Sleep Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

The Sleep Side of Aging and Alzheimer's Disease

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ARTICLE INFO

Article history:
Received 6 April 2020
Received in revised form
13 May 2020
Accepted 19 May 2020

ABSTRACT

As we age, sleep patterns undergo significant modifications in micro and macrostructure, worsening cognition and quality of life. These are associated with remarkable brain changes, like deterioration in synaptic plasticity, gray and white matter, and significant modifications in hormone levels. Sleep alterations are also a core component of mild cognitive impairment (MCI) and Alzheimer's Disease (AD). AD night time is characterized by a gradual decrease in slow-wave activity and a substantial reduction of REM sleep. Sleep abnormalities can accelerate AD pathophysiology, promoting the accumulation of amyloid-β (Aβ) and phosphorylated tau. Thus, interventions that target sleep disturbances in elderly people and MCI patients have been suggested as a possible strategy to prevent or decelerate conversion to dementia. Although cognitive-behavioral therapy and pharmacological medications are still first-line treatments, despite being scarcely effective, new interventions have been proposed, such as sensory stimulation and Noninvasive Brain Stimulation (NiBS). The present review outlines the current state of the art of the relationship between sleep modifications in healthy aging and the neurobiological mechanisms underlying age-related changes. Furthermore, we provide a critical analysis showing how sleep abnormalities influence the prognosis of AD pathology by intensifying Aβ and tau protein accumulation. We discuss potential therapeutic strategies to target sleep disruptions and conclude that there is an urgent need for testing new therapeutic sleep interventions.

1. Introduction

Growing older is associated with remarkable sleep disruption, characterized by reduced ability to transition from wakefulness to sleep and to stay asleep without waking up. In an extensive meta-analysis, Ohayon and colleagues (2004) highlighted some of the key aging-related sleep disturbances, such as delayed circadian rhythm, a lighter and more fragmented sleep pattern, lower δ activity, and less time spent in the deeper stage. Moreover, sleep features like sleep spindles (SS) and K-complexes (Kc) also dramatically drop in frequency and amplitude [1]. The authors suggest that many factors are involved in causing sleep changes with age. As an example, the aging-associated physiological and metabolic changes, as well as the increased susceptibility to environmental factors increase the risk to suffer from primary sleep disorders, such as Insomnia and Sleep Disordered Breathing [1].

Furthermore, disrupted sleep patterns are also a major risk factor for developing Mild Cognitive Impairment (MCI), which may convert to Alzheimer's Disease (AD). Sleep disruptions caused by cortical and environment modifications are often reported years before the clinical onset of the disease in elderly individuals, therefore making them a potential biomarker of the risk in AD. Then, after the onset and during the progression of MCI/AD, the sleep abnormalities undergo an even more accelerated worsening. These indicators suggest a complex bidirectional influence, for which sleep disruption may both causally contribute to AD development, and be a consequence of the onset. The current concept is

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https://doi.org/10.1016/j.sleep.2020.05.029
1389-9457/

that sleep quality reduction results from amyloid-beta (Aβ) aggregation that also triggers hippocampal degeneration and, ultimately, memory impairment. The hypothesis is that a reduction of slow-wave activity (SWA) during non-rapid eye movement sleep (NREM) partly arises from amyloid pathology and contributes to cognitive decline in elderly individuals [2]. Because the worsening of sleep quality is among the earliest observable symptoms of MCI and AD, current theories suggest examining sleep modifications in pursuit of a biomarker to identify the greater risk of developing dementia. Within this framework, a decreased duration of rapid eye movement (REM) and the general slowing down of electroencephalogram (EEG) activity in NREM sleep has been considered as a potential biomarker. It has been argued that the promotion of slow waves during the NREM stage in the elderly population may have a protective effect on AD risk by enhancing Aβ clearance [3]. On this line, it has been shown that elderly people with narcolepsy have a lower burden in amyloid deposits [4].

The up-regulation of SWA may even restore damage to proteins caused by oxidative stress, as demonstrated in animal models [5]. Further, the amplitude and duration of SWA during the NREM stage are important for the long-term consolidation of newly acquired memories. The current hypothesis is that sleep improvement would slow the decline in cognitive abilities in AD patients. Within this framework, restoring slow-wave sleep (SWS) quality and duration would be a fundamental step in addressing AD symptomatology. Recently, therapeutic attempts aiming at changing sleep oscillatory activity have been proposed. Light exposure in combination with melatonin administration may be a valid way to influence the sleep-wake cycle [6]. Auditory stimulation can enhance SWA and improve memory retention [7]. Recent evidence suggests that also noninvasive Brain Stimulation (NiBS) techniques might be able to restore the sleep quality and preserve or enhance physiologically-declining cognitive functions [8–11].

The present paper intends to review recent evidence of sleep modifications in healthy elderly individuals and AD patients along with the associated brain changes (for a comprehensive scheme see Fig. 1). We aim to foster an understanding of the tight bidirectional relationship between sleep quality, normal aging, and AD pathology. Further, we discuss potential therapeutic strategies targeting sleep disruptions using NiBS and sensory stimulation to restore sleep quality and thus possibly prevent cognitive decline in healthy aging and AD.

2. Sleep alterations in normal aging

In the next paragraph, we review age-associated sleep changes (Fig. 2) in circadian rhythms, macrostructure (eg REM-NREM cycle), microstructure, and EEG features (eg SWA), homeostatic sleep drive, and prevalence of sleep disorders. Albeit these modifications are so frequent to be an aging biomarker, individual variability, due to gender, ethnicity, race, and environment still plays a role in age-associated sleep abnormalities. In the following chapter, we will then discuss how these changes might be related to aging-related processes in the healthy brain such as atrophy.

2.1. Circadian rhythms

Huang and colleagues (2002) found that circadian sleep/wake rhythms (CR) were weakened and fragmented in the old and oldest groups as compared to the young and middle-aged groups [12]. Macrostructure and total sleep time (TST) were also significantly altered with age. Individuals shift from a mean of 7.4h in early life to 5.6h in old age [13], with some gender differences (men: 5.4h, women: 6h on average per night [14]. Münch et al. [15] reviewed the evidence for the effects of aging on CR and found age-related modifications in terms of amplitude, earlier phase, shortened repetition time, and worsened capacity to tolerate sudden phase shifts.

CR changes start to be visible in middle-age subjects with increased sleepiness during the evening and delayed sleep-onset latency (time required to fall asleep) [13]. As a consequence, regular diurnal napping increases, growing 25% after the 75th year and eventually resulting in a worsened cycle shift [16]. With aging, difficulties in falling asleep are present not only at the beginning but also after nighttime arousals (shifts from deeper to lighter stages). Elderly people usually spend twice as much overnight time in unwanted wakefulness [17] and this drastically drops sleep efficiency (% time in bed spent asleep). Elderly individuals are also more sensitive to the external environment, showing a lower arousal threshold to auditory stimuli [18]. Once sleep is interrupted (spontaneously or by external causes) transition from sleep to a fully awake state occurs also more rapidly in older subjects, thereby delaying the start of sleep again [19]. Further, the frequency of arousals is also remarkably higher in elderly people, with different prevalence between the various sleep stages; older subjects present significantly more shifts from SWS to N2 and from N2 to N1, while in younger subjects the typical pattern is from REM to N1 [20].

2.2. Macrostructure

Aging also influences the structure of REM-NREM cycles (Fig. 2, panel B); they are shorter and fewer, with a mean of 3.46 cycles per night compared to the usual 4-5 in adults and teenagers [20]. Noticeably, NREM changes are considered a reliable age-related biomarker. Elderly people spend less time in a deeper stage, N3, replaced by a greater amount in lighter phases, N1 and N2 [1,14,17,21–23]. SWS (or N3) reduction begins in middle age, gradually decreasing until disappearing after the 90th year [1,17]. The increase of time in lighter phases is greater in stage N1 than N2, but N2 microstructure undergoes more changes, with a decrement of sleep spindles and K-complexes (see below; [20]). Older women show a less marked difference in lighter and deeper stages, with a smaller decrement in SWS than men [1,17].

REM studies, on the other hand, are less developed and coherent. Some studies reported a slight REM decrease [1,14], but the drop is not as prominent and typical as the one in NREM sleep. Time spent in REM seems, indeed, to start its fall only after the 65th-70th year, while NREM starts around 4 decades before [1,14]. Even when reaching older age (around 70 years old), REM and NREM time decreases differentially: -24 minutes per decade of NREM compared to -10 minutes per decade for REM [21]. It is worth noticing that other studies failed to find a difference in REM and NREM sleep age-related modifications [22,23], leaving the discussion open.

2.3. Microstructure and EEG

Recent studies show how typical sleep oscillations are also dramatically modified on their fundamental components while growing older.

