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ORIGINAL ARTICLE

Poor Self-Reported Sleep is Related to Regional Cortical Thinning in Aging but not Memory Decline—Results From the Lifebrain Consortium

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Abstract

We examined whether sleep quality and quantity are associated with cortical and memory changes in cognitively healthy participants across the adult lifespan. Associations between self-reported sleep parameters (Pittsburgh Sleep Quality Index, PSQI) and longitudinal cortical change were tested using five samples from the Lifebbrain consortium ($n = 2205$, 4363 MRIs, 18–92 years). In additional analyses, we tested coherence with cell-specific gene expression maps from the Allen Human Brain Atlas, and relations to changes in memory performance. “PSQI # 1 Subjective sleep quality” and “PSQI #5 Sleep disturbances” were related to thinning of the right lateral temporal cortex, with lower quality and more disturbances being associated with faster thinning. The association with “PSQI #5 Sleep disturbances” emerged after 60 years, especially in regions with high expression of genes related to oligodendrocytes and S1 pyramidal neurons. None of the sleep scales were related to a longitudinal change in episodic memory function, suggesting that sleep-related cortical changes were independent of cognitive decline. The relationship to cortical brain change suggests that self-reported sleep parameters are relevant in lifespan studies, but small effect sizes indicate that self-reported sleep is not a good biomarker of general cortical degeneration in healthy older adults.

Key words: aging, atrophy, cortex, sleep

Introduction

Older adults with poor sleep are more likely to develop neurodegenerative disease (Prinz et al. 1982; Hatfield et al. 2004; Videnovic et al. 2014; Mander et al. 2016; Shi et al. 2018; Fan et al. 2019; Irwin and Vitiello 2019; Xu et al. 2020), and in a recent meta-analysis, it was argued that 15% of Alzheimer's Disease (AD) diagnoses in the population may be attributed to aspects of sleep (Bubu et al. 2017). It is, however, not known whether the relationship between sleep and neurodegeneration is causal, and little is known about the mechanisms that could mediate such a connection. For instance, the association might be bidirectional or reflect the operation of mechanisms (e.g., Raz and Daugherty 2018) affecting both sleep and brain change in normal and pathological aging. Also, older adults without dementia show differences in sleep patterns compared to younger adults (Ohayon et al. 2004; Scullin and Bliwise 2015; Mander et al. 2017), so it is important to know whether natural variations in sleep quality and quantity are related to brain changes across adult life. Here, we examine the relationship between multiple self-reported sleep variables, including sleep disturbances and sleep duration, and cortical changes across the adult lifespan. Participants from the Lifebbrain consortium assessed repeatedly (up to 7 assessments over 11 years) with MRIs were studied (Fjell et al. 2018a). In additional analyses, we tested coherence with cell-specific gene expression maps from the Allen Human Brain Atlas (AHBA), and with changes in memory performance.

Several studies have reported cross-sectional relationships between self-reported sleep parameters and structural properties of the cerebral cortex. Poor sleep tends to be associated with thinner cortex or smaller cortical volume (Table 1), but there is little agreement about which self-reported sleep measures and

cortical regions that are involved. The largest study to date found daytime sleepiness to be associated with thinner cortices in all lobes (Carvalho et al. 2017) but did not report results for other sleep variables. Three studies tested associations with longitudinal cortical change. In one, lower global sleep quality was related to greater cortical volume reduction in frontal, temporal, and parietal regions (Sexton et al. 2014) in participants above 60 years of age. Sleep duration was not associated with atrophy, in accordance with a recent study where duration measured five times over 28 years (Zitser et al. 2020) in 613 participants did not relate to global or regional gray matter volume measured at follow-up. In contrast, a second study found that sleep duration of more or fewer than 7 h was associated with frontotemporal cortical thinning (Spira et al. 2016). A third study of middle-aged and older adults reported shorter sleep duration to be related to more ventricular expansion, whereas no relationship was observed between a global sleep score and volumetric change in total cerebral, inferior or superior frontal volume (Lo et al. 2014). Thus, poor self-reported sleep tends to be modestly related to unfavorable cortical changes, but with little consistency across studies with regard to sleep parameters and brain regions.

Here we took advantage of five longitudinal MRI studies from the Lifebbrain consortium (Fjell et al. 2018a) to examine which self-reported sleep parameters were related to cortical changes and whether these associations were stable through adult life or increased in strength with age. We hypothesized stronger relationships between sleep and cortical changes in older compared to younger adults, mainly in frontal and temporal cortices. These hypotheses were speculative due to few longitudinal studies and highly divergent findings in previous publications. In additional analyses, we tested whether sleep

Table 1 Overview of representative studies testing self-reported sleep, sleep disturbances, and cortical volume or thickness

Reference	N	Population	Result	Comment
Patients with sleep disorders (patients/controls)				
Altena et al. (2010)	24/13	Chronic insomnia	+	Patients had a smaller volume of the left orbitofrontal cortex and in the anterior and posterior precuneus. VBM using SPM
Joo et al. (2013)	27/27	Chronic primary insomnia	-	Tendencies for reduced GM volume in patients, but no effects survived corrections. VBM using SPM8
Suh et al. (2016)	57/40	Persistent insomnia symptoms	+	Thinner cortex in anterior cingulate, precentral, and lateral prefrontal cortex in patients. Vertex-wise analyses using CIVET. PSQI for sleep
Spiegelhalder et al. (2013)	28/38	Primary insomnia	-	No significant relationships. ROI analyses using FreeSurfer (thickness and volume), and VBM using SPM8
Winkelmann et al. (2013)	20/15 and 21/20	Chronic primary insomnia	-	Larger normalized rostral anterior cingulate volume in patients in both sub-studies. Analyses using FreeSurfer
Morrell et al. (2003)	7/7	Obstructive sleep apnea	-	No differences outside hippocampus. VBM using SPM
Riemann et al. (2007)	8/8	Chronic insomnia	-	No differences outside hippocampus. Analyses of manual ROIs
Moon et al. (2018)	37	Heart failure	-	No relationship between PSQI global score and brain volume. VBM using SPM.
Normal controls				
Cross-sectional				
Alperin et al. (2019)	69	Older	+	Smaller left superior parietal lobule volume and thinner right frontal pole, superior frontal, and lateral orbitofrontal cortex in poor sleepers as measured by PSQI global score. Lower sleep duration was most highly correlated with cortical volume and thickness reductions among all subjects. ROI analyses using FreeSurfer (thickness and volume)
Branger et al. (2016)	51	Older	+	Number of nocturnal awakenings was negatively correlated with volume in the bilateral insula and inferior frontal gyri. VBM using SPM8. Custom made self-reported sleep instrument based on PSQI (sleep latency, duration, quality, and number of nocturnal awakenings)
Del Brutto et al. (2016)	290	Older (≥ 60 years)	+	PSQI global score was related to globally wider sulci based on qualitative ratings, especially in participants >67 years
Carvalho et al. (2017)	1374	Middle-aged/ older (>50 years)	+	Daytime sleepiness was associated with thinner cortex in the four lobes. Epworth Sleepiness Scale used for sleep. ROI analyses using FreeSurfer (four lobar ROIs)
Grau-Rivera et al. (2020)	366	Middle-aged/ older	+	Insomnia is associated with lower volume (left orbitofrontal, right middle temporal, bilateral precuneus, posterior cingulate), but did not survive FWE multiple comparison correction. World Health Organization Composite International Diagnostic Interview used for sleep. VBM using SPM12
Helfrich et al. (2018)	52	Young and old	+	GM volume in mPFC positively correlated with directional slow oscillation-spindle coupling. VBM using SPM8
Lim et al. (2016)	141	Older (mean age 82.9 years)	+	Sleep fragmentation is related to lower total cortical GM volume, and volume in lateral orbitofrontal and inferior frontal gyri pars orbitalis. Actigraphy.
Reinhard et al. (2014)	38	Unknown age	+	Analyses using FreeSurfer Positive association between EEG beta2 power and left caudal anterior cingulate cortex thickness. ROI analyses using FreeSurfer (thickness and volume)

