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GUEST EDITORIAL

# Sleeping well and staying in rhythm to stave off dementia

As society enjoys increased life expectancy, an unintended consequence is the rise in age-associated neurocognitive disorders, of which Alzheimer's disease (AD) and vascular dementia are the most common. More than 40 million people worldwide have dementia, and with an estimated 9.9 million new cases per year, the number of affected persons is expected to grow beyond 131 million by 2050 [1]. These staggering statistics, coupled with the lack of effective treatment for dementia, the devastating effect on quality of life, and strain on global health economies, have made staving off dementia one of the most urgent public health challenges in our modern society. In AD, the pathological changes, such as the accumulation of amyloid and tau proteins in the brain, precede clinical diagnosis by a decade or more [2]. Thus, key to winning this race against time is to identify the earliest possible modifiable risk factors for dementia and to develop strategies to address them. The prioritization of research on the biological mechanisms of dementia and approaches to prevent or delay cognitive impairment is essential for healthy aging. Sleep-wake disturbance is a hallmark symptom of dementia, affecting up to 39% of patients with dementia and up to 70% when including all sleep disorders [3,4]. Sleep Medicine Reviews contains two articles that provide compelling evidence for sleep and circadian rhythms as potential novel modifiable risk factors and therapeutic targets for incident dementia [5,6].

The concept that sleep and circadian rhythm disturbances are biologically plausible mechanisms involved in the expression of neurodegeneration has only recently gained the attention of the AD research community. In part, this may be due to the classical view that sleep and circadian disturbances are consequences of underlying neurodegeneration and represent targets limited to symptom management. However, emerging evidence indicates a need for a paradigm shift of this classical view. Sleep-wake disturbances precede clinical evidence of dementia by several decades and may represent early risk factors for its expression and development [7–9]. Recent epidemiological studies demonstrate that sleep fragmentation increases the risk for cognitive decline and support the view that sleep quality is a predictor of dementia [7,10–13]. The accumulating evidence for a complex bidirectional relationship between sleep and circadian rhythm disturbances and dementia opens up exciting possibilities for sleep- and circadian-based strategies to enhance successful aging.

Just in the last decade, advances in our understanding of the mechanisms linking sleep and circadian rhythms with cognitive aging and neurodegeneration [14–18] have fueled the research in this exciting area. There is strong evidence that sleep plays an important role in the regulation of neuronal synaptic strength and memory consolidation [19]. In particular, slow wave sleep and spindle activity, which decline with age, have been shown to be important for cognitive health [20]. A primary pathological feature of AD is the accumulation of extracellular amyloid-β (Aβ) and intraneuronal tau proteins in the brain. The seminal findings that Aβ levels in the cerebrospinal fluid (CSF) exhibit a diurnal rhythm [21] and that sleep-wake activity alters Aβ production and removal from the brain have provided mechanistic insights on how sleep and wake disturbances may act as risk factors for AD and other dementias [22–25]. Sleep disturbance [24], particularly slow wave sleep deprivation [26], results in both increased neuronal excitability and impairment of clearance of Aβ during sleep and can promote Aβ conversion into insoluble amyloid plaques [27,28]. Sleep fragmentation is also associated with neuronal loss in the intermediate nucleus of the hypothalamus, the human homologue of the rodent ventrolateral preoptic nucleus [29]. Neuronal loss in the intermediate nucleus was found to be more pronounced in people with AD [29], indicating that AD-associated sleep disturbances are the result of specific pathology in sleep-wake regulating centers.

Decreased stability and amplitude of circadian rhythms in sleep-wake activity and other rhythms, such as melatonin and core body temperature, increase with age and are even more pronounced in AD [30–32]. These changes may contribute to weakened synchronization between brain regions important for sleep and memory [33,34]; at the cellular level they increase oxidative stress, inflammation and possibly Aβ levels [24,28,35], leading to accelerated aging and neurodegeneration. Neuronal loss in the suprachiasmatic nucleus (SCN), the central circadian pacemaker, has been reported in humans after age 80 [36] but is notably more prominent in AD [30,37]. In addition, decreased melatonin secretion and/or receptors in the SCN may further contribute to AD-associated sleep-wake disturbances [38]. The paper in Sleep Medicine Reviews by Van Erum et al. demonstrates how AD pathology influences SCN anatomy and function at the molecular, cellular and systems levels [6]. The authors conclude that the pathological changes in the SCN play an important role in the dysregulation of sleep and wake centers, as well as other physiological and behavioral rhythms, which in turn contribute to the progression of AD pathophysiology [6]. Evidence from a mouse model of AD points to a causal relationship between amyloid and both rest-activity changes and neuronal loss in the SCN [39]. However, data from human studies are limited regarding a clear causal relationship. The human SCN appears more resistant to AD pathology; when seen, neuritic plaques are rare and differ from those in the hippocampus and neocortex [37], suggesting that pathology in the SCN may occur late in the disease. Interestingly, amyloid pathology can be seen in the intrinsically light sensitive melanopsin-containing retinal ganglion cells that directly project to the SCN [40]. Functional changes in the signaling cues,

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including light, activity, feeding and melatonin, to the SCN and directly or indirectly to peripheral clocks may represent additional mechanisms of circadian dysfunction in AD. These changes are particularly appealing because enhancement of clock function with timed exposure to light, physical activity, feeding and melatonin can be employed as single or combined approaches to improve sleep and circadian function as targets for disease modification.

