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Brain changes associated with sleep disruption in cognitively unimpaired older adults: a short review of neuroimaging studies.

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27 **Running title:** Ageing, sleep and brain integrity.

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33
Highlights:

• Sleep disruption is increasingly considered as a risk factor for Alzheimer’s disease.

• Poor sleep is associated with diffuse frontal, temporal and parietal gray matter atrophy.

• Alzheimer’s disease biomarkers are associated with several sleep parameters.

• However, the specificity, topography and causality of these links are unclear.
Abstract: Ageing is characterized by a progressive decline of sleep quality. Sleep difficulties are increasingly recognized as a risk factor for Alzheimer’s disease (AD), and have been associated with cognitive decline. However, the brain substrates underlying this association remain unclear. In this review, our objective was to provide a comprehensive overview of the relationships between sleep changes and brain structural, functional and molecular integrity, including amyloid and tau pathologies in cognitively unimpaired older adults. We especially discuss the topography and causality of these associations, as well as the potential underlying mechanisms. Taken together, current findings converge to a link between several sleep parameters, amyloid and tau levels in the CSF, and neurodegeneration in diffuse frontal, temporal and parietal areas. However, the existing literature remains heterogeneous, and the specific sleep changes associated with early AD pathological changes, in terms of topography and neuroimaging modality, is not clearly established yet. Notably, if slow wave sleep disruption seems to be related to frontal amyloid deposition, the brain correlates of sleep-disordered breathing and REM sleep disruption remains unclear. Moreover, sleep parameters associated with tau- and FDG-PET imaging are largely unexplored. Lastly, whether sleep disruption is a cause or a consequence of brain alterations remains an open question.
1. Introduction

As the worldwide population is ageing, preventing cognitive decline and the development of dementia represents an important challenge. Intense research aims at identifying modifiable lifestyle factors that might help to promote healthy ageing. Among them, sleep is receiving particular attention, as about 50% of older adults complain of poor sleep (Foley et al., 1995).

Age-related changes consist, at the circadian level, in advanced sleep timing and reduced amplitude of the circadian rhythms (Duffy et al., 2015; Kondratova and Kondratov, 2012). Sleep changes include longer sleep latency, decreased sleep duration, and increased number and duration of nocturnal awakenings, resulting in greater sleep fragmentation and lower sleep efficiency (Li et al., 2018; Ohayon et al., 2004). Remarkably, the amount of slow wave sleep (SWS), the deepest non-rapid eye movement (NREM) sleep stage, linearly decreases across the adult lifespan, contrasting with the increase of lighter NREM sleep (especially stage N1). Substantial changes in NREM sleep oscillations such as delta waves (Carrier et al., 2001; Landolt et al., 1996; Schwarz et al., 2017) and sleep spindles, key features of N2 sleep (Crowley et al., 2002; Schwarz et al., 2017) are also reported. Rapid-eye movement (REM) sleep time is reduced with age, albeit to a lesser extent and later in life than SWS (Floyd et al., 2007; Ohayon et al., 2004). Finally, 30 to 80% of older adults suffer from sleep-disordered breathing (SDB; Senaratna et al., 2017), a respiratory disorder defined by recurrent upper airway collapse during sleep, resulting in intermittent hypoxia episodes and sleep fragmentation, which may trigger neurodegenerative processes.

Sleep is essential for an optimal daytime cognitive functioning, notably for attention, executive functioning, memory, and synaptic plasticity (Buzsáki, 1996; Killgore, 2010; Lowe et al., 2017; Tononi and Cirelli, 2006). In older adults, growing evidence show that sleep disturbances may represent a risk factor for cognitive decline and dementia. Indeed, longitudinal studies indicate that poor self-reported sleep quality, short but also long sleep
duration (i.e., <7 or >8 hours of sleep), longer sleep latency, lower sleep efficiency, greater sleep fragmentation, decreased REM sleep, excessive daytime sleepiness and SDB are associated with cognitive decline and incident mild cognitive impairment or dementia diagnosis (Bubu et al., 2017; Diem et al., 2016; Foley et al., 2001; Gabelle et al., 2017; Leng et al., 2017; Lim et al., 2013a; Pase et al., 2017; Song et al., 2015; Virta et al., 2013). As Alzheimer’s disease (AD) pathology develops several years before the first clinical symptoms (Jack et al., 2018), it is crucial to better understand the associations between sleep disturbances and brain integrity (including AD biomarkers) in older adults who are still cognitively unimpaired. Thus, our objective was to summarize existing data about these associations, with an emphasis on their topography and causality, and discuss the potential underlying mechanisms. We focused the present short review on papers published during the last decade (i.e., between 2010 and November 2020), involving cognitively unimpaired older adults, with no history or current diagnosis of major neurological or psychiatric diseases, or any other major medical condition.