Continued

Table 1 Continued

Reference	N	Population	Result	Comment
Stoffers et al. (2012)	65	Adults (18–56)	+	Early morning awakenings were negatively related to orbitofrontal volume, but not relationships for initiating or maintain sleep. VBM using SPM. WHIRS and MCTQ for sleep
Zitser et al. (2020)	613	Adults (mean age 42.3 years)	–	No relationship between global GM volume and sleep duration measured over several years. Voxel-based analyses using FSL
Taki et al. (2012)	290	Children/adolescents	–	No relationship between sleep duration and GM outside the hippocampus. VBM
Aribisala et al. (2020)	457	Older (LBC)	±	DARTEL for volume analyses Weekend daytime sleep associated with reduced total brain volume, but no relationship to night-time sleep duration or daytime sleeping during weekdays
Longitudinal Sexton et al. (2014)	147	Adult lifespan, 3.5 years interval	+	PSQI global score is related to more volume reduction in widespread frontal, temporal, and parietal regions. Relationships were largely driven by older (>60 years) participants, and were stronger in longitudinal than cross-sectional analyses. Of PSQI sub-scores, efficiency and latency showed significant associations in post hoc analyses, while duration did not.
Lo et al. (2014)	119	Middle-aged/older (>55 years), longitudinal	–	Vertex-wise analyses using FreeSurfer No relationship with volumetric change in total cerebral, inferior, or superior frontal volume. Vertex-wise analyses using FreeSurfer. PSQI (duration and Global score) for sleep
Spira et al. (2016)	122	Older (56–86 years), 8 years interval	±	Sleep durations of <7 h and >7 h associated with more frontotemporal gray matter loss. Vertex-wise analyses using FreeSurfer

Note: Main result: “+” indicates no relationship between cortical volume/ thickness and sleep or an inverse relationship (e.g., higher volume in patients). “–” indicates the expected relationship between cortical volume/ thickness and sleep, for example, smaller volume in patients or a negative correlation between sleep problems and volume. Only results of cortical analyses are included in the table. ROI: Region of interest. SPM: Statistical Parametric Mapping (<https://www.fil.ion.ucl.ac.uk/spm/>). FSL: FMRIB Software Library (<https://fsl.fmrib.ox.ac.uk/fsl/fswiki/FSL>). GM: Gray matter. WHIRS: Women's Health Initiative Insomnia Rating. MCTQ: Munich Chronotype Questionnaire. VBM: Voxel-based morphometry. DARTEL: Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra.

Table 2 Descriptive variables of the Lifebrain samples providing data on self-reported sleep

Study	Unique participants	Observations	Mean follow-up length in years(SD)	Range of max follow-up length	Age range at baseline	Sex (female/male)
Barcelona	39	114	4.2 (0.5)	1.9–4.9	64.5–80.6	27/12
BASE-II	315	627	1.9 (0.7)	0.6–3.1	24.2–83.2	112/203
Betula	266	385	4.0 (0.3)	3–5	25–85	135/131
CamCAN	639	901	1.4 (0.7)	0.3–3.5	18.5–91.7	327/312
LCBC	946	2336	4.6 (2.7)	0.2–11.0	19.5–91.9	635/311
Total	2205	4363	3.2 (2.3)	0.2–11.0	18.5–91.9	1236/969

Note: Follow-up time is between MRIs.

and cortical thinning were preferentially associated in regions characterized by high rates of natural age changes, and whether such relationships were stronger in cortical regions characterized by higher expression of genes related to specific cell types—so-called “virtual histology” (Shin et al. 2018). Guided by results from animal experiments, overlap with regions of high expression of microglia, astrocytes, and oligodendrocyte genes could be expected. We also examined whether there was a relationship with memory decline. Longitudinal sleep observations were available only for a smaller subset of the data, and we were, therefore, not able to test change–change relationships directly. Note that sleep was measured based on self-reports, which is not always aligned with physiological recordings of sleep.

Materials and Methods

Sample

The sample was derived from the European Lifebrain project (<http://www.lifebrain.uio.no/>) (Fjell et al. 2018a), including participants from the Berlin Aging Study II (BASE-II) (Bertram et al. 2014; Gerstorf et al. 2016), the BETULA project (Nilsson et al. 1997), the Cambridge Centre for Ageing and Neuroscience study (Cam-CAN) (Shafto et al. 2014), the Center for Lifespan Changes in Brain and Cognition longitudinal studies (LCBC) (Walhovd et al. 2016; Fjell et al. 2018b), and the University of Barcelona brain studies (Vidal-Pineiro et al. 2014; Rajaram et al. 2016; Abellaneda-Perez et al. 2019). Self-reported sleep and structural MRIs from 2205 participants (18.5–91.9 years) yielding a total of 4363 observations were included (Table 2). Screening criteria were not identical across studies but participants were in general cognitively healthy and did not suffer from neurological conditions known to affect brain function, such as mild cognitive impairment/dementia, major stroke, and multiple sclerosis (Fjell et al. 2019b, and Supplementary Material). Depression symptoms were mapped using the Beck Depression Inventory (Beck and Steer 1984) (LCBC, except MADRS for $n = 91$), the Geriatric Depression Scale (Yesavage et al. 1982) 15 item version (BASE-II), the Center for Epidemiologic Studies Depression Scale (Radloff 1977) (Betula), and the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) (Cam-CAN).

Associations between sleep parameters and longitudinal memory change were tested in 1419 participants (2702 observations; Betula [$n = 138/276$ observations, baseline-age = 65, 55–85 years], LCBC [$n = 730/1480$ observations, baseline-age = 49, 19–89 years], BASE-II [$n = 512/830$ observations, baseline-age = 62, 24–92 years], Barcelona [$n = 39/116$ observations, baseline-

age = 69, 64–81 years]), by 30 min delayed free recall from the Verbal Learning and Memory Test (BASE-II), 30 min free recall from the California Verbal Learning Test (LCBC) (Delis et al. 1988), word recall (immediate free recall of words and sentences, and delayed cued recall of words from the previously learned sentences, Betula) (Nilsson et al. 1997; Pudas and Ronnlund 2019) and 30 min delayed recall from the Rey Auditory Verbal Learning Test (Ryan and Geisser 1986) (Barcelona).

