Whole brain network analysis of neural synchrony and information flow during transition from wakefulness to light non-rapid eye movement sleep

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ABSTRACT

Sleep is a highly stereotyped and reproducible phenomenon, requiring robust spatial and temporal coordination of neural activity. Understanding how the brain coordinates across local and long-range neural activity upon the transition to sleep is necessary as a foundation for research on the physiological functions subserved by sleep and pathologic phenomena associated with the sleep transition. In this study, we quantified whole brain network changes during the transition from wake to non-rapid eye movement (NREM) sleep using magnetoencephalography imaging in healthy subjects. In addition, we performed computational modeling to infer excitatory and inhibitory properties of local neural activity. Local and long-range neural synchrony in wake and light NREM sleep stages revealed that the transition to sleep is encoded in spatially and temporally specific patterns of regional neural activity. Patterns of information flow demonstrated that the mesial frontal regions receive hierarchically organized inputs from broad cortical regions in NREM as compared to wakefulness. Finally, biophysical neural mass modeling revealed that sleep onset was accompanied by a spatially heterogeneous change in cortical excitation-to-inhibition, highlighting a cortically-based homeostatic process with the transition to sleep. Together, these findings provide clear evidence for the structured corticocortical modulation in sleep-wake behavior and demonstrate the orchestration of local and long-range, frequency-specific cortical interactions that are fundamental to sleep onset.

INTRODUCTION

The transition to sleep is stereotyped and ubiquitous. Classical lesion and stimulation-based studies have identified sleep-wake transitions as modulated by distributed circuits originating in the brainstem and extending to the hypothalamus, thalamus, and basal forebrain[1,2]. Such bottom-up regulation of sleep and wake has led to a model whereby cortical structures are simultaneously activated by subcortical structures during global state transitions. More recent studies, however, have identified the presence of local cortical dynamics during sleep[3–7] and furthermore suggest that the neocortex may even play a top-down role in sleep-wake regulation[8,9]. In this context, structured corticocortical functional interactions during sleep, as yet defined, may have been overlooked and may ultimately support functions during sleep such as emotional regulation[10–12], memory consolidation[13–15], and recovery[16]. An accurate model of local and long-range corticocortical interactions occurring at sleep onset is therefore a necessary foundation for understanding cortically-based physiologic and pathologic phenomena that begin at sleep onset, including mechanisms of consciousness, cognitive functions subserved by sleep, or pathologic activity such as state-dependent epileptic spiking or insomnia.

For many decades, sleep electrophysiology has been characterized by recordings from a limited number of scalp electrodes, as traditionally used in polysomnography. Meanwhile, fMRI/PET[17–19] studies have provided key anatomical insights on whole-brain neural activation patterns of sleep. Such large-scale network analyses primarily using fMRI have revealed widespread increases in corticocortical connectivity and decreases in thalamocortical connectivity during light non-rapid eye movement (NREM)[20–22]; deep NREM has been associated with widespread decreases in functional connectivity (FC) and increased thalamocortical connectivity[20,21]. The diffuse increase in corticocortical FC from wakefulness to light NREM has been hypothesized to lead to reduced information integration, underpinning the loss of consciousness with sleep[23,24]. While fMRI/PET offer

high spatial resolution, these imaging modalities indirectly probe neural activity (e.g., fMRI measures blood flow and PET measures neural metabolic rate) and are limited by low temporal resolution.

Complementing prior fMRI methods, several key MEG/EEG[25–27] studies have elucidated frequency-specific patterns with sleep onset, including the robust increase in low frequency oscillations in midline anterior brain regions, which later propagate posteriorly. The increased corticocortical connectivity with sleep onset has been furthermore observed across multiple frequency bands using band-limited power correlations of MEG/EEG sensor time series[28]. To date, however, MEG/high-density EEG studies have been limited by the lack of a comprehensive assessment of simultaneous local and long-range neuronal synchrony and information flow with transition from wakefulness to sleep. Furthermore, amidst findings of global increases and decreases in FC, salient long-range cortical interactions have not previously been observed, which may reflect prior methodological limitations including: uninterpretable measures of connectivity due to the lack of source reconstruction[28]; temporal blurring due to the lack of simultaneous EEG for sleep-scoring in MEG studies; and correlational connectivity methods that may introduce effects of volume conduction or other sources of spurious connectivity.

In this study, we seek to identify local and long-range cortical structure that underlies global state transitions. We pursue three aims: 1) to determine which cortical areas are preferentially activated by local synchronization during sleep onset using MEG imaging; 2) to determine what cortical regions facilitate long-range synchronization observed upon the transition to sleep; and 3) to infer mechanisms underlying observed network physiology using biophysical models. We hypothesize that there are frequency-specific, spatial patterns of corticocortical synchronization and information flow upon transition to sleep. In addition, we hypothesize that the underlying corticocortical structure of neural synchrony supports a spatially heterogeneous homeostatic process, characterized by locally specific excitatory-inhibitory properties, during light NREM. To test these hypotheses, we leverage the high spatial and temporal sensitivity of MEG imaging to quantify spatial-temporal

patterns of local and long-range neural synchrony across oscillatory frequencies in healthy individuals. We employ simultaneous EEG recordings to enable accurate standardized sleep staging of corresponding MEG data, and examine three complementary metrics (i.e. spectral power, functional connectivity and information flow) using source-reconstructed time courses. Finally, we perform computational modeling of the underlying neurophysiology using a deterministic neural mass model (NMM) to quantify the cortical excitation-to-inhibition balance across sleep-wake states. Our findings reveal the orchestration of large-scale cortical interactions that are intrinsic to sleep onset and homeostasis that provide additional evidence for the role of corticocortical modulation in sleep.

MATERIALS AND METHODS

Study cohort

MEG and simultaneously obtained scalp EEG data were obtained from a set of 19 healthy controls. All participants underwent a complete history, physical examination, and neuropsychological evaluation. Exclusion criteria for this healthy cohort included any neurologic disorders by history or abnormal neurologic findings by exam. In addition, exclusion criteria included use of any chronic or acute neuroactive medications, including neuroleptics, benzodiazepines, SSRI/SNRIs, or sedatives. Inclusion criteria included achieving at least an aggregate of 60 seconds within each sleep-wake state (W, N1 and N2, segmented into 15 second epochs, see below) during the EEG/MEG study. Fourteen patients met inclusion criteria and were included in the study. Demographics of the healthy cohort are provided in Table 1s. In all subjects, the use of these data for research was approved by the University of California Institutional Review Board, and all subjects provided written informed consent prior to data collection.

*Data acquisition and preprocessin*g

EEG/MEG data were obtained for a period of 50-70 minutes of resting state, recorded at a sampling rate of 600 Hz. Before the start of the recording, subjects were instructed to close their eyes and attempt to sleep. Subjects did not engage in any tasks during the recording. Raw individual EEG and MEG traces were chunked into 15 second epochs. Each epoch was visually inspected and rejected if there was presence of movement artifacts. In a subset of subjects with metallic artifacts from non-cranial implants, a digital signal subspace project (DSSP) algorithm was used for denoising[29]. Epochs were scored into the appropriate sleep states based on scalp EEG criteria and using two-person validation according to American Academy of Sleep Medicine (AASM) criteria. The 15 second epochs of MEG data were then concatenated together to achieve at minimum, a 60 second time series representing each behavioral state. A maximum of the first eight artifact-free epochs, e.g. 120 second sensor time, were utilized in this analysis. Prior work demonstrated that 60 seconds of resting wake state is an adequate duration to reliably achieve stationarity for MEG time series[30].

