

# Physiologic Network Interactions: Novel Hallmark for Physiologic State and Function

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**Keck Laboratory for Network Physiology, Boston University  
and  
Division of Sleep Medicine  
Brigham and Women's Hospital & Harvard Medical School**

**BOSTON  
UNIVERSITY**

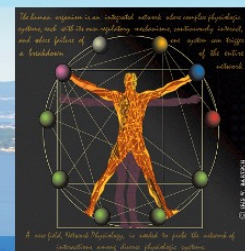


**HARVARD  
MEDICAL SCHOOL**



**Third International Summer Institute  
on Network Physiology (ISINP)**

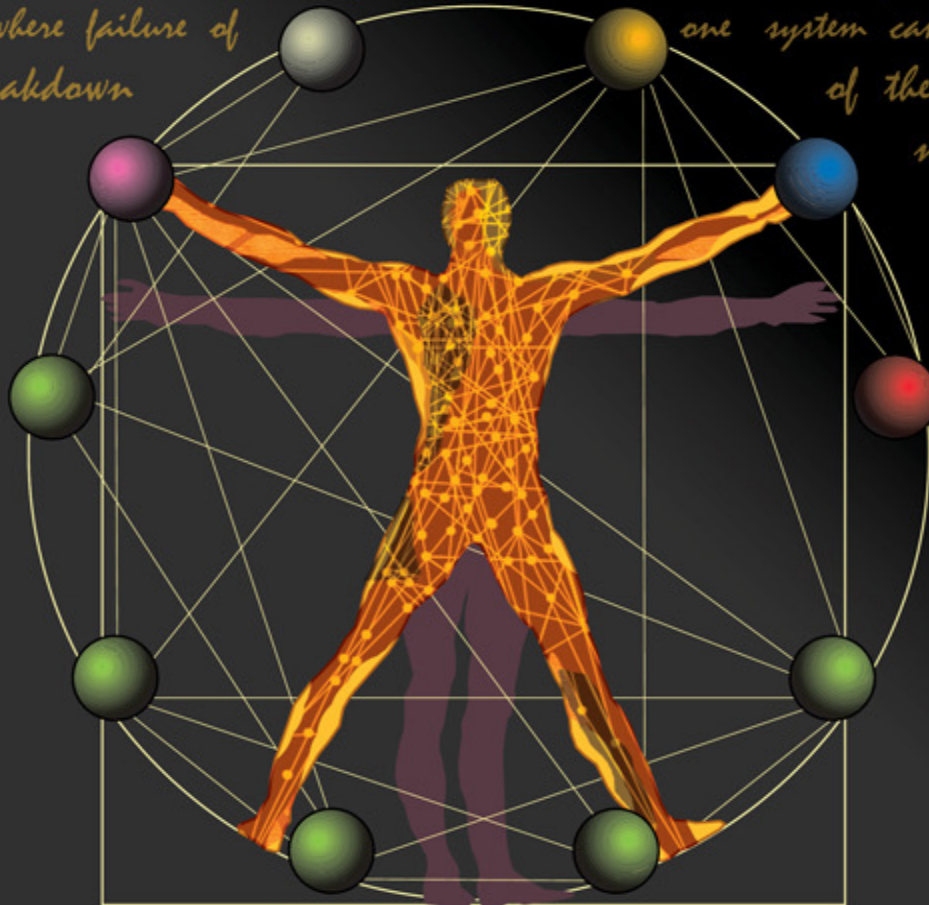
Lake Como School of Advanced Studies, 24 - 29 July 2022



## Our Research Program

# New Research Direction: Shifting the focus from single organ systems to the network of organ interactions

*The human organism is an integrated network where complex physiologic systems, each with its own regulatory mechanisms, continuously interact, and where failure of one system can trigger a breakdown of the entire network.*



*A new field, Network Physiology, is needed to probe the network of interactions among diverse physiologic systems.*

*A new field*

**Network Physiology**

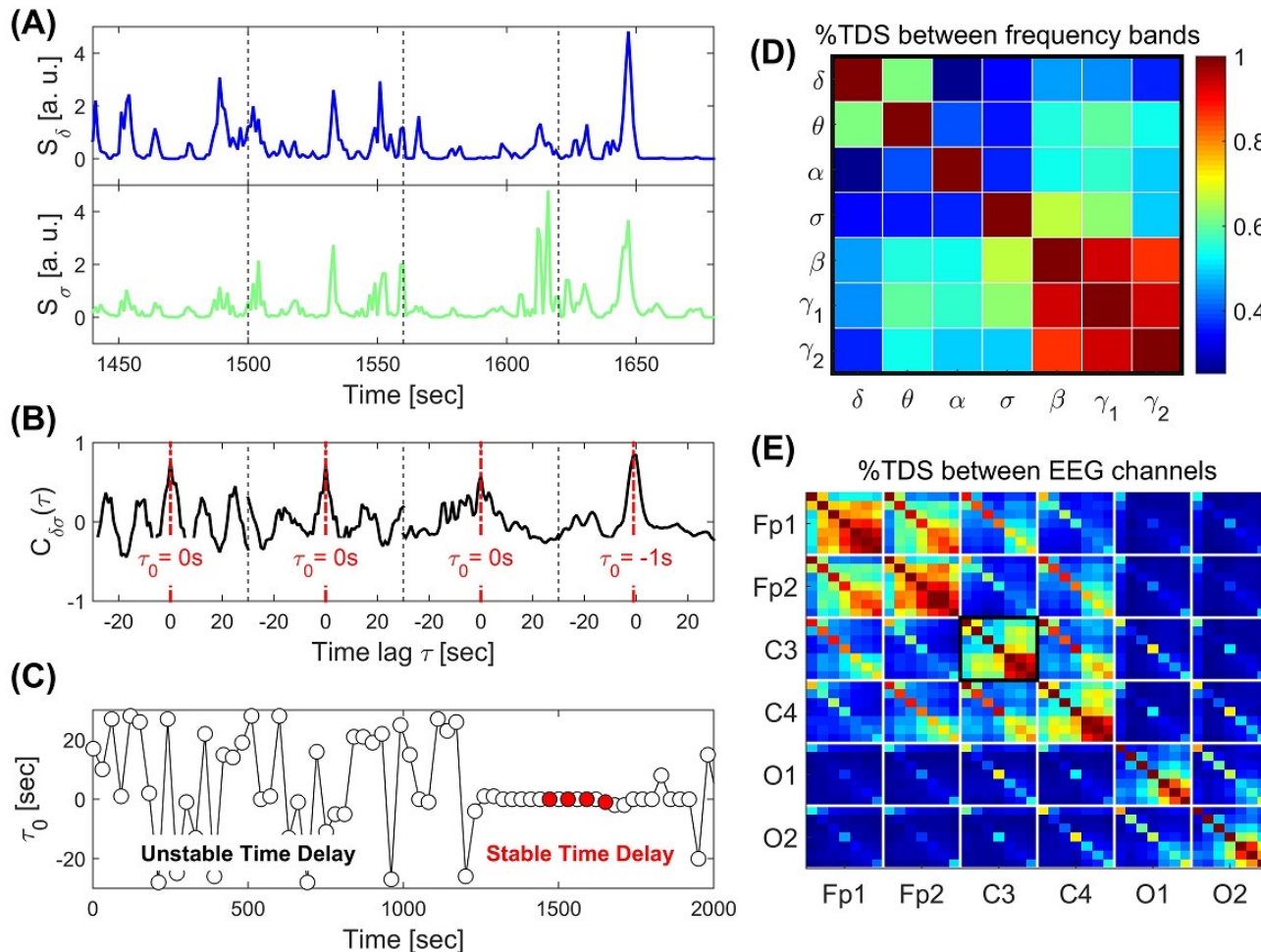
*needed to probe interactions among diverse physiologic systems.*

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Level 3:  
Networked  
Interactions

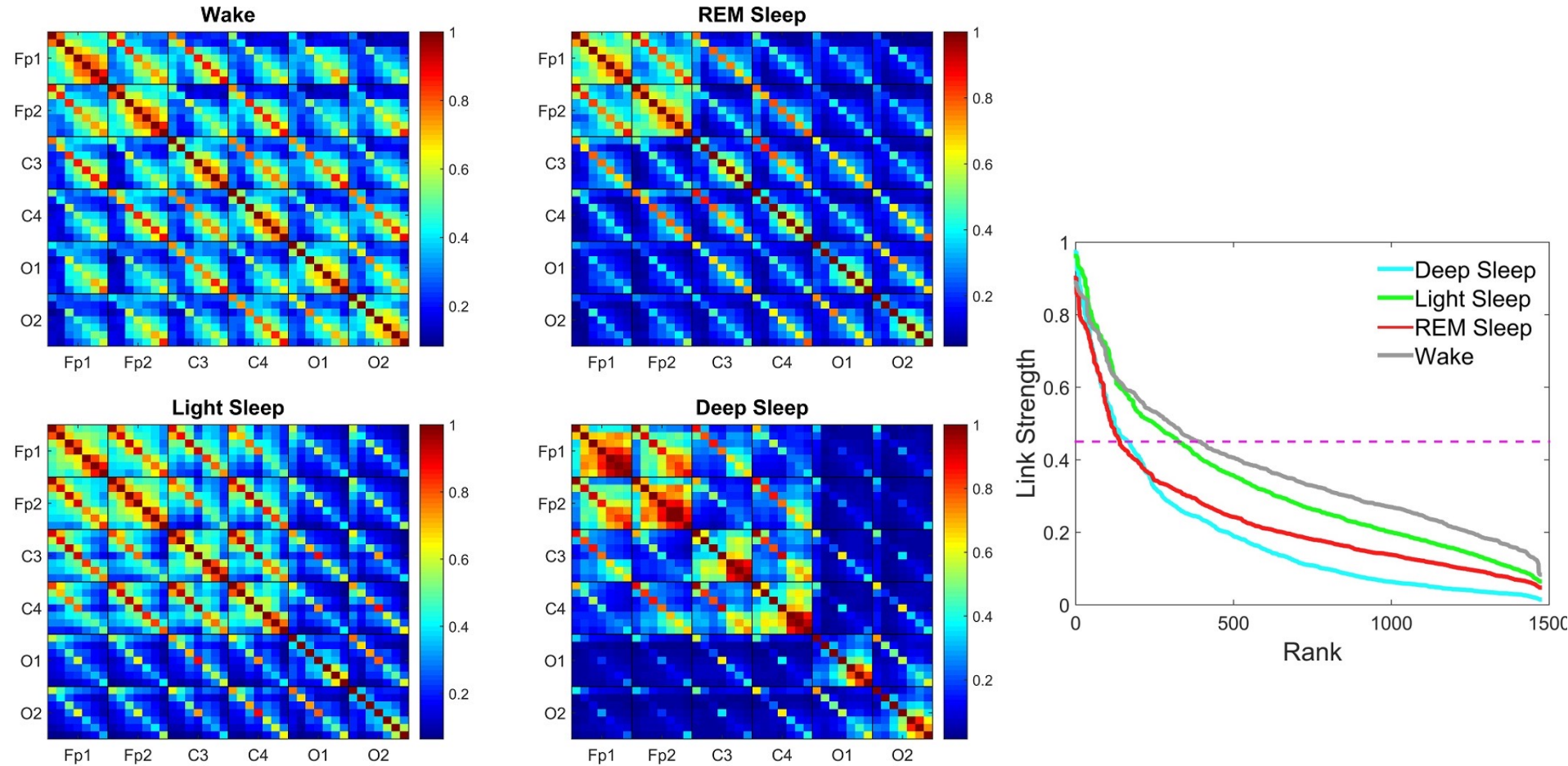
# Network Physiology: Implications for brain dynamics and neural plasticity

