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1 **Title page**

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

5

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

28

29 **Keywords:** Sleep, Ageing, Alzheimer's disease, Neuroimaging, Amyloid, Tau.

30

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33

34 **Highlights:**

- 35 • Sleep disruption is increasingly considered as a risk factor for Alzheimer's disease.
- 36 • Poor sleep is associated with diffuse frontal, temporal and parietal gray matter atrophy.
- 37 • Alzheimer's disease biomarkers are associated with several sleep parameters.
- 38 • However, the specificity, topography and causality of these links are unclear.

39

40

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

57

58 **1. Introduction**

59 As the worldwide population is ageing, preventing cognitive decline and the development of
60 dementia represents an important challenge. Intense research aims at identifying modifiable
61 lifestyle factors that might help to promote healthy ageing. Among them, sleep is receiving
62 particular attention, as about 50% of older adults complain of poor sleep (Foley et al., 1995).
63 Age-related changes consist, at the circadian level, in advanced sleep timing and reduced
64 amplitude of the circadian rhythms (Duffy et al., 2015; Kondratova and Kondratov, 2012). Sleep
65 changes include longer sleep latency, decreased sleep duration, and increased number and
66 duration of nocturnal awakenings, resulting in greater sleep fragmentation and lower sleep
67 efficiency (Li et al., 2018; Ohayon et al., 2004). Remarkably, the amount of slow wave sleep
68 (SWS), the deepest non-rapid eye movement (NREM) sleep stage, linearly decreases across
69 the adult lifespan, contrasting with the increase of lighter NREM sleep (especially stage N1).
70 Substantial changes in NREM sleep oscillations such as delta waves (Carrier et al., 2001;
71 Landolt et al., 1996; Schwarz et al., 2017) and sleep spindles, key features of N2 sleep (Crowley et
72 al., 2002; Schwarz et al., 2017) are also reported. Rapid-eye movement (REM) sleep time is
73 reduced with age, albeit to a lesser extent and later in life than SWS (Floyd et al., 2007; Ohayon
74 et al., 2004). Finally, 30 to 80% of older adults suffer from sleep-disordered breathing (SDB;
75 Senaratna et al., 2017), a respiratory disorder defined by recurrent upper airway collapse during
76 sleep, resulting in intermittent hypoxia episodes and sleep fragmentation, which may trigger
77 neurodegenerative processes.

78 Sleep is essential for an optimal daytime cognitive functioning, notably for attention,
79 executive functioning, memory, and synaptic plasticity (Buzsáki, 1996; Killgore, 2010; Lowe et
80 al., 2017; Tononi and Cirelli, 2006). In older adults, growing evidence show that sleep
81 disturbances may represent a risk factor for cognitive decline and dementia. Indeed,
82 longitudinal studies indicate that poor self-reported sleep quality, short but also long sleep

83 duration (i.e., <7 or >8 hours of sleep), longer sleep latency, lower sleep efficiency, greater
84 sleep fragmentation, decreased REM sleep, excessive daytime sleepiness and SDB are
85 associated with cognitive decline and incident mild cognitive impairment or dementia
86 diagnosis (Bubu et al., 2017; Diem et al., 2016; Foley et al., 2001; Gabelle et al., 2017; Leng et al.,
87 2017; Lim et al., 2013a; Pase et al., 2017; Song et al., 2015; Virta et al., 2013). As Alzheimer's
88 disease (AD) pathology develops several years before the first clinical symptoms (Jack et al.,
89 2018), it is crucial to better understand the associations between sleep disturbances and brain
90 integrity (including AD biomarkers) in older adults who are still cognitively unimpaired.
91 Thus, our objective was to summarize existing data about these associations, with an
92 emphasis on their topography and causality, and discuss the potential underlying mechanisms.
93 We focused the present short review on papers published during the last decade (i.e., between
94 2010 and November 2020), involving cognitively unimpaired older adults, with no history or
95 current diagnosis of major neurological or psychiatric diseases, or any other major medical
96 condition.