Source reconstruction was performed using adaptive spatial filtering methods[31] at an individual subject level, yielding voxel level source time series. Source reconstructions were co-registered to MNI template, and regional level time courses were extracted with alignment to the Brainnetome atlas[32], parcellated into 218 cortical regions of interests (ROIs). The data analysis pipeline is illustrated in Fig 1s.

Data analysis and neural mass model

Time series data were bandpass filtered into the following frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (12-15 Hz), and beta (15-30 Hz). Local neural synchrony was quantified by the spectral power of the canonical frequency bands within a given ROI. FC metrics were computed using imaginary coherence, an established spectral coherence measure of neural synchrony that is robust to volume conduction effects[33]. To quantify information flow, phase transfer entropy (PTE) was also computed to assess the pair-wise directional interaction between ROI time courses[34], and directional information was computed using directional phase transfer entropy (dPTE). Data analysis was performed using the FieldTrip Matlab Toolbox[35] and custom made MATLAB code (version R2019a).

In addition, we utilized a linear, deterministic neural mass model (NMM)[36] to gain mechanistic insights on the relative balance of excitatory and inhibitory inputs in observed spectra. This NMM captures the local neural activity, as measured by the power spectral density (PSD) across each ROI and sleep-wake state. In this implementation of the NMM, whole-brain dynamics are deterministically modeled in closed form within the Fourier domain, using a canonical rate model that considers local cortical neural activity.[36] For every ROI, based on the Brainnetome parcellation, a local signal is modeled as the summation of excitatory signals $x_e(t)$ and inhibitory signals $x_i(t)$. Excitatory and inhibitory signals are modeled by a decay of the respective signals, feedback inputs from both excitatory and inhibitory signals and noise. The excitatory and inhibitory signals for individual regions are modeled as below, where g_{ee}, g_{ii}, and g_{ei} are neural gains for the excitatory, inhibitory, and

alternating populations, respectively, τ_e and τ_i are characteristic time constants of the excitatory and inhibitory populations, respectively, $p(t)$ is the input Gaussian white noise, and $f_e(t)$ and $f_i(t)$ are Gamma-shaped ensemble average neural impulse response functions.

$$\frac{\mathrm{d}x_e(t)}{\mathrm{d}t} = -\frac{f_e(t)}{\tau_e} \star \left(g_{ee}x_e(t) - g_{ei}f_i(t) \star x_i(t)\right) + p(t) \quad (1)$$

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = -\frac{f_i(t)}{\tau_i} \star \left(g_{ii}x_i(t) + g_{ei}f_e(t) \star x_e(t)\right) + p(t) \quad (2)$$

The parameters, g_{ee}, g_{ii}, τ_e, and τ_i were estimated for each region-of-interest, while g_{ei} was fixed at 1. Optimization of the model was based on mean squared errors (MSE) between the actual PSD curve and modeled PSD curve, for each ROI, patient, and sleep-wake state. The closed-form expression of the modeled PSD is described further in the Supplementary Methods. Parameter optimization was done using the basin hopping global optimization algorithm in Python[37]. An empirical cumulative distribution function was constructed on the basis of MSE across all regions of interest, sleep-wake states, and patients; outliers were determined based on the threshold inclusion of 75% of the cumulative distribution (corresponding to MSE 37.6). Subsequent statistical testing to compare model parameters across state was performed using a repeated mixed models approach on a modular ROI level, accounting for subject, ROI, frequency, and state.

Group statistics

For statistical comparisons across states, the 218 cortical regional parcellation level spatial maps of the Brainnetome atlas were hierarchically configured to 44 modular level parcellation maps, giving rise to 990 functional connections, which includes the averaged measure (e.g. imaginary coherence) within each module. Linear mixed effects models with repeated measures were performed to identify statistically significant differences across two states for modules and modular connections, with statistics corrected for multiple comparisons (FDR level 0.05). Hierarchical clustering was performed to order brain regions that were most similar based on region-region FC based on linkage-complete metrics. Seed-based studies were additionally conducted to determine FC across select regions,

including the default mode network and precuneus/posterior cingulate, as determined by atlas-based network definitions[38], following module-level extraction.

RESULTS

Local neural synchrony across sleep states

Local neural synchrony, as measured by the spectral power, was averaged across all parcellations and revealed an expected alpha peak during wakefulness and a shift toward delta frequencies with transition to N1 and N2 (Fig. 1A). Source reconstructions of the mean relative spectral power demonstrated increased delta power predominantly over the bilateral prefrontal cortices with transition from wake to NREM (Fig. 1B). The anterior-posterior gradient in the alpha frequency band, as well as the central beta power, attenuated with transition from wake to light NREM (Fig. 2s). The spectral reconstructions are consistent with prior findings[39] and demonstrate the accurate designation of sleep-wake states.

Long-range neural synchrony maps across sleep states

Spatial maps of FC across classical frequency bands revealed frequency-specific patterns of long-range neural synchrony in light sleep as compared to wakefulness. Given the prominent shift to delta/theta frequencies with transition from wake to sleep (Fig. 1A), we focused on low frequency long-range neural synchrony patterns during sleep. Findings for other high frequency FC patterns are provided in the Supplementary Materials. Within the delta band, global FC diffusely increased (Fig. 1C) with prominent long-range connections within and across bilateral frontal regions (i.e. SFG, MFG, PrG) and between frontal-parietal regions (i.e. between MFG, SFG and IPL, SPL; Figs. 1D, E). Connectivity involving the mesial mid-posterior regions (i.e. PCL, L PCun, MVOcc, PCC and MCC) were most distinct from those of the temporal structures (i.e. AD, Hipp, PhG, FuG, ITG, and MTG; Fig. 1F) with transition from W to N1.

Mean global FC increased from W to N1 (Fig. 1G; $t=19.4$, $p<0.001$) and W to N2 ($t=15.3$, $p<0.001$), and decreased from N1 to N2 ($t=-4.2$, $p<0.001$) in the delta band. The spatial maps of the long-range and local synchrony were not correlated within each state (Fig. 1I; red, green, and purple lines; R^2 = 0.003-0.058), although there was an overall correlation *across* sleep-wakes states between long-

range and local synchrony (Fig. 1I; black line, R^2 = 0.586). These findings suggest that the spatial map of local synchrony does not reflect the degree of long-range synchrony of individual regions for a given sleep-wake state.

Within the theta frequency band, bilateral frontal and occipital regions (i.e. IFG, MFG, ACC, and MVoCC, LOcC, and Pcun) exhibited increased connectivity, while bilateral temporal regions were found to have reduced intra- and interhemispheric connectivity (i.e. STG, ITG, MTG, Hipp and Amyg) in N1 as compared to W (Figs. 2A-C). Based on the hierarchical clustering of regional FC spatial patterns, temporal structures were most similar to each other when comparing between N1 and W, while parietal-occipital regions were the most distinct (Fig. 2D). Mean global FC again was observed to increase from W to N1 (Fig 2F, t=7.55, p=<0.001) and to decrease from N1 to N2 (t=-9.16, p=<0.001). Mean global FC was not statistically different between W and N2 (t=-1.62, p=0.238). The mean global FC and spectral power were not correlated across states (R^2 = 0.158) nor again within sleep-wake states (R^2 = 0.098-0.204).

