

Circadian and sleep-wake modulation of EEG functional connectivity across brain states and Its associations with cognition in humans

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ABSTRACT

Sleep and circadian rhythms both influence human brain function, but their distinct contributions to large-scale network organisation remain unclear. We quantified the effect of brain state (wake, NREM, REM), sleep-wake history, and circadian phase on functional connectivity using over 1200 h of artefact-free EEG recorded during a 10-day forced-desynchrony protocol.

We derived principal components of functional connectivity and found that both sleep-wake history and circadian phase significantly modulated functional connectivity, with sleep-wake history exerting a broader influence. Complementary cosinor analyses further demonstrated circadian rhythmicity in several NREM and REM connectivity measures. Across sleep, global connectivity increased progressively during NREM sleep, particularly in the delta and sigma bands, but declined during REM sleep. During controlled resting wakefulness, increasing time awake was associated with higher global alpha-band connectivity, which was associated with poorer concurrent cognitive performance.

Connectivity during NREM sleep was also associated with subsequent cognitive performance, with lower global theta and, to a lesser extent, higher sigma connectivity linked to better performance. REM connectivity was not associated with these cognitive measures.

Together, these findings reveal opposing NREM and REM trajectories in large-scale EEG functional connectivity and show that these brain-state-specific network dynamics are shaped by both sleep-wake history and circadian phase and are associated with cognitive performance.

1. Introduction

Sleep is widely conceptualised as a recovery process, which returns neural network function degraded by prior wakefulness towards a baseline state (Tononi and Cirelli, 2014). Recovery may be understood mechanistically (e.g. synaptic downscaling) or functionally (e.g. restoration of information transfer and integration capability). Yet how recovery unfolds across sleep and circadian cycles remains poorly defined.

Oscillations in cortical electrical activity reflect the

neurophysiological mechanisms enabling the temporal organisation, transfer, and integration of information essential for waking performance (Buzsaki and Draguhn, 2004; Fries, 2005; Kahana, 2006; Nunez and Srinivasan, 2006).

These rhythms vary across and within brain states (wake, NREM, and REM) and is modulated by sleep-wake history and circadian rhythmicity (Cajochen et al., 2002; Dijk et al., 1997; Lázár et al., 2022). Prominent examples include the decline of slow-wave activity across NREM sleep and the increase in theta activity with elapsed time awake (Dijk and

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Czeisler, 1995; Finelli et al., 2000). These low-frequency EEG dynamics have been widely used as indicators of a recovery process during sleep and of accumulating sleep pressure during wakefulness (Borbely et al., 2016), yet how their dynamics relate to sleep-dependent recovery of waking brain function remains unclear.

Beyond local spectral power, the functional integration of brain regions can be characterised using phase-based connectivity metrics, which index non-instantaneous synchrony between distributed cortical areas (Nunez and Srinivasan, 2006; Stam et al., 2007; Vinck et al., 2011).

Such connectivity measures vary across brain states (Achermann et al., 2016; Bouchard et al., 2020; Imperatori et al., 2021; Massimini et al., 2005; Nielsen et al., 1990; Tagliazucchi et al., 2013) relate to cognitive performance, and are altered in neurodevelopmental and neurodegenerative disorders (Kahana, 2006; Koenig et al., 2005; Smailovic et al., 2022). Reduced responsiveness to external stimuli during sleep is accompanied by reduced functional connectivity (Massimini et al., 2005), underscoring their functional relevance.

However, whether functional connectivity (FC) is systematically modulated by sleep-wake history and circadian phase, and how such changes relate to well-established sleep- and circadian-dependent modulation of brain activity and waking cognitive performance (Muto et al., 2016; Santhi et al., 2016; Wyatt et al., 1999), remains unknown.

A central challenge is that under baseline conditions sleep-wake history and circadian rhythmicity are tightly coupled, preventing determination of their independent contributions. Forced-desynchrony protocols overcome this limitation by dissociating the sleep-wake cycle from circadian phase, indexed by melatonin, cortisol, and core body temperature rhythms (Czeisler et al., 1999; Dijk and Czeisler, 1995).

Using data from 34 healthy young adults collected during a 10-day forced-desynchrony protocol (Fig. 1A), we quantified the independent contributions of sleep-wake history and circadian rhythmicity to FC across brain states and oscillations using an improved index of phase synchronisation, the debiased weighted phase-lag index (Vinck et al., 2011) (Fig. 1B) and its association with cognition. FC was quantified across >1200 h of artefact-free NREM and REM sleep and nearly 90 h of wake EEG, alongside performance on tests of sustained attention and working memory (Fig. 1C and 1D). We identified a global connectivity component reflecting widespread synchronisation and a topographically differentiated component and examined their associations with cognitive performance.

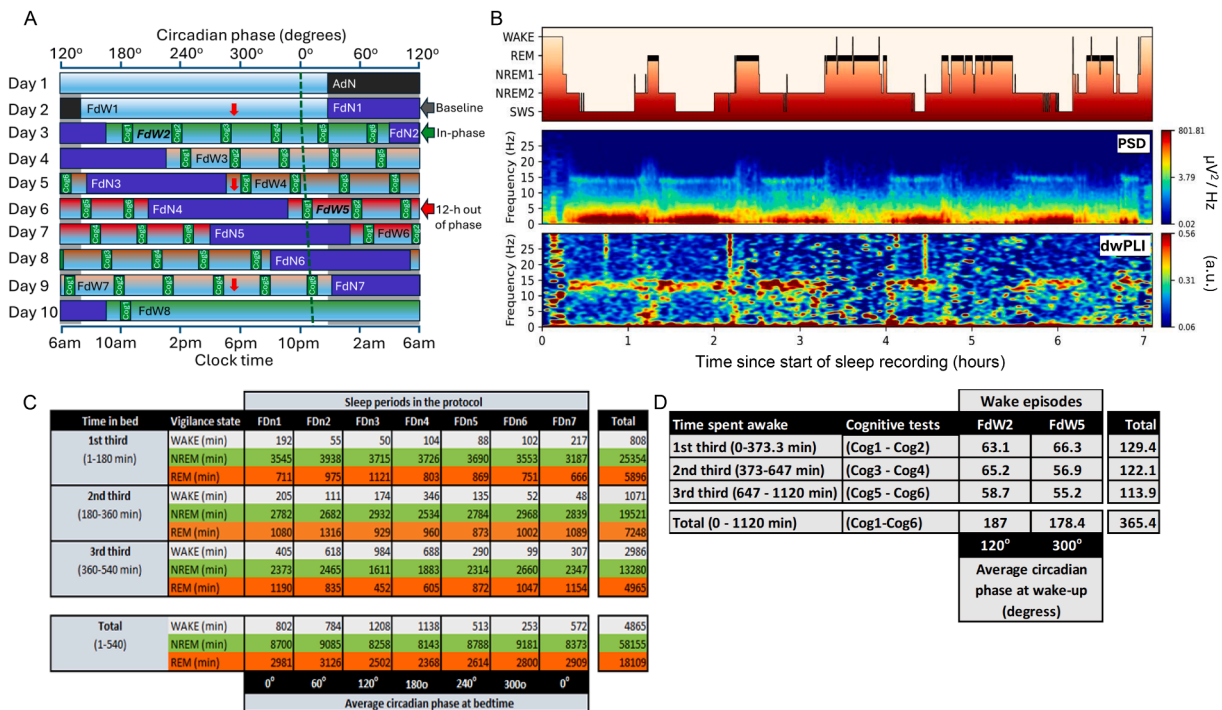


Fig. 1. Research protocol and EEG data analysis. (A) Raster plot of the 28-h forced desynchrony (FD) protocol with a representative example of sleep-wake schedule (habitual bedtime: 00:00). Following an 8-hour adaptation night (ADN) and adaption day (FdW1) participants were scheduled to a 28-h sleep-wake cycle, including 9 h and 20 min of sleep (horizontal dark blue bars) and 18 h and 40 min for wakefulness (horizontal light blue bars). The 24-h variation of plasma melatonin concentration was assessed on three occasions, at baseline (FdW1-FdN1), FdW4-FdN4, and FdW7-FdN7 to estimate the phase and period of the intrinsic circadian clock as indicated by the GREEN line, which represent the estimated onset of melatonin. The red arrow pointing indicates the start of each 24-hour-long melatonin sampling session. Vertical green bars indicate cognitive test sessions included in the current analysis. The gradient colour on the wake period, ranging from green (habitual timing) to red (12 h out of phase), indicates circadian alignment of the wake periods with the FD protocol. The green and red arrows to the right of the figure indicate the two wake periods (FdW2 and FdW5) included in the wake EEG analysis. During these two wake periods, each cognitive test session included two 2-minute Karolinska Drowsiness Tests (KDTs) to measure resting wake EEG at the start and end of the assessments. (B) Time course of sleep stages (top panel), power spectral density (PSD) (middle panel), and debiased weighted phase lag index (dwPLI) (bottom panel) measured during a baseline sleep episode in one participant. Warmer colours represent higher spectral power (logarithmic scale) and functional connectivity (FC) as measured by dwPLI. Temporal resolution is 10 s/pixel, each representing the average of the short-time Fourier transforms of four segments of 4-s long, Hanning tapered windows with 50% overlap. Power spectral density (PSD) values were obtained by also averaging over the 12 channels (FP1, Fp2, F3, F4, C3, C4, T3, T4, P3, P4, O1, and O2) whereas dwPLI values were averaged over all 66 electrode pairs. (C) The amount of artefact-free Wake, NREM, and REM sleep EEG data (in minutes) analysed for each sleep episode throughout the 10-day-long forced desynchrony study. (D) The amount of artefact-free Wake EEG data (in minutes) analysed for the baseline (FdW2) and the 12-h out-of-phase (FdW5) wake episodes.

2. Methods

2.1. Experimental design

The circadian and sleep-wake time-dependent modulation of EEG oscillations was assessed using a 10-day forced desynchrony (FD) protocol, conducted in the Surrey Sleep Research Centre at the University of Surrey. The protocol and associated procedures have been described in detail elsewhere (Lazar et al., 2015, 2013; Santhi et al., 2016). Briefly, following a baseline day (FdW1) and night (FdN1), participants were scheduled to a 28-h sleep-wake cycle comprising 18 h and 40 min of wakefulness in dim light (< 5 lx) and 9 h and 20 min of sleep opportunity in darkness (Fig. 1A). Throughout the 10-day period, participants resided in the clinical research facility and followed a standardised routine including scheduled mealtimes and cognitive testing sessions without access to information about clock time. Participants were continuously monitored during wake periods by a member of staff to ensure wakefulness and followed a strict schedule without physical exercise. During the scheduled wake periods, participants spent most of their time in a lounge where they were allowed to chat with each other or with a member of staff, listen to music, and watch movies and TV series from a pre-selected list.

2.2. The assessment of the circadian phase

Blood samples were collected hourly during the 1st, 4th, and 7th 28-h forced desynchrony sleep-wake cycles (FdW1, FdW4, and FdW7) for determination of melatonin concentrations and assessment of circadian phase (Lazar et al., 2015, 2013; Santhi et al., 2016) (Fig. 1A). Blood melatonin concentration was quantified using radioimmunoassay (Stockgrand Ltd, Guildford, UK). The time corresponding to the 25% of the daily melatonin amplitude range [dim light melatonin onset (DLMO)] was assigned circadian phase zero (Klerman et al., 2002; Lewy et al., 1985). Circadian period was derived from the linear regression fitted to the 3 DLMOs measured on Day 3, Day 6, and Day 9 for each participant, as shown in Fig. 1A ($\tau = 24$ h + slope) (Hasan et al., 2012).

