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Sleep, rest-activity fragmentation and structural brain changes related to the ageing process

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Increasing evidence suggests an association between typical age-related changes in sleep and brain structure. Here we review studies exploring the association between human histopathological and *in vivo* neuroimaging markers of brain structure and sleep-wake parameters in healthy older adults. Evidence from both large-scale epidemiological studies and in-lab quantification of specific sleep signatures are reviewed and advantages and pitfalls highlighted. Overall, the results point to an association between sleep-wake disruption and both local and diffuse changes in brain structure. The associative strength largely varies between studies and seems to partially depend on the sleep trait under investigation. The role of specific sleep-wake regulating mechanisms on human cognitive and brain fitness and more particularly their causal relationship remains to be disentangled.

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Introduction

Over the last few years, growing interest is observed in understanding the protective effects of sleep on health and quality of life, especially in the context of the ageing population. In humans, the gross framework to sleep and wakefulness alternation is provided by the interaction between a sleep-dependent homeostatic process and the circadian timing system responsible for endogenous modulations of sleep and wake propensity over the 24-hour day [1]. Those regulating processes act as important modulators for brain and behavior (e.g. [2]) and their potential implication in cognitive and brain ageing is increasingly considered ([3–5]; see also [6] for a review).

Here we review studies exploring the association between human *post-mortem* and *in vivo* magnetic resonance imaging (MRI) markers of brain structure and sleep-wake parameters in healthy older adults. As summarized in Table 1, brain structural measures include quantification of grey matter as well as white matter from cross-sectional and longitudinal designs, using whole-brain or regions of interest approaches. We will differentiate studies investigating sleep-wake parameters collected through (1) self-reported questionnaires, (2) polysomnography (sleep architecture and electrophysiological signatures), and (3) actimetry recordings (integrity of the temporal distribution of rest-activity cycles and estimated sleep fragmentation in real-life settings).

Association between brain structure and self-reported sleep

Sleep complaints are increasing while getting older including altered sleep perception, changes in sleep architecture or increased variability in the timing and duration of sleep [7]. Sleep questionnaires have been developed to provide a general overview of the subjective quality of sleep. While they are often used as a first diagnostic tool in clinical practice, qualitative assessments of sleep perception do not inform about specific sleep-regulating mechanisms and are the consequence of an amalgam of various biological and environmental factors, varying over time. However, they remain cost effective and easy to use allowing therefore the generation of large and representative samples by adopting epidemiological approaches.

Cross-sectional studies detected an association between poor self-reported sleep quality and reduced grey matter volume including orbitofrontal regions [8], insula [9], and age-related thalamic and hippocampal atrophy [10]. A longitudinal approach reported that grey matter atrophy of frontal, parietal and temporal, but not hippocampal regions was predictive for poor sleep quality at 3.5 years follow up [11]. Compared to sleep quality, reports on sleep duration have produced more mixed results. Most cross-sectional studies failed to observe a significant association between self-reported sleep duration and grey matter volume [9,12,13]. A longitudinal study reported that both short (<7 hours) and long (>7 hours) sleep durations were associated with higher rates of cortical thinning in fronto-temporal regions over eight years [14],

Table 1

Cross sectional and longitudinal studies of sleep-wake states and structural brain imaging