**Key question:** How brain rhythms dynamically communicate to facilitate physiologic states and functions?



### Level 3: Networked Interactions

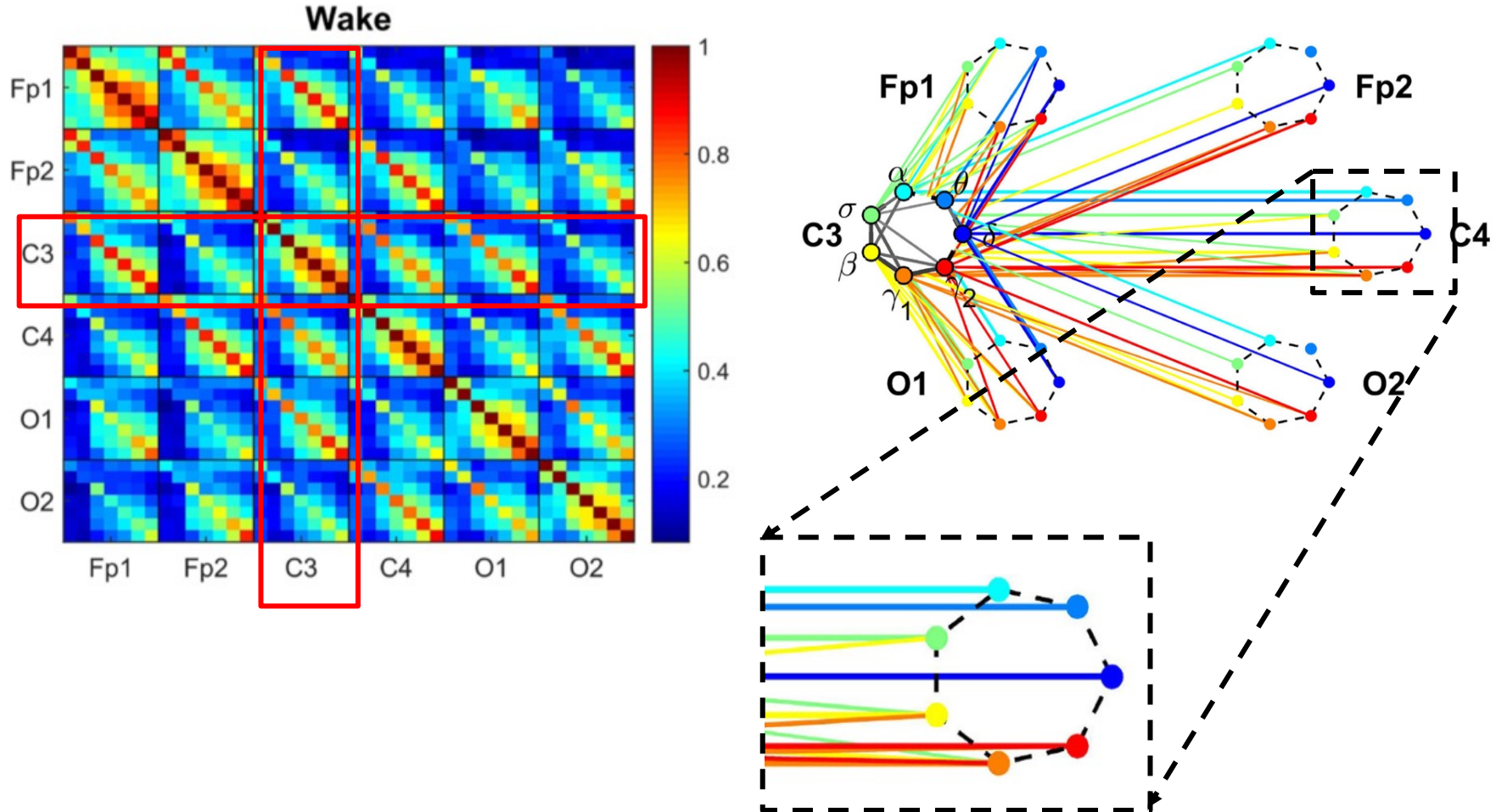
# Network Physiology: Networks of brain activity across sleep stages



Liu KKL, Bartsch RP, Lin A, Mantegna RN and Ivanov PCh (2015)

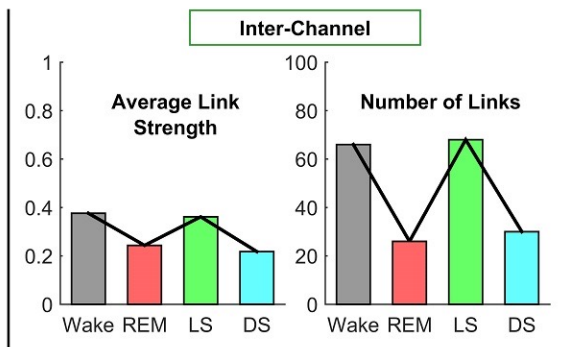
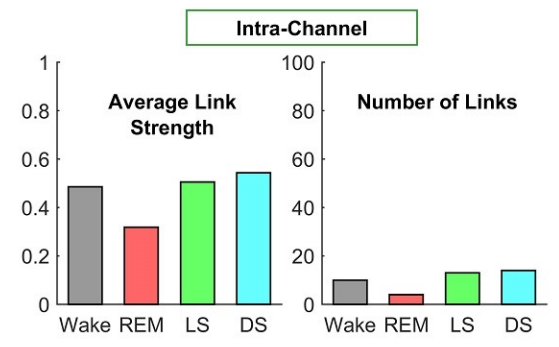
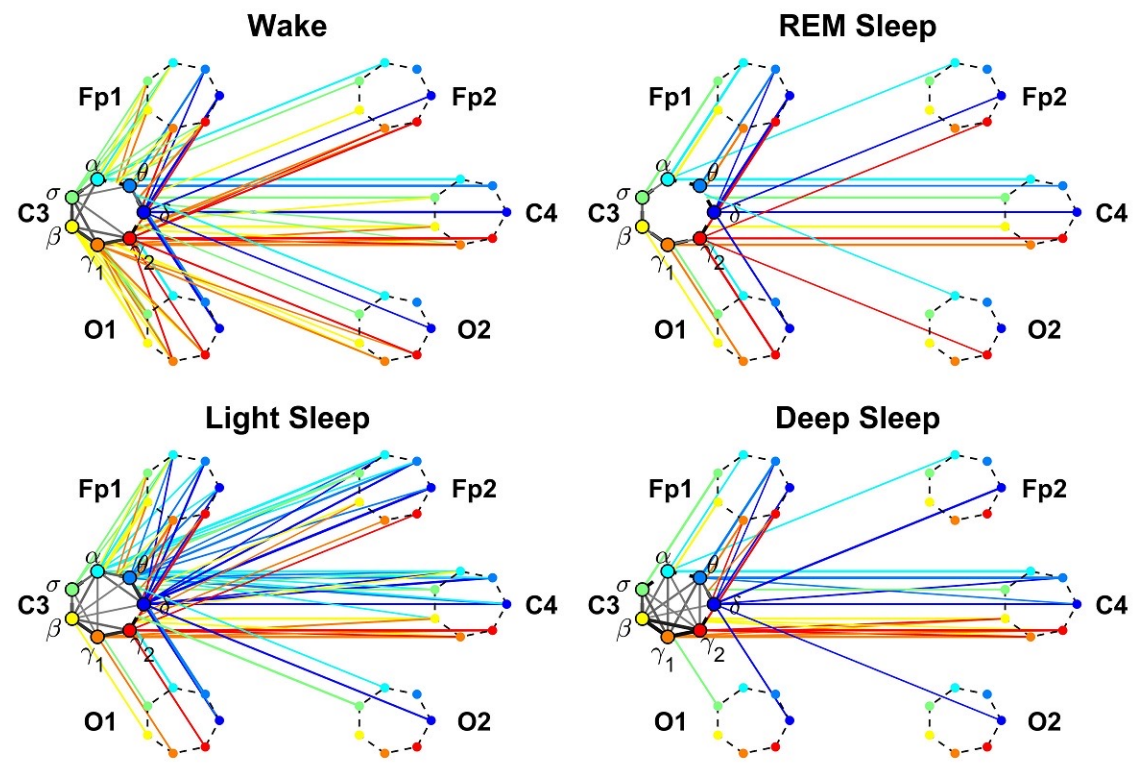
Plasticity of brain wave network interactions and evolution across physiologic states. *Front. Neural Circuits* 9:62.

## Visualization of channel specific sub-network



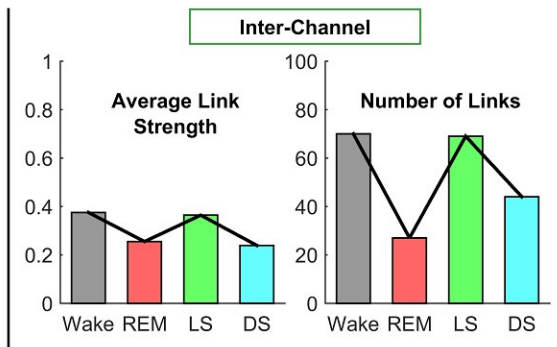
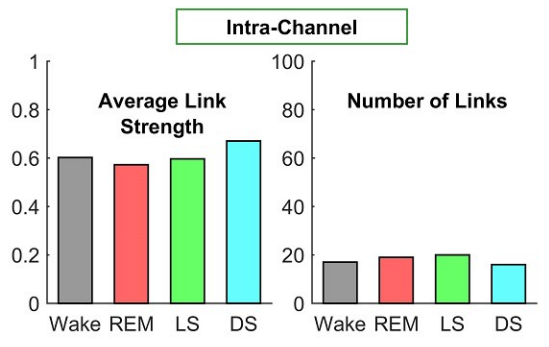
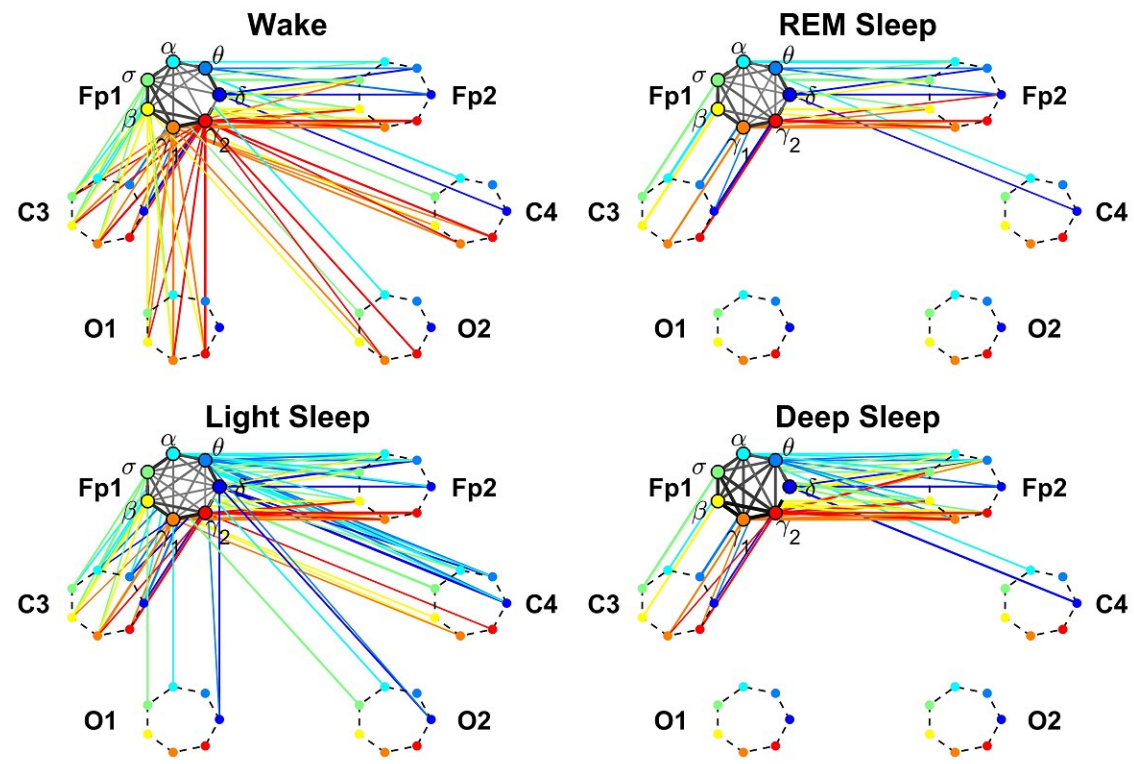
**Level 3:  
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Interactions**