2.3. Assignment of circadian phase and elapsed time in sleep and time in wake period to dependent variables

To estimate the independent contribution of circadian phase and time since the start of the sleep and wake episodes, to the outcome measures, we grouped the continuously recorded EEG data into time bins and assigned to each of those time bins a circadian phase and the sleep-wake dependent index as described earlier (Lazar et al., 2015; Santhi et al., 2016).

PSD and connectivity measures were computed for all consecutive 20-minute intervals from the start to the end of each sleep episode. We then assigned a circadian phase and a time since the start of the sleep episode to each of the 20-minute intervals. For this, we used the 9 h 20 min sleep episodes across FdN1 to FdN7 (Fig. 1A). In the next step, spectral and connectivity data were averaged separately for each brain state (NREM, REM, and wake within sleep episode) across consecutive 20-minute intervals, and then aggregated into six circadian phase bins (60° , ~ 4 h each) and three sleep-dependent time bins (~ 186.7 min each) for each sleep episode.

For the wake-duration-dependent EEG analysis, we used the resting state wake EEG data collected during the Karolinska Drowsiness Tests (KDT) with eyes open and fixating a point for two minutes. These KDT sessions were scheduled immediately before and after each of the six cognitive test sessions during the 2nd (FdW2) and 5th (FdW5) 18 h and 40 min wake periods. FdW2 began at habitual wake time (e.g., approximately 08:00), whereas FdW5 began 12 h later, i.e., 180° out of phase (Fig. 1A). Similar to the sleep-duration-dependent analyses, the wake data were averaged per third of the 18h-40 min wake periods.

2.4. Assessment of cognition

Participants completed approximately 40 minutes of computerised cognitive testing at three-hour intervals throughout the experimental protocol (Fig. 1A). For the present analyses, we examined subjective sleepiness using the Karolinska Sleepiness Scale (KSS; administered at the beginning and/or end of each session), objective vigilance and sustained attention via the 10-minute Psychomotor Vigilance Test (PVT), and working memory and executive function using 1-, 2-, and 3-back tasks. A detailed description of these measures has been published elsewhere (Lo et al., 2012; Santhi et al., 2016). The KSS is a 9-point Likert scale ranging from 1 (extremely alert) to 9 (very sleepy), with higher scores indicating higher levels of subjective sleepiness. From the PVT, we derived four outcome measures: mean reaction time (RT), number of lapses (RT > 500 ms), and the inverse of the slowest and fastest 10 % of RTs. For the n-back tasks, performed in four variants (integrated, pictorial, spatial, and verbal), we extracted two main outcome measures for each variant: RT and A' (A-prime). A' is a nonparametric sensitivity index that quantifies a participant's ability to discriminate targets (hits) from non-targets (false alarms), ranging from 0.5 (chance performance) to 1.0 (perfect discrimination).

2.5. Polysomnographic (PSG) and wake EEG assessment

The sleep EEG data acquisition has been described in detail elsewhere (Lazar et al., 2015). Briefly, EEG was recorded throughout the forced desynchrony protocol during both sleep episodes and repeated cognitive test sessions during the wake episodes. For the current analyses, we analysed the complete EEG data acquired during 231 sleep episodes from 34 participants (18 females, age: 25.1 ± 3.4). All participants presented a healthy sleep profile based on their baseline adaptation night which also served as a clinical sleep screening with a full clinical EEG-PSG setup (12 EEG channels, EOG, EMG, thoracic belt, a nasal airflow sensor, a microphone, and leg electrodes). During the scheduled sleep opportunities of the FD protocol, polysomnographic (PSG) data were recorded using Siesta 802 amplifiers (Compumedics, Abbotsford, Victoria, Australia) including basic polygraphy (EMG, ECG, and EOG) with extended monopolar EEG montage which covered the major brain areas (Fp1, Fp2, F3, F4, C3, C4, T3, T4, P3, P4, O1, and O2) following the international 10–20 system. The ground and common-reference electrodes were placed at FPz and Pz, respectively. Sleep staging was performed in 30 s epochs according to the Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968).

During the scheduled wake periods, resting wake EEG data were collected using the TEMEC Vitaport 3 system (TEMEC Instruments B.V., Kerkrade, the Netherlands) before and after each cognitive test session as part of the Karolinska Drowsiness Test. The EEG montage was similar to that used for the sleep recordings, except that Fp1 and Fp2 were excluded because of blink-related artefacts. For the present analysis, artefact-free wake EEG data were available from 12 of the 34 participants (nine men and three women). These recordings underwent manual artefact rejection because the wake EEG collected during the Karolinska Drowsiness Test was highly contaminated and required extensive pre-processing. Given that the primary focus of the study was the sleep EEG, the wake EEG analyses were treated as exploratory. Importantly, the participants included in the wake EEG analysis did not differ from the remainder of the sample in demographic characteristics or baseline sleep parameters.

Two offline referencing schemes were applied. For power spectral density analyses, which were conducted only on the sleep EEG data, derivations were re-referenced to the contralateral mastoid (A1 or A2), consistent with the established spectral-analysis approach used for these recordings. For the functional-connectivity analyses, both the sleep and wake EEG datasets were re-referenced using the same common-reference scheme across all channels and connectivity metrics.

To improve comparability between the sleep and wake EEG

recordings, which were acquired using different recording systems, both datasets were re-referenced to a common reference for the functional connectivity analyses. Contralateral mastoid referencing was not used for the wake connectivity analyses because it substantially increased artefact rejection, most likely owing to greater mastoid and neck muscle activity during wakefulness. This consideration was particularly important given that the resting wake recordings consisted of relatively short, two-minute sessions, for which the loss of artefact-free data could have had a disproportionate impact on the analyses. The common-reference approach also reduced the potential for hemispheric bias associated with contralateral mastoid referencing, whereby electrodes over the two hemispheres are referenced to different mastoid electrodes. Because the connectivity analyses included both intrahemispheric and interhemispheric channel pairs, differences between the A1 and A2 reference signals could otherwise have influenced the estimated phase relationships and introduced artificial hemispheric asymmetries.

2.6. EEG power spectrum and connectivity analyses

For each 20-minute interval (or 2 min for resting-state wake), spectral and connectivity estimates were derived from contiguous artefact-free EEG segments belonging to the sleep stages of interest (WAKE, NREM1, NREM2, SWS, REM). Within each segment, estimates were computed using 60-second epochs with 75% overlap (45 s). The resulting epoch-wise estimates were then averaged within each interval. Across the 231 sleep episodes spanning the period between lights out and lights on (9 h 20 min; 28 intervals), a total of 76,264 min (1271 h) of artefact-free sleep EEG data were analysed, comprising 58,155 min of NREM sleep and 18,109 min of REM sleep. An additional 4865 min of artefact-free wake EEG occurring within the sleep episodes were available (Fig. 1C and 1D). Separately, for the resting-state wake EEG data collected during the KDTs, two-minute EEG segments were extracted immediately before and after each cognitive test battery, yielding a total of 365 min of artefact-free EEG analysed across FdW2 and FdW5.

We chose spectral methods to enable direct examination of frequency-specific effects, allowing us to assess how the circadian-homeostatic interaction modulates functional connectivity in each canonical EEG band. While non-spectral methods combined with bandpass filtering can also provide frequency-resolved estimates, spectral methods offer native frequency resolution, well-defined phase estimates, and methodological transparency (Widmann et al., 2015).

Values were either analysed on a 0.5 Hz bin basis to investigate spectral profiles between 0.5 to 32 Hz or averaged over commonly used frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (16–25), and gamma (25–32 Hz). All measures were computed across standard EEG frequency bands (delta, theta, alpha, sigma, beta, gamma) and separately for each brain state. Computations were performed in Python using the standard scientific computing ecosystem, including NumPy and SciPy (Oliphant, 2007; Harris et al., 2020; Virtanen et al., 2020). Detailed descriptions of the Power Spectral Density and Local Connectivity measures are provided in the Supplementary Appendix.

2.7. Evaluation and selection of functional EEG connectivity metrics

While we ran the initial analysis characterising the spectral profile of FC across different brain states using five different connectivity measures (Supplementary Fig. S1), we chose to run the in-depth analysis using the debiased weighted phase lag index (dwPLI) (Vinck et al., 2011). These phase-based connectivity measures represent progressively refined approaches to estimating synchronisation while reducing the influence of instantaneous coupling that can arise from volume conduction. Imaginary coherence (ImCoh) retains only the imaginary component of coherency and therefore emphasises interactions with a non-zero phase lag (Nolte et al., 2004). The phase lag index (PLI) similarly focuses on non-zero-lag coupling by quantifying the

asymmetry of the distribution of instantaneous phase differences (Stam et al., 2007). The weighted phase lag index (wPLI) further weights phase leads and lags according to the magnitude of the imaginary component of the cross-spectrum, reducing sensitivity to noise and small perturbations around zero phase lag, while dwPLI additionally corrects for the sample-size bias of wPLI (Vinck et al., 2011). A detailed description of the derivation of these measures from the Fourier-transformed EEG signals is provided in the Supplementary Methods.

The choice of dwPLI as the primary connectivity metric is further supported by its correlation profile in our data. It exhibits a very high Pearson correlation with wPLI (0.95) and strong correlations with PLI (0.81) and ImCoh (0.66), indicating that it captures much of the phase-based connectivity structure shared across these measures. At the same time, its low correlation with phase coherence (0.10) indicates that the connectivity structure captured by dwPLI differs substantially from that obtained with a measure that also includes zero-phase-lag synchronisation. Together with its reduced sensitivity to volume conduction, noise, and sample-size bias (Vinck et al., 2011), these properties motivated our use of dwPLI for the subsequent analyses.

The selection of dwPLI was further supported by superior fit statistics for the mixed-effects model, specifically lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, compared to those obtained using ImCoh.

As an additional sensitivity analysis, we examined the extent to which dwPLI estimates were associated with the spectral power of the underlying EEG signal. Pearson correlations were calculated between dwPLI and log-transformed power spectral density (PSD) separately for each frequency band and brain state. This analysis was performed to assess whether variation in functional connectivity might systematically covary with spectral power and, indirectly, with signal-to-noise characteristics of the underlying oscillatory activity (Supplementary Fig. S2).

2.8. Principal component analysis

To reduce dimensionality, we applied principal component analysis (PCA) to the high-dimensional datasets of functional connectivity (FC) and cognitive measures.

2.8.1. Principal component analysis of functional brain connectivity

Given the large number of connectivity variables across the sleep (66 electrode pairs per brain state and frequency band) and wake (45 electrode pairs per frequency band) episodes, we applied PCA to functional connectivity (FC) estimates derived from dwPLI to reduce dimensionality and examine their underlying structure. PCAs were run separately for each brain state and frequency band. Observations containing missing values were excluded prior to PCA. All columns were z-score standardised to ensure equal contribution of variables. PCA was computed and the first 10 components were retained for inspection.

After fitting each PCA model, we extracted the component loadings and scores and calculated the explained-variance ratio for each component to quantify the proportion of total variance accounted for. Across the EEG connectivity matrices, PC1 accounted for the largest proportion of variance and was marked by a distinct elbow in the scree plot. In several frequency bands, PC2 also accounted for a relatively large share of variance (>10%), whereas subsequent components individually explained substantially less variance.

To further assess whether PC2 represented structure beyond that expected from random covariance, we compared its eigenvalue with the upper bound of the Marchenko-Pastur distribution, which characterises the expected eigenvalue spectrum of random covariance matrices (Marchenko and Pastur, 1967; Veraart et al., 2016). This analysis was performed separately for each NREM and REM frequency-band combination. PC2 exceeded the Marchenko-Pastur upper bound in all 12 combinations. Together with inspection of the scree plots, these findings supported retaining the first two components for the subsequent NREM and REM analyses (Supplementary Table S1).

