Chapter 10
Network Physiology: Mapping Interactions Between Networks of Physiologic Networks

Plamen Ch. Ivanov and Ronny P. Bartsch

Abstract The human organism is an integrated network of interconnected and interacting organ systems, each representing a separate regulatory network. The behavior of one physiological system (network) may affect the dynamics of all other systems in the network of physiologic networks. Due to these interactions, failure of one system can trigger a cascade of failures throughout the entire network. We introduce a systematic method to identify a network of interactions between diverse physiologic organ systems, to quantify the hierarchical structure and dynamics of this network, and to track its evolution under different physiologic states. We find a robust relation between network structure and physiologic states: every state is characterized by specific network topology, node connectivity and links strength. Further, we find that transitions from one physiologic state to another trigger a markedly fast reorganization in the network of physiologic interactions on time scales of just a few minutes, indicating high network flexibility in response to perturbations. This reorganization in network topology occurs simultaneously and globally in the entire network as well as at the level of individual physiological systems, while preserving a hierarchical order in the strength of network links. Our findings highlight the need of an integrated network approach to understand physiologic function, since the framework we develop provides new information which can not be obtained by studying individual systems. The proposed system-wide integrative approach may facilitate the development of a new field, Network Physiology.

P. Ch. Ivanov (✉)
Department of Physics and Center for Polymer Studies, Boston University, Boston, MA, USA
e-mail: plamen@buphy.bu.edu

P. Ch. Ivanov
Institute of Solid State Physics, Bulgarian Academy of Sciences, 1784 Sofia, Bulgaria

P. Ch. Ivanov · R. P. Bartsch
Harvard Medical School and Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA, USA
e-mail: bartsch.ronny@gmail.com

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10.1 Introduction

In contrast to the unorthodox diagnostic approaches of the fictional character Dr. Gregory House from the acclaimed US TV-series "House" who, in a detective-like manner, considers a variety of interactions between multiple physiologic systems and variables to understand origins of symptoms in order to reach the right diagnosis, health care specialists traditionally focus on a single physiological system. Cardiologists mainly examine the heart and consider ECG signals; pulmonologists check lung structure and function and probe respiratory patterns; and brain neurologists study EEG. However, the human organism is an integrated network of interconnected and interacting physiologic organ systems, where each system is a multi-component structural and regulatory network. The complex behavior of one physiological system may be affected by changes in the dynamics of other systems in the physiologic network of organ networks. Due to these interactions, failure of one system may trigger a breakdown of the entire physiologic network.

Multiple organ failure is often the reason for fatal outcome in critical clinical care [1, 2]. In fact, multiple organ dysfunction remains a leading cause of death in most intensive care units. Clinical medicine offers support for specific organ systems that has proven necessary but often insufficient to promote recovery. If the links between physiological organ systems remain substantially altered, recovery is unlikely even when the structure and function of a specific failed system is restored after treatment. Indeed, autopsy findings in patients who succumb to multiple organ failure usually show that tissue architecture is preserved, cells do not appear abnormal and there is no widespread thrombosis. Nor does organ function appear to be irretrievably lost for patients who survived multiple organ failure [3]. This underscores the importance of identifying and quantifying the interactions between physiological organ systems, and how these interactions change under different physiologic states, pathologic conditions and with medical treatment. Further, medications developed to treat one physiological system often influence the function and have side effects on other systems. While some of the interactions between organ systems are partially known at the qualitative level, more precise quantitative estimates are important especially in the context of evaluating the proper medication dosage. Thus, the framework we propose to investigate a network of physiologic interactions between organ networks may help (i) to uncover new hitherto unknown links between organ systems, and (ii) to quantify the degree and strength of physiologic coupling and interactions, and how they change under various physiologic states and pathologic conditions.

A defining feature of physiological organ systems is their complexity. Decoding the remarkable range of behaviors of living systems in health and disease has emerged as a major focus of contemporary medicine. Physiological systems under neural regulation exhibit nonstationary, intermittent, scale-invariant and nonlinear behaviors [4, 5]. Moreover, physiologic dynamics transiently change in time with different physiologic states and under pathologic conditions [6–8], in response to changes in the underlying control mechanisms. The structural and neuronal control networks that underlie each physiologic organ system lead to the the high degree of

complexity in the output signals of physiological systems. This complexity is further compounded by various coupling [9] and feedback interactions [10–12] among different systems, the nature of which is not well-understood. Quantifying these physiologic interactions is a challenge as one system may exhibit multiple simultaneous interactions with other systems where the strength of the couplings may vary in time.

Therefore, to understand physiologic function it is critical to identify the network of physiologic interactions, and to track its evolution under different physiologic states and pathological conditions. This enterprise requires collaboration among scientists with different backgrounds, and the need to foster multidisciplinary approaches to problems at the interface of physics and physiology. Modern methods of statistical physics and recent advances in the theory of complex networks have great potential to uncover and quantify the structural and dynamical characteristics of the physiologic network of organ networks. Here, we introduce a method to identify interactions between physiologic systems, and we propose an integrative approach to study the dynamical evolution of an entire network of physiologic interactions in relation to changes under different physiologic states.

The central task of statistical physics is to understand macroscopic phenomena that result from microscopic interactions among many individual components often driven by competing forces and nonlinear feedback mechanisms. This problem is akin to many investigations undertaken in physiology. In particular, physiological systems under neural regulation and their complex nonlinear interactions among each other are good candidates for a statistical physics approach, since (i) physiological systems include many individual components (nodes) connected through a network of nonlinear feedback interactions, as observed in certain physical systems, and (ii) each physiologic system has multiple simultaneous interactions with other systems, thus forming a network of physiologic networks.

