THEORETICAL REVIEW

Low-grade inflammation in the relationship between sleep disruption, dysfunctional adiposity, and cognitive decline in aging

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SUMMARY

Aging is characterized by a progressive increase in proinflammatory status. This state, known as inflammaging, has been associated with cognitive decline in normal and pathological aging. However, this relationship has been inconsistently reported, likely because it is conditioned by other factors also affected by the aging process. Sleep and adiposity are two factors in particular that show significant alterations with aging and have been related to both cognitive decline and inflammaging. Given the consequences this state also has for brain integrity and cognition, we discuss here evidence supporting the potential mediating role of chronic low-grade systemic inflammation in the complex relationship between impaired sleep, dysfunctional adiposity, and cognitive decline through the common pathway of neuroinflammation. This review proposes a multi-factor model of aging-related cognitive decline that highlights the reciprocal interactions between sleep, the circadian system, and inflammation on the one hand, and between sleep, adiposity, and hormone resistance on the other. The model identifies sleep and adiposity as modifiable lifestyle factors that can be targeted to maximize cognitive function and quality of life in the elderly.

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Glossary of terms

Adaptive immune response

The adaptive or acquired immune response is the response of antigen-specific lymphocytes to antigens that are able to evade or overcome innate immune defenses. This system uses an immunological memory to learn about the threat and enhance the immune response accordingly.

Adiposity

Excessive accumulation of fat in adipose tissue.

Forced desynchrony

Uncoupling between the circadian and homeostatic regulatory systems by imposing a wake-sleep (light–dark) cycle outside (much longer or shorter) the entrainment range of the biological clock.

Inflammasome

A multiprotein intracellular complex that detects pathogenic microorganisms and sterile stressors, and that activates the highly proinflammatory cytokines IL-1β and IL-18.

Innate immune response

It refers to a variety of defense mechanisms that are present at birth and ready to recognize and respond rapidly to the presence of certain antigens.

Insulin sensitivity

The insulin concentration required for a half-maximal response.

Insulin resistance

The decreased sensitivity and/or responsiveness to insulin-mediated glucose disposal and/or inhibition of hepatic glucose production.

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Leptin sensitivity

Unlike insulin sensitivity, leptin sensitivity is more difficult to define because it is not only predicted by leptin concentration. Other factors such as sex, body mass index, adiposity, and fat distribution, adiponectin and other circulating factors may predict different aspects of the efficacy of leptin.

Leptin resistance

It is generally defined as the failure of endogenous or exogenous leptin to promote anticipated healthful metabolic outcomes in states of over-nutrition or obesity.

Mild cognitive impairment

This condition refers to the symptomatic predementia phase of Alzheimer’s disease. Core clinical criteria include self- or informant-reported cognitive complaint, objective cognitive impairment, preserved independence in functional abilities and not fulfilling diagnostic criteria for dementia.

Primed microglia

With aging, microglia take on a ‘primed’ phenotype, which is characterized by an exaggerated and uncontrolled inflammatory response to an immune stimulus.

Introduction

It is generally understood that cognitive function declines with advancing age even in the absence of disease [1]. However, much evidence suggests that chronic diseases emerging in middle age after prolonged exposure to an unhealthy lifestyle may accelerate cognitive decline and dementia [2]. Dysregulation of the immune system, a common feature of both age and disease, is typically accompanied by a chronic subclinical condition of low-grade systemic inflammation that can be challenging to diagnose and treat [3]. Here we will show that this condition may become exacerbated by modifiable lifestyle factors strongly associated with cognitive decline in aging, notably impaired sleep and body fat redistribution.

In this review, we further delineate a model wherein the interaction between aging-related increases in systemic low-grade inflammation and concomitant changes in sleep and adiposity may combine to promote cognitive decline through the common mechanism of neuroinflammation (Fig. 1). The model also stresses the importance of reciprocal interactions between the immune and circadian systems for sleep regulation, and between impaired sleep, dysfunctional adiposity, and hormone resistance for low-grade inflammation. The information contained in this model might help in the development of novel targeted therapies and preventative approaches to slow cognitive decline in normal aging and Alzheimer’s disease (AD).

Contribution of low-grade inflammation to cognitive decline

Immunosenescence and inflammaging

The integrity of the immune system tends to deteriorate with age, leading to increased susceptibility to infection and other health problems. This condition, known as immunosenescence, is accompanied by a chronic low-grade proinflammatory environment at the cellular, tissue, and systemic level [4]. Low-grade systemic inflammation is characterized by enhanced production of reactive oxygen species, elevated levels of C-reactive protein (CRP), proinflammatory cytokines such as interleukins (e.g., IL-6) and tumor necrosis factors (e.g., TNF-α, TNF-β), as well as by a reduction of cytokines counteracting the inflammatory state (e.g., IL-10) [3]. This phenomenon, often referred to as “inflammaging”, has been demonstrated to be a crucial risk factor for morbimortality in the elderly, and for most aging-related systemic chronic diseases sharing an inflammatory pathogenesis [5]. Although a great deal of evidence supports a link between systemic low-grade inflammation and cognitive decline in aging, results across different studies are highly inconsistent.