2.8.2. Principal component analysis of cognition

To examine the association between FC and cognitive performance, PCA was conducted on cognitive data across all test sessions throughout the experimental protocol, in line with the approach used for FC. In total, 21 cognitive outcomes were included, spanning the Karolinska Sleepiness Scale, the Psychomotor Vigilance Test, and multiple N-back tasks (verbal, numerical, pictorial, and integrated at 1-, 2-, and 3-back levels). In line with the FC analysis, component loadings and scores were extracted from the fitted PCA model, and the explained variance ratio for each component was calculated to quantify the proportion of total variance explained.

2.9. Statistical analysis

Primary linear mixed-effects analyses were conducted in SAS 9.4. Principal component analyses and multivariable association analyses were conducted in Python (v3.8), while the mixed-effects cosinor analyses were implemented in Python using *pymr4* interfacing with the R packages *lme4* and *lmerTest*. Figures were generated using GraphPad Prism 9 and Python's Matplotlib package (Hunter, 2007), as appropriate.

2.9.1. Power and connectivity spectrum analysis

In the first analysis, the dependent variables were spectral power and electrode-pair connectivity, measured with five metrics (coherence [COH], imaginary coherence [ImCOH], phase-lag index [PLI], weighted PLI [wPLI], and debiased wPLI [dwPLI]), computed at 0.5 Hz resolution across each brain state (Wake during the entire time in bed period, NREM and REM). NREM included NREM2 and SWS. The PSD and connectivity outcome measures were averaged across all EEG channels and channel pairs, respectively, as topography was not evaluated at this stage. Linear mixed-effects models were used to examine the influence of circadian phase, elapsed time in sleep, and brain state on log-transformed PSD and connectivity measures across the frequency spectrum and all 231 scheduled sleep episodes. Fixed effects included three within-subject factors: circadian phase (six levels, 60° bins), elapsed time in sleep (three ~3.1-hour intervals), and brain state (Wake, NREM, REM), as well as their interactions. In an exploratory analysis, models were repeated with a finer-grained classification of sleep stages (Wake, NREM1, NREM2, SWS, REM). To account for the repeated-measures structure, observations were nested within participant and sleep episode, with a random intercept for participant. Repeated measures across occasions were modelled using a compound symmetry covariance structure. Degrees of freedom were estimated using the Kenward-Roger method to improve the accuracy of standard errors. The analysis focused on estimating and testing the main effects of each factor on connectivity as well as the two-way interactions of factors *brain state* (or *sleep stage*) with *circadian phase* and *elapsed time in sleep*. To control for Type I error, the significance threshold was adjusted to $\alpha = 0.01$ (see Section 2.9.5).

2.9.2. Topographical analysis of EEG connectivity

The topographical analysis comprised two consecutive steps. In the primary analysis, the dependent variables were the principal component (PC) scores derived from a PCA on dwPLI-based electrode-pair connectivity. Connectivity was calculated within six canonical frequency bands (delta, theta, alpha, sigma, beta, and gamma) across two consolidated brain states (NREM and REM) during 231 sleep episodes, and during baseline wakefulness (FdW2) and 12 h out-of-phase wakefulness (FdW5) in a subset of participants. Although the PCA reduced the 66 individual electrode-pair connectivity values to a smaller set of components, the original PC loadings enabled topographical interpretation of each component.

For the sleep episodes, we focused on the first two PCs, two consolidated brain states, and six frequency bands, yielding $2 \times 2 \times 6 = 24$ unique models. Each model examined a single PC, brain state and frequency-band combination. To control for Type I error, the

significance threshold was adjusted to $\alpha = 0.01$ (see section on 2.9.5).

For the wake EEG data, 24 individual KDT recordings were obtained per participant across FdW2 (in-phase wake episode) and FdW5 (12-h out-of-phase wake episode). Within each wake episode, two recordings were obtained for each of the six cognitive test sessions, one immediately before and one immediately after the cognitive test battery. The two KDT recordings associated with each cognitive session were combined for analysis, yielding up to 12 session-level wake EEG observations per participant. Here we again used the first two PCs but focused exclusively on the theta and alpha frequency bands, given their well-established associations with both sleep pressure (Finelli, Baumann et al. 2000) and circadian phase (Cajochen et al., 2002), resulting in $2 \times 2 = 4$ models, each examining a single PC-frequency-band combination. To balance statistical rigour with our small exploratory sample ($N = 12$) due to the intensive manual artefact rejection required, we limited the number of tests and set the significance threshold at $\alpha = 0.05$ (see Section 2.9.5).

In the second step, we conducted a more exploratory topographical analysis by examining dwPLI-measured connectivity for each electrode pair individually instead of PCs. For the sleep data, comprising 66 EEG channel pairs, two brain states (NREM and REM), and six frequency bands, this resulted in $66 \times 2 \times 6 = 792$ unique models. For the wake EEG data, no additional exploratory topographical analyses were conducted due to the pilot nature of the study and to limit the risk of Type I error.

In both the primary and the secondary topographical analyses of FC during the sleep episodes, we applied the same linear mixed-effects modelling approach across brain states and canonical frequency bands. We conducted linear mixed-effects modelling for each PC outcome across all scheduled sleep episodes. The fixed effects included two within-subject factors: circadian phase (six levels, using 60° bins) and elapsed time in sleep (divided into three approximately 3.1-hour intervals). To accommodate the repeated-measures structure of the data, observations were nested within participant and sleep episode. Random intercepts were included to account for inter-individual differences, and a compound symmetry covariance structure was specified to model within-subject correlations across repeated measurement occasions. To improve the accuracy of standard error estimates, we used the Kenward-Roger method for degrees of freedom estimation.

The categorical mixed-effects approach has been widely used in forced-desynchrony studies because it appropriately accommodates repeated observations within participants, unequal numbers of observations across circadian phases, missing observations, and inter-individual variability. In addition, modelling circadian phase as a categorical factor does not require the observed temporal pattern to conform to a predetermined sinusoidal waveform. To provide a complementary assessment of circadian rhythmicity, we also performed mixed-effects cosinor analyses to quantify circadian modulation of functional connectivity and assess the extent to which the observed phase-dependent patterns were consistent with an approximately 24-hour rhythm (see Section 2.9.3).

For the topographical analysis of functional connectivity (FC) during resting wake, we conducted linear mixed-effects modelling for each PC outcome, including two within-subject factors: time elapsed in wake (thirds of the day; ~6-hour intervals) and wake period (FdW2 and FdW5), indexing sleep pressure accumulation and circadian phase, respectively. The interaction between these factors was also included. To accommodate the repeated-measures structure of the data, observations were nested within participant and wake episode. Random intercepts were included to account for inter-individual differences, and a compound symmetry covariance structure was specified to model within-subject correlations across repeated measurement occasions. Degrees of freedom were estimated using the Kenward-Roger method.

2.9.3. Mixed-effects cosinor analysis

Population-level circadian rhythms were also estimated separately

for each principal component (PC1 and PC2), frequency band (delta, theta, alpha, sigma, beta and gamma), and sleep stage (NREM and REM) using linear mixed-effects cosinor models implemented in Python with the `pymr4` package interfacing with the R packages `lme4` and `lmerTest`. Each model included fixed cosine and sine terms describing the circadian rhythm together with random intercepts for subject and sleep nested within subject, and was fitted by restricted maximum likelihood (REML). Statistical significance of circadian rhythmicity was evaluated using a joint two-degree-of-freedom F-test of the cosine and sine coefficients with Satterthwaite denominator degrees of freedom. Circadian mesor, amplitude and acrophase were derived from the fitted coefficients. Confidence intervals for amplitude and acrophase were obtained by Monte Carlo sampling from the estimated covariance matrix of the fixed effects.

2.9.4. Association analysis between connectivity and cognition.

All multivariate analyses were conducted in Python (v3.8) (Rossum, 1995) using standard scientific computing libraries, including `numpy`, `scipy`, `pandas`, `scikit-learn`, `statsmodels`, and `shap` (Harris et al., 2020; McKinney, 2010; Virtanen et al., 2020). Functional connectivity was calculated using the debiased weighted Phase Lag Index (dwPLI), separately for NREM, REM, and resting wakefulness. For the cognition-association analyses, we used the first principal component (PC1), representing global connectivity, for each frequency-band $\times$ brain-state combination. Cognitive performance was likewise reduced through PCA across 21 behavioural outcomes spanning sleepiness ratings, sustained attention, and working memory tasks. The first cognitive component (PC1), interpreted as a general alertness and working memory factor, served as the target variable. For sleep analyses, PC1 scores were averaged across the six cognitive test sessions following each sleep episode.

To examine the relationship between functional connectivity and cognition, a two-step analysis was applied. In the exploratory phase, multivariate association was assessed using Ordinary Least Squares (OLS) regression via the `statsmodels` package, yielding estimated regression coefficients, p-values, and 95% confidence intervals.

In the follow-up phase, candidate predictors identified in the exploratory analysis were tested using univariate Spearman correlations with cognitive PC1 scores, calculated separately for each sleep-wake episode. Spearman correlations were performed in SAS 9.4.

2.9.5. Model outputs, effect sizes, and diagnostics

For each linear mixed-effects model, we extracted key analytical outputs, including estimated least-squares means for each predictor, Type III tests of fixed effects (F- and p-values), and model fit statistics (AIC, BIC). We also recorded residual skewness and whether the final model used a log-transformed or untransformed outcome variable. Omnibus significance tests were used to determine whether elapsed time in sleep, circadian phase, and their interactions were significantly associated with functional connectivity. The relative magnitude of these effects was not inferred from comparisons of p-values or F-statistics. Instead, we calculated Cohen's f^2 effect size (Cohen, 2013):

$$f^2 = u/v * F,$$

where u and v are the numerator and denominator degrees of freedom, respectively, of the F-statistic corresponding to each main or interaction effect in the linear mixed-effects model. This dimensionless effect-size measure incorporates the degrees of freedom associated with each effect and was used to compare the relative magnitude of effects of elapsed time in sleep and circadian phase. Estimated marginal means were used to characterise the direction and pattern of these effects.

During model selection, residual diagnostics and model convergence were assessed, and competing models were compared using AIC and BIC, with lower values indicating better fit.

2.9.6. Correction for multiplicity

We conducted a large number of statistical tests across several multivariate models. Although these tests were not entirely independent, we addressed the risk of Type I error through multiple strategies. First, we set a more stringent significance threshold at $\alpha = 0.01$. Second, in our primary topographical analysis, we further limited the number of comparisons by reducing dimensionality via a PCA and only the PCs derived from the dwPLI connectivity data were tested. Third, we then carried out an exploratory channel-pair analysis to characterise the topographical distribution of the primary effects, and throughout both stages we reported P values alongside standardised effect sizes, anchoring our main conclusions on the largest and most statistically robust effects.

To contextualise our chosen $\alpha = 0.01$ against a conventional multiplicity correction, we also applied the Benjamini-Hochberg procedure (FDR = 5%) across the 4240 P-values from the sleep connectivity analyses, including the complementary mixed-effects cosinor analyses reported in Supplementary Tables S2, S3, S5, S6, and S7. The largest P-value satisfying the Benjamini-Hochberg criterion was 0.0259. Thus, under Benjamini-Hochberg, tests with $P \leq 0.0259$ would be deemed significant. Our choice of $\alpha = 0.01$ therefore represents a more conservative approach than controlling the false discovery rate at 5%.

For the wake-episode data, given the limited statistical power of this exploratory analysis due to the smaller sample size, we aimed to balance Type I and Type II error risks. First, we restricted the number of statistical tests by focusing a priori on the theta and alpha frequency bands, given their established associations with sleep pressure (Finelli, Baumann et al. 2000) and circadian phase (Cajochen et al., 2002), and did not conduct additional exploratory topographical analyses. Second, we set the significance threshold at $\alpha = 0.05$ to maintain sensitivity while limiting the risk of Type II errors.