2. Sleep quality and gray matter volume changes

Cross-sectional studies show that lower grey matter (GM) volume within frontal areas is one of the brain changes most consistently associated with sleep quality in cognitively unimpaired older adults (Table 1). Sleep parameters associated with frontal atrophy include self-reported poor sleep quality (Sexton et al., 2014) and inadequate sleep duration (Lo et al., 2014; Westwood et al., 2017), early-morning awakenings (Stoffers et al., 2012), excessive daytime sleepiness (Killgore et al., 2012), greater sleep fragmentation obtained from actigraphy (Lim et al., 2016), and decreased slow wave activity (Dubé et al., 2015; Lareille et al., 2019; Mander et al., 2013).
In addition, reduced GM volume in lateral and medial temporal regions (including the hippocampus and the amygdala), the thalamus, and parietal cortex, have been associated with poor self-reported sleep quality (Alperin et al., 2019; Liu et al., 2018), inadequate sleep duration (Lo et al., 2014; Westwood et al., 2017) and excessive daytime sleepiness (Carvalho et al., 2017). Branger et al. (2016) also found an association between a higher number of self-reported nocturnal awakenings and lower GM volume in the insula. Importantly, these findings are supported by studies using actigraphy or polysomnography. Indeed, SWS integrity has been associated with GM volume in parietal and insular cortices (Dubé et al., 2015), and reduced GM volume in medial temporal areas has been related to greater sleep-wake rhythm fragmentation (Van Someren et al., 2019). GM volume changes associated with SDB in older adults vary importantly, some studies showing atrophy (Huang et al., 2019; Shi et al., 2017; Tahmasian et al., 2016; Weng et al., 2014) in frontal, temporal and parietal areas, while others rather report hypertrophy (André et al., 2020; Baril et al., 2017; Cross et al., 2018; Rosenzweig et al., 2013) in the same brain areas.

A few longitudinal studies reported that self-estimated poor sleep quality (Fjell et al., 2019; Sexton et al., 2014) and short sleep duration (Lo et al., 2014; Spira et al., 2016) are associated with an increased rate of atrophy within frontal, temporal (including the hippocampus) and parietal areas. However, long self-reported sleep duration (> 7h) has also been related to a higher rate of frontal GM atrophy (Spira et al., 2016).

3. Sleep, brain glucose metabolism and perfusion changes

Only a few studies have explored the associations between sleep quality and resting-state glucose metabolism using $^{18}$F-fluorodeoxyglucose (FDG) Positron Emission Tomography
(PET), or perfusion, using Arterial Spin Labeling (ASL) or Single Photon Emission Computed Tomography (SPECT) imaging (see Table 1).

In cognitively unimpaired older adults, if self-reported sleep measures were not associated to glucose metabolism (Branger et al., 2016), greater sleep fragmentation obtained from actigraphy was related to lower glucose metabolism within the ventromedial prefrontal cortex and the hippocampi (André et al., 2019). In addition, as for GM volume, SDB has been related to both lower (Baril et al., 2020, 2015; Innes et al., 2015; Kim et al., 2017; Nie et al., 2017) and greater (André et al., 2020; Baril et al., 2015; Nie et al., 2017) metabolism and/or perfusion mainly in frontal, temporal and parietal areas, including the precuneus and posterior cingulate cortex (Table 1).

4. Sleep and amyloid pathology

In animal models of Alzheimer’s disease and in humans, amyloid-ß peptide (Aß) levels fluctuate following a circadian pattern, increasing with wakefulness and decreasing during NREM sleep (Kang et al., 2009). Whether this effect is mainly attributable to decreased metabolic activity during SWS, and/or increased metabolites clearance through the “glymphatic system” (Tarasoff-Conway et al., 2015a; Xie et al., 2013) is still debated. Nevertheless, the circadian fluctuations of Aß levels in the cerebrospinal fluid (CSF) are attenuated with ageing and with increased Aß deposition (Huang et al., 2012; Roh et al., 2012).

