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Later-life sleep, cognition, and neuroimaging research: an update for 2020

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Abstract

This review summarizes recent studies of sleep and brain health in later life, focusing on cognitive and magnetic resonance imaging (MRI)-derived outcomes. The majority of older people report sleep problems, and over one-third have sleep-disordered breathing (SDB). The research described herein builds on work demonstrating that abnormal sleep duration, sleep fragmentation, and SDB are associated with memory impairment and executive dysfunction. Self-reported short sleep is linked with greater cortical thinning and lower white matter integrity, and objectively measured fragmentation and SDB are tied to gray matter atrophy and altered connectivity. Results suggest that brain changes mediate previously identified sleep-cognition associations. Additional clinical trials are needed to determine whether treating insomnia or SDB benefits cognition in this population.

Introduction

Aging is associated with changes in sleep, and complaints of poor sleep are common among older persons [1]. Compared to young adults, middle-aged and older adults have shorter sleep duration, lower sleep efficiency (i.e., less time in bed asleep), and longer sleep onset latency [2]. Insomnia and sleep-disordered breathing (SDB) also become more common with greater age, and are increasingly tied to Alzheimer's disease (AD) and vascular dementia [3–5].

Accordingly, this review highlights recent results linking poor sleep to cognitive impairment and decline, and to magnetic resonance imaging (MRI) indices of brain structure and

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function. We also review recent evidence for the effect of sleep interventions on cognitive outcomes.

Self-reported sleep duration and cognition

Prior studies of sleep duration and cognition reveal contradictory findings. Some tie shorter sleep, and others longer sleep, to poorer cognitive performance. Others link both short and long sleep (versus intermediate-duration sleep) to poorer cognition. Recent studies continue this tradition of mixed results. Cross-sectional findings in community-dwelling middle-aged and older adults tie reports of >7 hours sleep with poorer memory, and processing speed [6], and >9 hours sleep to executive dysfunction [7•]. Sleep >8 hours was also associated with poorer memory among cognitively normal older adults [8•]. A UK Biobank study, including participants aged 40–69, found both shorter (<7 hours) and longer (>9 hours) sleep duration were linked with poorer reasoning, reaction time, and memory performance [9]. Some studies have found an association between short sleep (<6 hours) and executive dysfunction [7•], while others still detected no associations of short sleep (i.e., <6 hours or <7 hours) with global cognition [10••] or cognitive performance among specific domains [6,8•]. Among the oldest-old (≥90 years), >8 hours (versus 7–8 hours) but not <7 hours sleep was tied to poorer memory, executive function, and global cognition[11•]; after stratifying by cognitive status, the only association was of long sleep with poorer memory among participants with cognitive impairment.

Insomnia and cognition

Clinical insomnia is characterized by difficulty falling, staying, or returning to sleep, plus daytime consequences [12,13]. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for insomnia disorder also include complaints regarding sleep quality or quantity and require that symptoms have occurred ≥3 times per week for ≥3 months [13]. For feasibility, epidemiologic studies typically are limited to questionnaire-measured insomnia symptoms. Up to 20% of community-dwelling older adults meet insomnia disorder criteria, and up to 50% report insomnia symptoms [14].

Three recent studies examined prospective associations of insomnia with global cognitive decline in cognitively normal older adults. In a representative U.S. cohort, there was no association of number of insomnia symptoms with 5-year cognitive decline [10••]. In pooled data from four Scandinavian cohorts, no association was found between mid-life insomnia symptoms and global cognition (assessed >20 years post-baseline) after adjusting for lifestyle and medical factors, but late-life sleep maintenance/terminal insomnia was independently associated with decline on the Mini Mental State Exam (MMSE) [15]. Another study, however, tied reports of difficulty maintaining sleep to ~3-year decline in global cognition [16].

A large (N > 28 000) cross-sectional Canadian study of cognitively normal middle-aged and older adults found that participants with probable insomnia disorder had poorer declarative memory than those without [17]. A cross-sectional study in the UK Biobank Cohort reported that frequent insomnia symptoms were associated with better cognition [9]. Importantly,

both studies contained both middle-aged and older adults, which may explain discrepancies with the aforementioned prospective studies.