3. Ethics statement

All aspects of the study were approved by the University of Surrey Ethics Committee on 3 November 2008 (EC/2008/61/FHMS) and were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation-Good Clinical practise guidelines. Written informed consent was obtained from all participants before participation in the study.

4. Results

4.1. Effect of brain states, homeostatic sleep pressure, and circadian phase on functional EEG connectivity spectra

Using linear mixed effects models (see Methods), we quantified the effects of the three consolidated brain states, NREM, REM sleep, and wake, during the sleep episodes as well as the effects of time elapsed in sleep (i.e., dissipation of sleep pressure) and circadian phase on power spectrum density (PSD) and EEG connectivity measures (Fig. 2). NREM included NREM2 and slow wave sleep (SWS) following common practise (Dijk and Czeisler, 1995; Lazar et al., 2015).

Wakefulness occurring within the sleep episodes was retained in this initial spectral comparison to provide a broad state-level reference against the well-characterised EEG spectral differences between wakefulness, NREM and REM sleep. However, because wakefulness within sleep episodes is inherently more heterogeneous in duration, timing and level of alertness across participants, it was not included in the subsequent detailed topographical connectivity analyses.

PSD averaged across EEG channels showed the known characteristics of brain states (Fig. 2A and Supplementary Table S2). Alpha activity was higher in wakefulness than in NREM and REM sleep; delta, theta, and sigma activity in NREM exceeded the corresponding values in REM.

The dwPLI also varied significantly across brain states and frequency (Fig. 2B; Supplementary Table S2). Its spectral profile showed

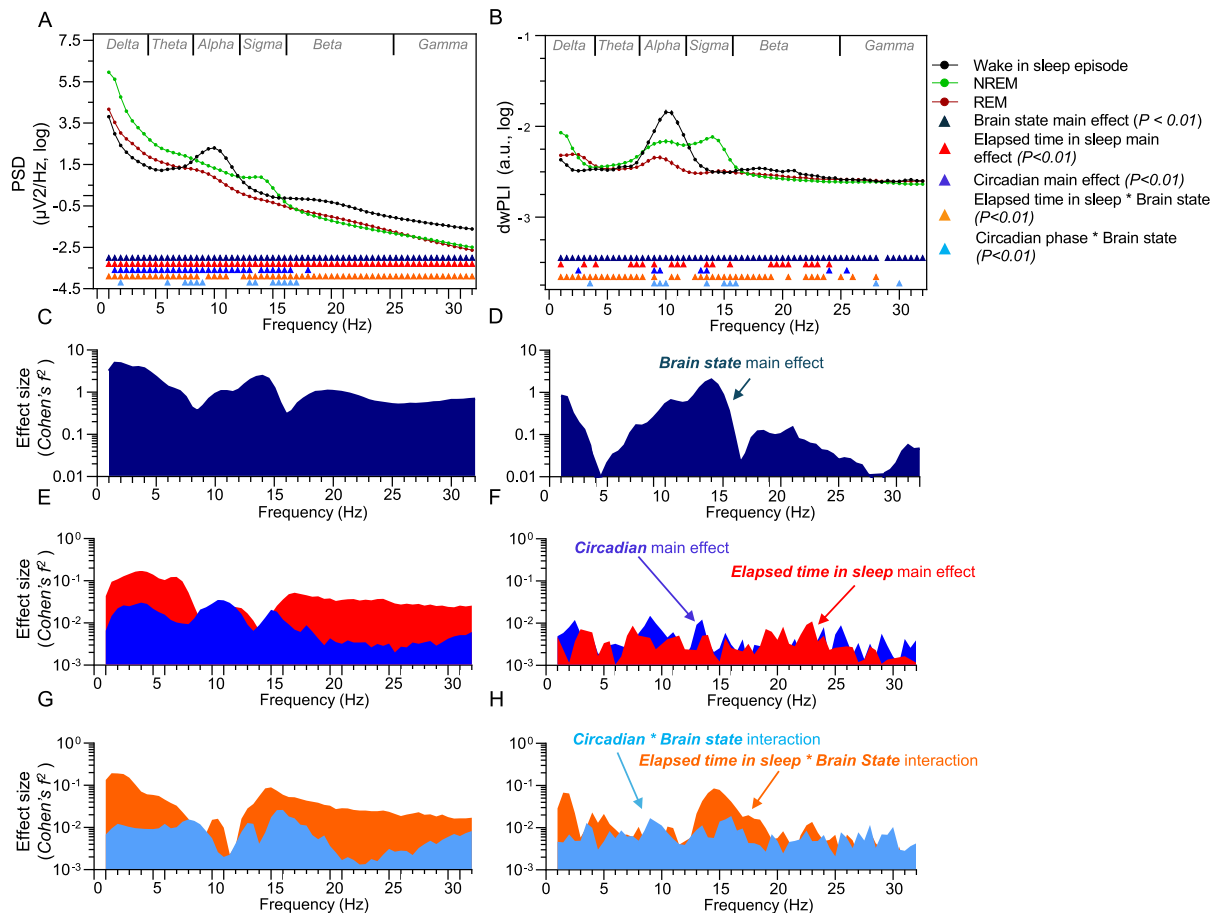


Fig. 2. Power spectral density and functional connectivity spectra across brain states and sleep episodes. The main effect of brain states on (A) power spectrum density (PSD) and (B) debiased weighted Phase Lag Index (dwPLI) across all sleep episodes (231 nights) and averaged across EEG channels and channel pairs, respectively. The upper panels represent least-square means (Lsmeans) and standard error of the mean (SEM). (C and D) Effect size (Cohen's f^2) of main effects of brain state on the PSD and dwPLI. (E and F) Effect size of main effects of Elapsed time in sleep (red) and Circadian phase (blue) on PSD and dwPLI. (G and H) Effect size of interactions between factors Elapsed time in sleep and Circadian phase on PSD and dwPLI. Coloured triangles in (A) and (B) indicate significant ($P < 0.01$) effects. Detailed statistical results are in Supplementary Table S2.

prominent peaks in the alpha and sigma bands and, unlike PSD, dwPLI values did not markedly decrease with increasing frequency. Brain state effects on dwPLI were most dominant in the alpha-sigma range as well as in the delta frequencies (Fig. 2B and 2D). Within the alpha band, dwPLI values were highest during wakefulness, lowest in REM sleep, and intermediate in NREM. In the sigma range (12–16 Hz), dwPLI peaked most strongly during NREM 2 and SWS. Overall, brain states were best distinguished by PSD in the delta and sigma bands (Fig. 2A and 2C) and by dwPLI values in the alpha and sigma bands (Fig. 2B and 2D). For exploratory purposes, we also repeated the same analysis including all NREM substages in the model (NREM1, NREM2, SWS as well as REM and wake during sleep) (Supplementary Fig. S3; Supplementary Table S3).

Mixed model analyses revealed significant ($P < 0.01$) main effects of Time Elapsed in Sleep and Circadian Phase on PSD across all frequencies (Fig. 2E; Supplementary Table S2). For dwPLI these effects were much smaller and restricted to specific frequency bands (Fig. 2F; Supplementary Table S2). The sleep-pressure and circadian effects on dwPLI were substantially smaller than the effects of Brain State (Fig. 2D and 2F). For PSD, the strongest sleep-pressure effects occurred in the delta and theta bands, reflecting the well-known decline of low-frequency power during sleep, while the largest circadian modulations peaked in the alpha (8–12 Hz) and sigma bands (Fig. 2E). Except near 10 Hz and 15 Hz, sleep-pressure effects on PSD exceeded circadian effects. For

dwPLI, sleep-pressure effects on connectivity were largest in the theta, and beta bands, with magnitudes similar to or larger than circadian effects (Fig. 2F; Supplementary Table S2). Circadian effects on dwPLI peaked in the low delta (0.5–3 Hz) and a narrow sigma band (~13 Hz). Overall, standardised effect sizes for dwPLI were generally smaller for circadian phase than for elapsed time in sleep. The interaction between brain state and both time elapsed in sleep and circadian phase showed more similar effect magnitudes across PSD and dwPLI (Fig. 2G and 2H). This indicates that the magnitude of sleep-dependent and circadian effects on FC also varied according to brain state.

All major effects were confirmed using additional phase-based connectivity metrics (imaginary coherence, phase coherence, phase-lag index, and standard weighted phase-lag index), indicating robustness to metric choice (Supplementary Fig. S4; Supplementary Table S2).

To further assess the relationship between spectral power and functional connectivity, we examined correlations between log-transformed PSD and dwPLI across frequency bands and sleep states (Supplementary Fig. S2). Associations were generally weak to moderate and varied substantially by frequency band and brain state rather than showing a consistent positive relationship. During NREM sleep, mean correlations ranged from -0.18 in the delta band to 0.26 in the alpha band, whereas during REM sleep they ranged from 0.11 in delta to 0.35 in gamma. Thus, although spectral power and dwPLI were not entirely independent, their relationship was neither uniform nor consistently

strong, arguing against a simple correspondence between spectral power and the observed connectivity patterns.

Because dwPLI provided a good balance between sensitivity to state-related changes and resistance to volume-conduction artefacts, we retained dwPLI and excluded the other connectivity measures from further analyses (see Methods). We did not pursue further topographical analyses of the elapsed-time-in-sleep and circadian modulation of PSD, as these effects have already been extensively characterised in previous work (e.g., [Dijk et al., 1995, 1997](#)). Instead, the supplementary PSD-dwPLI correlation analysis was used to assess the extent to which connectivity estimates covaried with spectral power.

4.2. Principal components of the topographical distribution of functional connectivity during NREM and REM sleep

In the next step, we investigated the direction and topography of significant main effects of elapsed time in sleep and circadian phase on

functional connectivity (FC) using PCA (see Methods).

We conducted separate PCAs for each consolidated brain state, NREM ([Fig. 3](#)) and REM ([Fig. 5](#)), and for each frequency band, resulting in a total of 12 analyses (see Methods [Sections 2.8 and 2.9.2](#)). Across the six frequency bands and two sleep states, the PCA consistently identified one dominant component (PC1), which explained 29–61% of the variance (mean: 42%) (Supplementary Table S1). The second principal component (PC2) accounted for 4–19% of the variance (mean: 9%). Importantly, PC2 exceeded the upper Marchenko-Pastur bound in all 12 NREM/REM $\times$ frequency-band combinations, with eigenvalues ranging from 2.4 to 10.4 times the corresponding upper bound, indicating that PC2 consistently captured structure beyond that expected from random covariance. The combined variance explained by the first two components was greater in NREM sleep (mean: 54%) than in REM sleep (mean: 47%) (Supplementary Table S1).

