

# Sleep in the Aging Brain

Maurizio Gorgoni <sup>1</sup> and Luigi De Gennaro <sup>1,2,\*</sup><sup>1</sup> Department of Psychology, Sapienza University of Rome, 00185 Rome, Italy; maurizio.gorgoni@uniroma1.it<sup>2</sup> IRCCS Fondazione Santa Lucia, 00179 Rome, Italy

\* Correspondence: luigi.degennaro@uniroma1.it; Tel.: +39-06-4991-7647

**Abstract:** We have entered an era of a steep increase in the absolute and relative number of older people. This well-come phenomenon represents a major challenge for health care. However, maturational changes in sleep associated with aging do not easily appear as main factors, even though sleep alterations in the aging process lead to many detrimental consequences. In this editorial paper, we summarize the present knowledge about the main aging-related sleep modifications and their relevance for health problems and cognitive decline. Then, we present the papers published in the Special Issue “Disturbances of Sleep Among Older People”.

**Keywords:** sleep; aging; cognitive decline; Alzheimer’s disease; EEG; sleepiness; insomnia; obstructive sleep apnea; sleep oscillations; health care

We have entered an era of a steep increase in the absolute and relative number of older people. This welcome phenomenon represents a major challenge for health care, which has to sustain the ability to stay healthy at any age. A healthy status also includes keeping high cognitive and physical functioning, and avoiding or at least minimizing disease and disability.

Among the targets that may be of interest, the maturational changes of sleep associated with aging do not easily appear as a main factor. Still, abnormalities in this maturational process lead to many consequences, such as sleepiness, cognitive impairment, and several cardiovascular events, thus spreading disabilities all over the body. From this viewpoint, exploring the links between normal and pathological modifications of sleep and the brain appears to be of utmost importance to the promotion of successful aging.

Large changes in sleep pattern characterize the elderly population. Age-related modifications in the sleep architecture mainly include advanced sleep timing (i.e., anticipation of both night sleep onset and morning awakening), longer sleep latency, shorter sleep duration, reduced sleep efficiency (i.e., the ratio of time spent asleep to time spent in bed), decreased ability to maintain sleep (i.e., greater sleep fragmentation), increased time spent awake after sleep onset, and reduction of deeper non-REM (NREM) sleep and (to a lesser extent) REM sleep (for a review, see [1,2]). Moreover, the circadian rhythms and the sleep homeostatic process appear less robust with aging [2]. Daytime napping is more frequent in the elderly [3–5], and a large proportion of older adults experience excessive daytime sleepiness [3,6,7] albeit several studies suggest a reduced vulnerability to sleep pressure in older subjects [8–10].

The electrophysiology of sleep is also affected by age at a microstructural level. In particular, the strongest age-related modifications can be observed in NREM sleep hallmarks, with reduced density and amplitude of slow waves [11–14], K-complexes [15–18] and sleep spindles [19–21]. Phase-locked synchrony between slow waves and sleep spindles is also affected by age [22,23]. Many primary sleep disorders like insomnia, restless leg syndrome, REM behavior disorder and sleep-disordered breathing are more frequent in older adults [24,25].

**Citation:** Gorgoni, M.; De Gennaro, L. Sleep of Aging Brain. *Brain Sci.* **2021**, *11*, 229. <https://doi.org/10.3390/brainsci11020229>

Received: 29 January 2021

Accepted: 8 February 2021

Published: 12 February 2021

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

Overall, many indices of impaired quality and quantity of sleep characterize aging. Moreover, it is worth noting that different factors associated with aging can have a negative impact on sleep in the elderly, like medical and psychiatric disorders, or environmental, social and lifestyle modification [2].

Such substantial age-related deterioration of the sleep pattern should be considered in light of the association between sleep problems and health. Indeed, many studies found a relationship between sleep duration and/or quality and several health problems like adiposity/obesity [26–29], diabetes [30–33], cardiovascular disease [34–38], and mortality [39,40]. A recent meta-analysis found a relationship between short sleep and mortality outcome, diabetes, cardiovascular disease, coronary heart disease and obesity [41]. More recently, another meta-analysis showed that difficulty in the falling-asleep process and nonrestorative sleep were associated with increased risk of mortality, and particularly with cardiovascular disease mortality [42]. Moreover, such a relationship was restricted to the middle- to older-aged population [42]. Starting from these findings, research on the link between sleep and health in the elderly appears essential at a clinical level: wider attention to sleep habits and problems in older subjects may help prevent many health diseases.