2.3.1. Slow Waves (SWA)

Evidence supports a reorganization in the N3 during aging. Slow Waves (δ waves) are oscillations with slow frequency (<2Hz) and high amplitude (>75μV) associated with a reduction of homeostatic sleep pressure [24] and protective effects from awakenings and arousal [25]. Δ waves have also been suggested to be implicated in learning and memory processing [26]. A drop in total SWA (spectral power density from 0.5 to 4.5Hz; or δ activity), is a particularly

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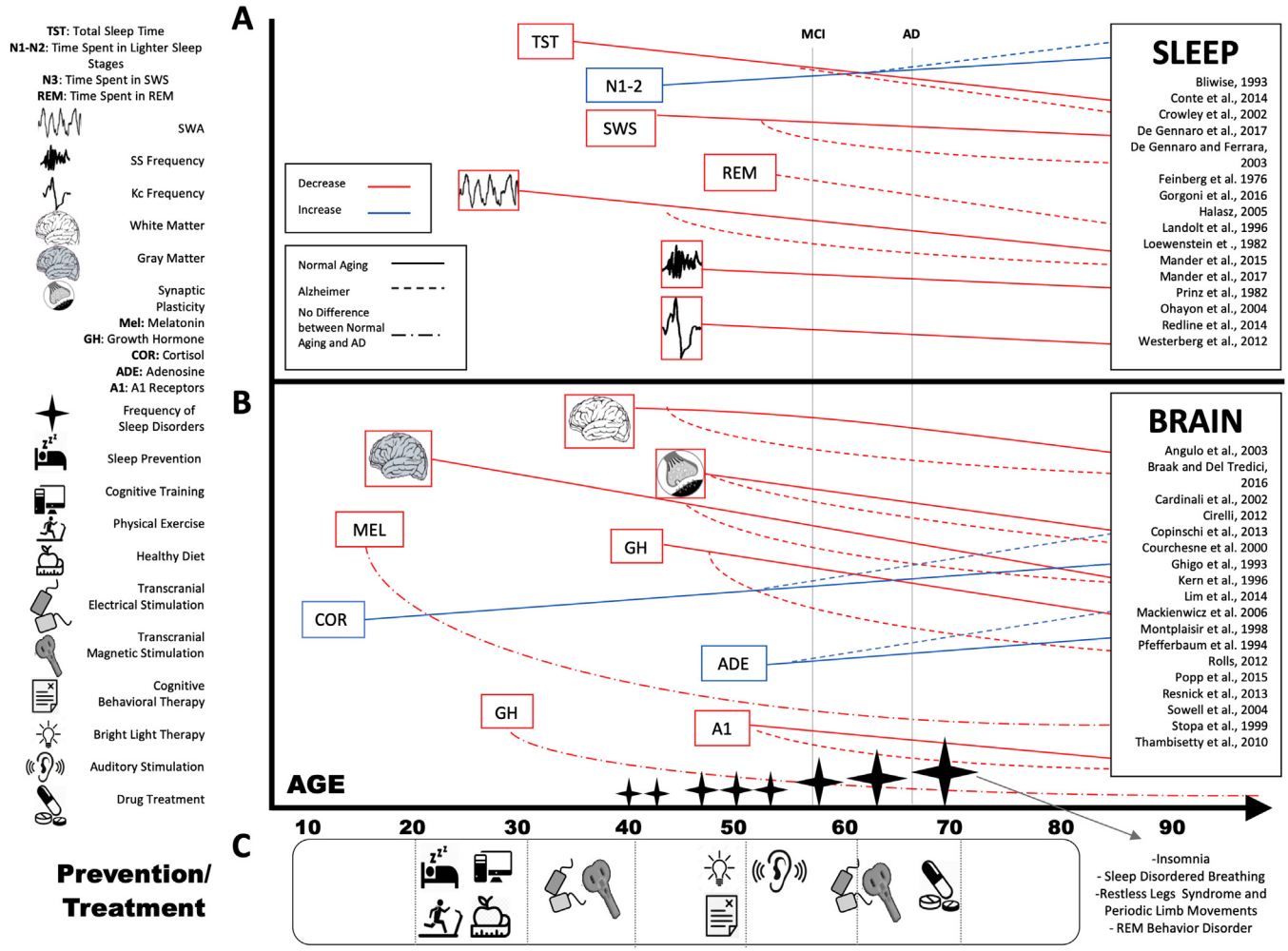

Fig. 1. Sleep and Brain changes in elderly and AD patients during the Lifespan. A comprehensive review of sleep modifications (panel A) and brain changes (panel B) in healthy aging individuals and AD patients. The items represent investigated and modified variables (*red* items show a decrease; *blue* items illustrate an increase). The mean age when MCI or AD is diagnosed is illustrated by *vertical black dotted lines*. The *horizontal lines* indicate the trajectories of sleep and brain changes. Sleep disruptions and cortical alterations start earlier than clinical symptoms' appearance. Horizontal line slopes depict differences in sleep and cortical abnormalities between healthy elderly and MCI/AD. *Black stars* show the prevalence of sleep disorders while growing older. Panel C shows when prevention and potential treatment efficacy would be optimal. NiBS techniques (such as transcranial magnetic stimulation and transcranial electrical stimulation) are represented at a different age for their applications in prevention and treatment. *Non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), slow-wave sleep (SWS), slow-wave activity (SWA), sleep spindles (SS), K-complexes (Kc), Total sleep time (TST).*

relevant consequence of aging and is used to test sleep quality and homeostatic sleep pressure [17,21–23]. The decrement of SWA is not spatially and temporally homogeneous across the night. There is a maximal decrease over the prefrontal cortex and in the first NREM cycle for elderly individuals [23,26]. Both SWA amplitude and density are significantly reduced in middle-aged adults, worsening during advancing age [26]. Further, age-related decrease in power density in θ and α frequencies has been shown [23]. Another qualitative change in older individuals is a homogeneous slowing of SWA of about 0.1 Hz across all scalp sensors [26].

2.3.2. Sleep spindles and K-complexes

While N2 total time is not different between young and elderly individuals, its EEG features undergo age-related modifications. Sleep Spindles expression deteriorates, indicating that sleep microstructure can change without a parallel modification in the macrostructure [27]. SS can be divided into slow (9-12Hz) and fast (13-15Hz), and these are differentially affected in aging [28]. While there is agreement about the age-related drop in fast spindles, changes in slower-frequency spindles are still not clear [23]. Total spindle frequency activity (sigma power) is significantly reduced in middle-aged and older adults compared to young participants [29] with a bigger drop in the last part of the night [23]. Previous studies analyzed spindle characteristics, finding that spindles also undergo a progressive decrement in density, amplitude, and duration with aging [13,23,26,29–32]. Spindle breakdown is most pronounced during final N2 cycles [29]. These results are indicative of a different propagation of spindles through the cortical network in the elderly compared to young individuals. Thus, SS alterations may be a sign of the difficulties experienced by elderly individuals in maintaining sleep during lighter NREM stages [33]. The incidence of both, spontaneous and elicited Kc, decrease growing older [34,35], with a significant drop in Kc amplitude evoked by auditory stimuli [13].

2.3.3. Fast oscillations

Faster frequencies, like β (from 15 to 25Hz) or γ range (from 30 to 120Hz), are a prominent feature of awake EEG and are typically associated with normal cognition. Although their presence in sleep

