



# Sleep Disturbances in MCI and AD: Neuroinflammation as a Possible Mediating Pathway

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Mild cognitive impairment (MCI) and Alzheimer's disease (AD) affect a high proportion of the elderly population with an increasing prevalence. Sleep disturbances are frequent in those with MCI and AD. This review summarizes existing research on sleep disturbances and neuroinflammation in MCI and AD. Although strong evidence supports various pathways linking sleep and AD pathology, the temporal direction of this central relationship is not yet known. Improved understanding of sleep disturbance and neuroinflammation in MCI and AD may aid in the identification of targets for their prevention.

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## INTRODUCTION

Alzheimer's disease (AD) is a leading public health problem (Ballard et al., 2011) affecting 24 million people worldwide (Ballard et al., 2011; Reitz and Mayeux, 2014). Descriptive evidence implies that sleep may play a crucial role in optimal daytime cognitive functioning, attention, executive functioning, and memory (Diekelmann and Born, 2010; Killgore, 2010). Disturbed sleep is associated with cognitive disorders (da Silva, 2015), and early observational data from institutionalized AD patients showed worse nocturnal sleep among those with more severe dementia (Bliwise et al., 1995). Epidemiological research among older adults has shown that both short and long sleepers have worse cognitive function (Potvin et al., 2012; Devore et al., 2014) and greater cognitive decline in contrast to adults sleeping 7 or 8 h per night (Keage et al., 2012; Benito-León et al., 2013). Thus, a U-shaped association between sleep duration and cognitive outcomes has been suggested (Yaffe et al., 2014). Both cross-sectional (Muangpaisan et al., 2008; Naismith et al., 2010; Guarnieri et al., 2012) and longitudinal studies (Westerberg et al., 2012), have shown that sleep disturbance is linked to mild cognitive impairment (MCI) and AD.

Patients with dementias, especially AD, often have disrupted nocturnal sleep. When monitored in overnight sleep studies (Vitiello et al., 1990; Montplaisir et al., 1998), they have earlier bedtimes and much more variable wake-up times than those without AD (Bliwise et al., 1992). Approximately

25–44% of patients with AD reported having sleep disturbances, although sleep was measured via self-report (Guarnieri et al., 2012). Nocturnal sleep disturbance is more frequent in dementia patients with Lewy bodies than in patients with AD, although nocturnal sleep disturbances in AD are more associated with advanced disease (Bliwise et al., 2011). There may also be a higher prevalence of sleep apnea in AD patients, though this remains a controversial area (Bliwise, 1996; Bliwise et al., 2019). Nevertheless, a potential causal role for sleep apnea in impaired cognition in the aged could be exacerbated by sleep fragmentation, inflammation, oxidative stress, and hypoxemia, all of which are features of disturbed respiration during sleep (Daulatzai, 2012, 2013). In this review, we examine relevant existing human research on neuroinflammation and sleep disturbance in MCI and AD.

## IMPORTANCE OF EXPLORING MICROGLIA, NEUROINFLAMMATION, AND SLEEP IN MCI AND AD

We propose a model in which disturbed sleep may play a crucial causal role for cognitive decline in old age. This places neuroinflammation as the most important mediating variable underlying many of the associations noted to date. Sleep disturbance may be a major risk factor for AD and is associated with increased inflammation (Hansson et al., 2006; Alvarez et al., 2007). The amyloid cascade hypothesis proposed by Hardy and Higgins (1992) postulates that the accumulation of insoluble amyloid  $\beta$  ( $A\beta$ ) is the primary driver of AD pathology. However, research has demonstrated neuroinflammatory responses connected to  $A\beta$  deposition common to both sleep disturbance and AD.

Microglia are a type of glial cell that is common in the central nervous system (CNS) and functions as a primary line of immune defense (Nayak et al., 2014). They manage immunosurveillance and mediate inflammation, both of which are suggested to be important in AD (Olsson et al., 2013). Activated microglia appear to have a beneficial effect in response to brain injury, although uncontrolled microglial activation that is part of aging may lead to neuronal dysfunction and cognitive decline (Ojo et al., 2015). Upon exposure to  $A\beta$ , microglia and astrocytes release cytokines, interleukins, nitric oxide, and other potentially cytotoxic molecules (McGeer and McGeer, 2010; Krabbe et al., 2013; Heneka et al., 2015). Twenty-four-hour sleep deprivation followed by 24-h recovery was associated with elevated levels of IL-6 and microglial activation in the mouse hippocampus, although not in the cortex (Zhu et al., 2012). Chronic sleep restriction and low-level microglial activation may promote neuroinflammation and increase the brain's vulnerability to insult (Atienza et al., 2018). Xie et al. (2019) have shown that chronic sleep fragmentation can induce dysfunction of intracellular protein degradation and activate microglia predominately in the hippocampus, which in turn may induce this pro-inflammatory response (Xie et al., 2019). Rodent models of chronic sleep deprivation have reported microglial morphological changes, including enlargement of the cell body and increased expression

of pro-inflammatory cytokines (Hsu et al., 2003; Wisor et al., 2011). Thus, microglial dysfunction and neuroinflammation may contribute to the pathophysiology of sleep disorders.