Three recent studies investigated self-reported sleep quality and cognition in older adults with mixed results. Among cognitively normal older adults, poor MOS Sleep Index II Questionnaire scores were tied to poorer memory performance [8•]. Yet, research among adults aged ≥90 found no association of sleep quality measures with global cognition, memory, or executive function [11•]. Before adjustment for health-related covariates, longer sleep onset latency was cross-sectionally associated with poorer visuospatial ability, processing speed, and memory in older adults aged ~76, but there was no association of nighttime sleep characteristics with subsequent 6-year change in cognition [18].

Objectively measured sleep and cognition

Three recent studies used wrist actigraphy to quantify sleep-cognition links in older adults. A cross-sectional study of older women linked longer (versus intermediate) total sleep time (TST) to lower global cognition and phonemic and semantic fluency, and greater wake after sleep onset (WASO) to poorer memory and semantic fluency, but some associations were accounted for by participants with dementia [19]. Another study in a cohort of older men and women linked several actigraphic measures of sleep disruption (i.e., WASO, sleep fragmentation, percentage sleep, number of wake bouts) to poorer global cognition cross-sectionally, and in a subset of sample re-assessed at 5-year follow-up, greater WASO, more fragmented sleep, lower sleep percentage, and shorter TST (i.e., <6 hours) were tied to increased odds of 5-year cognitive decline [10••]. A cross-sectional study found no independent associations of TST with cognition, but noted that greater WASO was linked with poor memory after adjustment for napping [20]. Furthermore, WASO moderated links of beta-amyloid with cognition, such that the association of amyloid with poorer memory was stronger in those with longer WASO [20].

Sleep-disordered breathing

SDB is defined by repeated pauses (apneas) or decreases in respiration (hypopneas) during sleep, resulting in sleep fragmentation and chronic intermittent hypoxemia. In obstructive sleep apnea (OSA), respiratory events occur despite efforts to breathe, due to airway collapse or other obstructions. OSA prevalence increases with age [21].

Individual observational studies link SDB to impairment in global cognition and deficits in attention, executive function, and memory [22,23]. However, a recent meta-analysis suggested only weak associations with poorer global cognition, memory, and processing speed among older adults with OSA [24], and another tied SDB to a greater risk of cognitive impairment and found weak associations with executive function and none with global cognition or memory [25]. The first meta-analysis was limited to older adults, and the latter combined results from middle-aged and older adults, which may account for different findings.

Two recent studies shed light on moderators and mechanisms linking SDB to cognition. A study of diverse middle-aged to older adults provided further evidence that the cognitive

effects of SDB are more pronounced among APOE-e4 carriers [26•], and consistent with prior research [27], a cross-sectional study suggested that, relative to sleep fragmentation, hypoxemia is more strongly tied to poorer cognition [28]. These results could have implications for treatment and prevention because they identify individuals at increased risk for SDB-related cognitive deficits and mechanisms that may serve as targets for prevention.

Sleep and neuroimaging outcomes

Efforts to identify mechanisms underpinning the sleep-cognition link have gained momentum with the publication of important papers linking sleep with AD pathology [29–32]. Recent studies have evaluated the role of sleep in later-life brain health using structural magnetic resonance imaging (MRI) methods, including volumetric or diffusion tensor imaging (DTI), or functional MRI of brain activity. Prospective studies tied both short and long self-reported sleep duration to greater cortical thinning over eight years [33], and linked short sleep to lower white-matter integrity (i.e., greater mean diffusivity; MD, lower fractional anisotropy; FA, greater hyperintensity volume) after five years [34]. Similarly, recent cross-sectional studies, using the Pittsburgh Sleep Quality Index [35], linked poorer sleep quality to greater global cortical atrophy [36,37•], hippocampal and thalamic atrophy [37•], and lower FA [38]. Moreover, a 2018 multimodal MRI study using combined resting state (rs)-fMRI and DTI data showed older individuals with poor sleep quality had lower structural and functional connectivity in temporal and occipital regions [39••].