Within the alpha frequency band, global synchrony increased over the bilateral frontal and temporal regions with relative sparing of the parietal-occipital region in N1 and N2, as compared to W. The increased synchrony in the alpha frequency band in N1 was spatially reduced with the transition to N2 and only involved the mesial-frontal regions (i.e. bilateral SFG) (Fig. 3s). The beta band demonstrated relatively increased synchrony in interhemispheric connectivity and anterior temporal regions, during N1 and N2 as compared to W (Fig. 3s).

The frequency-specific activation patterns in N1 and N2 were similar; however, N1 overall demonstrated an increase in long-range neural synchrony as compared to N2 (Fig. 4s). This trend in long-range synchrony contrasts with that of local synchrony, in which the averaged local synchrony of N1 lies in magnitude in between W and N2. This discordance between the trends in local and long-range synchrony is best observed in the delta frequency band delta, in which there was a

progressive increase in spectral power with transition from N1 to N2, but the global FC was statistically highest in N1 (Fig. 1F).

Default Mode Network (DMN) and PCC-Precuneus connectivity across sleep states

We additionally assessed specific FC changes both within and across the DMN and PCC/precuneus with transition from wake to sleep. Seeded analysis was performed to assess the relationship between the anterior and posterior regions of the DMN across sleep-wake states (Fig. 3A). Frequency specific coupling was observed with an increase in coupling in the delta band upon transition from W to N1 (Fig 3B; $t=7.762$, $p<0.001$) and a reduction from N1 to N2 ($t=-2.869$, $p=0.012$). Regional coupling within the anterior DMN was overall higher than within the posterior DMN in the delta band (Fig. 3B), consistent with the large-scale unseeded findings. In the alpha band, a trend of reduced anterior-posterior coupling from W to N1 (Fig. 3C; $t=-2.70$, $p=0.0192$) and increased coupling from N1 to N2 ($t=-2.69$, $p=0.0195$) was observed, but not statistically significant following multiple comparison corrections. These findings suggest that there is a spectral shift from alpha to delta frequencies in the coupling between anterior-posterior DMN during the transition from wake to light NREM and that the anterior-posterior DMN coupling has a unique pattern across sleep-wake states as compared to regional-level synchrony.

In addition, seeded analysis revealed distinct patterns of coupling intrinsic to the PCC-precuneus and between the PCC-precuneus and residual cortex (Fig. 4). While the coupling between the PCC-precuneus and the remainder of the brain largely reflected the patterns of global FC in delta and theta bands (Figs. 1H, 2F), the coupling within the PCC-precuneus was distinct. Notably, the intrinsic delta coupling within the PCC-precuneus during N1 was most similar to that in the wake state; in contrast, during N1 and N2, delta coupling was most similar between the PCC-precuneus and all other cortical structures. In addition, a statistically significant peak in the sigma band was identified in the cross-region couplings, but not in the intrinsic coupling within the PCC-precuneus.

Information flow across sleep-wake states

Information flow, as measured by dPTE, provides insight on the regional inputs and outputs that may influence local activity and synchronization. Within the delta band, the highest outflow was identified over bilateral occipital cortex (e.g. bilateral occipital polar cortex, lingual gyrus, inferior occipital gyrus, middle occipital gyrus, and ventromedial parietooccipital sulcus), and this outflow increased in magnitude when transitioning from W to N1 and from N1 to N2 (Fig. 5). Outflow from the bilateral occipital cortices were largely directed to the bilateral frontal regions. Strikingly, with transition to N2, the outflow from the posterior regions gave rise to primary inputs not only to the bilateral frontal lobe, but also to the bilateral temporal lobe, insula, and cingulate (Figs. 5C, F). In turn, indirect outflow regions (i.e. bilateral temporal lobe, insula, and cingulate) then provided inflow into the bilateral frontal region (Fig. 5C), representing a hierarchical organization of information flow that converges on the bilateral frontal regions. In comparison to W, N1 and N2 demonstrated increased information flow across broad cortical regions both directly and indirectly into the bilateral frontal region (Fig 5G, H), suggesting that the prominent anterior delta power seen at sleep onset is enabled through the inputs of broadly distributed and hierarchically organized cortical activity.

In alpha frequency band, there an overall reduction in the occipital-frontal information flow (Fig. 5s) with transition from wake to NREM. In addition, the strong outflow tracks seen from the precuneus and IPL attenuated with during the transition from W to N1 and from N1 to N2 (Fig. 5s). Importantly, these findings suggest that with the transition to sleep, the posterior-anterior information flow does not cease, but rather that there is a spectral shift to lower frequencies.

Neural mass modeling reveals cortical excitation and inhibition balance changes in sleep states

Finally, the balance between cortical excitation and inhibition was examined by modeling estimated regional spectral power using a deterministic NMM that captures local oscillatory dynamics (Fig 6A). The two indices of the NMM that were optimized to fit local electrophysiology included the characteristic time constants (τ_e, τ_i), representing the time-course of the underlying inhibitory and

excitatory drive, and the gain (g_{ee}, g_{ii}), representing the strength of recurrent local circuits. From wake to light NREM, both the g_{ee}/g_{ii} and the $\tau_e/\ \tau_i$ ratio was observed to increase; differences between N1 to N2 were not statistically significant (Fig. 6B). The resultant excitation-to-inhibition model neural ensemble ratio (X_e/X_i) revealed an increase in excitation-to-inhibition balance from wake to light NREM (N1-W, t=10.4, p<0.001; N2-W, t=8.2, p<0.001) and a trend toward decreasing magnitudes from N1 to N2, although non-significant (N1-N2, t=2.3, p = 0.052; Fig 6C). These findings suggest that the transitional period to sleep may comprise of a complex excitation-to-inhibition balance, in which *local* excitability-to-inhibition increases with the transition to NREM.

By modeling local dynamics, X_e/X_i was furthermore demonstrated to be heterogeneous across the cortical surface within sleep-wake states (Fig 6D). The cortical excitation-to-inhibition ratio was highest over the bilateral frontal lobes during N1, while relatively reduced during wakefulness (Fig 6E). Furthermore, the bilateral parietal regions exhibited relatively increased cortical excitation-to-inhibition during wakefulness, as compared to light NREM (Fig. 6E). Comparison of the raw spectra to the model spectra (Fig. 6F) revealed overall similarity in the profile of the spectra and peak frequencies. As homeostatic regulation during sleep has been thought be achieved through tuning of the synaptic strengths of excitatory and inhibitory circuits, our computational modeling using NMM illustrates that the local cortical dynamics identified during sleep onset ultimately yields a spatially heterogenous homeostatic cortical process at the sleep transition.

DISCUSSION

The characterization of whole-brain neural oscillations is essential to advancing our understanding of distributed network interactions underlying the transition to sleep. Descriptions of large-scale brain networks have relied chiefly on fMRI/PET imaging, which lack the temporal resolution and access to electrophysiology, and on EEG, which has with limited spatial coverage and sensor level analysis. By using MEG imaging, a whole-brain, high-density imaging methodology, to simultaneously evaluate spectral power, functional connectivity, and information flow, we identify local and long-range cortical structure that underlie the transition from waking to NREM sleep.