Complex networks have attracted enormous attention in the past decade in various fields of application. However, despite the importance to physiology and medicine, the network of interactions between diverse vertically- and horizontally-integrated organ systems is not known. Dynamical networks of physiologic interactions are particularly challenging because most physiological systems are multiple component complex systems with their own regulatory mechanism, and their function is affected by various interactions with other systems and by their integration in the human organism. Furthermore, physiologic dynamics and interactions continuously change in time due to changes in physiologic conditions. Thus, most of the complexities encountered in many of the networks studied so far are simultaneously present in physiological networks.

The interdisciplinary field of Network Physiology bridges two active fields of modern science: (A) the physics of complex networks, and (B) the organization and control of integrated physiologic organ systems. There are several fundamental questions that are critical for the development of both fields:

(A) In the field of complex networks: (A.1) it remains an unsolved problem how to identify and quantify networks comprised of *diverse* systems with very different types of interactions; (A.2) the relation between network topology and function is

hypothesized but has not been demonstrated yet on real systems; (A.3) there are no studies on real networks evolving in time and undergoing topological phase transitions from one state to another, and (A.4) the relation of network topology to network robustness and to the propagation of cascades of failure. These questions are even more challenging for networks of networks, where each subnetwork is characterized by different topology and dynamics of interactions with other subnetworks.

(B) In the field of integrated physiology: (B.1) it is not known how different physiologic organ systems simultaneously interact as a network in the human body; (B.2) whether different physiologic states are characterized by distinct networks of physiologic interactions; (B.3) how transitions across physiologic and pathologic states lead to transitions in the strength of physiologic interactions and in physiologic network topology, and (B.4) quantitative knowledge of the critical zone of physiologic coupling between multiple organ systems is essential to predict disintegration of the physiologic network leading to multiple organ failure and other pathologies.

10.2 Complex Networks Approach to Physiologic Interactions

Research in statistical physics of networks has identified networks with complex topologies [13, 14], and has focused on the role of topology for network function and robustness [15–17], on the evolution of network topology under varied conditions [18], emergence of self-organization and complex network behavior out of simple interactions [19], and more recently on critical transitions due to failure in the coupling of interdependent networks [20]. Recent advances in complex networks theory are of relevance to a broad range of real systems including industrial [20, 21], transportation [22, 23] and communication networks [24], food and ecological webs [19], financial systems and social interactions [21, 25–29] as well as biological systems at the microscopic level such as genetic and protein-interaction networks [30], biochemical [31], metabolic [32] and cell signaling networks [33]. However, understanding the relation between topology and dynamics of complex networks remains a challenge, especially when (i) the network evolves with links created or lost in time, (ii) links between different nodes have different functional form and strength/weight which change over time and (iii) network nodes are of different kind with different dynamical properties and types of links [34, 35]. A further challenge to the contemporary theoretical framework of complex networks is posed by real-world systems where each network node represents a multicomponent complex system, a network on its own, with its own topology and regulatory mechanism that can vary in time, and where the transient output dynamics of individual networks affect the entire "network of networks" by reinforcing (or weakening) the coupling between individual networks and changing network topology. A prime example of a network of networks is the human organism, where integrated physiologic systems, each representing a complex network, form a network of interactions that in turn affect physiologic function of individual systems or of the entire organism, and

where breakdown in the interaction between physiological systems under certain conditions may lead to a cascade of system failures [1, 2].

Physiological systems exhibit remarkable dynamic complexity where transient changes in the underlying control mechanisms associated with different physiologic states and conditions lead both to changes in their individual output characteristics as well as in their interactions [6, 36–46]. Here, we introduce a framework to study the network of interactions between physiological systems, and we focus on the topology and dynamics of this network and their relevance to physiologic function. We hypothesize that during a given physiologic state the physiologic network of organ networks may be characterized by a specific topology. Further, we hypothesize that even for networks with relatively stable topology associated with specific physiologic states, the coupling strength between physiologic systems may change in time due to the inherent variability in the regulation and output of these systems. Moreover, coupling strength and physiologic network topology may change with transition from one physiologic state to another, where physiologic interactions (network links) are established or lost leading to a completely new network configuration. Such transitions may also be associated with changes in the connectivity of specific network nodes, i.e., the number of systems to which a given physiologic system is connected can change, forming sub-networks of physiologic interactions. Thus, probing physiologic network connectivity and the stability of physiologic coupling may provide new insights on integrated physiologic function.

10.3 Time Delay Stability and Network of Physiologic Interactions

We introduce the concept of time delay stability (TDS) to identify and quantify dynamic links among physiological systems. The framework we propose allows (i) to quantify the topology and global dynamics of physiologic networks, taking into account the output of individual physiologic systems as well as the interactions among them, and (ii) to track the dynamical evolution of multiple interconnected systems undergoing transitions from one physiologic state to another (Fig. 10.1). We construct a network of interactions for an ensemble of key integrated physiologic systems (cerebral, cardiac, respiratory, ocular and muscle activity). We consider different sleep stages (deep, light, REM sleep and quiet wake) as examples of physiologic states. We demonstrate that sleep stages are associated with markedly different networks of physiologic interactions (Fig. 10.2) characterized by different number and strength of links (Fig. 10.3), and by specific node connectivity (Fig. 10.6). In particular, during deep sleep we find a much lower number of links in the physiologic network compared to light sleep (Figs. 10.2 and 10.3)—individual physiologic systems, such as the cardiac, are highly connected to other systems during light sleep while there are practically no TDS links during deep sleep (Fig. 10.6). Furthermore, the network links are much weaker during deep compared to light sleep (Figs. 10.3d