The present literature also points to the role of age-related sleep deterioration in cognitive decline [1]. Sleep is essential for memory processes and plastic mechanisms, with a crucial role of different sleep electrophysiological hallmarks like slow-wave activity (SWA) and sleep spindles [43]. Several studies suggest a reduced association between slow-wave sleep and memory in older adults [44,45]. Moreover, the age-related impairment of NREM SWA in older subjects predicts decreased overnight sleep-dependent memory consolidation [14,46], in relation to medial prefrontal cortex grey-matter atrophy [14]. Similarly, the reduction of prefrontal sleep spindles in older adults explains the degree of impaired episodic memory [20]. Age-related deterioration of white matter fiber tracts is associated with reduced sleep spindles, and the level of deterioration predicts whether sleep spindles can promote motor memory consolidation [47]. Crucially, a growing body of evidence suggests that sleep disruption may represent a risk factor for Alzheimer's disease (AD) [48,49]. AD, the most common age-related neurodegenerative disorder, is characterized by further pervasive sleep impairment compared to healthy aging, with marked alterations of sleep architecture and sleep-wake cycle [50]. The preclinical stage of AD, called Mild Cognitive Impairment (MCI), is also associated with stronger sleep disruption than normal aging [51]. Moreover, several signs of altered NREM and REM sleep electrophysiology in AD and MCI have been observed [48,52–59]. While sleep alterations have often been considered merely a consequence of AD, recent findings point to a bidirectional relation between sleep and AD [48,60,61]. Indeed, sleep disruption is associated with AD biomarkers like  $\beta$ -amyloid and phosphorylated tau in humans [58,62–68] and animals [69–71]. Moreover,  $\beta$ -amyloid levels increase with time spent awake in mice, while the clearance of  $\beta$ -amyloid is predicted by NREM sleep [72,73]. Sleep deprivation and selective SWS disruption in humans induce an increase of the cerebrospinal fluid levels of  $\beta$ -amyloid [74–76]. Furthermore, the sleep-wake cycle modulates interstitial fluid levels of tau, and sleep deprivation increases the cerebrospinal and interstitial fluid level of tau and tau spreading [77]. At a longitudinal level, sleep disruption in healthy older humans is associated with AD pathology-related outcomes [78–82], and the proportion of NREM SWA <1 Hz and sleep efficiency selectively predict the following  $\beta$ -amyloid deposition over time [83]. Finally, sleep disruption induces systemic inflammation [61], which is often considered an early event in the AD pathology [84,85]. Overall, the present literature suggests that sleep alterations represent both a risk factor and a marker of AD, raising the possibility that sleep assessment and management may be considered essential for AD prevention, diagnosis and treatment [48,60].

The present collection of articles introduces some critical topics associated with sleep and aging. Bartolacci et al. [86] investigated the influence of sleep quality, vigilance, and sleepiness on driving-related cognitive abilities in older people to identify how sleepiness

and sleep quality predict their driving-related cognitive skills. While results confirm some maturational changes of aging (i.e., lower sleep efficiency and lower performance in attention and perception tests), these changes do not necessarily imply a worsened driving ability. In fact, older adults show poorer attentional performance and perception skills in driving tasks while accepting minor risk than younger subjects.

A large study in patients with obstructive sleep apnoea syndrome (OSAS) [87] also debunks another common opinion and shows that OSAS may not necessarily be linked to morning headaches (MH). MH has been considered to be a symptom of OSAS for more than a century. Still, this study suggests that most clinical measures of OSAS parameters are not significantly associated with the probability of MH.

Moving toward a public health perspective with specific attention devoted to healthy lifestyle, another study in a large sample of older individuals living in the insular Mediterranean region [88] shows that midday napping is associated with higher levels of successful aging. Along the same vein, 8.5 h of sleep per day in total, not necessarily slept all together, are associated with the best successful aging level. Another article [89] investigated social and health determinants of insomnia among economically disadvantaged African-American older adults. This study's merit consists of showing that financial difficulty, smoking, pain intensity, depression, and a higher number of chronic diseases predict insomnia symptom frequency and are associated with higher odds of possible clinical insomnia.

Although the state of the art of existing knowledge should be considered very preliminary, the last article of this collection [90] critically introduces promising techniques to modulate specific sleep characteristics (mostly slow oscillations) with the aim to improve sleep and induce cognitive benefits. This narrative review suggests that techniques with minimal invasiveness, like auditory stimulations delivered during sleep, may be capable of modulating sleep electrophysiology in the elderly population without impacting sleep architecture and the subjective quality of sleep. Although pioneering and very preliminary, these promising studies point to the feasibility and effectiveness of using closed-loop auditory stimulation systems in older people. This approach's relevance is even greater in light of the mounting evidence on the role of specific sleep changes in the preclinical stage of AD in predicting the onset of cognitive decline [60]. According to this view, the development of intervention strategies and specific techniques effective in modulating sleep electrophysiology may reduce risk factors for AD. This novel view fits with the general notion that some brain plasticity-dependent processes could be improved managing sleep quality, while monitoring EEG during sleep may help to explain how specific rehabilitative paradigms work [91].