Association of CRP and IL-6 with cognitive decline in normal aging

Cross-sectional studies in the elderly have generally associated poor executive function and memory performance with elevated levels of CRP and IL-6 [6, 7]. Baseline levels of peripheral inflammation have also been found to predict cognitive decline, albeit inconsistently. Studies with follow-up periods ranging from 3 to 20 y have shown that both higher [8] and lower levels of baseline CRP predict cognitive decline over time [9], while higher levels of IL-6 are typically associated with decline of global cognition, executive function, and memory [6, 7, 9–11].

These studies rely on the idea that measurements of peripheral inflammation taken at a single time point reflect long-term inflammatory exposure. But longitudinal measurements of both peripheral inflammation and cognition have provided different results. For instance, increasing CRP levels over time was not associated with cognitive decline in a study by Singh-Manoux and colleagues [11], while others found that an association with CRP was only evident in those individuals not using statins at or before baseline [9].

Results derived from long-term changes in IL-6 are equally heterogeneous, with some studies reporting an association with the increased risk of cognitive decline and dementia [11], and others showing that neither baseline levels nor rate of change of IL-6 concentration are predictors of dementia [10]. In the latter study, only those subjects exhibiting high variability in IL-6 concentration over time appeared to be at a higher risk for cognitive impairment, an association that was partially mediated by the degree of aging-related hippocampal atrophy. Some research has even indicated that cross-sectional CRP and IL-6 levels appear to be more important in determining such risk than change in concentration of these compounds over time [12]. Importantly, once cognitive symptoms of neurodegeneration become evident, as in individuals with mild cognitive impairment (MCI), the association between increasing levels of these biomarkers and cognitive decline appears to be lost [13].
Association of TNF-α with cognitive decline in AD

The cytokine TNF-α has been shown to contribute to AD neuropathology. High levels of TNF-α in the brain of mouse models of AD have been associated with increased Aβ production, decreased Aβ clearance, synaptic dysfunction, and cognitive deficits; while TNF-α neutralization has been associated with the opposite outcomes [14]. Evidence indicates that inhibiting TNF-α signaling before the onset of amyloid plaque formation prevents hyperexcitability of glutamate synapses at a later stage in AD mouse model [15]. This finding suggests that administration of TNF-α inhibitors in asymptomatic stages of AD may help prevent later synaptic dysfunction and related cognitive decline. Unfortunately, there is not clear evidence that TNF-α concentration is increased in preclinical AD [16,17]. And the biologic TNF-α inhibitors that have been approved by the Food and Drug Administration for the treatment of peripheral inflammatory conditions present a limited blood–brain barrier (BBB) penetration. While new biologic inhibitors are currently under development [18], physical exercise might be a promising approach to reduce TNF-α levels and slow cognitive decline in normal aging and AD. Indeed, a reduction in TNF-α associated with physical exercise has been reported to have a beneficial effect on cognition in MCI patients [19].

The data reviewed here indicates a weak association between longitudinal changes in peripheral inflammation and cognition. This may be because the relationship is conditioned by a variety of factors including statin and nonsteroidal anti-inflammatory drug use, aging-related medial temporal lobe atrophy, and clinically silent AD pathology. In fact, evidence suggests that changes in peripheral levels of CRP and IL-6 are mainly linked to cognitive function in normal aging, while TNF-α emerges as a pivotal factor in AD-related cognitive decline, likely due to its influence on early synaptic disruption.

Beyond the influence of factors that might mediate or moderate the impact of low-grade inflammation on cognition, the disparity between the results of cross-sectional and longitudinal studies of normal aging and dementia may also be explained by the wide variety of potential sources of inflammmationing. These include immunosenescence, cellular senescence, accumulation of harmful products derived from oral and gut microbiota, and increasing activation of the coagulation system [3]. In the following sections, we review evidence suggesting that other factors that are modifiable by embracing a healthier lifestyle, such as impaired sleep and adiposity, may also favor inflammmating and aging-related cognitive decline.