In cognitively unimpaired older adults, various sleep parameters have been associated with greater global Aß levels measured in the CSF or using PET, including poorer self-reported sleep quality, both cross-sectionally (Sprecher et al., 2017) and longitudinally (Fjell et al., 2018), longer subjective (Brown et al., 2016) and objective (Ettore et al., 2019) sleep latency, both
insufficient and long self-reported sleep duration (Spira et al., 2013; Xu et al., 2020), lower sleep efficiency (Ettore et al., 2019; Ju et al., 2013; Molano et al., 2017), increased sleep fragmentation (Ettore et al., 2019; Lucey et al., 2019; Wilckens et al., 2018), excessive daytime sleepiness (Xu et al., 2020), and altered slow wave activity (SWA) (Ju et al., 2017; Varga et al., 2016; Winer et al., 2019) (Table 1). Furthermore, Mander et al., (2015) showed that amyloid burden in medial prefrontal areas disrupts SWA, negatively affecting sleep-dependent memory consolidation. In addition, Winer et al. (2020) showed that decreased SWA and sleep efficiency significantly predicted the subsequent Aβ accumulation over several years.

Studies using regional approaches have revealed that greater amyloid deposition in frontal and/or parietal areas, including the precuneus and posterior cingulate cortex, is associated with lower self-reported sleep quality (Sprecher et al., 2017), longer self-reported sleep latency (Branger et al., 2016), lower subjective sleep adequacy (Sprecher et al., 2015), corresponding to insufficient sleep quality and duration, and excessive daytime sleepiness, both cross-sectionally (Sprecher et al., 2015) and longitudinally (Carvalho et al., 2018). Short sleep duration has been associated with greater amyloid deposition in the precuneus (Spira et al., 2013), but this result failed replication by Gabelle et al. (2019).

Lastly, SBD has also been related to higher amyloid levels measured in the CSF or using PET imaging (both cross-sectionally and longitudinally) (Bu et al., 2015; Bubu et al., 2019; Jackson et al., 2020; Kong et al., 2020; Liguori et al., 2017; Sharma et al., 2018; Ylä-Herttuala et al., 2020), and specifically in the posterior cingulate cortex and the precuneus (André et al., 2020; Ylä-Herttuala et al., 2020; Yun et al., 2017).

5. Sleep and tau pathology
Besides Aβ deposition, sleep disruption may also exacerbate tau pathology in older adults without cognitive deficits, the second pathophysiological hallmark of AD (Holth et al., 2019). Self-estimated poor sleep quality and excessive daytime sleepiness have been associated with higher t-tau and p-tau/Aβ42 ratios (Sprecher et al., 2017). In addition, Fjell et al. (2018) showed that CSF tau levels predict poor sleep quality in amyloid-positive older adults. Moreover, CSF tau levels increased after one night of sleep deprivation (Holth et al., 2019), and are associated with greater sleep fragmentation (Lim et al., 2013b) and lower sleep efficiency (Ju et al., 2017). Interestingly, in this latter study, the association between sleep and tau was mainly driven by increased neuronal activity during sleep. Moreover, patients with SDB also exhibit increased CSF tau levels, both cross-sectionally (Bu et al., 2015; Kong et al., 2020; Liguori et al., 2017) and longitudinally (Bubu et al., 2019).

Recent studies using tau-PET imaging have provided mixed results (Table 1). Lucey et al. (2019) reported that both amyloid and tau pathologies are associated with decreased SWA, with a stronger link for tau. In contrast, Winer et al. (2019) did not report any direct association between tau in the medial temporal lobe and prefrontal SWA, but rather a relationship between medial temporal tau burden and altered coupling between slow waves and sleep spindles. However, research using tau-PET imaging is still in their infancy, and further studies are needed to unravel the associations between tau pathology and sleep quality.

6. Discussion

Poor sleep quality in cognitively unimpaired older adults is associated with diffuse and heterogeneous structural, functional and molecular brain changes in frontal, temporal and parietal areas. While some of these brain substrates are consistent with early pathological
changes observed in AD, other sleep-associated brain changes seem less suggestive of AD, both in terms of topography and nature of brain alterations involved.