We hope that these findings will stimulate interest for further basic and clinical investigations on the role of sleep in healthy and pathological aging, enhancing our knowledge on this research topic.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Mander, B.A.; Winer, J.R.; Walker, M.P. Sleep and human aging. *Neuron* **2017**, *94*, 19–36, doi:10.1016/j.neuron.2017.02.004.
- Li, J.; Vitiello, M.V.; Gooneratne, N. Sleep in normal aging. *Sleep Med. Clin.* **2018**, *13*, 1–11, doi:10.1016/j.jsmc.2017.09.001.
- Foley, D.J.; Vitiello, M.V.; Bliwise, D.L.; Ancoli-Israel, S.; Monjan, A.A.; Walsh, J.K. Frequent napping is associated with excessive daytime sleepiness, depression, pain, and nocturia in older adults: Findings from the National Sleep Foundation '2003 Sleep in America' Poll. *Am. J. Geriatr. Psychiatry* **2007**, *15*, 344–350.
- Fang, W.; Li, Z.; Wu, L.; Cao, Z.; Liang, Y.; Yang, H.; Wang, J.; Wu, T. Longer habitual afternoon napping is associated with a higher risk for impaired fasting plasma glucose and diabetes mellitus in older adults: Results from the Dongfeng–Tongji cohort of retired workers. *Sleep Med.* **2013**, *14*, 950–954.
- Milner, C.E.; Cote, K.A. Benefits of napping in healthy adults: Impact of nap length, time of day, age, and experience with napping. *J. Sleep Res.* **2009**, *18*, 272–281.
- Whitney, C.W.; Enright, P.L.; Newman, A.B.; Bonekat, W.; Foley, D.; Quan, S.F. Correlates of daytime sleepiness in 4578 elderly persons: The Cardiovascular Health Study. *Sleep* **1998**, *21*, 27–36.
- Jausent, I.; Bouyer, J.; Ancelin, M.L.; Berr, C.; Foubert-Samier, A.; Ritchie, K.; Ohayon, M.M.; Besset, A.; Dauvilliers, Y. Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep* **2012**, *35*, 1201–1207, doi:10.5665/sleep.2070.
- Adam, M.; Rétey, J.V.; Khatami, R.; Landolt, H.P. Age-related changes in the time course of vigilant attention during 40 hours without sleep in men. *Sleep* **2006**, *29*, 55–57, doi:10.1093/sleep/29.1.55.
- Duffy, J.F.; Willson, H.J.; Wang, W.; Czeisler, C.A. Healthy older adults better tolerate sleep deprivation than young adults. *J. Am. Geriatr. Soc.* **2009**, *57*, 1245–1251, doi:10.1111/j.1532-5415.2009.02303.x.
- Philip, P.; Taillard, J.; Sagaspe, P.; Valtat, C.; Sanchez-Ortuno, M.; Moore, N.; Charles, A.; Bioulac, B. Age, performance and sleep deprivation. *J. Sleep Res.* **2004**, *13*, 105–110, doi:10.1111/j.1365-2869.2004.00399.x62.
- Dijk, D.J.; Beersma, D.G.M.; Van Den Hoofdakker, R.H. All night spectral analysis of EEG sleep in young adult and middle-aged subjects. *Neurobiol. Aging* **1989**, *10*, 677–682, doi:10.1016/0197-4580(89)90004-3.
- Landolt, H.P.; Dijk, D.J.; Achermann, P.; Borbély, A.A. Effect of age on the sleep EEG: Slow-wave activity and spindle frequency activity in young and middle-aged men. *Brain Res.* **1996**, *738*, 205–212, doi:10.1016/s0006-8993(96)00770-6.
- Carrier, J.; Land, S.; Buysse, D.J.; Kupfer, D.J.; Monk, T.H. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology* **2001**, *38*, 232–242, doi:10.1111/1469-8986.3820232.
- Mander, B.A.; Rao, V.; Lu, B.; Saletin, J.M.; Lindquist, J.R.; Ancoli-Israel, S.; Jagust, W.; Walker, M.P. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat. Neurosci.* **2013**, *16*, 357–364, doi:10.1038/nn.3324.
- Crowley, K.; Trinder, J.; Colrain, I.M. An examination of evoked K-complex amplitude and frequency of occurrence in the elderly. *J. Sleep Res.* **2002**, *11*, 129–140.
- Crowley, K.; Trinder, J.; Kim, Y.; Carrington, M.; Colrain, I.M. The effects of normal aging on sleep spindle and K-complex production. *Clin. Neurophysiol.* **2002**, *113*, 1615–1622.
- Crowley, K.; Trinder, J.; Colrain, I.M. Evoked K-complex generation: The impact of sleep spindles and age. *Clin. Neurophysiol.* **2004**, *115*, 471–476.
- Kubicki, S.; Scheuler, W.; Jobert, M.; Pastelak-Price, C. The effect of age on sleep spindle and K complex density. *EEG EMG Z. Elektroenzephalogr. Elektromyogr. Verwandte Geb.* **1989**, *20*, 59–63.
- De Gennaro, L.; Ferrara, M. Sleep spindles: An overview. *Sleep Med. Rev.* **2003**, *7*, 423–440, doi:10.1053/smr.2002.0252.
- Mander, B.A.; Rao, V.; Lu, B.; Saletin, J.M.; Ancoli-Israel, S.; Jagust, W.J.; Walker, M.P. Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. *Cereb. Cortex* **2014**, *24*, 3301–3309, doi:10.1093/cercor/bht188.
- Martin, N.; Lafortune, M.; Godbout, J.; Barakat, M.; Robillard, R.; Poirier, G.; Bastien, C.; Carrier, J. Topography of age-related changes in sleep spindles. *Neurobiol. Aging* **2013**, *34*, 468–476, doi:10.1016/j.neurobiolaging.2012.05.020.
- Helfrich, R.F.; Mander, B.A.; Jagust, W.J.; Knight, R.T.; Walker, M.P. Old brains come uncoupled in sleep: Slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron* **2018**, *97*, 221–230, doi:10.1016/j.neuron.2017.11.020.
- Muehlroth, B.E.; Sander, M.C.; Fandakova, Y.; Grandy, T.H.; Rasch, B.; Shing, Y.L.; Werkle-Bergner, M. Precise slow oscillation-spindle coupling promotes memory consolidation in younger and older adults. *Sci. Rep.* **2019**, *9*, 1940, doi:10.1038/s41598-018-36557-z.
- Crowley, K. Sleep and sleep disorders in older adults. *Neuropsychol. Rev.* **2011**, *21*, 41–53.
- Rissling, M.; Ancoli-Israel, S. Sleep in aging. In *The Neuroscience of Sleep*; Stickgold, R., Walker, M.P., Eds.; Academic Press: London, UK, 2009; pp. 78–84.
- Knutson, K.L. Does inadequate sleep play a role in vulnerability to obesity? *Am. J. Hum. Biol.* **2012**, *24*, 361–371, doi:10.1002/ajhb.22219.
- Watanabe, M.; Kikuchi, H.; Tanaka, K.; Takahashi, M. Association of short sleep duration with weight gain and obesity at 1-year follow-up: A large-scale prospective study. *Sleep* **2010**, *33*, 161–167, doi:10.1093/sleep/33.2.161.
- Chaput, J.P.; Bouchard, C.; Tremblay, A. Change in sleep duration and visceral fat accumulation over 6 years in adults. *Obesity* **2014**, *22*, E9–E12, doi:10.1002/oby.20701.
- Chaput, J.P.; Despres, J.P.; Bouchard, C.; Tremblay, A. The association between sleep duration and weight gain in adults: A 6-year prospective study from the Quebec Family Study. *Sleep* **2008**, *31*, 517–523, doi:10.1093/sleep/31.4.517.