The correlation patterns between the principal components (PCs) and dwPLI values across individual electrode pairs indicated that higher

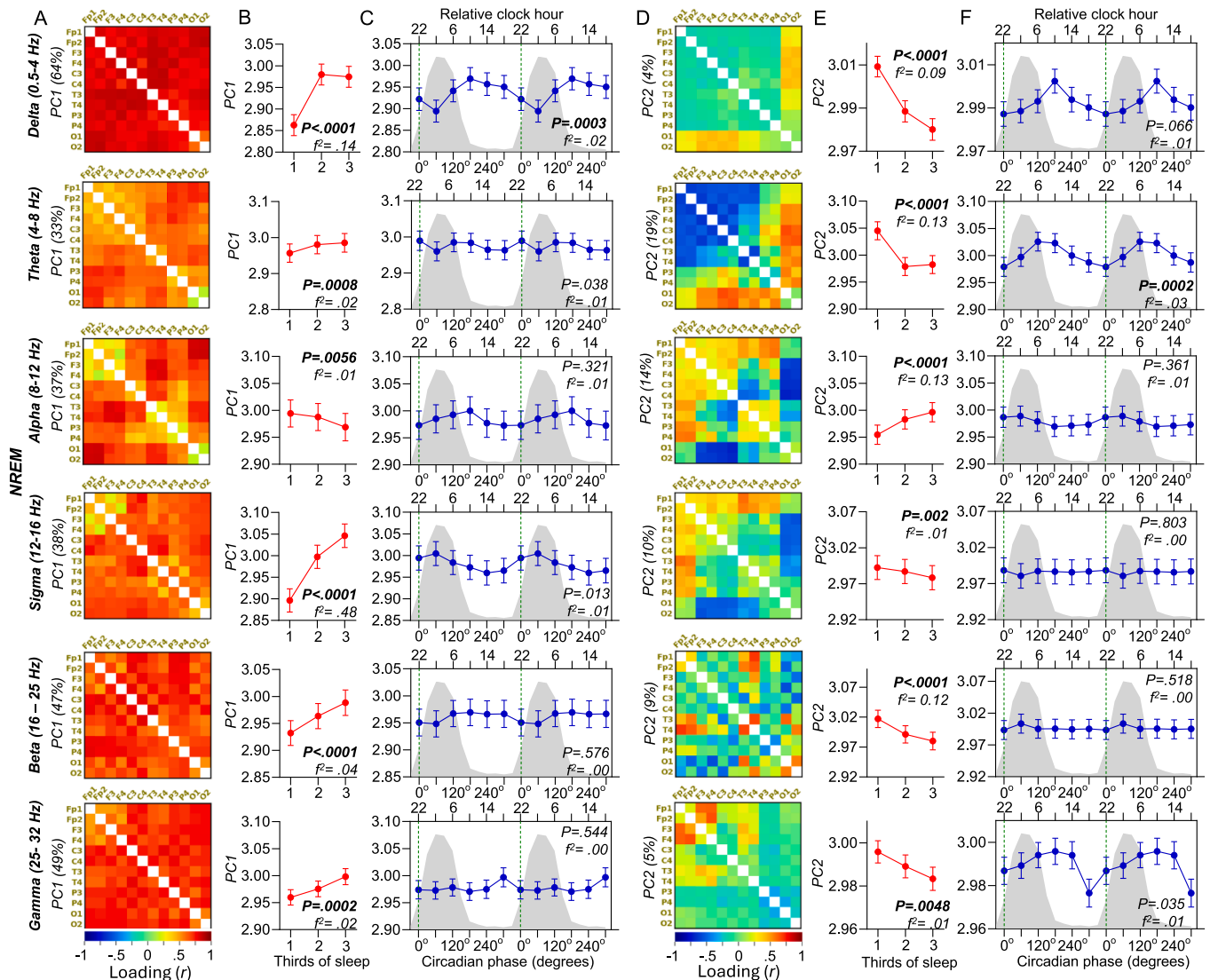


Fig. 3. Principal component analysis of functional connectivity (dwPLI) during NREM sleep: effects of sleep progression and circadian phase. (A and D) Loading values of individual electrode pairs on PC1 and PC2, for delta, theta, alpha, sigma, beta and gamma frequencies. Values between brackets along the vertical axes represent the variance explained by the PC. (B and E) The modulation of PC1 and PC2 by elapsed time in sleep. Least square means (LSMeans) and standard errors of the mean (SEM) are presented for each 186.7-minute interval (i.e., one-third of the sleep episode), averaged across all studied circadian phases. (C and F) the circadian modulation of PC1 and PC2, with LSMeans and SEM shown for each 60° (~4-hour) circadian phase bin, averaged across all sleep intervals. Data are double plotted to enhance the visualisation of circadian rhythms. The green vertical line marks the dim-light melatonin onset (DLMO; 0° circadian phase), and the grey shaded area represents the average melatonin profile. Type III fixed effects are reported, with only statistically significant p-values ($\alpha = 0.01$) indicated. Detailed statistical results are provided in Supplementary Table S5.

loadings on PC1 reflected increased ‘global connectivity,’ characterised by overall elevated dwPLI across all electrode pairs (Figs. 3A and 5A; Supplementary Table S4). This pattern was consistent for PC1 across all frequency bands and brain states. In contrast, PC2 exhibited a more differentiated topography, and the interpretation of high loadings varied by frequency band and brain state (Figs. 3D and 5D; Supplementary Table S4). PC2 was therefore interpreted more cautiously as a secondary component with heterogeneous topographical loadings that varied across frequency bands and brain states. We limited our subsequent analyses to the first two principal components to retain the principal non-random connectivity structure while limiting dimensionality and multiplicity.

4.3. Effects of sleep pressure dissipation on global and topographically distributed functional connectivity

We conducted two mixed model analyses: a primary analysis focusing on the two principal components (PCs) and an exploratory analysis examining connectivity in each electrode pair separately (see Methods).

The number, magnitude, and direction of the significant ($P < 0.01$) effects of elapsed time in sleep and circadian phase varied with brain state, frequency, and PC / topography (Figs. 3 and 5; Supplementary Table S5).

As the sleep episode progressed and sleep pressure decreased, global FC (PC1) during NREM sleep increased across most frequency bands, except for alpha, which showed a small but significant decrease (Fig. 3B; Supplementary Table S5). In contrast, the secondary topographical component (PC2) decreased across all frequency bands except alpha,

where it increased (Fig. 3E). Exploratory electrode-pair analyses were consistent with these findings, revealing widespread increases in coupling across the sleep episode (Fig. 4A and B; Supplementary Table S6). In line with the PC1 results the strongest and most widespread increases in connectivity with decreasing sleep pressure were observed in the delta and particularly the sigma band, with additional increases in the beta band (Fig. 4A). Theta, alpha, and beta bands showed topographically differentiated patterns, with some connexions increasing and others decreasing over time (Fig. 4A). In the theta band, long-range fronto-centro-temporal connexions increased in coupling over the course of the sleep episode, whereas fronto-occipital and centro-occipital connexions decreased. In the alpha band, elapsed-time-in-sleep-dependent increases were mainly interhemispheric between homologous regions, while decreases were concentrated in long-range fronto-occipital and fronto-centro-parietal connexion (Fig. 4A; Supplementary Table S6).

REM sleep (Fig. 5B and Supplementary Table S5), unlike NREM, showed a significant decrease in global FC (PC1) with elapsed time in sleep across most frequency bands, except for alpha, which showed no significant change. The secondary topographical component (PC2) showed no overall effect of sleep pressure, except in the delta and beta bands, where connectivity increased with time in sleep (Fig. 5E). Exploratory electrode-pair analyses corroborated the PC1 results, showing that all significant effects reflected decreases in coupling across the sleep episode (Fig. 6A and B; Supplementary Table S6). The largest number of connexions exhibiting a significant decrease in connectivity was observed in the sigma band.

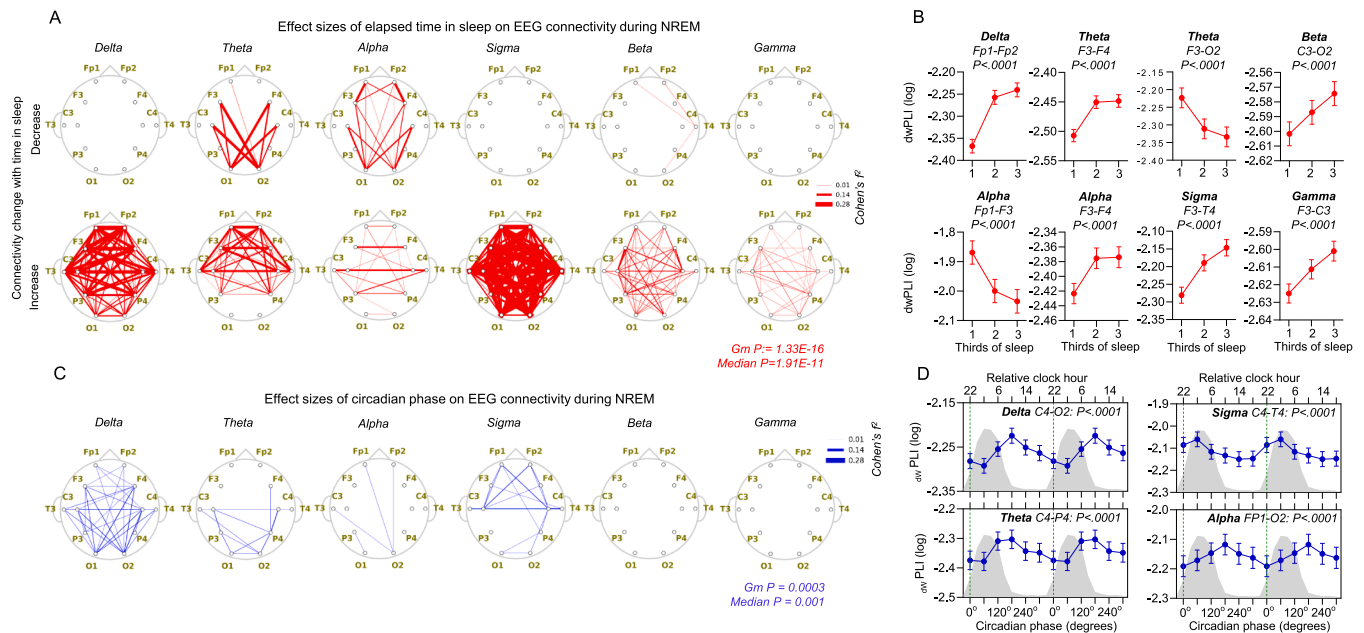


Fig. 4. Topographical patterns of functional connectivity (dwPLI) in NREM sleep as a function of sleep progression and circadian phase. (A) Red lines represent the magnitude of effect sizes for elapsed time in sleep for electrode pairs, where a significant main effect of this predictor was observed ($P < 0.01$). Effect sizes for electrode pairs that showed a time-in-sleep-dependent increase or decrease in functional connectivity are shown separately. The geometric mean and median p-value among all significant p-values are also indicated and highlighted in red. (B) Representative examples of the effects of elapsed time in sleep on dwPLI. Least square mean (LSmeans) and standard error of the mean (SEM) are presented indicating sleep-dependent estimates at each 186.7-minute interval (third of the sleep episode) measured across all studied circadian phases. (C) Blue lines represent the magnitude of effect sizes for elapsed time in sleep for electrode pairs, where a significant main effect of this predictor was observed ($P < 0.01$). The geometric mean and median p-value among all significant p-values are also indicated and highlighted in blue. (D) Representative examples of the effects of circadian phase on dwPLI. LSmeans and SEM indicate circadian phase-dependent estimates at 60 degrees (~4 h) bins measured across all studied sleep intervals and EEG derivations presenting a significant circadian modulation as shown in A. Data are double plotted to enhance the visualisation of circadian rhythms. The green vertical line marks the dim-light melatonin onset (DLMO; 0° circadian phase), and the grey shaded area represents the average melatonin profile. Type III fixed effects are reported, with only statistically significant p-values ($\alpha = 0.01$) indicated. Detailed statistical results are provided in Supplementary Table S6.