97

98 **2. Sleep quality and gray matter volume changes**

99 Cross-sectional studies show that lower grey matter (GM) volume within frontal areas is one
100 of the brain changes most consistently associated with sleep quality in cognitively unimpaired
101 older adults (**Table 1**). Sleep parameters associated with frontal atrophy include self-reported
102 poor sleep quality (Sexton et al., 2014) and inadequate sleep duration (Lo et al., 2014; Westwood
103 et al., 2017), early-morning awakenings (Stoffers et al., 2012), excessive daytime sleepiness
104 (Killgore et al., 2012), greater sleep fragmentation obtained from actigraphy (Lim et al., 2016),
105 and decreased slow wave activity (Dubé et al., 2015; Latreille et al., 2019; Mander et al., 2013).

106 In addition, reduced GM volume in lateral and medial temporal regions (including the
107 hippocampus and the amygdala), the thalamus, and parietal cortex, have been associated with
108 poor self-reported sleep quality (Alperin et al., 2019; Liu et al., 2018), inadequate sleep duration
109 (Lo et al., 2014; Westwood et al., 2017) and excessive daytime sleepiness (Carvalho et al., 2017).
110 Branger et al. (2016) also found an association between a higher number of self-reported
111 nocturnal awakenings and lower GM volume in the insula. Importantly, these findings are
112 supported by studies using actigraphy or polysomnography. Indeed, SWS integrity has been
113 associated with GM volume in parietal and insular cortices (Dubé et al., 2015), and reduced
114 GM volume in medial temporal areas has been related to greater sleep-wake rhythm
115 fragmentation (Van Someren et al., 2019). GM volume changes associated with SDB in older
116 adults vary importantly, some studies showing atrophy (Huang et al., 2019; Shi et al., 2017;
117 Tahmasian et al., 2016; Weng et al., 2014) in frontal, temporal and parietal areas, while others
118 rather report hypertrophy (André et al., 2020; Baril et al., 2017; Cross et al., 2018; Rosenzweig et al.,
119 2013) in the same brain areas.

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

125

126 **3. Sleep, brain glucose metabolism and perfusion changes**

127 Only a few studies have explored the associations between sleep quality and resting-state
128 glucose metabolism using ¹⁸F-fluorodeoxyglucose (FDG) Positron Emission Tomography

129 (PET), or perfusion, using Arterial Spin Labeling (ASL) or Single Photon Emission
130 Computed Tomography (SPECT) imaging (see **Table 1**).

131

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

140

141 **4. Sleep and amyloid pathology**

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

149 In cognitively unimpaired older adults, various sleep parameters have been associated with
150 greater global A β levels measured in the CSF or using PET, including poorer self-reported
151 sleep quality, both cross-sectionally (Sprecher et al., 2017) and longitudinally (Fjell et al., 2018),
152 longer subjective (Brown et al., 2016) and objective (Ettore et al., 2019) sleep latency, both

153 insufficient and long self-reported sleep duration (Spira et al., 2013; Xu et al., 2020), lower
154 sleep efficiency (Ettore et al., 2019; Ju et al., 2013; Molano et al., 2017), increased sleep
155 fragmentation (Ettore et al., 2019; Lucey et al., 2019; Wilckens et al., 2018), excessive daytime
156 sleepiness (Xu et al., 2020), and altered slow wave activity (SWA) (Ju et al., 2017; Varga et al.,
157 2016; Winer et al., 2019) (**Table 1**). Furthermore, Mander et al., (2015) showed that amyloid
158 burden in medial prefrontal areas disrupts SWA, negatively affecting sleep-dependent
159 memory consolidation. In addition, Winer et al. (2020) showed that decreased SWA and sleep
160 efficiency significantly predicted the subsequent A β accumulation over several years.