Self-Reported Sleep Assessment

Sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) representing self-reported sleep quality for the previous month. This assessed 7 domains (sleep quality, latency, duration, efficiency, disturbances, medication, and daytime tiredness) each scored from 0 to 3 and a global score (see Table 3 for an overview). High scores indicate worse sleep. Duration was also tested using the number of hours instead of the 0–3 scale. The sleep medication item was not analyzed, as most samples were screened for use of medications. The Karolinska Sleep Questionnaire (Nordin et al. 2013; Westerlund et al. 2014) was used for Betula and converted to PSQI (Supplementary Material, Fjell et al. 2019b). Although lifespan changes in sleep are pronounced (Gadde et al. 2017; Fjell et al. 2019b), mean changes as well as individual differences in change over a few years are rather small (Pillai et al. 2015; Zitser et al. 2020) and considered negligible here. PSQI was administered at baseline concurrently with the first MRI, or at a time between the first and the last MRI. If multiple observations were available, the mean value was used. Multiple administrations of the sleep inventory were only available for a small subsample of the participants only, and from only two sub-studies. Specifically, 94 LCBC participants had 2 and 19 had 3 sleep observations, and 119 Betula participants had 2. Mean interval between these PSQI time points was 3.54 years (SD 1.11 years). We calculated the intraclass correlation for PSQI global, which was 0.556, with subscales ranging from 0.25 (PSQI #7 Daytime dysfunction) to 0.49 (PSQI #2 Latency).

Magnetic Resonance Imaging (MRI) Acquisition and Analysis

MRI data originated from 8 different scanners (Table 4) and were processed with FreeSurfer v6.0 (<https://surfer.nmr.mgh.harvard.edu/>) (Dale et al. 1999; Fischl et al. 2002; Reuter et al. 2012; Jovicich et al. 2013), yielding maps of cortical thickness and volume. To avoid introducing possible site-specific biases, quality control measures were imposed and no manual editing

Table 3 PSQI sub-scales

Number	Name	Description
1	Subjective sleep quality	From «very good» (0) to «very bad» (3)
2	Sleep latency	Time taken to fall asleep (≤ 15 min [0] to > 60 min [3]) and how often you cannot get to sleep within 30 min
3	Sleep duration	From « > 7 h» (0) to « < 5 h» (3)
4	Habitual sleep efficiency	(Hours slept/Hours spent in bed) $\times 100$ ($> 85\%$ [0] to $< 65\%$ [3])
5	Sleep disturbances	Extent of nightly awakenings, need to use bathroom, uncomfortable breathing, snoring/coughing, feeling cold/hot, bad dreams, pain, other disturbances
6	Use of sleeping medication	Was not analyzed due to variance-reducing screening criteria
7	Daytime dysfunction	Trouble straying awake during driving/eating/social activities (never [0] to ≥ 3 times each week [3])
	Global	Sum of component 1–7 (total score 0–21)

Table 4 MR acquisition parameters

Sample	Scanner	Tesla	Sequence parameters
Barcelona	Tim Trio Siemens	3.0	TR: 2300 ms, TE: 2.98 ms, TI: 900 ms, slice thickness 1 mm, flip angle: 9°, FoV 256 \times 256 mm, 240 slices
BASE-II	Tim Trio Siemens	3.0	TR: 2500 ms, TE: 4.77 ms, TI: 1100 ms, flip angle: 7°, slice thickness: 1.0 mm, FoV 256 \times 256 mm, 176 slices
Betula	Discovery GE	3.0	TR: 8.19 ms, TE: 3.2 ms, TI: 450 ms, flip angle: 12°, slice thickness: 1 mm, FOV 250 \times 250 mm, 180 slices
Cam-CAN	Tim Trio Siemens	3.0	TR: 2250 ms, TE: 2.98 ms, TI: 900 ms, flip angle: 9°, slice thickness 1 mm, FOV 256 \times 240 mm, 192 slices
LCBC	Avanto Siemens	1.5	TR: 2400 ms, TE: 3.61 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240 \times 240 mm, 160 slices, iPat = 2
	Avanto Siemens	1.5	TR: 2400 ms, TE: 3.79 ms, TI: 1000 ms, flip angle = 8, slice thickness: 1.2 mm, FoV: 240 \times 240 mm, 160 slices
	Skyra Siemens	3.0	TR: 2300 ms, TE: 2.98 ms, TI: 850 ms, flip angle: 8°, slice thickness: 1 mm, FoV: 256 \times 256 mm, 176 slices
	Prisma Siemens	3.0	TR: 2400 ms, TE: 2.22 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 0.8 mm, FoV: 240 \times 256 mm, 208 slices, iPat = 2

Note: TR = repetition time; TE = echo time; TI = inversion time; FoV = field of view; iPat = in-plane acceleration.

was done. We previously have reported that across-scanner consistencies in estimated hippocampal volumes for the scanners used in Lifebrain are high. We nevertheless included “study site” as a fixed effect covariate to adjust for scanner differences (Fjell et al. 2019b). Additional post hoc analyses of Site \times sleep \times time were also run to test whether Site (Scanner) affected the relationship between sleep and cortical change.

Virtual Histology Analyses—Relationship With Cell-Specific Gene Expression Profiles

We tested how sleep-associated cortical thinning is related to regional gene expression profiles associated with specific cell types. As described in detail elsewhere (French and Paus 2015; Shin et al. 2018), gene expression data in ex-vivo left hemisphere brains were obtained from the AHBA (<http://www.brain-map.org>; Hawrylycz et al. 2012), mapped to 34 cortical regions of the Desikan-Killiany Atlas (Desikan et al. 2006). Genes were required to be regionally consistent across 6 donors and 2 datasets (AHBA, the BrainSpan Atlas) (Supplementary Material and French and Paus 2015). The resulting 2511 genes with consistent expression profiles were combined with a list of cell-specific genes from Zeisel et al. (2015), yielding the following cell-type panels: S1 pyramidal neurons ($n = 73$), CA1 pyramidal neurons ($n = 103$),

interneurons ($n = 100$), astrocytes ($n = 54$), microglia ($n = 48$), oligodendrocytes ($n = 60$), ependymal ($n = 84$), endothelial ($n = 57$), and mural ($n = 25$).

Statistical Analyses

See [Supplementary Material](#) for details.

Cortical Surface Analyses

Spatiotemporal linear mixed models (Bernal-Rusiel et al. 2013a; Bernal-Rusiel et al. 2013b) implemented in FreeSurfer v6.0.1 and running on MATLAB R2017a were used to test relationships between sleep variables and cortical thickness/volume change, accounting for the spatial correlation between residuals at neighboring vertices and the temporal correlation of residuals within repeated measurements of single participants. Surface results were tested against an empirical null distribution of maximum cluster size across 10 000 iterations using Z Monte Carlo simulations, yielding results corrected for multiple comparisons across space ($P < 0.05$) (Hagler et al. 2006). Baseline-age, time since baseline, site, and sex were included as covariates. Separate analyses included all two- and three-way interactions between PSQI, age, and time. The hierarchical nature of the data (repeated measurements nested within participants) was

Table 5 Cluster statistics

PSQI subscale	Hemisphere	Cluster number	Size (mm ²)	Cluster P	Peak effect location
PSQI #1	Right	1	2258	0.004	Inferior parietal
PSQI #5	Right	1	2248	0.004	Inferior parietal
PSQI #5 × age	Right	1	2810	0.0007	Middle temporal
	Right	2	2801	0.0007	Middle temporal
	Right	3	2347	0.003	Precentral
	Left	1	5329	0.0001	Inferior temporal

Note: PSQI #1 = subjective sleep quality; PSQI #5 = sleep disturbances.

accounted for using a random intercept term. Additional analyses were conducted, using a dichotomous indicator variable for age (\geq vs. < 60 years), creating a piecewise linear model for cortical thinning with a cut-point at 60 years. All follow-up analyses were run in R (R Core Team 2019). To assess relationships between PSQI and memory change, we ran generalized additive mixed models (Wood 2017) (GAMM) with a random intercept and random effects per study for time and sleep using the package “mgcv” using smooth terms for baseline-age. Additional models were run with PSQI \times time \times baseline-age and age \times sleep.

