The new frontier of Network Physiology: Emerging physiologic states in health and disease from integrated organ network interactions

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Abstract An intriguing question in the new field of Network Physiology is how organ systems in the human body dynamically interact to coordinate functions, to maintain healthy homeostasis, and to generate distinct physiological states and behaviors at the organism level. Physiological systems exhibit complex dynamics, operate at different time scales and are regulated by multi-component mechanisms, which poses challenges to studying physiologic coupling and network interactions among systems with diverse dynamics. We present a conceptual framework and a method based on the concept of time delay stability to probe transient physiologic network interactions in a group of healthy subjects during sleep. We investigate the multi-layer network structure and dynamics of interactions among (i) physiologically relevant brain rhythms within and across cortical locations, (ii) brain rhythms and key peripheral organ systems, and (iii) the network structure and dynamics among peripheral organ systems across distinct physiological states. We demonstrate that each physiologic state (sleep stage) is characterized by a specific network structure and link strength distribution. The entire physiological network undergoes hierarchical reorganization across layers with the transition from one stage to another. Our findings are consistent across subjects and indicate a robust association of organ network structure and dynamics with physiologic state and function. The presented Network Physiology approach provides a new framework to explore physiologic states under health and disease through networks of organ interactions.

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1 Introduction

The human organism consists of various physiological systems, each with its structural organization and exhibits complex dynamics with nonlinear and transient characteristics. States and functions at the organism level are traditionally defined by the dynamics of individual organ systems, and their modulation in response to internal and external perturbations. However, coordinated network interactions among organs are essential to generating distinct physiological states and maintaining health at the organism level. Manifested as synchronized bursting activities with certain time delays, these interactions occur through different coupling forms [1, 3], stochastic and nonlinear feedback across spatial-temporal scales and at multiple levels of integration to optimize and coordinate organ functions. Disrupting network communications can lead to dysfunction of individual systems or the collapse of the entire organism. Currently, there is no established theoretical framework, computational and analytic formalism to probe interactions between diverse systems in the human organism.

Here we present a new methodology adequate to identify and quantify the coupling of systems with different temporal characteristics and signal outputs. We apply Network Physiology approach [4, 14, 15] and the novel concept of time delay stability [2], and we demonstrate their utility to study transient synchronous bursts in systems dynamics as a fundamental form of physiologic network communications. We investigate new aspects of network interactions among brain rhythms across and within cortical locations, and their relation to neural plasticity in response to changes in autonomic regulation underlying different physiologic states. Further, we uncover dynamical features of brain-organ and organ-organ networks as a new signature of physiologic control and establish an association of network structure and dynamics with physiologic state and function. The presented methodology is an initial step in developing novel signal processing and computational tools and reported findings to establish building blocks of an atlas of dynamical interactions among key organ systems in the human body.

2 Method

2.1 Data

The data used in this work are multi-channel signals synchronously recorded from key physiological systems during night-time sleep with an average duration of 7.9h (EU SIESTA databases [18]). We analyze two subsets of the database: (i) 52 healthy subjects (26 female, 26 male, ages 20-34 years); (ii) 34 healthy subjects (17 female, 17 male, ages 20-40 years). All participants provided written informed consent. The research protocol was approved by the Institutional Review Boards of Boston Uni-

versity; data collection conducted according to the principles expressed in the Declaration of Helsinki; sleep stages scored in 30s epochs by certified technicians.

Standard polysomnogram recordings follow the American Academy of Sleep Medicine Manual [5]. Signals include EEG (channels Fp1, Fp2, C3, C4, O1 and O2), ECG, respiratory waves, EOG, EMG from chin and leg. From the raw signals we extract: spectral power in windows of 2s with 1s overlap for all physiologically relevant cortical rhythms (EEG frequency bands): δ (0.5-3.5Hz), θ (4-7.5Hz), α (8-11.5Hz), σ (12-15.5Hz), β (16-19.5Hz), γ_1 (20-33.5 Hz), γ_2 (34-99.5 Hz); variance of EOG and EMG in 2s windows with 1s overlap; heartbeat RR intervals and interbreath intervals are re-sampled to 1Hz after which values are inverted to obtain heart rate and respiratory rate. Thus, all time series have time resolution of 1s prior to analysis.

2.2 Time Delay Stability (TDS) Method

Physiological systems exhibit complex time-varying dynamics characterized by coherent bursts in activation across systems in response to modulation in physiologic state and condition (Fig. 1 Top left). We develop a new approach to (i) quantify pair-wise coupling and network interactions among diverse systems with bursting dynamics, and (ii) track the evolution of networks of organ interactions across states and conditions. We introduce a novel concept, Time Delay Stability (TDS), and a TDS method (Fig. 1) to study the time delay with which bursts of activity in a given system are consistently followed by corresponding bursts in the signal output of other systems. Within this framework, periods of TDS, i.e., constant time delay between bursts in the activation of two systems, indicate coupling.

To probe the interaction between two physiologic systems X and Y, we consider their output signals $\{x\}$ and $\{y\}$, each of length N. We divide signals $\{x\}$ and $\{y\}$ into N_L overlapping segments of equal length $L = 60$s. We chose an overlap of $L/2 = 30$s which corresponds to the time resolution of the conventional sleep-stage scoring epochs, and thus $N_L = [2N/L]$. Prior to analysis, each segment is normalized separately to zero mean and unit standard deviation to remove constant trends so that the estimated coupling between signals is not affected by relative amplitudes.