Indeed, frontal amyloid burden is associated with self-reported sleep difficulties (Branger et al., 2016; Sprecher et al., 2017, 2015). Moreover, SWS disruption appears to be robustly associated with amyloid pathology (Ju et al., 2017; Varga et al., 2016), notably in medial prefrontal areas (Mander et al., 2015). Interestingly, AD is defined by the presence of amyloid deposition (Jack et al., 2018) spreading from frontal areas, before the appearance of cognitive deficits.

Moreover, self-reported sleep difficulties (Alperin et al., 2019; Carvalho et al., 2017; Fjell et al., 2019) and greater fragmentation of the sleep/wake rhythm (Van Someren et al., 2019) have been linked to medial temporal lobe (MTL) atrophy. Of note, SDB has been related to both reduced (Huang et al., 2019; Tahmasian et al., 2016; Weng et al., 2014) and greater (Cross et al., 2018; Rosenzweig et al., 2013) MTL volume. It seems crucial to better characterize sleep parameters associated with MTL atrophy, as medial temporal areas are known to be affected by tau pathology and atrophied since AD pre-dementia stages (Braak and Braak, 1991; Villemagne and Chételat, 2016). In addition, beyond the MTL, tau pathology also affects the brainstem, which is involved in sleep-wake regulation and REM sleep generation (Horner and Peever, 2017).

REM sleep is reduced in AD patients (Brayet et al., 2016; Hassainia et al., 1997; Hita-Yañez et al., 2012; Montplaisir et al., 1995) and this alteration is predictive of cognitive decline in older adults (Pase et al., 2017). Liguori et al. (2020) have recently demonstrated that REM sleep reduction is associated with increased CSF tau levels, in a cohort of cognitively healthy older adults and patients with subjective cognitive decline, mild cognitive impairment and AD. However, due to the relatively recent emergence of tau-PET neuroimaging, the relationships between REM sleep changes and tau pathology in the brainstem and medial temporal areas remains to be clarified, specifically in cognitively normal older populations.
Lastly, the associations between sleep changes and glucose metabolism have been much less investigated. SDB has been associated with decreased metabolism and/or perfusion in posterior parietal areas (Baril et al., 2015; Yaouhi et al., 2009), but increases have also been reported (André et al., 2020). Taken together, it is unclear whether sleep quality is associated with the marked hypometabolism in posterior cingulate and precuneus areas observed in AD and mild cognitive impairment patients (Chételat et al., 2003; Minoshima et al., 1997; Schroeter et al., 2009).

Besides, sleep modifications have been linked to other brain changes which seem less directly suggestive of early AD pathological processes, and could rather reflect normal ageing processes. Indeed, GM atrophy in frontal and parietal areas is robustly associated with SWS disruption, in particular decreased slow wave activity (Dubé et al., 2015; Latreille et al., 2019; Mander et al., 2013). These results are consistent with the fact that these regions are involved in sleep physiology and the generation of slow waves (Massimini et al., 2004; Murphy et al., 2009). Moreover, greater sleep fragmentation is related to lower frontal GM volume (Lim et al., 2016) and fronto-hippocampal metabolism (André et al., 2019), two areas critical for sleep-dependent memory consolidation (Buzsáki, 1996; Maingret et al., 2016). The brain correlates of SDB appear however still conflicting, with both positive and negative associations with frontal GM volume and metabolism, MTL metabolism, and parietal GM volume (see Table 1). The pattern of SDB-related neuronal hyperactivity (i.e., greater GM volume, metabolism and perfusion) reported in some studies could reflect acute and early reactive processes, likely due to neuroinflammation in response to hypoxia. This neuronal hyperactivity may also reflect compensatory mechanisms due to greater individual brain reserve, which may help to maintain cognitive performance in the normal range by increasing brain activity. Importantly, these acute changes may only be temporary and may trigger neurodegeneration (i.e., GM
atrophy and hypometabolism) and the development of cognitive deficits over time. Longitudinal studies combining several neuroimaging modalities on large cohorts with various levels of SDB severity will be necessary to confirm this hypothesis.