# Neural Plasticity of Individual Brain Areas: Central Channel C3



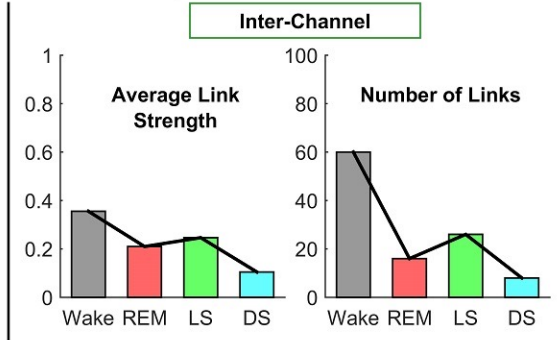
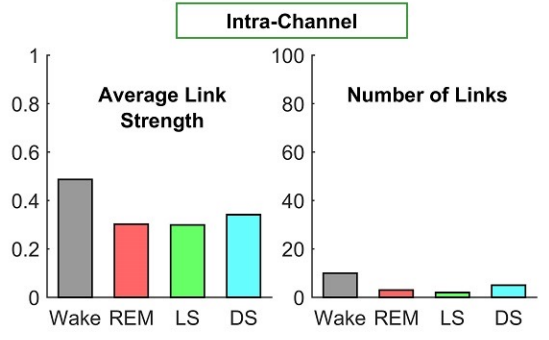
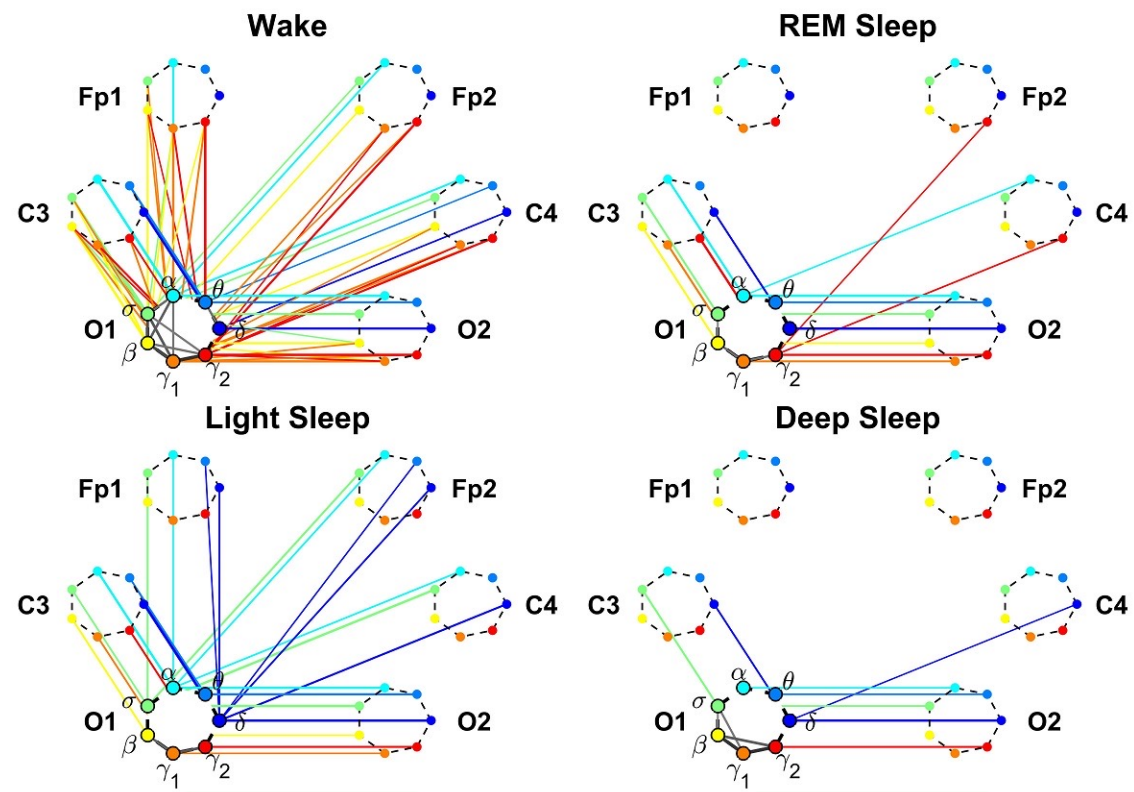
**Level 3:  
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# Neural Plasticity of Individual Brain Areas: Frontal Channel Fp1



**Level 3:  
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Interactions**

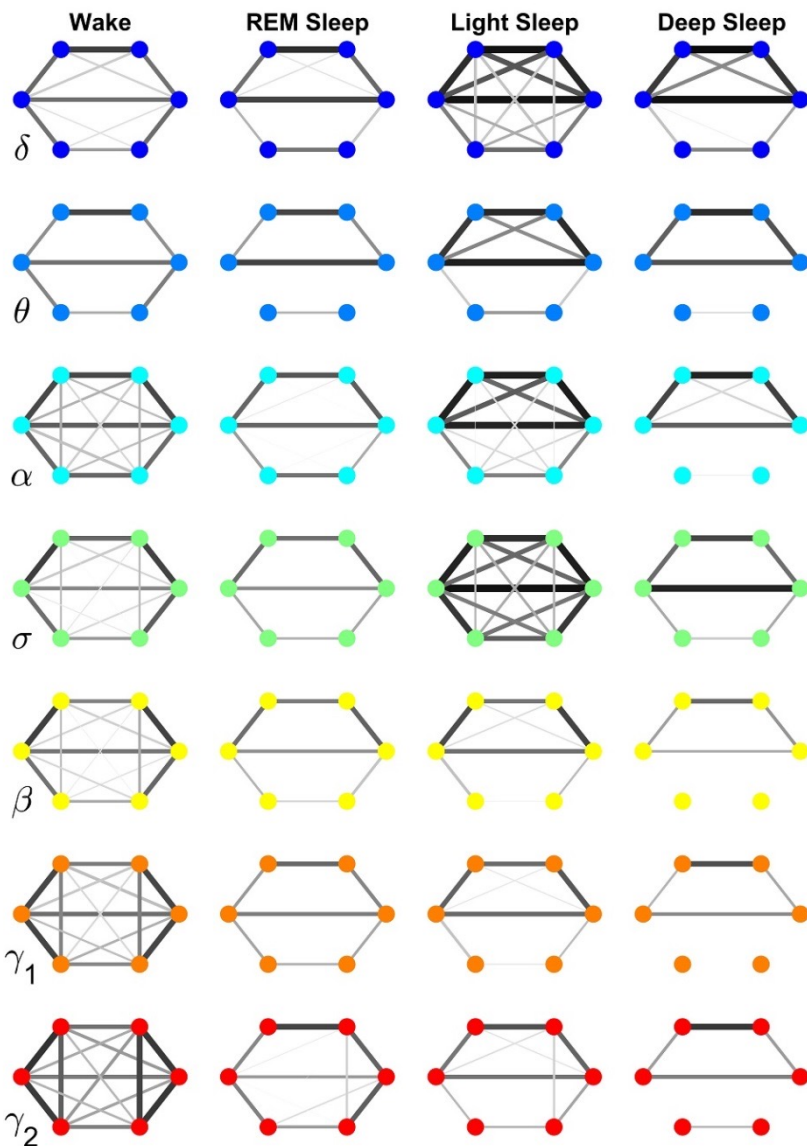
# Neural Plasticity of Individual Brain Areas: Occipital Channel O1