Recent cross-sectional studies employed objective sleep measures and MRI. One tied novel actigraphic indices of fragmented motor activity (and presumably sleep) to greater global and frontal atrophy [40]. Polysomnography (PSG) studies found individuals with OSA exhibited altered default mode network functional connectivity [41] and diffuse subcortical microvascular damage [42]. Although a recent PSG study tied oxygen desaturations to cortical thinning [43], others reported that hypoxemia [44•] and apnea-related sleep fragmentation [43] were linked to *greater* cortical thickness [44•] and subcortical volume [43], suggesting a potential adaptive response to SDB [44•].

Treating sleep to improve cognition

Recent randomized controlled trials (RCTs) have investigated whether treating insomnia or OSA improves cognition among older adults. The insomnia studies used Cognitive Behavioral Therapy for Insomnia (CBT-I) or Brief Behavioral Treatment of Insomnia (BBTI). CBT-I includes sleep restriction and stimulus control, as well as sleep hygiene instructions, and addresses dysfunctional sleep-related beliefs. BBTI focuses on behavioral rather than cognitive elements, and is of shorter duration. Continuous positive airway pressure (CPAP) is the standard OSA treatment.

RCTs of CBT-I [45] or BBTI [46,47] investigated their effects on cognition in older adults with insomnia (Table 1). All three RCTs demonstrated improvements in sleep-related outcomes. With respect to cognition, the only effect on cognition was a benefit of CBT-I on executive function (i.e., inhibition) among older adults with MCI [45]. Two RCTs investigated effects of CPAP on cognitive decline. One found that CPAP improved episodic

and short-term memory, and executive function [48]; the other found no cognitive effects [49] (Table 1). Contradictory results between the two CPAP studies may be due to different measures and heterogeneity of samples (i.e., differing OSA severity, enrollment criteria). A recent study, comparing older adults with OSA and MCI who were CPAP-adherent to those who were not, tied adherence to less 1-year decline in processing speed [50••].

Summary, conclusions, and future directions

We reviewed recent studies of self-reported and objectively measured sleep with cognitive and brain health in older adults, including investigations assessing the effect of treating sleep on cognition. With respect to cognition, results are mixed; some studies link short and long sleep duration to poorer performance, and others report no association. Similarly, some studies tie insomnia and poor sleep quality to poorer memory and global cognition, and others find null results or even better performance. More consistently, studies using objectively measured sleep link abnormal sleep duration and greater WASO to poorer memory and global cognition. Although many studies link SDB with poorer performance in multiple cognitive domains, two recent meta-analyses suggest less robust associations. However, SDB is linked to greater risk of developing cognitive impairment, providing further support that SDB may be an important modifiable risk factor for cognitive health in older adults. Moreover, growing evidence suggests that hypoxemia, as opposed to sleep fragmentation, is the primary driver for SDB-related cognitive deficits. Recent neuroimaging studies tie abnormal sleep duration and poor sleep quality to greater cortical thinning, reduced micro-structural integrity, and altered connectivity, and link objectively measured sleep fragmentation and SDB to brain atrophy and altered connectivity, suggesting that sleep-related changes in brain structure and function may mediate cognitive performance. RCTs for the treatment of insomnia (i.e., CBT-I, BBTI) and SDB (i.e., CPAP) consistently improved the targeted sleep outcomes, but had a less consistent effect on cognition. Findings from a recent pilot study suggest that adherence to CPAP treatment is an important factor to consider in future RCTs.

There are several important areas that future studies should consider to advance research on sleep and brain health. The first is to address the methodological heterogeneity of studies of aging, sleep, and brain health with respect to measures of sleep, cognition, and imaging. Such heterogeneity likely accounts for many of the discrepancies in results we observed and reduces the confidence with which we can draw conclusions concerning sleep disturbance as a modifiable risk factor for poor brain health outcomes [51]. By intentionally planning studies with harmonized subjective and objective sleep measures and shared cognitive measures, diagnostic criteria, and imaging parameters — or by harmonizing existing data from cohorts with different measures of sleep, cognition, or AD biomarkers — the field could more definitively answer critical research questions [52]. Second, although neuroimaging findings suggest that changes in brain structure and function likely mediate associations of sleep with cognitive performance [7•,41,43], few studies have formally evaluated this. Prospective studies using advanced neuroimaging techniques and rigorous cognitive measures will help address this gap. Third, because insomnia and SDB often co-occur with medical conditions associated with an increased risk of cognitive decline (e.g., diabetes, stroke), studies of the interaction of sleep with these additional cognitive risk