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

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

174

175 **5. Sleep and tau pathology**

176 Besides A β deposition, sleep disruption may also exacerbate tau pathology in older adults
177 without cognitive deficits, the second pathophysiological hallmark of AD (Holth et al., 2019).
178 Self-estimated poor sleep quality and excessive daytime sleepiness have been associated with
179 higher t-tau and p-tau/A β 42 ratios (Sprecher et al., 2017). In addition, Fjell et al. (2018) showed
180 that CSF tau levels predict poor sleep quality in amyloid-positive older adults. Moreover, CSF
181 tau levels increased after one night of sleep deprivation (Holth et al., 2019), and are associated
182 with greater sleep fragmentation (Lim et al., 2013b) and lower sleep efficiency (Ju et al., 2017).
183 Interestingly, in this latter study, the association between sleep and tau was mainly driven by
184 increased neuronal activity during sleep. Moreover, patients with SDB also exhibit increased
185 CSF tau levels, both cross-sectionally (Bu et al., 2015; Kong et al., 2020; Liguori et al., 2017) and
186 longitudinally (Bubu et al., 2019).

187 Recent studies using tau-PET imaging have provided mixed results (**Table 1**). Lucey et al.
188 (2019) reported that both amyloid and tau pathologies are associated with decreased SWA,
189 with a stronger link for tau. In contrast, Winer et al. (2019) did not report any direct association
190 between tau in the medial temporal lobe and prefrontal SWA, but rather a relationship
191 between medial temporal tau burden and altered coupling between slow waves and sleep
192 spindles. However, research using tau-PET imaging is still in their infancy, and further studies
193 are needed to unravel the associations between tau pathology and sleep quality.

194

195 **6. Discussion**

196 Poor sleep quality in cognitively unimpaired older adults is associated with diffuse and
197 heterogeneous structural, functional and molecular brain changes in frontal, temporal and
198 parietal areas. While some of these brain substrates are consistent with early pathological

199 changes observed in AD, other sleep-associated brain changes seem less suggestive of AD,
200 both in terms of topography and nature of brain alterations involved.

201 Indeed, frontal amyloid burden is associated with self-reported sleep difficulties (Branger et al.,
202 2016; Sprecher et al., 2017, 2015). Moreover, SWS disruption appears to be robustly associated
203 with amyloid pathology (Ju et al., 2017; Varga et al., 2016), notably in medial prefrontal areas
204 (Mander et al., 2015). Interestingly, AD is defined by the presence of amyloid deposition (Jack
205 et al., 2018) spreading from frontal areas, before the appearance of cognitive deficits.

206 Moreover, self-reported sleep difficulties (Alperin et al., 2019; Carvalho et al., 2017; Fjell et al.,
207 2019) and greater fragmentation of the sleep/wake rhythm (Van Someren et al., 2019) have been
208 linked to medial temporal lobe (MTL) atrophy. Of note, SDB has been related to both reduced
209 (Huang et al., 2019; Tahmasian et al., 2016; Weng et al., 2014) and greater (Cross et al., 2018;
210 Rosenzweig et al., 2013) MTL volume. It seems crucial to better characterize sleep parameters
211 associated with MTL atrophy, as medial temporal areas are known to be affected by tau
212 pathology and atrophied since AD pre-dementia stages (Braak and Braak, 1991; Villemagne and
213 Chételat, 2016). In addition, beyond the MTL, tau pathology also affects the brainstem, which
214 is involved in sleep-wake regulation and REM sleep generation (Horner and Peever, 2017).
215 REM sleep is reduced in AD patients (Brayet et al., 2016; Hassainia et al., 1997; Hita-Yañez et al.,
216 2012; Montplaisir et al., 1995) and this alteration is predictive of cognitive decline in older
217 adults (Pase et al., 2017). Liguori et al. (2020) have recently demonstrated that REM sleep
218 reduction is associated with increased CSF tau levels, in a cohort of cognitively healthy older
219 adults and patients with subjective cognitive decline, mild cognitive impairment and AD.

220 However, due to the relatively recent emergence of tau-PET neuroimaging, the relationships
221 between REM sleep changes and tau pathology in the brainstem and medial temporal areas
222 remains to be clarified, specifically in cognitively normal older populations.