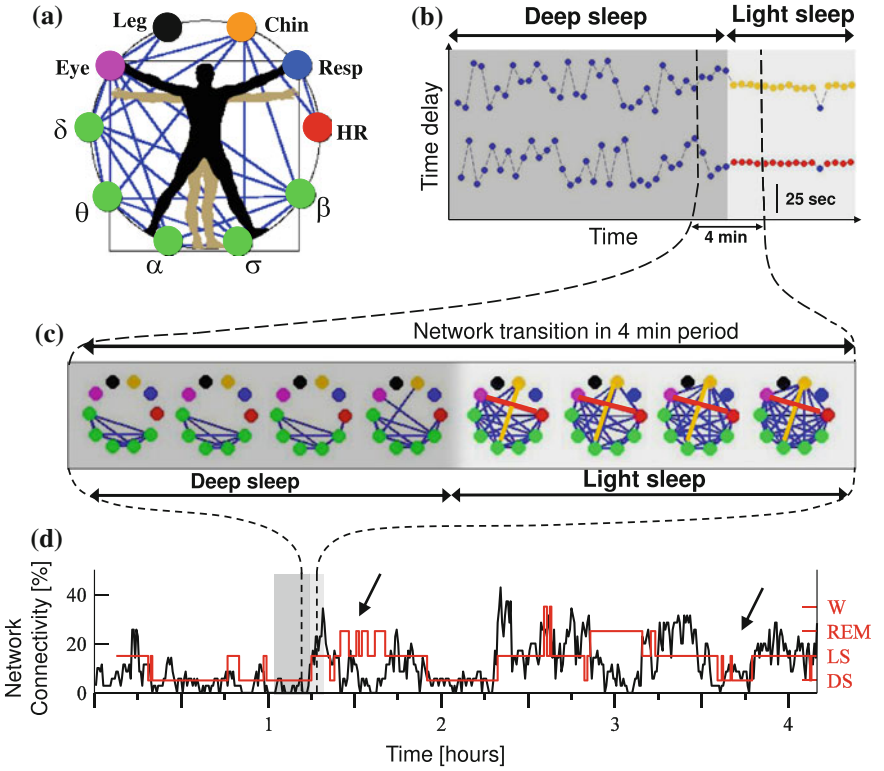

Fig. 10.1 Transitions in the network of physiologic interactions. **a** Dynamical network of interactions between physiological systems where ten network nodes represent six physiologic systems—brain activity (EEG waves: δ, θ, α, σ, β), cardiac (HR), respiratory (Resp), chin muscle tone, leg and eye movements. **b** Transition in the interactions between physiological systems across sleep stages. The time delay between two pairs of signals, (*top*) α-brain waves and chin muscle tone, and (*bottom*) HR and eye movement, quantifies their physiologic interaction: highly irregular behavior (*blue dots*) during deep sleep is followed by a period of time delay stability during light sleep indicating a stable physiologic interaction (*red dots* for the HR-eye and *orange dots* for the α-chin interaction). **c** Transitions between physiologic states are associated with changes in network topology: snapshots over 30 s windows during a transition from deep sleep (*dark gray*) to light sleep (*light gray*). During deep sleep the network consists mainly of brain-brain links. With transition to light sleep links between other physiologic systems (network nodes) emerge and the network becomes highly connected. The stable α-chin and HR-eye interactions during light sleep in (**b**) are shown by an *orange* and a *red* network link respectively. **d** Physiologic network connectivity for one subject during night sleep calculated in 30 s windows as the fraction (%) of present links out of all possible links. *Red line* marks sleep stages as independently scored in a sleep lab. Low connectivity is consistently observed during deep sleep (0:30–1:15 and 1:50–2:20 h) and REM sleep (1:30–1:45 and 2:50–3:10 h), while transitions to light sleep and wake are associated with a significant increase in connectivity [47]

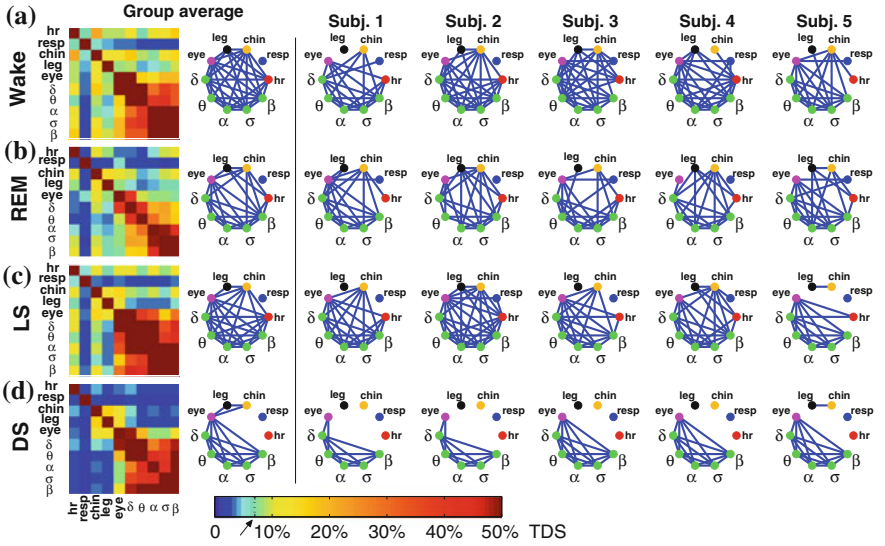

Fig. 10.2 Network connectivity across sleep stages. Group-averaged time delay stability (*TDS*) matrices and related networks of physiologic interactions during different sleep stages. Matrix elements are obtained by quantifying the TDS for each pair of physiologic systems after obtaining the weighted average of all subjects in the group. *Color code* represents the average strength of interaction between systems quantified as the fraction of time (out of the total duration of a given sleep-stage throughout the night) when TDS is observed. The physiologic network exhibits transitions across sleep stages—lowest number of links during deep sleep, higher during REM and highest during light sleep and quiet wake—a behavior observed in the group-averaged network as well as for each subject. Network topology also changes with sleep-stage transitions: from predominantly brain-brain links during deep sleep to a high number of brain-periphery and periphery-periphery links during light sleep and wake

and 10.5a). Traditionally, differences between sleep stages are attributed to modulation in the sympatho-vagal balance with dominant sympathetic tone during wake and REM [48]: spectral, scale-invariant and nonlinear characteristics of the dynamics of individual physiologic systems indicate higher degree of temporal correlations and nonlinearity during wake and REM compared to NREM (light and deep sleep) where physiologic dynamics during exhibit weaker correlations and loss of nonlinearity [6, 45]. In contrast, the network of physiologic interactions shows a completely different picture: the network characteristics during light sleep are much closer to those during wake and very different from deep sleep (Figs. 10.2 and 10.3). Specifically, network connectivity and overall strength of physiologic interactions are significantly higher during wake and light sleep, intermediate during REM and much lower during deep sleep. Thus, our empirical observations indicate that while sleep-stage related modulation in sympatho-vagal balance plays a key role in regulating individual physiologic systems, it does not fully account for the physiologic network topology and dynamics across sleep stages, showing that the proposed framework captures principally new information.