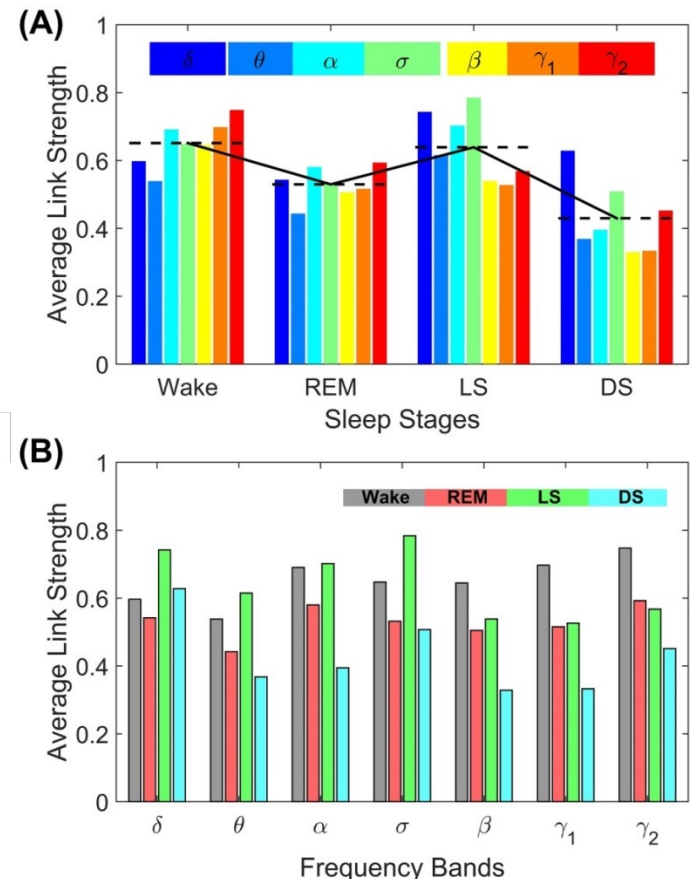


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Interactions**

# Brain-Wave Network Interactions: Frequency Specific Networks



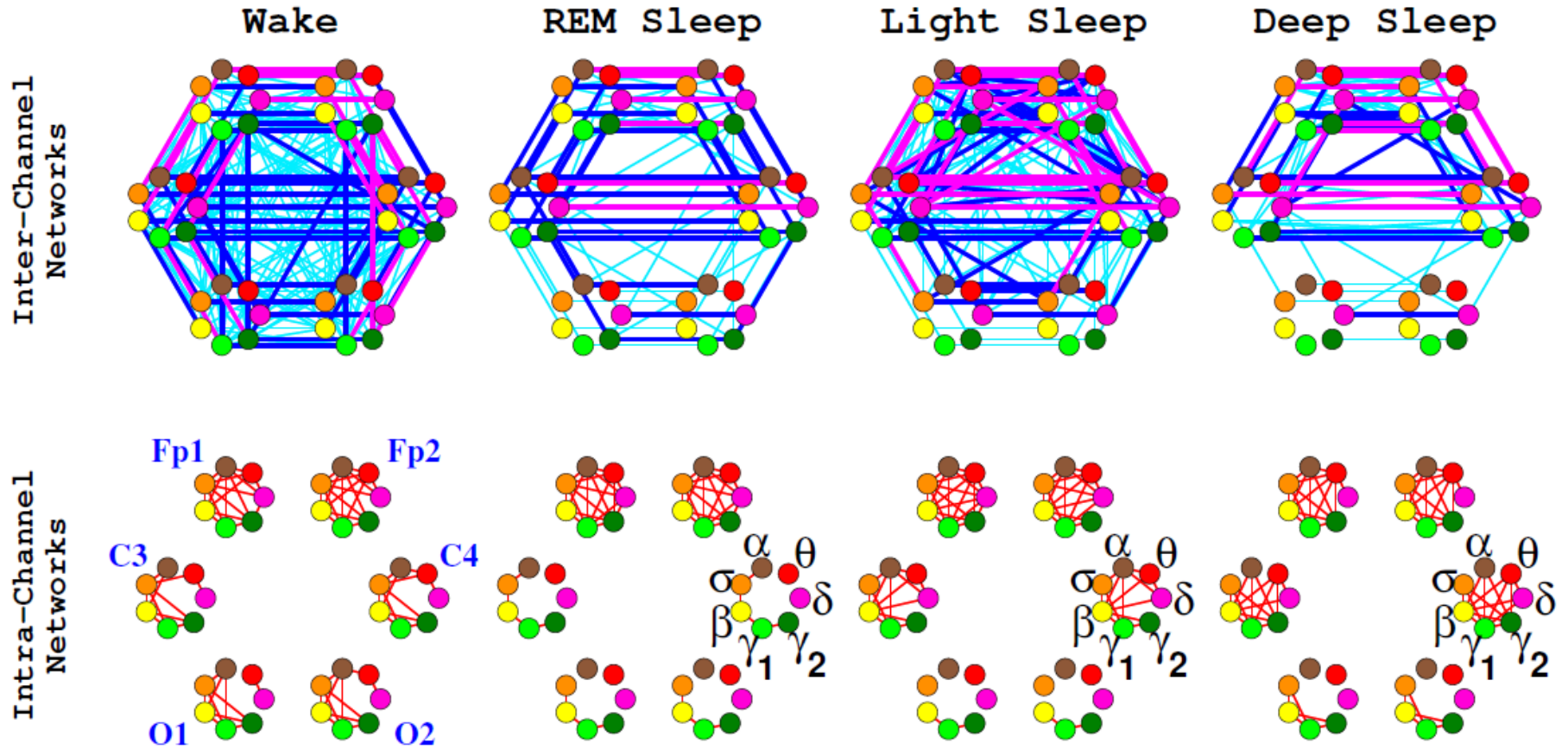
Functional network of brain waves coordination



**Plasticity of individual brain rhythms:  
complex transitions in frequency-specific  
networks across physiologic states**

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Interactions

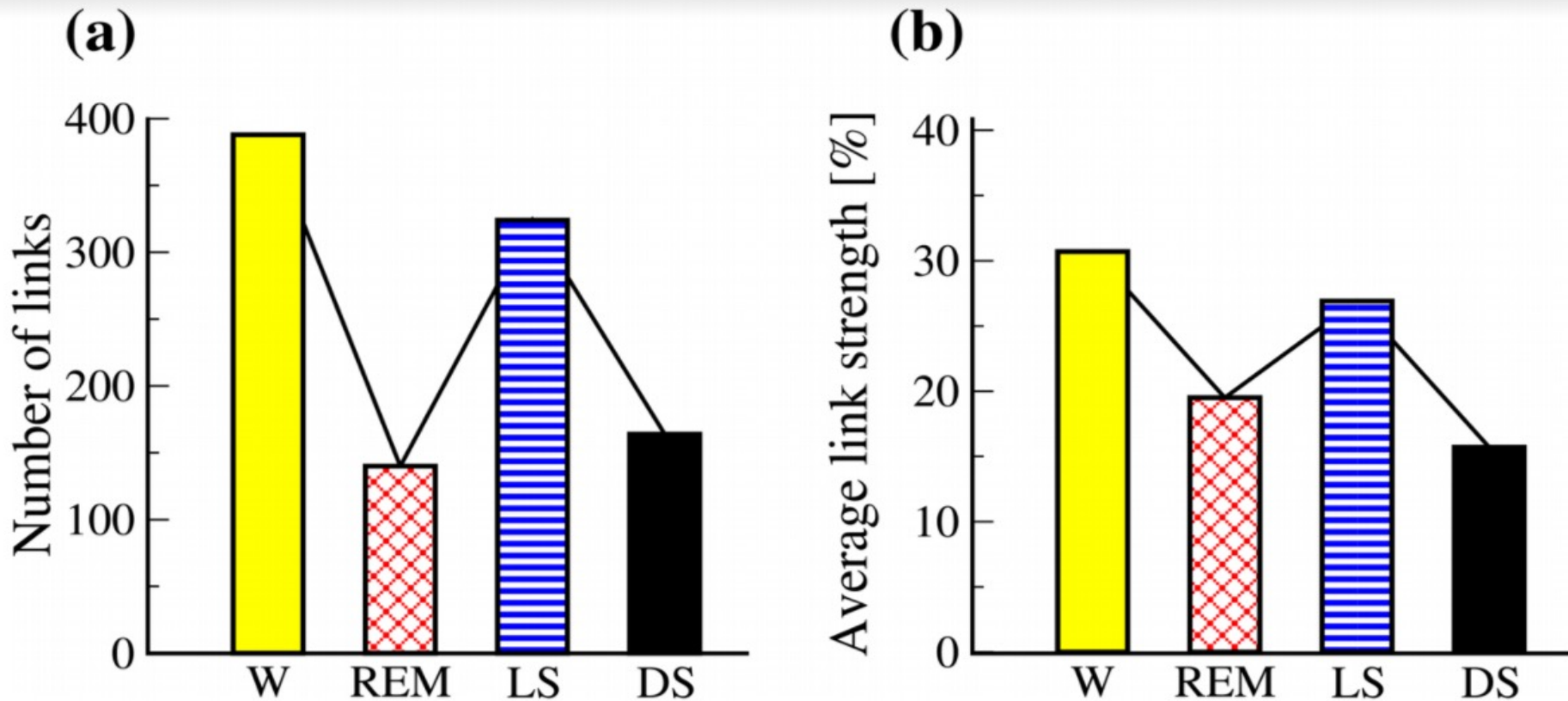
# Network Physiology: Implications for brain dynamics and neural plasticity



Phase transition in link strength and network topology

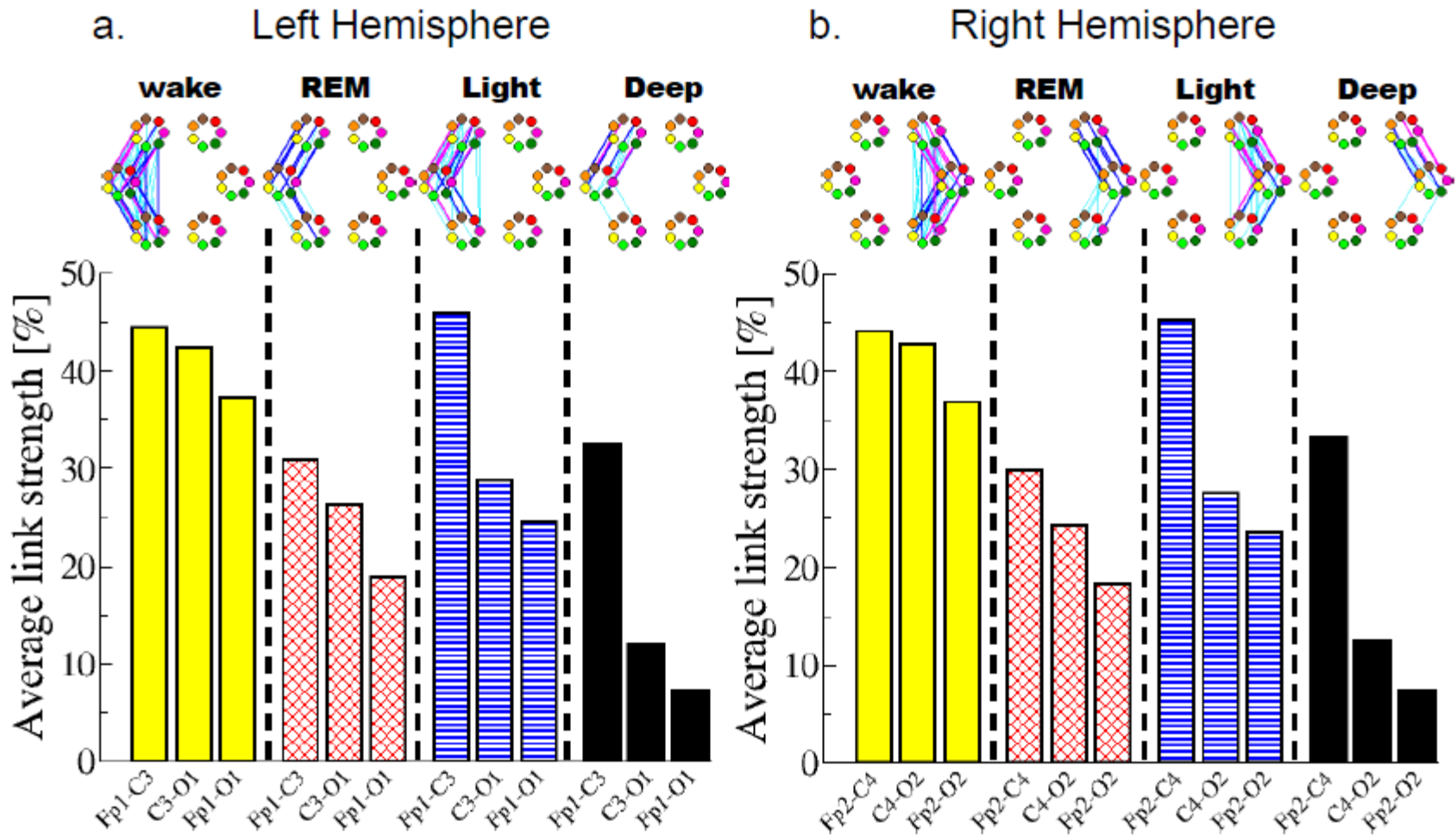
# Network Physiology: Implications for brain dynamics and neural plasticity