Paper	Design	n, mean age ± SD Project	Brain measures	Main findings
		Sleep questionnaire studies		
Stoffers [8]	Cross sectional	$n = 65$, 40.5 ± 9.7 Netherlands study of depression and anxiety	GM volume – VBM8, voxel wise analysis	EMA was associated with low volume within the left OFC. No association with DIS, DMS
Branger [9]	Cross sectional	$n = 51$, 64.1 ± 10.6 Multimodal imaging of early stage Alzheimer's disease	GM volume – VBM5, voxel wise analysis	High number of nocturnal awakenings was related to low insular volume. No association with sleep latency, duration and quality
Liu [10]	Cross sectional	$n = 54$ young, 21.6 ± 1.6 $n = 94$ older, 66.2 ± 5.1 Independent sample	GM, WM, hippocampal and thalamic volumes – VBM8	Poor sleep quality was associated with age-related GM, hippocampal and thalamic atrophy
Sexton [11]	Longitudinal 3.5 years	$n = 147$, 53.9 ± 15.5 Cognition and plasticity through the lifespan	Cortical volume – Freesurfer, vertex wise analysis Hippocampal volumes – Freesurfer	Low volume within the right superior frontal cortex (cross sectional) and increased rate of atrophy within frontal, temporal, and parietal regions (longitudinal) was predictive for poor sleep quality. No association with hippocampal volume or atrophy
Lo [12]	Longitudinal 2 years	$n = 66$, 67.4 ± 5.8 Singapore-longitudinal aging brain study	GM, WM, hippocampal, ventricles, inferior and superior frontal gyri volumes – Freesurfer	Short sleep duration was related to increased ventricular expansion. No association with other brain volumes and sleep quality
Lutsey [13]	Cross sectional	$n = 312$, 61.7 ± 5 The atherosclerosis risk in communities study	Frontal, temporal, parietal and occipital cortical volume. Hippocampal, and deep grey matter volume – Freesurfer WMH volume and brain infarcts	No association between sleep duration and MRI measures
Spira [14]	Longitudinal 8 years	$n = 122$, 66.6 ± 8 Baltimore longitudinal study of aging	Cortical thickness – Freesurfer, vertex wise analysis	Long sleep duration was associated with low cortical thickness in the inferior occipital gyrus and sulcus of the left hemisphere (cross sectional). Long and short sleep duration were associated with increased rate of cortical thinning in fronto-temporal area (longitudinal)
Carvalho [15]	Cross sectional	$n = 1374$, >50 Mayo clinic study of aging	Frontal, parietal, temporal and occipital cortical thickness and hippocampal volume – Freesurfer	Excessive daytime sleepiness was associated with low cortical thickness in frontal, parietal, temporal and occipital regions and hippocampal volume
Del Brutto [16]	Cross sectional	$n = 237$, 70 ± 8 Atahualpa project	WMH volume, lacunar infarcts and deep microbleeds	Poor sleep quality was associated with WMH presence and severity. No association with silent lacunar infarct or deep microbleeds
Kocevska [17]	Longitudinal 5 years	$n = 2{,}529$, 55.8 ± 6.0 Rotterdam study	FA, MD – tractography	Sleep complaints were related to decreased FA in the middle cerebellar peduncle and medial lemniscus over time. Short sleep duration was related to increased WMH burden over time and high sleep efficiency with high WMH volume at follow up. No association between WM measures at baseline and changes in sleep complaints
Sexton [19]	Cross sectional	$n = 448$, 69.2 ± 5.1 Whitehall II imaging substudy	FA, AD, RD - FSL, TBSS, voxel wise analysis WMH volume	Poor sleep quality was related to low FA, high AD and RD values in frontal lobe. No association with sleep duration, sleep efficiency, WMH volume and persistence of poor sleep 16 years prior brain imaging

Table 1 (*Continued*)