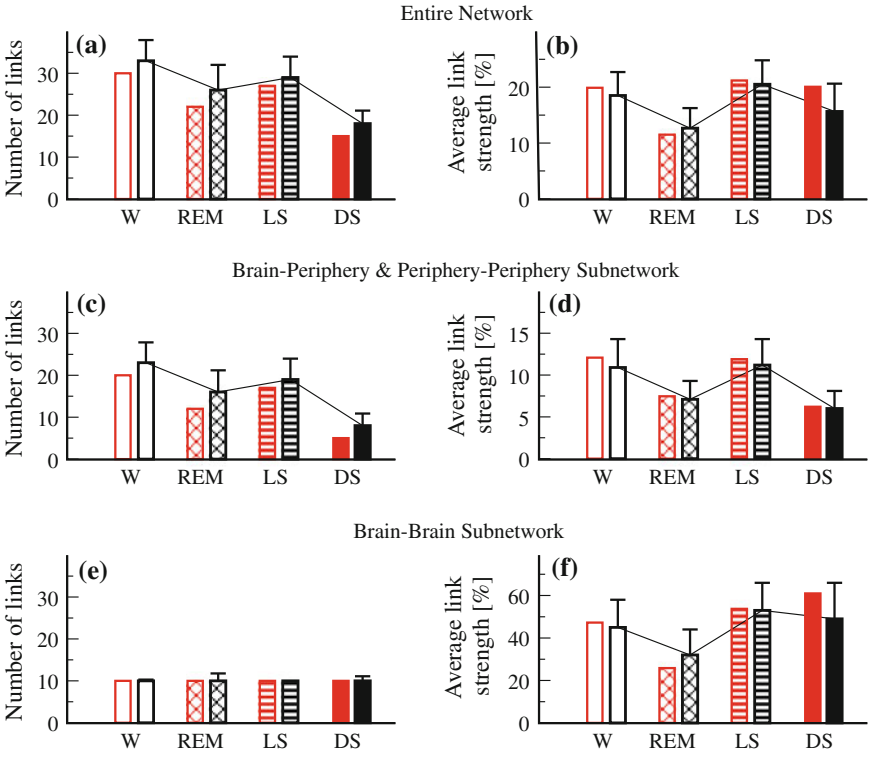

Fig. 10.3 Sleep-stage stratification pattern in network connectivity and network link strength. Group-averaged number of links (**a**) and averaged link strength (**b**) are significantly higher during wake and light sleep compared to REM and deep sleep. There is no significant difference between wake and light sleep. This pattern is even more pronounced for the subnetwork formed by the brain-periphery and periphery-periphery links shown in (**c**) and (**d**). In contrast, the number of brain-brain links remains practically unchanged with sleep-stage transitions (**e**), and the average brain-brain link is $\approx$5 times stronger in all sleep stages compared to the other network links (**f**). The group-averaged patterns in the number of network links and in the average link strength across sleep stages (*black bars*) are consistent with the behavior observed for individual subjects (*red bars* in all panels represent the same subject). The average link strength represents the average strength of all links in a network obtained from a given subject during a specific sleep stage which then is averaged over all subjects. Error bars indicate standard deviation

To quantify the interaction between physiologic systems and to probe how this interaction changes in time under different physiologic conditions we study the time delay with which modulations in the output dynamics of a given physiologic system are consistently followed by corresponding modulations in the signal output of another system. Periods of time with approximately constant time delay indicate a stable physiologic interaction, and stronger coupling between physiologic systems results in longer periods of time delay stability (TDS). The TDS method is general, and can be applied to diverse systems. It is more reliable in identifying physio-

logic coupling compared to traditional cross-correlation and cross-coherence analyses (Fig. 10.7) which are not suitable for heterogeneous and nonstationary signals, and are affected by the degree of auto-correlations in these signals [49]. Utilizing the TDS method we build a dynamical network of physiologic interactions, where network links between physiological systems (considered as network nodes) are established when the time delay stability representing the coupling of these systems exceeds a significance threshold level, and where the strength of the links is proportional to the percentage of time when time delay stability is observed. This dynamic network approach provides an integrated view of the simultaneous interactions of multiple physiologic systems, where transient changes in physiologic conditions of the human organism are reflected in continuous fluctuations in the strength of network links, variations in the connectivity of individual network nodes, and emergence or loss of specific links in response to changes in physiologic function—all leading to transitions in network topology.

10.4 Transitions in Network Topology with Physiologic Function

We apply this new approach to a group of young subjects with continuously recorded multi-channel physiologic data during sleep which allows us to track the dynamics and evolution of the network of physiologic interactions during different sleep stages and sleep-stage transitions (Fig. 10.1). We focus on physiologic dynamics during sleep since sleep stages are well-defined physiological states, and external influences due to physical activity or sensory inputs are reduced during sleep. While earlier studies have identified how sleep regulation influences aspects of the specific control mechanism of individual physiologic systems (e.g., cardiac or respiratory [6, 7, 45, 48]), the dynamics and topology of an entire physiologic network have not been studied so far. Utilizing sleep data as an example we demonstrate that a network approach to physiologic interactions is necessary to understand how modulations in the regulatory mechanism of individual systems translate into reorganization of physiologic interactions across the human organism.

