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Sleep as a window to understand and regulate Alzheimer's disease: emerging roles of thalamic reticular nucleus

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Introduction: Alzheimer's disease (AD) is a common neurodegenerative disorder and the primary cause of dementia. Considerable evidence supports the "amyloid hypothesis," stating that the pathogenesis of AD is primarily caused by the deposition of amyloid-β (Aβ), which drives tau phosphorylation, neuroinflammation, and neurodegeneration in the brain. The amyloid hypothesis is strengthened by the significant and moderate benefit of lecanemab, a humanized antibody through an anti-amyloid mechanism, showing slowed clinical decline (van Dyck et al., 2023). The recent positive results of anti-amyloid trials have brought back focus on the amyloid hypothesis through biochemical, genetic, and pharmacological approaches (Zhang, 2023). As a complex disease, AD neuropathology and risk are heterogeneous and regulated by aging, genetics, and sex, in combination with other risk-modifying factors. Among the risk factors of AD, sleep disturbance is an important factor that may occur early in AD and last throughout the disease.

Sleep is tightly regulated throughout the lifespan and has plausible protective effects against various human disorders, besides AD. Insufficient or disrupted sleep is a challenge to brain health and a major public health issue - more than a third of American adults do not get enough sleep regularly and significant sleep disorders associated with disruption (e.g., apnea, insomnia) impact at least a third of the adult population. The bidirectional relationship between sleep disturbances and AD is well known. For example, sleep deprivation in humans leads to $A\beta_{42}$ abnormality in cerebrospinal fluid; on the other hand, with Aβ overproduction in sleep-regulating brain regions, both mice and humans exhibit shorter and fragmented sleep. Other mediators of the sleep-AD cycle include pathologic tau, microglia activation, impaired blood-brain barrier, impaired glymphatic system, loss of nighttime blood pressure dipping, and sleep hypoxia. Because sleep disturbance represents a significant threat to brain health and AD, the neuroanatomical structures by which sleep disturbance may be associated with AD have become a focus of recent research. One candidate brain region involved in AD pathophysiology is the thalamic reticular nucleus (TRN). The TRN receives inputs from multiple brain regions involved in the arousal-sleep system, including the ventrolateral preoptic area, laterodorsal tegmentum, reciprocal connections from the thalamus, and the cortex. Therefore, it integrates these signals to regulate sleep. TRN specifically inhibits thalamocortical relay neurons, reducing the transmission of sensory inputs to the cortex and promoting slow-wave sleep. Another important function of TRN is to serve as the pacemaker for sleep spindles during non-rapid eye movement sleep. During non-rapid eye movement sleep, the GABAergic neurons in TRN fire in a bursting mode, leading to post-inhibitory rebound spikes in thalamocortical neurons, which provide feedback to the cortex and the TRN, creating sleep spindles.

Because of the important roles of TRN in sleep, recent studies have not only tried to elucidate molecular mechanisms of TRN underlying the pathogenesis of AD but also attempted to uncover TRN-related therapeutic potential for AD. Below we will provide our perspectives regarding the use of sleep as a window to better understand and regulate AD through the TRN (**Figure 1**).

Thalamic reticular nucleus function is impaired in Alzheimer's disease and is linked to sleep disturbance: How TRN function is impaired by AD is unclear and has been recently explored. TRN-related sleep properties were analyzed in the $APP^{Swedish/Indiana}$-containing AD transgenic J20 mice that contain amyloid neuropathology (Jagirdar et al., 2021). The TRN in these mice displayed reduced neuronal activity, but the nucleus itself is not the site of primary Aβ deposition. In human thalamic tissue, there were fewer FosB/ΔFosB-expressing cells in the TRN in AD, while showing a gradient at different AD stages. Based on the literature, the results support two major hypotheses for the mechanism of TRN impairment in AD pathology. First, activity dyshomeostasis and hyperexcitability proposed in the firing homeostasis and plasticity hypothesis are key ingredients in pre-symptomatic AD (Styr and Slutsky, 2018; Slutsky, 2024), which may be accompanied by reduced inhibition from the TRN and epileptic spikes inhibiting sleep spindles. Second, genetic factors, such as the mutations in ABCA7, contribute to both Aβ deposition and abnormalities in GABAergic neurons and microglia ceramide signaling in the TRN (Liu et al., 2021; Hijazi et al., 2023). The role of tau, neurodegeneration, and neuroinflammation in TRN impairment is elusive at the moment.

TRN impairment in AD is linked to sleep disturbance (Weng et al., 2020). In the J20 mice, sleep fragmentation was found to occur early during or before 4–5 months of age, including increased sleep fragmentation and decreased slow-wave sleep time, followed by memory deficits. TRN impairment in AD also leads to reduced sleep spindles, which impairs memory consolidation and worsens AD dementia, completing the vicious cycle. The noradrenergic input from the locus coeruleus to TRN is also impaired in AD, leading to unstable sleep and unfavorable autonomic and cardiovascular outcomes. This is because the locus coeruleus imposes an infraslow oscillation at 0.02 Hz during non-rapid eye movement sleep measured from the sigma band power at 11–16 Hz in the brain wave, synchronized with cyclic alternating patterns in brain wave, pupil size, breathing, and heart rate (Osorio-Forero et al., 2021).