Contribution of aging-related sleep changes to low-grade inflammation

Sleep changes in aging

Along with the phase advance, fragmentation, and flattening of the sleep-wake rhythm [20], older individuals show a reduced homeostatic sleep pressure that may account for the marked aging-related changes observed in sleep physiology [21]. As illustrated in Fig. 2a, elderly adults show a linear decrease in total nocturnal sleep time, increases in daytime naps, and augmented sleep fragmentation that ultimately result in reduced sleep quality [22]. These changes are further accompanied by decreases in slow-wave sleep (SWS) and REM sleep paralleled by increased light sleep (Fig. 2b) [22]. Fig. 2 also illustrates the typical reduction in the density of electroencephalographic (EEG) events occurring during NREM sleep such as prefrontal slow-wave activity (SWA, Fig. 2c) and sleep spindles (Fig. 2b) [23,24]. Most of these aging-related sleep changes progressively worsen from the preclinical phase [25] to the prodromal [26,27] and clinical stages of AD [28], and are further associated with faster cognitive decline and a higher risk of developing AD [28,29].

Mechanisms by which impaired sleep may contribute to inflammation

Evidence suggests that sleep and immune responses are reciprocally linked [30]. Sleep loss impairs the immune response [31], while some cytokines such as TNF-α, IL-1β, and IL-6 act as sleep regulatory substances [32]. There is however a great degree of individual variability involved in this bidirectional relationship [31]. Although many factors may modulate the circulating levels of sleep-related cytokines, the circadian system might be an important contributor [33]. For instance, Bjarström and colleagues [34] found that elevated expression of TNF-α and IL-6 in the evening correlated with better sleep maintenance and higher SWS percentage in older adults; while these sleep measures were associated with lower expression of the same proinflammatory cytokines the next morning.

Here we hypothesize that the reciprocal association between sleep, immune responses, and circadian factors may combine to promote low-grade inflammation in aging. After sleep deprivation, older adults fail to activate the typical homeostatic rebound increase in SWS and SWA during sleep recovery [21]. In these circumstances, circulating proinflammatory compounds may continue to be elevated the next morning, contributing to...
inflammaging if sleep is shortened over a prolonged period of time [39]. At the same time, these elevated levels of peripheral inflammatory markers might inhibit further activation of immune cells [36], ultimately preventing the countervailing relationship of sleep maintenance and sleep depth with evening and morning levels of cytokines production. In line with this hypothesis, elderly subjects do not exhibit the increase in inflammatory cytokine production that has been observed in young adults following acute sleep restriction [37].

From these results, we can infer that an intervention targeting sleep, inflammation, or immune response could plausibly have an effect on the other two processes. This assumption is supported by evidence showing that 6 months of moderate exercise training has beneficial effects on sleep quality and the cytokine profile of older individuals [38]. After training, participants showed decreased REM latency, decreased time awake, and increased sleep efficiency parallelled by decreased levels of IL-6 and TNF-α, and increased levels of IL-10. However, it is still unclear whether changes in the cytokine profile mediate the link between sleep and inflamming.

The reviewed evidence is consistent with the idea that reciprocal influences between sleep, the circadian system, and the immune response may indeed contribute to inflamming. Though no study to our knowledge has addressed if greater low-grade systemic inflammation is present in older individuals with disordered circadian rhythm, this phenomenon might be particularly exaggerated under conditions of chronic sleep restriction (<6 h/d). The reduced and inefficient homeostatic response to chronic sleep restriction, further facilitated by the aging-related decline in circadian output, might contribute to elevated circulating levels of proinflammatory cytokines. Some of these cytokines are involved in the biochemical cascades responsible for homeostatic processes during NREM sleep by acting both on sleep-regulatory networks and local circuits depending on prior activation of these functional connections [39]. Therefore, aging-related changes in circulating cytokine levels may affect not only sleep continuity and sleep depth but also the wake- and sleep-like state of certain cortical networks, with potential consequences for cognition.

**Contribution of aging-related changes in adipose tissue to low-grade inflammation**

**Fat redistribution in aging**

The primary site of storage for excess energy in the human body is adipose tissue, a specific type of connective tissue composed mostly of adipocytes. These cells collectively form a highly active metabolic and endocrine organ, capable of synthesizing a variety of inflammatory mediators that contribute to metabolic homeostasis. Appropriately regulated adipocyte function is thus critical for health. The imbalance between proinflammatory and anti-inflammatory cytokines, in addition to contributing to inflamming, is thought to drive aging-associated changes in adipose tissue [40]. This reciprocal relationship is illustrated in Fig. 3. Indeed, elevated circulating levels of both IL-6 and TNF-α prevent the normal differentiation of preadipocytes into mature adipocytes, leading to decreased adipogenesis and increased susceptibility to lipotoxicity, proinflammatory cytokine production, and activation of the innate and adaptive immune response [40]. As a result, the adipocyte becomes dysfunctional, and a redistribution of adipose tissue from lower-body subcutaneous depots to central visceral depots is observed in aging [41].

