabolites produced throughout the day. Over time, the reduced levels of SWS lead to accumulation of the Aꞵ peptides that form plaques associated with AD, and contribute to disease progression. (Bottom right) Therapeutic activation of the TRN in AD mice restored sleep maintenance and enhanced SWS, effectively normalizing the sleep patterns of the mice. Activating the TRN each day when the mice went to sleep led to sustained improvement in sleep, and reduced the accumulation of plaques in the brain, effectively slowing disease progression. Credit: Jeannie Chin and Rohan Jagirdar

Multiple studies in humans and mouse models indicate that sleep disruptions raise the risk of Alzheimer's disease (AD) by increasing the accumulation of disease-relevant proteins such as amyloid-beta (A-beta) in the brain. In the current study, a team led by researchers at Baylor College of Medicine discovered that, in an animal model of Alzheimer's disease, restoring normal sleep by returning to normal the activity of the thalamic reticular nucleus (TRN), a brain region involved in maintaining stable sleep, reduced the accumulation of A-beta plaques in the brain.

Published in the journal *Science Translational Medicine*, the study suggests that TRN not only may play a previously unsuspected driving role in symptoms associated with Alzheimer's, but also that restoring its normal activity could be a potential therapeutic approach for this severe condition.

The TRN is quiet in AD

"Our interest in studying the TRN in the context of Alzheimer's disease began when we observed in an animal model that TRN activity was generally reduced when compared to the TRN activity of animals

without the condition," said corresponding author Dr. Jeannie Chin, associate professor of neuroscience at Baylor.

When we sleep, the TRN is in general more active than when we are awake, Chin explained. This increased TRN activity reduces the perception of peripheral sensory information. Consequently, when we sleep, we typically are not aware of sounds, lights and other sensations, which helps us get a good night sleep.

"Observing that the TRN in our animal model was less active than in animals without the condition, we investigated the possibility that a quiet TRN could be a reason for the sleep interruptions that are common in people with Alzheimer's disease," said first author Dr. Rohan Jagirdar, an instructor in the Chin lab.
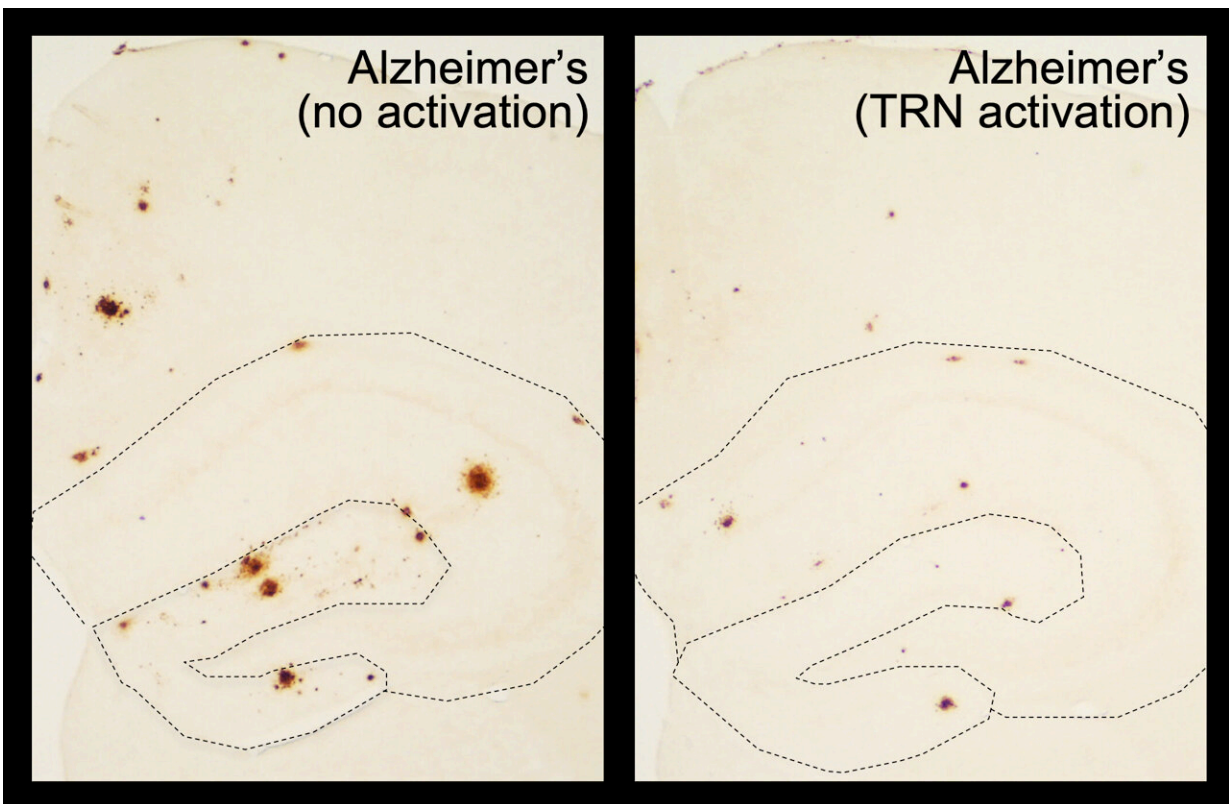
In the brains of mice and humans with Alzheimer's disease (AD), amyloid plaques build up, as seen here in the brains of AD mice. Activating a specific part of the brain called the thalamic reticular nucleus (TRN) in mice with AD decreased sleep fragmentation and increased slow wave sleep, the deep restorative sleep during which the brain clears out toxins and metabolites produced throughout the day. Activating the TRN each day when the mice went to sleep led to sustained improvement in sleep, and reduced the accumulation of plaques in the brain, effectively slowing disease progression. Credit: Rohan Jagirdar