We find that the network of interactions between physiologic systems is very sensitive to sleep-stage transitions. In a short time window of just a few minutes the network topology can dramatically change—from only a few links to a multitude of links (Fig. 10.1c)—indicating transitions in the global interconnectivity between physiological systems. These network transitions are not associated with random occurrence or loss of links but are characterized by certain organization in network topology where given links between physiological systems remain stable during the transition while others do not—e.g., brain-brain links persist during the transition from deep to light sleep while brain-periphery links significantly change (Fig. 10.1c). Further, we find that sleep-stage transitions are paralleled by abrupt jumps in the total number of links leading to higher or lower network connectivity (Fig. 10.1c, d). However, even during stable physiologic conditions within a specific sleep stage, the network of physiologic interactions does not remain static and undergoes continuous dynamical changes with small fluctuations in the number of network links. These

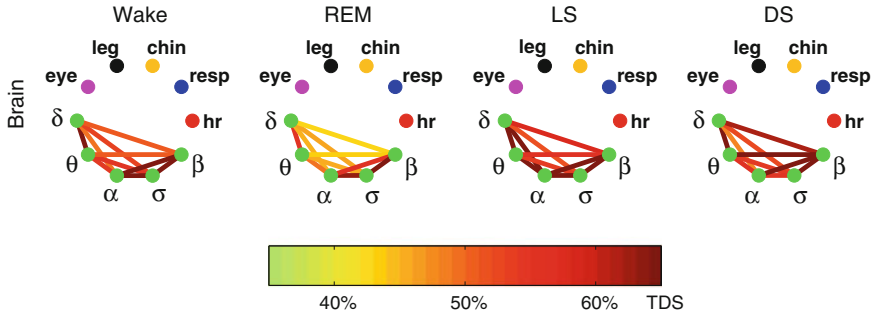

Fig. 10.4 Network connectivity and link strength of the brain-brain subnetwork for different sleep stages. While the topology of the brain subnetwork does not change, the strength of network links significantly changes with strongest links during light sleep and deep sleep (*brown* and *dark red color*), intermediate during wake (*red* and *orange color*) and weakest links during REM sleep (*yellow color*)

network dynamics are observed for each subject in the database, where consecutive episodes of sleep stages (scored from standard polysomnographic recordings) are paralleled by a level of connectivity specific for each sleep stage, and where sleep-stage transitions are consistently followed by transitions in network connectivity throughout the course of the night. Indeed, the network of physiologic interactions exhibits a remarkable responsiveness as network connectivity changes even for short sleep-stage episodes (Fig. 10.1d).

To identify the characteristic network topology for each sleep stage we obtain group-averaged time delay stability matrices, where each matrix element represents the percentage of time with stable time delay between two physiological systems, estimated over all episodes of a given sleep stage throughout the night. Matrix elements with values above a threshold of statistical significance determined by surrogate analysis, indicate stable interactions between physiologic systems represented by network links (Fig. 10.2). We find that matrix elements greatly vary for different sleep stages with much higher values for wake and light sleep, lower values for REM and lowest for deep sleep. This is correspondingly reflected in higher network connectivity for wake and light sleep, lower connectivity for REM and significantly reduced number of links during deep sleep (Fig. 10.3a). Further, the time delay stability matrices indicate separate subgroups of interactions between physiologic systems—brain-periphery, periphery-periphery and brain-brain interactions—which are affected differently during sleep stages and form different sub-networks. Specifically, matrix elements representing interactions between peripheral systems (cardiac, respiratory, chin, eye, leg) and the brain as well as interactions among the peripheral systems are very sensitive to sleep-stage transitions, leading to networks of very different topology for different sleep stages (Fig. 10.2). We find sub-networks with high number of brain-periphery and periphery-periphery links during wake and light sleep, lower number of links during REM and a significant reduction of links at

deep sleep (Fig. 10.3c). In contrast, matrix elements representing brain-brain interactions form a subnetwork with the same number of brain-brain links (Fig. 10.3e), and stable topology consistently present in the physiologic network during all sleep stages (Fig. 10.2). These sleep-stage related transitions in network connectivity and topology are not only present in the group-averaged data but also in the physiologic networks of individual subjects, suggesting universal behavior (Fig. 10.2). Notably, we find a higher number of brain-periphery links during REM compared to deep sleep despite inhibition of motoneurons in the brain leading to muscle atonia during REM [50]. Further, the empirical observations of significant difference in network connectivity and topology during light sleep compared to deep sleep are surprising, given the similarity in the output dynamics of physiologic systems during light and deep sleep [6, 7, 45, 48] (both stages traditionally classified as NREM), and indicate that previously unrecognized aspects of sleep regulation may be involved in the control of physiologic network interactions.

10.4.1 Physiologic States and Network Link Strength Stratification

Networks with identical connectivity and topology can exhibit very different strength of their links. We find that not only network connectivity but also the average strength of network links changes with sleep-stage transitions: network links are significantly stronger during wake and light sleep compared to REM and deep sleep—a pattern similar to the behavior of the network connectivity across sleep stages (Fig. 10.3a, b). Further, subgroups of physiologic interactions exhibit different relationship between their respective subnetwork connectivity and the average link strength. Specifically, the subnetwork of brain-periphery and periphery-periphery interactions is characterized by significantly stronger links (and also higher connectivity) during wake and light sleep, and much weaker links (with lower network connectivity) during deep sleep and REM (Fig. 10.3c, d). In contrast, the subnetwork of brain-brain interactions exhibits very different patterns for the connectivity and the average link strength—while the group average subnetwork connectivity remains constant across sleep stages, the average link strength varies with highest values during light and deep sleep and a dramatic $\approx$40 % decline during REM. The observation of significantly stronger links in the brain-brain subnetwork during NREM compared to REM sleep is consistent with the characteristic of NREM as EEG-synchronized sleep and REM as EEG-desynchronized sleep [50]. During NREM sleep adjacent cortical neurons fire synchronously with a relatively low frequency rhythm [51] leading to coherence between frequency bands in the EEG signal, and thus to stable time delays and strong network links (Fig. 10.3f and 10.4). In contrast, during REM sleep cortical neurons are highly active but fire asynchronously [51] resulting in weaker links (Fig. 10.3f and 10.4). Our findings of stronger links in the brain-brain subnetwork during NREM indicate that bursts in the spectral power of one EEG-frequency band are consistently synchronized in time with bursts in a different EEG-frequency band, thus leading to periods of longer time delay stability. This can explain some seemingly surprising