Next, we calculate the cross-correlation function,

$$C_{xy}^{\nu}(\tau) = \frac{1}{L}\sum_{i=1}^{L} x^{\nu}_{i+(\nu-1)\frac{L}{2}}\; y^{\nu}_{i+(\nu-1)\frac{L}{2}+\tau}, \tag{1}$$

within each segment $\nu = 1, \ldots, (N_L - 1)$ by applying periodic boundary conditions. For each segment ν we define the time delay τ_0^{ν} corresponding to the maximum in the absolute value of $C_{xy}^{\nu}(\tau)$ in this segment:

$$\tau_0^{\nu} = \tau|_{|C_{xy}^{\nu}(\tau)| \geq |C_{xy}^{\nu}(\tau')| \;\; \forall \tau'}. \tag{2}$$

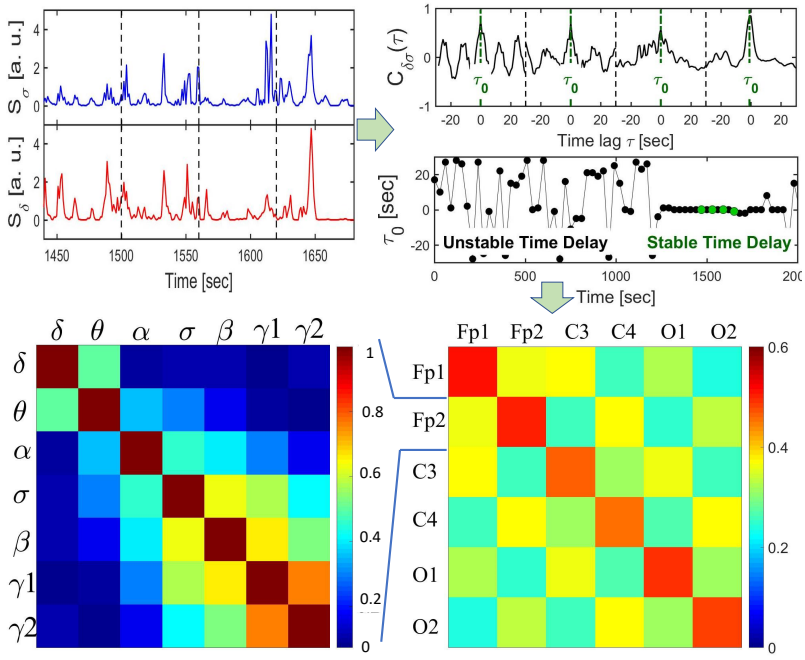

Fig. 1 Degree of coupling between brain rhythms quantified by Time Delay Stability (TDS). Schematic presentation of the TDS method. (Top left) Segments of time series representing EEG spectral power $S(\sigma)$ and $S(\delta)$ of the σ and δ cortical rhythms shown for consecutive 60s windows (vertical dashed lines). (Top right) Coordinated synchronous bursts in $S(\sigma)$ and $S(\delta)$ lead to pronounced cross-correlation $C_{\delta\sigma}$ with dominant peak within each time window located at time lag τ_0, representing the time delay between the two signals. Time delay τ_0 between $S(\sigma)$ and $S(\delta)$ is plotted for consecutive 60s windows with step of 30s (green dots mark τ_0 for the windows shown in the $C_{\delta\sigma}$ plot). Note the transition at $\sim$ 1200s from a segment with strongly fluctuating τ_0 to a stable time delay regime with $\tau_0 \approx$ constant. Such regime of time delay stability (TDS) indicates the onset of physiological coupling. The fraction of time (%) in the EEG recording when TDS is observed quantifies the degree of coupling strength (%TDS). (Bottom left) TDS matrix representing the degree of coupling between different brain rhythms (δ, θ, α, σ, β, γ_1, and γ_2) derived from two cortical locations (Fp1 and Fp2 EEG channels). Matrix elements represent the coupling strength, measured as %TDS, for each pair of brain rhythms. (Bottom right) TDS matrix representing the average coupling of all brain rhythms across each pair of EEG channels (Fp1, Fp2, C3, C4, O1, O2). Matrix elements show cortical rhythms interactions for one representative healthy young subject during Wake. Color code indicates the average coupling strength.

Time periods of stable interrelation between two signals are represented by segments of approximately constant τ_0 in the newly defined series of time delays, $\{\tau_0^\nu\}_{\nu=1,\ldots,N_L-1}$. In contrast, absence of stable coupling between the signals corresponds to large fluctuations in τ_0 (Fig. 1 Top right).

Third, we identify two systems as linked if their corresponding signals exhibit a time delay that does not change by more than $\pm$1s for several consecutive segments ν. We track the values of τ_0 along the series $\{\tau_0^\nu\}$: when for at least four out of

five consecutive segments ν (corresponding to a window of 5×30s) the time delay remains in the interval $[\tau_0 - 1, \tau_0 + 1]$ these segments are labeled as stable. This procedure is repeated for a sliding window with a step size one along the entire series $\{\tau_0^\nu\}$. The TDS value is finally calculated as the fraction (%TDS) of stable points in the time series $\{\tau_0^\nu\}$. Thus, longer periods of TDS between the output signals of two systems reflect more stable interaction and stronger coupling between these systems, and the links strength in physiologic networks is determined by the percentage of time when TDS is observed: higher %TDS means stronger links.

We have tested several different values for the window size L, i.e., $L = 30$, 60, 120, and 180s with non-overlapping windows as well as window overlaps $L/2$ and $L/4$. The overall TDS results were not significantly different for the different combinations of L and overlap, however, there was a tendency to noisier τ_0 vs t signals for shorter windows and less overlap (Fig. 1 Top left). On the other hand larger windows reduce the time resolution of the TDS.