**Contribution of hormone resistance to fat redistribution**

Accumulation of abdominal visceral fat predicts an age-related reduction in insulin sensitivity in humans [42]. At the same time, insulin resistance has been associated with the release of additional proinflammatory compounds via mitochondrial dysfunction, suggesting the existence of a possible feedback loop between body fat redistribution, insulin resistance, and inflammation in late life [43].

The hormone leptin may also be relevant for aging-related fat redistribution. Unlike IL-6 and TNF-α, leptin is almost exclusively

![Fig. 2. Age-related changes in sleep.](image)

- **A** Linear decrease in total sleep time (TST) and sleep onset latency (SOL) is paralleled by an exponential increase in wake after sleep onset (WASO). These changes explain the decline in sleep efficiency (SE) to below 90% seen after age 45 (based on [22]).
- **B** Top panel: Longitudinal changes in different sleep spindle parameters, especially evident after age 35. Bottom panel: changes in sleep stage proportion with age (based on [22]). A prominent decrease in SWS and increase in N2 sleep is observed across the lifespan (modified from [23]).
- **C** Top panel: Correlation of age with slow-wave activity (SWA) power (log µV²) in NREM sleep for left central and frontal derivations. A decline in power is most remarkable in frontal electrodes. Bottom panel: scalp distribution of the association of age with absolute and relative power of SWA averaged across the first three sleep cycles of NREM sleep (modified from [24]).
expressed by adipocytes, produced mainly in subcutaneous adipose tissue in proportion to the size of the fat depots [44]. Although leptin regulates a multitude of physiological processes, it is mainly known as a catabolic regulator of food intake and energy expenditure, and subsequently body weight [45]. In normally-functioning adipose tissue, leptin induces anorexia and increases metabolic rate and body temperature by interacting with receptors in areas associated with the control of feeding-related behavior and energy expenditure like different nuclei in the hypothalamus, midbrain and brainstem [46]. Leptin also modifies adipocyte metabolism (i.e., suppression of lipogenesis, increase of lipolysis, and increase in fatty acid and glucose oxidation) through activation of sympathetic efferents to white adipose tissue [47]. Consequently, the loss of subcutaneous fat with advancing age results in a reduced capacity for leptin to trigger oxidation of free fatty acids in peripheral tissues, favoring visceral and ectopic fat redistribution [48].

Circulating leptin levels are abnormally high in overweight older adults, yet a resistance to leptin action in the brain has been
consistently observed in these individuals [49]. Though the causes of leptin resistance are not fully understood, the phenomenon may stem from defective transport of leptin to the brain, down-regulation of the leptin receptor, failures in intracellular leptin signaling, and/or impairments in leptin target neurons [50]. There is also evidence that aging impairs both central leptin access and cellular leptin signaling in rats [51]. However, it is unclear whether leptin resistance can be attributed to the increased adiposity associated with aging, to aging alone, or involves the interaction of both of these factors. Pétervári and colleagues [52] found evidence that the hypermetabolic and anorexigenic actions of leptin are differentially affected by aging and obesity. They showed that resistance to leptin affected the hormone’s hypermetabolic action in older but not younger rats, and that increased adiposity reduced both hypermetabolism and anorexia, while caloric restriction enhanced anorexigenic action only in older animals. These results suggest that obesity in aging favors leptin’s contribution to low-grade systemic inflammation. In support of this hypothesis, leptin concentration has been found to be highly correlated with plasma levels of soluble TNF-α receptors in morbidly obese patients after controlling for the effects of body mass index (BMI) and sex [53]. This leptin-induced upregulation of TNF-α production, mediated by activation of B cells [54], T cells, and macrophages [55], may in turn play a pivotal role in mediating insulin resistance with advancing age [56].

**Contribution of sleep to fat redistribution**

Growing evidence supports the idea that sleep may be an additional factor contributing to fat redistribution with age. Indeed, in normal individuals aged 18–64 y, after controlling for BMI, those with shorter sleep duration gained more abdominal adiposity over the course of 6 y [57]. This association is also supported by cross-sectional studies conducted in normal older adults [58]. However, others have found that shorter sleep is associated with more subcutaneous fat tissue rather than visceral fat [59]. Chaput and colleagues [60] examined the association between changes in self-reported sleep duration and visceral fat accumulation over a 6-y period. After controlling for age, sex, BMI, personal characteristics, energy intake, and physical activity, both short (<6 h/night) and long (≥9 h/night) sleepers gained more visceral fat than those sleeping 7–8 h a night. Although sleep duration was unrelated to changes in visceral fat in the whole sample, those individuals showing a spontaneous improvement in sleep duration also showed decreasing visceral fat accumulation over time. The above findings suggest a U-shaped curve in the relationship between sleep duration and visceral fat accumulation that, interestingly, parallels the relationship of sleep duration with cognitive decline [61], and with mortality [62].