30. Barone, M.T.; Menna-Barreto, L. Diabetes and sleep: A complex cause-and-effect relationship. *Diabetes Res. Clin. Pr.* **2011**, *91*, 129–137, doi:10.1016/j.diabres.2010.07.011.
31. Bopparaju, S.; Surani, S. Sleep and diabetes. *Int. J. Endocrinol.* **2010**, *2010*, 759509, doi:10.1155/2010/759509.
32. Zizi, F.; Jean-Louis, G.; Brown, C.D.; Ogedegbe, G.; Boutin-Foster, C.; McFarlan, S.I. Sleep duration and the risk of diabetes mellitus: Epidemiologic evidence and pathophysiologic insights. *Curr. Diabetes Rep.* **2010**, *10*, 43–47, doi:10.1007/s11892-009-0082-x.
33. Shan, Z.; Ma, H.; Xie, M.; Yan, P.; Guo, Y.; Bao, W.; Rong, Y.; Jackson, C.L.; Hu, F.B.; Liu, L. Sleep duration and risk of type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care* **2015**, *38*, 529–537, doi:10.2337/dc14-2073.
34. Grandner, M.A.; Chakravorty, S.; Perlis, M.L.; Oliver, L.; Gurubhagavatula, I. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. *Sleep Med.* **2014**, *15*, 42–50, doi:10.1016/j.sleep.2013.09.012.
35. Altman, N.G.; Schopfer, E.; Jackson, N.; Izci-Balaserak, B.; Rattanaumpawan, P.; Gehrman, P.R.; Patel, N.P.; Grandner, M.A. Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. *Sleep Med.* **2012**, *13*, 1261–1270, doi:10.1016/j.sleep.2012.08.005.
36. Meng, L.; Zheng, Y.; Hui, R. The relationship of sleep duration and insomnia to risk of hypertension incidence: A meta-analysis of prospective cohort studies. *Hypertens. Res.* **2013**, *36*, 985–995, doi:10.1038/hr.2013.70.
37. King, C.R.; Knutson, K.L.; Rathouz, P.J.; Sidney, S.; Liu, K.; Lauderdale, D.S. Short sleep duration and incident coronary artery calcification. *JAMA* **2008**, *300*, 2859–2866, doi:10.1001/jama.2008.867.
38. Cappuccio, F.P.; Cooper, D.; D’Elia, L.; Strazzullo, P.; Miller, M.A. Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *Eur. Heart J.* **2011**, *32*, 1484–1492, doi:10.1093/eurheartj/ehr007.
39. Gallicchio, L.; Kalesan, B. Sleep duration and mortality: A systematic review and meta-analysis. *J. Sleep Res.* **2009**, *18*, 148–158, doi:10.1111/j.1365-2869.2008.00732.x.
40. Cappuccio, F.P.; D’Elia, L.; Strazzullo, P.; Miller, M.A. Sleep duration and all-cause mortality: A systematic review and meta-analysis of prospective studies. *Sleep* **2010**, *33*, 585–592, doi:10.1093/sleep/33.5.585.
41. Itani, O.; Jike, M.; Watanabe, N.; Kaneita, Y. Short sleep duration and health outcomes: A systematic review, meta-analysis, and meta-regression. *Sleep Med.* **2017**, *32*, 246–256, doi:10.1016/j.sleep.2016.08.006.
42. Ge, L.; Guyatt, G.; Tian, J.; Pan, B.; Chang, Y.; Chen, Y.; Li, H.; Zhang, J.; Li, Y.; Ling, J.; et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. *Sleep Med. Rev.* **2019**, *48*, 101215, doi:10.1016/j.smr.2019.101215.
43. Klinzing, J.G.; Niethard, N.; Born, J. Mechanisms of systems memory consolidation during sleep. *Nat. Neurosci.* **2019**, *22*, 1598–1610, doi:10.1038/s41593-019-0467-3.
44. Scullin, M.K. Sleep, memory, and aging: The link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychol. Aging* **2013**, *28*, 105–114, doi:10.1037/a0028830.
