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Sleep and resting-state functional magnetic resonance imaging connectivity in middle-aged adults and the elderly: A population-based study

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Abstract

Sleep problems increase with ageing. Increasing evidence suggests that sleep problems are not only a consequence of age-related processes, but may independently contribute to developing vascular or neurodegenerative brain disease. Yet, it remains unclear what mechanisms underlie the impact sleep problems may have on brain health in the general middle-aged and elderly population. Here, we studied sleep's relation to brain functioning in 621 participants (median age 62 years, 55% women) from the population-based Rotterdam Study. We investigated cross-sectional associations of polysomnographic and subjectively measured aspects of sleep with intrinsic neural activity measured with resting-state functional magnetic resonance imaging on a different day. We investigated both functional connectivity between regions and brain activity (blood-oxygen-level-dependent signal amplitude) within regions, hierarchically towards smaller topographical levels. We found that longer polysomnographic total sleep time is associated with lower blood-oxygen-level-dependent signal amplitude in (pre)frontal regions. No objective or subjective sleep parameters were associated with functional connectivity between or within resting-state networks. The findings may indicate a pathway through which sleep, in a 'real-life' population setting, impacts brain activity or regional brain activity determines total sleep time.

KEYWORDS

BOLD, epidemiology, fMRI, rs-fMRI

1 | INTRODUCTION

Sleep is a homeostatic process serving vital functions for the brain to support performance the next day. As adults age, they increasingly experience sleep problems (Foley et al., 1995). Sleep problems have been hypothesized to impair brain health, as they are associated with developing stroke (Wu, Chen, Yu, Wang, & Guo, 2017) and dementia (Shi et al., 2018). It is therefore important that we increase our understanding how sleep, beyond its homeostatic, night-to-day effect, may impact brain health in the general middle-aged and elderly population.

How sleep affects the brain can be investigated well by studying brain functional connectivity. Brain functional connectivity can be studied non-invasively with functional magnetic resonance imaging (fMRI), which measures intrinsic neural activity indirectly through blood oxygenation. Applying fMRI when individuals are not engaged in a task ('resting-state' fMRI (rs-fMRI)) reveals how brain regions spontaneously communicate with each other in connected networks

(Biswal, Yetkin, Haughton, & Hyde, 1995). Intrinsic neural activity as measured with rs-fMRI can provide measures of activity between cortical regions, or within them. The organization of intrinsic neural activity in networks is remarkably robust and present across various conditions (Smith et al., 2009).

That sleep is relevant for waking rs-fMRI neural activity has been shown using various approaches. Experimental sleep deprivation studies showed immediate widespread changes in functional connectivity during subsequent wakefulness (Nilsonne, 2017; Yeo, Tandi, & Chee, 2015), including an increase of global fMRI-signal variability (Nilsonne et al., 2017), also known as signal amplitude. Importantly, observational studies that associated habitual sleep quality or duration, or a sleep disorder such as insomnia, with rs-fMRI measures suggest that sleep may impact intrinsic neural activity beyond the short term (Bijsterbosch et al., 2017; Khalsa et al., 2016; Khazaie et al., 2017; Killgore et al., 2015; Stoffers et al., 2014; Van Essen et al., 2013). Yet, only a few studies measured sleep objectively to minimize misclassification or used large samples to increase statistical power and decrease the chance that significant associations are overestimated. Findings from large-scale, population-based studies are more equivocal, reporting no associations of sleep quality with connectivity between networks (Stephen et al., 2016) or of self-reported sleep duration with signal amplitude in the often-studied 'default mode' network (Bijsterbosch et al., 2017).

It is therefore unclear if variations in sleep, including total sleep time and duration of individual sleep stages, are related to intrinsic neural activity during daytime, measured as functional connectivity between or neural activity within different brain regions, in the general middle-aged and elderly population. We aimed to fill this knowledge gap using sleep parameters measured with polysomnography and the Pittsburgh Sleep Quality Index, and rs-fMRI measures from the population-based Rotterdam Study cohort. We explored associations between sleep and intrinsic neural activity using a hierarchical approach from global to more spatially specific analyses, and subsequently examined associations of total sleep time more regionally based on initial findings.

2 | METHODS

2.1 | Study setting

The Rotterdam Study, starting in 1990, is a prospective population-based cohort of inhabitants of a suburban district in Rotterdam aged 45 years or over (Ikram et al., 2017). Participating inhabitants were interviewed at home and subsequently visited the research centre. These examination rounds were repeated every 4–5 years. The cohort was expanded twice, in 2000 with persons aged ≤55 and in 2006 with persons aged ≤45. We studied individuals from all three inclusion rounds who participated in a polysomnography (PSG) study between January 2012 and September 2014, and also underwent a resting state fMRI (rs-fMRI) scan. Rs-fMRI has been implemented routinely since 2012 (Zonneveld et al., 2019).

The Rotterdam Study (RS) has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272–159521-PG). The RS has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. The study was conducted in accordance with the guideline proposed in the World Medical Association Declaration of Helsinki. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

2.2 | Study sample

We invited 1,750 persons that visited the research centre for in-home PSG; 928 consented. Invitees were deemed able to understand the study purpose and instructions. Twenty-seven recordings failed or were of insufficient quality for sleep scoring. Of these, 724 persons without MRI contraindications also underwent rs-fMRI. We excluded participants with poor quality (Zonneveld et al., 2019) rs-fMRI data (n = 49), cortical brain infarcts (n = 20) or with prevalent dementia or missing dementia screening (n = 2). From the remaining 653, we included in our main analyses 621 participants with a time interval between PSG and rs-fMRI of 1 year or less. From this population, we included 560 participants for analyses of PSG spectral power due to failure of critical EEG leads in 61 individuals. Similarly, we included 603 participants for analyses on global PSQI score due to missing data of more than one component (see 'Sleep assessments' below).

2.3 | Sleep assessments

We recorded one night of PSG at home during weeknights. Polysomnography was applied by trained research assistants according to the American Association of Sleep Medicine (AASM) criteria (Iber, 2007), including six electroencephalography (EEG) channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2 and O2/A1), bilateral electro-oculography, chin electromyography, electrocardiography, respiratory belts on the chest and abdomen, oximetry, and a nasal pressure transducer and oronasal thermocouple. Participants were instructed to spend the night as normally as possible, without restrictions on bedtimes and use of alcohol, coffee or sleep medication. They pressed a button to signal when intending to go to sleep ("lights out") and getting out of bed ("lights on").

