PERSPECTIVE

Insights from human sleep research on neural mechanisms of Alzheimer's disease

Alzheimer's disease (AD) is considered as the major cause of dementia and affects about 50 million people in world population, with an expected increase of 27% in the coming decades, as reported by the most recent AD statistics.

The fast-growing empirical evidence is highlighting the close relationship between sleep and AD since the preclinical stage of the disease, pointing to an important role of sleep in the occurrence and progression of AD. A summary of the current research strategies and approaches to this topic is illustrated in the **Figure 1**.

Typically, sleep changes with aging, in terms of more fragmented sleep, decrease in total sleep time spent in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, shorter sleep duration, minor efficiency and more difficulty to fall asleep (Yaffe et al., 2014). In case of AD and mild cognitive impairment (MCI) patients, sleep changes are similar, but they seem to be more robust and severe. Together with the poorer sleep, recent data sustain the occurrence of sleep disturbances in AD/MCI patients: insomnia, sleep-wake cycle alterations, sundowning and REM sleep behaviour disorder are frequent and persistent in AD pathology (Peter-Derex et al., 2015).

Most evidence on the relationship between sleep and AD derives from sleep deprivation (SD) studies. The theoretical assumption starts from the stringent association between sleep loss and consequent impairment in cognitive domains. Recent contributions underline the growing advancements in this research line, both in human and animal models, increasing the complexity of experimental protocols. These investigations evaluated SD effects on the main AD pathological features [beta amyloid (Aβ) accumulation in the brain and tau protein hyperphosphorylation and consequent neurofibrillary tangle formation] and systematically introduced longitudinal protocols to characterize the pathophysiology and progression of AD (Cordone et al., 2019). Reviewing the literature of the last decades, it is evident that the relationship between sleep and Aβ has been deeper investigated compared to tau accumulation, mainly due to the evidence deriving from the "amyloid cascade hyphothesis" that considers Aβ burden as the principal triggering event of AD.

Although more experimental confirmations are needed, available findings provide important contribution for research in the field of human SD in relation to AD. It is interesting to note that different SD protocols have dissimilar effects on the main pathological hallmarks of AD. In particular, different results have been obtained as a function of the SD extent. Indeed, one night of total SD in a healthy population affected the physiological morning decrease of the $A\beta_{42}$ levels, in contrast with the stable levels detected in $A\beta_{40}$ and tau protein (Ooms et al., 2014). On the other hand, Holth et al. (2019) demonstrated that the cerebrospinal fluid levels of tau in a healthy population were 50% higher after 36 hours of SD when compared with control night of sleep.

The importance of sleep in relation with AD led investigators to also explore the role of the different electrophysiological features of NREM and REM sleep components in different perspectives. In particular, studies in healthy elderly populations combined different methodological measurements, in order to provide specific and complex interactions between the different aspects that characterize the relationship between sleep and AD since its preclinical stage. At this purpose, Mander et al. (2013, 2015) analyzed changes in sleep oscillations of NREM sleep, such as slow oscillations (< 1 Hz frequency) and sleep spindles, together with other neuropsychological and anatomical measures. In their first study, Mander et al. (2013) showed that the atrophy found in the prefrontal gray matter predicted the disruption of NREM slow wave activity (SWA) disruption. Furthermore, the interaction between those measures also predicted cognitive performance in episodic memory retention. The results obtained from functional MRI measures during memory task underlined that memory failure was associated to continuous hippocampal activation and reduction in connectivity between hippocampus and prefrontal cortex (Mander et al., 2013).

A successive study of the same group (Mander et al., 2015) evaluated whether the degree of Aβ (measured through carbon 11–labeled Pittsburgh compound B PET scanning) at the medial prefrontal cortex level was associated with a decrement of NREM SWA (spectral electroencephalogram power during SWS in the frequency range from 0.5 to 4.5 Hz). The results of this study represent the first indication of a correlation between cortical Aβ and impaired generation of NREM SWS. In turn, these measures predicted successive decline in hippocampal-neocortical memory transformation and related overnight memory retention.

At electrophysiological level, it emerges a crucial distinction within the delta frequency range (1–4 Hz): the association that concerns Aβ and NREM SWA refers only to the low-frequency range of SWA (0.6–1 Hz), suggesting that only slowest EEG oscillations could be related to Aβ pathology.

Considering also the NREM transient oscillatory activity in the 12–15 Hz range (sleep spindles), Mander et al. (2014) combined electroencephalogram and functional MRI recordings and found that the extent of reduced prefrontal sleep spindles predicted the degree of impaired episodic learning in healthy elderly peolple. More in detail, the capacity of sleep in restoring next day encoding learning abilities was associated to the activity of fast-frequency sleep spindles over the left prefrontal cortex. The results of this study underlined that the decrement in prefrontal sleep spindle sta-

