REVIEWS

Sleep Science

Sleep and the aging brain. A multifaceted approach

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ABSTRACT

In the current review we provide a theoretical background on studies examining the association between sleep and brain function. We focus on the association between sleep and cognitive performance, cognitive changes over time and incident dementia as well. We then present some data on the link between sleep and subjective cognitive complaints, in participants without any objective clinical cognitive decline. We conclude with investigating the association between sleep and brain biomarkers, by highlighting the importance of specific genes and specific brain regions' morphometry. The role of sleep is vital in maintaining a healthy aging brain, and multiple factors should be taken under account when investigating this association.

Keywords: Sleep; Cognition; Dementia; Brain; Aging.

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Changes in sleep patterns are common among the aging population. Approximately 5% of older adults meet the criteria for clinically significant insomnia disorders and 20% for sleep apnea syndromes[1]. Self-reported sleep problems seem to reflect poor overall quality of sleep, which in turn has been associated with changes in cognition[2-6]. Some cross-sectional studies have reported that sleep problems, especially daytime sleepiness, are related to poor cognitive function[7-9]. For example, excessive daytime sleepiness has been associated with impaired memory, orientation, and attention[8]. Narcolepsy also, which is linked to daytime sleepiness, has been associated with executive control deficits in different studies, however, as most of the narcoleptic patients are under treatment, it is difficult to clarify the directionality and the exact power of the results[10].

Although a number of cross-sectional studies have investigated the relationship between sleep problems and cognitive functioning in older adults, there is a relative paucity of longitudinal research on this relationship[11-16]. From the few longitudinal studies that do exist, findings suggest that self-reported daytime sleepiness, in particular, is a major risk factor for[11], and a possible early marker of cognitive decline[12]. Some results of the existing longitudinal literature, however, are contradictory. No longitudinal association between self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women was reported in one study[17]. Also, on a different study, results about the association between sleep problems and cognitive decline did not survive after controlling for depression[11].

Many of the previous longitudinal studies have some apparent research gaps. For example, it is unclear whether sleep problems are related to specific cognitive abilities, as most of the existing studies used short global measures of cognitive function[13,16,18] or a telephone-based screening battery[19-21]. One large longitudinal study that did investigate the association of sleep with a specific cognitive domain (i.e. memory) used a single memory test (i.e. Delayed Word Recall Test) in addition to the Mini Mental State Examination (MMSE)[22], which may not provide a complete picture of cognitive function. Furthermore, many of the previous longitudinal studies did not include a comprehensive clinical evaluation. Some of the studies had also a relatively small sample size[13,23,24] or used specific sex-groups, i.e. only male participants[15,25], limiting the generalizability of the results.

Our group examined the association between self-reported sleep problems and cognition, both cross-sectionally and longitudinally in a large sample of older adults. Sleep was measured by the Medical Outcomes Study-Sleep Scale (MOS-SS), while cognition was examined through an extensive neuropsychological evaluation. Results indicated that daytime sleepiness was linked to slow speed of processing cross-sectionally but also after a 3.2 years follow-up[26]. This relationship did not change even after excluding demented participants at baseline, indicating that specific sleep problems such as increased daytime sleepiness can be an early sign of cognitive decline in the elderly. We also examined the above cross-sectional association in a different group of older adults, with a different geographical background (Greece) but with a similar study design. Poor sleep quality, as a general sleep problems variable, and long sleep duration appeared to be associated with poor memory performance in older adults, even after excluding the participants with dementia or Mild Cognitive Impairment (MCI)[27].

After examining the association between sleep and cognition/cognitive changes over time, a question that arises is what is the relationship between sleep problems and incident dementia. Daytime sleepiness has been associated with incident dementia in several longitudinal studies[19,28-30]. Another study found that daytime sleepiness predicted vascular dementia in a sample of older men[30]. In addition, 'sleep fragmentation' (high activity during sleep) has been linked to incident Alzheimer's disease (AD)[23] in older adults. Prolonged sleep duration has been also linked to an increased risk of dementia in a large population based study[31]. A specific meta-analysis suggests insomnia to be a risk factor for AD, while Sleep-Disordered Breathing (SDB) to be a risk factor for not only AD, but also vascular and all-cause dementia[32]. Examination of the above association in our large multiethnic group of cognitively normal older adults, showed that 7.2% of the participants became demented in a 3-year follow-up. Daytime sleepiness and sleep inadequacy appeared to be significant risk factors for developing dementia, even after adjusting for multiple demographic factors and comorbidities[33].

Based on the existing literature, we conclude that sleep problems are associated with cognition, cognitive changes over time and incident dementia as well. Multiple clinical, neurobiological, and demographic factors could play a significant role to these links. Disrupted circadian rhythms could affect both sleep regulation and cognitive performance[34,35]. Amyloid-β deposition, especially in cortical areas and the precuneus, is another factor which could affect the relationship between sleep and cognition/ risk for dementia[36,37]. We could speculate that sleep problems are causing cognitive decline, however, reverse causality could be also true; sleep dysregulation could be an early symptom of an upcoming neurodegeneration.

After examining the relationship between sleep and objective cognitive decline, it is plausible to examine any possible association between sleep and subjective cognitive decline (SCD), which might be an early indicator of upcoming cognitive changes. Of the studies that have examined sleep in relation to SCD, one showed that sleep loss was associated with increased severity of SCD[38]. Poor sleep quality and daytime sleepiness were also linked to SCD in older adults[39,40]. Our group examined this relationship in two different cohorts –the ones mentioned before showing the association between sleep and objective cognitive changes-, and results revealed links between sleep and SCD even after controlling for objective cognitive status[41]. At any given level of objective cognition, sleep disturbance is accompanied by subjective cognitive impairment. Personality, mood, and attitudinal factors could significantly affect this association.