Sleep was scored (Iber, 2007) by a registered polysomnographic technologist to determine total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE), and the duration of the sleep stages non-rapid eye movement (NREM) 1 (N1), N2, N3 and REM.

We calculated spectral power and spindles in the C3/A2 derivation using PRANA software (PhiTools). For spectral power, bandpass filtering (0.125–128 Hz) and automated removal of artifacts were applied. Spectral analysis was performed using 4-s epochs with 50% overlap, averaged over 30-s epochs. We calculated the absolute spectral power in the delta (0.75–4.00 Hz), beta (15.50–22.50 Hz) and gamma (22.50–40.00 Hz) frequency bands.

Apneas were defined as an airflow reduction of ≥90% of baseline for ≥10 s, and a hypopnea was defined as an airflow reduction of ≥30% of baseline for ≥10 s and a desaturation of ≥3% from baseline or an arousal(Iber, 2007). The apnea–hypopnea index (AHI) was automatically calculated as the number of apneas and hypopneas per hour of sleep.

Subjective sleep quality during the past 4 weeks was measured with the PSQI during the home interview. The PSQI has good test–retest reliability and validity in a non-clinical sample of older adults (Mollayeva et al., 2016). Items, including self-reported sleep duration, were scored to provide a global PSQI score ranging from 0 to 21. Higher scores indicate poorer sleep quality. We weighted the PSQI score for 36 out of 603 individuals with one component score missing, by multiplying scores by 7/6.

To validate our findings for polysomnography sleep measures and assess a possible first-night effect we used actigraphy (Van Den Berg et al., 2008). On the night of polysomnography, participants also wore an actigraph (ActiWatch model AW4, Cambridge Technology Ltd), and were invited to wear it for 7 days and also keep a sleep diary. Of 621 participants, 428 completed at least four consecutive nights (recording duration, 153 ± 16 hr [median = 144]). We used diary-derived times of 'lights out' and getting up the next morning to estimate time in bed. Within the time in bed, total sleep time was estimated using a validated algorithm with a threshold of 20 activity counts, and was averaged over all available nights per participant to estimate habitual total sleep time.

2.4 | Neuroimaging

Brain imaging was performed with a 1.5-tesla MRI scanner (Signa Excite II, GE Healthcare) at the research centre. Resting state fMRI acquisition time was 7 min 44 s (repetition time = 2,900 ms, echo time = 60 ms, field of view = 21 cm^2, 31 axial slices, matrix size = 64 x 64, slice thickness = 3.3 mm, 165 volumes). Details of rs-fMRI preprocessing and connectivity analyses are provided elsewhere (Zonneveld et al., 2019). In brief, participants were prompted before the start of the fMRI sequence to lie still, keep their eyes open and stay awake. Preprocessing of resting-state data was performed with the FMRIB Software Library FEAT package (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Subject-specific artifact removal was conducted using independent components, which were automatically classified. We excluded scans showing absolute head displacement >3 mm and/or mean relative framewise displacement >0.2 mm. Also, as mild ghosting artefacts were introduced during rs-fMRI acquisition, we did not include scans with a ghost-to-signal ratio >0.1 and added this ratio as a covariate in analyses (Zonneveld et al., 2019).

For functional connectivity analyses, we generated a study-specific functional parcellation using independent component analysis (Smith et al., 2015; Zonneveld et al., 2019), resulting in 50

TABLE 1 Characteristics of the study population

Characteristics (unit)	Value
Covariates	
Age (years)	62 (58; 66)
Female	340 (55%)
Time interval measurements (days) MRI–PSG	6 (−12; 22)
No. of participants <1 month	450 (72%)
MRI – PSQI	150 (104; 191)
No. of participants <6 months	438 (69%)
Habitual alcohol consumption (gr/day)	8 (4; 11)
Physical activity (MET, hr/week)	50 (24; 78)
Systolic blood pressure (mm Hg)	133 ± 18
Body mass index (kg/m^2)	27 ± 4
History of diabetes mellitus	73 (12%)
Supratentorial grey matter volume (cm^3)	538 ± 55
Intracranial volume (cm^3)	1,141 ± 115
Depressive symptoms (CES-D score)	12 (10; 15)
Use antidepressant/hypnotic medication during PSG	29 (5%)
Self-reported sleep duration (min)	408 ± 73
Apnea–hypopnea index (events/hr of sleep)	9 (5; 13)
Sleep parameters	
Total sleep time (min)	380 ± 65
Sleep onset latency (min)	14 (8; 23)
Wake after sleep onset (min)	71 ± 48
Sleep efficiency (%)	81% ± 11
Sleep stage duration (min)	
N1	49 ± 25
N2	203 ± 52
N3	48 ± 37
REM	79 ± 26
Absolute spectral power ($\mu V^2/Hz$)	
Delta (range: 0.75–4.50 Hz)	106 (72; 155)
Beta (range: 15.50–22.50 Hz)	2.5 (1.7; 3.7)
Gamma (range: 22.50–40.00 Hz)	1.9 (1.3; 2.9)
Missing	61 (10%)
Subjective sleep quality (PSQI score)	3 (1; 6)
Missing	18 (3%)

Note: Values are frequency (%) for categorical variables and mean ± standard deviation or median (first quartile; third quartile) for continuous variables, calculated over 621 participants unless specified otherwise. Values include imputed values for covariates.

Abbreviations: CES-D, Center for Epidemiological Studies – Depression Scale; MET, metabolic equivalent of task; MRI, magnetic resonance imaging; *N*, sample size; *N*[x], non-REM stage x; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; TST, total sleep time.

components of interest or functional nodes (hereafter: nodes). A node thus is a region where voxels show the same temporal blood-oxygen-level dependent (BOLD)-signal pattern. This template was used to derive node-level time series and obtain values for the full temporal correlations per subject for all nodes. Using hierarchical clustering of the group-level node correlations (Smith et al., 2015), we concatenated these nodes into nine large-scale networks, labelled anterior default mode, posterior default mode, frontoparietal, dorsal attention, ventral attention, sensorimotor, visual, subcortical and temporal networks (Zonneveld et al., 2019). Networks thus contain multiple nodes showing similar temporal patterns. Defining small nodes and clustering them into networks allowed studying in more detail the functional specialization within networks, as well as large-scale networks as a whole (Smith et al., 2013).