Our findings reveal that the transition to sleep is accompanied by specific cortical patterns of neural synchrony that are coordinated in frequency and spatial extent (e.g. local, long-range, and network based) and that are suggestive of hierarchically structured corticocortical interactions. With the descent to sleep, frequency-dependent long-range patterns of connectivity are distinct from that of local synchrony (Figs. 1I, 2G). Furthermore, the underlying organization of neural oscillations reveals a multilevel hierarchical flow of information (Figs. 5C, F). Finally, by deploying a NMM optimized to the measured local electrophysiology, we demonstrate spatially heterogeneous excitatory-to-inhibitory contributions with the transition to sleep, suggestive of local homeostatic processes.

In fact, studies from the past decade have revealed that sleep onset is not a homogenous process[3,40–43]. Seminal PET studies provided the initial evidence of differential deactivation of cortical association regions with transition from W to NREM, including in the prefrontal cortex, anterior cingulate, precuneus and mesial temporal structures, in addition to the deactivation of subcortical structures[44,45]. Slow wave activity using EEG/MEG has been identified to originate in anterior medial regions[40,46], later involving parietal, temporal and occipital regions in an anterior to posterior direction[40]. The initial sparing of sensory regions, such as the occipital cortex, are thought to explain perceptual experiences that may occur at sleep onset[4]. The onset of slow wave activity coincides with an early rise in delta activity in the frontal regions[25,27,46], as measured by spectral power, and an

increase in theta synchrony in the occipital region[41,46]. Our spectral reconstructions similarly revealed prominent mesial frontal delta power (Fig. 1B), consistent with prior spectral reconstructions[39]. However, across all frequency groups, the correlations between the spatial maps of spectral power and global synchrony were poor (e.g. Figs. 1F, 2F), indicating that local oscillatory activity did not fully reflect the aggregation of long-range interactions.

Large-scale functional connectivity studies using fMRI[20,21,24] and MEG[28] have demonstrated widespread increases in FC from W to N1 and N1 to N2, and a subsequent breakdown in global FC with transition to N3[20,21,47]. The widespread, homogenous synchronization across large spatial distances has been associated with decreased global integration[48], theorized to account for loss of consciousness. The suggestion of a “horizontal” corticocortical synchronization process, complementing the “bottom-up” subcorticocortical arousal system[40], raises the possibility of structured long-range cortical oscillations. In contrast to prior studies, our findings demonstrate that long-range interactions were evident during light NREM with predominant bifrontal and fronto-parietal interactions in the delta band (Figs. 1D, E), and fronto-occipital and fronto-parietal interactions in the theta band (Figs. 2B, C). Importantly, prior work with MEG[28] revealing widespread increases in coherence have been limited by sensor-based FC mappings, which suffers from overlapping lead fields and spurious connectivity and may conceal underlying structure. Furthermore, fMRI connectivity studies are limited by temporal blurring. Our findings ultimately reveal the orchestration of not only local but also intrinsic long-range subnetworks of regions across multiple frequency bands (Figs. 1C-F, 2A-D), complementing the host of other circuit-specific oscillations of NREM[49].

Our findings additionally confirm prior studies[20,21,28,50] reporting that the overall connectivity in N1 is increased as compared to in W and N2 in the delta band. In contrast, spectral power demonstrates a monophasic increase from W to N1 and N1 to N2. These findings suggest that N1 composes a

unique state that is not strictly transitional, which may account for unique behavioral observations of N1, including sleep mentation or lucid dreaming.

Complementing large-scale functional connectivity which quantifies the strength of neural interactions, we also assessed the directionality of interactions, as measured by information flow. Previously, dominant posterior to anterior patterns of information flow of alpha frequencies have been identified during resting state[51]. Our findings confirm the posterior to anterior patterns of information flow during resting state for higher frequencies (Fig. 5s), and furthermore newly demonstrate increasing organization and magnitude of information flow in the delta frequency band with transition from wake to light NREM. The findings of a dominant posterior to anterior pattern of information flow (i.e. from parietal-occipital regions to frontal regions), in addition to information flow from posterior regions to bilateral temporal regions, which secondarily flow to the bilateral frontal lobes (Figs. 5C, F), demonstrate multilayer circuitry of neural information flow or sequence of assemblies[49,51,52].

In contrast to prior EEG-based studies revealing an inversion of directionality from occipital-to-frontal to frontal-to-occipital during sleep onset[26,53,54], our findings suggest a spectral shift in the prominent organizational pattern, while maintaining the posterior-to-anterior information flow. In addition to the increased number of sensors for source reconstruction approaches, MEG provides a reference free methodology for computing information flow, thereby preventing the potential bias associated with referenced based methods such as EEG.

Interestingly, our work does qualitatively suggest a broad hemispheric difference in FC across different frequency bands (Fig 6s). Prior work has demonstrated the presence of frequency-specific interhemispheric information flow with sleep onset[55]. Future larger-sample studies would be of great interest to assess how the laterality of hemispheric FC relates to language lateralization and dominance.

In addition to large-scale, unseeded analyses, we performed seeded analyses on key resting-state targets. The DMN has garnered significant interest over the last two decades due to its robust activation during resting state and deactivation with externally mediated attention and tasks[56,57]. As such, the DMN has been thought to play a role in internally mediated cognitive processing and self-referential behavior[56], reflecting or arguably mediating a critical component of conscious content[58,59]. PET/fMRI studies have identified that the intrinsic coupling of the DMN remains intact with light NREM[17,19] and REM[58], while the anterior and posterior regions of the DMN decouple in deep NREM[18,58,60,61]. To complement these studies, our findings probing the intrinsic coupling between anterior-posterior regions of the DMN reveal frequency specificity with transition to light NREM. In contrast to EEG-based studies that have revealed anterior-posterior decoupling at sleep onset[53,61], we identified that the anterior-posterior connectivity exhibits a spectral shift from higher to lower frequencies with transition to light NREM (Fig 3). As PET/fMRI power modulation has previously been associated with ultraslow amplitude modulation of higher frequency neural oscillations, including beta[62], gamma[63], or multiple frequency bands[22,64,65], shifts to lower frequency bands may not be captured with these imaging modalities. In addition, prior EEG-based studies demonstrating decoupling probed neural activity at the sleep onset transition without sleep staging and utilized referenced-based information flow metrics, which may account for differences in findings[53,61]. Here, via both FC (Fig. 3) and information flow (Fig. 5C), we identify increased activity in the delta frequency band with the transition to sleep. Future work to probe deeper stages of sleep is a great interest.

Within the DMN, the PCC/precuneus has been implicated as a low frequency synchronizer[61] and central hub involved in conscious processing with the external environment[66–68] and conscious self-awareness[68–70]. We demonstrate that the connectivity between the PCC/precuneus and the remainder of the cortex is distinct from the intrinsic coupling within the region. Specifically, within the delta frequency band, the intrinsic coupling within the PCC/precuneus during N1 was most

consistent with that of wakefulness (Fig. 4B), whereas the interactions between the PCC and the residual cortex mimicked the trends seen with global FC. This finding suggests that the intrinsic connectivity within the PCC/precuneus, particularly in the delta frequency band, which has been demonstrated to have increasingly robust organization during sleep, is delayed with an increase in intrinsic delta FC with transition to N2 rather than to N1. This finding may reflect the concept that self-reflective activity reduces gradually, rather than acutely, with progression to deeper stages of sleep[16,18].