The TDS method is general, and can be applied to diverse systems with bursting dynamics. It is more reliable in identifying physiological coupling compared with traditional cross-correlation, cross-coherence, and classical Granger causality approaches, which are not suitable for heterogeneous non-stationary signals with time varying coupling, and are affected by the degree of auto-correlations and irregular bursts embedded in these signals [4, 23]. Several relevant signal processing techniques have been developed for automated pattern discovery (e.g., dynamic time wrapping method used for machine learning and information retrieval), which may perform well when time-series are at a similar scale with low noise. They are not tailored for high-frequency bursting signals in multiple-channel polysomnogram recordings that exhibit transient dynamics and strong stochastic fluctuations.

2.3 Averaging procedure for assessing links strength in physiological networks

We introduce a procedure to quantify the group average strength of a particular network link for a physiological state (sleep stage). A standard averaging procedure, where the strength of a network link during a given sleep stage is first calculated for one subject and is then averaged for all subjects, would give equal weight for all subjects in the group average. However, we note that the total duration of each sleep stage (sum of all episodes of a given stage) during night-time sleep varies from subject to subject. Thus, we perform a weighted averaging procedure where the contribution of each subject in the group average link strength for a sleep stage is weighted proportionally to the total duration of that sleep stage during the night.

Specifically, links in our network analysis are obtained by quantifying TDS for each pair of physiological systems after calculating the weighted average for all subjects during a given physiological state (sleep stage): $\%\text{TDS} = (\Sigma_i s_i / \Sigma_i S_i) \times 100$ where S_i indicates the total duration of a given sleep stage for subject i, and s_i is the total duration of TDS within S_i for the considered pair of physiological signals.

Artifacts related to specific behaviors of individual subjects (excessive movement, respiratory perturbations, etc.) or to the quality of recording of specific channels (due to loose lead contact) may lead to outliers in the estimate of some links strength in the network for a given subject. Further, links that are outliers in the physiological network of one subject may not be outliers in the network of another subject (same artifacts may not repeat for different subjects). To address this problem, for each pair of physiological signals (specific network link) we obtain the distribution and standard deviation of %TDS values (link strength) derived from all subjects in the group. Subjects for whom the considered network link has %TDS value above the group average + 2 are then removed, and a weighted average for the link is obtained based on the remaining subjects in the group, thus removing outliers in the calculation of the group-averaged link strength. This procedure is repeated for each link in the network. Considering all network links for all subjects in our database during a given physiologic state, this procedure led to $< 3\%$ of links removed as outliers in the calculation of the reported group average results for the different physiological networks.

To avoid unreal couplings due to small cross-correlation peaks, we only look at stable periods of TDS – only when four out of five consecutive segments with maximal correlation appear at the same delay do we consider them to be stable. A network link between two systems is defined when their interaction is characterized by TDS value above a significance threshold determined by a surrogate analysis test. For each link in a given sleep stage, 200 surrogates are generated considering signals from two distinct and randomly chosen subjects, and a surrogate average link strength (%TDS) is obtained. The procedure is repeated for each network link to obtain a distribution of surrogate link strengths in each sleep stage. For each distribution, the mean μ_{surr} and standard deviation σ_{surr} are estimated. The significance threshold at 95% confidence level for network links strength is defined as $\mu_{\text{surr}} + 2\sigma_{\text{surr}}$ for each sleep stage. The %TDS thresholds in surrogate tests are around 2.5% which are much lower than those in real empirical data (around 50-60%), validating our method's effectiveness.

3 Results

We focus on physiological systems network dynamics during sleep because sleep stages are well-defined physiological states with specific neuroautonomic regulation, and external influences due to physical activity or sensory inputs are reduced. The structure of our database, comprising of multi-channel synchronously recorded signals from different organ systems, allows to investigate the dynamics of interactions among organ systems and their network organization during different physiological states (sleep stages). Using the TDS method, specially tailored to probe interactions among systems with diverse dynamics, we aim to quantify coupling between organ systems and their network characteristics. It is essential to understand how physiologic regulation underlying a given state influences the dynamics of or-

