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Editorial

## Editorial

# Disturbances in rest-activity rhythms and their neurobiological correlates: implications for Alzheimer's disease and dementia

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The circadian system orchestrates biological and physiological processes to align with the recurring near 24-h environmental changes such as the light-dark cycle [1]. With aging, circadian rhythms gradually dampen [2], leading to daily behavioral changes including alterations in rest-activity rhythms (RARs)—the cycles of rest and wakefulness. In older adults, common RAR disturbances include irregular or fragmented sleep-wake patterns, reduced day-night differences in activity levels, and mistimed sleep [3]. These disruptions tend to be more pronounced in individuals with Alzheimer's disease (AD) and dementia [4]. Additionally, prospective studies have shown that disturbances in RAR can precede the clinical onset of AD and are associated with an increased risk of developing dementia, independent of traditional risk factors such as age, sex, and comorbidities [5, 6]. However, the neurobiological mechanisms, especially neuroanatomical changes in the brain linking circadian dysfunction to the development of AD and dementia, remain poorly understood.

In the current issue of SLEEP, Espinosa et al. investigated the relationship between non-parametric RAR measures and cortical thickness in 143 older adults enrolled in a memory clinic [7]. The study found that greater RAR fragmentation was associated with reduced cortical thickness in the *cuneus*, *middle frontal gyrus*, and *lateral orbitofrontal cortex*. Additionally, lower RAR stability was associated with reduced cortical thickness in regions such as the *superior frontal gyri*, *anterior cingulate cortex*, and *medial orbitofrontal* areas.

These findings suggest that anatomical changes across multiple brain regions may contribute to altered RAR patterns. This is not entirely unexpected. Although the suprachiasmatic nucleus (SCN) in the hypothalamus serves as the "master circadian clock," numerous other brain regions also contribute to circadian regulation [8], forming an interconnected network that governs a wide array of biological and physiological processes. This network also provides a foundation for understanding the potential link between circadian dysfunction and neurodegenerative diseases, i.e. neurodegeneration may disrupt circadian regulation through its effects on brain regions that communicate with the SCN [9].

It is worth noting that certain brain regions that have previously been linked to RAR alterations were not observed in the study. For instance, RAR fragmentation has been shown to account for a significant portion of the variance in *medial temporal lobe* atrophy—a region critical for memory and frequently associated with memory complaints in older age—exceeding the effect of age [10]; more fragmented RAR has been linked to reduced gray matter volume in *posterior parietal* cortex, a region commonly affected by dementia [11], and lower gray matter volumes in *lateral orbital* and *inferior frontal* regions have also been associated with nighttime RAR or sleep fragmentation [12]. One possible explanation is that different measures were used in different studies to assess anatomical changes. Compared to cortical thickness, gray matter volume accounts for both thickness and surface areas, while atrophy is assessed based on the combined information from gray matter, white matter, and cerebrospinal fluid volumes. Additionally, the study presented cortical thickness differences across tertiles of RAR using the "maximum gamma value," a nonstandard measure of effect size, which may limit the clarity and generalizability of the findings.

It is important to interpret RAR measures with caution. For instance, Espinosa et al. interpreted RAR stability as an indicator of synchronization [of the circadian rhythms] with the 24-h light-dark cycle, which is questionable. More importantly, RAR could be driven by behavioral factors and daily schedules that are known to introduce a *masking effect*, complicating the use of RAR measures as proxies to intrinsic circadian regulation. For this reason, the effects of employment and working schedules as well as other timed events should be considered and controlled in circadian studies. An alternative approach to address the masking effects is to use certain RAR analyses that are less affected by

scheduled events [13]. Fractal analysis is one of the examples, and it has been introduced to capture RAR fluctuation patterns across multiple time scales (rather than just the 24-h cycle), which appears to be independent of physical activity level and more resilience to different daily behavioral schedules [14–17]. Research has shown that disrupted fractal activity patterns are associated with reduced gray matter volumes in seven regions commonly affected by AD [18], including lateral orbitofrontal, supra marginal, isthmus cingulate, superior temporal, fusiform, and accumbens areas. Nevertheless, the theoretical basis for the fractal regulatory function of the circadian network has yet to be validated [16, 19].

While the study by Espinosa et al. provided intriguing findings and valuable datasets supporting the circadian-dementia link, several limitations should be noted. The lack of a clinical evaluation of subjective cognitive decline may have introduced heterogeneity into the sample. Additionally, the analyses were exploratory rather than hypothesis-driven, involving all cortical regions and relying on Bonferroni correction to control for multiple comparisons, which may have led to false negative findings. Another limitation is the timing discrepancy between actigraphy and imaging assessments, with intervals extending up to 3 months, which introduces an additional source of variability and potential confounding.

Several unanswered questions remain, warranting further investigation.

Evidence regarding a causal relationship between circadian function and neurodegeneration in humans remains limited. Findings from animal studies have demonstrated that circadian disruption is associated with the formation of amyloid-β (Aβ) plaque [20]. The circadian clock also influences Aβ metabolism through its effects on macrophage and microglia behaviors, which are essential for Aβ clearance [21, 22]. These findings imply a direct connection between circadian function and Aβ dynamics. Prior human studies reported associations between RAR disturbances and AD pathological burden [23, 24]. A randomized clinical trial also investigated the acute effects of suvorexant, a dual orexin receptor antagonist known to improve circadian rhythms, on AD pathology. The study found that that suvorexant decreased tau phosphorylation and Aβ levels in the central nervous system, underscoring potential causal and therapeutic roles of circadian regulation in mitigating AD-related pathologies [25]. Further research is necessary to establish causality between RAR disturbances and AD, which could inform the development of targeted interventions.

Also, the biological mechanisms underlying the relationship between circadian rhythms and AD require further exploration. Several pathways have been implied, including the time-sensitive clearance of Aβ, regulation of tau protein homeostasis, modulation of neuroinflammation, circadian regulation of antioxidants, oxidative stress, and cerebral vascular perfusion [26, 27]. For example, mice lacking the circadian transcription factor BMAL1 exhibit increased reactive oxygen species in various organs [28] including the brain [29] and show heightened vulnerability to neurodegeneration [27]. Additionally, during slow wave sleep, the brain's glymphatic system—a waste clearance mechanism—becomes more active, with a significant increase in interstitial fluid volume that facilitates Aβ clearance [30]. Neuroinflammation is another critical factor in neurodegeneration, driven by the activation of astrocytes and microglia, which exhibit circadian variations [31, 32]. Peripheral macrophages, regulated by the circadian clock display clock-modulated inflammatory response and monocyte trafficking [33, 34]. Evidence also suggests that proinflammatory cytokine production in macrophages is regulated by REV-ERBα, a direct target of the BMAL1 transcription factor [35]. Conversely, inflammatory stimuli, such as lipopolysaccharide, can suppress the expression of BMAL1 and REV-ERBα, adversely affecting neurons and glia, particularly in the hippocampus [36].

Given the multifaceted nature of these biological and physiological processes, future studies should consider employing systems biology approaches, leveraging molecular-level and system-level evidence to comprehensively elucidate the underlying biological and physiological mechanisms in human pathophysiology. Such approaches could provide critical insights into the complex interplay between circadian rhythms and AD pathogenesis, paving the way for innovative therapeutic strategies.

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## Data availability

Data sharing is not applicable to this editorial as no new data were created or analyzed.

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