Additionally, intrinsic molecular clock control within microglia regulates sleep–wake cycle-dependent changes in synaptic strengths (Hayashi et al., 2013). This intrinsic circadian control within microglia is an example of a peripheral clock of the circadian sleep–wake system. These are centrally directed from the suprachiasmatic nucleus (SCN), which controls metabolomic changes and synchronizes tissues within the body in response to internal and external “zeitgebers” such as light (Musiek, 2017). These cellular circadian rhythms are often expressed through a transcriptional–translational feedback loop (TTFL) in which the transcriptional factors CLOCK and BMAL1 heterodimerize and bind to E-box sequences in target gene promoters to drive rhythmic expression of Period (Per1–3) and Cryptochrome (Cry1–2) proteins. These Per and Cry proteins then form a complex to return to the nucleus and inhibit CLOCK- and BMAL1-mediated gene expression, completing the feedback loop (Eckel-Mahan and Sassone-Corsi, 2013; Gachon et al., 2017). Studies in mice show that when *Bmal1* or *Clock* is deleted or deficient, they produce arrhythmic circadian cycles in the SCN (Eckel-Mahan and Sassone-Corsi, 2013; Krishnaiah et al., 2017). This process may be disrupted in AD patients, as differences in the phase of these clock gene rhythms have been observed in the brains of individuals with AD when compared to controls (Cermakian et al., 2011; Weissova et al., 2016). Additionally, Ni et al. (2019) show that reduced expression of BMAL1 (a clock gene) is responsible for increased expression of an inflammatory type of microglia in APP knockout mice (Ni et al., 2019). This circadian rhythm dysfunction links AD and sleep disturbance pathology (Musiek, 2017).

Recent research has demonstrated the importance of a missense mutation in the triggering receptor expressed on myeloid cells 2 (TREM2) in increasing one's risk for AD (Guerreiro et al., 2013; Jonsson et al., 2013; Wang et al., 2015). The R47H variant of the gene confers a 2–4.5-fold increased risk of developing late-onset AD. Behind the APOE  $\epsilon$ 4 gene, these results place *Trem2* as the strongest associated risk gene for AD (Guerreiro et al., 2013; Jonsson et al., 2013). In studies of mice with  $A\beta$  accumulation, deletion of *Trem2* significantly reduced the number of plaque-associated macrophages (Jay et al., 2015). Deletion of *Trem2* also led to decreases in astrocytosis and declines in inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (Jay et al., 2017). Additionally, studies have shown that microglia and macrophages lacking TREM2 have a reduced ability to clear  $A\beta$  and apoptotic cells from the brain (Savage et al., 2015). In addition to TREM2, research has explored other microglia-specific receptors and their role in immune response in AD. CX3CL1 is an inhibitory chemokine that binds to CX3CR1 on the surface of microglia, regulating microglial activity and migration in injury conditions (Limatola and Ransohoff, 2014). CX3CL1 may also dose-dependently reduce expression of nitric oxide, IL-6, and TNF- $\alpha$ , and suppress neuronal death induced by microglial activation. Disrupting the receptor can lead to system inflammation and microglial neurotoxicity (Jung et al., 2000; Zujovic et al., 2000; Mizuno et al., 2003; Cardona et al., 2006).

Plasma levels of CX3CL1 have been shown to be elevated in patients with AD and more so in patients with MCI, possibly due to increased inflammation preceding AD pathology (Kim et al., 2008). Additionally, postmortem analysis shows significantly lower levels of CX3CL1 in the hippocampus of AD brains compared to controls without dementia (Cho et al., 2011). Microglia, particularly those that have been activated, exhibit GABA<sub>B</sub> receptors (Kuhn et al., 2004). This is important as GABA decreases the release of pro-inflammatory cytokines IL-6 and TNF- $\alpha$  by activating astrocytes and microglia through this receptor (Lee et al., 2011).