**Interaction between sleep and hormone resistance**

Common sleep alterations in aging may also be related to increased systemic inflammation via the effects of hormonal resistance. For instance, insomnia [63] and longer sleep duration in the elderly are associated with a greater risk for insulin resistance [64], whereas longer sleep onset latency in middle-aged adults is correlated with insulin resistance along with higher peripheral levels of IL-6 and CRP [65]. The aging-related reduction in SWS may also contribute to increased low-grade inflammation via insulin resistance. This is compatible with the association found between SWS suppression and insulin resistance in young adults [66], and between SWS reduction and increased waist circumference in older men [67]. A link between leptin resistance and sleep alterations may also exist. Objectively measuring sleep duration in middle-aged adults has shown that shorter total sleep time is proportionally related to increased serum leptin concentration [68]. Notably, sleep fragmentation induced in a mouse model led to hyperphagic behaviors and reduced leptin signaling in the hypothalamus, indicating a state of leptin resistance [69]. Still, the association between poor sleep and leptin resistance suggested by these studies must be confirmed in older adults.

As insulin and leptin resistance coincide with aging-related changes in both sleep and body fat distribution, inflammatory consequences may reinforce the reciprocal link between impaired sleep, dysfunctional adiposity, and inflammation. This complex relationship may also be influenced by sex, which has been associated not only with differences in sleep disturbance and body composition, but also with insulin and leptin resistance [70]. The following section reviews evidence supporting the hypothesis that alterations in both sleep and adiposity may influence cognitive decline late in life differently in men and women through the common pathway of low-grade inflammation (see the subsection entitled “Aging-related changes in adiposity are linked to cognitive decline”).

**Low-grade inflammation may link aging-related changes in sleep and adiposity to cognitive decline**

The evidence presented thus far indicates that low-grade systemic inflammation is linked to cognitive decline, interactions between the immune and circadian systems are at the core of sleep regulation, and that reciprocal links between the immune system, sleep, and fat redistribution contribute to inflamming. In this section, we outline findings suggesting that both sleep changes and body fat redistribution in aging are also closely associated with cognitive decline. Although the mechanisms responsible for each of these associations are not yet clear, the impact of low-grade inflammatory status on BBB disruption has emerged as a critical factor. Indeed, it has been suggested that increased BBB permeability and related neuroinflammation may be induced by either the aging process per se [71], neurodegeneration [72], and/or by inflammatory mediators in the brain and periphery resulting from chronic sleep restriction [73] or accumulated abdominal visceral fat in aging [74]. Increased BBB permeability in aging may moreover augment the impact of low-grade inflammation on cerebral integrity and in turn mediate the relationship between disrupted sleep, dysfunctional adiposity, and impaired cognition. The extent to which changes in sleep and adiposity are associated with different aspects of cognitive decline in normal aging and AD is discussed below.

**Aging-related sleep changes are linked to cognitive decline**

**Contribution of sleep to cognitive decline in normal aging.** A growing body of evidence links disrupted sleep to cognitive decline in normal and pathological aging [75]. These results are summarized in Table 1. Self-report data indicates that especially short and long sleep is associated with worse cognitive functioning in nondemented elderly subjects both cross-sectionally and longitudinally [61]. However, others argue that it is sleep quality rather than sleep duration that more consistently relates to cognitive dysfunction in aging [28,76,77]. Paradoxically, some studies have suggested that cognition in older adults is less sensitive to restriction [78] and deprivation of sleep [79]. These protocols do not allow us to know if age is affecting the wake-dependent and/or the circadian influences. This distinction is possible with the forced desynchrony paradigm, which has been used to schedule the subject to a rest–activity cycle duration much shorter or much longer than 24 h [80]. In this study, the two regulatory processes influenced cognitive performance in both young and older adults, but the circadian process showed a greater adverse effect on young than older individuals. Although the reason behind this finding is not clear, it has been associated with aging-related changes in the
circadian system and/or in the homeostatic process controlling sleep and wakefulness [81].

Much evidence supports a close relationship between aging-related disruption of sleep architecture and cognitive function. Reduced REM sleep in aging has been linked to cognitive decline [81,82], while alterations in SWS (i.e., reduction, fragmentation) have been associated with aging-related deficits in sleep-dependent memory consolidation [83–85]. Furthermore, the relationship between SWA and memory appears to be causative in nature, not only because this EEG activity mediates age effects on memory [83], but also because manipulating SWA during sleep in older adults leads to greater overnight memory retention benefits [84,85]. The impact of aging on SWA, in turn, seems to be mediated by the structural integrity of the medial prefrontal cortex [83,85], a region particularly involved in aging-related cognitive decline. Dube and colleagues [88] have shown that decreased density and amplitude of SWA in older adults can be explained by cortical thinning in regions implicated in the generation and propagation of this sleep oscillatory activity. Prefrontal sleep spindles have also been shown to mediate the effects of aging on next-day hippocampal activation during encoding and subsequent impaired episodic learning [84]. Hippocampal activity during successful memory retrieval in turn appears to mediate the relationship between circadian activity rhythms and memory in older adults [89]. Together, these findings indicate that both the differential rate of aging-related changes in frontal brain regions and sleep spindles may be crucial mechanisms contributing to inter-individual variability in SWA and cognitive decline.