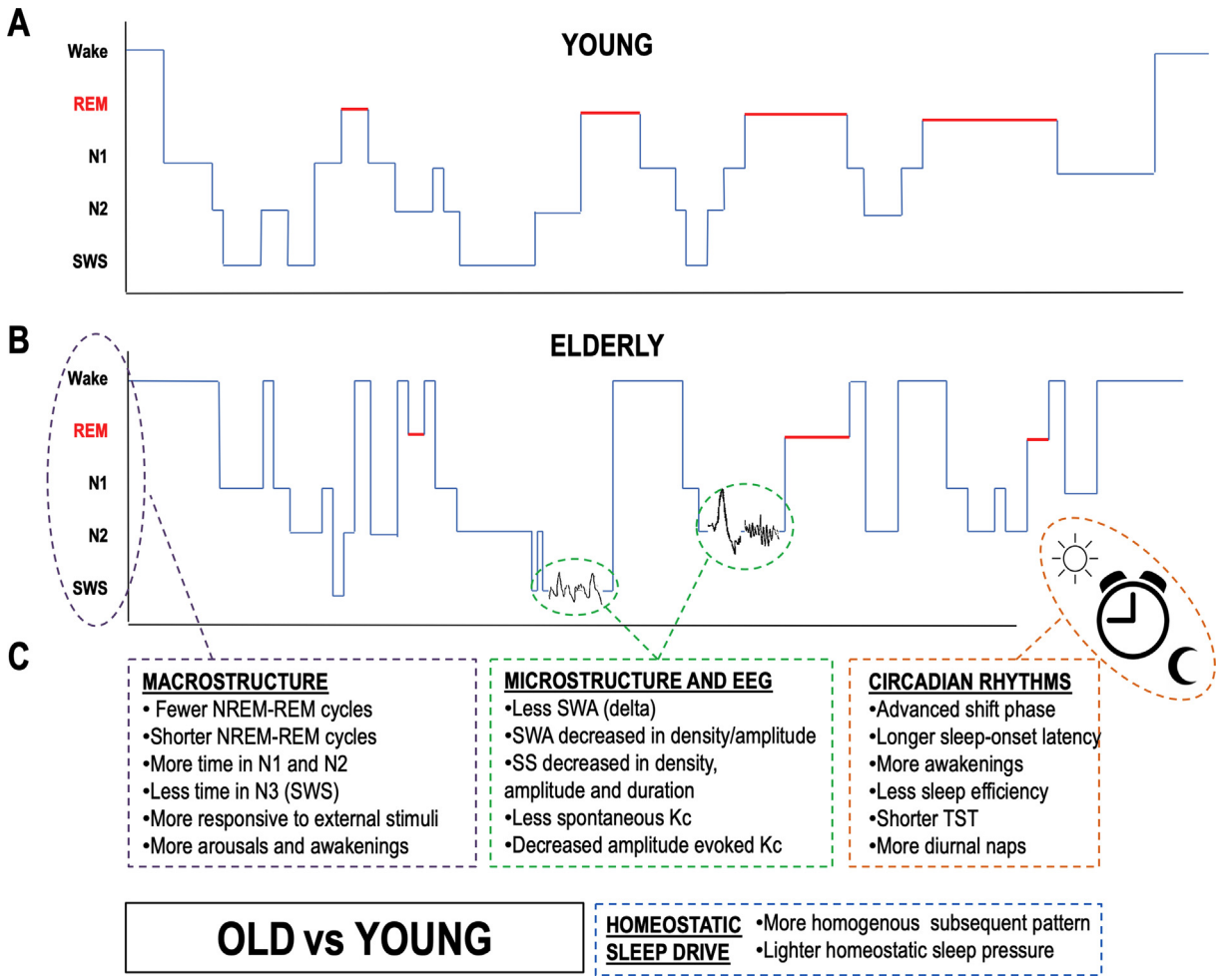

Fig. 2. Sleep Differences in Elderly versus Young Individuals. Polysomnographic (PSG) data showing sleep architecture in a young healthy adult (panel A) and an older healthy adult (panel B). The elderly show a more fragmented and less integrated sleep, shifting from deeper to lighter sleep stages multiple times during nighttime. Schematic illustration comprehensive of all sleep differences found in healthy elderly compared to young individuals (panel C). *Non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), slow-wave sleep (SWS), slow waves (SW), slow-wave activity (SWA), sleep spindles (SS), K-complexes (Kc), Total sleep time (TST).*

has been studied, results are contradictory [36–38]. Sleep deprivation-related EEG slowing over the frontal region during wakefulness also results in a concurrent reduction in β/γ rhythms [38,39], thereby partially explaining the cognitive impairment associated to sleep deprivation. As aging is associated with a progressive reduction in sleep quantity and quality, several researchers investigated whether age-related cognitive decline might be related to β/γ reduction; while old studies surprisingly highlighted increased in β activity [40–42], newer paradigms show no differences between age groups at 65 years [36], leaving the question open.

Spontaneous γ rhythm mostly occurs coupled with θ rhythms during REM sleep [43,44], with a higher presence of low γ when eye movements are present [45]. Importantly, γ seems to promote synaptic plasticity when coupled with θ, [46,47] specifically for phasic REM states, where the synchrony between θ and γ is enhanced; this suggests that tonic REM phases support offline mnemonic processing, while phasic bursts of activity may promote memory consolidation [48,49]. As a recent study with cortical and intracortical EEG on epileptic patients under age 50 suggested a higher presence of γ activity during SWS than REM [37], different roles of γ-band may be suggested in NREM and REM (memory consolidation vs. dreaming state). Sprecher and colleagues (2016) analyzed results gathered with high-density (256 channels) EEG in a cohort of 18-65 y/o participants and found greater high γ (define frequency range) power in the older group compared to the younger one. Unfortunately, this result was secondary to SWA and sigma (12-15 Hz) drop [36]. Moreover, because the experimental paradigm involved participants under age 65, new studies are required to find some clarity regarding high-frequency activity in older adults.

2.3.4. REM Sleep

Past studies found no changes [50,51], or a decrease [52] in REM-related eye movement patterns across the lifespan. Further, it has been shown a reduced duration of movement bursts in elderly individuals [50] and a reduction in δ-θ range (0.25-7Hz) and low α (8.25-10Hz) during REM stages [23].

2.4. Homeostatic sleep drive and subjective complaints

Homeostatic sleep drive is a time-awake dependent process so that the longer the time spent awake, the greater the drive to fall asleep. In healthy adult people, longer sleep deprivation and time spent in wakefulness leads to a more pressing homeostatic sleep drive, with a consequent increase in SWA and NREM during the following night [24]. The homeostatic pressure is reflected by SWA in the first NREM cycle during the initial part of sleep recovery and

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a progressive reduction of SWA during other cycles [23,24]. Indeed, Kc and SWA reduction supports the idea that homeostatic sleep pressure decreases across adulthood [51]. Current evidence supports the notion that, in elderly people, SWA is less influenced by longer-term wakefulness in comparison to younger control groups [15,53]. These are indicative of a lighter homeostatic sleep drive in elderly individuals [28].

Even though the consequences of sleep deprivation seem to be blunted in the elderly, the prevalence of subjective complaints increases significantly and steadily with advancing age (40-50% of the entire older population). The most common complaints involve overnight awake states, light sleep, less total time asleep, early waking up, and excessive daytime sleepiness [54,55]. Strangely, even if sleep is qualitatively and quantitatively more disrupted in men, women complain more about subjective difficulties [1]. Only half of healthy older adults complain of chronic sleep disruptions, albeit age-related changes occur in all "optimally aged" elderly. This means that even those who do not complain of sleep problems show poor sleep efficiency and quality [56].

2.5. Sleep disorders

Elderly individuals are at increased risk of suffering from primary sleep disorders, such as insomnia and sleep-disordered breathing. Insomnia prevalence, in particular, reaches 40% in over 65 y/o individuals, with greater frequency in women [54]. If untreated, insomnia aggravates depression and significantly worsen cognitive skills [57]. As aforementioned, adulthood arousal threshold progressively declines, resulting in more awakenings even in deeper sleep stages like N3 and REM, therefore worsening insomnia condition [18]. SDB shows also a higher prevalence in elderly subjects. In a randomly selected cohort of 427 participants (age range 65-95) 62% of the cohort showed an SDB diagnosis [58].

3. Aging-related neurobiological modifications

The aging process contributes to a great number of quantitative and qualitative modifications in the brain, starting from the reduction of synaptic density and plasticity, neuronal loss, and cortical atrophy, accompanied by hormonal and extracellular changes. As a consequence of these modifications, sleep and cognition are highly disrupted. In this section, we address the main age-related brain modifications, linking them to specific age-related sleep disruptions and cognitive impairment.

3.1. Synaptic plasticity

A reduction of cognitive activity in the elderly, and a subsequent modification in synaptic plasticity, is one of the first causative factors in SWA decline. SWA involves large populations of healthy neurons able to produce oscillations and also efficient synaptic connections among them [59]. Current evidence shows that a rapid increase or decrease in synaptic strength during awake states give rise to a subsequent enhancement or decline in SWA. During sleep, slow oscillations renormalize neural activity in the N3 stage, promoting synaptic depression by low levels of norepinephrine, serotonin, and acetylcholine (for a review see Ref. [60]). As aforementioned, previous studies showed a positive correlation between SWA during sleep and the number of potentiated synapses during wakefulness. The authors argued that learning and motor tasks trigger greater SWA during sleep that might be explained by plasticity mechanisms. In line with this, an age-related drop in brain plasticity and a lack of cognitive activity would account for a reduction of SWA in the elderly.

3.2. Deterioration of gray matter and functional consequences on sleep-related EEG

The most characteristic biomarker of the aging brain is the so-called "shrinking brain phenomenon" [28], a marked decrease in cortical volume [61–64] that has been measured through different parameters, such as the total volume of the brain, cerebrospinal fluid (CSF), gray and white matter, cortical thickness, surface area, cell loss, and neuronal shrinkage (for a comprehensive review see [65]).

The brain reaches its maximum volume in early adolescence, then it declines steadily and linearly from early through middle adulthood, with an accelerated rate after 55 years. Around age 71-80 the whole-brain volume has already dropped by 26% compared to the volume in children, while, concurrently, the total intracranial CSF volume increases [61]. Volume decline does not occur to the same degree in all brain regions: while white matter decrease affects the whole brain, gray matter deterioration mostly affects the frontal and parietal lobes [63,64].

As SWA results from the synchronization of a large population of neurons, SWA modifications may be a result of shrinking in specific regions and not a consequence of general whole brain atrophy [66]. Several studies demonstrated that neuronal loss in the lateral and medial prefrontal cortex (PFC) predicted impairment in slow oscillations generation and propagation [67,68]. It has been also shown that prefrontal regions in older individuals have lower resting metabolic activity compared to the brain of younger subjects [69]. These results are in line with the aforementioned maximal reduction of slow-wave density and amplitude in frontal EEG derivations in the elderly [23,26]. Moreover, it has been demonstrated that neuronal loss in the medial PFC and the middle frontal gyrus predicts a decrement in SWA amplitude, while density is correlated with deterioration of the areas surrounding the lateral fissure [67].

The neuronal loss might also account for the decrement in SS and Kc. Indeed, spontaneous Kc is considered an expression of slow oscillations at the level of the neural membrane potential. This link would explain the lower Kc frequency when δ oscillations are impaired [13,30]. Furthermore, neuronal loss in the hippocampus predicts the severity of reduction in SS density and duration in older individuals [27]. As regard to gender differences, a reduction of PFC volume is more pronounced in men than women [14,66]. These results suggest a gender discrepancy, with reduced SWA and sleep efficiency in men compared to women [13].