Using the functional parcellation of 50 nodes, we calculated functional connectivity between node regions and brain activity within node regions. For functional connectivity, we calculated correlations between the BOLD-signal time series of each of the 50 nodes with all others. At the network level, we obtained between-network functional connectivity by averaging correlation values between all nodes from one network with all nodes from the other network, for 9 x 9 networks. Within-network functional connectivity was thus defined by averaging correlations of node pairs within that network. We investigated brain activity within regions as the variability of that region's BOLD signal, by calculating the standard deviation (*SD*) of each node's time series (hereafter: signal amplitude). Analogous to functional connectivity, network-level signal amplitude was obtained by averaging amplitudes across nodes within that network. Global signal amplitude was obtained by averaging over all 50 nodes (Table 1).

2.5 | Potential confounders

We adjusted for potential confounders selected based on relevant publications (Liu, 2013; Zonneveld et al., 2019): age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume.

The sensitivity analysis included additionally adjusting the main analyses for depressive symptoms and use of any antidepressant or hypnotic medication during PSG.

Details of measurements are provided in the Supplementary Text, Appendix S1.

2.6 | Statistical analyses

Details are described in the Supplementary Text, Appendix S1. We investigated cross-sectional associations of 12 sleep determinants (TST, WASO, SOL, SE, duration of stages N1, N2, N3, REM, spectral delta, beta and gamma power, and global PSQI score) with both functional connectivity between regions (and within where possible) and signal amplitude within regions. We used non-parametric permutation testing (n = 5,000) implemented in FSL's 'randomise', with family-wise error (FWE)-corrected p-values.

We hierarchically tested associations to examine regional heterogeneity if significant at a global level: we investigated associations with functional connectivity at the network level, and further analysed node-level associations if nominally significant. Similarly, we first investigated associations with mean signal amplitude on a global level, and further analysed the nominally significant associations on a network level. Furthermore, we investigated significant network-level associations on a node level.

As tests in 'randomise' are by default performed one-sided, we further Bonferroni-corrected the alpha level of 0.05 to $p_{\text{FWE-corrected}} < .025$ (nominal significance level). As we tested multiple sleep determinants, we defined a more stringent threshold for significance at $p_{\text{FWE-corrected}} < .00277$ (number of effective independent tests = 9.23).

As a sensitivity analysis, we repeated the analyses in persons with a shorter time interval between imaging and sleep measurements (<1 month for PSG parameters; <6 months for PSQI score). Also, we additionally adjusted analyses for (a) depressive symptoms and use of any antidepressant or hypnotic medication during PSG and (b) AHI.

In post-hoc analyses based on initial findings for total sleep time, we (a) explored associations of separate sleep stages with amplitude on a node level, (b) assessed possible non-linearity by analysing five equal-sized categories (quintiles) of total sleep time and modelling a quadratic term, and (c) repeated analyses with actigraphy-estimated total sleep time in n = 428 with valid actigraphy data, and with self-reported sleep duration assessed in the PSQI (Figure 1; Table 2).

3 | RESULTS

We included 621 participants (median age = 62 years [range 52–95 years], 55% women). The median absolute time interval between PSG and rs-fMRI was 17 days. Excluded participants did not differ from included participants by age, sex, head motion parameters or duration of sleep stages. Correlations amongst sleep and fMRI parameters are provided in Table S1.

FIGURE 1 Colours and sizes of blocks correspond to beta coefficients: red indicates positive and blue indicates negative associations. Values are obtained using linear regression, adjusted for age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume. No associations were significant at the level of $p_{\text{FWE-corrected}} < .025$. Abbreviations: DAN, dorsal attention network; FPN, frontoparietal network; DMNa, anterior default mode network; DMNp, posterior default mode network; N[x], non-REM sleep stage x; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SMN, sensorimotor network; Subcort, subcortical network; Temp, temporal network; VAN, ventral attention network; Vis, visual network