Another major source of sleep-wake disturbances is the high prevalence of sleep disorders, such as insomnia and sleep disordered breathing (SDB) in older adults, and even more prominently in those with dementia [3,4,41]. An important question is whether these sleep disorders increase the risk for cognitive impairment and dementia [42–44]. The article by Shi et al. in this issue is the first to systematically review the literature to address whether sleep disturbances and specific subtypes increase the risk for dementia disorders [2]. Intrinsic to meta-analyses, there are limitations, such as the ability to adjust for relevant co-variates, such as depression, physical activity levels, and medications. In addition, the majority of the studies used self-reported assessments of sleep quality. These limitations should not distract us from the strengths of this meta-analysis, which include 18 prospective studies with a sample size of approximately a quarter of a million participants at baseline and a prospective mean follow up of nearly 10 y, making this the most definitive systematic assessment to date. The findings demonstrate that sleep disturbances as a whole predicted incident all-cause dementia, and specifically AD and vascular dementia. An interesting finding was from the subtype analyses, showing that insomnia was only associated with incident AD, while SDB was a risk factor for all-cause dementia, AD and vascular dementia [5]. These differences suggest that the multiple mechanisms link sleep and circadian disturbances to dementia and offer insight into the potential of sleep and circadian strategies as precise therapeutic targets for dementia. Insomnia as a risk factor for incident AD is consistent with previous studies that found associations between short sleep duration and fragmentation with incident mild cognitive impairment and dementia [15,45]. This evidence includes the experimental data that sleep loss increases neuronal activity, leading to increased release and impaired clearance of Aβ, thereby promoting amyloid plaque formation [24], which may in turn further disrupt sleep [9]. In mice, intermittent hypoxia upregulates β-secretase, resulting in increased cleavage of amyloid precursor protein and Aβ formation [46], particularly its more toxic form $A\beta_{42}$ [47]. People with SDB have abnormal CSF markers similar to those seen in AD (lower $A\beta_{42}$ and higher lactate and tau protein); these markers correlate with memory impairment. In addition, people with SDB have decreased CSF $A\beta_{40}$ which may reflect impaired clearance of Aβ from the brain interstitial fluid to the CSF due to the sleep fragmentation [16]. In SDB, besides the sleep loss, factors such as shared genetic vulnerability with AD (ApoE ε4) [48], intermittent hypoxemia and inflammation [19] may also play a role in the association with vascular dementia (for a review, see Ref. [49]).

The preponderance of the scientific evidence from experimental and epidemiological studies point to sleep and circadian disturbances as risk factors for dementia, with the strongest evidence in AD. Discrepancies among previous studies may be due to the lack of standardized definitions of sleep quality, self-reported measures of sleep disturbance, confounding variables in populations studies (that were not intended to assess sleep and circadian rhythms), and small sample sizes in the majority of experimental human studies. Weeding through these limitations, sleep and circadian rhythms stand as potentially modifiable risk factors for dementia and represent an opportunity for improving brain health. To date, clinical trials using sleep and circadian based approaches to study their disease modifying potential are generally lacking. However, environmental and behavioral approaches to strengthen circadian amplitude of the sleep-wake rhythm, using timed bright light exposure, scheduled social and physical activities [50–55] and supplementation with exogenous melatonin [56], have shown promise and may reduce cognitive deterioration in patients with dementia [52]. These interventions warrant research on innovative technologies to measure and deliver them to older adults in their own living environments. Studies on the effects of treatment of insomnia in older adults or in those with dementia and the association with cognitive outcomes are also generally lacking. However, there is evidence that treatment of SDB with continuous positive airway pressure may improve cognitive function in adults with and without dementia [57–61] and merits further study. Advances in our understanding of the molecular, cellular and neural network mechanisms involved in sleep and circadian regulation offer unparalleled opportunities for drug and device development focused on sleep and circadian rhythms as diagnostic and therapeutic targets in AD prevention and treatment studies. It is evident that there is a need for clinical trials of sleep- and circadian-based interventions in dementia, as well as for incorporating sleep and circadian rhythm measurements as health outcomes in dementia prevention and treatment trials.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2018.01.007.

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