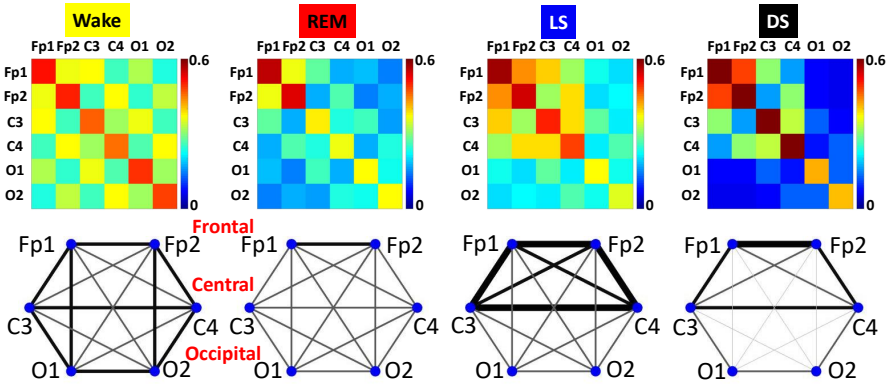

Fig. 2 Dynamic networks of brain rhythms interactions across cortical locations and transitions with physiological states. (Top) Time Delay Stability (TDS) matrices representing the average strength of coupling among all cortical rhythms (EEG frequency bands) across EEG channels, obtained from continuous overnight recordings for different sleep stages and averaged for a group of healthy subjects. Color code for matrix elements marks the coupling strength (%TDS). Transitions across sleep stages lead to changes in the average coupling strength of brain rhythm interactions across cortical locations and associated reorganization in TDS matrix structure characterized by stronger interactions during Wake and LS (warmer colors) compared to REM and DS (colder colors). (Bottom) Network representation of the group average TDS matrices for different sleep stages. Network nodes indicate cortical areas: Frontal (Fp1 and Fp2), Central (C3 and C4) and Occipital (O1 and O2). Each network link represents the coupling strength averaged over all pairs of rhythms from two different cortical areas, where wider and darker links indicate stronger coupling. Links are separated in four modules (with %TDS $<$12%; 12%-30%; 30%-38%; $>$38%). Dramatic reorganization in network structure is observed with transition from one sleep stage to another, with more homogeneous links (coupling strength) distribution during Wake and REM, heterogeneous and modularized links during LS and DS. Reorganization in network links heterogeneity is paralleled by a pronounced sleep-stage stratification pattern – average network links strength is significantly different comparing all four sleep stages (one-way ANOVA rank test $p \leq 0.001$), and pairwise comparisons of Wake vs REM and LS vs DS both show significant difference (Mann-Whitney test $p \leq 0.001$).

gan network communications, and how integration of organ systems as a network leads to emergent behaviors and physiological functions at the organism level [16].

3.1 Networks of brain rhythms interactions across cortical locations

We first investigate the network of interactions among different brain rhythms. Sleep stages are traditionally defined by the presence of dominant brain rhythms in cortical EEG dynamics. However, little is known whether and how brain rhythms across cortical locations interact as a network to generate sleep stages [22]. We consider seven distinct cortical rhythms from six cortical areas (EEG channels) that are traditionally used in sleep-stage scoring. Our TDS analysis shows pronounced coupling

for all pairs of rhythms, well above the significance threshold at 2.5%TDS, indicating physiologically relevant network interactions. Further, we find that the complex network of brain rhythms interactions across locations changes with transition from one sleep stage to another. A clear sleep-stage stratification is observed when we coarse-grain the network by averaging the coupling strength over all pairs of rhythms for each two cortical areas – globally the network is characterized by much stronger coupling among brain rhythms during Wake and LS compared to REM and DS, as demonstrated by the coarse-grained TDS matrix in Fig. 2. Moreover, there is a pronounced reorganization in network topology with transition across physiologic states, where each sleep state is characterized by specific modules of cortical locations with strong or weak interactions (Fig. 2).

3.2 Network interactions among brain rhythms within cortical areas

We next investigate the network of brain rhythms interactions within each of the six cortical locations separately. We find that higher frequency brain rhythms exhibit stronger coupling (i.e. more synchronous bursting activity) – a behaviour which is consistently observed for all six cortical locations and sleep stages, as shown by the TDS matrices in Fig.3. With transition from one sleep stage to another, there is a significant reorganization in both links strength and topology for all local networks of brain rhythms interactions: while Wake is characterized by similar network link strength and topology for all six cortical areas, local networks of brain rhythms interactions during REM, LS and DS exhibit different structure with higher connectivity and link strength in the Frontal areas compared to the Central and Occipital areas.

The existing literature focuses on how a given rhythm (such as δ) interacts with itself across different brain locations. Since neuronal populations in six cortical layers generate different brain rhythms that project onto the scalp, cross-frequency coupling naturally occurs at the same location, manifesting neuronal populations' synchronous activities and quantifying inter-layer coordination between cortical neurons. Moreover, in the next section, we will discuss specific functional forms of couplings among cortical rhythms in the same brain area [21].

3.3 Coexisting networks of brain rhythm interactions represent different types of physiologic coupling

In contrast to Fig. 3 where network links represent %TDS (Method), network links in Fig. 4 [21] represent the degree of synchronous or asynchronous modulation in the spectral power amplitude of different (dominant and non-dominant) brain rhythms. To probe the collective behavior of brain rhythms in relation to physiologic states, we construct networks of positive and anti-correlated interactions from equal-