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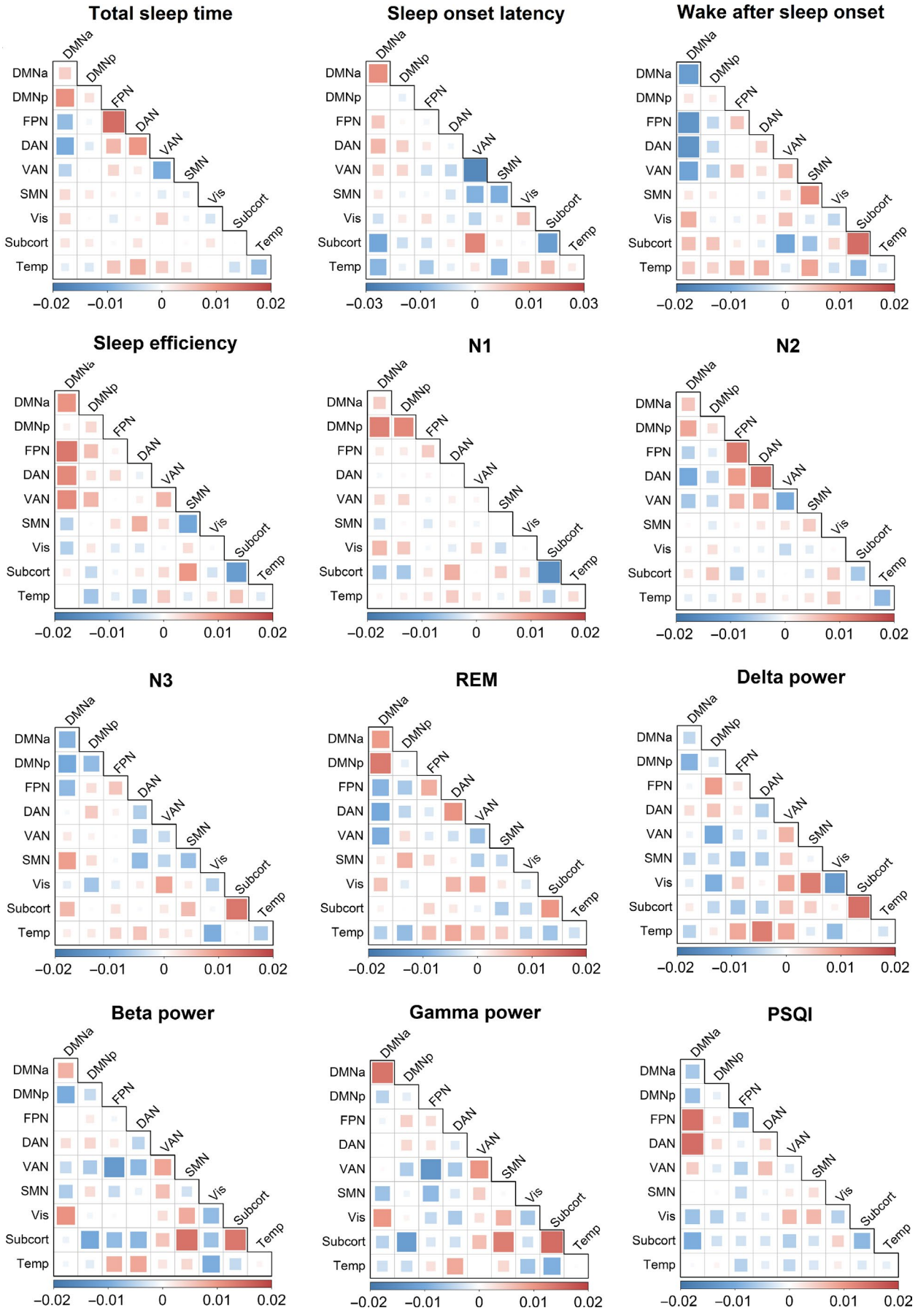

TABLE 2 Associations of sleep parameters with global mean signal amplitude

Sleep measures	Beta (95% CI)	*p*-value
Objective		
Sleep continuity measures		
Total sleep time	**−0.025 (−0.044; −0.006)**	**5.0e−3**
Sleep onset latency	0.015 (−0.020; 0.049)	.19
Wake after sleep onset	−0.001 (−0.022; 0.019)	.45
Sleep efficiency	−0.014 (−0.038; 0.010)	.14
Sleep stage duration		
N1	−0.013 (−0.034; 0.007)	.10
N2	−0.013 (−0.032; 0.005)	.08
N3	−0.009 (−0.030; 0.013)	.21
REM	−0.015 (−0.034; 0.004)	.05
Spectral power		
Delta power	0.004 (−0.024; 0.032)	.39
Beta power	0.013 (−0.013; 0.038)	.16
Gamma power	0.003 (−0.023; 0.029)	.41
Subjective		
Sleep complaints (global PSQI score)	0.009 (−0.010; 0.028)	.18

Note: Values represent difference (95% CI) in mean signal amplitude on a whole-brain level, per standard deviation increase in the determinant. Estimates are obtained using linear regression models adjusted for age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume.

Bold values indicate statistical significance at $p < .025$. Please note that *p*-values were uncorrected as only the 'global' region was tested.

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; Nx, non-REM sleep stage x; REM, rapid eye movement.

3.1 | Network connectivity

We found no associations of objective or subjective sleep parameters with functional connectivity between or within resting state networks (all $p_{FWE\text{-}corrected} > .025$; Figure 1, Table 3).

3.2 | Signal amplitude

We observed an association of longer total sleep time with lower mean global signal amplitude (beta per *SD* increase, −0.025 [95% CI, −0.044, −0.006]; $p = 5.0e\text{-}3$; Table 2).

Investigating the regional heterogeneity of this association at a network level, we found it was present in the ventral attention, sensorimotor, subcortical and temporal networks (Table 3). In the ventral attention network, the association remained after correcting for testing multiple sleep parameters (−0.051 [95% CI −0.077, −0.024]; $p_{FWE\text{-}corrected} = 1.2e\text{-}3$; Figure S1).

We further investigated associations of total sleep time with signal amplitude within aforementioned networks at the node level. We only observed associations of longer total sleep time with lower signal amplitude in nodes of the ventral attention network, distributed mainly in (pre)frontal regions (Figure 2). The association in 'node 32' remained after correcting for multiple testing (−0.051 [95% CI −0.075, −0.027]; $p_{FWE\text{-}corrected} = 1.6e\text{-}3$). This node corresponds bilaterally to the anterior cingulate gyrus and the juxtapositional lobule cortex (formerly: supplementary motor cortex; Figure 2).

Other sleep parameters were not associated with mean global signal amplitude, yet direction of effect sizes was mostly congruent with indicating 'poor' sleep (e.g., sleep onset latency, beta spectral power) versus 'good' sleep (e.g., sleep efficiency).

3.3 | Sensitivity analysis

Restricting associations to persons with a shorter time interval between sleep and rs-fMRI measurement showed more pronounced effect sizes for the association of longer total sleep time with lower mean signal amplitude ($n = 450$, Table S2). Associations remained statistically significant in 'node 32' (−0.063 [95% CI −0.091, −0.034]; $p_{FWE\text{-}corrected} = 1.0e\text{-}3$) and 'node 23' (−0.080 [95% CI −0.120, −0.040]; $p_{FWE\text{-}corrected} = 2.0e\text{-}3$), corresponding mainly to the frontal pole and the anterior cingulate gyrus (Figure 2). Longer stage N2 sleep was related to lower global mean signal amplitude, driven mostly by the ventral attention and temporal networks (Table S2), yet no node-level associations survived correction for multiple testing.