network links—for example, we find a strong link between α and δ brain activity during NREM sleep (Fig. 10.2) although α waves are greatly diminished and δ waves are dominant [50]. Since the spectral densities of both waves are normalized before the TDS analysis, the presence of a stable α–δ link indicates that a relative increase in the spectral density in one wave is followed with a stable time delay by a corresponding increase in the density of the other wave—an intriguing physiologic interaction which persists not only during deep sleep but is also present in light sleep, REM and quiet wake (Fig. 10.2). Notably, the average link strength of the brain-brain subnetwork is by a factor of 5 higher compared to all other links in the physiologic network (Fig. 10.3d, f).

Our finding that after averaging over all links in the physiologic network the resulting average link strength exhibits a specific stratification pattern across sleep stages, with strongest links during light sleep and wake, and weaker links during deep sleep and REM (Fig. 10.3), raises the question whether the underlying distribution of the network links strength is also sleep-stage dependent. To this end and to probe the relative strength of individual links we obtain the rank distribution of the strength of the brain-periphery and periphery-periphery network links for each sleep stage averaged over all subjects in the group (Fig. 10.5a). The link strength shown in the rank plots in Fig. 10.5a is determined by the degree of time delay stability, quantified as the fraction of time when TDS is observed. We find that the rank distribution corresponding to deep sleep is vertically shifted to much lower values for the strength of the network links, while the rank distribution for light sleep and wake is for all links consistently higher than the distribution for REM. Thus, the sleep-stage stratification pattern we find for the average strength of the network links (Fig. 10.3d) originates from the systematic change in the strength of individual network links with sleep-stage transitions as demonstrated by the rank analysis. Notably, although the strength of individual network links changes significantly with sleep stages, the rank order of the links does not significantly change. Remarkably, after rescaling the rank distributions for all sleep stages, we find that they collapse to two distinct functional forms: (i) a slow and smoothly decaying rank distribution for REM and wake, and (ii) a much faster decaying rank distribution for deep sleep and light sleep with a characteristic plateau in the mid rank range indicating a cluster of links with similar strength (Fig. 10.5b). Despite the similarity in the functional form of the distributions and in the rank order in the strength of individual network links, our analyses show a significant difference in the average strength of network links during deep sleep compared to light sleep and REM compared to wake (Fig. 10.3d).

10.4.2 Local Topology and Connectivity of the Physiologic Network

Our observations that physiologic networks undergo dynamic transitions where key global properties such as network connectivity and average link strength significantly change with sleep-stage transitions following a robust stratification pattern, raise the question whether local topology and connectivity of individual network nodes also

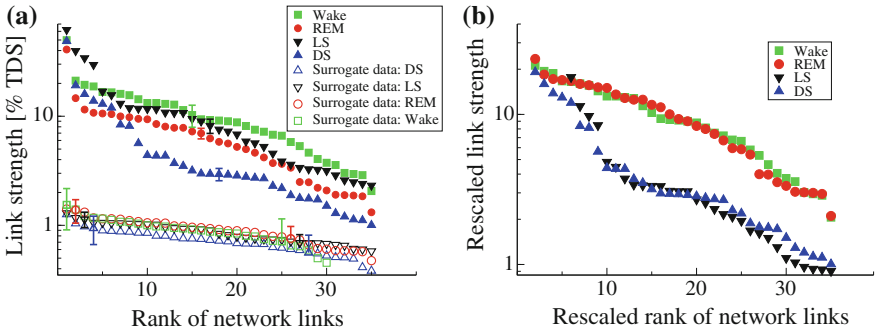

Fig. 10.5 Rank distributions of the strength of network links. Group-averaged strength of individual physiologic network links for different sleep stages. Rank 1 corresponds to the strongest link in the network, i.e., highest degree of time delay stability (*TDS*) (shown are all periphery-periphery and brain-periphery links). **a** The rank distributions for different sleep stages are characterized by different strength of the network links—consistently lower values for most links during deep sleep, higher values during REM and highest during light sleep and wake, indicating that the stratification pattern in Fig. 10.3d is present not only for the average link strength (when averaging over different types of links in the network) but also for the strength of individual links. Indeed, links from all ranks are consistently stronger in light sleep compared to deep sleep and REM: such rank-by-rank comparison of links across sleep stages is possible because the rank order of the links does not change significantly from one sleep stage to another. A surrogate test based on TDS analysis of signals paired from different subjects, which eliminates endogenous physiologic coupling, leads to significantly reduced link strength ($p < 10^{-3}$) and close to uniform rank distributions with no difference between sleep stages (*open symbols*), indicating that the TDS method uncovers physiologically-relevant information. Error bars indicate standard error. **b** Rescaling the plots reveals two distinct forms of rank distributions: a slow decaying distribution for wake and REM, and a fast decaying distribution for light sleep and deep sleep with a pronounced plateau in the middle rank range corresponding to a cluster of links with similar strength, most of which related to the cardiac system

change during these transitions. Considering each physiologic system (network node) separately, we examine the number and strength of all links connecting the system with the rest of the network. For example, we find that the cardiac system is highly connected to other physiologic systems in the network during wake and light sleep (Fig. 10.6). In contrast, during deep sleep we do not find statistically significant time delay stability in the interactions of the cardiac system, which is reflected by absence of cardiac links (Fig. 10.6). Further, we find that the average strength of the links connected to the cardiac system also changes with sleep stages: stronger interactions (high % TDS) during wake and light sleep and significantly weaker interactions below the significance threshold during deep sleep (Fig. 10.6). Such 'isolation' of the cardiac node from the rest of the network indicates a more autonomous cardiac function during deep sleep—also supported by earlier observations of breakdown of long-range correlations and close to random and more linear behavior in heartbeat intervals in this sleep stage [6]. With transition to light sleep, REM and wake where the average link strength and connectivity of the cardiac system is significantly higher, indicating increased interactions with the rest of the network that lead to cor-

