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Editorial

Mounting Evidence on the Relationship between Sleep and Alzheimer's Disease

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The relationship between sleep and Alzheimer's disease (AD) has become increasingly apparent in recent years with the results of new scientific investigations and with AD being viewed as a multidimensional disease. One of the aims of researchers and clinicians is to identify AD biomarkers in the preclinical phase of the disease. The histopathological signs of AD during this phase (e.g., deposition of insoluble plaques of extracellular beta amyloid (Aβ) in the brain, aggregation of tau protein into intracellular neurofibrillary tangles [1] precede the appearance of cognitive symptoms by many years. The multidimensionality of AD means that modifiable factors contribute to the development and progression of this disease. Sleep has long been part of this scenario, given the high incidence of sleep disorders in the AD population [2]. The views of the research community towards AD and the experimental procedures employed have changed profoundly over the past 15 years. With regard to prevention and the preclinical phase of the disease, healthy elderly populations and populations with mild cognitive impairment (MCI) have become crucial targets of AD research. Moreover, longitudinal studies follow the evolution of normal and pathological ageing over time.

The main neuropathological events that characterize AD are evident during the preclinical stage. Changes in sleep patterns are closely related to the accumulation of Aβ and tau protein [3] and are considered to be predictive risk factors for neurodegeneration [2].

The relationship between sleep and AD is bidirectional, with the two conditions influencing each other [4]. The most promising research topics in this field are: (i) the study of mechanisms that could explain how sleep promotes or reduces the risk of AD; (ii) the effects of sleep deprivation on features related to AD; (iii) the role of Obstructive Sleep Apnoea Syndrome (OSAS); (iv) the role of slow wave sleep (SWS) in relation to AD; (v) the relationship between sleep electroencephalographic (EEG) components and the neuropathological and cognitive characteristics of AD; and (vi) the implementation of sleep-based treatments in elderly, MCI and AD patients.

With regard to the mechanisms by which sleep could promote AD, many studies have shown that Aβ levels and tau concentrations increase over time in sleep-related disorders that affect healthy elderly populations (Lucey *et al.*, 2023 [5]). Of particular relevance, it has been suggested that OSAS and AD could share some mechanisms and influence each other [6]. OSAS and AD clearly share risk factors such as age, gender, cardiovascular comorbidities, and genetic background [7]. In short, the typical respiratory effort of apnoea episodes could worsen the drainage of cerebrospinal fluid (CSF), leading to harmful impacts on cognition [8].

Variations in the sleep-wake cycle, together with increased Aβ and tau levels, are particularly important as these are linked to changes in hypothalamic function and specifically to orexinergic neuropeptides. It has been suggested that blocking orexin could modulate the amyloid burden in the brain, although the effect on tauopathy is still inconclusive [5].

Many of the novel concepts regarding the relationship between sleep and AD are derived from longitudinal studies employing different sleep deprivation protocols, in association with different subtypes of cognitive impairment. Sleep deprivation generally increases tau levels in the interstitial fluid (ISF) of mouse brain and in the CSF of humans, while chronic deprivation accelerates the spread of aggregated tau in specific brain networks [2]. The importance of sleep deprivation is highlighted by the recent discovery that sleep plays a role in clearing the brain of toxic metabolic by-products, including Aβ [9]. Therefore, if sleep ensures the clearance of toxic metabolic by-products, the lack of sleep, or disturbed sleep, are hypothesised to reduce clearance activity and thus promote the accumulation of Aβ.

The role of sleep in clearing Aβ is particularly evident in stages that are characterised by SWS. One quantification of slow waves involves the measurement of spectral EEG power in the 0.5 to 4.5 Hz range during SWS, also known as Slow Wave Activity (SWA). The largest decrease was noted during non-rapid eye movement (NREM) in the first part of the night within the prefrontal cortex (PFC) [10]. SWS is related to grey matter within specific PFC regions, and atrophy in these areas appears to predict the extent of change in the NREM slow-wave characteristics in elderly populations [10]. A series of studies by Westerberg and col-

leagues [10,11] combined several measurements to reveal a loss of brain volume in the grey matter of the medial PFC (mPFC), which is a crucial area for NREM sleep regulation. This measure was able to predict the loss of SWA in healthy elderly people. Loss of spindles and SWA are predictive risk factors for age-related declines in memory retention and cognition [10].

What happens to the specific EEG components of NREM? Both K-complexes and spindles undergo changes in healthy elderly, MCI and AD populations. Furthermore, these alterations are associated with changes in cognition and with structural integrity of the brain. K-complexes react to external stimuli during sleep, and protect sleep during the essential synchronisation part of NREM. These decrease significantly in AD/MCI patients and also correlate positively with global cognitive status scores [12]. At a frequency range of 13–15 Hz, fast spindles (EEG features of NREM related to cognition and sleep-dependent memory consolidation) decrease in association with learning and memory abilities [10]. They are also negatively associated with the structural integrity of the brain (reduction in hippocampal subcortical grey matter) that predicts the extent of the reduction in frontal lobe spindle density in the elderly [13].

The different emerging dimensions on the commonalities between sleep and AD make it difficult to suggest specific sleep-based interventions. Sleep assessment should be routinely included in at-risk populations, in the preclinical phases of the disease, and in the diagnostic phase in MCI and AD. In order to develop therapeutic strategies, it is important to distinguish between different sleep-related problems and to implement targeted interventions according to patient characteristics. In general, the sleep-based treatments considered to be effective for healthy elderly and MCI/AD patients are sleep hygiene guidelines, combined interventions, and bright light therapy (BLT). Another promising therapeutic approach may also be direct modulation of NREM sleep electrophysiology, with different targets for specific AD phases. Several non-invasive techniques (Transcranial Current Stimulation, tCS; and repetitive Transcranial Magnetic Stimulation, rTMS) are able to modulate EEG oscillations during sleep and could have beneficial effects on memory [14].

The current research findings on the importance of sleep in relation to normal and pathological ageing still need to be translated into improved clinical practice. Longitudinal studies on adults and elderly populations are expected to continue, with increasingly structured integration of electrophysiological, anatomical, neuropsychological and clinical data. Future research should deepen the mechanisms linking sleep and AD and test the efficacy of sleep-based interventions on large populations of healthy subjects and MCI/AD patients.

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LG and SC wrote the manuscript and conducted a literature review. Both authors read and approved the final manuscript.

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Conflict of Interest

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