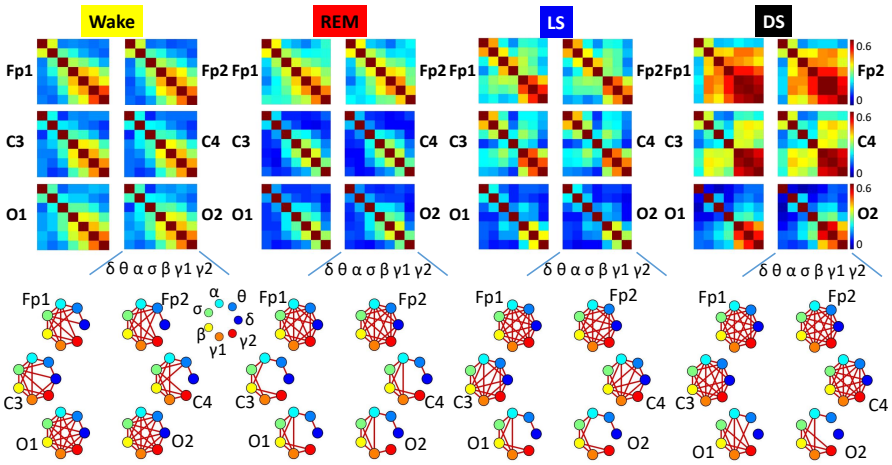

Fig. 3 Plasticity in network interactions among brain rhythms at specific cortical locations as function of physiologic state. (Top) Time Delay Stability (TDS) matrices quantify interactions for specific pairs of cortical rhythms (EEG frequency bands δ, θ, α, σ, β, γ_1, and γ_2) within six cortical areas (EEG channels: Frontal Fp1 and Fp2, Central C3 and C4, Occipital O1 and O2). Color code of matrix elements marks the coupling strength for each pair of brain rhythms averaged over a group of healthy subjects. Changes in TDS matrix structure for different brain areas and sleep stages indicates plasticity of brain rhythms interactions as function of physiologic state. (Bottom) Network presentation of the TDS matrices at six cortical locations for different sleep stages. Network nodes in color mark cortical rhythms derived from a given EEG channel representing a cortical location. Network links (in red) represent the strength of interaction for each pair of brain rhythms at a given EEG channel location (only links with %TDS$\geq$ 25% are shown). Network connectivity significantly changes at cortical locations during a given sleep stage, as well as with transition across stages (one-way ANOVA tests $p \leq 0.001$), indicating a complex reorganization and plasticity in brain rhythm interactions necessary to facilitate physiologic functions associated with distinct physiologic states.

time cross-correlation among brain rhythms, and we track their evolution across sleep stages. This network approach helps to visualize and dissect brain wave interactions where positive- and anti-correlated behaviors coexist [21]. It also provides a first demonstration of how brain rhythms coordinate collectively as a network to generate distinct physiologic states.

During DS, we observe a pronounced network cluster of anti-correlated interactions between the δ wave and all other brain waves (Fig. 4). We also identify a coexisting complementary network during DS comprised of only positively-correlated interactions between all brain waves except δ (Fig. 4). With the transition from DS to LS, REM, and wake, the links strength in the anti-correlated cluster between δ and all other brain waves decreases. In contrast, new positively-correlated links emerge, indicating a complex reorganization among brain rhythms across physiologic states. We note that links in the positively-correlated networks represent parallel coordination of brain wave activation, whereas links in the anti-correlated networks correspond to brain wave interactions of reciprocal and complementary

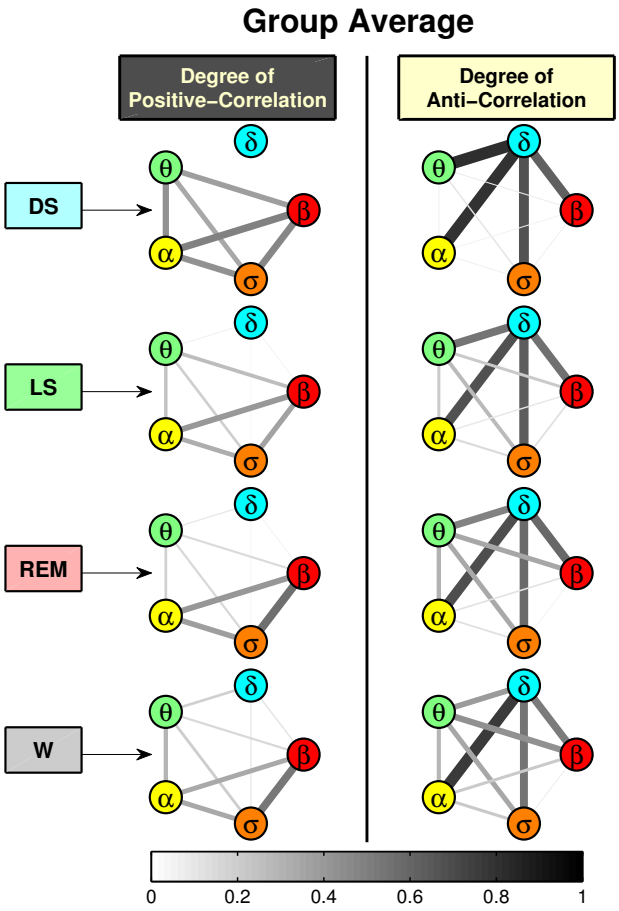

Fig. 4 Coexisting networks of brain rhythm interactions at channel C3 represent different types of physiologic coupling and exhibit distinct topology across sleep stages. Network nodes represent brain waves (EEG frequency bands) and network links indicate the degree of equal-time cross-correlations for each pair of brain waves (line thickness and darkness correspond linearly to link strength). Two types of networks are shown: left column, where links strength reflects the fraction of time when significant positive correlation (with $C > 0.5$) is found between a given pair of brain waves; right column, where links strength corresponds to the fraction of time when significant anti-correlation (with $C < -0.5$) is observed. These networks of interactions evolve across sleep stages – the links strength in the anti-correlated cluster between δ and all other brain waves decrease, while new positively-correlated links emerge. Remarkably, the coexistence of both positively- and anti-correlated networks of brain waves interactions within each physiologic state indicates a transient on/off nature of brain-wave communications, where links of different nature can emerge during different periods of time within the same physiologic state. The specific topology and clustering of brain wave networks during different sleep stages demonstrate a direct association between brain wave communications and physiologic state and function.

nature (opposite direction of modulation). Specifically, the δ-α interaction is always characterized by strong anti-correlation during all sleep stages, and there is

no δ-α link in the positively-correlated networks (Fig. 4). This observation is consistent with the traditional understanding of δ and α waves as the predominant brain rhythms for two opposite physiologic states, i.e., sleep vs. wake. However, the classical description of these physiologic states does not address the nature of δ-α interaction. Our analyses reveal the complex dynamics of reciprocal and competing nature in the coupling between δ and α waves, which transcends all physiologic states. In contrast to δ-α interactions, links associated with the θ wave that show positive correlations during DS become increasingly anti-correlated during LS and REM, indicating a very different role of θ-wave interactions compared to α- and δ-wave. Note that network links represent the fraction of time when a specific type of cross-correlation (positive or negative) is observed. Thus, the coexistence of both positively- and anti-correlated networks of brain-wave interactions within each physiologic state indicates a transient on/off nature of brain rhythms communications, where links of different nature can emerge during different times in the same physiologic state.