223 Lastly, the associations between sleep changes and glucose metabolism have been much less
224 investigated. SDB has been associated with decreased metabolism and/or perfusion in
225 posterior parietal areas (Baril et al., 2015; Yaouhi et al., 2009), but increases have also been
226 reported (André et al., 2020). Taken together, it is unclear whether sleep quality is associated
227 with the marked hypometabolism in posterior cingulate and precuneus areas observed in AD
228 and mild cognitive impairment patients (Chételat et al., 2003; Minoshima et al., 1997; Schroeter et
229 al., 2009).

230

231 Besides, sleep modifications have been linked to other brain changes which seem less directly
232 suggestive of early AD pathological processes, and could rather reflect normal ageing
233 processes. Indeed, GM atrophy in frontal and parietal areas is robustly associated with SWS
234 disruption, in particular decreased slow wave activity (Dubé et al., 2015; Latreille et al., 2019;
235 Mander et al., 2013). These results are consistent with the fact that these regions are involved
236 in sleep physiology and the generation of slow waves (Massimini et al., 2004; Murphy et al.,
237 2009). Moreover, greater sleep fragmentation is related to lower frontal GM volume (Lim et al.,
238 2016) and fronto-hippocampal metabolism (André et al., 2019), two areas critical for sleep-
239 dependent memory consolidation (Buzsáki, 1996; Maingret et al., 2016). The brain correlates of
240 SDB appear however still conflicting, with both positive and negative associations with
241 frontal GM volume and metabolism, MTL metabolism, and parietal GM volume (see **Table**
242 **1**). The pattern of SDB-related neuronal hyperactivity (i.e., greater GM volume, metabolism
243 and perfusion) reported in some studies could reflect acute and early reactive processes, likely
244 due to neuroinflammation in response to hypoxia. This neuronal hyperactivity may also
245 reflect compensatory mechanisms due to greater individual brain reserve, which may help to
246 maintain cognitive performance in the normal range by increasing brain activity. Importantly,
247 these acute changes may only be temporary and may trigger neurodegeneration (i.e., GM

248 atrophy and hypometabolism) and the development of cognitive deficits over time.
249 Longitudinal studies combining several neuroimaging modalities on large cohorts with
250 various levels of SDB severity will be necessary to confirm this hypothesis.

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

264 However, it is likely that the links between sleep and brain alterations are bidirectional (Ju et
265 al., 2014). Indeed, the consequence of disrupted sleep is to increase the amount of wakefulness
266 during sleep and to decrease the amount of sleep *per se*. Subsequently, greater neuronal
267 activity and reduced brain clearance function may result in greater amyloid and tau release
268 (**Fig. 1**). If increased activity and reduced clearance are likely to co-exist, their respective
269 contributions are unclear. A pilot study in humans showed that these links are mainly driven
270 by increased A β secretion, and not by decreased clearance (Lucey et al., 2018). However, the
271 study of brain clearance mechanisms is a recent area of research. In mice, clearance through
272 the blood brain barrier and interstitial fluid bulk-flow seem to be both implicated in amyloid

273 clearance and related to sleep quality (Rasmussen et al., 2018; Tarasoff-Conway et al., 2015b; Xie
274 et al., 2013). Notably, the glymphatic system hypothesis proposes that arterial pulsations drive
275 waste clearance through a directional convective flow of CSF, from periarterial areas in the
276 deep brain parenchyma to the perivenous spaces. This process implicates water channels, like
277 aquaporin-4, located in glial cells (Iliff et al., 2013, 2012; Nedergaard, 2013), and is facilitated
278 during sleep (Xie et al., 2013). Nevertheless, several aspects of this model are currently debated
279 (Mestre et al., 2020), and most findings in mice are pending replication in humans, as non-
280 invasive neuroimaging tools of clearance mechanisms are still under development. Moreover,
281 the associations with AD pathology remain to be confirmed. In healthy young subjects, a
282 promising recent study demonstrated that slow waves during NREM sleep are followed by
283 hemodynamic oscillations, which are in turn coherent with large waves of CSF (Fultz et al.,
284 2019).

285

286 **7. Conclusion**

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

297 pathophysiological mechanisms and may represent a modifiable lifestyle factor contributing
298 to healthy ageing.