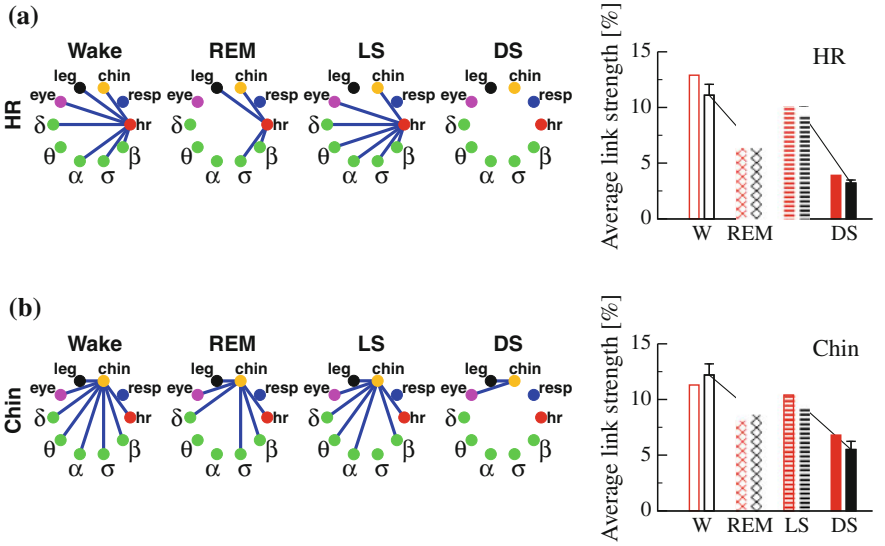

Fig. 10.6 Transitions in connectivity and link strength of individual network nodes across sleep stages. The number of links to specific physiologic systems (network nodes) significantly changes, with practically no links during deep sleep, a few links during REM and much higher connectivity during light sleep and wake. Notably, the average strength of the links connecting a given network node is also lowest during deep sleep and highest during light sleep and wake. Shown are connectivity and average link strength for two network nodes, heart and chin. This sleep-stage stratification pattern in individual physiologic system (node) connectivity and in the average strength of the links connecting a specific network node is consistent with the transitions of the entire network across sleep stages shown in Fig. 10.3. Networks for heart and chin are obtained by averaging the corresponding networks for all subjects. During deep sleep no links to the heart are shown since the strength of each link averaged over all subjects is below the significance threshold. *Right bars* in the panels represent for different sleep stages the group mean of the average strength of network links connecting heart and chin respectively, and error bars show the standard deviation. *Left bars* represent an individual subject

respondingly higher degree of correlations and nonlinearity in cardiac dynamics [6]. Similarly, respiratory dynamics also exhibit high degree of correlations during REM and wake, lower during light sleep and close to random behavior during deep sleep [45]. Such transitions in the number and strength of links across sleep stages we also find for other network nodes (for example chin, Fig. 10.6). Moreover, the sleep-stage stratification pattern in connectivity and average link strength for individual network nodes (Fig. 10.6) is consistent with the pattern we observe for the entire network (Fig. 10.3). Our findings of significant reduction in the number and strength of brain-periphery and periphery-periphery links in the corresponding sub-networks during deep sleep indicate that breakdown of cortical interactions, previously reported during deep sleep [52], may also extend to other physiologic systems under neural regulation. Indeed, the low connectivity in the physiologic network we find in deep sleep may explain why people awakened during deep sleep do not adjust immediately

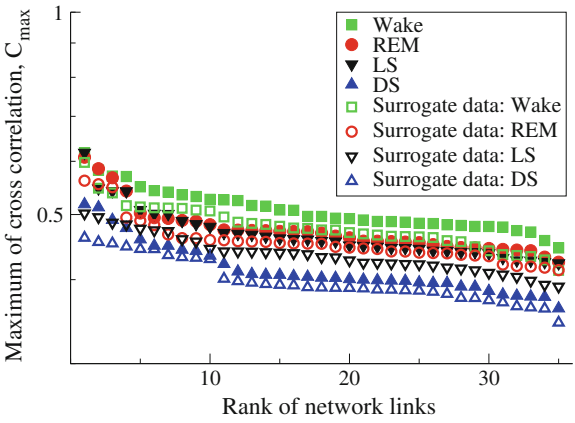

Fig. 10.7 Cross-correlation and surrogate analysis. Rank plots obtained from cross-correlation analysis show no statistically significant differences between real and surrogate data, indicating that cross-correlation is not a reliable measure to identify physiologic interactions

and often feel groggy and disoriented for a few minutes. This effect is not observed if subjects are awakened from light sleep when we find the physiologic network to be highly connected (Fig. 10.2). Further, the fact that deep sleep in primates dominates at the beginning of the night and not close to dawn, when many large predators preferably hunt, may have been evolutionarily advantageous.