The traditional paradigm in brain research focuses on exploring the temporal dynamics and role of individual brain rhythms, and their association with specific physiologic states and functions [10, 26]. It is motivated by observations of quasi-steady-state behavior of brain rhythms at large time scales within a given physiologic state (e.g., sleep or wake, sleep stages) [6, 28], and changes in the amplitude (i.e., spectral power) of individual brain rhythms, their synchrony and coherence across cortical areas with the transition from one physiologic state to another [7, 11, 12, 30]. Our study aims to address the question of how dominant and non-dominant brain rhythms dynamically interact. We demonstrate that synchronous short-term modulations in the amplitude of brain rhythms that occur on top of their quasi-steady-state behavior at large time scales carry key information about the coupling among brain rhythms that are essential characteristics of a physiologic state. The presented here approach can detect higher-order interactions among both dominant and non-dominant brain rhythms embedded in their fine temporal structure at small time scales. It can quantify the change in brain rhythms network communications with transition across distinct sleep stages (Fig. 4). The uncovered coupling forms and network coordination among brain rhythms provide new insights into intrinsic physiologic interactions.

3.4 Dynamics of brain-organs interactions

Brain dynamics play an important role in the neuroautonomic regulation of organ systems. However, it remains unknown how brain rhythms simultaneously coordinate the function of different organs. We analyze the coupling of all seven brain rhythms from all six cortical locations with five key organ systems: heart, lungs, chin, eye and leg.

There are several key questions related to the nature of brain-organ interactions: (i) how different brain areas (EEG-channel locations) are involved in the commu-

nications and control of each organ system, (ii) which brain-wave frequency bands mediate the brain-organ communications, and (iii) how the networks of brain-organ interactions evolve with transitions across physiologic states. To this end, we apply the TDS method to identify and quantify dynamical links in the networks, which would serve as unique physiological maps of brain-organ interactions.

3.4.1 Brain-heart interactions

To demonstrate the rich dynamical features in brain-organ communications, let us first examine the network of brain-heart interactions. As indicated by the radar chart inside the heart hexagon in Fig. 5 [2], the network exhibits a relatively symmetric distribution of the average links strength for different brain areas, with a slight prevalence in strength for the links between the heart and the Central brain areas (C3 and C4). The spatial symmetry in the average brain-heart link strength holds for all sleep stages. Systematically investigating the links strength in the brain-heart network for all seven frequency bands and different sleep stages, we find that the average link strength for the entire network of brain-heart interactions is highest during W and LS, lower during REM and lowest during DS (Fig. 5). Further, this sleep-stage stratification pattern is consistently observed for all three sub-networks representing the Frontal-heart, Central-heart and Occipital-heart links across all frequency bands. Thus, our analysis shows that the strength of all links in the brain-heart network, regardless of brain areas or frequency bands, is modulated in the same way with transitions across sleep stages.

3.4.2 Sub-networks of brain-organ interactions

We find that sub-networks of brain rhythms interacting with distinct organ systems exhibit different average links strength, indicating a more synchronous activity and stronger coupling of brain rhythms with the dynamics of some organ systems compared to others, as shown by different size of network nodes in Fig. 6.

Further, we find that while all brain rhythms play certain role in the network of brain-organs interactions, a particular rhythm serves as the main mediator of network communications for a given organ system. Thus, a very structured dynamic network of brain-organs interaction emerges, where different brain rhythms are involved as main mediators of the function of different organ systems during a given physiological state (marked by different node circumference color in Fig.6). With transition from one sleep stage to another, a different brain rhythm may take the role as the main mediator in network interaction with a given organ system – e.g., brain-heart network interactions are mediated by γ_2 rhythms during Wake, γ_1 and β rhythms during REM and LS, and δ rhythms during DS, reflecting previously unrecognized aspects in the autonomic regulation of organ systems (Fig. 6) [2, 20].