299

300 **8. Competing interests**

301 None declared.

302

303 **9. References**

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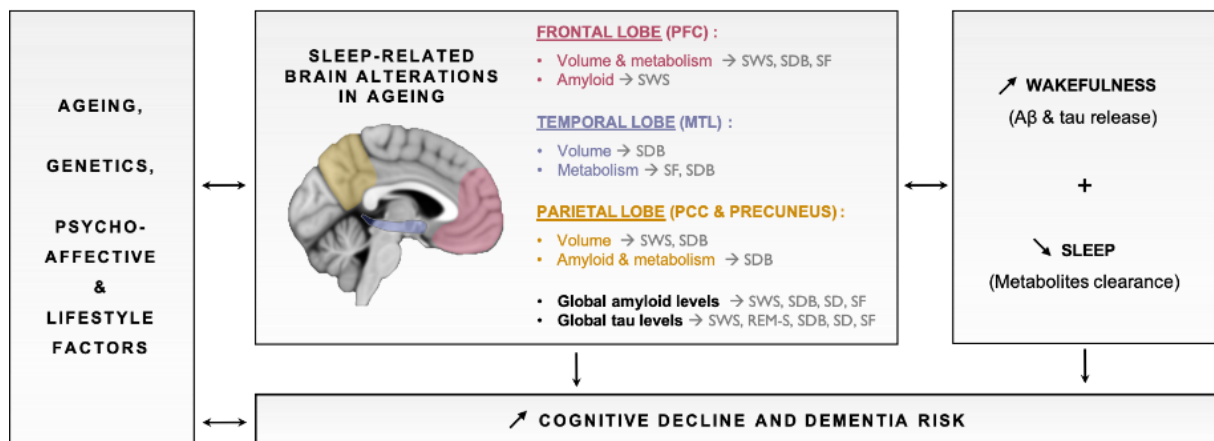
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702

703 **Figure 1**



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705

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

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

711 Studies show that poor sleep quality in older adults is associated with decreased gray matter volume in
712 frontal, temporal and parietal areas, increased global, frontal, and parietal amyloid levels, as well as
713 increased global tau levels. These brain areas are both sensitive to ageing and Alzheimer's disease,
714 and some of them (notably frontal areas) are involved in the generation and maintenance of sleep
715 oscillations. Their alteration contributes to the aggravation of amyloid and tau pathologies and may
716 explain why poor sleep quality is associated with an increased risk of cognitive decline.

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Sleep parameter	Method	Grey matter volume	Perfusion and glucose metabolism ¹	Amyloid pathology ²	Tau pathology ³
Sleep deprivation	Objective			Global levels (Ooms 2014)	Global levels (Holth 2019)
↘ Global sleep quality	Self-reported	Frontal (Sexton 2014), hippocampus (Alperin 2018, Liu 2018), thalamus (Liu 2018), parietal and amygdala (Alperin 2018). <i>Longitudinal: frontal, temporal and parietal (Sexton 2014), hippocampus (Fjell 2019)</i>		Global levels (Sprecher 2017), frontal & parietal (Sprecher 2017) <i>Longitudinal: global levels (Fjell 2018)</i>	Global levels (Sprecher 2017) <i>Longitudinal: global levels (Fjell 2018)</i>
↗ Excessive daytime sleepiness	Self-reported	MTL, frontal, parietal and occipital (Carvalho 2017)		Global levels (Xu 2020), frontal & parietal (Sprecher 2015). <i>Longitudinal: global levels (Spira 2018), anterior and posterior cingulate & precuneus (Carvalho 2018)</i>	Global levels (Sprecher 2017)
↗ Sleep latency	Self-reported			Global levels (Brown 2016), frontal (Branger 2016)	
	Objective			Global levels (Ettore 2019)	
↘ Sleep efficiency	Objective			Global levels (Ju 2013, Molano 2017, Ettore 2019) <i>Longitudinal: global levels (Winer 2020)</i>	Global levels (Ju 2017)
Short sleep duration	Self-reported	Global atrophy (Lo 2014). <i>Longitudinal: fronto-temporal (Spira 2016: <7h)</i>		Global levels (Spira 2013, Xu 2020: ≤6h) & precuneus (Spira 2013: ≤6h)	
Long sleep duration	Self-reported	Global atrophy (Westwood 2017: ≥9h), occipital (Spira 2016: >7h). <i>Longitudinal: frontal (Spira 2016: >7h)</i>		Global levels (Xu 2020: ≥6h)	
↗ Nocturnal awakenings & sleep fragmentation	Self-reported	OFC (Stoffers 2012, early awakenings), insula (Branger 2016, nocturnal awakenings)			
	Objective	Frontal (Lim 2016)	Frontal & hippocampus (André 2019)	Global levels (Wilckens 2018, Lucey 2019, Ettore 2019)	<i>Longitudinal: global levels (Lim 2013)</i>
Sleep-wake rhythm fragmentation	Objective	MTL (Van Someren 2018)			
↘ Slow wave sleep	Objective	Frontal (Mander 2013, Dubé 2015, Latreille 2019), parietal & insula (Dubé 2015)	PFC (Wilckens 2016)	Global levels (Ju 2017, Varga 2016, Winer 2019), PFC (Mander 2015) <i>Longitudinal: global levels (Winer 2020)</i>	Global levels (Lucey 2019, Liguori 2020)
↘ Sleep spindles	Objective				Global levels (Kam 2019: spindles density); MTL (Winer 2019: spindles/slow waves coupling)