**Contribution of sleep to cognitive decline in AD.** Evidence also links poor sleep quality and disruption of SWA to AD pathology in a bidirectional manner [90]. Acute sleep deprivation in transgenic animal models of AD has been demonstrated to increase Aβ concentration while chronic sleep deprivation accelerates Aβ aggregation [91], likely due to a reduction in the efficiency of Aβ clearance that typically occurs during sleep [92]. Neuronal activity-related Aβ release has also been proposed to be significantly reduced during SWS because of silent periods of hyperpolarization that characterize SWA [90]. This hypothesis was recently tested by disrupting SWA in a group of adults aged 35–65 y after monitoring their sleep with actigraphy for 1–2 wk [93]. A selective increase of cerebrospinal fluid Aβ40 associated with SWA disruption was observed, along with a corresponding total tau increase associated with worse home sleep quality. Similarly, disturbed sleep in cognitively normal elderly individuals has been associated with increases in Aβ42 [94]. Given that Aβ-associated brain atrophy and cognitive decline only appears to occur in the presence of elevated phosphorylated tau levels [95–97], poor sleep quality is expected to be strongly associated with poor cognition in MCI patients. This hypothesis is supported by evidence shown in Table 1 [98–100]. However, no association has been found between changes in sleep stages and cognition in MCI patients [26]. This may be because this kind of alteration in sleep mainly affects Aβ clearance and deposition, which is not on its own strongly associated with cognitive impairment [101].

These studies indicate that sleep quality and cognitive performance are associated in a remarkably consistent fashion in both normal aging and AD. Conversely, disruption of sleep architecture is not always shown to be related to cognitive impairment in either normal or pathological aging. Only alteration of frontal brain activity during SWS, likely as a result of aging effects on frontal lobe structure, appears to be a crucial determining factor of cognitive outcomes in normal aging as well as in AD.

**Aging-related changes in adiposity are linked to cognitive decline**

As reviewed above, changes in regional fat distribution with age have consequences for the development of insulin and leptin resistance, metabolic dysfunction, and inflammation, and may thus constitute a mechanism by which aging leads to a decline in cognitive abilities. Evidence summarized in Table 2 suggests that fat mass deposited in different parts of the body may be differentially related to the risk of cognitive decline in normal aging [102,103] and AD [104]. Taken together, these studies implicate visceral fat, rather than body mass per se, in aging-related changes in body composition associated with the loss of brain integrity and subsequent cognitive impairment.

Despite the link between visceral fat and aging-related cognitive decline, some degree of variability is also evident across studies. This may be partially explained by sex differences in the influence of steroid hormones on age-related adipose redistribution (Table 2). Accordingly, practically all measures of adiposity are associated with declining cognitive function in men after controlling for metabolic disorders, adipocytokines, and sex hormone levels [107], whereas subcutaneous fat [108], lean mass [109], and glynnoid fat [102] may in fact help protect against cognitive decline in women. Some of the variability in the relationship between visceral fat and cognition in normal aging may also be due to the decreased capacity of leptin to act as a regulator of body fat distribution. In the elderly, the hypermetabolic effects of leptin are largely dependent on fat accumulation, such that obesity enhances resistance to leptin
while intentional weight loss enhances leptin sensitivity [110]. This finding might help to explain how leptin interacts with central obesity to shape cognitive decline. In the non-obese, higher baseline serum leptin levels have been associated with better cognitive performance over time for older adults with a small waist circumference [111]. But leptin sensitivity may potentially be increased in elderly subjects following caloric restriction, as intentional weight loss through diet has been shown to be associated with cognitive improvement in obese MCI patients, especially in those carrying the ε4 allele in the APOE gene [112].

These findings indicate that the interaction between body fat distribution and sex likely influences cognitive function in the elderly. However, the effect of obesity itself on cognition in the elderly should not be discounted altogether, given that this condition may decrease leptin sensitivity and/or increase leptin resistance with its subsequent effects on cognitive function. We next review evidence supporting the idea that the effect of aging-related changes in sleep and adiposity on cognitive decline might be mediated by systemic low-grade inflammation through the common mechanism of neuroinflammation.