45. Baran, B.; Mantua, J.; Spencer, R.M. Age-related Changes in the Sleep-dependent Reorganization of Declarative Memories. *J. Cogn. Neurosci.* **2016**, *28*, 792–802, doi:10.1162/jocn\_a\_00938.
46. Varga, A.W.; Ducca, E.L.; Kishi, A.; Fischer, E.; Parekh, A.; Koushyk, V.; Yau, P.L.; Gumb, T.; Leibert, D.P.; Wohlleber, M.E.; et al. Effects of aging on slow-wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol. Aging* **2016**, *42*, 142–149, doi:10.1016/j.neurobiolaging.2016.03.008.
47. Mander, B.A.; Zhu, A.H.; Lindquist, J.R.; Villeneuve, S.; Rao, V.; Lu, B.; Saletin, J.M.; Ancoli-Israel, S.; Jagust, W.J.; Walker, M.P. White matter structure in older adults moderates the benefit of sleep spindles on motor memory consolidation. *J. Neurosci.* **2017**, *37*, 11675–11687, doi:10.1523/jneurosci.3033-16.2017.
48. Mander, B.A.; Winer, J.R.; Jagust, W.J.; Walker, M.P. Sleep: A novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer’s disease? *Trends Neurosci.* **2016**, *39*, 552–566, doi:10.1016/j.tins.2016.05.002.
49. Cordone, S.; De Gennaro, L. Insights from human sleep research on neural mechanisms of Alzheimer’s disease. *Neural Regen. Res.* **2020**, *15*, 1251–1252, doi:10.4103/1673-5374.272579.
50. Peter-Derex, L.; Yammine, P.; Bastuji, H.; Croisile, B. Sleep and Alzheimer’s disease. *Sleep Med. Rev.* **2015**, *19*, 29–38, doi:10.1016/j.smr.2014.03.007.
51. D’Rozario, A.L.; Chapman, J.L.; Phillips, C.L.; Palmer, J.R.; Hoyos, C.M.; Mowszowski, L.; Duffy, S.L.; Marshall, N.S.; Benca, R.; Mander, B.; et al. Objective measurement of sleep in mild cognitive impairment: A systematic review and meta-analysis. *Sleep Med. Rev.* **2020**, *52*, 101308, doi:10.1016/j.smr.2020.101308.
52. Hassainia, F.; Petit, D.; Neilsen, T.; Gauthier, S.; Montplaisir, J. Quantitative EEG and statistical mapping of wakefulness and REM sleep in the evaluation of mild to moderate Alzheimer’s disease. *Eur. Neurol.* **1997**, *37*, 219–224, doi:10.1159/000117446.
53. Petit, D.; Gagnon, J.F.; Fantini, M.L.; Ferini-Strambi, L.; Montplaisir, J. Sleep and quantitative EEG in neurodegenerative disorders. *J. Psychosom. Res.* **2004**, *56*, 487–496, doi:10.1016/j.jpsychores.2004.02.001.
54. Rauchs, G.; Schabus, M.; Parapatics, S.; Bertran, F.; Clochon, P.; Hot, P.; Denise, P.; Desgranges, B.; Eustache, F.; Gruber, G.; et al. Is there a link between sleep changes and memory in Alzheimer’s disease? *Neuroreport* **2008**, *19*, 1159–1162.
55. Gorgoni, M.; Lauri, G.; Truglia, I.; Cordone, S.; Sarasso, S.; Scarpelli, S.; Mangiaruga, A.; D’Atri, A.; Tempesta, D.; Ferrara, M.; et al. Parietal fast sleep spindle density decrease in Alzheimer’s disease and amnesic mild cognitive impairment. *Neural Plast.* **2016**, *2016*, 8376108, doi:10.1155/2016/8376108.
56. De Gennaro, L.; Gorgoni, M.; Reda, F.; Lauri, G.; Truglia, I.; Cordone, S.; Scarpelli, S.; Mangiaruga, A.; D’Atri, A.; Lacidogna, G.; et al. The Fall of Sleep K-Complex in Alzheimer Disease. *Sci. Rep.* **2017**, *7*, 39688, doi:10.1038/srep39688.