Astrocytes reside in the extracellular space (ECS) of the CNS and are also involved in the clearance of metabolites from the brain. They are responsible for clearing A $\beta$  from parenchyma through the recently described glymphatic system (Jessen et al., 2015). There is a 60% increase in the ECS during sleep, allowing increased flow of interstitial fluid from para-arterial to para-venous space that doubles the rate of A $\beta$  clearance at night (Cedernaes et al., 2017; Mander et al., 2016). In order for this to occur, low adrenergic input is required to the area. The locus coeruleus (LC), best known for its role in alertness and attention and as a center of noradrenergic neurons, acts as the main driver of metabolite clearance in the brain by reducing its adrenergic input (Mander et al., 2016). Any activation of the LC during the night, which occurs in obstructive sleep apnea (OSA), may affect its role in sleep-mediated memory consolidation (Twigg et al., 2010; Rosenzweig et al., 2016). Conversely, normal activation of adrenergic neurons in the LC during the day is neuroprotective, as noradrenaline (NA) is anti-inflammatory and anti-oxidative (Heneka et al., 2015). NA is also responsible for reducing TNF- $\alpha$  expression in microglia, interferon  $\gamma$ -induced expression of class II antigens in astrocytes, and cytokine induction of type 2 nitric oxide synthase expression in astrocytes and microglia (Feinstein et al., 2016). The number of neurons in the LC naturally declines with age, but this occurs more significantly in individuals with AD (Robinson, 1975; Heneka et al., 2015). In fact, this reduction in LC neurons is significantly correlated with the number of plaques, the number of neurofibrillary tangles, and the severity of dementia (Bondareff et al., 1981, 1987). It is hypothesized that increased damage to the LC in AD pathology results from hyperphosphorylated tau, which appears before tau lesions or A $\beta$  accumulation in the cortex (Braak et al., 2011).

Melatonin, a major hormone controlling circadian rhythm and the sleep-wake cycle, is decreased significantly in the cerebrospinal fluid (CSF) and blood of individuals with AD (Zhou et al., 2003; Wu and Swaab, 2005). Additionally, reductions of MT2, a melatonin receptor, are found in the hippocampus of AD patients (Savaskan et al., 2005, 2002). In addition to its role in the sleep-wake cycle, melatonin inhibits tau phosphorylation (Deng et al., 2005) and reduces the release of APP from neurons (Lahiri, 1999), both hallmarks of AD. Melatonin also plays an anti-inflammatory role by inhibiting the activation of nuclear factor kappa B (NF- $\kappa$ B) (Tamura et al., 2009) and reducing adherence of leukocytes and neutrophils to endothelium, preventing vascular permeability (Lotufo et al., 2006). Melatonin is released from the pineal gland, which can be reduced in volume or undergo calcification in AD (Bumb et al., 2013, 2014).

When A $\beta$  interacts with toll-like receptors in the pineal gland, subsequent release of pro-inflammatory factors inhibit synthesis of melatonin through the NF- $\kappa$ B pathway (Cecon et al., 2015). These pineal gland volume and function changes in AD are also significantly associated with sleep disturbances and insomnia (Matsuoka et al., 2017).

TNF- $\alpha$  plays an important role as a pro-inflammatory cytokine and is elevated in the brains and plasma of individuals with AD (Chang et al., 2017). TNF- $\alpha$  binds to TNFR1 or TNFR2 to activate a cytokine cascade. Overexpression of TNFR1 in the hippocampi of mice resulted in activation of A $\beta$ -induced apoptosis, while mice lacking the receptor exhibited reduced microglial activation and improved cognition performance (He et al., 2007; Li et al., 2004). As noted above, microglia produce TNF- $\alpha$  in response to A $\beta$ . Perpetuating this cycle, TNF- $\alpha$  can then promote A $\beta$  production through upregulation of  $\beta$ -secretase (Liao et al., 2004). IL-1 $\beta$  is another pro-inflammatory cytokine involved in A $\beta$  plaque development that is found in increased levels in the hippocampus and prefrontal cortex of individuals with AD (Cacabelos et al., 1994). IL-6 is a cytokine whose overproduction can lead to neuroinflammation (Rothaug et al., 2016). Elevated levels in midlife predict cognitive decline 10 years later and are elevated in the CSF and plasma of individuals with AD (Blum-Degen et al., 1995; Singh-Manoux et al., 2014). In addition to its release by glial cells in response to A $\beta$ , activation of IL-6 receptors enhance APP transcription and expression (Chong, 1997; Ringheim et al., 1998). Elevated levels of these pro-inflammatory cytokines have also been linked to sleep disturbances, such as excessive daytime sleepiness (EDS), obstructive sleep apnea, and narcolepsy (Vgontzas et al., 1997; Okun et al., 2004). Studies simulating acute sleep loss in humans have shown TNF- $\alpha$ , IL-6, and cellular adhesion molecules to be dysregulated (Vgontzas et al., 2004; Frey et al., 2007; Chennaoui et al., 2011). Even modest sleep restriction is associated with secretion of IL-6 in both men and women and TNF- $\alpha$  in men (Mullington et al., 2016).

It is believed that impaired permeability of the blood-brain barrier (BBB) may be related to neuroinflammation and sleep disruption (Atienza et al., 2018). Specifically, chronic restriction of either total sleep time (He et al., 2014) or REM sleep results in a reduction in BBB integrity (Montagne et al., 2015). Sleep fragmentation may lead to age-related disruption of the BBB's ability to block proinflammatory compounds (Atienza et al., 2018). Increased BBB permeability in aging may augment low-grade inflammation on cerebral integrity and mediate the relationship between disrupted sleep, dysfunctional adiposity, and impaired cognition (Atienza et al., 2018). These results suggest that disturbed sleep may play a causative role in neuroinflammation and subsequent cognitive decline.