Virtual Histology

Pearson correlations were computed between the thinning coefficients and the median interregional profile of gene expression levels for each marker gene. Using a resampling-based approach (Shin et al. 2018), the average expression–thinning correlation for each group of cell-specific genes served as the test statistic. False discovery rate was used to account for 9 cell-types.

Results

Self-Reported Sleep is Associated With Accelerated Cortical Thinning

Associations of PSQI scales and cortical atrophy are shown in Figure 1 and Table 5. PSQI #1 Subjective sleep quality was related to cortical thinning in the right middle temporal gyrus, extending posteriorly, so that lower quality was associated with faster thinning. A similar relationship for PSQI #5 Sleep disturbances was found in an overlapping region, bordering angular gyrus, with more disturbances being associated with faster thinning. For this subscale, extensive age-interactions were found (Fig. 2), with three large lateral clusters in the right hemisphere, located in the temporal, inferior parietal, and inferior/middle prefrontal cortex, and one cluster in the left (lateral, inferior, and medial temporal cortex). More sleep disturbances were related to accelerated cortical thinning from about 60 years of age (see below). For the remaining PSQI components and the global score, no effects were found. No relationships with cortical volume change were seen. Follow-up analyses were performed to test whether sleep duration showed a quadratic relationship with atrophy. Here, duration was measured in the number of hours instead of using the PSQI #3 Sleep duration 0–3-point scale. There were no significant quadratic relationships or age-interactions for the number of hours slept.

As can be seen in Figure 2, the association between “PSQI #5 Sleep disturbances” and cortical thinning emerged from around 60 years of age. To assess the size of this age interaction, we calculated mean cortical thinning (Δ thickness mm/year) as a function of the amount of sleep disturbances in 60 years old

and 80 years old (Fig. 3). For participants with minor sleep disturbances (“PSQI #5 Sleep disturbances” = 0), annual cortical thinning was low and close to identical for 60 years old and 80 years old; ≈ 0.05 mm/year or -0.20% . In contrast, for participants with severe sleep disturbances (PSQI #5 Sleep disturbances = 3), annual cortical thinning was almost twice as large in the oldest group, equal to -1.03% (0.027 mm/year) compared to -0.55% (0.014 mm/year), respectively.

To assess the regional specificity of the effects in Figures 1 and 2, p-maps thresholded at $P < 0.05$ not corrected for multiple comparisons were inspected (see Supplementary Material for full results). These revealed that the apparent hemispheric differences seen in the corrected maps were exaggerated by the applied correction procedure. The uncorrected maps showed bilateral and in general less localized effects, affecting all four lobes. Thus, the results should not be interpreted as showing anatomically specific sleep–atrophy relationships.

PSQI #5 SLEEP Disturbances-Related Cortical Thinning is not Stronger in Regions Showing the Most Atrophy

To test whether the age-interactions for “PSQI #5 Sleep disturbances” were strongest in regions showing the most atrophy in aging, we calculated the vertex-wise spatial correlations between the age \times “PSQI #5 Sleep disturbances” interaction coefficients and cortical thinning in participants above 60 years. The correlations were 0.04 for the left and -0.003 for the right hemisphere. These very low correlations suggest that “PSQI #5 Sleep disturbances” are not more related to cortical thinning with higher age in the regions undergoing the most thinning per se, although bootstrapping showed that the left hemisphere relationship was significantly greater than expected by chance ($P < 0.001$).

Sleep-Related Thinning and Expression of Oligodendrocytes and S1 Pyramidal Cell Genes

Virtual histology was used to test whether the age-dependent associations between “PSQI #5 Sleep disturbances” and cortical thinning were related to interregional gene expression profiles associated with specific cell types (Table 6, Fig. 4). The results showed overlap with regions with higher expression of genes related to oligodendrocytes and S1 pyramidal cells ($P_{\text{fdr}} < 0.05$). Note that these analyses were performed vertex-wise, and were not restricted to regions with significant sleep \times time \times age-interactions.

No Relationship With Memory Change

GAMMs were performed with memory score as the outcome, PSQI \times time as the main term of interest, with sex and

#1 Subjective sleep quality #5 Sleep disturbances

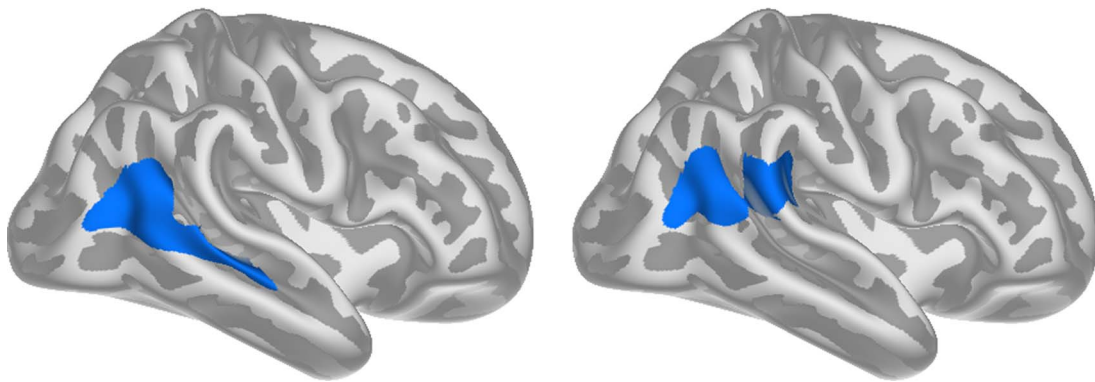


Figure 1. Effects of sleep on cortical thinning Clusters where PSQI #1 Subjective sleep quality and PSQI #5 Sleep disturbances were related to cortical thinning after corrections for multiple comparisons across space.