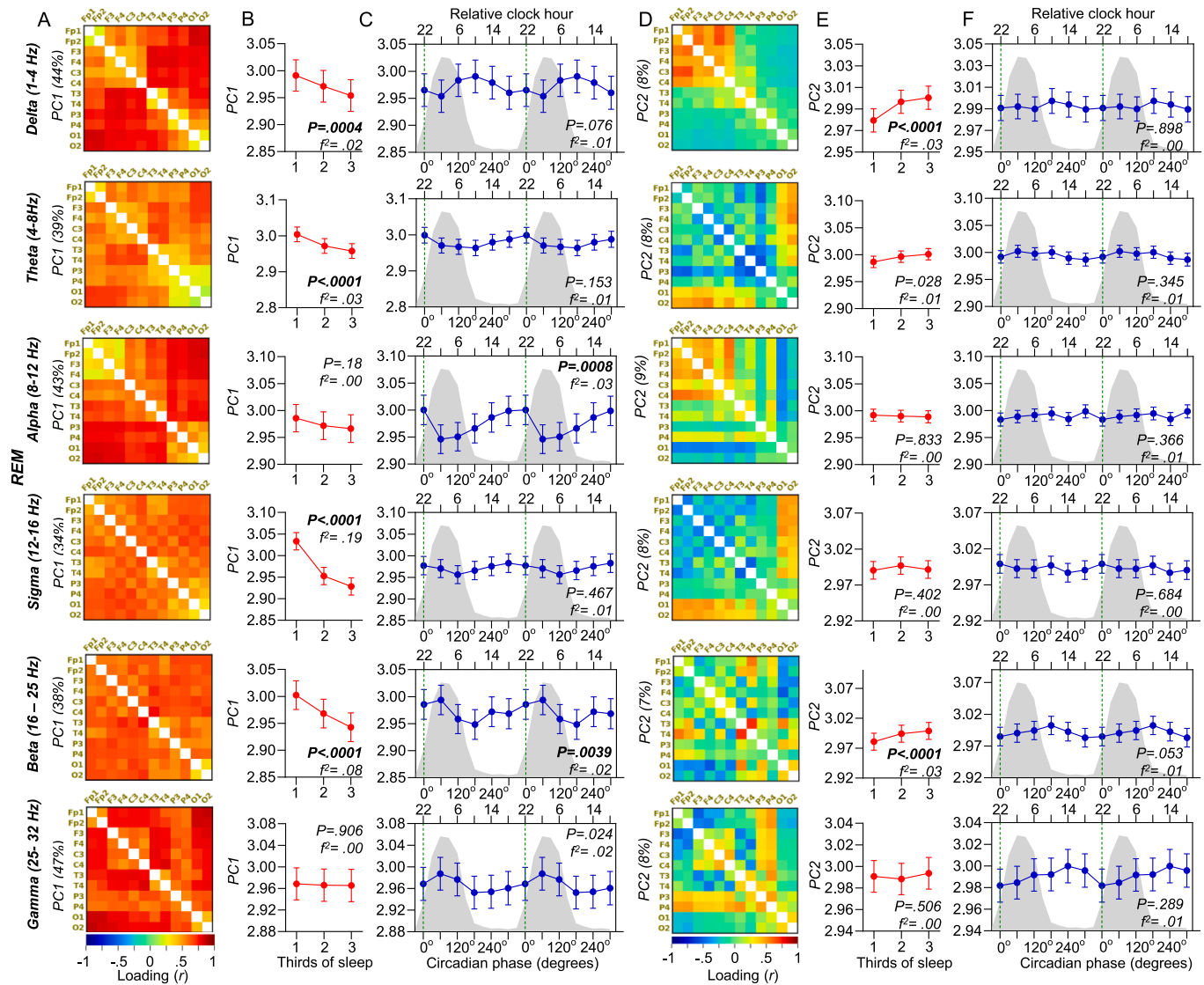


Fig. 5. Principal component analysis of functional connectivity (dwPLI) during REM sleep: effects of sleep progression and circadian phase. (A and D) Loading values of individual electrode pairs on PC1 and PC2, for delta, theta, alpha, sigma, beta and gamma frequencies. Values between brackets along the vertical axes represent the variance explained by the PC. (B and E) The modulation of PC1 and PC2 by elapsed time in sleep. Least square means (LSMeans) and standard errors of the mean (SEM) are presented for each 186.7-minute interval (i.e., one-third of the sleep episode), averaged across all studied circadian phases. (C and F) the circadian modulation of PC1 and PC2, with LSMeans and SEM shown for each 60° (~4-hour) circadian phase bin, averaged across all sleep intervals. Data are double plotted to enhance the visualisation of circadian rhythms. The green vertical line marks the dim-light melatonin onset (DLMO; 0° circadian phase), and the grey shaded area represents the average melatonin profile. Type III fixed effects are reported, with only statistically significant p-values ($\alpha = 0.01$) indicated. Detailed statistical results are provided in Supplementary Table S5.

4.4. Circadian modulation of global and topographically differentiated functional connectivity is brain-state- and frequency-specific

Circadian modulation of FC varied across brain states and frequency bands and was generally smaller in magnitude than elapsed-time-in-sleep effects based on standardised effect-size estimates (Supplementary Table S5).

In NREM sleep, global FC (PC1) in the delta band (Fig. 3C) and topographically distributed FC (PC2) in the theta band (Fig. 3F) showed significant circadian modulation, both peaking during the circadian day, i.e. when plasma melatonin levels are low (Supplementary Table S5). Exploratory electrode-pair analyses were consistent with the PCA findings and further characterised their topographical distribution, revealing significant circadian modulation in some electrode pairs across all frequency bands except beta and gamma (Fig. 4C; Supplementary Table S6). In the theta band, significant electrode pairs were

primarily clustered over centro-posterior cortical regions, whereas in the sigma band, effects were more prominent over fronto-central areas. FC generally peaked during the circadian day, except in the sigma band, where FC was highest during the circadian night, i.e. when plasma melatonin concentrations are high (Fig. 4D).

In REM sleep, only global FC (PC1) in the alpha and beta bands showed significant circadian modulation, peaking at the end of the circadian day, i.e. near the onset of the nocturnal surge in melatonin (Fig. 5C; Supplementary Table S5). Exploratory analysis confirmed strong circadian modulation in the alpha band across multiple electrode pairs, peaking in the second half of the circadian day (Fig. 6C and D; Supplementary Table S6). In contrast, beta and gamma bands exhibited circadian modulation that peaked during the circadian night (Fig. 6D).

The complementary cosinor analysis corroborated the findings of the primary analysis. All 24 mixed-effects cosinor models converged successfully. Significant circadian rhythmicity was detected in several

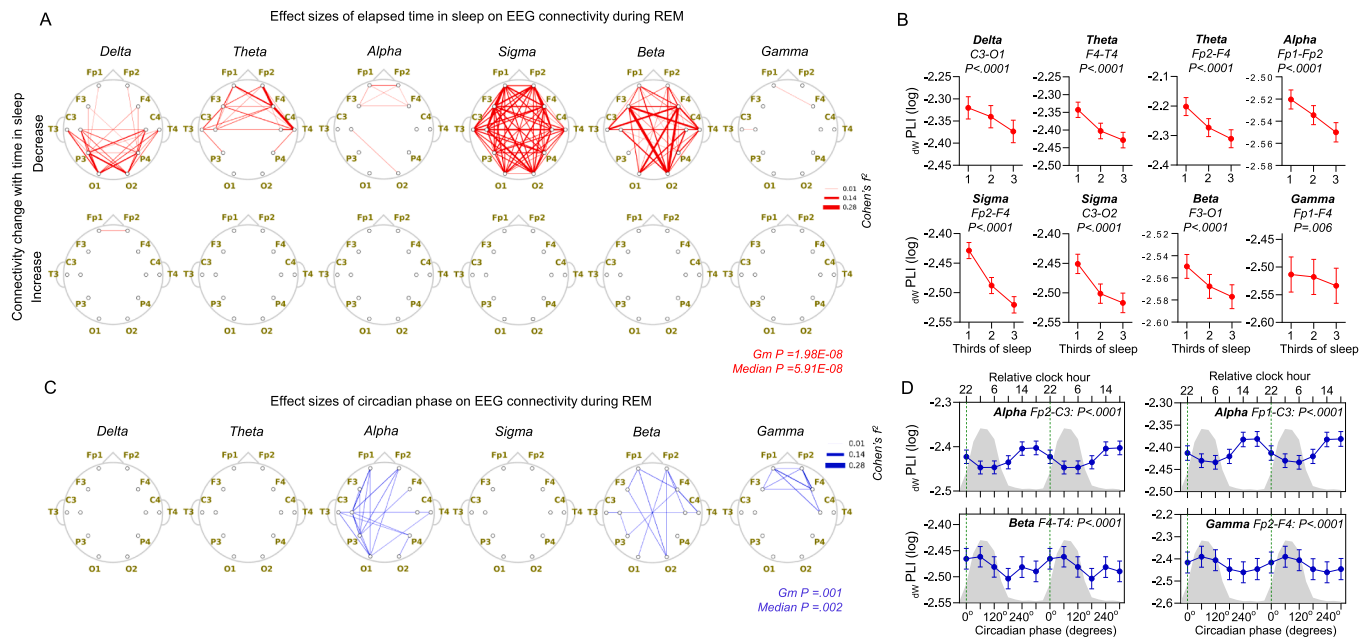


Fig. 6. Topographical patterns of functional connectivity (dwPLI) in REM sleep as a function of sleep progression and circadian phase. (A) Red lines represent the magnitude of effect sizes for electrode pairs, where a significant main effect of this predictor was observed ($P < 0.01$). Effect sizes for electrode pairs that showed a time-in-sleep-dependent increase or decrease in functional connectivity are shown separately. The geometric mean and median p-value among all significant p-values are also indicated and highlighted in red. (B) Representative examples of the effects of elapsed time in sleep on dwPLI. Least square mean (LSmeans) and standard error of the mean (SEM) are presented indicating sleep-dependent estimates at each 186.7-minute interval (third of the sleep episode) measured across all studied circadian phases. (C) Blue lines represent the magnitude of effect sizes for elapsed time in sleep for electrode pairs, where a significant main effect of this predictor was observed ($P < 0.01$). The geometric mean and median p-value among all significant p-values are also indicated and highlighted in blue. (D) Representative examples of the effects of circadian phase on dwPLI. LSmeans and SEM indicate circadian phase-dependent estimates at 60 degrees (~ 4 h) bins measured across all studied sleep intervals and EEG derivations presenting a significant circadian modulation as shown in A. Data are double plotted to enhance the visualisation of circadian rhythms. The green vertical line marks the dim-light melatonin onset (DLMO; 0° circadian phase), and the grey shaded area represents the average melatonin profile. Type III fixed effects are reported, with only statistically significant p-values ($\alpha = 0.01$) indicated. Detailed statistical results are provided in Supplementary Table S6.

principal component $\times$ frequency band $\times$ brain state combinations, with the strongest effect observed for PC1 in NREM delta activity (amplitude = 1.14, $F(2787.7)=36.7$, $p < 0.0001$, Cohen's $f^2=0.093$). Significant rhythms were also observed for PC1 in REM alpha, beta and sigma activity, and for several PC2 measures, particularly NREM delta, theta, alpha, beta and gamma. Most significant effects corresponded to small-to-moderate effect sizes, whereas the NREM delta rhythm of PC1 showed the largest effect. Estimated acrophases differed across frequency bands and sleep stages, indicating that the timing of peak circadian modulation depends on both oscillatory component and vigilance state. The fitted population-level cosinor curves generally followed the empirical phase-bin means, supporting an approximately sinusoidal description of the observed circadian variation. Complete parameter estimates, confidence intervals, effect sizes and model diagnostics are provided in Supplementary Fig. S5 and Supplementary Table S7.

In summary, the circadian phase of peak FC in NREM and REM sleep varied by frequency band and principal component / topography.

4.5. Alpha-band-specific global FC during wakefulness increases with time awake and is modulated by the circadian timing of the wake period

We next investigated whether an increase in sleep pressure associated with time elapsed since waking up from a major sleep episode leads to changes in connectivity in wakefulness and whether these changes are opposite to the changes observed when sleep debt dissipates.