57. Reda, F.; Gorgoni, M.; Lauri, G.; Truglia, I.; Cordone, S.; Scarpelli, S.; Mangiaruga, A.; D'Atri, A.; Ferrara, M.; Lacidogna, G.; et al. In Search of Sleep Biomarkers of Alzheimer's Disease: K-Complexes Do Not Discriminate between Patients with Mild Cognitive Impairment and Healthy Controls. *Brain Sci.* **2017**, *7*, 51, doi:10.3390/brainsci7050051.
58. Lucey, B.P.; Mccullough, A.; Landsness, E.C.; Toedebusch, C.D.; Mcleland, J.S.; Zaza, A.M.; Fagan, A.M.; McCue, L.; Xiong, C.; Morris, J.C.; et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci. Transl. Med.* **2019**, *11*, eaau6550, doi:10.1126/scitranslmed.aau6550.
59. Liu, S.; Pan, J.; Tang, K.; Lei, Q.; He, L.; Meng, Y.; Cai, X.; Li, Z. Sleep spindles, K-complexes, limb movements and sleep stage proportions may be biomarkers for amnesic mild cognitive impairment and Alzheimer's disease. *Sleep Breath.* **2020**, *24*, 637–651, doi:10.1007/s11325-019-01970-9.
60. Cordone, S.; Annarumma, L.; Rossini, P.M.; De Gennaro, L. Sleep and  $\beta$ -amyloid deposition in Alzheimer disease: Insights on mechanisms and possible innovative treatments. *Front. Pharmacol.* **2019**, *10*, 695, doi:10.3389/fphar.2019.00695.
61. Irwin, M.R.; Vitiello, M.V. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol.* **2019**, *18*, 296–306, doi:10.1016/S1474-4422(18)30450-2.
62. Liguori, C.; Romigi, A.; Nuccetelli, M.; Zannino, S.; Sancesario, G.; Martorana, A.; Albanese, M.; Mercuri, N.B.; Izzi, F.; Bernardini, S.; et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurol.* **2014**, *71*, 1498–1505, doi:10.1001/jamaneurol.2014.2510.
63. Mander, B.A.; Marks, S.M.; Vogel, J.W.; Rao, V.; Lu, B.; Saletin, J.M.; Ancoli-Israel, S.; Jagust, W.J.; Walker, M.P.  $\beta$ -amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat. Neurosci.* **2015**, *18*, 1051–1057, doi:10.1038/nn.4035.
64. Spira, A.P.; Gamaldo, A.A.; An, Y.; Wu, M.N.; Simonsick, E.M.; Bilgel, M.; Zhou, Y.; Wong, D.F.; Ferrucci, L.; Resnick, S.M. Self-reported sleep and  $\beta$ -amyloid deposition in community-dwelling older adults. *JAMA Neurol.* **2013**, *70*, 1537–1543, doi:10.1001/jamaneurol.2013.4258.
65. Sprecher, K.E.; Bendlin, B.B.; Racine, A.M.; Okonkwo, O.C.; Christian, B.T.; Kosciak, R.L.; Sager, M.A.; Asthana, S.; Johnson, S.C.; Benca, R.M. Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. *Neurobiol. Aging* **2015**, *36*, 2568–2576, doi:10.1016/j.neurobiolaging.2015.05.004.
66. Sprecher, K.E.; Kosciak, R.L.; Carlsson, C.M.; Zetterberg, H.; Blennow, K.; Okonkwo, O.C.; Sager, M.A.; Asthana, S.; Johnson, S.C.; Benca, R.M.; et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology* **2017**, *89*, 445–453, doi:10.1212/WNL.0000000000004171.
67. Varga, A.W.; Wohlleber, M.E.; Giménez, S.; Romero, S.; Alonso, J.F.; Ducca, E.L.; Kam, K.; Lewis, C.; Tanzi, E.B.; Tweardy, S.; et al. Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid A $\beta$ 42 Levels in Cognitively Normal Elderly. *Sleep* **2016**, *39*, 2041–2048, doi:10.5665/sleep.6240.