In the total sample of $n = 621$, additional adjustment for depressive symptoms and use of antidepressant and hypnotic medication during PSG did not change estimates on the global level (−0.025 [95% CI 0.044, −0.006]; $p = 5.0e\text{-}3$) or network level (ventral attention network: −0.051 [95% CI −0.078, −0.025]; $p_{FWE\text{-}corrected} = 1.2e\text{-}3$; other networks: all $p_{FWE\text{-}corrected} > 8.6e\text{-}3$). Additionally adjusting analyses for AHI did not influence global and network-level associations (Table S3), and the association within 'node 32' remained highly similar (−0.051 [95% CI −0.075, −0.027]; $p_{FWE\text{-}corrected} = 1.2e\text{-}3$; Figure 3).

3.4 | Post-hoc explorative analyses for total sleep time

We explored the contribution of individual sleep stages to the association of total sleep time with mean signal amplitude found in four networks, at both the network and node level. As most of total sleep time was spent in stages REM and N2, these stages contributed most to the association (Figure 3), yet no association survived multiple testing correction.

Analysing categorized total sleep time did not suggest non-linearity in the relation with signal amplitude at a global or network level (Table S4), which was supported by testing quadratic terms of total sleep time (global: $p = .27$; networks: all $p_{FWE\text{-}corrected} > .025$).

TABLE 3 Associations of total sleep time and mean signal amplitude in networks

Total sleep time	Beta (95% CI)	*p*-value	$p_{FWE\text{-}corrected}$
Networks			
1: Default mode – anterior	**−0.046 (−0.083; −0.010)**	**5.8e−3**	.04
2: Default mode – posterior	−0.017 (−0.039; 0.006)	.08	.30
3: Frontoparietal	−0.013 (−0.040; 0.013)	.16	.49
4: Dorsal attention	−0.014 (−0.041; 0.013)	.15	.48
5: Ventral attention	**−0.051 (−0.077; −0.024)**	**4.0e−4**	**1.2e−3**
6: Sensorimotor	**−0.030 (−0.049; −0.010)**	**1.6e−3**	**8.8e−3**
7: Visual	−0.013 (−0.033; 0.008)	.12	.39
8: Subcortical	**−0.021 (−0.036; −0.005)**	**4.2e−3**	**2.5e−2**
9: Temporal	**−0.032 (−0.053; −0.011)**	**1.2e−3**	**8.4e−3**

Note: Values represent difference (95% CI) in mean signal amplitude on a network level, per standard deviation increase in total sleep time. Estimates are obtained using linear regression models and permutation tests, adjusted for age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume.

Bold indicates statistical significance at $p < .025$.

Actigraphy-estimated longer total sleep time was also associated with lower mean signal amplitude at a global level, driven by similar networks to when derived from PSG (Table S5).

Self-reported sleep duration was not associated with mean signal amplitude on a global level (−0.011 [95% CI −0.028, 0.004]; $p = .07$), nor on a network level (all $p_{FWE\text{-}corrected} > .025$).

4 | DISCUSSION

In this population-based study, we found that PSG-determined longer total sleep time was associated with a lower mean BOLD-signal amplitude during the daytime, primarily in the ventral attention network. In contrast, no objective or subjective sleep parameter was associated with functional connectivity between or within networks.

No study previously investigated the relation of objectively measured sleep with intrinsic neural activity measured at median 17 days apart, using a population-based design. In a large-scale study using UK biobank data, self-reported total sleep time was negatively correlated with signal amplitude in networks labelled as sensory/motor, not attentional networks (Bijsterbosch et al., 2017). We found no association for self-reported sleep duration assessed with the PSQI, but to the extent that PSG-derived total sleep time measured a similar construct, differences in study-specific parcellation, attributing the same functional node to different networks, may explain regional differences between studies.

Both sleep and rs-fMRI were not meaured within a 24-hr timeframe, which makes the association more robust to biases due to variable recording conditions of PSG and rs-fMRI. The association was more pronounced in persons who underwent measurements within a shorter, 1-month time interval, suggesting that effects were short-lived. Yet, both sleep (De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005; Tafti, 2009) and resting-state measures (Finn et al., 2015; Xu et al., 2016) exhibit 'trait'-like, time-stable properties, supporting that our association may extend beyond a night-to-day effect. Our findings were specific to BOLD-signal amplitude. Momentary increases in the BOLD signal may reflect local, task-triggered neural activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). This amplitude does not refer to momentary increases but to increased *fluctuations over time*. Although its correlates have not been well characterized, several observations suggest it is representative of a sleep-deprived state or lower vigilance (Chee & Zhou, 2019; Wong, Olafsson, Tal, & Liu, 2013; Yeo et al., 2015). After sleep deprivation, increased lapses in maintenance of attention can be observed (Krause et al., 2017) and such lapses may be accompanied by repeated intrusions of sleep (Chee & Zhou, 2019).

Alternatively, the amount of wakefulness could equally well underlie the association of total sleep time and signal amplitude as it was not driven by a specific sleep stage, and was also found when using actigraphy-estimated habitual total sleep time. Extended wakefulness increases synaptic potentiation (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008) and low-frequency EEG power (Tinguely, Finelli, Landolt, Borbely, & Achermann, 2006), indicative of more synchronized activity. This power increase is most pronounced medio-frontally, as was our association. Also, high amplitude activity on EEG observed in deep sleep indicates more synchronized fluctuations in membrane potential (Van Someren, Van Der Werf, Roelfsema, Mansvelder, & da Silva, 2011). Against this background, we speculate that the association with BOLD-signal amplitude may also result from more synchronized, infra-slow neural activity during wakefulness.