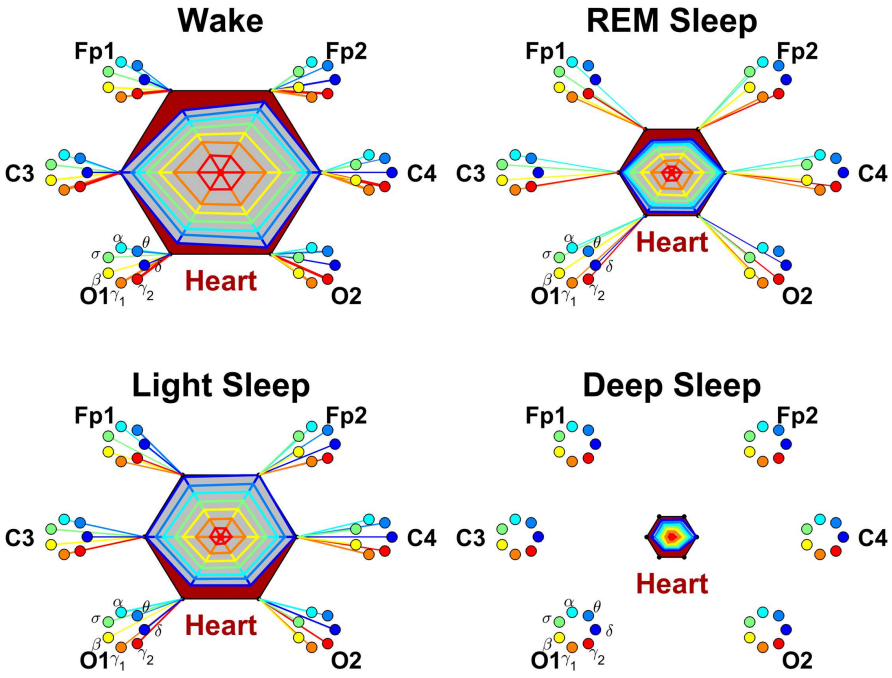

Fig. 5 Networks of brain-heart interactions during different physiologic states. Brain areas are represented by Frontal (Fp1 and Fp2), Central (C3 and C4) and Occipital (O1 and O2) EEG channels. Network nodes with different colors represent seven frequency bands ($\delta, \theta, \alpha, \delta, \beta, \gamma_1, \gamma_2$) in the spectral power of each EEG channel. Network links between the heart (red hexagon) and EEG frequency nodes at different locations are determined based on the TDS measure, and links strength is illustrated by the line thickness. Shown are links with strength 5%TDS. Radar-charts centered in each hexagon represent the relative contribution of brain control from different brain areas to the strength of network links during different sleep stages. The length of each segment along each radius in the radar-charts represents TDS coupling strength between the heart and each frequency band at each EEG channel location. These segments are shown in the same color as the corresponding EEG frequency nodes. During W and REM, the brain-heart network interactions are mediated mainly through high-frequency γ_1 and γ_2 bands (orange and red links), while during LS and DS, the interactions are mediated uniformly through all frequency bands. The brain-heart network is characterized by relatively symmetric links strength to all six brain areas, as shown by the symmetric radar-charts in each hexagon. A pronounced stratification pattern is observed for the overall strength of network links—stronger links during W and LS (larger hexagons) and weaker links during REM and DS (smaller hexagons). Notably, there are no links in the brain-heart network during DS (all links $<$ 5%TDS).

3.4.3 Networks of organ interactions

Finally, we apply our TDS analysis to probe interactions among organ systems. We find that pairs of organ systems are characterized by different coupling and correspondingly by different group average network links strength. As in the cases of brain-brain and brain-organs interactions, our analyses show that each sleep stage is characterized by a specific network topology of organ interactions (Fig. 6). The re-

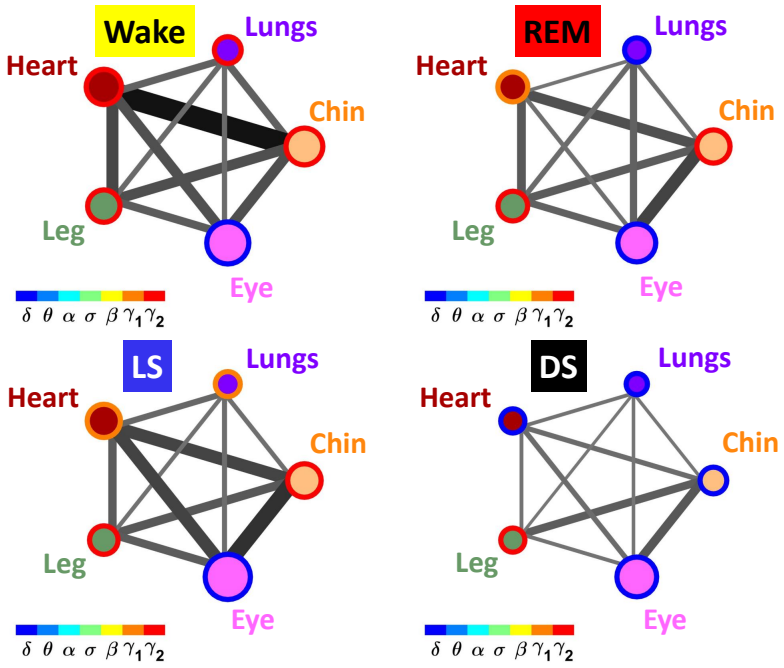

Fig. 6 Dynamic networks of organ interactions across sleep stages. Interactions among organ systems are represented by weighted undirected graphs, where network links between organ systems reflect the strength of dynamic coupling measured as %TDS and averaged for a group of healthy subjects. Darker and thicker links correspond to stronger interaction with higher %TDS. Network nodes represent key organ systems. The size of each organ node is proportional to the strength of the overall interaction of the organ with all brain rhythms at six cortical EEG channel locations (see Fig. 3). Color bars represent physiologically relevant cortical rhythms (EEG frequency bands). The circumference color of each organ node corresponds to the cortical rhythm exhibiting dominant coupling with the organ system when averaged over all cortical locations. Significant reorganization in network topology (links strength) for different sleep stages (all stages comparison one-way ANOVA rank test $p \leq 0.001$, and pairwise comparisons of Wake vs REM and LS vs DS with Mann-Whitney test $p \leq 0.003$) indicates an association between organs network interactions and physiologic function.

sults for the group average network characteristics (topology and link strength) are consistent with results obtained for individual subjects in our database, indicating a robust association of organ network interactions with physiologic state and function.