Paper	Design	n, mean age ± SD Project	Brain measures	Main findings
Yaffe [21]	Cross sectional	*n* = 613, 45.4 Coronary artery risk development in young adults	Frontal, parietal, temporal and occipital FA, MD WMH volume	Short sleep duration was associated with high MD values in frontal, parietal and temporal regions and high parietal WMH volume
Ramos [22]	Cross sectional	*n* = 1,244, 70.0 ± 9.0 Northern Manhattan study	WMH volume	Long sleep duration was associated with high WMH volume only in older adults suffering from diabetes
		Polysomnographic studies		
Gelber [28]	Cross sectional	*n* = 167, 83.7 (79–95) Honolulu-Asia aging study	Brain autopsy	Greater SWS duration was associated with less brain atrophy
Dubé [29]	Cross sectional	*n* = 30 young, 23.49 ± 2.79 *n* = 33 older, 60.35 ± 5.71 Independent sample	Cortical thickness – CIVET, voxel wise analysis	Higher SW density was associated with age-related insular, superior temporal, parietal and middle frontal thickness. Higher SW amplitude was associated with age-related middle frontal, medial prefrontal, and medial posterior thinning
Mander [30]	Cross sectional	*n* = 18 young, 20.4 ± 2.1 *n* = 18 older, 72.4 ± 6.1 Independent sample	mPFC volume – VBM8	Reduced SWA was associated with age-related mPFC atrophy
Varga [31]	Cross sectional	*n* = 18 young, 18–23 *n* = 13 older, 51–85 Independent sample	mPFC volume – Freesurfer	Reduced frontal SWA was associatd with age-related mPFC atrophy
Helfrich [32•]	Cross sectional	*n* = 20 young, 20.4 ± 2.0 *n* = 32 older, 73.7 ± 5.3 Independent sample	mPFC, dlPFC, lateral orbitofrontal cortex, thalamic and hippocampal volumes – VBM8	Impaired slow wave-spindle coupling was related to age-related mPFC atrophy. No association with hippocampus, thalamus, lateral OFC and dlPFC
Fogel [33]	Cross sectional	*n* = 13 young, 24.1 ± 3.5 *n* = 15 older, 62.2 ± 3.8 Independent sample	GM volume – FSL, voxel wise analysis	Sleep spindles were related to grey matter volume within the hippocampus, cerebellum, cingulate and parietal cortex in young but not older adults
Mander [34]	Cross sectional	*n* = 20 young, 20.4 ± 2.0 *n* = 31 older, 73.5 ± 5.2 Independent sample	MD - FSL, TBSS, voxel wise analysis	Decreased in fast spindle density was associated with age-related increased MD values in commissural and projecting fiber tracts
Gaudreault [35]	Cross sectional	*n* = 30 young, 22.9 ± 2.7 *n* = 31 older, 59.8 ± 5.4 Independent sample	FA, MD, AD, RD - FSL, TBSS, voxel wise analysis	Sleep spindles were related to WM modifications over frontal regions in young but not older adults
		Actigraphic studies		
Lim [37]	Cross sectional	*n* = 45, 33 healthy older and 12 AD, 89.4 (85.2–93.5) Rush memory and aging project	Brain autopsy	High fragmentation of sleep and active states was related to low galanin-immunoreactive neurons in the intermediate nucleus. No association with self-reported sleep duration, DIS, DMS
Lim [38•]	Cross sectional	*n* = 315 older, 90.4 ± 6.1 Rush memory and aging project	Brain autopsy	High sleep fragmentation was associated with severe arteriolosclerosis and subcortical macroscopic infarcts
Wang [39•]	Cross sectional	*n* = 17, 10 healthy older and 7 AD, 90.4 ± 5.5 Rush memory and aging project	Brain autopsy	Low rest-activity amplitude was associated with low VIP-immunoreactive neurons in the suprachiasmatic nucleus

Table 1 (*Continued*)

Paper	Design	n, mean age ± SD Project	Brain measures	Main findings
Lim [40]	Cross sectional	*n* = 141, 82.9 (median, IQR 77.4–87.4) Rush memory and aging project	Volume, surface and area of Desikan-Killiany atlas regions – Freesurfer	High sleep fragmentation was related to low volumes within the lateral orbitofrontal and inferior frontal pars orbitalis and thickness within the right inferior frontal pars orbitalis. No association with cortical area, subcortical and WM volume, self-reported sleep duration and nocturnal awakenings
André [41]	Cross sectional	*n* = 30 cognitively unimpaired, 73.3 ± 7 *n* = 36 SCD and/or MCI, 71.5 ± 8.2 IMPAP + study	GM volume – SPM12, voxel wise analysis	High variability of sleep fragmentation during the first part of the night was related to low volume within the thalamus in cognitively unimpaired older adults. No association with sleep fragmentation intensity
van Someren [42]	Cross sectional	*n* = 138, 69.1 ± 8.5 Independent sample	Medial temporal lobe and global cortical atrophy – visual ratting scales	High rest-activity fragmentation was associated with medial temporal lobe atrophy
Baillet [43•]	Cross sectional	*n* = 58, 76.1 ± 0.5 (SEM) AMImage study	GM volume – VBM8, voxel wise analysis FA, MD, RD, AD - FSL, TBSS, voxel wise analysis WMH volume	Low rest-activity amplitude and high sleep fragmentation were related to low FA, high MD and RD values in the whole WM. This association was partly associated with WMH. No association with rest-activity fragmentation, stability of activity rhythms, sleep duration and GM volume
Kocevska [44•]	Longitudinal 5.8 years	*n* = 1,201, 59.3 ± 7.9 Rotterdam study	FA, MD – tractography	Short sleep duration, high WASO and low sleep efficiency were related to WM modifications in several WM tracts up to seven years after brain imaging. No association with sleep latency and with WM modification changes over time
Oosterman [45]	Cross sectional	*n* = 162, 69.1 ± 8.6 Independent sample	WMH volume – visual rating scale	Low rest-activity amplitude and unstable activity rhythms were associated with frontal deep WMH. No association with periventricular WMH and rest-activity fragmentation
Zuurbier [47]	Cross sectional	*n* = 970, 59.2 ± 7.5 Rotterdam study	WMH volume, lacunar infarcts and cerebral microbleeds	Rest-activity fragmentation was associated with high WMH volume and cerebral microbleeds. No association with stability of activity rhythms, sleep duration, WASO, self-reported sleep quality and lacunar infarcts