The researchers began by determining whether their Alzheimer's disease mice would wake up more often than mice without the disease during normal sleeping hours. Using a wireless system to record the animals' brain activity, the researchers discovered that, indeed, the Alzheimer's mice woke up 50% more times than non-Alzheimer's mice. Moreover, the Alzheimer's mice got less than the normal amount of slow wave sleep, the deep restorative sleep during which waste products and metabolites are cleared from the brain. This was observed in the early stages of disease progression, before the animals developed memory deficits.

"This finding is relevant to the human condition, as research has shown that sleep fragmentation and other sleep disturbances in cognitively normal people are associated with increased Alzheimer's disease risk," Chin said. "When AD mice got older, reaching about three to five months, their sleep continued to be disrupted and they also presented with memory deficits."

Quiet TRN linked to A-beta plaque load

In the AD animal model, measurable levels of A-beta began to appear in the brain when the mice reached about one month of age and began to

deposit into plaques by approximately six months of age.

"We assessed whether the sleep fragmentation and reduction of slow wave sleep that we observed in our AD mouse model might be associated with the accumulation of A-beta at later stages, by examining mice at six to seven months of age," Jagirdar said. "We found that the magnitude of sleep fragmentation was directly related to plaque load in the brains of six-month-old AD mice."

Taken together, these findings show that AD mice present disruptions in sleep that could influence the accumulation of proteins involved in disease progression.