Existing human studies on microglia and neuroinflammation are limited in that they do not measure sleep explicitly (Schuitemaker et al., 2009; Olsson et al., 2013) but may hold relevance for possible causal pathways linking poor sleep to cognitive decline. CSF YKL-40, a glycoprotein and biomarker of glial inflammation, is associated with a cerebral structural signature distinct from that related to p-tau

neurodegeneration at the earliest stages of cognitive decline due to AD (Gispert et al., 2016). In order to investigate if microglial markers could differentiate between AD and controls, and secondly between stable MCI and those progressing to AD, the Olsson et al. study quantified YKL-40 and sCD14 in CSF from 96 AD patients, 65 healthy controls, and 170 patients with MCI from baseline and over 5.7 years (Olsson et al., 2013). YKL-40, and not sCD14, was significantly elevated in AD compared with healthy controls ( $p = 0.003$ ). Furthermore, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Olsson et al., 2013), YKL-40 and sCD14 were increased in MCI patients who converted to vascular dementia (VaD) ( $p = 0.029$  and  $p = 0.008$ ), but not to AD. However, when stratified according to CSF levels of tau and A $\beta$ 42, YKL-40 was elevated in those with an AD-indicative profile compared with stable MCI with a normal profile ( $p = 0.037$ ). In addition, YKL-40 and sCD14 were very stable in AD patients with strong correlation between time-points ( $r = 0.94$ ,  $p = 3.4 \times 10^{-25}$ ;  $r = 0.77$ ,  $p = 2.0 \times 10^{-11}$ ) and the cortical damage marker T-tau (Olsson et al., 2013). Thus, microglial markers appear stable for monitoring CNS inflammation and microglia activation in clinical trials (Olsson et al., 2013). Moreover, YKL-40 differentiates between AD and controls, between stable MCI to AD, and those that convert to AD and VaD. In order to clarify the role of disturbed sleep and its impact on neuroinflammation, it will be important to measure sleep explicitly in future studies.

Studies conducted in human subjects have demonstrated that neuroinflammation, which includes microglia activation and increases in the levels of pro-inflammatory cytokines in the brain, may lead to cognitive function decline (Schuitemaker et al., 2009). Schuitemaker et al. (2009) conducted a study examining levels of pro-inflammatory cytokines in patients with MCI and probable AD. In this study, 145 subjects had probable AD and 67 had MCI. Patients were diagnosed with MCI according to Petersen et al. (1999): failing in one or more cognitive domains or a greater cognitive decline than that expected for the person's age or education but not interfering notably with daily activities (Petersen et al., 1999). Patients were diagnosed with probable AD according to McKhann et al. (1984): the gradual worsening of specific cognitive functions such as language, motor skills, and perception (McKhann et al., 1984). The MCI patients were further classified as having either a low-risk or high-risk for AD according to their A $\beta$ 42 and tau levels in CSF, with cut-off values from previously published work (Schoonenboom et al., 2005). High risk CSF consisted of A $\beta$ 42  $\leq$  494 pg/mL and tau > 356 pg/mL and low risk CSF consisted of A $\beta$ 42 > 494 pg/mL and tau > 356 pg/mL. CSF and serum CRP levels were significantly higher in MCI compared to AD patients after adjustment for age, APOE  $\epsilon$ 4 genotype, and cardiovascular diseases. This difference remained present in patients with a low-risk biomarker profile for AD after adjustment for the abovementioned covariates. CSF IL-6 levels were also significantly higher in MCI patients with a low-risk CSF profile (Schuitemaker et al., 2009). Again, these studies have not assessed sleep *per se* but do suggest that associations between

cognitive impairment and sleep noted in the literature may well be reflecting such mediational effects.

## SLEEP DISTURBANCES IN ALZHEIMER'S

The adverse effects of sleep on the production and clearance of proteins have been seen in neurodegenerative diseases such as AD (Ju et al., 2017; Olsson et al., 2018; Shokri-Kojori et al., 2018). Sleep has a role in regulating neuronal activity that affects the release of glymphatic proteins, A $\beta$ , and  $\tau$  (Huang et al., 2012). The brain relies on the glymphatic clearance pathway to remove these waste materials (Xie et al., 2013). Studies have shown positive associations between sleep deprivation, OSA, and increased efflux of these proteins in the brain. Spira et al. (2013) found that older adults with shorter sleep duration have an increase in A $\beta$  (Spira et al., 2013). Another study conducted with healthy volunteers revealed that a night of total sleep deprivation led to a physiological increase in cerebral A $\beta$ 42, an isoform of A $\beta$  (Ooms et al., 2014). A 2-year prospective longitudinal study conducted in community-dwelling healthy older adults found that OSA was associated with markers of increased amyloid burden (Sharma et al., 2018). A study of OSA patients from the Korean Genome and Epidemiology Study revealed significant Pittsburgh compound B (PiB) deposition compared to controls at the right posterior cingulate gyrus and the right temporal cortex; there was no area of higher uptake in the controls compared with the OSA group (Yun et al., 2017). The study found that OSA accelerates amyloid deposition, contributing to the development or progression of AD (Yun et al., 2017).