Despite the smaller dataset, PCA applied to the 45 electrode pairs across up to 12 session-level resting-wake EEG observations per participant, each obtained by combining the KDT recordings acquired before and after a cognitive test session, revealed two principal components

(Supplementary Table S1), with interpretations similar to those observed in the sleep analyses. Based on the PC loadings PC1 reflected a global FC component (Supplementary Fig. S6A), while PC2 showed a more heterogeneous topographical loading pattern (Supplementary Fig. S6C; Supplementary Table S4). Mixed-effects modelling (see Methods) revealed a significant main effect of time elapsed in wake on PC1 in alpha and a significant interaction in both alpha and theta (Supplementary Fig. S6B and Supplementary Table S8). In the alpha band, global FC showed a steep increase during the 12-hour out-of-phase wake period and followed a non-monotonic pattern during the baseline day. In the theta band, global FC decreased during the baseline wake period, whereas during the 12-hour out-of-phase condition it did not decline and remained higher overall than during baseline (Supplementary Fig. S6B). No significant effects were observed on PC2 (Supplementary Fig. S6D; Supplementary Table S8).

4.6. Association of Sleep- and wake-dependent functional connectivity with cognition

Finally, we examined whether EEG-based functional connectivity (FC) measured during sleep (NREM, REM) and resting wake was associated with cognitive performance, measured in 1421 cognitive test sessions collected across the forced desynchrony protocol (Fig. 7). To reduce dimensionality, 21 cognitive outcomes were included in the analysis, spanning the Karolinska Sleepiness Scale, the Psychomotor Vigilance Test, and multiple N-back tasks (verbal, numerical, pictorial, and integrated at 1-, 2-, and 3-back levels) (Fig. 7B). Two principal components emerged (PC1 = 29% variance; PC2 = 18%) over an eigenvalue of 1, but only PC1 was retained for subsequent analyses due to its robust loadings and interpretability with higher scores indicating

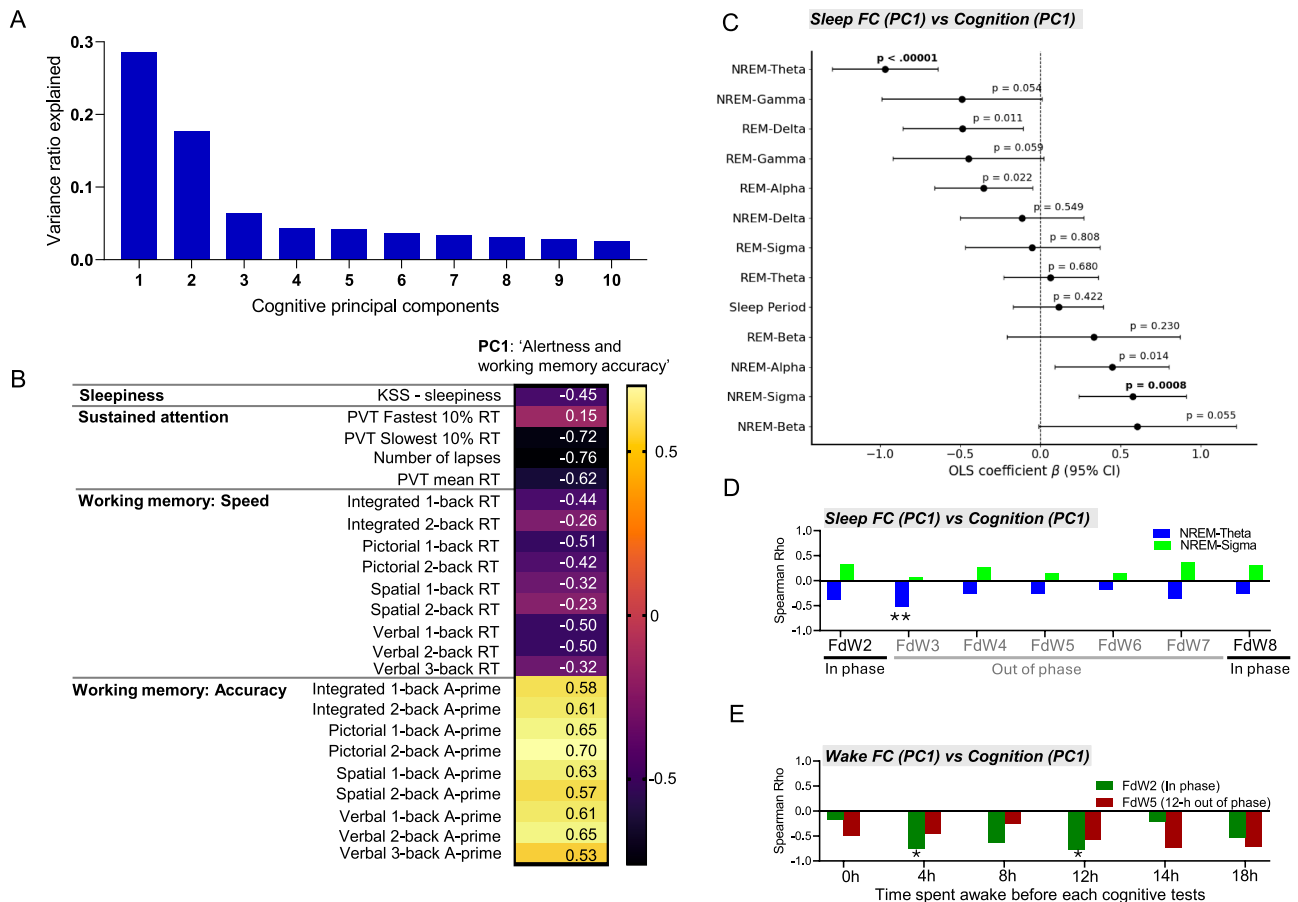


Fig. 7. Principal component analysis of cognitive performance and associations with sleep and wake functional connectivity. Cognitive performance was assessed during scheduled wake periods, with six cognitive test batteries conducted during each wake episode. **(A)** Explained variance ratios for the first 10 principal components derived from 21 cognitive outcome measures spanning subjective sleepiness (Karolinska Sleepiness Scale, KSS), vigilance/sustained attention (Psychomotor Vigilance Test, PVT), and working memory (N-back tasks). **(B)** Loadings of the 21 cognitive outcome measures on cognitive PC1, representing higher alertness and working memory accuracy. Warmer colours indicate stronger positive and colder colours stronger negative loadings. **(C)** Multivariable ordinary least-squares (OLS) regression examining associations between sleep functional connectivity (FC) and subsequent cognitive performance ($N = 34$; 226 sleep-episode observations). Predictors included FC PC1 scores, representing global dwPLI-based connectivity across 66 channel pairs, for each of six frequency bands in NREM and REM sleep, together with sleep period. Points represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and corresponding p-values are shown. **(D)** Follow-up Spearman correlations between cognitive PC1 and global FC PC1 in the NREM theta and sigma bands, examined separately across sleep-wake periods. Negative correlations for NREM theta indicate that higher theta connectivity was associated with poorer subsequent cognitive performance, whereas NREM sigma showed weaker positive associations. **(E)** Follow-up Spearman correlations between global alpha-band FC measured during resting wakefulness (Karolinska Drowsiness Test) and cognitive PC1, examined separately across the six cognitive test sessions during the in-phase wake episode (Fdw2) and the 12-h out-of-phase wake episode (Fdw5) ($N = 12$). Full statistical results are reported in Supplementary Tables S9-S12. Asterisks indicate the statistical significance of the Spearman correlations in panels D and E: * = $p < 0.05$ and ** = $p < 0.01$.

higher alertness and working memory accuracy (Fig. 7A and 7B). Similarly, FC was represented by the PC1 for each brain state and frequency band extracted as described before, only to reduce multiplicity.

To investigate the relationship between NREM- and REM-dependent FC (PC1 - 'global connectivity') and cognitive performance (PC1 - 'alertness and working memory accuracy') on the subsequent day, we first performed exploratory multivariable analyses, followed by targeted follow-up analyses (see Methods). In the exploratory step, we applied multivariable ordinary least squares (OLS) regression to identify connectivity features showing the strongest independent associations with cognitive performance (see Methods).

The exploratory model included FC PC1 scores across six frequency bands in both NREM and REM sleep (12 connectivity predictors), together with sleep period (Fdw1-Fdw7) as an additional predictor ($N = 34$; 226 observations in total) (Fig. 1A). The model explained 29% of the variance in cognitive performance ($R^2 = 0.29$). NREM theta connectivity showed the strongest negative association with cognition ($\beta = -0.97$, $p < 0.00001$), whereas NREM sigma connectivity was positively associated with cognitive performance ($\beta = 0.57$, $p = 0.0008$)

(Fig. 7C; Supplementary Table S9).

In follow-up analyses, we examined Spearman correlations between the two FC measures showing the strongest associations in the exploratory model (NREM theta and NREM sigma) and cognitive PC1, separately for each sleep-wake period. NREM theta connectivity showed a consistent negative association with cognitive PC1. The positive association between NREM sigma connectivity and cognitive performance was weaker and did not reach significance when examined separately across sleep-wake periods. The strength of these associations varied across sleep-wake periods and their circadian timing (Fig. 7D; Supplementary Table S10).

We next examined the relationship between wake-dependent FC PC1 scores measured during resting wakefulness in the Karolinska Drowsiness Test (KDT) across six test sessions and two wake periods, habitual wake (Fdw2) and 12-h out-of-phase wake episodes (Fdw5), and the corresponding cognitive PC1 scores in a smaller pilot sample ($N = 12$; 133 observations in total). The initial exploratory multivariable linear regression included four predictors: wake FC PC1 (global connectivity) scores in the alpha and theta bands, wake episode (Fdw2, in-phase;

FDW5, out-of-phase), and test number (COG1-COG6). The dependent variable was the PCA-derived cognitive PC1 score for each individual test session and wake episode. The model explained 19% of the variance in cognitive performance ($R^2 = 0.19$). Higher wake alpha connectivity showed the strongest independent association with poorer cognitive performance ($\beta = -0.647$, 95% CI $[-0.99, -0.30]$, $p = 0.00031$). Test number was also negatively associated with cognitive performance ($\beta = -0.484$, 95% CI $[-0.82, -0.15]$, $p = 0.0053$), whereas wake episode and wake theta connectivity were not significantly associated with cognitive performance (Supplementary Table S11).

Follow-up Spearman correlation analyses examined the association between wake alpha connectivity and cognitive PC1 separately across test sessions and wake episodes. These analyses showed a negative association between global alpha-band FC and cognitive performance, with the strength of the association varying across test sessions and between the two wake episodes (Fig. 7E; Supplementary Table S12).

In summary, higher NREM theta connectivity and higher wake alpha connectivity showed the most consistent associations with poorer cognitive performance, while higher NREM sigma connectivity showed a weaker positive association with performance.

5. Discussion

By dissociating sleep-wake history from circadian phase, we show that large-scale functional connectivity is modulated by both processes, with standardised effects of sleep-wake history generally larger and more widespread than those associated with circadian phase. NREM and REM sleep showed opposing sleep-dependent connectivity trajectories, and selected connectivity measures during sleep and controlled wakefulness were associated with subsequent or concurrent cognitive performance.

5.1. Functional EEG connectivity across brain states

Although previous studies have reported sleep stage-dependent differences in EEG functional connectivity, this is the first study to assess brain-state effects while simultaneously controlling for elapsed time in sleep and circadian phase. As a result, the state-specific differences observed here may not align precisely with earlier reports but provide a characterisation of functional connectivity across wake, NREM, and REM sleep while accounting for elapsed time in sleep and circadian phase.

Wake EEG was characterised by a dominant peak in alpha-band connectivity, which was reduced in NREM sleep and lowest in REM sleep. However, wakefulness did not consistently show higher connectivity across all frequency bands. Sigma-band connectivity, reflecting sleep spindle activity, was highest during NREM sleep, whereas across alpha and sigma bands functional connectivity in REM sleep was lower than in slow-wave sleep, with no frequency band showing higher connectivity in REM than in all other states. These patterns were consistent across connectivity measures and support earlier findings indicating that reduced large-scale functional connectivity, particularly in the alpha band, distinguishes wakefulness from REM sleep and may reflect functional disconnection from the external environment (Massimini et al., 2005).