68. Winer, J.R.; Mander, B.A.; Helfrich, R.F.; Maass, A.; Harrison, T.M.; Baker, S.L.; Knight, R.T.; Jagust, W.J.; Walker, M.P. Sleep as a Potential Biomarker of Tau and  $\beta$ -Amyloid Burden in the Human Brain. *J. Neurosci.* **2019**, *39*, 6315–6324, doi:10.1523/JNEUROSCI.0503-19.2019.
69. Roh, J.H.; Huang, Y.; Bero, A.W.; Kasten, T.; Stewart, F.R.; Bateman, R.J.; Holtzman, D.M. Disruption of the sleep-wake cycle and diurnal fluctuation of  $\beta$ -amyloid in mice with Alzheimer's disease pathology. *Sci. Transl. Med.* **2012**, *4*, 150ra122, doi:10.1126/scitranslmed.3004291.
70. Menkes-Caspi, N.; Yamin, H.G.; Kellner, V.; Spires-Jones, T.L.; Cohen, D.; Stern, E.A. Pathological Tau disrupts ongoing network activity. *Neuron* **2015**, *85*, 959–966, doi:10.1016/j.neuron.2015.01.025.
71. Holth, J.K.; Mahan, T.E.; Robinson, G.O.; Rocha, A.; Holtzman, D.M. Altered sleep and EEG power in the P301S Tau transgenic mouse model. *Ann. Clin. Neurol.* **2017**, *4*, 180–190, doi:10.1002/acn3.390.
72. Kang, J.E.; Lim, M.M.; Bateman, R.J.; Lee, J.J.; Smyth, L.P.; Cirrito, J.R.; Fujiki, N.; Nishino, S.; Holtzman, D.M. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* **2009**, *326*, 1005–1007, doi:10.1126/science.1180962.
73. Xie, L.; Kang, H.; Xu, Q.; Chen, M.J.; Liao, Y.; Thiyagarajan, M.; O'Donnell, J.; Christensen, D.J.; Nicholson, C.; Iliff, J.J.; et al. Sleep drives metabolite clearance from the adult brain. *Science* **2013**, *342*, 373–377, doi:10.1126/science.1241224.
74. Ju, Y.S.; Ooms, S.J.; Sutphen, C.; Macauley, S.L.; Zangrilli, M.A.; Jerome, G.; Fagan, A.M.; Mignot, E.; Zempel, J.M.; Claassen, J.A.H.R.; et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid- $\beta$  levels. *Brain* **2017**, *140*, 2104–2111, doi:10.1093/brain/awx148.
75. Lucey, B.P.; Hicks, T.J.; McLeland, J.S.; Toedebusch, C.D.; Boyd, J.; Elbert, D.L.; Patterson, B.W.; Baty, J.; Morris, J.C.; Ovod, V.; et al. Effect of sleep on overnight cerebrospinal fluid amyloid  $\beta$  kinetics. *Ann. Neurol.* **2018**, *83*, 197–204, doi:10.1002/ana.25117.
76. Ooms, S.; Overeem, S.; Besse, K.; Rikkert, M.O.; Verbeek, M.; Claassen, J.A. Effect of 1 night of total sleep deprivation on cerebrospinal fluid  $\beta$ -amyloid 42 in healthy middle-aged men: A randomized clinical trial. *JAMA Neurol.* **2014**, *71*, 971–977, doi:10.1001/jamaneurol.2014.1173.
77. Holth, J.K.; Fritschi, S.K.; Wang, C.; Pedersen, N.P.; Cirrito, J.R.; Mahan, T.E.; Finn, M.B.; Manis, M.; Geerling, J.C.; Fuller, P.M.; et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* **2019**, *363*, 880–884, doi:10.1126/science.aav2546.
78. Sexton, C.E.; Storsve, A.B.; Wallhovd, K.B.; Johansen-Berg, H.; Fjell, A.M. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology* **2014**, *83*, 967–973, doi:10.1212/WNL.0000000000000774.