## Brain-Brain Interactions

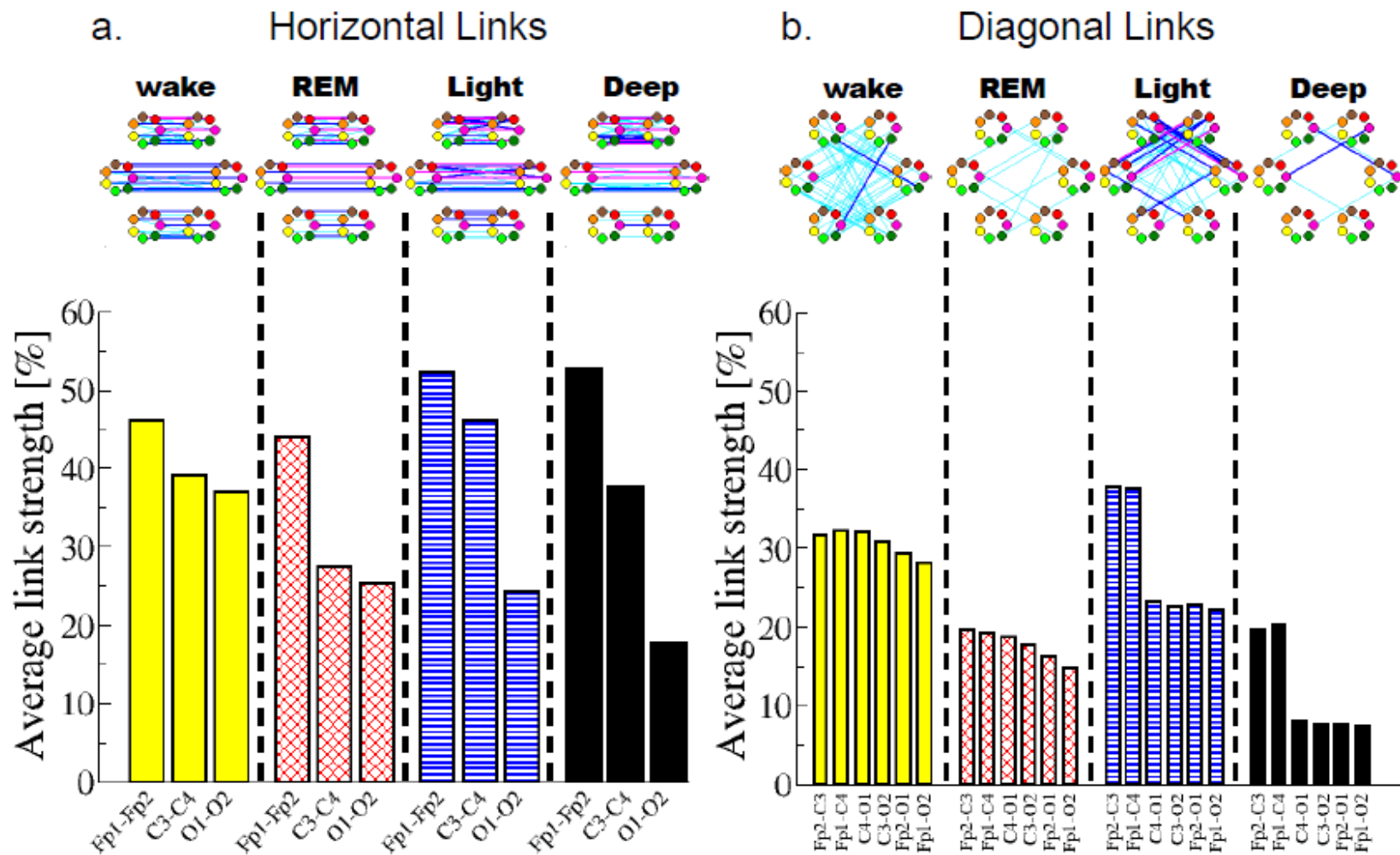


Phase transition in link strength and network topology

## Links within Brain Hemispheres

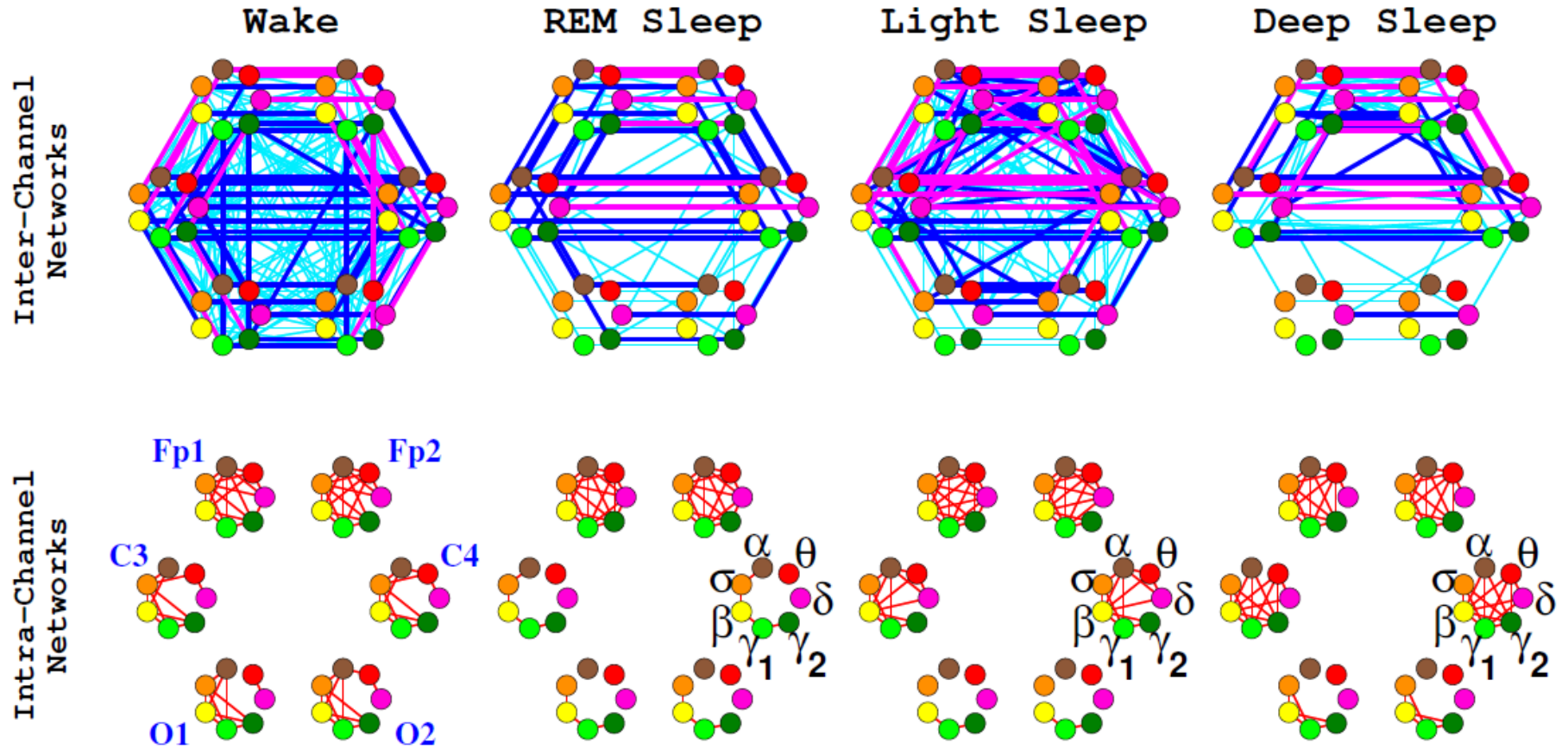


## Links across Brain Hemispheres



Level 3:  
Networked  
Interactions

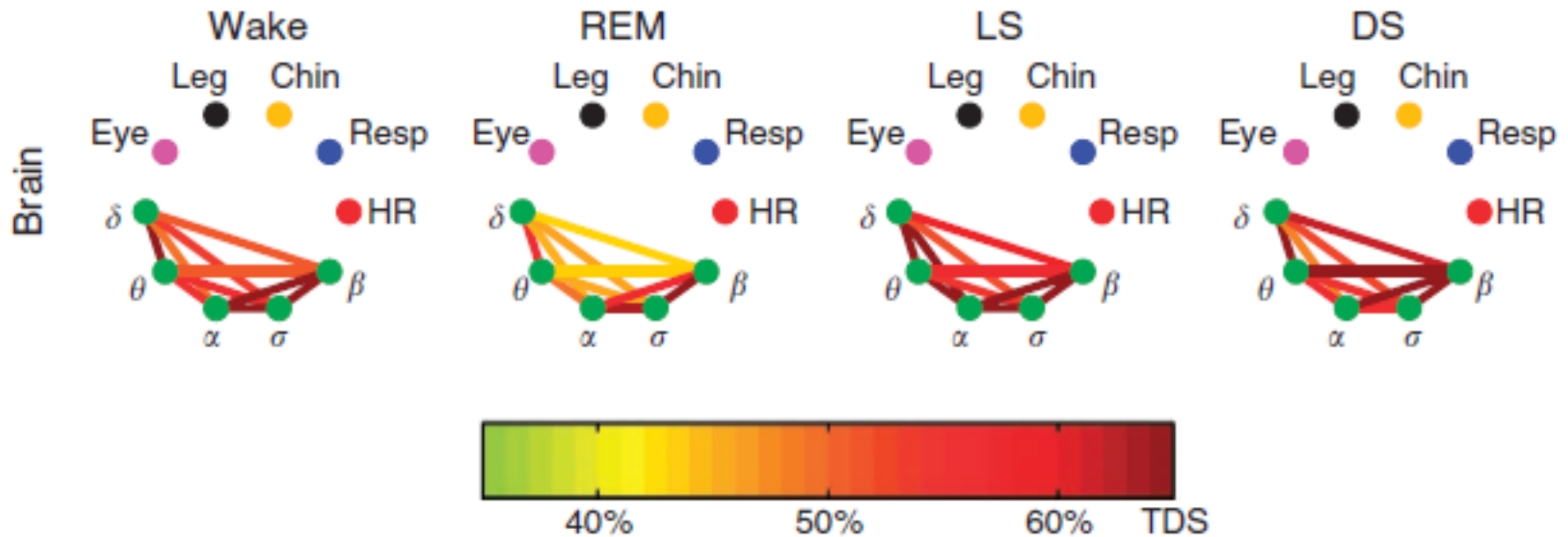
# Network Physiology: Implications for brain dynamics and neural plasticity