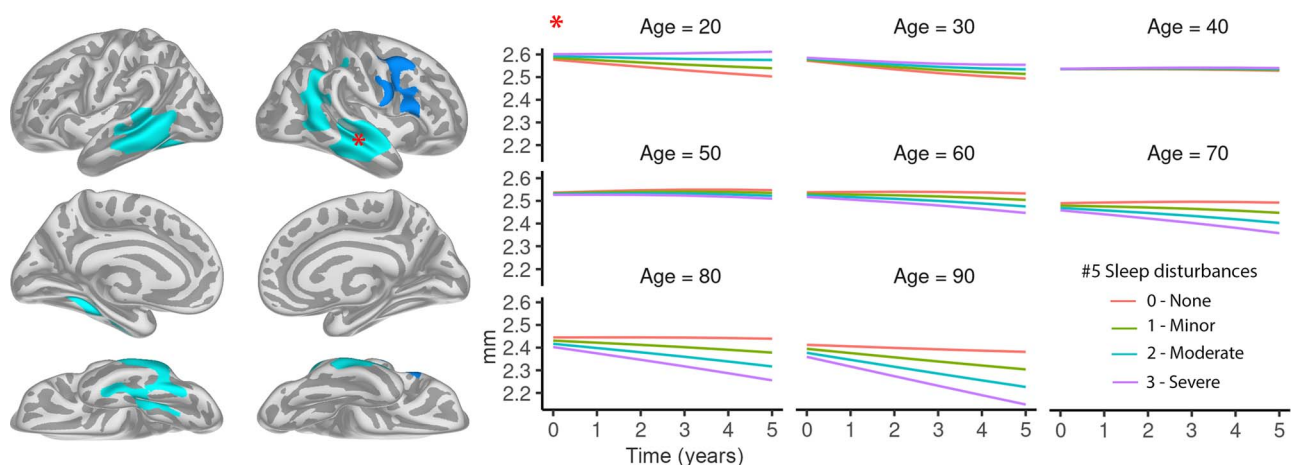


Figure 2. Age-interactions; left panels: clusters where PSQI #5 Sleep disturbances are significantly more strongly related to cortical thinning in older than younger adults. Average cortical thickness in the cluster in the right middle temporal gyrus—marked by the red asterisk—was extracted and used to illustrate the age-interactions in the right panels. Right panels: model predicted cortical thickness in the right middle temporal cluster in the left panel as a function of age, time, and amount of sleep disturbances (0: none, 3: severe). Participants reporting more sleep disturbances show more cortical thinning in the older age ranges but not in the younger. CIs around the curves were removed for improved viewing and are presented in the [Supplementary Material](#), along with similar curves for the other three significant clusters. These plots are used for illustrating the effects in the surface analyses. Statistical analyses were conducted using age as a continuous variable.

baseline-age as covariates. No significant relationships were found (all P 's ≥ 0.22). Effect estimates are presented in the [Supplementary Material](#), showing that the largest effect was found for PSQI #4 Habitual sleep efficiency, for which the efficiency (scale 0–3) \times time (in years) interaction on change in memory scores (SD) was -0.022 , that is, high sleep efficiency (PSQI #4 score “0”) was associated with 0.33 SD less decline in memory score over a 5-year interval compared to low efficiency (PSQI #4 score “3”). We tested the three-way interaction PSQI \times time \times baseline-age, with no significant effects (all P 's ≥ 0.58). Finally, we ran models with the smooth interaction between age at testing and PSQI. Here the longitudinal and cross-sectional information is combined in the test age variable, and because chronological age has much more variance than ages at repeated measures, this analysis is skewed toward cross-sectional effects. Here, age \times “PSQI #5 Sleep disturbances” showed a weak but significant relationship with memory change ($P = 0.039$, uncorrected). None of the other PSQI components showed this, with “PSQI #3 Sleep duration”

($P = 0.086$) and “PSQI #4 Habitual sleep efficiency” ($P = 0.099$) scales yielding the lowest P -values, and “PSQI global score” the highest ($P = 0.96$).

Post Hoc Analyses: Controlling for body mass index and Depression

We performed post hoc analyses testing whether body mass index (BMI) or preclinical depression affected the observed “PSQI 5 Sleep disturbances”—cortical change relationship (see [Supplementary Material](#) for details). BMI was available at the time of analysis from the LCBC, CamCAN, and Betula datasets ($n = 1717$), and depression scores from the LCBC, CamCAN, Betula, and BASE-II datasets ($n = 1637$). As seen in [Figures 5 and 6](#), controlling for BMI or depression symptoms did not affect the relationship between “PSQI #5 Sleep disturbances” and cortical change, except for some offset effects for BMI in the 50ties and 60ties, not affecting the actual slope.

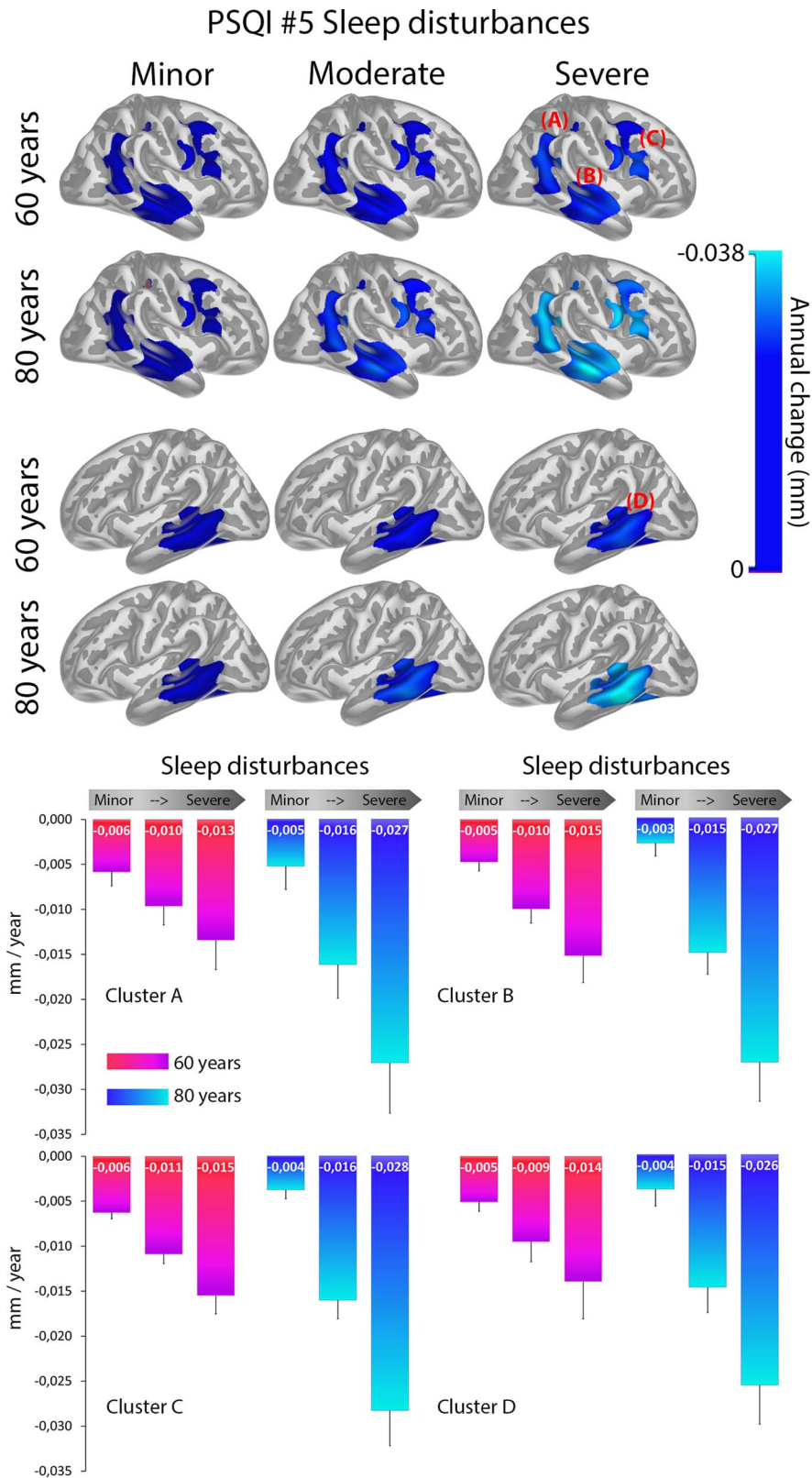


Figure 3. Cortical thinning as a function of sleep disturbances and age; top panel: mean cortical thinning (mm/year) in the clusters with a significant effect of age \times sleep on thickness change broken up by score on PSQI #5 Sleep disturbances and age group. Bottom panel: mean cortical thinning in the same regions as a function of score on PSQI #5 Sleep disturbances and age group. Error bars denote 1 SD.