**Systemic low-grade inflammation may link aging-related changes in sleep and adiposity to cognitive decline via neuroinflammation**

**Association between systemic inflammation, neuroinflammation, and cognitive decline.** Though inflamming is observed in both the brain and the periphery, it is unknown to what extent neuronal and systemic low-grade inflammation resulting from chronic sleep disruption and/or changes in body fat distribution are associated with specific physiological and cognitive outcomes. It is likely that communication between the immune system and the central nervous system heightens the brain’s inflammatory response observed in aging [113]. This reciprocal process may ultimately have consequences for cognitive integrity. Thus, although activated microglia exert a beneficial effect in response to brain injury and acute infection in the periphery, the uncontrolled microglial activation characteristic of aging, as illustrated in Fig. 4, may lead to neuronal dysfunction and cognitive decline over time [114].

The effect of systemic inflammation on primed microglia might occur via both neural and humoral pathways, leading to enhanced synthesis of proinflammatory mediators. This may help explain cognitive deficits in individuals suffering from mild infections. Findings from animal studies indicate that higher levels of systemic proinflammatory compounds are associated with increased inflammation in the brain, negatively affecting cognitive processes in aging. Inducing a systemic inflammatory response via injection of lipopolysaccharides leads to greater neuroinflammation in aged mice than in young animals, as evidenced by enhanced microglial response and increased expression of IL-6 and IL-1β [115]. In humans, inflammation in the hippocampus has also been shown to mediate the association between memory impairment and elevated uric acid, considered a possible proinflammatory activator [116]. Hippocampal inflammation not only contributes to reduced neurogenesis, synaptic function, and plasticity with age [114], but may also contribute to Ca2+ dysregulation, which has itself been directly linked to age-related changes in synaptic plasticity [117]. In fact, it has been postulated that interaction between Ca2+ signaling and inflammatory mechanisms may exacerbate neuronal vulnerability to AD, leading to faster cognitive decline [117].

In addition to its effect on the hippocampus, aging-related impairment in microglial function may contribute to myelin damage in the frontal lobe. In a recent study, Shobin and colleagues [118] found in aged rhesus monkeys that neuroinflammation and phagocytic microglial activation increased with age within the white matter pathways of the frontal lobe including the cingulum bundle, corpus callosum, and frontal white matter, likely in response to accumulating myelin pathology. However, cognitive impairment was correlated with an increase in phagocytic microglial activation only in frontal white matter. Although the cause of this regional specificity is not clear, it is consistent with the idea that white matter regions that myelinlate later in development deteriorate earlier in aging. Moreover, the loss of white matter integrity in anterior cortical regions may contribute to a disconnected state that is associated with decline in episodic memory, executive function, and processing speed in the elderly [119].

**Sleep and neuroinflammation.** Animal evidence has shown that sleep disturbance may too induce microglial activation and neuroinflammation. For instance, 24 h of sleep deprivation followed by 24 h of recovery were accompanied by increased levels of IL-6 and induced microglial activation in the mouse hippocampus, but not in the cortex [120]. Sleep disruption over the course of a week in mice also resulted in increased inflammation, altered vascular reactivity, decreased glucose transporter, and impaired BBB permeability [121]. However, a recent study reported increased activation and phagocytosis of microglial cells in the frontal cortex of mice subjected to 4.5 d of chronic sleep restriction but without signs of neuroinflammation in cerebrospinal fluid [122]. Together, these results suggest that both acute and chronic sleep disruption can lead to a proinflammatory state in the absence of overt infection and/or injury, but that such a response likely depends on factors...
such as sleep debt, age, and other pathology. Still, chronic sleep restriction and related low-level sustained microglial activation might ultimately promote neuroinflammation and increase the brain’s vulnerability to other forms of insult. Indeed, mild sleep restriction over a period of 6 wk in a mouse model of AD increased levels of Aβ peptides and phosphorylated tau, correlating with impaired memory performance [123].

Although it is not yet fully clear what mechanisms link sleep disruption to neuroinflammation, alterations in the permeability of the BBB emerge as a likely candidate. This is consistent with findings that chronic restriction of either total sleep time [121] or REM sleep in particular [124] results in a reduction in BBB structural and functional integrity. A recent study has further demonstrated that the impact of sleep on BBB permeability depends largely on age [125]. Specifically, the authors found that sleep fragmentation led to an age-related disruption of the BBB’s ability to block proinflammatory compounds, as TNF-α transport into the brain was seen to a greater extent in aged than in young mice. However, BBB disruption alone might be insufficient to induce brain dysfunction. Montagne and colleagues [126] showed that hippocampal BBB permeability increased with age in the absence of cognitive impairment, while this increase was more marked in MCI patients. Pathogenic factors intrinsic to the hippocampus like Aβ accumulation and tau hyperphosphorylation, which are closely tied to cognitive malfunction, are also likely to be influenced by age-related sleep disruption. Recent evidence suggests that the lymphatic system for clearance of interstitial toxic metabolites is most active during sleep [127], and reduced clearance of AD pathology may be affected by sleep alterations in aging [128]. Finally, the aging-related decline in different neurotransmitter systems involved in anti-inflammatory and neuroprotective actions could also play a crucial role in cognitive decline and neurodegenerative disease [129].