Clarifying the underlying causes of sleep disturbances in AD can help to improve quality of life and understanding of disease progression. A prior study by Lee et al. (2007) investigating whether reports of daytime sleepiness in AD were correlated with lower functional status showed that EDS is linked to lower quality of life in AD subjects (Lee et al., 2007). EDS has been reported to range from 44.5 (Guarnieri et al., 2012) to 52.1% (Park et al., 2011) in AD patients. Despite this high prevalence, there is a lack of research on the mechanistic causes of sleepiness in AD, which will have important implications for improving quality of life and disease progression.

Recent research reveals a correlation between self-reported EDS and A $\beta$  deposition in cognitively normal subjects (Carvalho et al., 2018; Spira et al., 2018). Spira et al. (2018) showed that EDS is associated with more than 2.5 times the odds of A $\beta$  deposition at follow-up 15.7 years later in 124 cognitively normal subjects (Spira et al., 2018). However, they did not look at objectively measured sleepiness and did not adequately control for variables such as sleep quality, which may be linked to higher CSF A $\beta$  (Ooms et al., 2014); sleep duration, which may influence A $\beta$  accumulation (Spira et al., 2013); or sleep apnea, which is linked to sleepiness and may influence A $\beta$  (Spira et al., 2014; Bu et al., 2015). Another study of 2,172 subjects found that baseline EDS is associated with a longitudinal increase in A $\beta$  accumulation [measured by Pittsburgh compound

B positron emission tomography (PiB-PET)] in elderly persons without dementia (Carvalho et al., 2018). One study of 1,041 non-demented participants over 65 years found that increased daytime sleepiness and sleep inadequacy was a risk factor for development of dementia, which occurred in 78 participants over the following 3 years (Tsapanou et al., 2015). Additionally, increased A $\beta$  deposition in the brainstems of patients with more frequent nocturnal awakenings is associated with cognitive impairment (You et al., 2019). Prior studies have confirmed this link between poor sleep and/or sleep disturbance and cognitive impairment (Blackwell et al., 2006; Tworoger et al., 2006; Xu et al., 2011; Yaffe et al., 2011). A $\beta$  deposition as a result of less adequate sleep, more sleep problems, and greater daytime somnolence has been reported in AD-sensitive brain regions and is associated with greater AD pathology (Sprecher et al., 2015, 2017). This relationship between sleep and A $\beta$  accumulation has also been demonstrated in subjects with pre-clinical AD (Ju et al., 2013). A cross-sectional study of 145 cognitively normal individuals (half of which had a parental history of late-onset AD) measured sleep quality using wrist actigraphy and A $\beta$  levels in CSF samples (Ju et al., 2013). 22% of the sample met their definition of “preclinical” AD, in which CSF A $\beta$ 42 levels were 500 pg/mL or less. This group experienced worse sleep quality and more frequent napping (Ju et al., 2013).

The apolipoprotein (APOE)  $\epsilon$ 4 allele significantly increases one's risk for developing AD. One copy of the allele can increase risk of developing AD by nearly threefold, while two alleles may increase one's risk by 8–15 times (Corder et al., 1993). APOE  $\epsilon$ 4 has also been linked to sleep disturbances. For example, Koo et al. (2019) showed that carriers of the gene more frequently experienced disrupted sleep as compared to non-carriers (Koo et al., 2019). Sleep quality measured by polysomnography (PSG) and wrist actigraphy was also shown to be lower in individuals with APOE  $\epsilon$ 4 as compared to non-carriers (Drogos et al., 2016). Additionally, APOE  $\epsilon$ 4 has been linked to an increased risk of developing sleep apnea (Kadotani et al., 2001; Gottlieb et al., 2004).

## SLEEP DISTURBANCES IN MCI

Sleep disturbances are not restricted to those with AD but are also prevalent in patients with MCI (da Silva, 2015). MCI is viewed as a transitional stage between normal decline of cognitive aging to dementia, which is a general term for loss of memory and other cognitive abilities severe enough to interfere with daily life (Muangpaisan et al., 2008). The specific transition between normal aging and MCI can be subtle and the distinction between MCI and very early dementia is challenging (da Silva, 2015). Patients affected with this condition have a higher conversion rate to AD, with an estimated average rate of 10–15% annually (Muangpaisan et al., 2008). MCI patients may show intermediate levels of electroencephalographically (EEG) defined sleep instability relative to AD patients (Maestri et al., 2015). Sleep disturbance is prevalent and may be predictive of cognitive decline in older adults and in those with neurodegenerative disorders (da Silva, 2015). Though these studies suggest linkage