Abbreviations: GM = grey matter, WM = white matter, OFC = orbitofrontal cortex, mPFC = medial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, VIP = vasoactive intestinal polypeptide neurons, WMH = white matter hyperintensities, VBM = voxel based morphometry, FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, AD = axial diffusivity, TBSS = tract based spatial statistics; EMA = early morning awakenings, DIS = difficulty initiating sleep, DMS = difficulty maintaining sleep, SWS = slow-wave sleep, SWA = slow-wave activity, WASO = wake after sleep onset.

while an association between short sleep duration and ventricular expansion over two years was detected in another study [12]. Beside sleep, Carvalho *et al.* reported that excessive daytime sleepiness was associated with reduced hippocampal volume and cortical thickness, particularly in temporal regions, suggesting that not only altered sleep but also resulting daytime sleepiness may be related to brain structure [15].

Regarding white matter, poor sleep quality has been associated with the presence of white matter hyperintensities (WMH) in cross-sectional and longitudinal studies [16,17]. WMH are commonly observed during ageing and reflect white matter tissue injury such as demyelination, axonal loss and gliosis [18]. Importantly, WMH have been related to cognitive decline, especially executive dysfunction, and incident dementia [18]. Another study

observed that poor sleep quality, and especially long sleep latency, was associated with modifications of Diffusion Tensor Imaging (DTI) parameters, particularly radial diffusivity (RD), but not with WMH volume. Persistence of poor sleep quality sixteen years prior MRI was however not associated with white matter measures [19]. Of note, ageing is related to reduced fractional anisotropy (FA) and increased diffusivity parameters (mean diffusivity, MD and RD; less prominent for axial diffusivity, AD) reflecting impaired fiber integrity due to a loss of coherence on a preferred direction and an increase of diffusion rate. Changes in RD are assumed to reflect myelin damage while changes in AD presumably reflect axonal damage [20]. Kocevska *et al.* revealed no significant association between white matter measures at baseline and changes in sleep complaints over time, but observed that sleep complaints at baseline were associated with decreased FA values in brainstem tracts over a five-year longitudinal design; thereby suggesting that sleep complaints may predict future age-related white matter modifications [17]. With respect to sleep duration, shorter durations (<6 hours) have been associated with high WMH volume in parietal areas [21] and increased WMH burden over time [17]. Short self-reported sleepers presented also higher MD values mainly in frontal, parietal and temporal white matter regions and, higher prevalence of vascular risk factors compared to moderate sleepers [21]. Other studies did not observe a significant association between self-reported sleep duration and WMH in older adults [13,22]; note that Ramos *et al.* reported an association between long sleep duration (>9 hours) and WMH volume only in older adults suffering from diabetes [22].