Finally, we investigated whether the identified neural oscillatory patterns may be attributed to a mechanistic heterogeneity in the degree of cortical excitability, as reflected in the ratio of modeled excitatory to inhibitory activity. Cortical excitability has been demonstrated to increase with time awake or sleep deprivation[71,72] and decrease during sleep and the circadian cycle[72–74], as measured by neuronal firing rates, synchronization, and propagation of transcranial magnetic stimulation (TMS)[72,75]. In our study, by utilizing a NMM to model the cortical excitation-to-inhibition balance, we demonstrate that the observed physiology manifests a global increase in *local* cortical excitability with the transition from wake to light NREM, consistent with prior methods using TMS[76]. Specifically, prior TMS findings revealed an enhancement of early or local TMS-EEG responses during sleep, followed by an global attenuation reflecting an overall global breakdown in effective cortical connectivity[76]. The amplified early TMS-EEG response, which has also been observed with visual, auditory and sensory stimulation[77], supports the conception of increased *local* excitability during NREM and has been hypothesized to relate to an increased drive of post-synaptic excitatory neurons or a reduction in synaptic depression, synchronization of local cortical populations or activation of thalamocortical circuits[76,78,79].

By employing local NMM modeling and leveraging whole-brain local field potential, cortical spatial maps of excitability can be fully elaborated, in contrast to seeded processes, e.g. TMS impulses[72,75,80,81], magnetic resonance spectroscopy[82], or direct measurements of excitatory and

inhibitory neurotransmitters[83,84]. We thereby further demonstrate for the first time that the degree of excitability across the cortex is non-uniform (Fig. 6D, E). We identify that the primary local excitation occurs in the bilateral frontal lobes during light NREM, which is largely decreased during wakefulness. Meanwhile, the primary local excitation is within the parietal-occipital regions during wakefulness. Our findings reinforce the conception that sleep is composed of spatially heterogeneous network dynamics that furthermore reflect complex homeostatic patterns within the cortex.

This work does have limitations, including the quality of sleep captured and the relatively modest sample size. Due to the noisy environment and time-limitations of a recording session within the MEG scanner, the sleep quality in the healthy participants was at times fragmented. In addition, deep NREM stages were not obtained across all patients and thus not included in the analysis. To address the sleep fragmentation, shortened epochs of 15s were utilized and concatenated together to formulate the most faithful representations of sleep-wake states. Future efforts may benefit from overnight or sleep-deprived recording sessions to obtain longer, continuous periods of sleep-wake states. In addition, this study incorporates a modest sample size of fourteen patients, who are older in age (Table 1s). A future research direction includes the characterization of differences in local and long-range sleep electrophysiology across age. Although MEG imaging offers improved spatial resolution as compared to other EEG modalities, source reconstruction methodologies, including adaptive beamformers[31], are still an active area of research with respect to modeling spontaneous neural activity; thus as compared to other modalities (e.g. fMRI and intracranial EEG), there are trade-offs with respect to high spatial resolution and acquiring electrophysiology or whole-brain coverage. Finally, although the linear NMM can capture the frequency spectra directly through a

closed form solution, the primary limitations of the NMM employed in this study include its inability to capture non-linear complexities of the brain.

In summary, our work identifies cortical oscillations structured across space on multiple scales (i.e. local, long-range, and network) and hierarchically organized across time (e.g. frequency-specific interactions) with the transition to NREM sleep. Multilayer information flow from broad cortical regions are directed to the mesial frontal regions in the delta frequency, contributing to the synchronization of local oscillations. Finally, the captured electrophysiology supports a spatially heterogenous increase of cortical excitability relative to inhibition with transition to sleep. Together, our findings suggest that the transition to sleep is accompanied by coordinated, frequency and spatially (e.g. local, long-range, and network based) specific cortical patterns of activity suggestive of hierarchically structured corticocortical interactions, which complement bottom-up sleep-onset mechanisms modulated at the subcortical and brainstem level. These findings may ultimately explain pathologic phenomena, including why the propensity of seizure activity is spatially heterogenous across the cortex in NREM[85,86], an avenue of future direction.

Acknowledgments

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations: Amyg = amygdala; CG = cingulate gyrus; FC = functional connectivity; FuG = fusiform gyrus; Hipp = hippocampus; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; INS = insula; ITG = inferior temporal gyrus; IQR = interquartile range; LOcC = lateral occipital cortex; MEG = magnetoencephalography; MFG = middle frontal gyrus; MTG = middle temporal gyrus; MVOcC = medioventral occipital cortex; NREM = non-rapid eye movement; N1 = stage 1 sleep (NREM); N2 = stage 2 sleep (NREM); OrG = orbital frontal gyrus; PCL = paracentral lobule; Pcun = precuneus; PhG = parahippocampal gyrus; PoG = postcentral gyrus; PrG = precentral gyrus; pSTS = posterior superior temporal sulcus; ROI = region of interest; SFG = superior frontal gyrus; SPL = superior parietal lobule; STG = superior temporal gyrus; W = wake