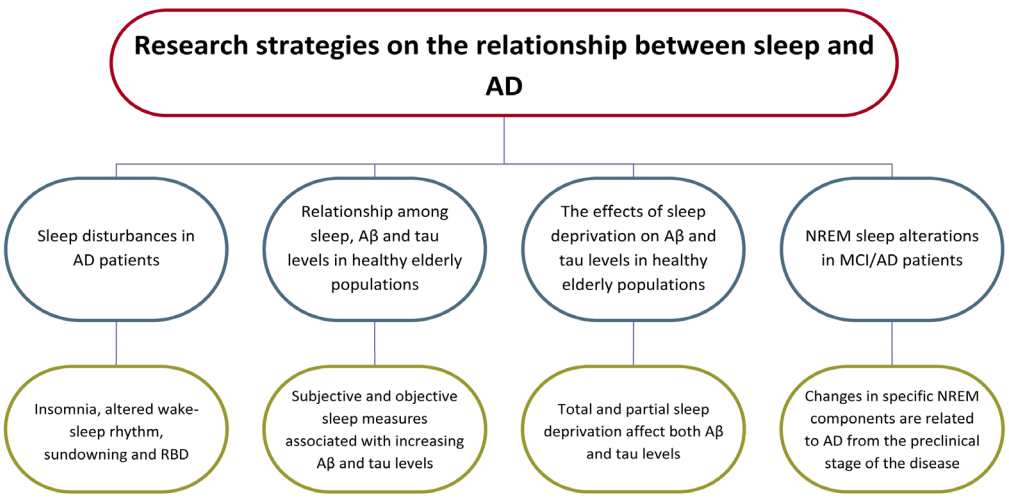

Figure 1 Summary of the main research strategies on the relationship between sleep and AD.
Aβ: Beta amyloid; AD: Alzheimer's disease; MCI: mild cognitive impairment; NREM: non rapid eye movement; RBD: rapid eye movement sleep behavior disorders.

tistically mediated the effect of old age on next day episodic learning and the amount of this impairment in learning ability could be due to the degree of the decrement in prefrontal sleep spindles.

Taken together, the contribution of Mander et al. (2014) provide a robust confirm to the hypothesis that the disruption of sleep physiology plays a relevant role in the age-related cognitive impairment in later life.

A more recent contribution, in early AD, with participants predominantly at normal cognitive level, showed that NREM SWA had an inverse relationship with tauopathy, and that this relation was most evident at the lowest frequencies of NREM SWA (Lucey et al., 2019). Authors suggest that changes in NREM SWA (with particular reference to 1 to 2 Hz), could be able to discriminate tau pathology and cognitive impairment since the preclinical stages of AD.

While the above-mentioned studies were mostly conducted on healthy elderly population, other recent contributions derive from experimental protocols conducted in AD and MCI patients. Starting from the previous results obtained by Mander et al. (2015), De Gennaro et al. (2017) examined both frontal K-complexes (KCs) and SWA in AD patients (n = 20) and healthy controls (n = 20), in order to clarify the apparent contradiction that showed a decrease of 0.6–1 Hz activity during NREM. The authors hypothesized a possible overlap between 0.6–1 Hz activity and KCs. Specifically, authors hypothesized that KC density could better discriminate patients from healthy elderly than ≤ 1 Hz SWA. The results confirm a 40% decrease of KC density, with a correct classification of 80% and a strong association with cognitive decline. The KC density decrement was detected in the same areas (at frontal level) in which ≤ 1 Hz SWA activity was higher.

The same research group (Reda et al., 2017) extended these findings, with an experimental protocol that had the aim of understanding the beginning of the KC decrease in the course of AD degeneration. The data of 20 MCI patients were compared to AD (n = 20) and healthy controls (n = 20). The results showed that, while AD patients had a significant decrease of KC density when compared with both MCI and healthy controls, no differences were observed between MCI and healthy controls. Furthermore, KC decrease also positively correlated with cognitive global status, measured through Mini Mental Stat Examination. Therefore, the results of this study suggest that the robust KC density decrease starts in the advanced state of AD pathology and can not be referred to the early stage of the disease.

The first study that evaluated the density of fast- and slow-frequency spindles in AD/MCI patients (Gorgoni et al., 2016) showed that parietal sleep spindle density significantly decreased in both AD and MCI patients compared with healthy controls. The decrement also positively correlated with the cognitive mental status (measured with Mini Mental Stat Examination). The innovation of this study contributes to improve the knowledge about the frequency and localization of AD-related to changes in spindle density.

Although the available findings do not provide any direct evidence of a causal relationship between sleep deterioration and AD, the empirical evidence on electroencephalogram changes in relation with AD pathology is guiding investigators to extend their results, considering the above mentioned NREM components as possible contributors to future innovative treatments. Actually, the steps forwards are at the very beginning, but encouraging results have been reported. Although there is no evidence of its long term effectiveness, the enhancement of < 1 Hz NREM SWA during NREM sleep seems to have a positive impact in improving restorative characteristics of sleep. In particular, a closed-loop in phase auditory stimulation at low intensity is candidate to be a novel approach also in case of sleep disturbance.

The current research in the field of sleep and AD is increasing in importance, denoting a possible innovative future in terms of non-invasive and early interventions and prevention strategies. The above-mentioned results on sleep electroencephalogram in relation with AD have to be considered as preliminary reports, because other confirmations are needed. Future researches should propose complex and integrated experimental protocols, in order to provide concurrent electrophysiological, behavioral, anatomical and neuropsychological data. At this purpose, longitudinal studies that follow the entire course of the pathology, since the preclinical stage of the disease are needed. Further investigations on the role of specific NREM sleep components are also required, with the aim of confirming the original and promising existing evidence.

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