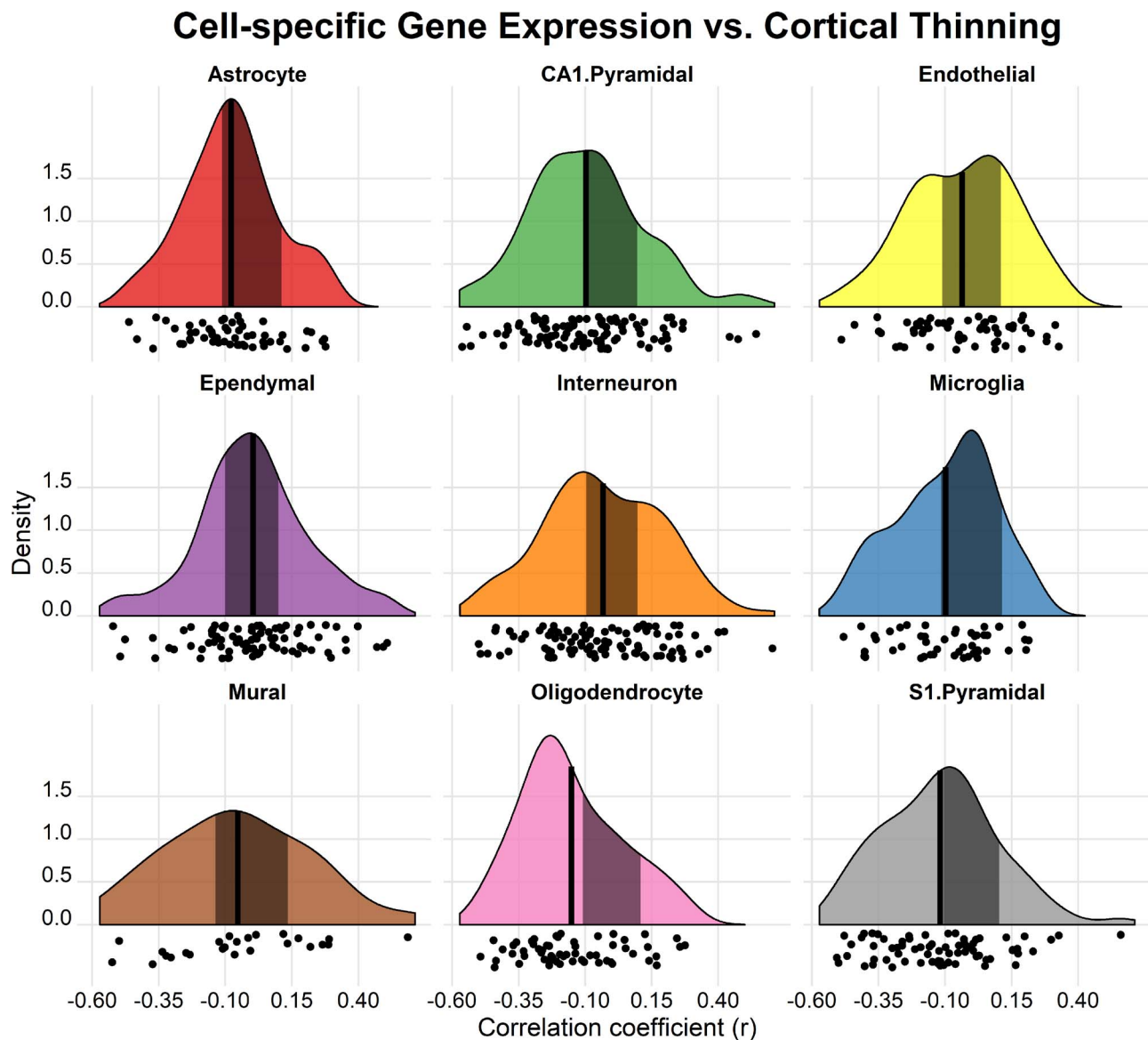


Figure 4. Virtual histogram; significantly higher expression of genes characteristic of specific cell types (oligodendrocytes and S1 pyramidal) in vertices where the age-related association between PSQI #5 Sleep disturbances and cortical thinning are the strongest (vertex-wise thickness effects from the age \times time \times sleep interaction; see surface plots in Figure 2). The black vertical lines represent the mean association, and the shaded area represents the empirical null distribution for each of the 9 cell types. The x-axes indicate the coefficients of correlation between the thinning and the gene expression profiles. The y-axes indicate the estimated probability density for the correlation coefficients. Panels, where the mean of the target ROIs is outside the null distribution 95% CI, are considered to show a correlation greater or smaller than predicted. See Allen et al. (2019) for the creation of raincloud plots.

Post Hoc Analyses: Site Differences

Differences in MR scanners and sequences are expected to affect cortical thickness estimates. Here site was included as a covariate in all analyses, which controls for main effects of scanner/sequence ("Site") on cortical thickness. As an additional test, for each of the identified clusters listed in Table 5, we reran the models, including a Site \times Sleep \times Time interaction as an additional term to directly test whether the sleep–thickness change relationship differed between sites. Only for "PSQI #5 Sleep disturbances" \times Cluster 4 (left lateral temporal cortex) was the interaction significant. The estimated effect of sleep on cortical thinning had the same sign as the reported and was still significant. Thus, we cannot exclude the possibility that

the relationship between sleep and thickness change is stronger for some sites than others for this specific effect, although the nature of the relationship did not change when controlling for site \times sleep \times time. For all other models, the site \times sleep \times time interaction was not significant.

Discussion

Lower self-reported sleep quality and more sleep disturbances were associated with more regional cortical thinning, independently of depressive symptoms and BMI, after the age of 60 years. These relationships were stronger in regions with higher expression of genes related to oligodendrocytes and S1 pyramidal cells.