3.3. Hypothalamus and brainstem nuclei: the sleep state switching process

The switch between sleep and wakefulness is regulated by a complex network within the brainstem and hypothalamic nuclei. This system is differentially affected by age on many levels (for a comprehensive review see Ref. [70]) In particular, age-related changes in four areas are responsible for disruptions in circadian rhythms: the wake-promoting lateral hypothalamic area (LHA) and the locus coeruleus (LC) help to maintain stable periods of wakefulness, while the preoptic area (POA) modulates LHA and LC function, sending inhibitory input to initiate and maintain sleep [71]. The hypothalamic suprachiasmatic nucleus (SCN) is the endogenous clock promoting wakefulness and regulating sleep [66,72]. Age-related neuronal loss affects these nuclei, disrupting the balance in sleep and wakefulness. The age-related deterioration of hypothalamic and brainstem nuclei does not occur to the same extent in all nuclei involved in sleep and wake control. For example, serotoninergic neurons in the raphe nucleus undergo minimal age-related changes and do not predict sleep disruptions [70].

Please cite this article as: Romanella SM et al., The Sleep Side of Aging and Alzheimer's Disease, Sleep Medicine, https://doi.org/10.1016/j.sleep.2020.05.029

3.3.1. Suprachiasmatic nucleus

The SCN coordinates hormonal and behavioral rhythms as a circadian pacemaker and is dramatically affected by the aging process. Modifications involve alterations in neuronal network functionality, membrane properties, and modifications of constituents in cellular nuclei (for a complete review see Ref. [73]). Post mortem examinations showed a decrement in SCN volume and cell number in the elderly [74,75]. Specific neuronal subpopulations are particularly affected by this shrinking, including those expressing vasoactive intestinal peptide (VIP). These neurons receive direct light input from the retina and regulate synchronicity between endogenous rhythms and the external light-dark cycle [73]. Loss of VIP-ergic neurons would lead to a lower influence from light to internal rhythms, loosing circadian control from SCN [72], therefore inducing modifications in a phase shift, nighttime movements, and the number of awakenings. Impairment in SCN function also reflects a desynchronized melatonin secretion cycle (see paragraph 2.6.1).

3.3.2. Hypothalamic preoptic area

The POA plays a major role in promoting, initiating, and maintaining sleep. POA is formed by cells expressing inhibitory neuropeptide galanin [71] and undergoes a significant decline in aging. The degree of cell loss in the POA predicts the severity of sleep fragmentation in older adults [76]. The POA shrinkage results in abnormalities in overnight sleep consolidation [76].

3.3.3. Lateral hypothalamic area and locus coeruleus

The LHA contains neurons expressing hypocretin and orexin which connects to other nuclei of the brainstem ascending arousal system. LHA together with the LC collectively maintains stable wake states [71]. Both undergo a reduction of their neuronal subpopulations during the aging process. Elderly individuals show a 10% loss in the number of LHA hypocretin-orexin neurons [77] and a significant neuronal reduction in LC volume [78]. Deterioration in these two structures and their interconnection with the POA is partially responsible for fragmentation and fragility of sleep, higher frequency arousal, and greater sleepiness during awake states in the elderly.

3.4. Deterioration of white matter

Aging also causes white matter (WM) deterioration, although it generally is less marked compared to changes in grey matter. By age 70-80, the former is decreased by 13%, and the latter 26% compared to the average volume in children [61]. WM does not reach its volume plateau until the 4th decade, and only after it starts declining in volume [61]. This has been confirmed by studies using diffusion tensor imaging (DTI; [79]). This deterioration can also be seen in investigations of the total length of myelinated fibers. Thinner fibers, like small collaterals, are more damaged than thicker, as main axons [80]. Literature reported how the structural properties of white matter tracts affect the brain network's ability to synchronizing themselves to produce SWA [81]. As an example [82], correlated a steeper slope of slow waves, suggestive with a higher axial diffusivity in major frontal regions, an indicator of better white matter integrity. SWA disruptions typical of the elderly may, indeed, be partially caused by loss of white matter tracts able to maintain higher cerebral synchronicity during sleep. Furthermore, specific aging deterioration of the body and splenium of the corpus callosum predicts the severity of SS frequency decline in the elderly [66].

3.5. Adenosine

Adenosine is a metabolic byproduct that accumulates during wakefulness. It promotes homeostatic sleep drive, including SWA after sleep deprivation. Previous studies show a decrease in homeostatic drive and lower homeostatic EEG response in older subjects, suggesting lower levels of adenosine in elderly subjects. On the contrary, animal models found higher extracellular adenosine levels in older mice, with a focus on brainstem sleep and wake-promoting nuclei [83]. This contradiction could be explained by reduced A1 receptor gene expression and widespread loss of adenosine A1 receptors in cortical, thalamic, and hippocampal areas occurring in advanced age [84,85]. This would then result in the higher extracellular concentration of adenosine, but fewer receptors able to interact with it, leading to lighter homeostatic sleep drive and SWA rebound for sleep deprivation.

3.6. Hormones

The sleep process across the life span is affected by age-related endocrine metabolic alterations. In the next section, we review the role of three hormones associated with promoting and maintaining sleep and we discuss how they are modified by the aging process.

3.6.1. Melatonin

Melatonin plays an important role in sleep regulation controlled by the SCN via a complex pathway (for a comprehensive review see Ref. [86]). The endogenous melatonin peak is 2 hours before habitual bedtime. The aging process attenuates overnight melatonin secretion in older individuals, while diurnal secretion is similar in elderly and young subjects [15,87,88]. Its overnight decrement is linked to nocturnal light exposure in the elderly. Light exposure during the night results in a dose-dependent suppression of melatonin secretion [86]. By contrast, insufficient daytime light exposure, often seen in the elderly due to spending most of the time home, elicits a desynchronization of the melatonin secretion cycle [89], concurrent with the shift in the sleep-wake cycle.

3.6.2. Growth hormone (GH)

GH functions include control of glucose concentration and cell reproduction [90]. Normally, GH secretion follows a tight circadian schedule closely linked to SWS [88]. In aging, a significant reduction in the GH secretor peak predicts a shorter time spent in N3 [91].

3.6.3. Cortisol

There are age-related alterations in cortisol levels with a rising trend which is probably linked to less sleep duration and more awakenings in older individuals [91]. Moreover, variations in cortisol secretion timing have been demonstrated. Specifically, there is a delayed shift in cortisol secretion in the elderly compared to younger subjects. It has been suggested that these age-related alterations could have a strong relationship with REM sleep. In this vein, a previous study demonstrates that, with aging, plasma cortisol levels progressively increase while REM sleep decreases [88].

4. The relationship between sleep and protein clearance

Several studies showed a strong relationship between sleep quality and Aβ alterations in MCI/AD and healthy elderly subjects [92–94]. It has been demonstrated that sleep disruptions are, indeed, a crucial factor affecting the severity of cortical Aβ burden and the levels of phosphorylated tau in the CSF (Fig. 3). In this paragraph, we review the causal relationship between sleep abnormalities, like the aforementioned ones explained in the last

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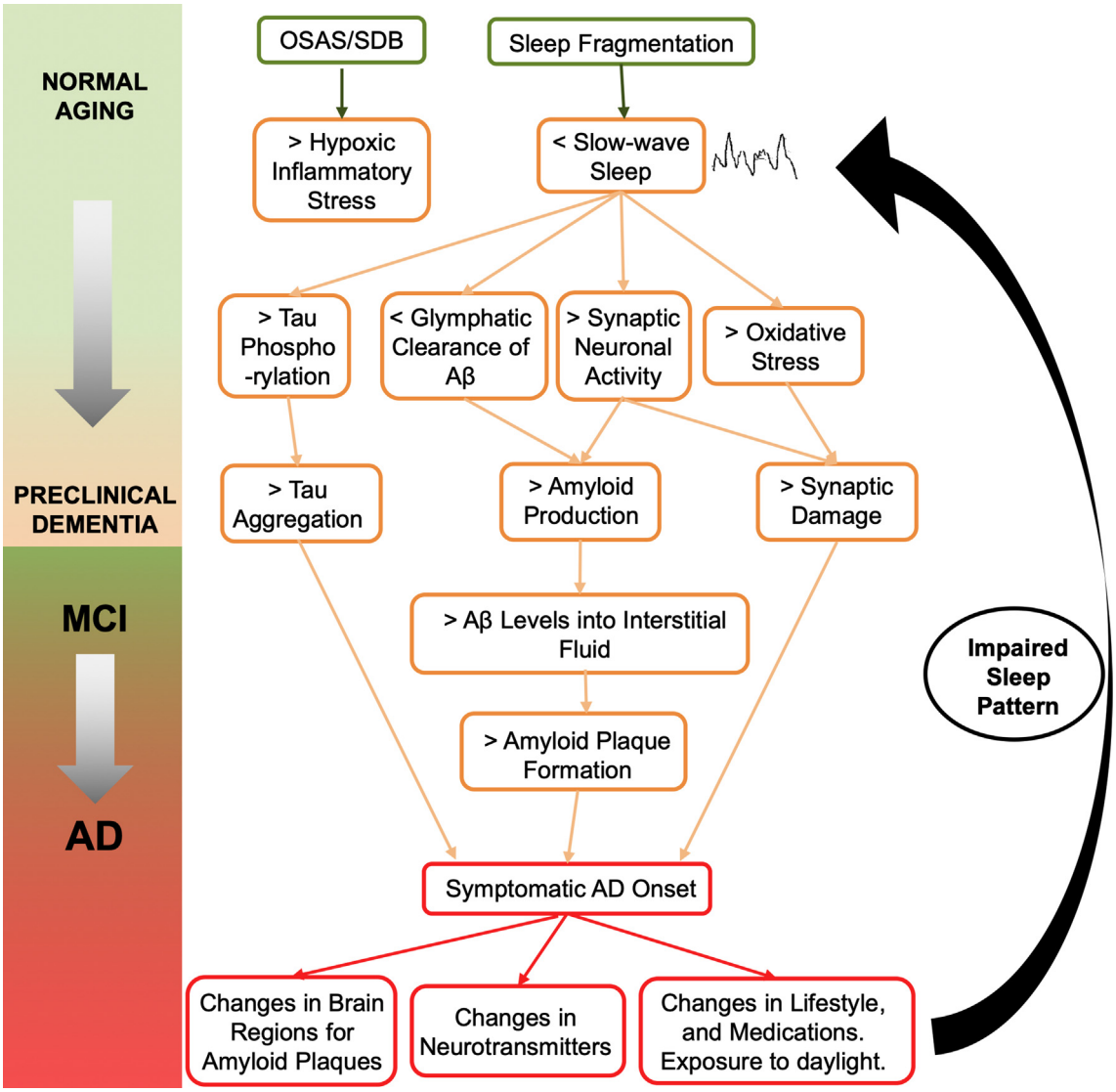