Sleep as a treatment response when targeting thalamic reticular nucleus in Alzheimer's disease: Restoring TRN function may reduce AD pathology. There are only a few methods reported to restore impaired TRN functions, which are far from clinical translation. First, selective activation of TRN using DREADDs (designer receptor exclusively activated by designer drugs) increased time in deep sleep, and importantly reduced amyloid plaque load in both the hippocampus and cortex (Jagirdar et al., 2021), which suggests a loss-of-function mechanism of TRN in AD. The AD pathology reduction achieved by restoring TRN function may be mediated by improved sleep quality. Second, a recent study (Ding et al., 2023) showed that N-arachidonoyl dopamine (NADA), an endocannabinoid, was reduced in TRN in a pain-related chronic sleep disturbance mouse model. Along the same line of targeting TRN in the J20 animal model, local NADA administration restored TRN-related functions, attenuated hyperalgesia, and improved sleep in chronic sleep disturbance mice. Thus, the endocannabinoid system is implicated in AD as a potential treatment target,

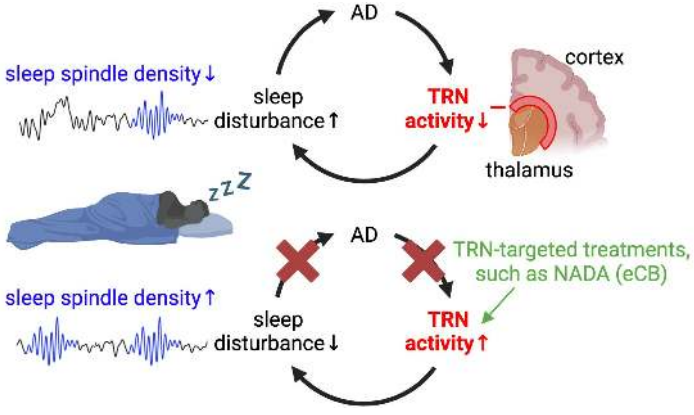

Figure 1 | **Role of TRN in AD, with sleep being a window in understanding and regulating TRN and AD.**
Created with BioRender.com. AD: Alzheimer's disease; eCB: endocannabinoid; NADA: N-arachidonoyl dopamine; TRN: thalamic reticular nucleus.

which may function through potential mechanisms by regulating microglial activation, protecting against neuroinflammation, reducing neuronal damage, promoting cell survival, and potentiating GABAergic neurons. TRN has a high density of CB1 receptor which is sensitive to NADA. Reduced NADA in TRN is one of the possible ways that may connect sleep disturbance and AD pathology.

At the same time, sleep microstructures can be used as treatment response elements when restoring TRN function. Spindle density during N2 sleep is a natural choice as the treatment response due to TRN's role in spindle generation. Sigma band power at 11–16 Hz is an alternative to spindle density, which integrates both spindle density and amplitude and does not require fine-tuning the spindle detection parameters. In addition, spindle-slow oscillation coupling reflects the intactness of thalamocortical circuits involving TRN. The most accurate treatment response may be better achieved by combining multiple sleep microstructure measurements. Taken together, TRN is a possible target in AD, and sleep may function as a treatment response biomarker state in AD and potentially other disorders involving TRN.

Future directions and steps toward clinical translation: Future direction 1: As shown in Jagirdar et al. (2021), the TRN is not the primary site for Aβ plaque or phosphorylated tau, yet TRN activation is reduced in AD which contributes to sleep fragility or fragmentation. More work is needed to clarify how the TRN fits into the bidirectional relationship between sleep and AD, such as the connection between the TRN and other brain regions manifesting primary Aβ plaque or phosphorylated tau deposition. This line of research is within the larger context of inhibitory neuron pathology in AD (Carello-Collar et al., 2023).

Future direction 2: Going beyond Aβ and tau, the roles of neuroinflammation and neurodegeneration on TRN in AD or sleep pathophysiology are unknown. For example, TRN has a high density of CB1 receptors, which is hence modulated by the endocannabinoid system. NADA represents a promising molecule but is only recently validated in a mouse chronic sleep disturbance-mediated pain model. Owing to the functions of the endocannabinoid system in regulating the nervous system and neuroinflammation, it represents a potential therapeutic for AD as well as sleep disturbance-related disorders.

Future direction 3: Several Food and Drug Administration (FDA)-approved medications for AD, including acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor partial antagonists, are only palliative with modest symptomatic relief and do not slow progression. Recent FDA approval of lecanemab has brought new hopes for AD patients, along with promising clinical trials of other antibodies such as donanemab (not yet approved by FDA by April 2024). It warrants future investigations focusing on TRN and sleep changes under these treatments.

Future steps toward clinical translation: It is expected that ergonomic sleep measurement devices will become widely available in the near future, including those at home. As mentioned above, sleep spindles can be used as a treatment response marker when restoring TRN function. However, there are two categories of sleep spindles: fast (> 13 Hz) and slow (< 13 Hz) (Fernandez and Luthi, 2020). They display different spatial and temporal distributions and only fast spindles are correlated with cognition and memory. It is not clear if the fast and slow spindles are merely two manifestations of the same source from the TRN or not. Future studies targeting TRN will need to investigate fast and slow spindles to determine which one is a better treatment response indicator. In addition, other sleep-related metrics are proposed, including K-complex, cyclic alternating pattern, spindle-slow oscillation coupling, infraslow oscillation, and sleep depth. Combining multiple sleep metrics as a sensitive and specific TRN treatment response may require artificial intelligence-based approaches. These metrics should be analyzed to understand their potential association with the TRN in AD and optimize clinical decision-making.

Conclusion: We review and highlight a loss-of-function mechanism of the TRN in the bidirectional interactions between sleep and AD. Recent data has provided proof of concept supporting that the TRN is a potential treatment target for AD and potentially other disorders, such as by enhancing the endocannabinoid system in TRN. Other possibilities of TRN regulation include enhancing spindles through GABAergic mechanisms. Sleep can also be used as the treatment response system when targeting TRN in AD. A clear understanding of molecular and circuitry-level mechanisms of TRN and sleep disturbance in AD will provide a window into the understanding and regulation of AD.

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