Phase transition in link strength and network topology

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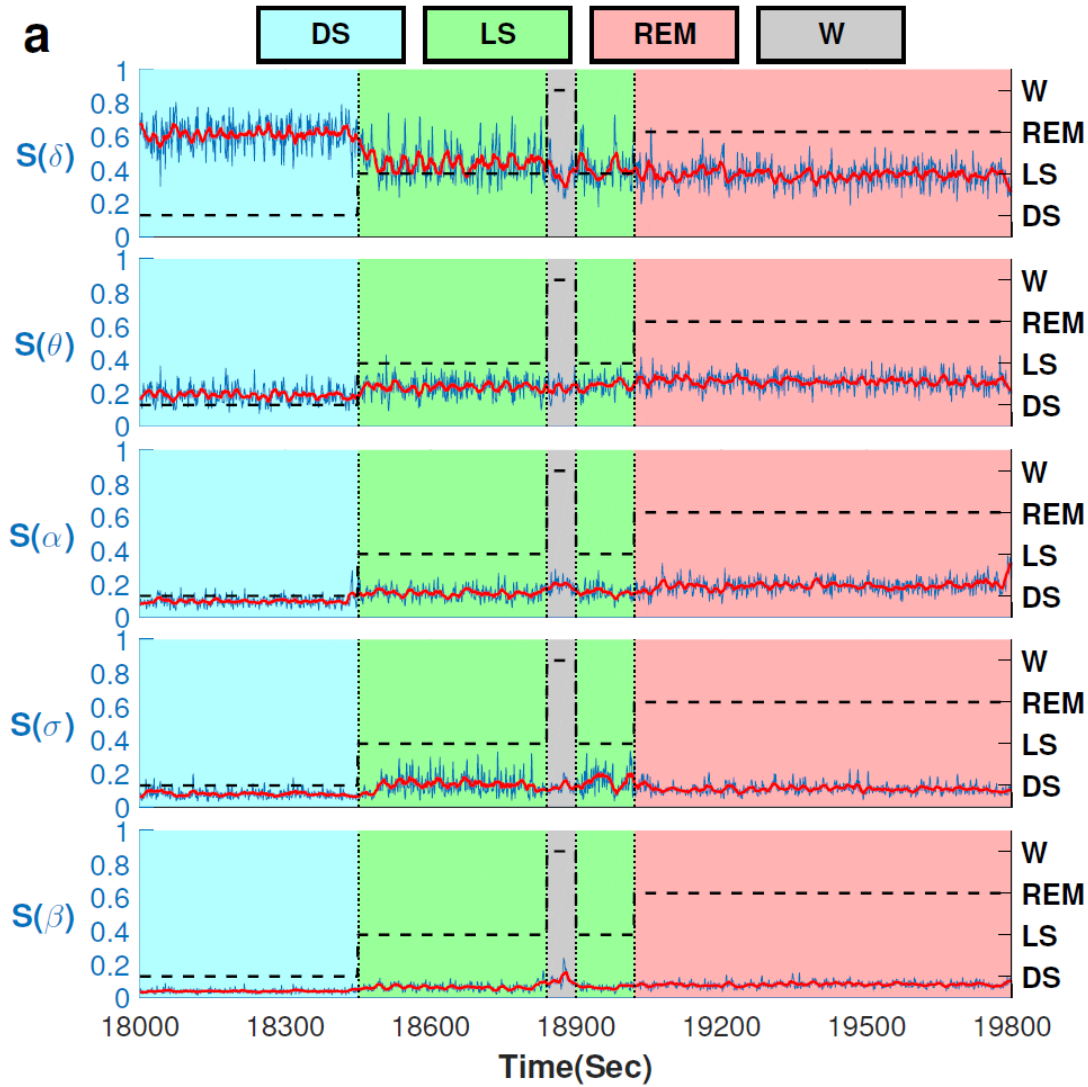
# Network connectivity and link strength of the brain–brain sub-network for sleep stages



Topology of brain-brain sub-network → no change  
Strength of network links → significant change

# Network Physiology: Implications for brain dynamics and neural plasticity

Complex temporal dynamics and distinct profiles of brain wave interactions.



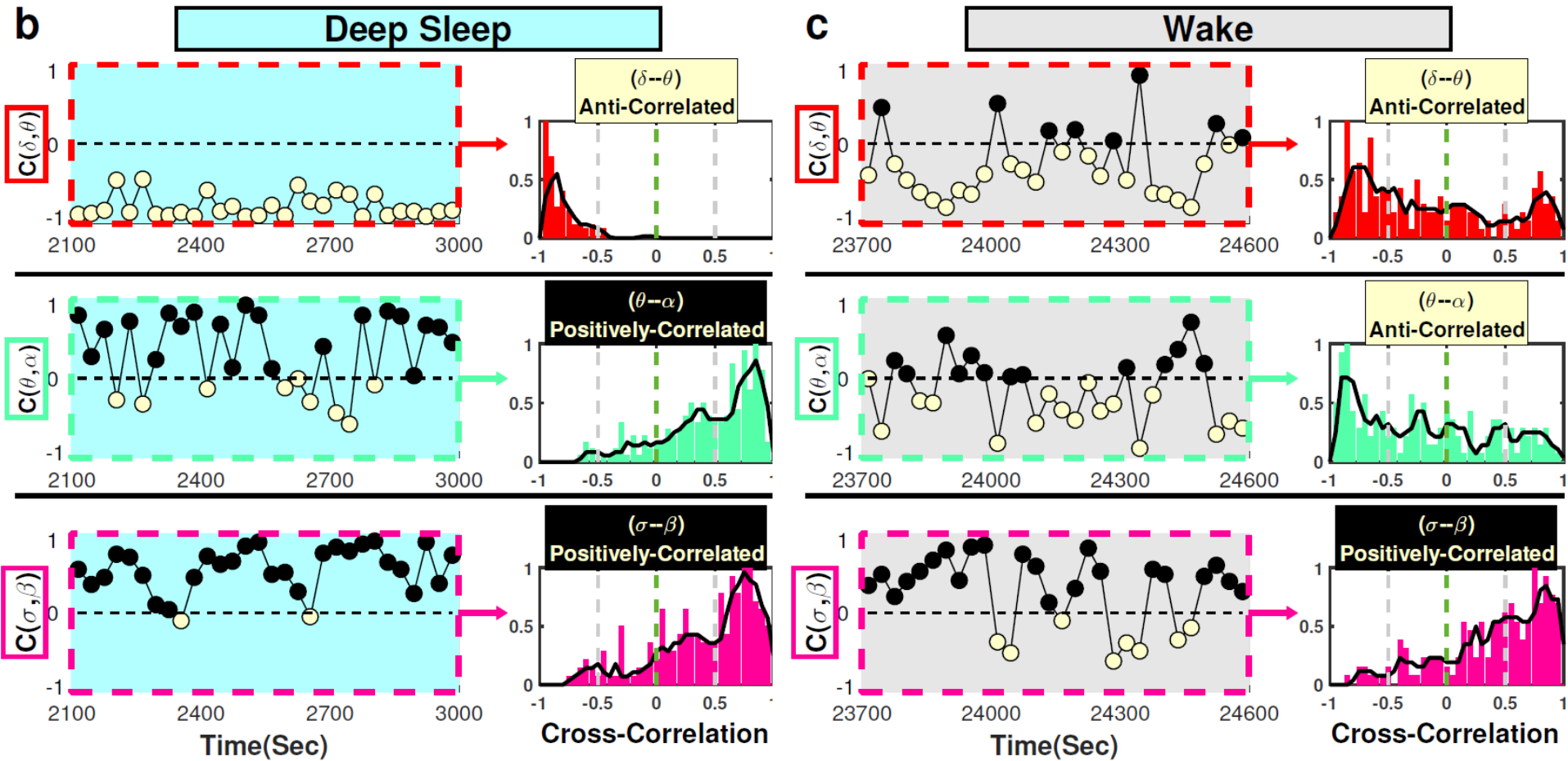




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Interactions**

# Network Physiology: Implications for brain dynamics and neural plasticity

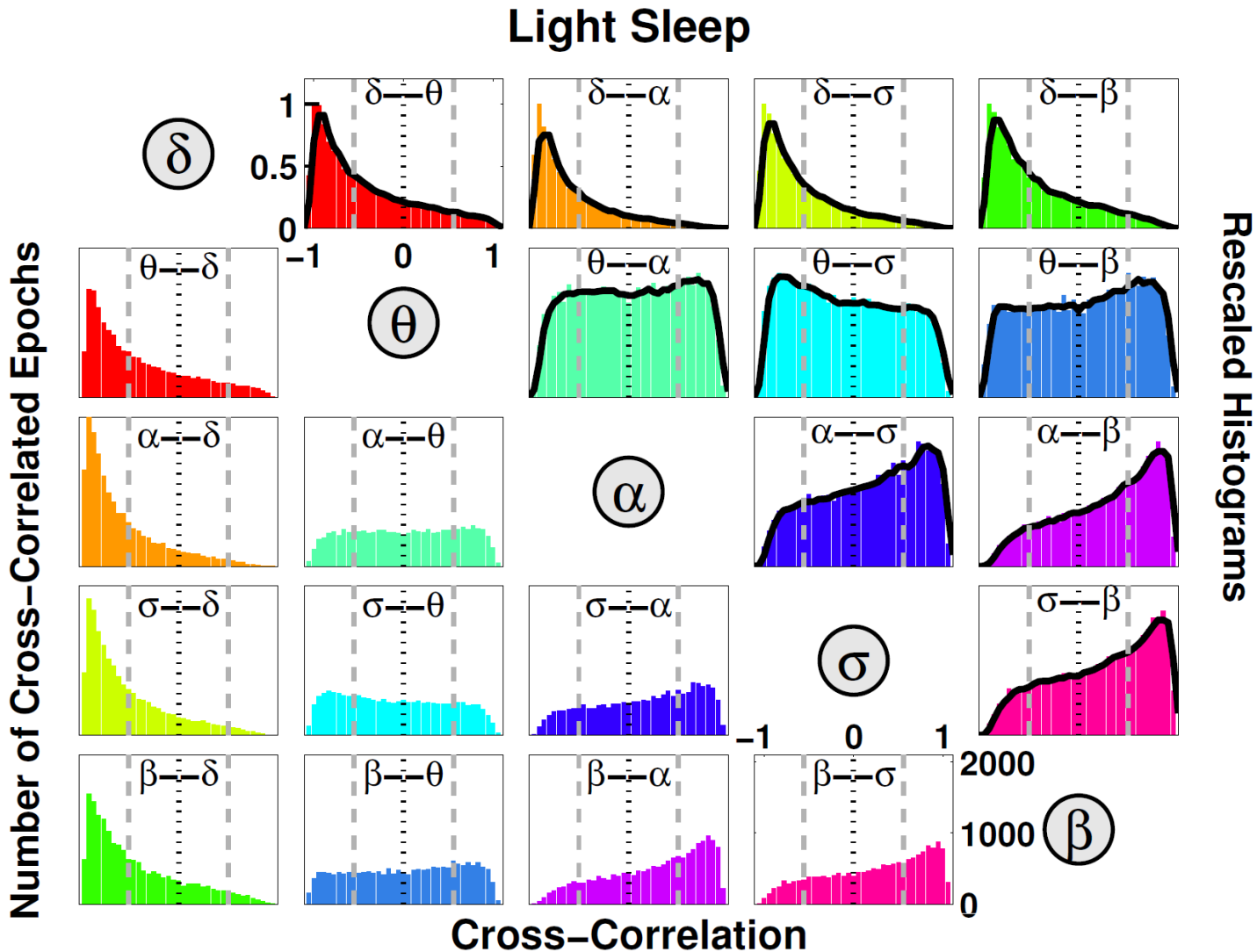
Complex temporal dynamics and distinct profiles of brain wave interactions.