Fig. 3. Bidirectional Link between Sleep, Aβ Levels, and MCI/AD Onset. Sleep fragmentation is a key factor that triggers a cascade of pathological processes before clinical onset. Modifications in brain regions, neurotransmitter levels, and lifestyle due to AD diagnosis and prognosis will then worsen sleep patterns establishing a vicious cycle feeding itself. OSAS: Obstructive sleep apnea syndrome. SDB: Sleep-disordered breathing. MCI: Mild cognitive impairment. AD: Alzheimer's Disease.

paragraph, and Aβ plaques, neurofibrillary tangles, and Apolipoprotein Epsilon (ApoE), the three main hallmarks of AD pathology.

4.1. Amyloid-β and glymphatic system

In a murine animal model-based study [95], discovered that Aβ and other metabolites are cleared during sleep through a perivascular pathway. They called this system the "lymphatic pathway". Crucially, these results suggest that at least one physiological function of sleep is the clearance of toxic substances that build up during daytime activities. Spira and colleagues [93] recruited 70 older adults in cross-sectional study design (mean age = 76; range 53 - 91). The authors assessed the Aβ burden using the Pittsburgh Compound B (PiB) positron emission tomography and found greater Aβ burden in the individuals who self-reported shorter sleep duration and lower sleep quality. Conversely, patients with narcolepsy have a lower burden of amyloid in the brain [4].

To better understand the relationship between sleep, Aβ, and tau protein, Ju and colleagues (2017) examined 17 healthy adults (age 35 to 65) who reported no sleep or cognitive issues. Actigraphy was recorded for at least 5 successive nights, after which participants spent one night in a climate-controlled sleep room. Half of the subjects were randomly assigned to have their SWS disrupted by a series of beeps (administered through headphones). This process was repeated approximately one month later, except that those who previously had their sleep disrupted were allowed to sleep through the night uninterrupted, and those who were previously allowed to sleep through the night had their sleep disrupted. Participants underwent a spinal tap after both nights to measure the levels of Aβ and tau protein in the CSF. The authors found an approximately 10% increase in Aβ following the disrupted night's sleep. Participants also consistently reported feeling tired after having their SWS disrupted, despite they only rarely recalled being awakened by stimuli.

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The increase in Aβ levels might be due to increased production of Aβ by neurons, or decreased clearance of Aβ by the lymphatic system (see Refs. [96,97] for an overview of brain lymphatic). In a subsequent study [98], administered sodium oxybate -which causes an increase in SWA- in one group, comparing it with another group of sleep-deprived subjects and normal sleeping control participants. They found that sleep deprivation increased Aβ levels through increased overnight Aβ production and argued that, despite lymphatic clearance might contribute to the protective effects of sleep against AD, changes in Aβ production rate indeed have a major role.

Pase and coworkers [99], followed a cohort of 321 (67 +/- 5 years old) for 19 years. They found a relation between REM disruptions and dementia in 32 cases, 24 of which were likely AD. Although the mechanisms behind the relationship between Aβ and REM are still unclear, disruptions of REM sleep might coincide with the onset of cognitive impairment. A previous study showed evidence of a relation between REM sleep disruption and Aβ levels in healthy elderly and AD patients [100]. These results may be mediated by the degeneration of cholinergic transmission within the brainstem and basal forebrain, which also plays a role in the regulation of REM sleep. Indeed, in both healthy older adults and MCI/AD patients, the degree of cortical Aβ burden was correlated with the degree of basal forebrain atrophy [101].

4.2. Tau-associated neurofibrillary tangles (NFTs)

Tau-associated neurofibrillary tangles (NFTs) are formed by hyperphosphorylation and intercellular aggregation of tau protein and are the second well-known hallmark of AD [102,103]. Tau pathology has been suggested as the earliest neurodegenerative feature linked to AD with abnormal tau phosphorylation and aggregation in the locus coeruleus, beginning during early adulthood. It then spreads into different cortical areas such as dorsal raphe, tuberomammillary nucleus, parabrachial nucleus, and basal forebrain (for a review see Ref. [104]) before Aβ burden could even be detected [100,105–107]. Furthermore, NFTs in the LC are found in AD patients [108], and later on, phosphorylated tau levels in the CSF also predict cognitive decline in preclinical and clinical AD [109]. The mediation of the LC between AD and NFTs is strongly linked to its excitatory role in the cortical ascending arousal system. In healthy individuals, noradrenergic neurons in the LC inhibits sleep [110], on the contrary, LC neurons are lost in AD. Interestingly, it has been shown that the number of LC neurons is correlated with cognitive decline in a cohort of healthy elderly [111].

NFTs are particularly disrupting considering the hippocampus's ability to generate ripples linked to the expression of NREM SS and SWA, and how these two features have been shown to support sleep-dependent memory processing [112]. Studies on animals showed that hippocampal ripples are diminished and less synchronized due to the accumulation of tau in the medial temporal lobe, therefore changing neural oscillatory pattern [113]. Tau has been associated with abnormally long hyperpolarized down states during SWA [114], explaining part of the correlation between CSF tau levels and SWS drop in patients with AD [100]. Furthermore, chronic sleep restriction, already known to be a risk factor for illness progression, impairs hippocampus-dependent memory and increases insoluble tau, helping NFTs formation [115,116]. Ju and colleagues [2] reported no increase in tau levels after only one night of disrupted SWS, whereas they found increased CSF tau levels in participants reporting poor sleep during several nights. Conversely, the lymphatic system during sleep promotes tau clearance, explaining why the elderly with a good sleep quality showed fewer NFTs at autopsy [117,118].

4.3. Apolipoprotein epsilon

ApoE is a class of protein essential to combine fats to form lipoprotein. Lipoproteins are important to preserve and remodel neuronal membranes. ApoE is polymorphic, with three major alleles: ApoE-ε2, ApoE-ε3, and ApoE-ε4. The latter is well known to be a genetic risk factor for developing AD [119–121]. ApoE-ε4 has been associated with reduced Aβ clearance with consequent pathological accumulation [122]. Normal cognitive elderly individuals with the ApoE-ε4 allele have shown a risk for developing MCI or dementia seven times higher [123]. Sleep disturbances appear to be linked to ApoE-ε4 in MCI/AD patients, especially concerning REM decrease [124] and delay in circadian rhythms [125]. It has also been proposed that increased sleep disturbances in ApoE-ε4 patients could result from alterations in melatonin production [126]. Besides, ApoE-ε4 has been associated with an increased risk of SDB and cognitive impairment in patients with OSAS [127–129].

While some studies suggested that ε4 allele may be the major cause of sleep disruptions in elderly people at risk for dementia [127,130], others stressed that sleep deficits and ApoE genotype may just amplify each other's negative effects [131,132]. The debate on ApoE-ε4 is still open given the fact that some studies showed no influence [133] or even a protective role of ApoE genotype on sleep patterns, raising the question of the true nature of this association [134]. Even though more investigation is required, current theories propose that better sleep consolidation could attenuate the increased risk conferred by the ApoE genotype [117,118].