↘ REM sleep latency	Objective			Global levels (Lucey 2019)	
SDB	Self-reported			Global levels (Elias 2018)	
	Objective	Frontal (↘ : Shi 2017, Huang 2019 ; ↗: Baril 2017), MTL (↘: Weng 2014, Huang 2019, Tahmasian 2016 ; ↗: Cross 2018, Rosenzweig 2013), temporo-parietal (↘: Weng 2014, Shi 2017), parieto-occipital (↗: Baril 2017, Cross 2018, André 2020), insula (↘: Tahmasian 2016)	Parieto-occipital (↘: Yaouhi 2009, Baril 2015, Joo 2007, Kim 2017; ↗: André 2020), frontal (↘: Yaouhi 2009, Innes 2015, Kim 2017, Shiota 2014, Nie 2017, Baril 2020; ↗: Nie 2017), temporal & MTL (↘: Innes 2015, Kim 2017, Joo 2017, Nie 2017, Baril 2020), thalamus (↘: Innes 2015), insula (↘: Baril 2020; ↗: Baril 2015), basal ganglia & limbic regions (↗: Baril 2015)	Global levels (Osorio 2014, Bu 2015, Liguori 2017, Jackson 2020, Ylä-Herttuala 2020, Kong 2020), posterior cingulate, precuneus & temporal (Yun 2017, André 2020, Ylä-Herttuala 2020). <i>Longitudinal: global levels (Sharma 2018, Bubu 2019)</i>	Global levels (Ju 2016, Osorio 2014, Bu 2015, Liguori 2017, Motamedi 2018, Kong 2020). <i>Longitudinal: global levels (Bubu 2019)</i>

720

721 **Table 1. Summary of the associations between sleep parameters and brain integrity in older adults.**

722 Abbreviations: ASL: Arterial Spin Labeling, CSF: cerebrospinal fluid, FDG: ¹⁸F-fluorodeoxyglucose, MTL: medial temporal lobe, OFC: orbitofrontal cortex,
723 PET: Positrons Emission Tomography, PFC: prefrontal cortex, SDB: sleep-disordered breathing, SPECT: Single Photon Emission Computed Tomography.

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

726 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,*
727 *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*).

728 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.,*
729 *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*
730 *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;*
731 *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.,*
732 *2019, André et al., 2020; Jackson et al., 2020; Ylä-Herttuala et al., 2020*).

733 ³ 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*
734 *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
735 PET imaging (*Lucey et al., 2019; Winer et al., 2019*), or at autopsy (*Lim et al., 2013b*).

736