Level 3:  
Networked  
Interactions

# Network Physiology: Implications for brain dynamics and neural plasticity

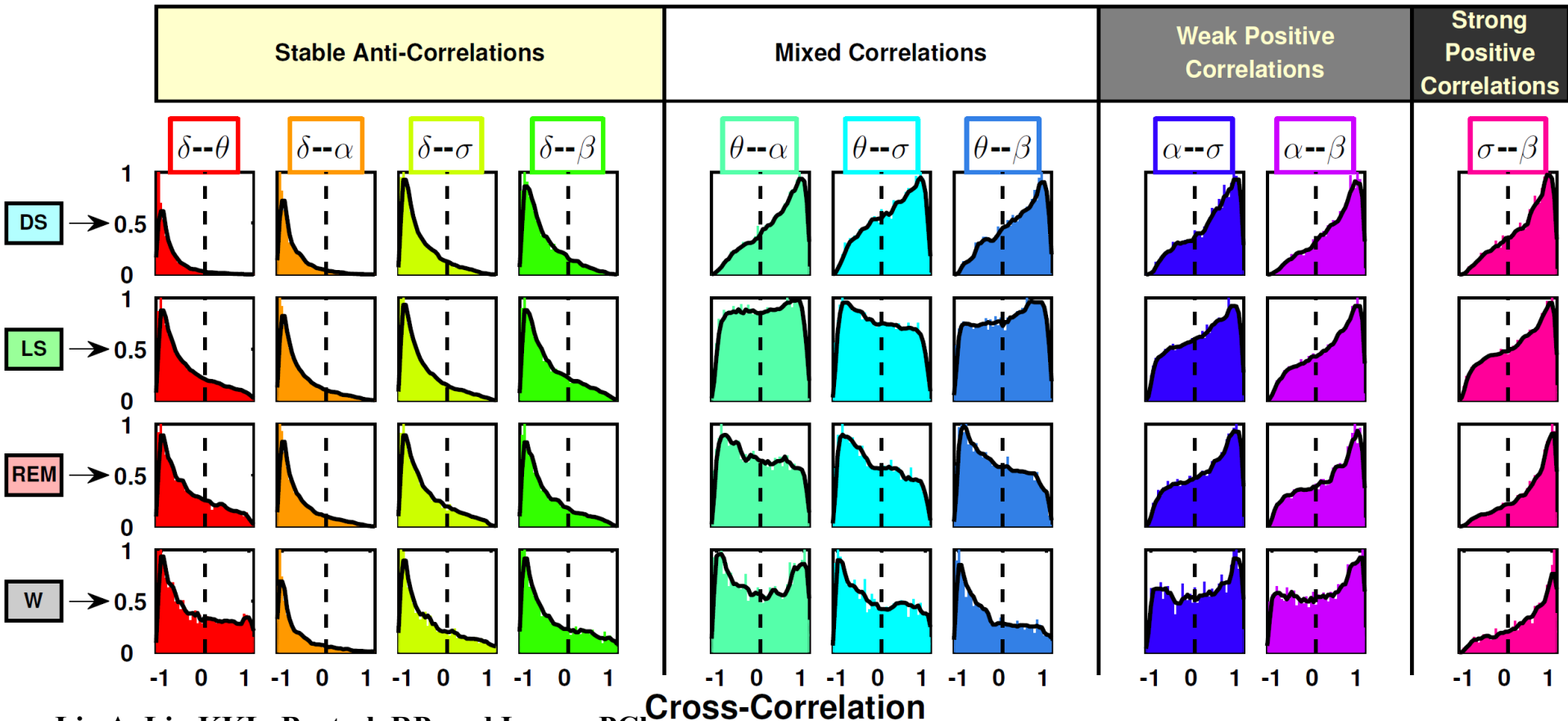
Alphabet of brain-wave interactions as a signature of physiologic state.



# Network Physiology: Implications for brain dynamics and neural plasticity

Transitions in brain-wave interactions across physiologic states.

## Distinct classes of brain wave interaction patterns



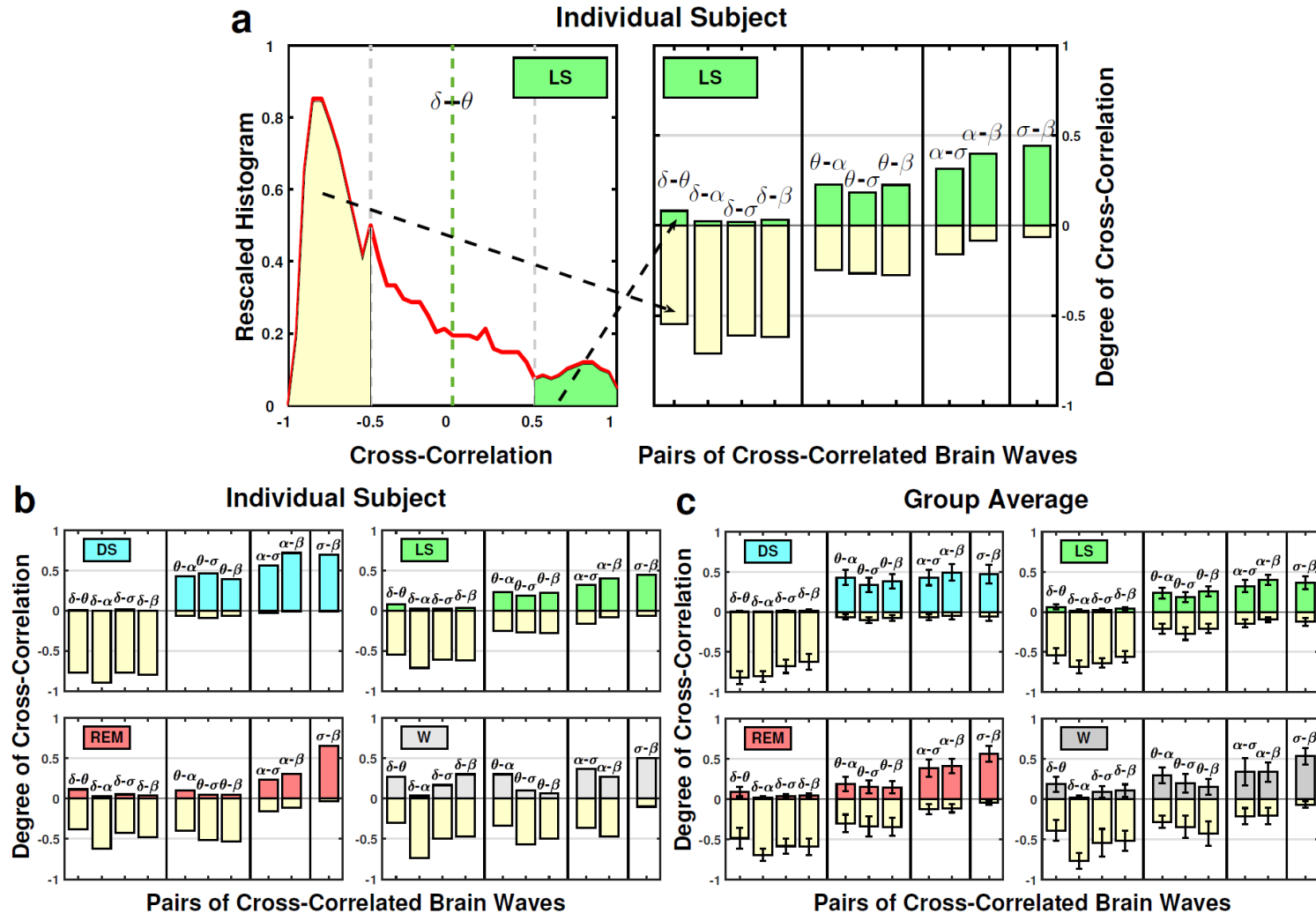
Lin A, Liu KKL, Bartsch RP, and Ivanov PCh.

Dynamic network interactions among distinct brain rhythms as a hallmark of physiologic state and function.

*Communications Biology*, 2020; 3: 197.

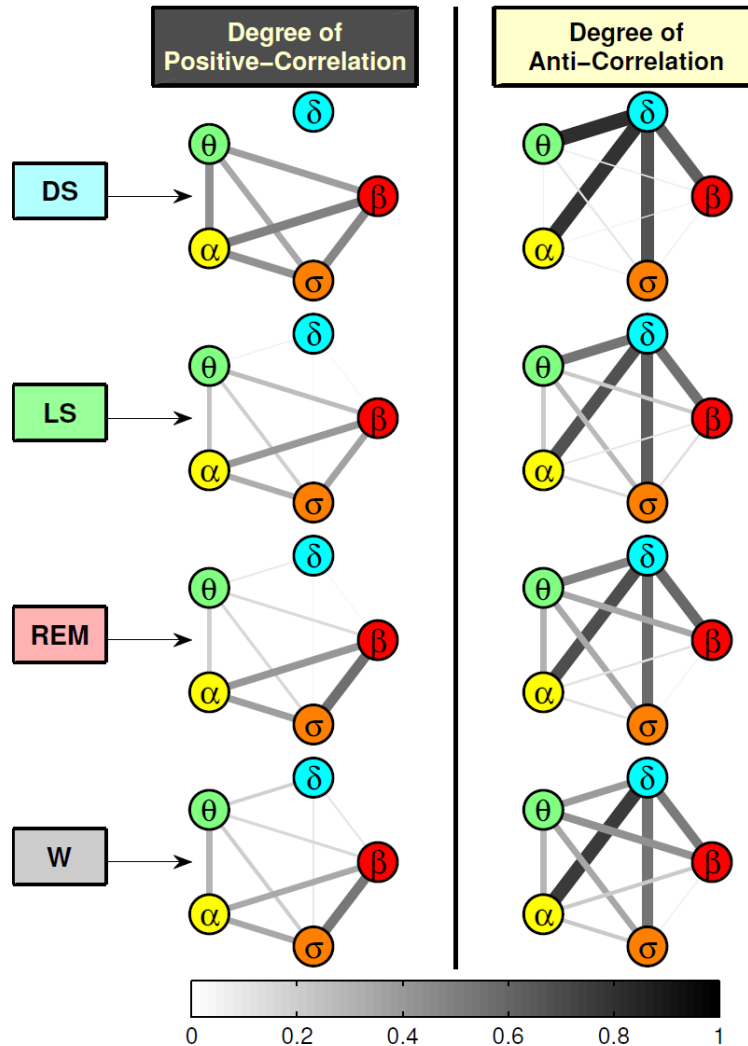
# Network Physiology: Implications for brain dynamics and neural plasticity

Robust sleep-stage stratification in the degree of cross-correlation for different pairs of brain rhythms.