5. The bidirectional link between sleep and Alzheimer's disease

As aforementioned, the current concept is that sleep disruptions accelerate AD pathogenesis by enabling Aβ and tau protein accumulation. Because sleep disruption also appears to be among the earliest observable symptoms of a wide range of neurodegenerative diseases, such as AD, Parkinson's Disease, and Multiple Sclerosis [135,136], its function as a biomarker to identify elderly at greater risk has been suggested [66]. Below we discuss modifications in sleep patterns, macro and microstructure in MCI and AD, and how these disruptions predict clinical symptoms and cognitive performance in patients. As aforementioned, Fig. 1 illustrates sleep and brain modifications in healthy and pathological aging.

5.1. Circadian Rhythms

MCI and AD patients show significantly disrupted sleep [137] and complain about poor sleep more frequently than healthy elderly (27.6% vs 18.3%; [138]). AD patients tend to spend more time awake during the night, due to increased sleep latency and higher frequency of nocturnal awakenings [139], thus resulting in more daytime sleepiness and decreased sleep efficiency [104,139]. Severe sleep fragmentation generally corresponds with the emergence of a syndrome called sundowning, that is characterized by behavioral symptoms such as hostility, anxiety, agitation, and confusion occurring at the end of the day, and has a great impact on cognitive skills and quality of life [140]. Visual hallucinations during wakefulness are also reported by AD patients. However, hallucinations are reported in one-third of the patients during specific phases of the sleep-wake cycle. Vivid dreams are also reported, together with aggressive sleep-related and dream-related behaviors [141].

Even before clinical onset, sleep disturbances have relevance to the development of cognitive dysfunctions. A previous study in community-based populations showed a link between delay and reduction of sleep-wake cycles and the probability of developing

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dementia [142]. Age-related sleep fragmentation is associated with a 1.5-fold increased risk of developing dementia in the following 6-year follow-up period [117,118]. Furthermore, a longitudinal cohort study showed that sleepiness is related to twice the risk of developing dementia [143], suggesting that daytime sleepiness is also a predisposing factor for developing dementia.

It has been argued whether part of these disruptions is caused by neuronal and synaptic loss occurring in the early clinical stages of dementia. An earlier study in AD showed that alterations of sleep-wake cycles are mainly mediated by degeneration of the SNC [144]. Stopa and colleagues determined that SNC is highly damaged in AD and that the astrocyte/neuron ratio is an accurate marker of SNC pathology [144]. Additionally, AD post-mortem studies have established that neurofibrillary tangles located in the hypothalamic preoptic area correlate with the severity of fragmented sleep [76]. Tau deposition is also present in the LC and the basal forebrain of healthy older adults [145]. It has been suggested that tau within these regions may trigger sleep disruptions years before symptomatic onset, and this may be used as an early diagnostic biomarker [104].

Changes in CSF melatonin levels are also a major cause of sleep pattern disruptions in AD patients. It was proposed that this may be due to modification in suprachiasmatic nucleus functionality [146], or due to alteration of melatonin secretion itself [147]. Sleep disruptions may also be linked to changes in CSF cortisol concentrations. MCI and AD patients show a significantly higher level of cortisol, strongly correlated with faster clinical worsening and cognitive decline [148]. Going further, pathophysiology seems to induce hypothalamic orexin neurodegeneration seen in later AD stages with consequences on sleep-wake rhythms [92]. In MCI and early AD, orexin levels are higher and predict longer sleep latency, more fragmented sleep, and shorter REM duration [100]. With disease progression, orexin levels decrease and are associated with more fragmented daytime wakefulness [149].

5.2. REM sleep

While REM sleep seems to be relatively preserved in normal aging, it is significantly reduced in AD patients [150] and characterized by shorter epochs [151]. AD patients also show a delayed REM sleep onset and a blunted rebound of REM sleep following selective deprivation [150,152]. It has been suggested that the specific degeneration of cholinergic neurons transmission in AD may constitute the basis of REM sleep changes [153]. The degree of basal forebrain atrophy is correlated with the degree of cortical Aβ burden, not only in MCI and AD patients but also in healthy elderly individuals [101]. Moreover, there is a general slowing of high-frequency oscillations in AD patients (for a review [154,155]). This phenomenon includes an increase in diffuse SWA and θ activity not only during wakefulness, but also during REM sleep [3,156,157], and this is larger in temporoparietal and frontal regions [151].

REM sleep can also predict neuropsychological impairment in older adults and AD patients [100]. It has also been shown that REM sleep has a role in emotional regulation and mood states. Thus, the manifestation of hostility, depression anxiety, emotional dysregulation, and memory retention impairment [158] could be attributed to poor REM sleep quality.

Therefore, a therapeutic intervention aiming at improving REM sleep quality is particularly important, due to the influence of REM sleep on cognition and mood. Cholinesterase inhibitors aimed at promoting REM sleep quality and duration and their efficacy predicts the degree of memory improvement in AD patients (see below; [159]).

5.3. Slow wave sleep

MCI patients show a decrease in time spent in NREM related to healthy elderly controls, which already have diminished SWA during normal aging [160]. NREM sleep progressively decreases after the onset and during illness progression [161]. Tau and Aβ protein levels measured in CSF predict the degree of reduced SWA time in AD patients, together with a drop in sleep efficiency and REM sleep duration [100]. SWA reduction strongly correlates with Aβ accumulation in the medial prefrontal cortex [92], which is one of the earliest regions damaged by Aβ plaques [162]. EEG slowing also predicts disrupted hippocampal memory consolidation [92]. New studies tried to find an answer to this apparent contradiction, explaining that SWA decrease may reflect changes in K-complexes. Following this explanation, <1Hz SWA would not change significantly from healthy age-matched subjects and AD patients, as previously shown.

5.4. Sleep spindles and K-complexes

AD patients show a dramatic reduction, over 40%, in Kc density compared to healthy elderly controls [163]. Normal aging is associated with a decrease in both spontaneous and evoked Kc, while AD patients present mainly a decrease of spontaneous Kc in the frontal cortex [150,164]. Lower Kc activity is also correlated with a lower Mini-Mental State Examination (MMSE) score [163]. AD patients showed faster mean θ frequency in both REM and SWS during post-learning sleep versus elderly controls. This significant difference was associated with the better delayed episodic recall, probably enabling a compensatory mechanism to sustain memory performance [165]. Similar to the reduction in Kc, various studies found a significant SS reduction in AD patients compared to healthy controls [17,150,164], mostly involving fast parietal spindle density [160]. Results suggest that pathology-related spindle alterations start in the early stages of the disease, possibly even in preclinical stages. In support of this theory, MCI patients often show a massive decrease in SS [166]. This reduction comes with cognitive deterioration in patients with dementia, as with many other specific disrupted EEG features. The relationship involves mostly fast central sleep spindles intensity and impaired immediate episodic recall in AD patients [167]. It has been suggested that thalamic damage [168] and disruptions in pathways of memory consolidation between the hippocampus and neocortical areas may account for spindle density drop.

5.5. Sleep disordered breathing and AD

Sleep disorders are often co-morbid with neurodegeneration. Over 60% of MCI/AD patients are diagnosed with at least one clinical sleep disorder, mostly SDB or insomnia, during illness progression [169]. Importantly, successful treatment of sleep disorders can delay MCI onset [170] and improves cognitive function when a patient is already in severe stages of AD [159].

There is a complex interaction between SDB and dementia. Although previous investigations showed an increased incidence of OSAS with aging, AD patients are particularly affected, with 40-70% having five or more apneas and hypopneas per hour of sleep [171,172]. A diagnosis of SDB is linked with a major risk of developing dementia [173]. Other studies found that SDB patients had an 85% increased risk to develop AD and MCI [174]. Furthermore, individuals with sleep apnea convert to MCI and AD more frequently and also at a younger age [170]. After clinical onset, AD stage, and SDB severity positively correlate, worsening together during progression [58].

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After the clinical onset of SDB, AD patients with a diagnosis of OSAS show sleep with less REM and SWS, and more frequent awakenings compared to AD patients without OSAS [175]. Frequent apneas and hypopneas during sleep are associated with deficits in memory, attention, and executive tasks. Some authors suggested that cognitive deterioration may be mediated by SDB's effect on daytime sleepiness [176]. Alternatively, SDB could also directly contribute to neuronal dysfunction through hypoxia, or it may be a consequence of AD-associated neurodegeneration in brainstem respiratory centers. Possible other explanations involve SDB's relation to increasing vascular risk, which is itself an independent risk factor for AD [177].

6. Sleep treatments in aging and AD

Along these lines, it has been suggested that treating sleep dysfunctions in young elderly and MCI patients could slow or prevent the progression of dementia [178]. Consolidating the sleep quality, increasing total sleep time and SWA have been reported to decrease the incidence of AD onset in the elderly community [117,118]. Current pharmacological therapies, such as cholinesterase inhibitors, hypnotic and antidepressants, can have important side effects in older individuals, for example impairing alertness, cognitive skills, and producing psychomotor effects; therefore, their use must be considered as a last resort (for a review see Ref. [179,180]). Therefore, the first line of treatment should prioritize a combination of sleep hygiene intervention and cognitive-behavioral therapy (CBT; [180]). It has been demonstrated that both interventions are highly effective and with no negative consequences [180]. Other combination therapies have been proposed, for example, bright light therapy with melatonin has been shown to stabilize the sleep/wake cycle. More recently, the application of Noninvasive Brain Stimulation, like transcranial electrical stimulation (tES) to manipulate SWS and sleep quality has been proposed as a promising intervention. In the following section, we will review evidence of innovative sleep therapies, discussing their efficacy in tackling sleep disruptions in healthy elderly and MCI/AD patients.