**Dysfunctional adiposity and neuroinflammation.** Given that alterations in sleep, low-grade systemic inflammation, and cognition are all associated with changes in regional fat distribution during aging, it is plausible that BBB disruption also mediates the impact of aging-related changes in adiposity on cognitive decline. The mediating role of the BBB would thus be expected to be more evident when brain integrity is more compromised. Indeed, evidence from in vivo human studies indicates that BBB vulnerability to systemic inflammation is increased in diseased brains as revealed by the presence of cerebrospinal fluid abnormality [130]. No study to our knowledge has specifically investigated the mediating effect of BBB disruption in the relationship between aging-associated body fat redistribution and cognition. Still, Bourassa and colleagues [131] recently found that systemic inflammation might indeed mediate the association between obesity and cognitive decline in older adults. They showed that greater overall obesity was indirectly associated with a decline in memory and executive functioning over 6 y via the mediating influence of CRP concentration. This finding led them to conclude that chronic low-grade inflammation represents a biologically-plausible mechanism through which differences in body mass might influence changes in

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**Fig. 4.** Mediating role of low-grade systemic inflammation in the effect of sleep disruption and dysfunctional adiposity on aging-related cognitive decline through the common pathway of neuroinflammation. The aging process and its consequences for sleep and regional fat redistribution contribute to low-grade inflammation in the periphery. Systemic inflammation primes microglia through neural (vagal afferent) and humoral pathways (diffusion across the blood-brain barrier, BBB or blood-cerebrospinal fluid barrier, BCSFB). Primed microglia are activated to enhance synthesis of proinflammatory compounds that ultimately damage the neuron and contribute to cognitive decline. M1: classic macrophage activation; M2: alternative macrophage activation.

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cognitive decline among aged adults. Nevertheless, further studies investigating the specific mediating role of systemic inflammation in the relationship between sex, central visceral fat, and cognition are necessary. Given the previously mentioned sex differences in fat redistribution with advancing age, it is likely that systemic inflammation mediates the relationship between adiposity and cognition differently in men and women.

From these results, it seems that aging-related adiposity may be relevant for inflammatory processes not only in the periphery but also in the brain. Indeed, a high-fat diet in rats leads to a greater expression in the hypothalamus of a number of proinflammatory compounds [132]. These neuroinflammatory changes associated with obesity may also have consequences for hypothalamic regulatory behaviors such as food intake. Adiposity-related neuroinflammation in aging may be present in extrahypothalamic regions as well. In a mouse model of high-fat diet-induced obesity, neuroinflammation was exacerbated in older animals, as evidenced by increased microglial activation, hippocampal proinflammatory cytokines, and oxidative stress responses [74]. Furthermore, obesity combined with Adi infusion promoted neuroinflammation in the hippocampus, predicting impaired object recognition memory in a mouse model of obesity [133]. As a whole, the evidence reviewed here suggests that neuroinflammation might represent a critical pathway by which changes in sleep and body fat distribution lead to altered cognitive function in the aging brain.

Conclusions

This review proposes a model (Fig. 1) that focuses on low-grade systemic inflammation as a critical mediator for dysfunctional adiposity and sleep disruption in aging. The model further hypothesizes a number of components that all mutually influence each other to exacerbate the negative impact on cognitive function. That is, inflammation likely affects adiposity and sleep in a reciprocal fashion to reinforce the processes described here. Alterations in the circadian clock with advancing age may represent an underlying impetus for changes observed in the interrelated components of this framework. Although the proposed model is based on evidence derived from a wide variety of research, the variability introduced by several confounding factors must be taken into account in future empirical evaluation, including the role of age, baseline cognition, AD pathology, and other general health conditions. Moreover, the substantial differences between cross-sectional and longitudinal studies as well as between men and women in the processes described here stipulate future studies that are carefully designed to account for these effects. Importantly, aspects of sleep and adiposity in aging have a central role in this review as lifestyle factors that could be effective targets of interventions aimed at improving quality of life in the elderly. Future research should address the inconsistent findings noted here and explore further variability in these highly interrelated processes.

Practice points

- Reciprocal influences between sleep, the circadian system, and the immune response contribute to inflammation via the effects of insulin and leptin resistance.
- The association of disturbed sleep and dysfunctional adipose tissue with cognitive decline in aging might be mediated by chronic low-grade systemic inflammation through the common pathway of neuroinflammation.


Bourassa K, Sharrar DA. Body mass and cognitive decline are indirectly associated via inflammation among aging adults. Brain Behav Immun 2017;60:53–70.