As we could now consider the exploration of the links between sleep and cognition quite established, the main interest transfers to the possible neurobiological connections underlying these associations. Several studies have suggested a familial aggregation of obstructive sleep apnea/ hypopnea (OSA/H)[42,43], snoring, and daytime hypersomnolence[44]. Results from a large longitudinal twin study showed that insomnia is moderately heritable (14%-38%)[45], suggesting that there might be a strong genetic contribution to sleep disturbances. Apolipoprotein E gene (*ApoE*) is known as a major risk factor for late-onset AD[46,47].

However, studies assessing whether *ApoE* gene may contribute to the risk of disturbances in sleep have been scarce, and results are often contradictory. One study suggests that apnea/hypopnea is linked to chromosome 19, a region that contains the *ApoE* gene[48], while different studies suggest that individuals carrying the *ApoE*-ε4 locus have an increased risk of developing OSA/H[49]. At the same time, OSA *ApoE*-ε4 carriers appear to have demonstrated an increased risk of impaired spatial working memory[50]. *ApoE*-ε4 has also been associated with SDB[51-53]. On the other hand, studies with OSA patients showed that the frequency of the *ApoE*-ε4 allele is the same as in a random population[54-56]. According to a study which compared individuals with different degrees of SDB, there was no association between SDB and *ApoE*-ε4[57]. More existing studies found no association between *ApoE*-ε4 and OSAS[55,58]. A different study investigating the association among napping, *ApoE*-ε4, and dementia revealed that napping for up to 60 minutes had an apparently protective effect against developing AD, especially for the *ApoE*-ε4 carriers[59]. Interestingly, our data analyses in a large group of non-demented older adults indicated that *ApoE*-ε4 carriers had less snoring and subjective sleep apnea, even after controlling for multiple covariates[60,61]. A complex etiology combining multiple environmental and genetic causes could affect the association between sleep and *ApoE*-ε4, leaving space for more research on the field.

Different genes have been also related to sleep regulation. The most common genes linked to sleep regulations are *circadian locomotor output cycles kaput (CLOCK)* which is mostly associated with insomnia and circadian rhythms, *PERIOD (PER)*, linked to sleep homeostasis and circadian alertness, *Brain and Muscle Arnt-Like 1* (*BMAL1)* linked to sleep deprivation, and *crystal (CRY)* linked to sleep homeostasis[62]. Associations have been found between most of these genes and their mutations with cognitive phenotypes such as memory formation, consolidation, and cognitive alertness[62,63]. A different review reports that the rhythmic expression of specific sleep genes (*BMAL1*, *CRY1*, and *PER1*) is lost in neurodegenerative diseases such as MCI and AD[64]. Combining sleep, genes, and cognition, a review reports that specific molecular clocks in different brain regions and their circadian phases and anatomical relationships to the central brain pacemakers indicate new ways for understanding the mechanisms of interaction between circadian clocks, sleep and cognition[62]. A recent study suggests that a Polygenic Risk Score (PRS), which is calculated based on variation in multiple genetic loci and their associated weights, can identify associations between sleep duration and specific diseases such as congestive heart failure and obesity[65]. Thus, the association among sleep, genes, and cognition remains to be explored further, with studies combining all the three factors and including multiple genes.

Apart from genetic factors, most recent studies examining sleep regulation and the brain focus their research on brain morphology. Age-related medial prefrontal cortex gray matter atrophy has been associated with reduced non-REM slow-wave activity in older adults, mediating the impairment of overnight sleep-dependent memory retention[66]. According to a different study, short sleep duration was associated with greater age-related brain atrophy and cognitive decline in older adults[67]. Based on a review, sleep deprivation and hippocampal vulnerability could cause changes in both neuronal plasticity, neurogenesis, and cognitive function[68]. Sleep deprivation has also been found to impair memory and frontal lobe function in insomnia patients[69]. Cortical thinning in the superior frontal lobe has been noted in female OSA patients[70], while the hippocampus also shows lateralized and sex-specific, OSA-related regional volume differences[71]. Among cognitively normal older adults, both short and long sleep duration can increase the rate of subsequent frontotemporal gray matter atrophy[72].

Preliminary results from our elderly group revealed significant associations between self-reported daytime sleepiness and total gray matter and cortical volume, while longer sleep duration was associated with low left entorhinal thickness[73]. From the fewer studies on sleep and functional connectivity, insomnia and more precisely difficulty in falling asleep has been linked to increased functional connectivity between sensory-motor brain regions[74]. Self-reported sleep duration has been also negatively correlated with prefrontal-amygdala connectivity in young adults[75]. Highlighting the role of sleep in brain function, a recent study reports that sleep-wake cycle regulates brain interstitial fluid tau in mice, and cerebro-spinal fluid tau in humans[76]. Hence, exploration of the links between sleep and brain morphometric factors can lead us to a better understanding of the neurobiology of sleep, and subsequently to a better understanding of how cognition works.

The importance of maintaining a normal sleep regulation is highlighted through the extensive literature. Sleep deprivation affects circadian clock gene expression in the cerebral cortex parallel electroencephalographic differences in an animal study[77], promoting the need for similar research which combines information about sleep, genes, and brain morphometry, in humans. As sleep problems, especially short and long sleep duration, and obstructive sleep apnea as well, have been linked to even increased risk for mortality[78,79], limiting the factors affecting negatively sleep regulation is of vital importance. Although in the current review we focused on sleep and cognition, as well as factors affecting this relationship, different factors could also play an important role to both sleep regulation and the brain function. Diet, light exposure, overall lifestyle, and multiple environmental elements could also contribute significantly to the association between sleep and brain[80-82], indicating the need for further investigation, combining sleep, genes, brain biomarkers, and cognitive factors.

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