6.1. Pharmacological medications

Current pharmacological treatments in sleep disruptions are effective for transient insomnia and when sleep disruption is secondary to a pathology (for a comprehensive review see Ref. [181]). Chronic drug therapies can lead to serious adverse effects and tolerance development, frequently affecting daytime alertness and cognitive ability [182]. Pharmacological therapy should be considered only in situations where a definite medical condition is diagnosed, or where the use of the behavioral approach has failed.

6.1.1. Cholinesterase Inhibitors

Memory and vigilance impairments are largely caused by a disruption in the cholinergic transmission. The concentration of acetylcholine is high during wakefulness and REM sleep, while it declines during SWS [183]. It has been shown that the timing of administration of cholinesterase inhibitors plays a crucial role, morning administration causes less negative side effects (eg nightmares; [175,184,185]). While positive modifications in sleep patterns due to cholinesterase inhibitors are difficult to replicate, improvement in memory consolidation and clinical global functioning in AD seems to be significant [175,184,185].

6.1.2. Hypnotics, antidepressants, and antipsychotics

Although hypnotics, whether benzodiazepines (eg Triazolam, Estazolam, Lorazepam, Temazepam, Flurazepam, Quazepam) or non-benzodiazepines (eg Zaleplon, Zolpidem, Eszopiclone) are effective in accelerating sleep onset and prolong overall time asleep, their side effects can be detrimental. They drastically modify sleep microarchitecture and may cause confusion and ataxia during awake states. Benzodiazepines may even cause paradoxical effects in the elderly [157]. Non-benzodiazepines cause fewer negative side effects but in general, they are not generally recommended, except in cases of acute and severe insomnia [157].

Sedating antidepressants may be helpful in those clinical situations where sleep difficulties are caused by depressive symptoms. On the other hand, some of these drugs (eg Trazodone) have also been administered in neurodegenerative diseases, such as AD or Lewy body dementia without characteristic depressive symptoms. Antidepressants result in higher overall time spent asleep and greater sleep efficiency, although side effects, such as diurnal sleepiness and dizziness, must be considered. The first choice antidepressant should be Serotonin Selective Re-uptake inhibitors (SSRIs) for their relative safety [182], although also Trazodone or Mirtazapine proved to be effective to treat insomnia [186].

Antipsychotics are usually administered to treat behavioral and psychiatric manifestations of AD, but they seem to also be effective on insomnia. Atypical antipsychotics, such as risperidone, olanzapine, and quetiapine, should be preferred over typical antipsychotics though, as the latter may cause extrapyramidal effects [187]. Particular attention should be given to the administration of particular antipsychotics (eg quetiapine) also due to excessive diurnal sedation and increase the risk of falling [188].

6.2. Sleep hygiene and cognitive-behavioral therapy

Sleep hygiene is an intervention that manipulates daily habits to influence sleep quality by preserving a regular sleep/wake schedule (ie with the same rise time every day and avoiding diurnal nap) and reducing pre-sleep tension and sleep-onset latency [180]. Sleep hygiene might be facilitated by creating a non-disruptive sleep environment. For example, the use of earplugs and "white noise" in a dark and comfortable temperature room decreases nocturnal awakenings and arousals [180]. Physical exercise combined with a healthy diet is also an important contributing factor for efficient sleep hygiene. Locomotor activity in the daytime activates neuronal feedback loops in the SCN, and, as a result, the sleep/wake cycle is regulated [189].

Cognitive-behavioral therapy for insomnia (CBT-I) consists of six to ten sessions supervised by a trained therapist. CBT-I aims to change maladaptive behaviors and cognitive beliefs that perpetuate insomnia and includes relaxation techniques and tips to reduce the arousal before bedtime (eg avoiding watching TV, using smartphones in bed) [180]. Various studies in healthy elderly, MCI, and early-stage AD patients proved the high efficacy of CBT-I in improving sleep efficacy, prolonging TST, and shortening sleep-onset. Importantly, CBT-I results, unlike pharmacotherapy, last at least 6 months after the end of the treatment [190–192]. However, further studies need to clarify whether CBT-I is also able to modify physiological sleep oscillations (eg enhancing SWA) or to regulate Aβ regulation.

6.3. Melatonin

Although melatonin has no negative reactions, it is still unclear whether its administration causes significant and direct beneficial effects. Actigraphy, polysomnography, subjective reports, sleep logs, and clinical observations have been used to investigate melatonin's effects in both healthy subjects and subjects diagnosed with AD, with varied results; some studies did not find a significant improvement, while others found a significant effect of melatonin

Please cite this article as: Romanella SM et al., The Sleep Side of Aging and Alzheimer's Disease, Sleep Medicine, https://doi.org/10.1016/j.sleep.2020.05.029

as a hypnotic and circadian controller, mostly when in combination with Bright Light Therapy [6,193–196]. Importantly, a significant slowing in cognitive decline has been found in AD patients when treated with prolonged-release melatonin [197]. Furthermore, melatonin seems to protect against several mechanisms of neuronal death and able to prevent Aβ toxicity, an effect probably linked to its cytoprotective and antioxidant effects (for a review see Ref. [147]).

6.4. Bright light therapy

Elderly people tend to spend less time exposed to daylight, aggravating sleep problems. Bright light therapy (BLT) consists of exposing healthy elderly individuals and patients to light with the aid of a full spectrum lightbox for a minimum of 30 minutes per day, preferably during the morning. It has been shown that BLT results in a reduction in overnight awakenings, increased sleep consolidation, and increased TST [198]. Moreover, BLT also reduces daytime sleepiness and increases daytime alertness [198,199]. BLT efficacy is even greater when circadian rhythms are severely impaired. The combined administration of BLT and melatonin amplifies efficacy in more severely impaired subjects [6] while showing less improvement in subjects with less severe disturbances [200].

6.5. Auditory stimulation

Auditory stimulation is applied overnight during the N3 stage aiming to enhance <1Hz SWA with the rationale of regulating hippocampus-dependent memory consolidation and in sleep stabilization. A promising application is auditory closed-loop stimulation, where short auditory stimuli are presented at the same frequency as endogenous slow oscillations. Ngo and colleagues [201] used an auditory closed-loop feedback system based on an adaptive amplitude threshold method, to detect online SWA to send a brief auditory stimulation (50ms bursts of pink noise). While white noise has equal power per hertz throughout all frequencies, the power per hertz in pink noise decreases as the frequency increases, creating a deeper and more balanced sound. The authors demonstrated a significant increase of SWA, an enhancement of phase-locked spindle activity during slow oscillations up-state, and amelioration of memory performance after closed-loop auditory stimulation. These results were replicated in a subsequent study by the same group [202] and by other groups that used auditory closed-loop systems [203–205]. All these studies increased SWA in young adults during daytime naps, in contrast, Papalambros and colleagues (2017) tested an automated and adaptive algorithm in 13 older participants (60–84yo) during one night of acoustic stimulation and one night of sham stimulation in random order. Pulses of pink noise were administered during slow-wave upstate. Promisingly, the authors found an increase in SWA and spindle activity for the active stimulation intervals compared to sham intervals. Furthermore, verbal memory was tested before and after sleep and overnight improvement in word recall was significantly greater with acoustic stimulation compared to sham and was correlated with changes in SWA [7].

6.6. Noninvasive brain stimulation

NiBS techniques, such as transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS), and oscillatory transcranial direct current stimulation (otDCS), can improve sleep quality and, in turn, cognitive functioning by promoting sleep-dependent plasticity through the modulation of SWA. The idea of targeting slow oscillations during sleep is based on the long-established relationship between sleep and memory consolidation [112,206]. Two major pieces of evidence provide an insight into this tight connection. According to the active system consolidation model, during NREM sleep, declarative memory representations transition from a hippocampus-dependent state to a hippocampus-independent state [112]. As memories get consolidated in the neocortex through replay, the hippocampus frees space to encode new memories. SWS, spindles, and Sharp Wave Ripples (SWRs) play a major role in this consolidation process, as shown by the disruptive effects of spindles and SWRs blockage on memory consolidation and retention [207].

At the synaptic level, the synaptic homeostasis hypothesis (SHY) [208] argues that sleep is a necessary tool to maintain the brain plastic as it renormalizes the net synaptic strength potentiated by learning. By preventing the synaptic downscaling (decrease of strength), sleep deprivation would impair not only memory consolidation but even subsequent learning. Tangible indirect biological markers of the disruption of this sleep-wake dependent homeostatic regulation of synaptic strength are enhanced awake EEG θ activity, cortical excitability, and short-interval intracortical facilitation (a marker of synaptic strength). These would lead to deficient long-term potentiation inducibility and, ultimately, to cognitive impairment, two features that characterize AD pathology [209]. Despite the different perspectives taken by these theoretical accounts, both stress the pivotal importance of sleep for memory functioning, pushing researchers to target sleep to address memory impairment both in healthy and pathological populations. NiBS techniques are particularly promising tools as they can be safely used to directly enhance/disrupt oscillatory activity during sleep (tES) or to modulate the activity of one cortical area or more functionally connected regions by changing their excitability (repetitive Transcranial Magnetic Stimulation or rTMS).