Association between brain structure and electrophysiological signatures of sleep

Sleep architecture is characterized by the ultradian alternation between rapid eye movement (REM) and non-REM (NREM) sleep as assessed by polysomnographic (PSG) recordings. Standard PSG-assessed variables and more particularly frequency-band specific spectral power exhibits stable and trait-like-interindividual differences (e.g. [23]) which make them interesting candidates for brain-behavior correlations. Sleep spindles have for example been proposed to reflect features of trait and time-varying properties of neuroplasticity [24] and have been associated with general intelligence (e.g. [25]). Compromised generation and propagation of sleep oscillations (spindles and slow waves) have been linked to age-related cortical thinning [26].

Post-mortem assessments from the Honolulu-Asia Aging Study [27] revealed that short slow-wave sleep (SWS) duration was associated with more global grey matter atrophy at death [28]. *In vivo* MRI studies similarly revealed that during adulthood, changes in slow waves density and amplitude were associated with age-related cortical thinning in frontal, temporal, parietal and insular regions [29]. Importantly, age-related grey matter atrophy within the medial prefrontal cortex (mPFC) has been related to decreased slow-wave activity [30,31] and slow wave — sleep spindle coupling [32•], both associated with overnight sleep-dependent memory impairment. Note however that another study reported significant associations between sleep spindle characteristics and grey matter volume in younger adults only [33]. With respect to white matter, Mander *et al.* observed that age-related increase of MD values in several white matter tracts, such as the corpus callosum, was associated with a loss of frontal fast sleep spindles. This white matter modification moderated the impairment of overnight sleep spindle-dependent motor memory consolidation [34]. Another study failed to observe such association in a younger age range [35].

Association between brain structure and rest-activity cycles

The application of in-lab approaches allow to uncover processes underlying different sleep phenotypes. At contrast, field actigraphy enables monitoring of masked 24-hour rest-activity cycles over days, weeks or even months. Difficulty however remains in the inference of physiologically meaningful sleep phenotypes. Strength of this approach is that, unlike single-night polysomnographic recordings, it allows a rather unique assessment of the temporal profiles of rest-activity patterns and thereby the inferences about putative temporal disruption of sleep-wake states. As such, not only sleep, but also the temporal organization of rest-activity cycles has been associated with cognitive functioning (e.g. [3–5]).

Knowledge on histopathological changes related to rest-activity cycles in ageing mainly arises from actigraphic studies of the Rush Memory and Aging Project [36]. In the latter, Lim *et al.* observed that higher rest-activity fragmentation was related to a lower number of galanin-immunoreactive neurons within the intermediate nucleus of the hypothalamus (homologue of the sleep-promoting ventrolateral preoptic nucleus in rodents; [37]). Furthermore, higher sleep fragmentation was associated with more severe arteriolosclerosis and subcortical macroscopic infarcts at autopsy (27% and 31% higher odds for each 1 standard deviation increase of sleep fragmentation; [38•]). Finally, Wang *et al.* reported that a lower 24-hour cycle amplitude (i.e. less differentiation between day-time activity and night-time rest) was related to a lower number of vasoactive intestinal polypeptide neurons of the suprachiasmatic nucleus implicated in the maintainance of a high-amplitude circadian output and photic resetting [39•].

Few studies evaluated the association between actigraphy-derived rest-activity parameters and grey matter in older adults. High sleep fragmentation has been associated with low grey matter volume over lateral orbital