Although we could not assess temporality in our cross-sectional study, these potential mechanisms favour a temporal association from sleep, or wakefulness, to brain intrinsic neural activity. Yet, the topographical overlap of our findings to the regions involved in the generation and propagation of sleep itself (Murphy et al., 2009;

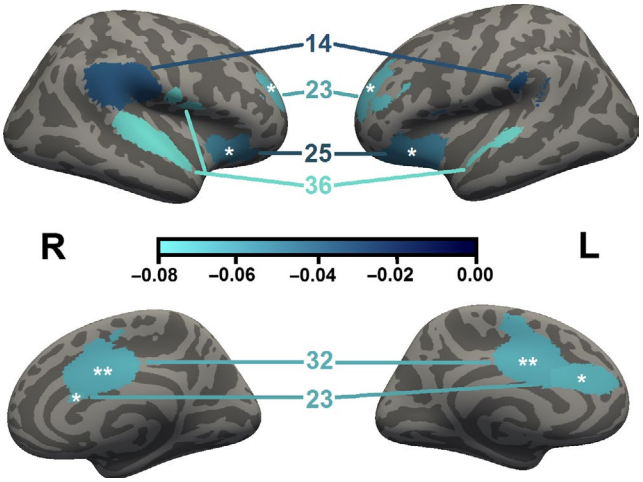

FIGURE 2 Negative associations of total sleep time with signal amplitude are shown for all five nodes of the ventral attention network on inflated right and left hemispheres, from a lateral (top row) and medial (bottom row) perspective. Lighter colours correspond to larger negative effect sizes (beta coefficients). Asterisks denote statistical significance as: $^{*}p_{\text{FWE-corrected}}$ <.025; $^{**}p_{\text{FWE-corrected}}$ <.00277. Please note that significance levels differ from effect sizes. Values represent difference in signal amplitude in that node per standard deviation increase in total sleep time, and are obtained through linear regression and permutation testing. Coefficients are adjusted for age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume. Nodes correspond to the following regions (labelled using the probabilistic Harvard-Oxford cortical atlas found at https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; top three overlapping regions): node 14, parietal operculum (16%), posterior (16%) and anterior (16%) supramarginal cortex; node 36, superior temporal cortex (21%), temporal pole (9%), central opercular cortex (9%); node 25, frontal orbital cortex (28%), insular cortex (17%) and frontal pole (8%); node 23, frontal pole (29%), cingulate cortex - anterior division (9%), and paracingulate cortex (6%); node 32, cingulate cortex – anterior division (24%), juxtapositional lobule (formerly: supplementary motor cortex) (13%) and paracingulate cortex (5%). Threshold of node borders was set at z, 5.0

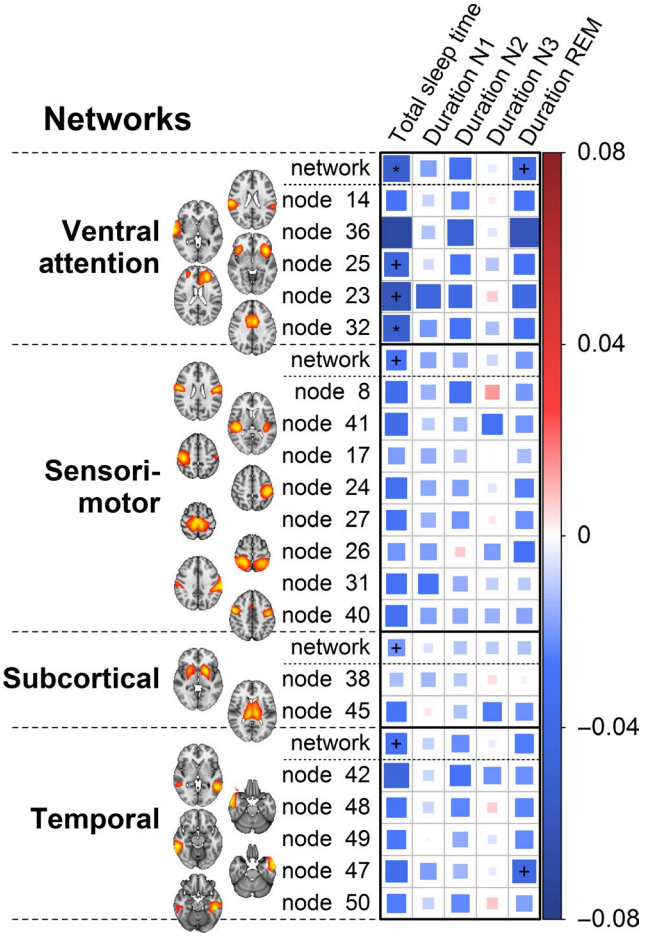

FIGURE 3 Associations of total sleep time and sleep stages with (mean) signal amplitude are shown for the four networks with a statistically significant relation. Corresponding nodes are depicted in the axial plane (right = anatomical left) at the level of highest node intensity. Colours and sizes of blocks correspond to effect sizes (beta coefficients): red indicates positive and blue indicates negative associations. Values are obtained through linear regression and permutation testing. Coefficients represent difference in signal amplitude in that network or node per standard deviation increase in the sleep parameter, adjusted for age, sex, mean framewise head displacement, ghost-to-signal ratio, time interval between sleep and rs-fMRI measurement, habitual alcohol consumption, physical activity, systolic blood pressure, body mass index, history of diabetes mellitus, supratentorial grey matter volume and total intracranial volume. FWE-corrected P-values for networks were corrected over all nine networks, and for nodes were corrected for all 50 nodes. Symbols denote: $+p_{\text{FWE-corrected}}$ <.025; $^{*}p_{\text{FWE-corrected}}$ <.00277. Please note that significance levels differ from effect sizes. Abbreviations: Nx, non-REM sleep stage x; REM, rapid eye movement

Saletin, van der Helm, & Walker, 2013) may also suggest that signal amplitude determines total sleep time in a population-based, 'non-laboratory' setting. The temporality of the association of objectively estimated total sleep time and regional brain activity, or shared causes, should be studied further.

No sleep parameter was associated with network functional connectivity, in line with previous findings for the PSQI score (Stephen et al., 2016). The findings differ from experimental sleep deprivation studies that show a consistent impact on subsequent (e.g., within-network) connectivity of the default mode network (Nilsonne, 2017). Possibly, the effects of sleep deprivation may be too short-lived to be detected here. Furthermore, such effects inherently differ from our sleep measures, which are more indicative of chronic, stable aspects of sleep. Importantly, methodological heterogeneity in, for example, study design, imaging processing or modelling approaches, may also explain finding null results in contrast to other literature, as concluded recently for insomnia neuroimaging findings (Tahmasian et al., 2018). Also, bias due to lack of adequate control for potential confounders or use of seed-based approaches (Tahmasian et al., 2018) may have made previous studies more prone to finding false-positive results.