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FIGURES

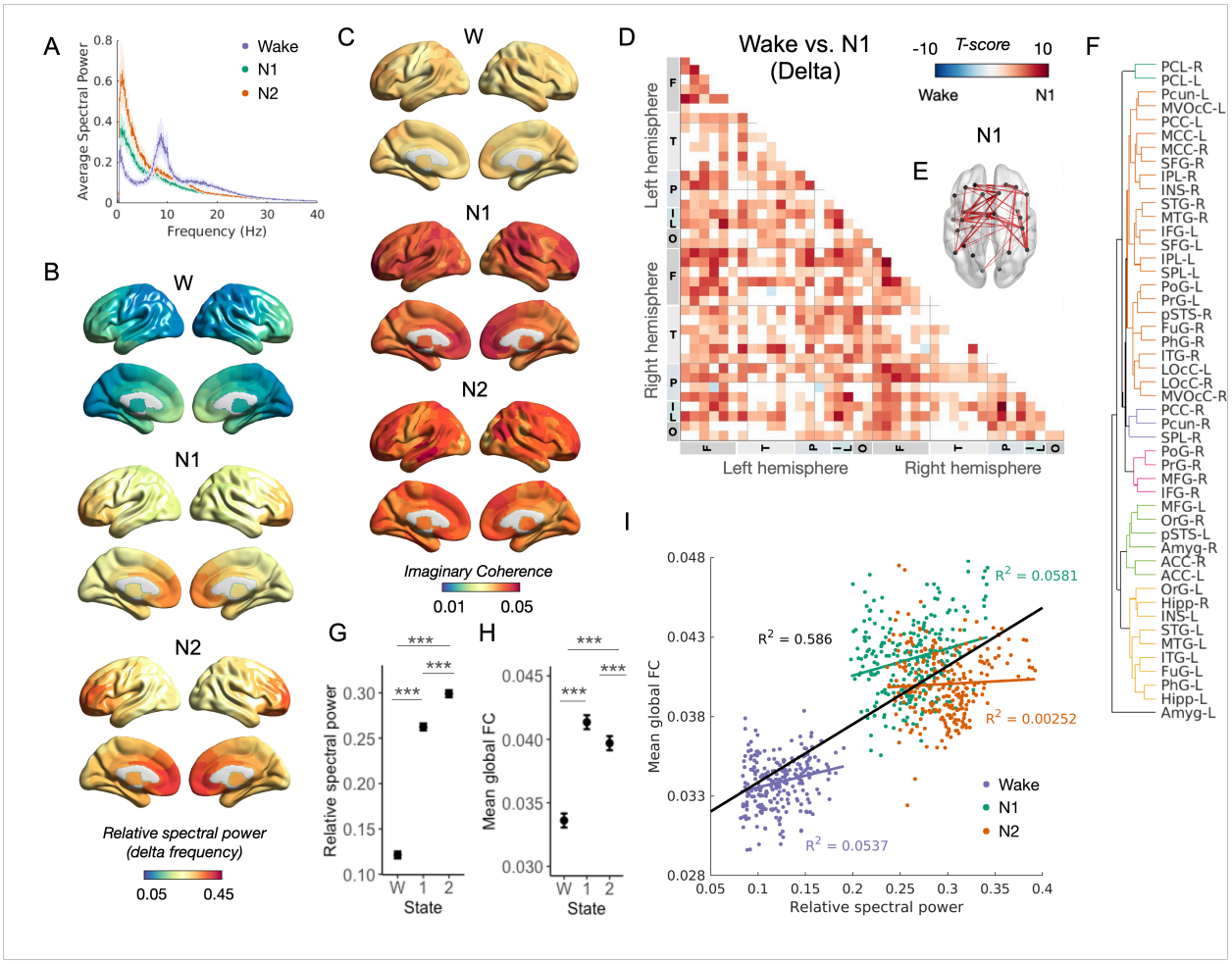

Figure 1. Spectra and spatial FC maps between sleep-wake states in delta frequency band. A) Mean relative spectral power, averaged across regions and patients in wake (purple), N1 (green), and N2 (orange). Light shading represents the standard error across patients. B) Spatial maps of relative spectral power in sleep-wake states. C) Spatial map of global synchrony in W, N1, and N2 within the delta band, as measured by imaginary coherence. D) T-score map of differences in regional FC between W and N1 within the delta band. Lobar regions delineated on x- and y- axis are further described in Table 1s. E) Top 50 highest positive functional connections, favoring N1. F) Regions specified with laterality ordered via hierarchical clustering of highest similarity in FC across regions. G) Mean relative spectral power in the delta band, averaged across regions and patients, for sleep-wake states. Error bars represent the SD across patients. H) Mean global FC in the delta

band across region and patients, for sleep-wake states Error bars denote 95% CI from the least-square mean. I) Association between the spatial maps of mean global FC and relative spectral power in the delta band. Linear regression and correlations of the mean global FC and relative spectral power for individual ROIs are provided for within sleep-wake state and across state (black) populations.

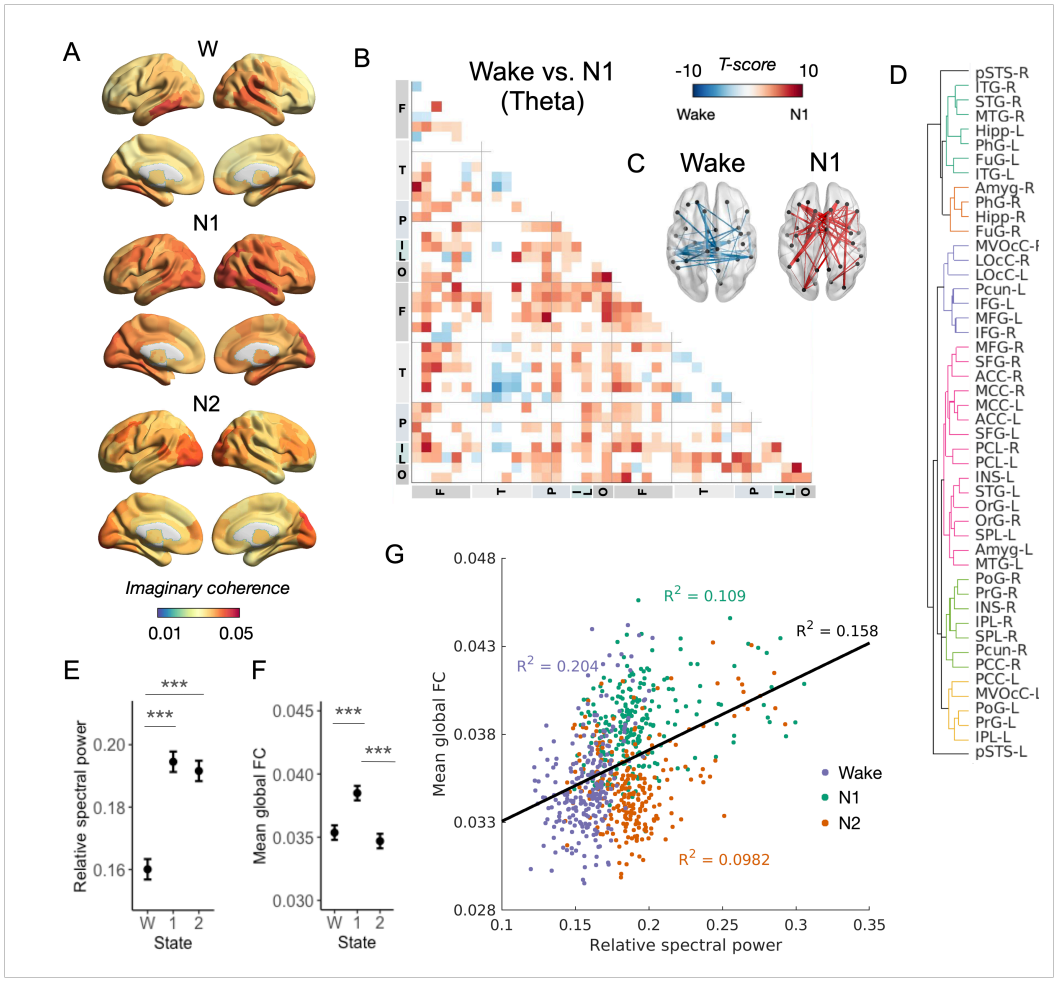

Figure 2. Spatial FC maps between sleep-wake states in theta frequency band. A) Spatial map of global synchrony in W, N1, and N2 within the theta band, as measured by imaginary coherence. B) T-score map of differences in regional FC between W and N1 within the theta band. C) Top 50 highest positive and negative functional connections, favoring N1 (red) and W (blue), respectively. D) Regions specified with laterality ordered via hierarchical clustering of highest similarity in FC across regions. E) Mean relative spectral power in the theta band, averaged across regions and patients, for sleep-wake states. Error bars represent the SD across patients. F) Mean global FC in the theta band, averaged across region and patients, for sleep-wake states. G) Association between the spatial maps of mean global FC and relative spectral power in the theta band.