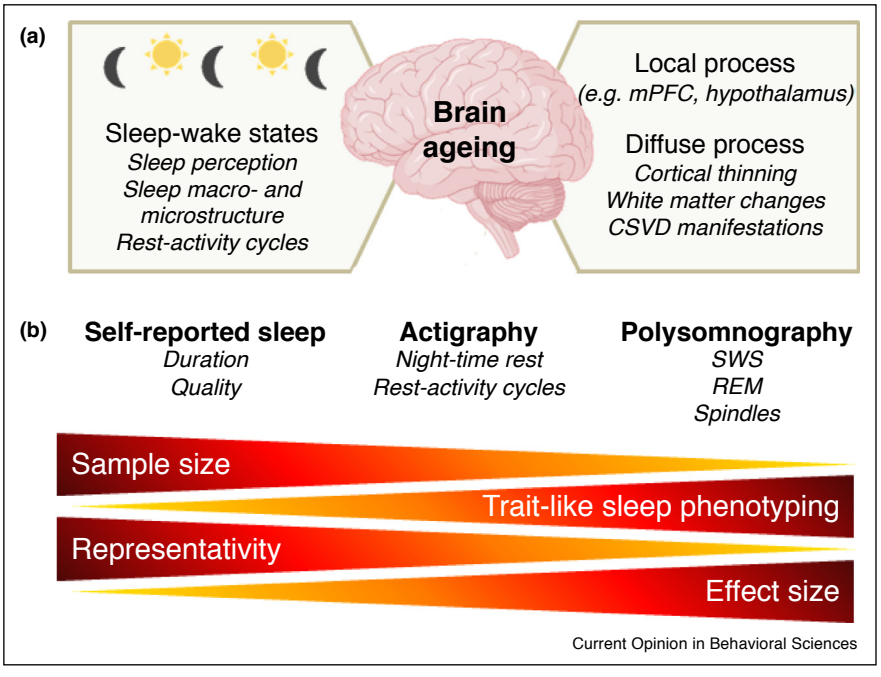
and inferior frontal regions [40], and its variability during the first part of the night with low thalamic volume [41]. Recently, van Someren *et al.* reported that rest-activity fragmentation accounted for 19% of the variance in medial temporal lobe atrophy, evaluated with a visual rating scale [42]. In contrast, another study did not observe any significant association between actigraphic measures of rest-activity cycles and grey matter volume [43•].

Regarding white matter, a population-based study reported that actigraphic derived poor sleep quality and short sleep duration were related to white matter modifications (high FA and low MD) up to seven years later but not with the evolution of DTI parameters over time. However as actigraphic recordings were not performed at baseline, causality between sleep and brain structure remains difficult to infer at this stage [44•]. Three cross sectional actigraphic studies provided first evidence that rest-activity disturbances observed in older adults are related to cerebral small vessel disease manifestations. Oosterman *et al.* observed that a lower 24-hour rest-activity amplitude, especially decrease in daytime activity, and unstable activity rhythms were related to higher deep WMH volumes in frontal regions [45]. In more than 900 participants of the Rotterdam Study [46], rest-activity fragmentation has been associated with WMH volume and cerebral microbleeds but not with the number of lacunar infarcts [47]. In the only study using DTI, Baillet *et al.* observed that low 24-hour rest-activity amplitude and high sleep fragmentation were both associated with diffuse white matter modifications (low FA, high MD and RD) and WMH volume. Interestingly, rest-activity amplitude remained associated with white matter properties when accounting for sleep fragmentation, suggesting a specific effect of the temporal distribution of rest and activity over the 24-hour day [43•].

Discussion

Ageing is associated with modifications of brain structure, sleep-wake regulation and cognition but how these factors are related to each other remains to be determined. At this stage, it might appear premature to draw firm conclusions regarding region-specific implications (see also Figure 1a for a conceptual representation). Regions of interest based approaches mainly targeted on frontal, temporal, hippocampal, and thalamic grey matter volume, considering the predominant implication of those regions in brain ageing trajectory but also in sleep-wake regulation or more specifically, in the generation and/or coupling of slow oscillations and sleep spindles. Of thirteen MRI studies including subcortical structures [8–13,15,32•,33,40–42,43•], only four reported a positive association between sleep-wake patterns and hippocampal [10,15,42] or thalamic volumes [10,41]. In contrast, all polysomnographic studies included in this

Figure 1



Conceptual representation of **(a)** results from studies reporting an association between sleep-wake states and MRI-derived brain structure and **(b)** methodological considerations.
Abbreviations: mPFC = medial prefrontal cortex, CSVD = cerebral small vessels disease, SWS = slow-wave sleep, REM = rapid eye movement

review suggest that a decrease in slow waves parameters is associated with cortical atrophy, including the medial prefrontal cortex [29–31,32•] suggesting a possible neuroanatomical substrate to explain sleep-related cognitive impairment. Rather consistent results were observed regarding white matter, and especially with actigraphic rest-activity patterns and cerebral small vessel disease manifestations as WMH, cerebral microbleeds and related cerebrovascular pathologies [38•,43•,45,47]. Acting as a diffuse process, these manifestations disrupt not only the normal appearing white matter but also connected cortical regions through secondary neurodegeneration disrupting efficient information transfer in brain networks [48]. Cerebral small vessel disease is underlined by reduced cerebral blood flow and blood-brain dysfunction and associated with vascular risk factors [48], suggesting that rest-activity disturbances may be related to vascular abnormalities.