3.5 Network integration of interactions between the brain and peripheral organ systems

After separately investigating the networks of interactions between the brain and different organ systems, we integrate all brain-organ interactions into a single net-

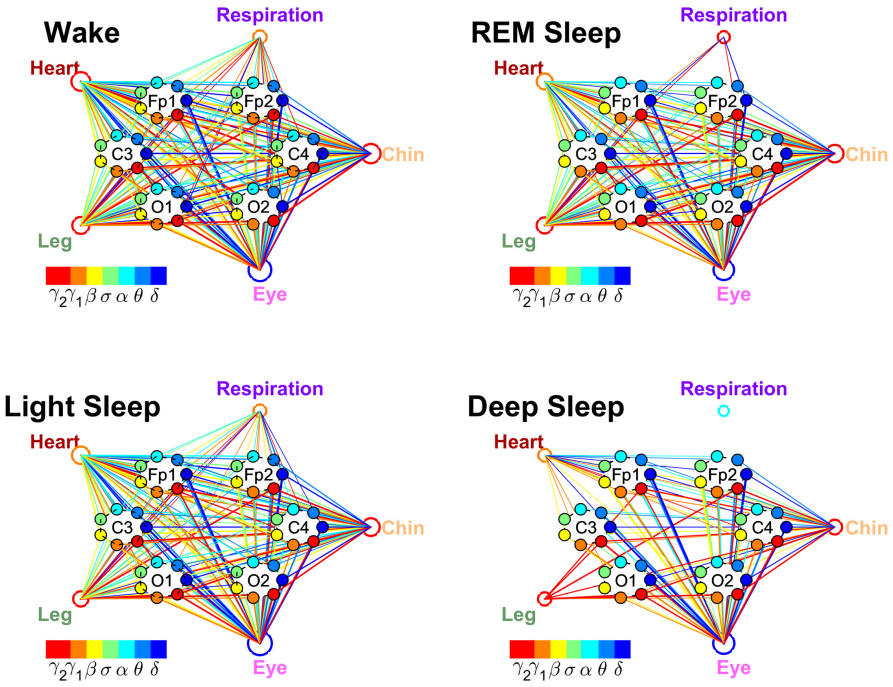

Fig. 7 Networks of physiologic interactions between brain areas and key organ systems during different physiologic states. Brain areas are represented by Frontal (Fp1 and Fp2), Central (C3 and C4) and Occipital (O1 and O2) EEG channels. Interactions between brain channels and organ systems are represented by weighted undirected graphs. The size of each organ node in the network is proportional to the strength of the overall brain-organ interaction as measured by the summation of the TDS links strength for all frequency bands and EEG channel locations. The color of each organ node corresponds to the dominant frequency band in the coupling of the organ system with the brain. The width of each link reflects the strength of dynamic coupling as measured by %TDS, and colors of the links correspond to the colors of the nodes representing the different frequency bands (color bars). Plotted are only links with strength 3%TDS. Thicker links correspond to stronger coupling and higher time delay stability. The physiological network exhibits transitions across sleep stages – lowest number of links during DS, higher during REM, and highest during LS and W. For different organs, brain-organ interactions are mediated through different dominant frequency bands, e.g., the chin and the leg are predominantly coupled to the brain through the high frequency γ_2 band during all sleep stages whereas brain-eye network interactions are mediated mainly through low-frequency δ band. The complex networks of dynamic interactions between key organ systems and the brain undergoes a hierarchical reorganization across different sleep stages, indicating a previously unknown mechanism of regulation.

work. It allows us to simultaneously compare several essential characteristics of the global network. Specifically, we track the number of links, their strength, the brain areas and frequency bands involved in the interactions between the brain and the group of organ systems and how this global brain-organs network evolves across physiologic states (Fig. 7) [2].

This integrative approach makes it possible to compare the predominant frequency band through which the interaction between the brain and different organs is mediated for several organ systems simultaneously during a given physiologic state. We find that the heart, leg and chin always interact with the brain mainly through the high-frequency γ_1 and γ_2 bands (red-colored links in Fig. 7, whereas the brain-eye interactions are mediated through lowest-frequency δ band (blue colored links in Fig. 7). There is no single dominating frequency for the brain-respiration interaction. The interaction between brain and the respiratory system is always weaker than other brain-organ interactions, indicating a relatively weak physiologic coupling between brain and respiration compared to other organs at the time scales (> 2.5 min) over which the TDS analysis is performed. Further, with transitions across sleep stages, we observe a complex hierarchical reorganization in both the number and the strength of links in the integrated brain-organs network – lowest number of links during DS (sparse network), higher during REM, and highest number of links involving most of the frequency bands during LS and W. Remarkably, this structural reorganization of the integrated brain-organs network is consistent with the sleep-stage stratification patterns observed for each organ system, indicating a previously unknown rule for neural regulation of organ systems.

4 Summary

We show that the concept of time delay stability and the TDS method we developed can be successfully employed to quantify the coupling and network interactions of systems with complex time-varying and diverse dynamics. Utilizing continuous recording during sleep from healthy young subjects, we demonstrate that each sleep stage is uniquely characterized by a network of physiologic interactions across scales in the human organism – from coupling among brain rhythms within and across cortical locations to networks of organ interactions. We find that with the transition from one state to another, physiologic network structure undergoes a consistent reorganization that occurs across scales. The dynamical networks method and empirical findings provide new insights into the mechanisms of autonomic regulation underlying physiologic states and, more importantly, opens the door to an emerging field of Network Physiology [4, 14], where recent developments uncover rich patterns in human physiology [8, 13, 17, 27, 31] and various clinical conditions [9, 19, 24, 25, 29]. Thus, the proposed Network Physiology approach [2, 15, 16], reveals fundamental new laws of physiologic regulation and can enhance our understanding of how behaviors and functions emerge at the organism level out of integrated network interaction among diverse systems.

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