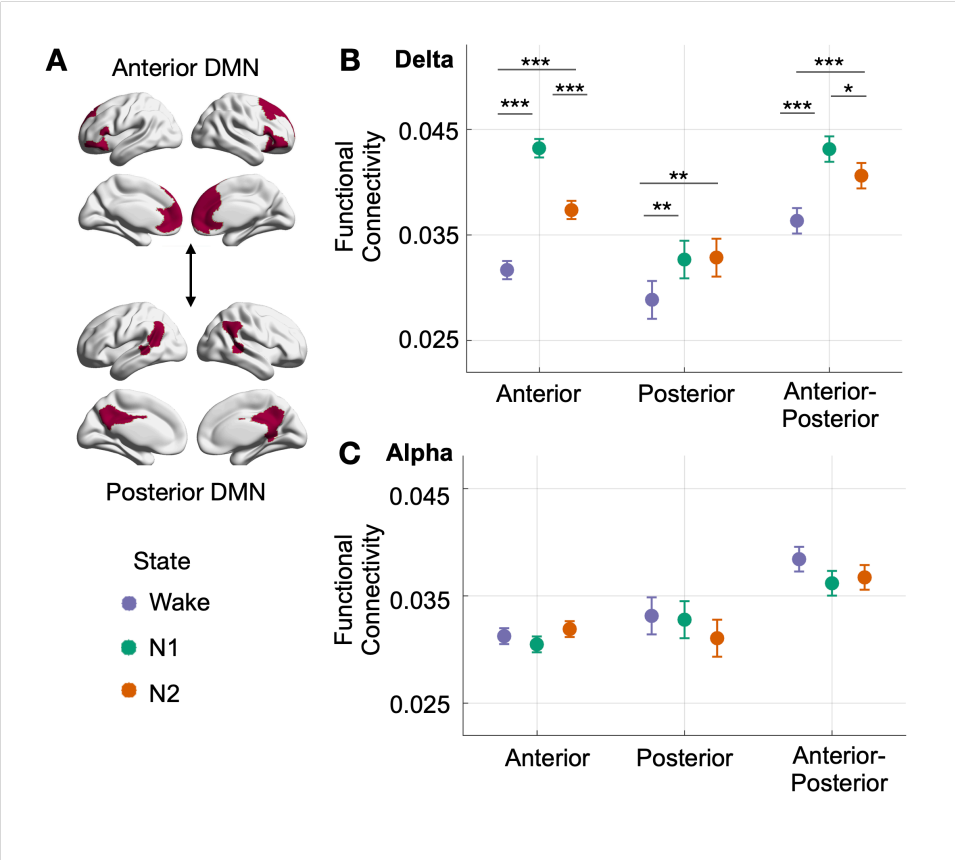

Figure 3. Seeded study evaluating the FC between anterior and posterior regions of the DMN. A) Voxels (red) that are involved and the anterior (*top*) and posterior (*bottom*) DMN. The anterior-posterior coupling as indicated by the arrows evaluates the interactions between anterior DMN voxels and posterior DMN voxels. B) Intrinsic FC within the anterior (*left*) and posterior (*middle*) DMN, and anterior-posterior coupling of the DMN (*right)* within the delta band and C) alpha band. Significance testing performed on multiple comparison testing across all regions (FDR level 0.5).

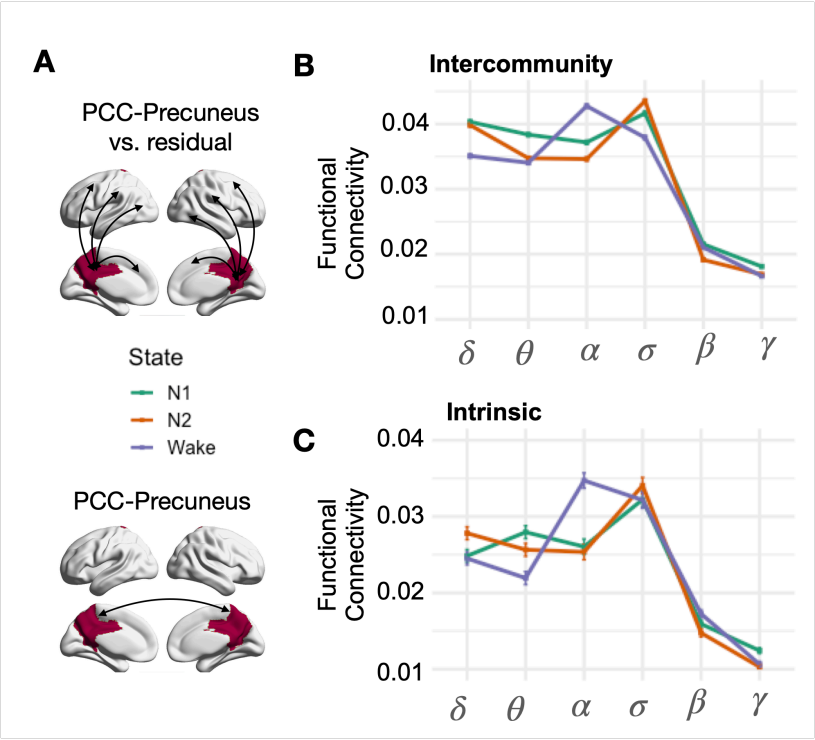

Figure 4. Seeded study evaluating the FC between the PCC-precuneus and residual cortical structures (intercommunity) and within the PCC-precuneus (intrinsic). A) Voxels (red) that are involved in the PCC-precuneus with arrows indicating intercommunity (*top*) and intrinsic connectivity (*bottom*). B) FC relative to frequency bands for intercommunity and C) intrinsic connectivity.