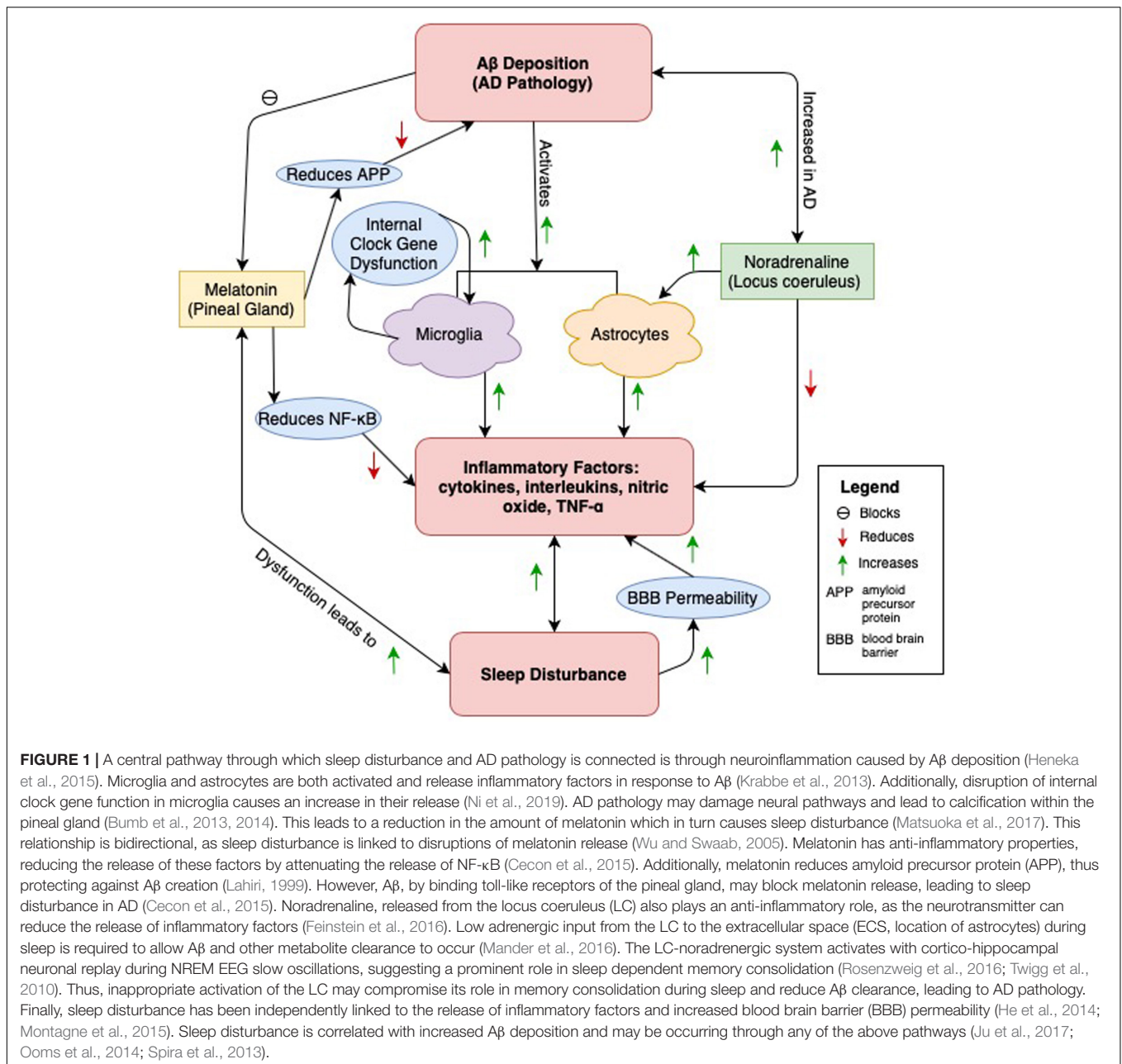
between sleep disturbance and MCI, the underlying mechanisms of sleep disturbances remain unclear.

A prior small case-control study of 16 older adults and 8 MCI subjects found that amnesiac MCI (aMCI) patients had lower delta and theta power during non-REM sleep and spent less time in slow-wave sleep. This is concerning since the sleep changes common in aMCI may interfere with sleep-dependent memory consolidation (Westerberg et al., 2012). Brayet et al. (2016) reported slower EEG frequencies during REM, particularly for amnesiac- relative to non-amnesiac MCI (Brayet et al., 2016). Additionally, at least one study has indicated that the associations between disrupted sleep and impaired cognition in MCI may be, at least in part, moderated by APOE genotype (Hita-Yanez et al., 2012).