Several methodological considerations deserve mention. First, we did not monitor sleep during rs-fMRI acquisition and cannot rule out contamination of our measures by sleep (Tagliazucchi & van Someren, 2017). Even light sleep stages (Larson-Prior et al., 2009) involve increases in global signal amplitude, consistent over networks. Individuals with a short total sleep time may have been at increased likelihood of falling asleep in the scanner, which may have biased our estimates. However, several observations suggest that contamination is less likely to explain our findings: (a) we found no non-linearity in our associations for total sleep time, indicating that results were not driven by short sleepers only; (b) total sleep time was not correlated with head motion, which may indicate sleepiness in the scanner (Curtis, Williams, Jones, & Anderson, 2016); (c) even light stages of sleep involve substantially altered network connectivity (Horovitz et al., 2008; Tagliazucchi & van Someren, 2017). This suggests that, if sleeping in the scanner drove our results for signal amplitude, one might expect to also find associations with functional connectivity between or within networks. Yet, we found none, indicating that it is likely that few participants slept during rs-fMRI acquisition. We ensured, by addressing participants, that they were awake at the start of rs-fMRI acquisition. Further monitoring of vigilance with concomitant EEG was not deemed necessary nor feasible due to the population-based nature of our study. Second, we could not assess the influence of sleep on the night preceding rs-fMRI acquisition. Third, performing fMRI at 1.5T instead of higher field strengths, and not controlling for variable conditions during rs-fMRI acquisition, may have reduced our sensitivity to detect associations. Similarly, retrospective assessment of sleep with the PSQI over the previous 4 weeks may have reduced chances to detect cross-sectional associations for PSQI-derived measures. Third, we could not assess how local differences in grey matter influenced our estimates beyond global volume. Study strengths include using PSG to study sleep over a broad and 'real-life' spectrum in a population-based setting, having substantial statistical power to detect small effect sizes and adjusting for multiple potential confounders.

We conclude that, in the general middle-aged and elderly population, total sleep time affects the repertoire of (pre)frontal brain activity, or vice versa, beyond a night-to-day effect. At the same time, our results suggest there is no clear association of objective and subjective measures of sleep with functional connectivity between or within resting-state networks.

CONFLICT OF INTERESTS

No conflicts of interest declared.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work. Data were acquired under supervision of MAI, MWV and HT. Data analysis was performed by TSL, HIZ and RLM. All authors interpreted the data and contributed to drafting the main manuscript text and substantially revising it. Figures and tables were prepared by TSL, HIZ and RLM. All authors approved the final submitted version of this manuscript.

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REFERENCES

Bijsterbosch, J., Harrison, S., Duff, E., Alfaro-Almagro, F., Woolrich, M., & Smith, S. (2017). Investigations into within- and between-subject resting-state amplitude variations. *NeuroImage*, *159*, 57–69. https://doi.org/10.1016/j.neuroimage.2017.07.014

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Chee, M. W. L., & Zhou, J. (2019). Functional connectivity and the sleep-deprived brain. *Progress in Brain Research*, *246*, 159–176. https://doi.org/10.1016/bs.pbr.2019.02.009

Curtis, B. J., Williams, P. G., Jones, C. R., & Anderson, J. S. (2016). Sleep duration and resting fMRI functional connectivity: Examination of short sleepers with and without perceived daytime dysfunction. *Brain and Behavior*, *6*(12), e00576. https://doi.org/10.1002/brb3.576

De Gennaro, L., Ferrara, M., Vecchio, F., Curcio, G., & Bertini, M. (2005). An electroencephalographic fingerprint of human sleep. *NeuroImage*, *26*(1), 114–122. https://doi.org/10.1016/j.neuroimage.2005.01.020

Finn, E. S., Shen, X., Scheinost, D., Rosenberg, M. D., Huang, J., Chun, M. M., … Constable, R. T. (2015). Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nature Neuroscience*, *18*(11), 1664–1671. https://doi.org/10.1038/nn.4135

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*, *18*(6), 425–432. https://doi.org/10.1093/sleep/18.6.425

Horovitz, S. G., Fukunaga, M., de Zwart, J. A., van Gelderen, P., Fulton, S. C., Balkin, T. J., & Duyn, J. H. (2008). Low frequency BOLD fluctuations during resting wakefulness and light sleep: A simultaneous EEG-fMRI study. *Human Brain Mapping*, *29*(6), 671–682. https://doi.org/10.1002/hbm.20428

Iber, C. (2007). *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. Darien, IL: American Academy of Sleep Medicine.

Ikram, M. A., Brusselle, G. G. O., Murad, S. D., van Duijn, C. M., Franco, O. H., Goedegebure, A., … Hofman, A. (2017). The Rotterdam Study: 2018 update on objectives, design and main results. *European Journal of Epidemiology*, *32*(9), 807–850. https://doi.org/10.1007/s10654-017-0321-4

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Khalsa, S., Mayhew, S. D., Przezdzik, I., Wilson, R., Hale, J., Goldstone, A., … Bagshaw, A. P. (2016). Variability in cumulative habitual sleep duration predicts waking functional connectivity. *Sleep*, *39*(1), 87–95. https://doi.org/10.5665/sleep.5324

Khazaie, H., Veronese, M., Noori, K., Emamian, F., Zarei, M., Ashkan, K., … Rosenzweig, I. (2017). Functional reorganization in obstructive sleep apnoea and insomnia: A systematic review of the resting-state fMRI. *Neuroscience and Biobehavioral Reviews*, *77*, 219–231. https://doi.org/10.1016/j.neubiorev.2017.03.013

Killgore, W. D. S., Vanuk, J. R., Knight, S. A., Markowski, S. M., Pisner, D., Shane, B., … Alkozei, A. (2015). Daytime sleepiness is associated with altered resting thalamocortical connectivity. *NeuroReport*, *26*(13), 779–784. https://doi.org/10.1097/WNR.0000000000000418

Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., & Walker, M. P. (2017). The sleep-deprived human brain. *Nature Reviews Neuroscience*, *18*(7), 404–418. https://doi.org/10.1038/nrn.2017.55

Larson-Prior, L. J., Zempel, J. M., Nolan, T. S., Prior, F. W., Snyder, A. Z., & Raichle, M. E. (2009). Cortical network functional connectivity in the descent to sleep. *Proceedings of the National Academy of Sciences*, *106*(11), 4489–4494. https://doi.org/10.1073/pnas.0900924106

Liu, T. T. (2013). Neurovascular factors in resting-state functional MRI. *NeuroImage*, *80*, 339–348. https://doi.org/10.1016/j.neuroimage.2013.04.071

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–157. https://doi.org/10.1038/35084005

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C. M., & Colantonio, A. (2016). The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *25*, 52–73. https://doi.org/10.1016/j.smrv.2015.01.009

Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences*, *106*(5), 1608–1613. https://doi.org/10.1073/pnas.0807933106

Nilsonne, G. (2017). Sleep deprivation and intrinsic brain connectivity - a near-systematic review. Retrieved from https://doi.org/10.6084/m9.figshare.5024507.v1.