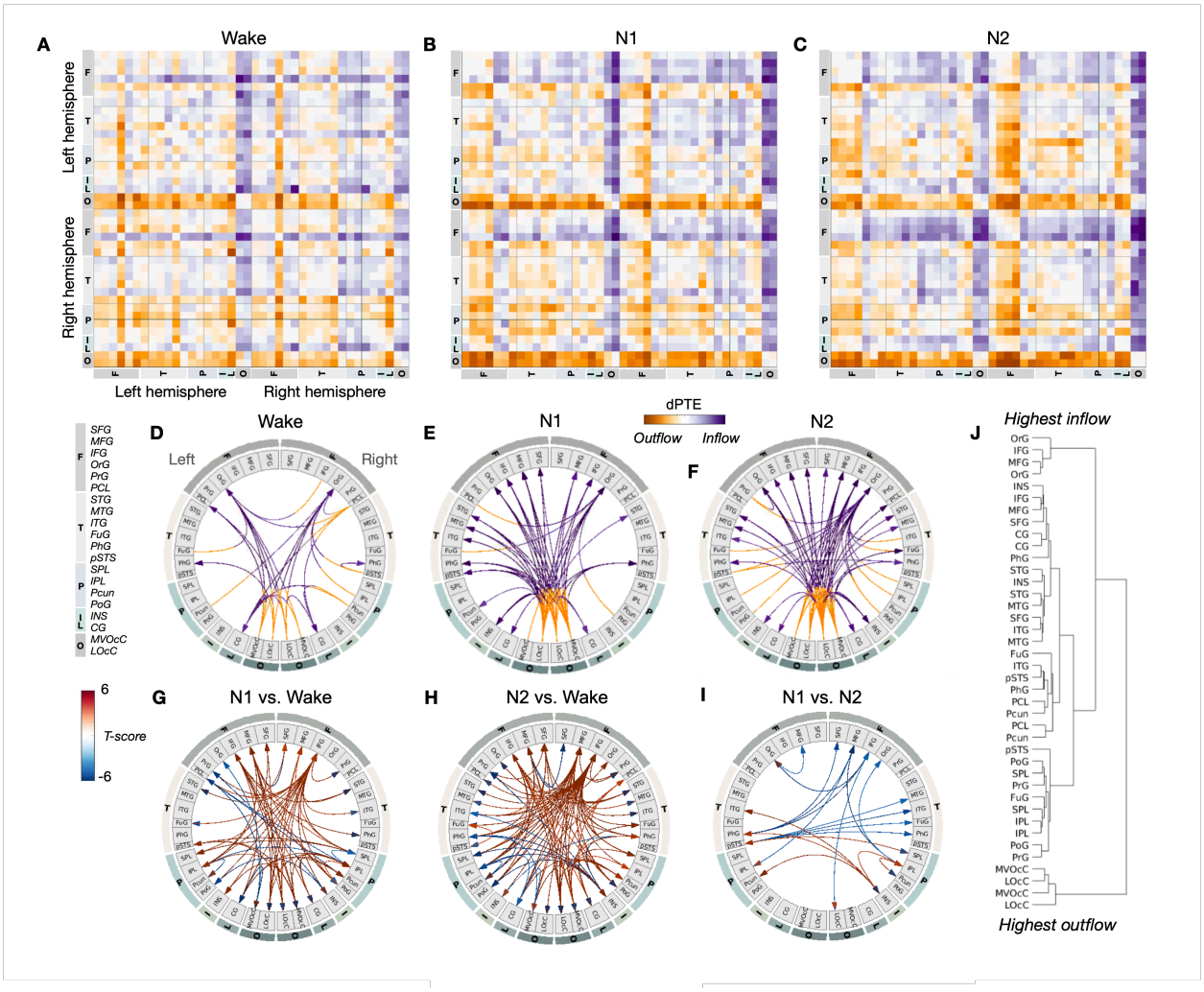

Figure 5. Directed information flow of sleep-wake states in the delta frequency band. A-C) Directed FC as measured by directional phase transfer entropy (dPTE) across W, N1, and N2. From W to N1 and N2, there is increasing magnitude of dPTE with an aggregative inflow into the bilateral frontal regions. D-F) Alternate visualization of directed FC colored by orange (outflow) and purple arrow (inflow). The visualization across W, N1, and N2 using a common threshold for depicting increased magnitudes and trajectories of the directed FC. G-I) T-scores plotted indicating magnitude changes between specified states. (FDR threshold 0.5) J) Hierarchical cluster representation of regions with common directed FC activations. CG reflects the anterior-posterior gradient of the CG; see Fig 6s to see decomposition.

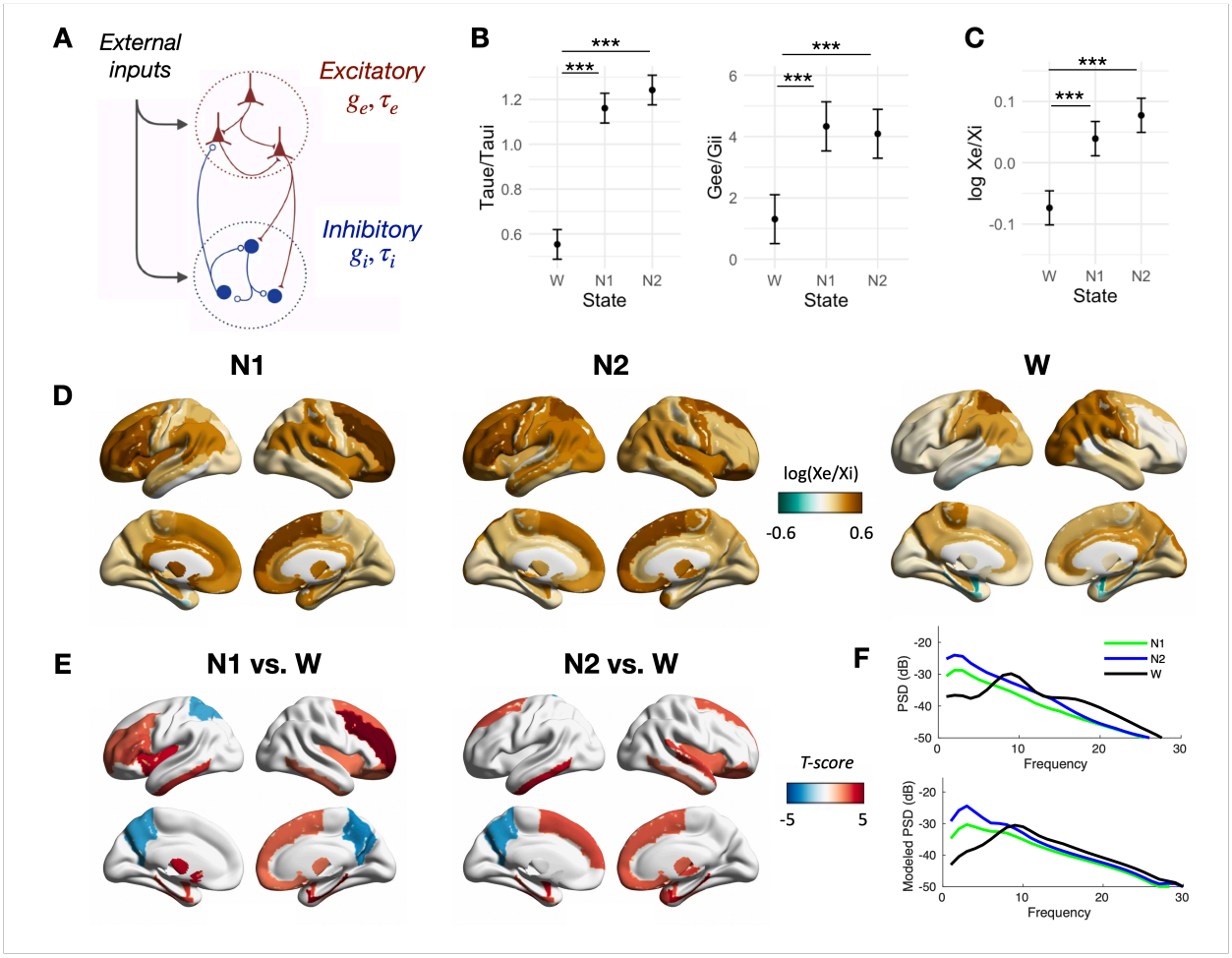

Figure 6. Biophysical model across sleep-wake states demonstrated reduced excitation-inhibition with transition to sleep. A) Depiction of NMM, comprised of both excitatory and inhibitory inputs and modeled with time constants (τ) and gain (g) parameters. B) Optimized parameters of g_{ee}/g_{ii} and τ_e/τ_i across sleep-wake states. C) Excitatory-inhibitory ratio (X_e/X_i) across sleep-wake states, revealing reduced excitation with transition to sleep. D) Spatial maps of X_e/X_i across sleep-wake states, revealing cortical heterogeneity in excitability. E) T-scores reflecting differences between N1 vs. W (*left*) and N2 vs. W (*right*) across different ROIs. Depicted T-scores are thresholded to account for multiple comparison testing (FDR level of 0.05). F) Actual (*top*) and modeled (*bottom*) power spectral density curves across sleep-wake states.

SUPPLEMENTARY MATERIALS.

Figures

1. Methods flow chart
2. Spatial map of all spectral changes across state
3. FC changes for alpha/beta frequencies
4. FC changes between N1 and N2
5. Information flow for alpha frequency
6. Hemispheric differences

Table

1. Demographics of healthy individual cohort

Methods

1. Neural mass modeling expanded methods: Closed form expression of modeled PSD