## INTEGRATION OF EVIDENCE: NEUROINFLAMMATION AS A MEDIATOR OF THE ASSOCIATION OF SLEEP DISTURBANCE WITH AD

We propose neuroinflammation as the mediator between AD and sleep disturbance. AD and sleep disturbance, as described in **Figure 1**. Evidence has accumulated linking sleep disturbance to A $\beta$  deposits in the brain, particularly in regions that A $\beta$  is typically found in AD. A $\beta$  also serves as a target of inflammatory response, attracting microglia that release cytokines, interleukins, and other potentially cytotoxic molecules. Other pathological changes in melatonin and NA release, both serving roles in sleep-wake neural circuitry and functioning in anti-inflammatory responses, reduce the brain's ability to respond to inflammation generated by A $\beta$  deposition. Sleep disturbances also independently promote a rise in inflammatory cytokines and interleukins and are separately linked to cognitive decline and AD. Fewer studies, however, have examined all three outcomes – AD, sleep disturbance, and inflammatory markers – within a human population. Most have addressed only one or two of these relationships at a time.

Two studies have examined all three outcomes within mouse models. Ni et al. (2019) studied APP knock-in (APP-KI) and wild-type (WT) mice injected with an agonist for REV-ERB designed to reduce expression of *BMAL1*, a central clock gene (Ni et al., 2019). This disruption of CLOCK/BMAL1-driven transcriptional loops impaired microglia in APP-KI mice. This led to NF- $\kappa$ B activation, increasing expression of pro-inflammatory genes (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) (Ni et al., 2019). This study demonstrates that clock gene disturbance in microglia is involved in early onset of AD by inducing chronic neuroinflammation (Ni et al., 2019). Thus, disturbed sleep and its subsequent triggering of inflammatory responses may play a critical role in AD pathology development. Cecon et al. (2015) also studied these outcomes in a mouse model. They treated rat pineal glands with A $\beta$ <sub>1–40</sub> or A $\beta$ <sub>1–42</sub> before inducing melatonin synthesis with NA (Cecon et al., 2015). They found that A $\beta$  interfered with melatonin binding. Additionally, 52 inflammatory genes were upregulated in



response to A $\beta$ . Through the NF- $\kappa$ B pathway, these inflammatory factors inhibited synthesis of melatonin, reducing production of the hormone by 75% (Cecon et al., 2015). This study demonstrates a way in which A $\beta$ , a hallmark of AD, may interfere with sleep regulation through disruption of melatonin via inflammatory pathways.

We have included a summary of the key human and animal studies discussed above in **Table 1**. It is unclear whether sleep disturbance leads to AD through inflammation or whether AD pathology leads to inflammation and subsequent sleep disturbance. The amyloid cascade hypothesis has provided a platform for researchers to target A $\beta$  in hopes of developing effective AD drugs. Given that A $\beta$  deposition triggers

inflammation in the brain, it is hypothesized that treatment of A $\beta$  would solve both problems. However, clinical trials in this area have been lacking. Others have instead focused on the brain's inflammatory response to A $\beta$ , specifically whether non-steroidal anti-inflammatory drugs (NSAIDs) may reduce AD risk or stop progression of the disease. These studies have also been inconclusive (Miguel-Álvarez et al., 2015). Largely missing from the literature are human studies examining all three outcomes: AD pathology, sleep disturbance, and inflammatory markers. Additionally, randomized studies examining the effect of treating sleep disturbance on AD risk would aid in determining the temporal relationship between AD and sleep (Irwin and Vitiello, 2019).