Nilsonne, G., Tamm, S., Schwarz, J., Almeida, R., Fischer, H., Kecklund, G., … Åkerstedt, T. (2017). Intrinsic brain connectivity after partial sleep deprivation in young and older adults: Results from the Stockholm Sleepy Brain study. *Scientific Reports*, *7*(1), 9422. https://doi.org/10.1038/s41598-017-09744-7

Saletin, J. M., van der Helm, E., & Walker, M. P. (2013). Structural brain correlates of human sleep oscillations. *NeuroImage*, *83*, 658–668. https://doi.org/10.1016/j.neuroimage.2013.06.021

Shi, L., Chen, S. J., Ma, M. Y., Bao, Y. P., Han, Y., Wang, Y. M., … Lu, L. (2018). Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *40*, 4–16. https://doi.org/10.1016/j.smrv.2017.06.010

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., … Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Smith, S. M., Nichols, T. E., Vidaurre, D., Winkler, A. M., Behrens, T. E. J., Glasser, M. F., … Miller, K. L. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nature Neuroscience*, *18*(11), 1565–1567. https://doi.org/10.1038/nn.4125

Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., … Van Essen, D. C. (2013). Functional connectomics from resting-state fMRI. *Trends in Cognitive Sciences*, *17*(12), 666–682. https://doi.org/10.1016/j.tics.2013.09.016

Stephen, S., Vidaurre, D., Glasser, M., Winkler, A., McCarthy, P., Robinson, E., Van Essen, D. (2016). Second beta-release of the HCP Functional Connectivity MegaTrawl - April 2016 "HCP820-MegaTrawl" release. The WU-Minn Human Connectome Project (Washington University, University of Minnesota). Retrieved 07–10-2018, from Human Connectome Project https://db.humanconnectome.org/megatrawl/HCP820_MegaTrawl_April2016.pdf

Stoffers, D., Altena, E., van der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Astill, R. G., … Van Someren, E. J. (2014). The caudate: A key node in the neuronal network imbalance of insomnia? *Brain*, *137*(Pt 2), 610–620. https://doi.org/10.1093/brain/awt329

Tafti, M. (2009). Genetic aspects of normal and disturbed sleep. *Sleep Medicine*, *10*(Suppl 1), S17–21. https://doi.org/10.1016/j.sleep.2009.07.002

Tagliazucchi, E., & van Someren, E. J. W. (2017). The large-scale functional connectivity correlates of consciousness and arousal during the healthy and pathological human sleep cycle. *NeuroImage*, *60*, 55–72.

Tahmasian, M., Noori, K., Samea, F., Zarei, M., Spiegelhalder, K., Eickhoff, S. B., … Eickhoff, C. R. (2018). A lack of consistent brain alterations in insomnia disorder: An activation likelihood estimation meta-analysis. *Sleep Medicine Reviews*, *42*, 111–118. https://doi.org/10.1016/j.smrv.2018.07.004

Tinguely, G., Finelli, L. A., Landolt, H. P., Borbely, A. A., & Achermann, P. (2006). Functional EEG topography in sleep and waking: State-dependent and state-independent features. *NeuroImage*, *32*(1), 283–292. https://doi.org/10.1016/j.neuroimage.2006.03.017

Van den berg, J. F., Van rooij, F. J., Vos, H., Tulen, J. H., Hofman, A., Miedema, H. M., … Tiemeier, H. (2008). Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. *Journal of Sleep Research*, *17*(3), 295–302. https://doi.org/10.1111/j.1365-2869.2008.00638.x

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., & Ugurbil, K., & Consortium, W. U.-M. H. (2013). The WU-Minn Human Connectome Project: An overview. *NeuroImage*, *80*, 62–79. https://doi.org/10.1016/j.neuroimage.2013.05.041

Van Someren, E. J., Van Der Werf, Y. D., Roelfsema, P. R., Mansvelder, H. D., & da Silva, F. H. (2011). Slow brain oscillations of sleep, resting state, and vigilance. *Progress in Brain Research*, *193*, 3–15. https://doi.org/10.1016/B978-0-444-53839-0.00001-6

Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nature Neuroscience*, *11*(2), 200–208. https://doi.org/10.1038/nn2035

Wong, C. W., Olafsson, V., Tal, O., & Liu, T. T. (2013). The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. *NeuroImage*, *83*, 983–990. https://doi.org/10.1016/j.neuroimage.2013.07.057

Wu, Z., Chen, F., Yu, F., Wang, Y., & Guo, Z. (2017). A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep and Breathing*, *22*(3), 729–742. https://doi.org/10.1007/s11325-017-1604-4

Xu, T., Opitz, A., Craddock, R. C., Wright, M. J., Zuo, X. N., & Milham, M. P. (2016). Assessing variations in areal organization for the intrinsic brain: from fingerprints to reliability. *Cerebral Cortex*, *26*(11), 4192–4211. https://doi.org/10.1093/cercor/bhw241

Yeo, B. T., Tandi, J., & Chee, M. W. (2015). Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation. *NeuroImage*, *111*, 147–158. https://doi.org/10.1016/j.neuroimage.2015.02.018

Zonneveld, H. I., Pruim, R. H. R., Bos, D., Vrooman, H. A., Muetzel, R. L., Hofman, A., … Vernooij, M. W. (2019). Patterns of functional connectivity in an aging population: The Rotterdam Study. *NeuroImage*, *189*, 432–444. https://doi.org/10.1016/j.neuroimage.2019.01.041

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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