Trends in Neurosciences

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Review

Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease?

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Sleep disruption appears to be a core component of Alzheimer's disease (AD) and its pathophysiology. Signature abnormalities of sleep emerge before clinical onset of AD. Moreover, insufficient sleep facilitates accumulation of amyloid-β (Aβ), potentially triggering earlier cognitive decline and conversion to AD. Building on such findings, this review has four goals: evaluating (i) associations and plausible mechanisms linking non-rapid-eye-movement (NREM) sleep disruption, Aβ, and AD; (ii) a role for NREM sleep disruption as a novel factor linking cortical Aβ to impaired hippocampus-dependent memory consolidation; (iii) the potential diagnostic utility of NREM sleep disruption as a new biomarker of AD; and (iv) the possibility of sleep as a new treatment target in aging, affording preventative and therapeutic benefits.

Trends

A bidirectional, causal interaction exists between NREM sleep and Aβ pathophysiology that may contribute to Alzheimer's disease (AD) risk and progression.

The disruption of NREM sleep may represent a novel pathway through which cortical Aβ impairs hippocampus-dependent memory consolidation.

The disruption of NREM sleep physiology offers potential diagnostic utility in the form of a non-invasive biomarker of Aβ pathology, AD risk, and/or AD pathophysiological progression.

Evidence implicates sleep disturbance as a consequence and cause of AD progression; one that is modifiable, offering preventative and therapeutic treatment potential.

Alzheimer's Disease and the Emerging Interaction with Sleep

AD is one of the largest public health and economic challenges of the 21st century. One in 10 adults over the age of 65 suffer from AD, representing a worldwide epidemic. As a result, there is a pressing need to develop sensitive biomarkers facilitating early detection, and effective treatment interventions [1]. Only by achieving both can the goals of prevention and therapeutic intervention be accomplished [1]. One emerging candidate that may fulfill all of these objectives is sleep. In this review we evaluate evidence linking sleep disturbance with AD and its pathophysiology, especially Aβ pathology. We further outline the cognitive consequences of sleep disruption as a novel mechanistic conduit contributing to cognitive decline associated with AD pathophysiology. Finally, we explore the potential of sleep to serve as both a biomarker of AD and as a new therapeutic and preventative strategy for lowering AD risk.

Sleep, Aβ, and Alzheimer's Disease

Sleep in Aging

A physiological hallmark of advancing age is the decline of sleep, wherein NREM slow wave sleep (SWS) declines are particularly significant [2]. These impairments begin in midlife, and in many older adults age 75 years or older, less than 10% of SWS time remains [2]. Similar reductions in the quality of SWS are observed, measurable in the electroencephalographic (EEG) signature of slow wave activity (SWA; ~0.5–4.5 Hz) [3,4]. These age-related decreases in NREM SWS quantity and quality are paralleled by increasing amounts of time spent awake

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at night, with sleep becoming more fragmented [2]. The prevalence of primary sleep disorders, including insomnia and sleep apnea, also increases with advancing age [5], further impairing the restorative quality of sleep.

Importantly, however, sleep disruption is not uniformly observed across older adults of equivalent age [5]. There are marked differences in the ability to generate sleep, including NREM SWS [2,5]. Similar variability is observed in the prevalence of sleep disorders [5–7]. This has led to the suggestion that underlying pathological factors, such as those associated with abnormal aging and AD, may partially determine the type and severity of sleep deterioration in later life and, with it, the cognitive faculties supported by sleep [4,8].

Sleep in Abnormal Aging

Impairments of sleep structure are markedly exaggerated in those with mild cognitive impairment (MCI), and in those suffering from AD [9–11], relative to cognitively normal older adults. Analogous sleep impairments are present in older adults at highest biological risk for developing AD, such as carriers of the *APOE4* allele; the most prominent genetic risk factor for late-onset AD [9]. In addition, the decline in physiological NREM sleep quality, specifically slow wave oscillatory activity, is accelerated in AD patients relative to age-matched controls [10].

Indicating clinical and etiological relevance, the magnitude of sleep disruption progresses in unison with the severity of AD symptomatology and pathology [6,10,12]. For example, tau and Aβ protein levels measured in cerebrospinal fluid (CSF) predict the degree of reduced SWS time in AD patients, together with decreases in sleep efficiency and REM sleep [12]. Sleep disturbance also appears to be among the earliest observable symptoms of AD, being present before and soon after MCI and AD diagnosis [9,10,13–16]. Beyond sleep disruption, clinical sleep disorders are strongly co-morbid with MCI and AD. Over 60% of patients with MCI and AD have at least one clinical sleep disorder [6,7], with sleep apnea and insomnia being most common. Furthermore, *APOE4* genotype is known to significantly increase the risk of developing sleep apnea [17].

The physiological decline of sleep, particularly NREM sleep quantity and quality, is therefore a common feature of advancing age, but the onset, severity, and nature of these impairments are all significantly accelerated in those with AD and in those at highest risk for AD. Although these sleep disturbances have long been considered robust symptoms of AD, new evidence indicates that this relationship between AD and sleep disruption may be causal and bi-directional, representing an integral part of the disease and potentially its treatment.

Bidirectional Links Between Sleep and Aβ Pathology

Insomnia and sleep apnea are not only more prominent in AD, but conversely increase the risk of developing MCI and AD [15,16], suggesting a reciprocal relationship between sleep disturbance and AD pathophysiology. Furthermore, individuals with sleep apnea convert to MCI and AD at a younger age [18]. By contrast, successfully treating sleep disturbance can delay the age of onset into MCI [18] and improve cognitive function in AD [19,20]. While additional evidence is required, these findings point to a potential causal and bidirectional link between sleep disorders and AD. As this reciprocal model would further predict, older adults with superior sleep quality have a significantly lower risk of developing MCI and AD, and also maintain cognitive function for longer [13,14]. Together, these findings indicate that healthier quality of sleep in later life may confer resilience to AD.

The bidirectional link between sleep disturbance and Aβ pathology is observed before clinical onset of AD, and can occur independently of insomnia or apnea [12,14,21–23]. This indicates that the association between sleep and Aβ pathology is not merely a consequence of a primary sleep disorder or of end-stage neurodegeneration. Instead, emerging evidence links specific sleep