Together, these findings challenge the characterisation of REM sleep as a paradoxical wake-like state and instead suggest that REM showed the least wake-like connectivity profile among the states examined.

5.2. Changes in functional EEG connectivity with time elapsed in sleep

The sleep-dependent decline in low-frequency power, particularly slow-wave activity (0.75–4.5 Hz) during NREM sleep, has long been used as a canonical EEG marker of sleep homeostasis and recovery (Finelli et al., 2000). These indices have been linked to synaptic strength and synaptic downscaling, forming the basis of the synaptic homeostasis

hypothesis (Tononi and Cirelli, 2014). Our data extend this framework by demonstrating that dissipation of sleep pressure also has pronounced effects on functional connectivity during NREM sleep across a wide frequency range.

Given that both spectral power and connectivity depend on synaptic processes, we expected parallel dynamics. Contrary to this expectation, functional connectivity in NREM sleep increased with dissipation of sleep pressure in all frequency bands except alpha. This finding is consistent with reports of increasing connectivity across successive sleep cycles in young participants (Bouchard et al., 2020) but contrasts with studies reporting decreases in NREM2 connectivity across the night (Migliorelli et al., 2019) which did not control for circadian phase and focused on a single NREM stage. Our results further show that while NREM sleep is characterised by a global increase in connectivity, particularly in the sigma band, there is substantial topographical heterogeneity, suggesting region-specific network reorganisation. Although PC2 exceeded the upper Marchenko-Pastur bound in all NREM/REM $\times$ frequency-band combinations, its loading pattern varied substantially across frequency bands and brain states; we therefore interpret it as a non-random secondary topographical component rather than as a single stable functional network.

The dissociation between sleep-dependent changes in spectral power and connectivity is consistent with their partly distinct neurophysiological bases. Power spectral density primarily indexes the amplitude of local oscillatory activity, whereas phase-based connectivity measures the consistency of phase relationships across distributed regions (Bastos and Schoffelen, 2015; Nunez and Srinivasan, 2006). Nevertheless, phase-based connectivity estimates may still be influenced by the amplitude and signal-to-noise characteristics of the underlying EEG signal. In our sensitivity analysis, correlations between log-transformed PSD and dwPLI were generally weak to moderate and varied substantially across frequency bands and sleep states, rather than showing a uniform positive relationship. This argues against a simple one-to-one correspondence between spectral power and the observed connectivity patterns, although it does not exclude an influence of signal amplitude or signal-to-noise ratio on individual dwPLI estimates. Finally, the opposing effects of sleep pressure on NREM and REM connectivity underscore the brain-state specificity of sleep-dependent network dynamics, a distinction not evident in spectral power measures, which show similar lower frequency range changes across both states (Dijk and Czeisler, 1995).

5.3. Circadian modulation in connectivity

Functional connectivity showed circadian-phase-dependent modulation that varied according to brain state, frequency band, and topography. Complementary mixed-effects cosinor analyses provided evidence for approximately 24-h rhythmicity in several NREM and REM principal-component $\times$ frequency-band combinations, with the strongest effect observed for global NREM delta connectivity. Significant rhythms were also observed for global connectivity in REM alpha, beta, and sigma bands and for several secondary NREM connectivity components. Estimated acrophases differed across frequency bands and brain states, indicating that the timing of peak circadian connectivity is not uniform across oscillatory components. These findings extend previous observations of circadian modulation of EEG measures, including slow-wave activity, sleep spindle activity, REM alpha activity, and markers of synaptic strength such as slow-wave slope, particularly under forced-desynchrony conditions (Cajochen et al., 2002; Dijk and Czeisler, 1995; Lazar et al., 2015, 2013; Santhi et al., 2016). Importantly, although distinct circadian connectivity effects were evident, their standardised effect sizes were generally smaller and less widespread than those associated with elapsed time in sleep. In the controlled resting-wake recordings, connectivity also differed according to wake episode and time awake, particularly in the alpha and theta bands; however, because only two wake episodes with different circadian

timing were examined, these findings should not be interpreted as a complete characterisation of circadian rhythmicity in waking connectivity.

5.4. Functional connectivity and cognitive performance

Functional connectivity during sleep, particularly NREM sleep, and during controlled wakefulness showed frequency-specific associations with cognitive performance. In the exploratory multivariable sleep analysis, lower global NREM theta connectivity and higher global NREM sigma connectivity were associated with better subsequent cognitive performance after accounting for the other connectivity predictors included in the model. NREM theta showed the strongest and most consistent association in follow-up analyses, whereas the positive association with NREM sigma connectivity was weaker and did not reach significance when examined separately across sleep-wake periods. Increased sigma coupling may reflect more effective thalamocortical interactions, whereas the mechanisms linking reduced NREM theta connectivity to subsequent cognitive performance remain unclear.

Previous work has shown that theta-band functional connectivity increases with age, whereas sigma-band connectivity decreases (Ujma et al., 2019), a pattern consistent with age-related cognitive decline. Related findings in clinical populations, including obstructive sleep apnea, further suggest that elevated theta activity during NREM sleep is associated with poorer cognitive performance (Qin et al., 2023). Together, these observations are consistent with the possibility that associations between sleep physiology and subsequent cognition involve frequency-specific patterns of oscillatory coupling, with distinct roles for sigma- and theta-band synchrony.

During controlled wakefulness, higher global alpha connectivity was associated with poorer concurrent cognitive performance, consistent with reports linking excessive alpha synchrony to reduced neural efficiency and cognitive flexibility (Babiloni et al., 2016; Klimesch, 2012). The reduction of global alpha connectivity across sleep, followed by its rebound with extended wakefulness, may therefore reflect sleep-dependent restoration and wake-related deterioration of network efficiency. Alternatively, these associations may partly reflect stable, trait-like relationships between large-scale functional organisation and cognition (Seitzman et al., 2019; Touroutoglou et al., 2015).

5.5. Speculative interpretation of the results - connectivity and criticality of brain states

Previous work suggests that optimal functional connectivity, and thus optimal brain performance, emerges when neural systems operate near a critical state that balances stability and flexibility, enabling efficient information processing (Lee, 2019; Xu et al., 2024).

Deviations from this regime, such as during anaesthesia, sleep deprivation, or disorders of consciousness, are associated with altered large-scale connectivity and impaired cognition. Within this framework, sleep has been proposed to restore network dynamics towards a more optimal operating range (Xu et al., 2024). Our findings are compatible with this framework, although they do not directly test neural criticality. Across brain states, alpha-band connectivity was highest during wakefulness and lower during sleep, while during controlled wakefulness global alpha connectivity increased with extended time awake, particularly during the out-of-phase wake episode. Higher wake alpha connectivity was also associated with poorer concurrent cognitive performance. These observations are consistent with, but do not establish, the possibility that excessive large-scale alpha synchrony accompanies reduced cognitive efficiency.

Although sleep recovery likely involves global synaptic renormalization, as proposed by synaptic homeostasis theory, the brain-state-specific patterns observed here, rising connectivity during NREM and declining connectivity during REM, suggest that restoration of large-scale network interactions is a coordinated, multi-phase process rather

than a uniform downscaling. This interpretation aligns with models proposing complementary roles of NREM and REM sleep in recalibrating neural integration and information-processing capacity (Tucker et al., 2025).

5.6. Limitations and strengths of the current study

The present study is based on a rigorous forced-desynchrony design and a large dataset, but several limitations should be noted. We used sensor-level EEG without high-density recordings or source reconstruction, limiting direct inference about specific functional brain networks. In addition, experimental manipulation was restricted to sleep-wake timing, and neural activity was not perturbed using electrical or magnetic stimulation. Several analytical limitations should also be considered. First, although the supplementary PSD-dwPLI analysis showed only weak-to-moderate and frequency-dependent associations, it cannot exclude an influence of signal amplitude or signal-to-noise ratio on individual phase-connectivity estimates. Second, although PC2 consistently exceeded the upper Marchenko-Pastur bound, we did not assess the stability of its loadings across individual participants; PC2 should therefore be interpreted as a non-random secondary topographical component rather than as a stable functional network. Third, modelling circadian phase categorically avoids imposing a sinusoidal waveform but remains dependent on the choice and number of phase bins. The complementary mixed-effects cosinor analyses provided additional evidence for circadian rhythmicity in several NREM and REM connectivity measures but do not imply that all phase-dependent effects were sinusoidal. Fourth, wakefulness occurring within sleep episodes is inherently heterogeneous and was therefore retained only for the initial state-level spectral comparison and excluded from the detailed topographical analyses. Finally, the cognition analyses were association analyses and do not establish causality or out-of-sample prediction. The controlled-wake cognition analyses were additionally based on a smaller subsample ($N = 12$) and should therefore be regarded as particularly exploratory.

Despite these limitations, our data reveal aspects of sleep-dependent network dynamics that have not previously been demonstrated. Specifically, this study provides a unique characterisation of the separate contributions of sleep-wake history and circadian rhythmicity to functional connectivity across wake, NREM, and REM sleep. In contrast to prior work based on smaller samples, sleep deprivation paradigms, or comparisons between discrete brain states or sleep stages, our repeated-measures design enabled us to examine within-state connectivity dynamics across the sleep episode. This approach is particularly relevant for understanding sleep-dependent recovery of brain function and was implemented in an unbiased manner by assessing connectivity across a broad range of frequency bands.

5.7. Concluding remarks

In summary, large-scale EEG functional connectivity shows opposing sleep-dependent trajectories across NREM and REM sleep and is also modulated by circadian phase. NREM sleep is characterised by progressive increases in global connectivity across most frequency bands, whereas REM sleep shows predominantly declining connectivity, indicating distinct state-dependent network dynamics. Sleep-wake history exerts a broader influence on connectivity than circadian phase, while circadian modulation remains evident in several frequency- and brain-state-specific patterns. Importantly, these connectivity patterns are associated with cognitive performance, as lower theta and, to a lesser extent, higher sigma connectivity during NREM are associated with better subsequent cognitive performance, whereas higher alpha connectivity during controlled wakefulness is associated with poorer concurrent performance. Together, these findings provide a systems-level account of how sleep reorganises large-scale brain networks and link these dynamics to cognitive performance.

These findings further suggest that alignment between sleep-wake

timing and circadian phase may support the maintenance of optimal large-scale brain connectivity. Given existing evidence that circadian misalignment adversely affects cognitive performance (Chellappa et al., 2018; Santhi et al., 2016), our findings raise the possibility that altered large-scale network coupling may represent one of the neural mechanisms through which such misalignment contributes to cognitive impairment. This possibility may be particularly relevant to conditions characterised by disturbed sleep and circadian rhythms.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, AI-based tools were used to assist with language editing and clarity. All content was reviewed and approved by the authors.

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Data availability statement

De-identified participant data supporting the findings of this study are available from the corresponding author upon reasonable request and subject to institutional ethical approval and applicable data protection regulations. Analysis code sufficient to reproduce the reported results is available from the first author upon reasonable request. EEG spectral and functional connectivity analyses pipeline was implemented in Python and relied on the standard scientific computing stack (NumPy, SciPy, Pandas, Matplotlib). Statistical analyses were conducted primarily in SAS 9.4, with additional multivariable association analyses were conducted in Python. Reproduction of the analyses requires the corresponding software environments and package dependencies.

CRediT authorship contribution statement

Alpar S Lazar: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Zsolt I Lazar:** Writing – review & editing, Software, Formal analysis. **Nayantara Santhi:** Writing – review & editing, Investigation. **June C Lo:** Writing – original draft, Investigation. **John A Groeger:** Writing – review & editing, Conceptualization. **Derk-Jan Dijk:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2026.122301](https://doi.org/10.1016/j.neuroimage.2026.122301).

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