Most of the studies exploring the association between sleep and structural brain changes at older age relied on questionnaire-based subjective assessments of sleep duration and quality. This might at least partially explain the variability in observed results with respect to brain structural changes over the ageing process. It might be assumed that replicability of structural brain-behavior associations critically relies upon the definition and precision of the sleep trait under investigation (e.g. [49]). It is thus important to complete population-based samples with in-lab measurements of more unmasked sleep phenotypes while controlling for prior sleep-wake history. Within this context, trait-like and thus replicable characteristics have been attributed for example to electrophysiological-derived sleep characteristics (e.g. [50]). Those studies, testing for an association between electroencephalographic-derived spectral power measures (mainly slow-wave activity, spindle density and their coupling) and brain structure mostly revealed strong effect sizes ([29–31,34] but see [33,35]). Adding complexity to such phenotypes, as for instance taking into account the dynamic interaction between REM and NREM sleep when testing for putative associations will complete the picture about the importance of sleep on brain ageing [51]. It was recently observed for example that NREM and REM sleep stages differently affect cognitive outputs linked to the ageing process (e.g. [52]) thereby re-emphasizing on REM sleep as an important contributor to brain function.

Finally, the role of the circadian clock on shaping human brain ageing has been widely underestimated. This appears surprising because of its widespread implication and regulation of cognitive brain function [2]. Even though not assessing the internal clock, actigraphy allows to infer about temporal profiles of rest-activity patterns. Note that most studies have focused on sleep and its disturbances without considering it as a part of a 24-hour cycle. Of seven [40,41,42,43,44,45,47] studies using MRI and actigraphy, only four described rest-activity patterns [42,43•,45,47] and most of them emphasized an association with white matter properties. Furthermore, post-mortem studies provide evidence that actigraphic rest-activity patterns are associated with degeneration of hypothalamic neurons implicated in circadian timing and sleep-wake regulation, regions not easily reachable with conventional MRI [37,39•]. These studies hint to the importance of the temporal framework given to sleep regulation for brain fitness at older age. Older adults present an advanced phase of circadian rhythms (e.g. classical endocrine markers such as melatonin secretion), leading to earlier sleep times and a reduced amplitude in both circadian sleep and wake consolidation [53], putatively leading to more fragmented active and sleep states (i.e. intrusion of sleep into daytime activities and fragmentation of night-time sleep by wake periods or nocturnal arousals; e.g. [54]). Note that a tool regrouping currently available analysis methods was recently developed in our lab in order to catch such temporal specificities in actigraphy-derived rest-activity data, making this type of analysis openly available for future studies (Pyactigraphy, doi: https://doi.org/10.5281/zenodo.2537921).

As summarized in Figure 1b, both large-scale epidemiological studies but also controlled in-lab quantification of specific sleep phenotypes present strengths and pitfalls such that their respective outputs should not be taken as equal but rather used in a complementary manner. In the same vein, inferences were mostly based on cross-sectional correlations between brain and sleep variables. Longitudinal designs are decisive to differentiate between intraindividual and inter-individual variability and thereby offer the possibility to determine whether sleep-wake disturbances have a predictive value on cognitive and brain changes. In subjective cognitive decline population, defined as preclinical stage of AD, poor sleep quality has for example been reported to precede medial temporal lobe atrophy [55].

Note that our review focuses on possible contributions of sleep-wake states on non-symptomatic age-related changes in brain structure. Insights from positron emission tomography imaging studies, not included in this review, revealed for example that poor sleep and fragmented rest-activity cycles are related to Aβ and Tau burden (e.g. [56]; see also [57] for a review). The latter might partially account for the modification in brain structure, opening new avenues to explore the association between sleep and age-related changes in brain integrity.

Conflict of interest statement

Nothing declared.

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