factors are needed to help clinicians prioritize the treatment of sleep in these populations [53]. Finally, additional randomized trials of sleep interventions — with neuroimaging measures and other biomarkers to detect effects upstream of cognitive change, and harmonized measures when possible—are needed to assess the effect of treating sleep disorders on later-life brain health. Given the aging of the population, the prevalence of sleep disorders, and the personal, social, and economic threats posed by cognitive decline and dementia, this is a public health imperative.

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prior research linking wake after sleep onset with subsequent cognitive decline. Contrary to existing literature, no significant cross-sectional or longitudinal associations with cognitive functions were found for self-reported sleep. This finding brings attention to the effect of discrepancies between self-report and objective measures of sleep, and demonstrates the utility of using both subjective and objective sleep measures.

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Table 1

RCTs investigating cognitive effects of treating insomnia or sleep-disordered breathing

Treatment (Publication Year)	Sample Characteristics	Sleep measure	Cognitive outcomes	Results
Insomnia				
BBTI (4 weeks) [47] (2016)	Community-dwelling older adults with insomnia (N = 79; mean age = 71.7; 68.3% female; 91.1% white)	Chronic insomnia (DSM-IV-TR) or general insomnia disorder (ICSD-2), verified by questionnaires and clinician interviews.	Episodic memory: Logical Memory Working memory: Letter-Number Sequencing Abstract reasoning: Test of Non-Verbal Intelligence	No effect on cognition.
Adapted CBT-I (six, 1-hour sessions) [45] (2018)	Older adults with mild cognitive impairment and insomnia in two residential facilities (N = 28; mean age = 89.4; 85.7% female)	DSM-5 criteria for insomnia disorder.	Verbal memory: Hopkins Verbal Learning Test Executive function: Trail Making Test A and B Inhibition/switching: Delis Kaplan Executive Function System	Improved inhibition, a subdomain of executive function.
BBTI (4 weeks) [46] (2018)	Community-dwelling older adults with insomnia (N = 62; mean age = 69.5 ± 7.7; 67.7% female; 82.3% white)	Insomnia complaints ≥3 nights/week for >6 months; sleep onset or awake time during night >30 min ≥ 6 nights during 2-week baseline period per sleep diary.	Overall cognitive functioning: Mini-Mental Status Exam, Wechsler Adult Intelligence Scale-III (vocabulary, digit symbol) Attention and Processing speed: Trail Making Test A Language: COWA (semantic verbal fluency), Boston Naming Test Memory: California Verbal Learning Test, Rey-Osterreith Complex Figure Test, Wechsler Memory Scale (logical memory) Executive function: COWA (phonemic fluency), Trail Making Test B	No effect on cognition.
Sleep-Disordered Breathing				
CPAP (3 months) [48] (2015)	Older adults with newly diagnosed severe OSA syndrome (N = 33; mean age = 71.3 ± 5.5; 30.3% female)	Polysomnography	Memory: Rey Auditory Verbal Learning Test Attention: digit span forward Executive function: digit span backward, digit symbol substitution test, Trail Making Test A and B, verbal fluency	Improved episodic and short-term memory, and processing speed.
CPAP (3 months) [49] (2019)	Older adults with moderate OSA (N = 145; mean age = 74.9 ± 4.6; 34.5% female)	PSG or respiratory polygraphy.	Executive function: Trail Making Test A and B Working memory: digit symbol substitution test, digit span backward	No effect on cognition.

Notes. BBTI = Brief Behavioral Treatment for Insomnia; CBT-I = Cognitive Behavioral Therapy for Insomnia; COWA = Controlled Oral Word Association; CPAP = continuous positive airway pressure; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ICSD-2 = International Classification of Sleep Disorders, 2nd Edition; OSA = Obstructive Sleep Apnea; PSG = polysomnography.