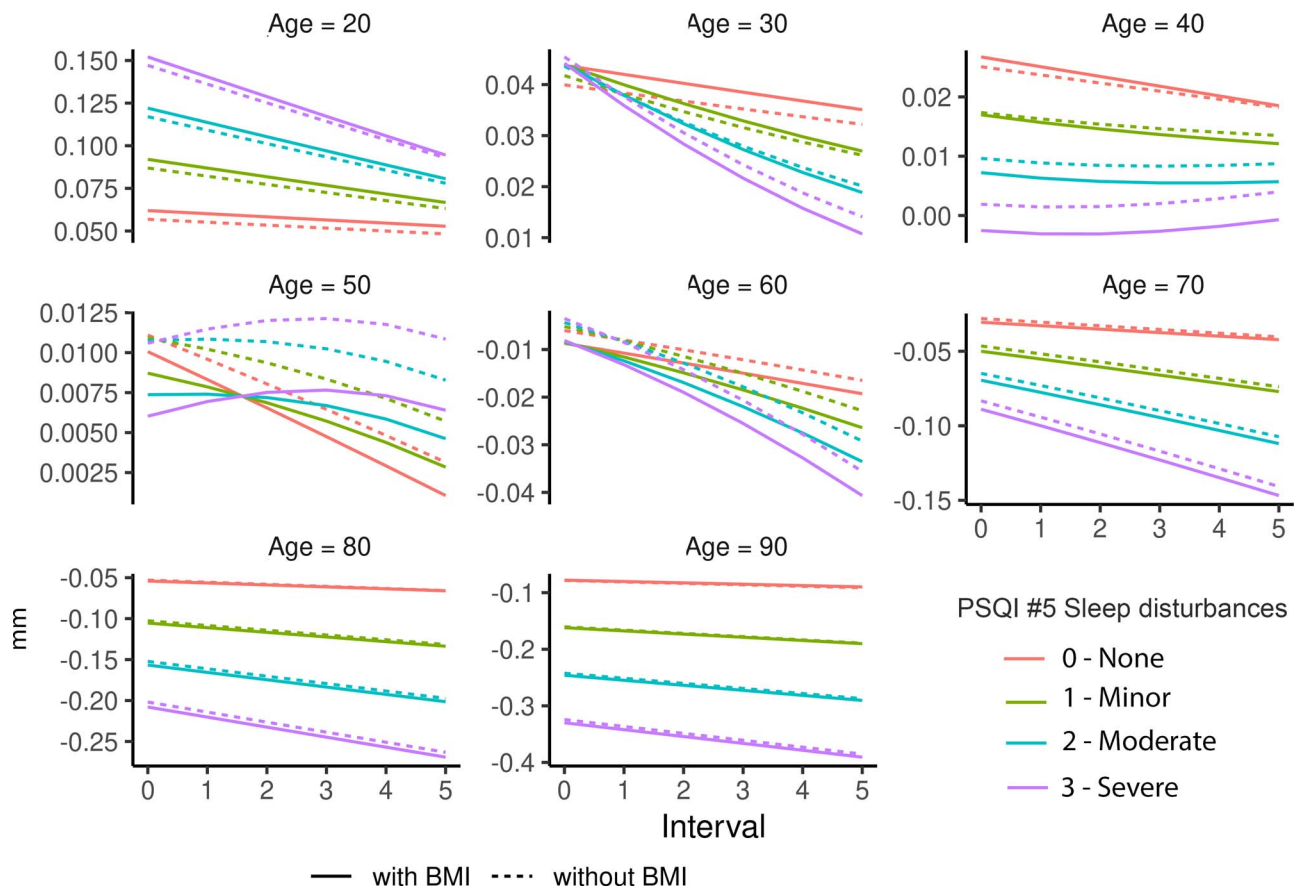


Figure 5. Controlling for BMI; BMI did not affect the relationship between PSQI #5 Sleep disturbances and cortical thinning across age, as can be seen from the overlapping solid and dotted lines. Plotted effects are from Cluster B (Figure 3); see [Supplementary Material](#) for additional clusters. Note that the y-axes are fitted to each plot to facilitate the detection of possible differences between curves visually, and therefore vary between plots.

It should be noted that effect sizes were modest, there were no significant associations with PSQI Global sleep score or sleep duration measured in hours or by “PSQI #3 Sleep duration,” and there was no significant association with memory change.

Sleep Disturbances and Cortical Thinning

Lower sleep quality and more sleep disturbances were related to cortical thinning in the right middle temporal gyrus, extending posteriorly. “PSQI #1 Subjective sleep quality” is based on the participants’ overall evaluation of their sleep, whereas “PSQI #5 Sleep disturbances” includes items such as nocturnal awakenings, bad dreams, and trouble breathing. In previous work on a subsample of the current sample, we found “PSQI Global sleep score” to be related to volume reductions in overlapping regions (Sexton et al. 2014) in older adults. Although worse sleep may accelerate cortical atrophy in aging, stronger relationships were not found in the regions that showed the most cortical thinning. This suggests that worse sleep does not simply relate to general patterns of cortical atrophy that are typical in aging but more regionally specific patterns of cortical decline. Alternatively, these results, together with previously reported unspecific relationships between sleep, cognition, and neurodegeneration (Ohayon et al. 2004; Scullin and Bliwise 2015; Mander et al. 2017), suggest that worse sleep results from multiple changes in the aging brain. Sleep and brain decline are probably linked

through complex interactions with multiple other factors, some involving atrophy and some not (Fjell et al. 2018b).

It is important to stress that effect sizes were small. Even with 4363 MRIs, only two aspects of self-reported sleep were significantly associated with a change in cortical thickness. Thus, the standard self-report sleep metrics do not seem to have much clinical relevance as markers of cortical atrophy. For participants in their 1960s, the transition from minor to severe sleep disturbances was weakly but reliably associated with cortical thinning. For 80-years-old participants that same transition was accompanied by a rather substantial increase in cortical thinning. However, as participants were not followed over time with repeated sleep measures, we do not know whether these group effects translate to relationships within individuals. Thus, although our findings are interesting as they demonstrate an age-dependent relationship between aspects of sleep and cortical thinning, the mechanisms driving this age dependency in the strength of the association between sleep and cortical thinning await further study. One important caveat is that sleep was observed at a one-time point or averaged across time points, and we were, thus, not able to assess whether a change in sleep was related to atrophy. Previous studies have found a change in sleep patterns to be predictive of atrophy (Fjell et al. 2018b) and declining cognition (Ferrie et al. 2011), and future studies should directly test such change–change relationship across the cortex.