Frontal, temporal and posterior parietal regions thus constitute common brain substrates between sleep physiology and AD pathology, but a critical question is whether sleep disturbances are causal and/or consecutive to brain alterations. First, AD pathology located in frontal, medial temporal and brainstem areas, involved in sleep rhythms, could disrupt sleep quality, eventually impairing cognitive performance. Supporting this hypothesis, atrophy and amyloid burden within medial prefrontal areas have been shown to disrupt SWS (Mander et al., 2015, 2013), ultimately impairing sleep-dependent memory consolidation. Moreover, sleep disruption may also mediate or moderate the association between brain alterations and cognitive performance. Indeed, poor self-estimated sleep quality (Molano et al., 2017) and increased nocturnal wakefulness (Wilckens et al., 2018) moderate the association between amyloid burden and memory performance. Lastly, greater sleep fragmentation mediates the association between fronto-hippocampal hypometabolism and poorer executive functioning (André et al., 2019).

However, it is likely that the links between sleep and brain alterations are bidirectional (Ju et al., 2014). Indeed, the consequence of disrupted sleep is to increase the amount of wakefulness during sleep and to decrease the amount of sleep per se. Subsequently, greater neuronal activity and reduced brain clearance function may result in greater amyloid and tau release (Fig. 1). If increased activity and reduced clearance are likely to co-exist, their respective contributions are unclear. A pilot study in humans showed that these links are mainly driven by increased Aβ secretion, and not by decreased clearance (Lucey et al., 2018). However, the study of brain clearance mechanisms is a recent area of research. In mice, clearance through the blood brain barrier and interstitial fluid bulk-flow seem to be both implicated in amyloid
clearance and related to sleep quality (Rasmussen et al., 2018; Tarasoff-Conway et al., 2015b; Xie et al., 2013). Notably, the glymphatic system hypothesis proposes that arterial pulsations drive waste clearance through a directional convective flow of CSF, from periarterial areas in the deep brain parenchyma to the perivenous spaces. This process implicates water channels, like aquaporin-4, located in glial cells (Iliff et al., 2013, 2012; Nedergaard, 2013), and is facilitated during sleep (Xie et al., 2013). Nevertheless, several aspects of this model are currently debated (Mestre et al., 2020), and most findings in mice are pending replication in humans, as non-invasive neuroimaging tools of clearance mechanisms are still under development. Moreover, the associations with AD pathology remain to be confirmed. In healthy young subjects, a promising recent study demonstrated that slow waves during NREM sleep are followed by hemodynamic oscillations, which are in turn coherent with large waves of CSF (Fultz et al., 2019).

7. Conclusion

Age-related sleep disruption is associated with brain changes mainly in frontal, temporal and parietal areas, some of them being suggestive of early AD pathological changes. These links may explain why sleep disruption is related to lower cognitive performance and steeper cognitive decline. However, the specific aspects of sleep disruption involved in these associations, the impact on tau pathology, and the associations with disrupted brain clearance mechanisms during sleep remain to be further explored. In addition, if we only discussed the associations between sleep disruption and regional GM integrity and functioning, sleep-related changes in structural and functional connectivity specifically in cognitively unimpaired older adults are a promising area of research. From a clinical perspective, it is crucial to screen for sleep problems in older adults, as they may exacerbate AD.
pathophysiological mechanisms and may represent a modifiable lifestyle factor contributing to healthy ageing.

8. Competing interests

None declared.

9. References


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Figure 1. Summary of the associations between sleep, brain and cognitive integrity in older adults.

Abbreviations: PFC: prefrontal cortex; MTL: medial temporal lobe; PCC: posterior cingulate cortex; REM-S: rapid eye movement sleep; SD: sleep deprivation; SDB: sleep-disordered breathing; SF: sleep fragmentation; SWS: slow wave sleep.