Introducing a framework based on the concept of TDS we identify a robust network of interactions between physiologic systems, which remains stable across subjects during a given physiologic state. Further, changes in the physiologic state lead to complex network transitions associated with a remarkably structured reorganization of network connectivity and topology that simultaneously occurs in the entire network as well as at the level of individual network nodes, while preserving the hierarchical order in the strength of individual network links. Such network transitions lead to the formation of sub-networks of physiologic interactions with different topology and dynamical characteristics. In the context of sleep stages, network transitions are characterized by a specific stratification pattern where network connectivity and link strength are significantly higher during light compared to deep sleep and during wake compared to REM. This can not be explained by the dynamical characteristics of the output signals from individual physiologic systems which are similar during light and deep sleep as well as during wake and REM. The observed stability in network topology and rank order of links strength during sleep stages, and the transitions in network organization across sleep stages provide new insight into the role which individual physiologic systems as well as their interactions play during specific physiologic states. We note that traditional methods based on cross-correlation or cross-coherence analysis lead to spurious detection of interrelations and coupling in signals of different origin and with different autocorrelations, and fail to identify and quantify a the network of physiologic interactions (Fig. 10.7). While we

demonstrate one specific application, the framework we develop can be applied to a broad range of complex systems where the TDS method can serve as a tool to characterize and understand the dynamics and function of real-world heterogeneous and interdependent networks.

10.5 Summary

We introduce a new framework to investigate a network of interactions between complex physiological systems, each representing a separate regulatory network. This proves useful to uncover key aspects of physiologic dynamics and coupling in the context of the integrated function of diverse physiological systems in the human organism, and may facilitate novel theoretical approaches to study dynamical processes on networks of networks. These investigations constitute a first step in the development of a new field we call Network Physiology.

Specifically:

1. This is the first study of a network comprised of diverse complex systems.
   Earlier studies have focused on networks where (i) all nodes are of the same type, and (ii) network links are static and do not change in time. This is not the case in many real networks. Further, such "idealized" networks can not exhibit transitions in topology, and thus do not allow investigation of key questions such as the relation between network topology and function.
   Quantifying networks comprised of different types of nodes, where the nodes are not identical and simple units, but represent complex multi-component dynamical systems with their own regulatory mechanisms, is a major challenge which has not been addressed so far. The reason that network interactions between such complex systems have not been studied is that different types of systems have output signals with very different characteristics, which can also change in time. Thus, current methods tailored to probe the interaction/coupling between two similar systems do not work for a pair of different systems. This is a strong limitation when studying real-world networks.
   To overcome this limitation we developed a framework, based on a novel concept of time delay stability (TDS), to probe interactions among diverse systems by quantifying interrelations between their transient signal outputs. Utilizing this new approach we identify a dynamic network that represents the global behavior of a group of complex systems (networks) even when the links between these systems are not a-priori known. Our approach is general, and can be applied to many real dynamical systems and networks.
2. We present the first physiologic network. Specifically, we identify and quantify a network of interactions between key integrated physiologic systems: cerebral, cardiac, respiratory, ocular and motor system. These are diverse and complex systems, with their own regulatory neuronal networks, and with very different types of output signals.

This discovery provides a first dynamical map of the human organism as an integrated network of interacting physiological systems. Utilizing the physiologic network we can track how the behavior of one organ system can be affected by changes in the dynamics of other systems. Further, this approach allows to estimate whether, under certain conditions, failure of one system may trigger a breakdown of the entire network of physiologic systems. This network information is critical to understand physiologic function and uncovers new aspects of the mechanisms of physiologic regulation, and cannot be obtained by traditional studies focusing on individual systems.

The new physiologic information we obtain is relevant and may be utilized for clinical applications in critical care units, in situations of multiple organ failure, or in assessing side effects of pharmacological treatment when targeting a specific system may also affect other systems via the network of physiologic interactions.

3. Of importance to complex networks, we show that there is a robust interplay between network topology and function. In network theory it is hypothesized that network function is influenced by network structure, however, examples on real networks did not exist prior to these investigations.

   We demonstrate that each physiologic state is associated with a specific network of physiologic interactions that is characterized by a given topology, node connectivity, number and strength of network links. A similar network topology and strength of network links is consistently observed for individual subjects in the same physiologic state, indicating *universal* behavior.

   In particular, relating physiologic function to network topology we show that during deep sleep several integrated systems (e.g., cardiac, respiratory and brain) act as if disconnected from each other. This is a principally new information, which can explain (i) why earlier studies have found that correlations and scaling properties in heartbeat intervals break down and exhibit close to random behavior during deep sleep (as it would be the case of a denervated heart), and (ii) why people awakened during deep sleep do not adjust immediately and often feel groggy and disoriented for a few minutes.

   Since specific mechanisms regulate physiologic function during each physiologic state, our observations provide a first empirical evidence on a real network of a robust relation between network structure and function.

4. We identify phase transitions in network topology. There is no precedent of such behavior. We quantify the process of transition by tracking the network evolution in time.

   We find that with transition from one physiologic state to another (for example across sleep stages), network topology dramatically changes within a short time window of 2–3 min—from only a few links to a multitude of links—indicating a remarkable flexibility in the interaction between physiologic systems in response to change in physiologic regulation. Such change in network structure in response to change in the mechanisms of control during different physiologic states indicates that our findings reflect *intrinsic* features of physiologic interaction.

   Further, we find that transitions from one physiologic state to another trigger a remarkably-structured reorganization of physiologic interactions. This

reorganization occurs simultaneously and globally in the entire network as well as at the level of individual network nodes (physiologic systems), while preserving a hierarchical order in the strength of network links.

Although our study is limited to a data-driven approach the empirical findings may facilitate future efforts on developing and testing network models of physiologic interactions. In relation to critical clinical care, where multiple organ failure is often the reason for fatal outcome [1, 2], our framework may have practical utility in assessing whether dynamical links between physiological systems remain substantially altered even when the function of specific systems is restored after treatment [3]. While we demonstrate one specific application, the framework we developed can be applied to a broad range of complex systems where the TDS method can serve as a tool to characterize and understand the dynamics and function of real-world heterogeneous and interdependent networks. The established relation between dynamical network topology and network function has not only significant medical and clinical implications, but is also of relevance for the general theory of complex networks, including the emerging field of networks of networks.

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