79. Benedict, C.; Byberg, L.; Cedernaes, J.; Hogenkamp, P.S.; Giedratis, V.; Kilander, L.; Lind, L.; Lannfelt, L.; Schiöth, H.B. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimer's Dement.* **2015**, *11*, 1090–1097, doi:10.1016/j.jalz.2014.08.104.
80. Lim, A.S.; Kowgier, M.; Yu, L.; Buchman, A.S.; Bennett, D.A. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* **2013**, *36*, 1027–1032, doi:10.5665/sleep.2802.
81. Lim, A.S.; Yu, L.; Kowgier, M.; Schneider, J.A.; Buchman, A.S.; Bennett, D.A. Modification of the relationship of the apolipoprotein E  $\epsilon$ 4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol.* **2013**, *70*, 1544–1551, doi:10.1001/jamaneurol.2013.4215.
82. Lysen, T.S.; Luik, A.I.; Ikram, M.K.; Tiemeier, H.; Ikram, M.A. Actigraphy-estimated sleep and 24-hour activity rhythms and the risk of dementia. *Alzheimer's Dement.* **2020**, *16*, 1259–1267, doi:10.1002/alz.12122.
83. Winer, J.R.; Mander, B.A.; Kumar, S.; Reed, M.; Baker, S.L.; Jagust, W.J.; Walker, M.P. Sleep Disturbance Forecasts  $\beta$ -Amyloid Accumulation across Subsequent Years. *Curr. Biol.* **2020**, *30*, 4291–4298, doi:10.1016/j.cub.2020.08.017.
84. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune attack: The role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **2015**, *16*, 358–372, doi:10.1038/nrn3880.
85. Wood, H. Dementia: Peripheral inflammation could be a prodromal indicator of dementia. *Nat. Rev. Neurosci.* **2018**, *14*, 127, doi:10.1038/nrneurol.2018.8.
86. Bartolacci, C.; Scarpelli, S.; D'Atri, A.; Gorgoni, M.; Annarumma, L.; Cloos, C.; Giannini, A.M.; De Gennaro, L. The Influence of Sleep Quality, Vigilance, and Sleepiness on Driving-Related Cognitive Abilities: A Comparison between Young and Older Adults. *Brain Sci.* **2020**, *10*, 327, doi:10.3390/brainsci10060327.
87. Spałka, J.; Kędzia, K.; Kuczyński, W.; Kudrycka, A.; Małolepsza, A.; Białasiewicz, P.; Mokros, Ł. Morning Headache as an Obstructive Sleep Apnea-Related Symptom among Sleep Clinic Patients—A Cross-Section Analysis. *Brain Sci.* **2020**, *10*, 57, doi:10.3390/brainsci10010057.
88. Foscolou, A.; D'Cunha, N.M.; Naumovski, N.; Tyrovolas, S.; Rallidis, L.; Matalas, A.-L.; Polychronopoulos, E.; Sidossis, L.S.; Panagiotakos, D. Midday Napping and Successful Aging in Older People Living in the Mediterranean Region: The Epidemiological Mediterranean Islands Study (MEDIS). *Brain Sci.* **2020**, *10*, 14, doi:10.3390/brainsci10010014.
89. Bazargan, M.; Mian, N.; Cobb, S.; Vargas, R.; Assari, S. Insomnia Symptoms among African-American Older Adults in Economically Disadvantaged Areas of South Los Angeles. *Brain Sci.* **2019**, *9*, 306, doi:10.3390/brainsci9110306.
90. Salfi, F.; D'Atri, A.; Tempesta, D.; De Gennaro, L.; Ferrara, M. Boosting Slow Oscillations during Sleep to Improve Memory Function in Elderly People: A Review of the Literature. *Brain Sci.* **2020**, *10*, 300, doi:10.3390/brainsci10050300.
91. Gorgoni, M.; D'Atri, A.; Lauri, G.; Rossini, P.M.; Ferlazzo, F.; De Gennaro, L. Is sleep essential for neural plasticity in humans, and how does it affect motor and cognitive recovery? *Neural Plast.* **2013**, 103949, doi:10.1155/2013/103949.