Studies show that poor sleep quality in older adults is associated with decreased gray matter volume in frontal, temporal and parietal areas, increased global, frontal, and parietal amyloid levels, as well as increased global tau levels. These brain areas are both sensitive to ageing and Alzheimer’s disease, and some of them (notably frontal areas) are involved in the generation and maintenance of sleep oscillations. Their alteration contributes to the aggravation of amyloid and tau pathologies and may explain why poor sleep quality is associated with an increased risk of cognitive decline.
<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>Method</th>
<th>Grey matter volume</th>
<th>Perfusion and glucose metabolism(^1)</th>
<th>Amyloid pathology(^2)</th>
<th>Tau pathology(^3)</th>
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<tr>
<td>Sleep deprivation</td>
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<td>Global levels (Ooms 2014)</td>
<td>Global levels (Holth 2019)</td>
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<tr>
<td>Excessive daytime sleepiness</td>
<td>Self-reported</td>
<td>MTL, frontal, parietal and occipital (Carvalho 2017)</td>
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<td>Global levels (Xu 2020), frontal &amp; parietal (Sprecher 2015)</td>
<td>Global levels (Sprecher 2017)</td>
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<td>Sleep latency</td>
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<td>Global levels (Brown 2016), frontal (Branger 2016)</td>
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<td>Sleep efficiency</td>
<td>Objective</td>
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<td>Global levels (Ju 2013, Molano 2017, Ettore 2019)</td>
<td>Global levels (Ju 2017)</td>
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<td>Short sleep duration</td>
<td>Self-reported</td>
<td>Global atrophy (Lo 2014), <em>Longitudinal: fronto-temporal (Spira 2016: ≤7h)</em></td>
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<td>Global levels (Spira 2013, Xu 2020: ≤6h) &amp; precuneus (Spira 2013: ≤6h)</td>
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<td></td>
<td>Self-reported</td>
<td>Global atrophy (Westwood 2017: ≥9h), occipital (Spira 2016: &gt;7h), <em>Longitudinal: frontal (Spira 2016: &gt;7h)</em></td>
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<td>Long sleep duration</td>
<td>Self-reported</td>
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<td>Global levels (Xu 2020: ≥6h)</td>
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<td>Nocturnal awakenings &amp; sleep</td>
<td>Self-reported</td>
<td>OFC (Stoffers 2012, early awakenings), insula (Branger 2016, nocturnal awakenings)</td>
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<td>Global levels (Wilckens 2018, Lucey 2019, Ettore 2019)</td>
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<td></td>
<td>Objective</td>
<td>Frontal (Lim 2016)</td>
<td>Frontal &amp; hippocampus (André 2019)</td>
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<td>Sleep-wake rhythm fragmentation</td>
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<td>MTL (Van Someren 2018)</td>
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<td>Objective</td>
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<td>Sleep spindles</td>
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Table 1. Summary of the associations between sleep parameters and brain integrity in older adults.

<table>
<thead>
<tr>
<th>REM sleep latency</th>
<th>Objective</th>
<th>Global levels (Lucey 2019)</th>
<th>Global levels (Elias 2018)</th>
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<td>Self-reported</td>
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<td>SDB</td>
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Table 1. Summary of the associations between sleep parameters and brain integrity in older adults.


When meta-analyses (in bold) were available, original studies showing the same results were not mentioned. Objective sleep measures encompass actigraphy and polysomnography measures. Longitudinal studies are indicated in italics.

1 Brain perfusion was measured using ASL (Innes et al., 2015; Nie et al., 2017) or SPECT imaging (Joo et al., 2007; Shiota et al., 2014; Baril et al., 2015, 2020; Kim et al., 2017), and brain glucose metabolism using FDG-PET (Yaouhi et al., 2009; Wilckens et al., 2016; André et al., 2019, 2020).

2 Amyloid levels were measured in the CSF (Ju et al., 2013; Ooms et al., 2014; Osorio et al., 2014; Varga et al., 2016; Liguori et al., 2017; Sprecher et al., 2017; Molano et al., 2017; Ju et al., 2017; Fjell et al., 2018; Sharma et al., 2018; Bubu et al., 2019; Liguori et al., 2020; Kong 2020; Xu 2020), the blood (Bu et al., 2015) or using PET imaging (Spira et al., 2013; Mander et al., 2015; Sprecher et al., 2015; Branger et al., 2016; Brown et al., 2016; Yun et al., 2017; Elias et al., 2018; Wilckens et al., 2018; Spira et al., 2018; Carvalho et al., 2018; Lucey et al., 2019; Ettore et al., 2019; Winer et al., 2019, 2020; Bubu et al., 2019, André et al., 2020; Jackson et al., 2020; Ylä-Herttuala et al., 2020).
Tau levels were measured in the CSF (Osorio et al., 2014; Ju et al., 2016; Liguori et al., 2017; Sprecher et al., 2017; Ju et al., 2017; Fjell et al., 2018; Bubu et al., 2019; Ju et al., 2019; Holth et al., 2019; Kam et al., 2019; Liguori et al., 2020; Kong 2020), the blood (Bu et al., 2015; Motamedi et al., 2018), using PET imaging (Lucey et al., 2019; Winer et al., 2019), or at autopsy (Lim et al., 2013b).