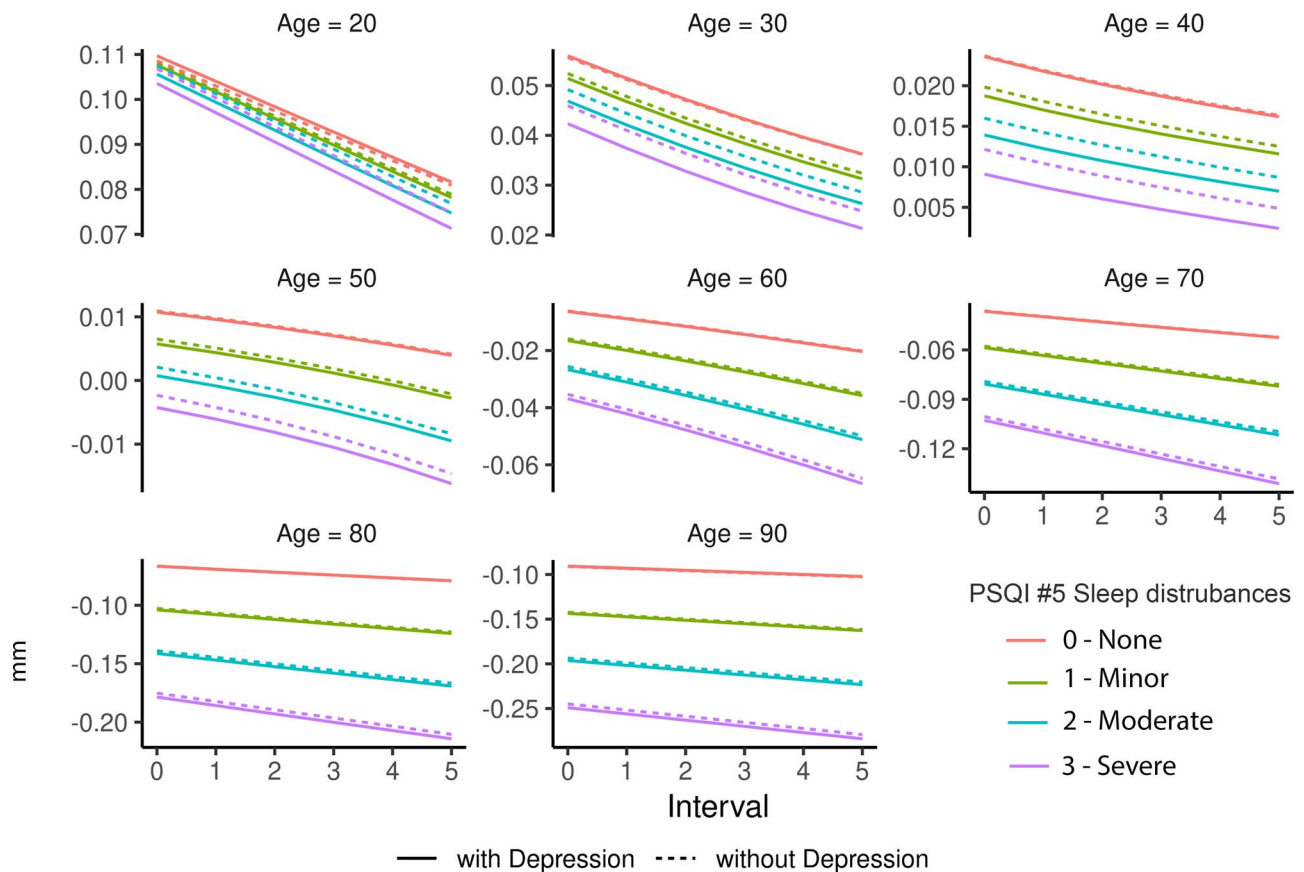


Figure 6. Controlling for depression; depressive symptoms did not affect the relationship between PSQI #5 Sleep disturbances and cortical thinning across age, as can be seen from the overlapping solid and dotted lines. Plotted effects are from Cluster B (Figure 3); see [Supplementary Material](#) for additional clusters. Note that the y-axes are fitted to each plot to facilitate the detection of possible differences between curves visually, and therefore vary between plots.

Virtual Histology—A Possible Role of Oligodendrocytes

The age-dependent sleep association overlapped with regions characterized by higher expression of genes related to oligodendrocytes and S1 pyramidal cells. These results do not reveal any direct mechanistic relationships but yield useful information for interpretation of the findings, especially regarding genes related to oligodendrocytes. Several genes involved in the synthesis and maintenance of myelin are expressed at higher levels during sleep, and sleep loss may negatively impact oligodendrocyte physiology (Bellesi 2015). Specifically, genes involved in phospholipid synthesis and myelination tend to be transcribed preferentially during sleep (Bellesi et al. 2013). For instance, gene expression analysis performed on oligodendrocyte-enriched samples of mouse forebrain showed that several genes changing their expression in sleep and awake were oligodendrocyte precursor cell (OPC)-specific genes (Bellesi et al. 2013). Genes promoting OPC proliferation were mainly upregulated during sleep whereas OPC differentiation was mainly upregulated during awake. Such studies suggest that sleep is important for myelination (de Vivo and Bellesi 2019). Myelin properties around the GM/WM boundary affect cortical thickness estimates (Walhovd et al. 2017; Natu et al. 2019) and change through the lifespan (Westlye et al. 2009; Vidal-Pineiro et al. 2016). Thus, regions with higher expression of oligodendrocyte-related genes could be more vulnerable to poor sleep, explaining the overlap between the expression of

oligodendrocyte-related genes and sleep-age-related cortical thinning. Although speculative, experimental, and large-scale genetic studies could address this.

No Relationship Between Cortical Thinning, Sleep Duration, and Memory Change

Sleep duration as measured in hours or by “PSQI #3 Sleep duration” was not associated with cortical thinning. Sleep duration is the most frequently investigated sleep measure in relation to health (Watson et al. 2015) and is potentially modifiable. It has been suggested that we have a “global epidemic of sleeplessness” (Lyon 2019; Walker 2019), and the United States National Sleep Foundation (NSF) provides sleep duration recommendations (Consensus Conference Panel et al. 2015; Hirshkowitz et al. 2015). Previous studies have, however, not provided conclusive evidence about a role for sleep duration in brain change (Lo et al. 2014; Sexton et al. 2014; Spira et al. 2016; Fjell et al. 2019b). We found no indication that sleep duration was related to cortical change, supporting previous Lifebank results on hippocampal atrophy (Fjell et al. 2019b). In that study, however, participants from the UK Biobank reporting short (< 5 h) and long (> 9 h) sleep duration showed smaller hippocampal volume. Although we cannot conclude with confidence that extremely short or extremely long sleep duration is unrelated to cortical atrophy, our results demonstrate that within normal ranges of sleep duration, there is no association with cortical change.

Scores on the sleep scales were not related to changes in memory function. The only significant result was the interaction between PSQI #5 Sleep disturbances and age, which would not survive correction for multiple comparisons. Experimental studies often report negative effects of short-term sleep restriction on cognition (Lim and Dinges 2010), but it is unclear whether such effects are relevant in the long run and in a naturalistic setting. Meta-analytic studies have reported poorer episodic memory in people with insomnia (Fortier-Brochu et al. 2012), whereas epidemiological studies have yielded mixed results, and the largest study to date—based on 477,529 participants from the UK Biobank—found no relationship between insomnia and any cognitive function (Kyle et al. 2017). The possibility remains that longitudinal changes in self-reported sleep could be related to declining memory over time (Fjell et al. 2018b), and stronger relationships could potentially be seen with other measures of sleep (Cavuto et al. 2016; Muehlroth et al. 2019). Still the present results, based on 1419 participants and 2702 memory tests, suggest that if a relationship between self-reported sleep and memory decline does exist, the effect size of this association can be expected to be small.

Limitations

Causes and appearance of age-related changes in sleep are manifold and diverse (Muehlroth and Werkle-Bergner 2020). There is no perfect way to measure sleep without disrupting routine (Lauderdale et al. 2008). Self-reports of sleep duration are only moderately correlated with actigraph measures (Regestein et al. 2004; Lauderdale et al. 2008; Wrzus et al. 2012), whereas actigraphs themselves tend to overestimate sleep duration compared to polysomnography (Ancoli-Israel et al. 2003; de Souza et al. 2003; Hedner et al. 2004; Sivertsen et al. 2006; Jackson et al. 2018). Still, self-report measures continue to be important in sleep studies, and epidemiological studies and the NSF recommendations are primarily based on self-reports (Hirshkowitz et al. 2015). Although we acknowledge the uncertainty of self-reports, this is currently the only viable option for testing sleep-brain relationships in large samples. Also, we are not able to distinguish between the effects of short- versus long-term sleep patterns, as PSQI only index sleep over the last month. Another possible limitation is that data were pooled across studies using partly different measures. Whereas this may introduce noise, it also reduces the risk of non-representative and biased samples and greatly increases statistical power. Finally, including different memory measures than delayed free recall could yield other results.

Conclusion

Worse self-reported sleep was related to an increased rate of cortical thinning in restricted regions after the age of 60 years. These regions are characterized by higher expression of genes related to oligodendrocytes and S1 pyramidal cells. This makes self-reported sleep a relevant variable in studies of brain aging. Small effect sizes and lack of relationship to episodic memory decline call for modesty in the implications drawn. Future studies should also directly test whether a change in self-reported sleep parameters over time shows stronger relationships to regional cortical atrophy.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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