In addition, Chin, Jagirdar and their colleagues analyzed postmortem tissues from patients who had either Alzheimer's disease, mild cognitive impairment or none of those conditions. They discovered that, as they had found in the mouse model, neurons in the TRN of Alzheimer's patients showed signs of having been less active when compared to the controls. Also, the brains of AD patients with the least active TRN had the highest A-beta plaque deposition. These findings support the possibility of a relationship between reduced TRN activity and increased accumulation of disease-causing proteins in AD.
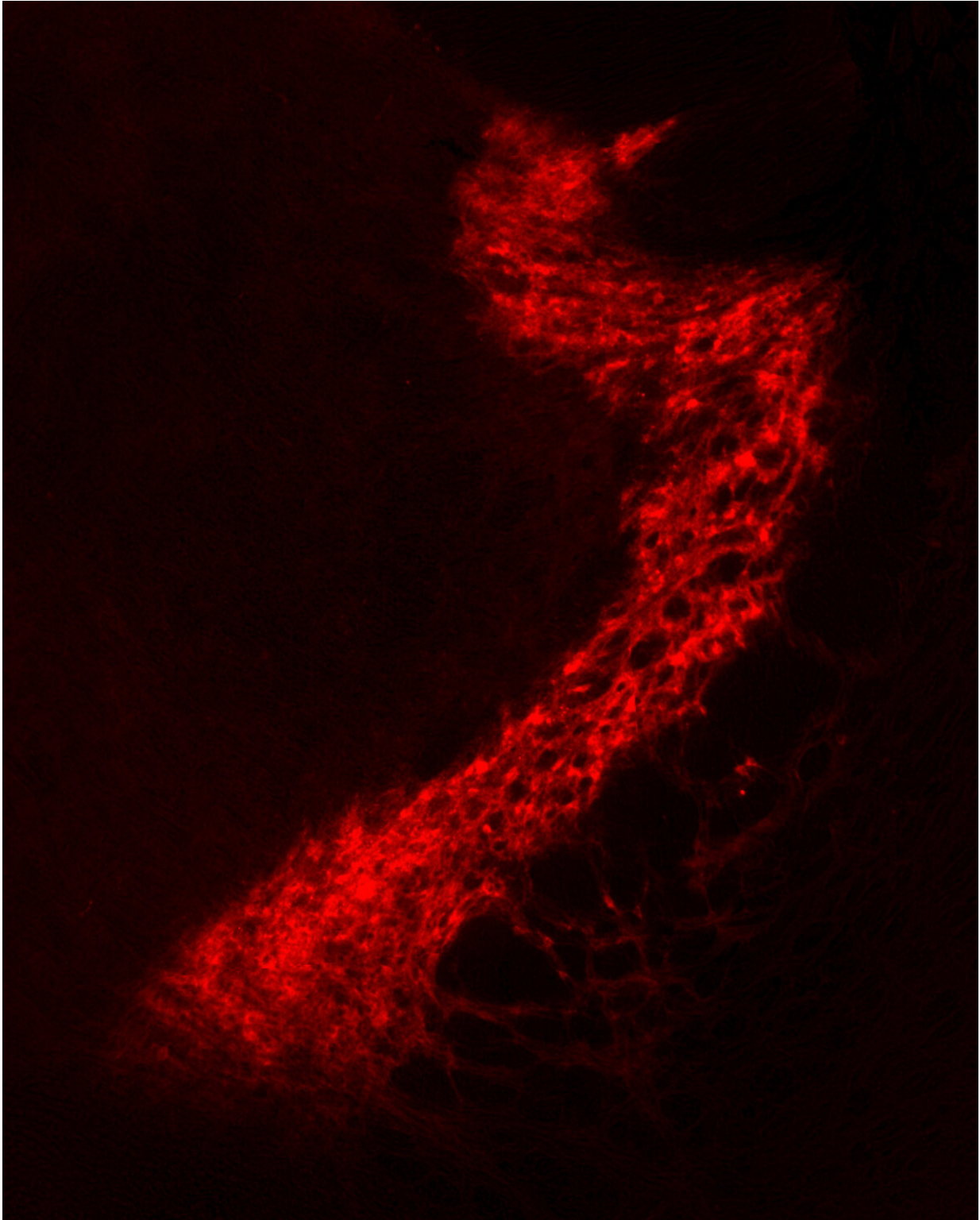
Image shows a specific region of the brain called the thalamic reticular nucleus (TRN, in red), which is less active in mice and patients with Alzheimer's disease

(AD). Activating the TRN in mice with AD decreased sleep fragmentation and increased slow wave sleep, the deep restorative sleep during which the brain clears out toxins and metabolites produced throughout the day. Activating the TRN each day when the mice went to sleep led to sustained improvement in sleep, and reduced the accumulation of plaques in the brain, effectively slowing disease progression. Credit: Rohan Jagirdar

Could reactivating TRN improve the condition?

Using a chemogenetic system, a technology that allows one to chemically activate specific cells, the team activated TRN neurons in the animal model. After a single round of chemogenetic activation of the TRN, the AD-mice woke up less often and spent more time in slow wave sleep, signs of improved sleep activity.

"It was exciting to see that, after receiving chemogenetic activation of the TRN daily for a month, the AD mice showed sustained activation of TRN neurons, consistent improvements in sleep and, remarkably, reduced accumulation of A-beta," Chin said.

The researchers point out that, although this approach seems to improve sleep disruption and A-beta deposition in this mouse model of Alzheimer's disease, not all sleep disturbances involve TRN.

"Sleep disturbances are associated with a number of disorders and arise from diverse causes," Jagirdar explained. "Targeting the TRN may not be as effective if the sleep disturbance is due to unrelated causes, such as obstructive sleep apnea or restless leg syndrome."

"Our findings support that selective activation of the TRN is a promising therapeutic intervention to improve sleep disturbances and slow the

accumulation of A-beta in AD," Chin said.

  More information: Restoring activity in the thalamic reticular nucleus improves sleep architecture and reduces Aβ accumulation in mice, *Science Translational Medicine* (2021). www.science.org/doi/10.1126/scitranslmed.abh4284

Provided by Baylor College of Medicine

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