Transcranial Electrical Stimulation. Two tES protocols seem to be particularly suitable for sleep modulation: tACS and otDCS. tACS delivers alternating current that continuously shifts between positive and negative voltages [210], thus inducing periodic shifts in the transmembrane potential, alternating depolarizing and hyperpolarizing effects, therefore, enabling the entrainment of intrinsic brain oscillations due to its sinusoidal waveform [211,212]. Differently, transcranial direct current stimulation (tDCS) sends a monophasic baseline voltage, modulating cortical tissue towards a subthreshold depolarization and therefore promoting endogenous oscillations (anodal) or hyperpolarization, suppressing it (cathodal; [212]. Oscillatory-tDCS combines the rhythmic oscillating current of tACS while still riding a directional voltage component, as tDCS creating an anodal or cathodal oscillating stimulation. In particular, these protocols drive cortical populations to oscillate at the same natural frequency as the one delivered by the stimulation itself, with a greater amplitude thanks to the resonance phenomenon. Marshall and coworkers (2006) administered anodal slow otDCS at 0.75Hz frequency over the prefrontal cortex (PFC) intending to interact with SWA during the N3 stage in young healthy participants. The author found a significant increase in δ power which was accompanied by a significant increase in declarative memory retention [10]. Some other attempts implemented innovative NiBS protocols, like the closed-loop system, to test the relationship between SWA and memory [8,9]. NiBS during sleep usually requires the experimenter to start the stimulation after 3-4 minutes of ongoing EEG typical of N2 or N3. A closed-loop algorithm can independently start the stimulation when the subject is in N3 [8,9,213]. This algorithm for augmentation of slow-wave sleep first detects the presence of SW oscillations, computing the mean of the power spectra of SW. The frequency of sinusoidal wave produced by tACS is then set to individualized SW frequency mean to match the stimulation frequency and phase with the natural ongoing SW

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activity. Further developments in transcranial stimulation protocols, and optimization and personalization of the current implemented, are necessary to precisely target SWA to study declarative memory consolidation (for a review of [214]).

Slow frequency otDCS mimicking slow-wave activity has been tested in older adults during afternoon naps. Westerberg targeted SWA with a subsequent improvement in word-pair performance [11], while Ladenbauer enhanced 1Hz oscillations and fast sleep spindles power, leading to a benefit in a visual memory task [215]. Other studies with slow-wave tACS and otDCS administered overnight in the elderly failed to replicate the beneficial enhancement of SWA and memory consolidation [216,217]. Authors found increased SWA and spindles activity, similar to previous results on young individuals, but no beneficial effects in the consolidation of visuospatial and verbal memories [217]. This may be due to crucial differences in overnight memory consolidation processes between young and aged individuals or differences in protocols (waveform of electrical stimulation).

Following a different lead, Marshall and colleagues found that θ-otDCS during REM sleep, instead of NREM, did not affect consolidation, yet causes a significant increase of γ power [218]. To date, during wakefulness, θ and γ oscillatory activity coupled during memory encoding/retrieval [219,220], while γ activity predominates during retrieval [221] and may play a role in memory consolidation during REM. Prominent REM θ rhythm coupled with γ have been seen in rodents [222,223] and monkeys [224]. γ seems to promote synaptic plasticity, supported by θ [46,47]. Stimulating θ and γ during REM may, therefore, help consolidate mnemonic traces as well as SWS stimulation.

Nonetheless, these promising findings need further studies with larger numbers of healthy participants and follow-ups, both during NREM and REM states. Interestingly, recent evidence encourages an experimental application in neurodegenerative diseases. Ladenbauer and colleagues (2017) enrolled 16 MCI amnestic patients in a crossover design. Patients were asked to sleep for 90 minutes while electrical stimulation was applied at 0.75 Hz over the prefrontal cortex. The authors found an enhancement of overall SWA and spindle power. Moreover, participants showed a significantly improved visual declarative memory during stimulation as compared with sham [225]. This study suggests that an individualized protocol may be effective to enhance the performance of visual declarative memory even in MCI patients.

Repetitive Transcranial Magnetic Stimulation. Compared to tES protocols, trains of TMS pulses (rTMS) can directly affect cortical neural plasticity by facilitating or preventing long-term potentiation (LTP) or long-term depression (LTD). This results in longer-lasting effects, which might help the patient comply with the treatment and enable off-line interventions. The literature on off-line rTMS extensively showed its feasibility in the treatment of several sleep disorders (for a recent review see Ref. [226]). Although rTMS during wakefulness does not directly elicit slow oscillations, evidence of endogenous SWA enhancement on the stimulated region during the subsequent sleep makes offline rTMS protocols a promising approach for addressing sleep disturbances in the long-term [227]. This possibility is particularly exciting also considering the positive effects of rTMS in promoting cognitive functioning in the elderly [228,229], and improving AD/MCI clinical outcomes [230,231]. Unfortunately, to the best of our knowledge, none of the published studies tacking cognitive impairment in AD or sleep disorder with rTMS included, respectively, an analysis of the subsequent sleep activity or a pre-post cognitive assessment. As more insights about the relationship between cognition and sleep could guide new interventions for AD, future investigations may further probe this relationship. New research on rTMS protocols in AD is also desirable to address some important safety concerns. Although rTMS is considered a safe tool [232], the lack of extensive knowledge of the biological mechanisms of rTMS may pose a threat to the AD population. As an example, basic research evidence showed that the release of Aβ is regulated by the amount of neural activity [233] and that low-frequency rTMS in AD-transgenic mice reduces amyloid secretion [234]. This raises doubts about the applicability of high-frequency rTMS to improve sleep and cognition in AD. Vice versa, the use of low-frequency rTMS to tackle Aβ deposition (that might also affect sleep quality) is challenged by a possible cognitive burden.

Differently from tES protocols that are feasible to use during sleep, rTMS 'online' interventions are currently limited by the device itself. In addition to the possibility of the machine overheating with prolonged use, rTMS also requires to keep the head in position for the entire protocol to precise target the region of stimulation. This requirement makes online rTMS protocols challenging even during a quiet night of sleep, and can, therefore, be prohibitive for both people suffering from sleep disorders (eg parasomnias), and the elderly population that is frequently affected by nocturia. Moreover, the noise produced by the coil (requiring earplugs/sound masking) can further disrupt sleep.

Despite these practical limitations that may hold back the researcher from studying the effects of TMS on the ongoing sleep oscillatory activity, the scant available evidence supports its online modulatory effects on SWA in the healthy population. Strong state-dependent slow oscillations can be elicited by single-pulse [235], paired-pulse with 100ms inter-stimulus-interval (ISI) [236] and rTMS delivered during NREM sleep [237]. Importantly, such response is amplified when delivered on the up-state (global depolarization) of the endogenous slow-wave, when the faster rhythms (spindles, gamma, and hippocampal ripples) are concentrated and the hippocampal-neocortex transfer of memories is thought to occur [238]. However, it is still unclear whether the externally triggered slow-oscillations could compensate or even replace the endogenous ones by producing the same beneficial effects on cognition.

7. Conclusions

In this review, we highlighted how sleep disturbances are a key factor impacting quality of life and cognition in normal aging, as well as a risk factor for MCI/AD development and prognosis. Earlier studies considered sleep abnormalities as a consequence of the neurodegenerative processes, while recent studies suggest that sleep degradation emerges in the prodromal phase, acting as both a risk factor and collateral cause of AD exacerbation. In this framework, finding reliable biomarkers in elderly individuals at risk, such as specific micro and macro-structural sleep features may potentially slow the progression of MCI to AD. Going further, the strong link between sleep abnormalities and Aβ/Tau protein accumulation suggests that sleep research might be pivotal in addressing AD pathogenesis and promoting healthy aging. Sleep research could guide the creation of rehabilitative and/or cognitive enhancement interventions to improve the quality of life of healthy elderly, detect individuals at risk, and even slow disease progression.

ACKNOWLEDGMENTS

Emiliano Santarnecchi is supported by the BROAD Institute at Harvard-MIT (Boston, MA, USA) via 2016P000351. Emiliano Santarnecchi is supported by Defence Advanced Research Projects Agency (DARPA) Emiliano Santarnecchi HR001117S0030. Emiliano Santarnecchi is supported by the Beth Israel Deaconess Medical Center (BIDMC) via the Chief Academic Officer (CAO) grant 2017 and by NIH via R01 AG060981-01. Emiliano Santarnecchi is

partially supported by R01 MH117063-01, P01 AG031720. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of Harvard University and its affiliated academic health care centers, the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2020.05.029.

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Please cite this article as: Romanella SM et al., The Sleep Side of Aging and Alzheimer's Disease, Sleep Medicine, https://doi.org/10.1016/j.sleep.2020.05.029

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Please cite this article as: Romanella SM et al., The Sleep Side of Aging and Alzheimer's Disease, Sleep Medicine, https://doi.org/10.1016/j.sleep.2020.05.029

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Please cite this article as: Romanella SM et al., The Sleep Side of Aging and Alzheimer's Disease, Sleep Medicine, https://doi.org/10.1016/j.sleep.2020.05.029