**TABLE 1** | Key studies examining AD, MCI, sleep disturbance and/or inflammation.

Title	Author	Methods	Results	Conclusion
<b>Human studies (AD)</b>				
Microglial markers are elevated in the prodromal phase of Alzheimer's disease and vascular dementia	Olsson et al., 2013	CSF measured from 96 AD patients, 65 healthy controls, and 170 patients with MCI from baseline and over 5.7 years.	When stratified according to CSF levels of tau and A $\beta$ 42, YKL-40 was elevated in those with an AD-indicative profile compared with stable MCI with a normal profile. YKL-40 was significantly elevated in AD subjects and both YKL-40 and sCD14 were increased in MCI patients who converted to vascular dementia.	Biomarker of glial inflammation may be used to differentiate between AD patients, controls, and MCI. Supports microglial inflammation in AD.
Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PIB PET	Spira et al., 2018	One hundred and twenty-eight participants of the Baltimore Longitudinal Study of Aging Neuroimaging Substudy completed subjective excessive daytime sleepiness (EDS) questionnaire, PIB PET scan and MRI. Analysis focused on mean cortical DVR (index of global amyloid deposition) in the frontal, cingulate, lateral temporal, parietal, and lateral occipital regions of the brain.	Patients with EDS had more than 2.5 times the odds of having A $\beta$ deposition an average of 15.7 years later.	Sleepiness may be related to AD pathology and contribute to A $\beta$ deposition.
<b>Human studies (MCI)</b>				
Inflammatory markers in AD and MCI patients with different biomarker profiles	Schuitmaker et al., 2009	Plasma serum and CSF levels of IL-6, ACT, CRP, A $\beta$ 42, p-tau, and total tau taken from 145 patients with probable AD and 67 with MCI. High to low risk MCI was established using A $\beta$ 42/tau profile.	CSF and plasma CRP levels higher in MCI patients ( $p < 0.01$ ), even in those with a low-risk biomarker profile. CSF IL-6 levels higher in MCI patients with low-risk profile.	Inflammation may be involved in AD/cognitive decline before A $\beta$ and tau pathology appears.
<b>Animal studies</b>				
Amyloid $\beta$ peptide directly impairs pineal gland melatonin synthesis and melatonin receptor signaling through the ERK pathway	Cecon et al., 2015	Adult male Wistar rats were kept under 12 h light, 12 h dark cycle. Pineal glands were harvested and then treated with A $\beta$ <sub>1-40</sub> or A $\beta$ <sub>1-42</sub> before stimulation of melatonin synthesis with noradrenaline. HEK293 cells were transfected to express melatonin receptors MT1 and MT2. After A $\beta$ incubation, glands were processed to nuclear protein extraction and supershift assay was performed by incubating protein extracts. TNF content was measured by ELISA kits. Real-time RT-PCR, radioligand binding experiments, microplate BRET assay, and SDS-page were conducted.	Glands incubated with A $\beta$ <sub>1-40</sub> (75% reduction) or A $\beta$ <sub>1-42</sub> (40% reduction) showed impaired noradrenaline-induced NAS and melatonin production. Aarnt mRNA levels were reduced in those treated with A $\beta$ <sub>1-40</sub> . Those treated with A $\beta$ also showed dose-dependent increases in NF- $\kappa$ B. Fifty-two inflammatory genes related to the TLR family, TLR adaptors, MAP kinases of the JNK family, and most cytokine-related genes were upregulated in treated glands. TNF release peaked in response to A $\beta$ . Melatonin receptor MT1 binding sites were reduced by 40% in HEK293 cells treated with A $\beta$ .	A $\beta$ interferes with melatonin binding and signaling and stimulates inflammation in the pineal gland.
An impaired intrinsic microglial clock system induces neuroinflammatory alterations in the early stage of amyloid precursor protein knock-in mouse brain	Ni et al., 2019	Inflammatory and clock genes examined in microglia isolated from 2 month old male amyloid precursor protein knock-in (APP-KI) and wild-type (WT) mice using CAGE deep sequencing and PCR. Mice were kept in dark-light conditions where Zeitgeber time 0 (ZT0) was lights on and ZT12 was lights off. All mice were administered SR9009 (synthetic agonist for REV-ERB) for 14 days. Brain cortical tissues collected from APP-KI mice with and without SR9009 injection. mRNA from isolated microglia of each group at different time points subjected to RT-PCR. Locomotor activity was tested after 14 days of treatment and novel object recognition and Y-maze tests were conducted.	Expression of cortical clock genes occurred at different time points in APP-KI mice, suggesting impaired transcriptional feedback loops. mRNA expression of inflammatory genes were significantly higher in cortical microglia of APP-KI mice, particularly during ZT14. Expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were significantly higher during the day in APP-KI mice. A significant increase in REV-ERB $\alpha$ mRNA was detected in APP-KI after treatment with SR9009. A $\beta$ deposition were observed in hippocampus and cerebral cortex of 6 month old, but not 2 month old, APP-KI mice, but treatment with SR9009 increased expression in 2 month old APP-KI.	Expression of clock genes and pro-inflammatory genes (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) increased in microglia of APP-KI mice. Clock gene disturbance in microglia is involved in onset of AD pathology through the induction of chronic neuroinflammation.

## CONCLUSION

Sleep disturbances are common in both MCI and AD. There is a need to better evaluate the role of neuroinflammation associated with sleep disturbance in the progression of MCI and AD. There are methodological limitations of existing studies that must be acknowledged. Results are supported by a small number of studies, have small sample sizes, often do not differentiate between different subgroups of MCI (amnesiac versus non-amnesiac), and do not consistently address confounders, including several common comorbidities in older adults such as depression or OSA, which could also negatively impact sleep quality and AD biomarkers. Large scale human studies with more comprehensive and objective sleep measures are needed. Future studies should consider the important biological/metabolic signatures associated with sleep disturbance and neuroinflammation, and subsequent

cognitive decline with age. From a clinical perspective, a better understanding of the associations between sleep disturbances, cognitive integrity, and brain integrity in older adults may allow for more targeted preventive strategies that promote healthy aging.

## AUTHOR CONTRIBUTIONS

VP, S-HO, DB, NK, KR, and FO wrote and edited the manuscript.

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**Conflict of Interest:** DB was a consultant for Merck, Eisai, and Ferring in the last 12 months.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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