# Network Physiology: Implications for brain dynamics and neural plasticity

Network communications and topological clustering of brain rhythms.  
Group Average

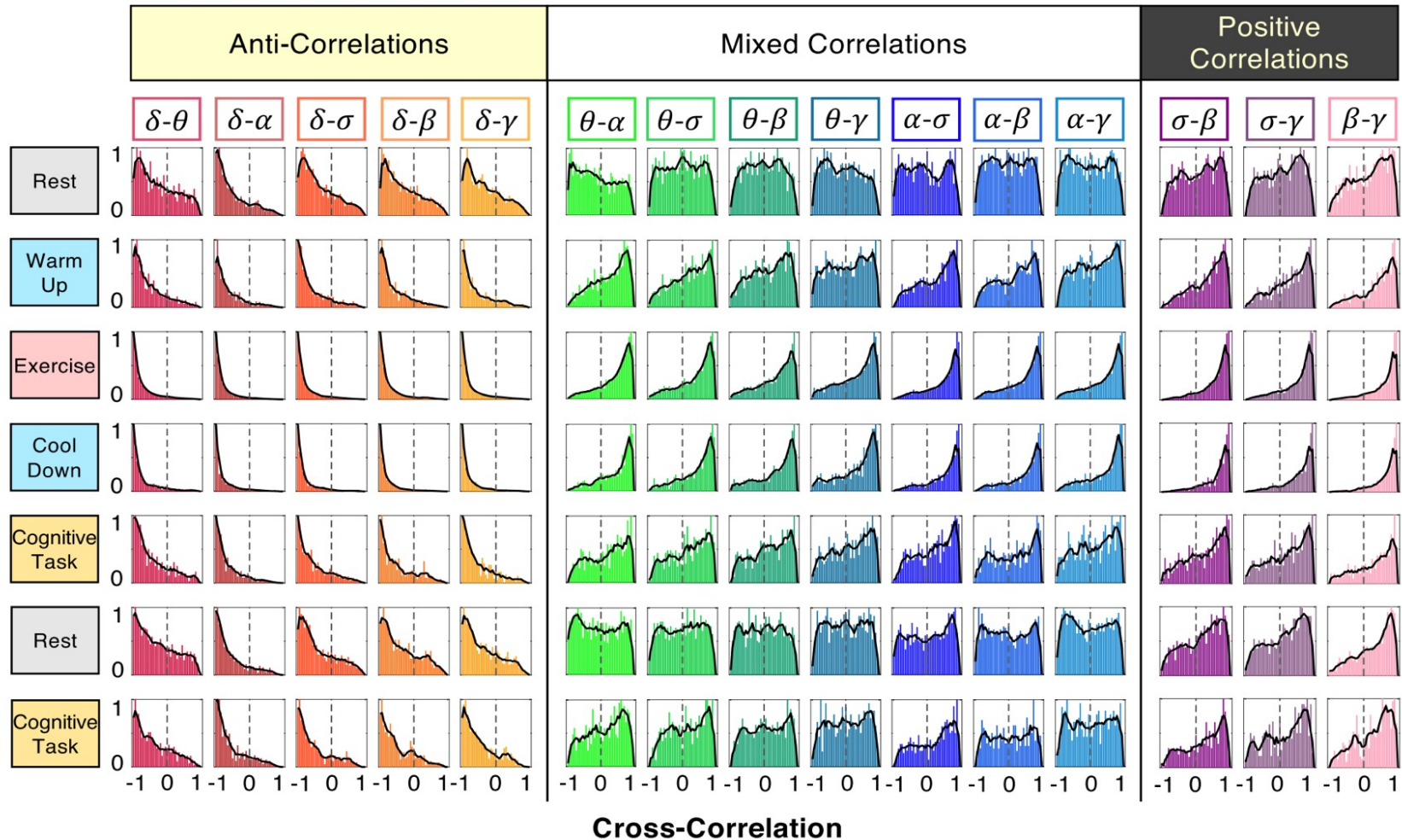


Lin A, Liu KKL, Bartsch RP, and Ivanov PCh.  
Dynamic network interactions among distinct  
brain rhythms as a hallmark of physiologic state  
and function.

*Communications Biology*, 2020; 3: 197.

**Level 3:  
Networked  
Interactions**

# Network Physiology: Implications for brain dynamics and neural plasticity



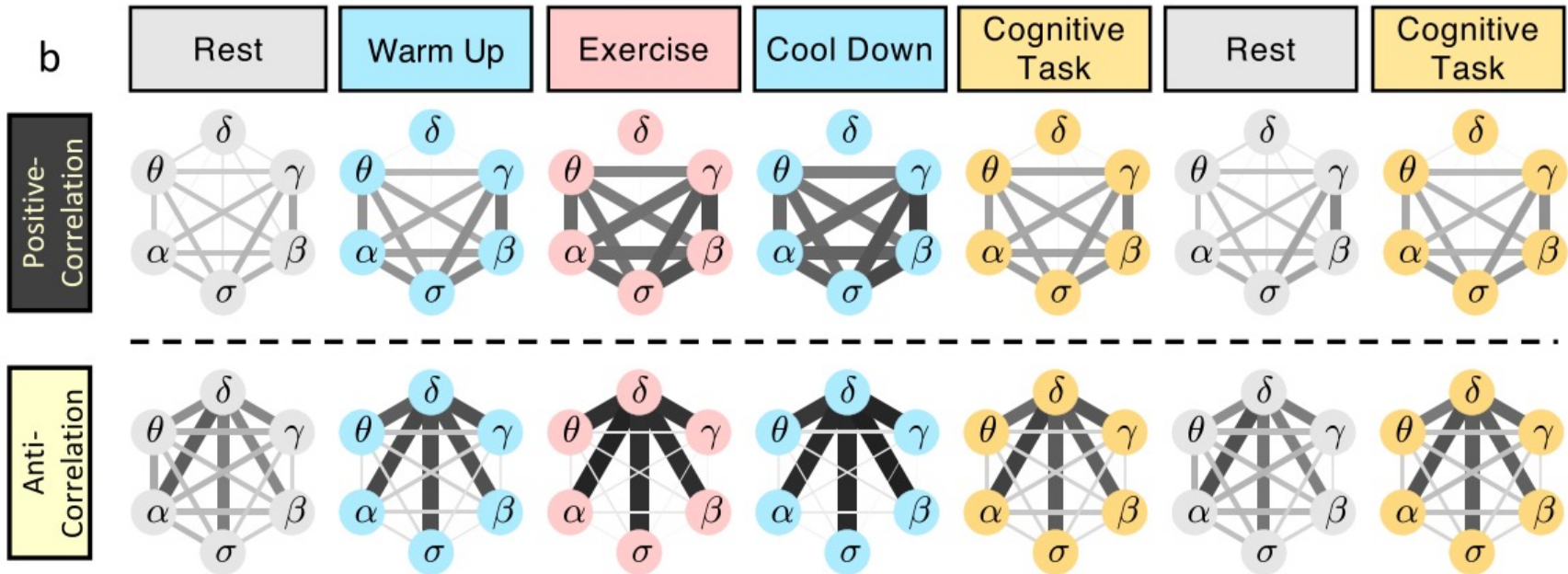
**Transitions in brain-wave interactions across physiologic states.**

Chen B, Ciria L, Hu C, and Ivanov PCh.

Ensemble of coupling forms and networks among brain rhythms as function of states and cognition.

*Communications Biology*, 2022;53: 82.

# Network Physiology: Implications for brain dynamics and neural plasticity



Network of cortical rhythm interactions and their evolution  
across physiological states.

Chen B, Ciria L, Hu C, and Ivanov PCh.

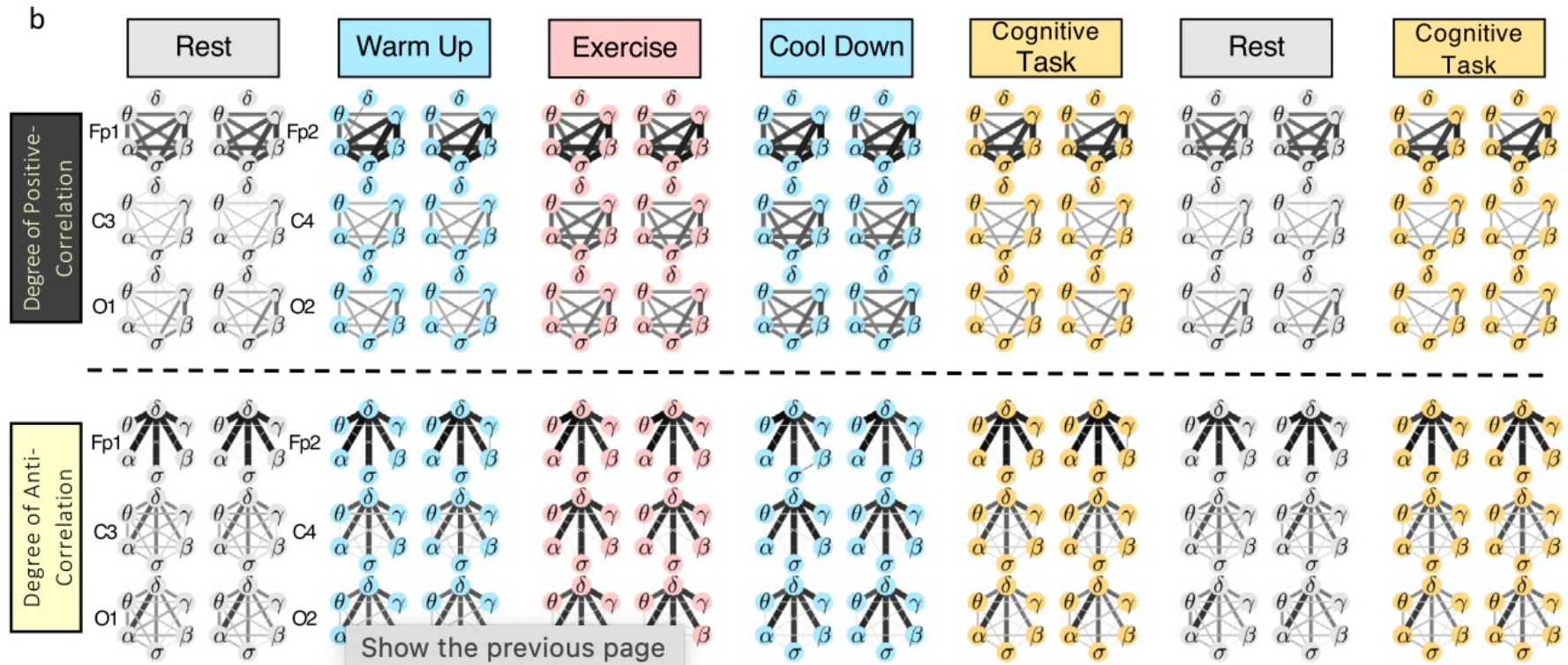
Ensemble of coupling forms and networks among brain rhythms as function of states and cognition.

*Communications Biology*, 2022;53: 82.



# Level 3: Networked Interactions

# Network Physiology: Implications for brain dynamics and neural plasticity



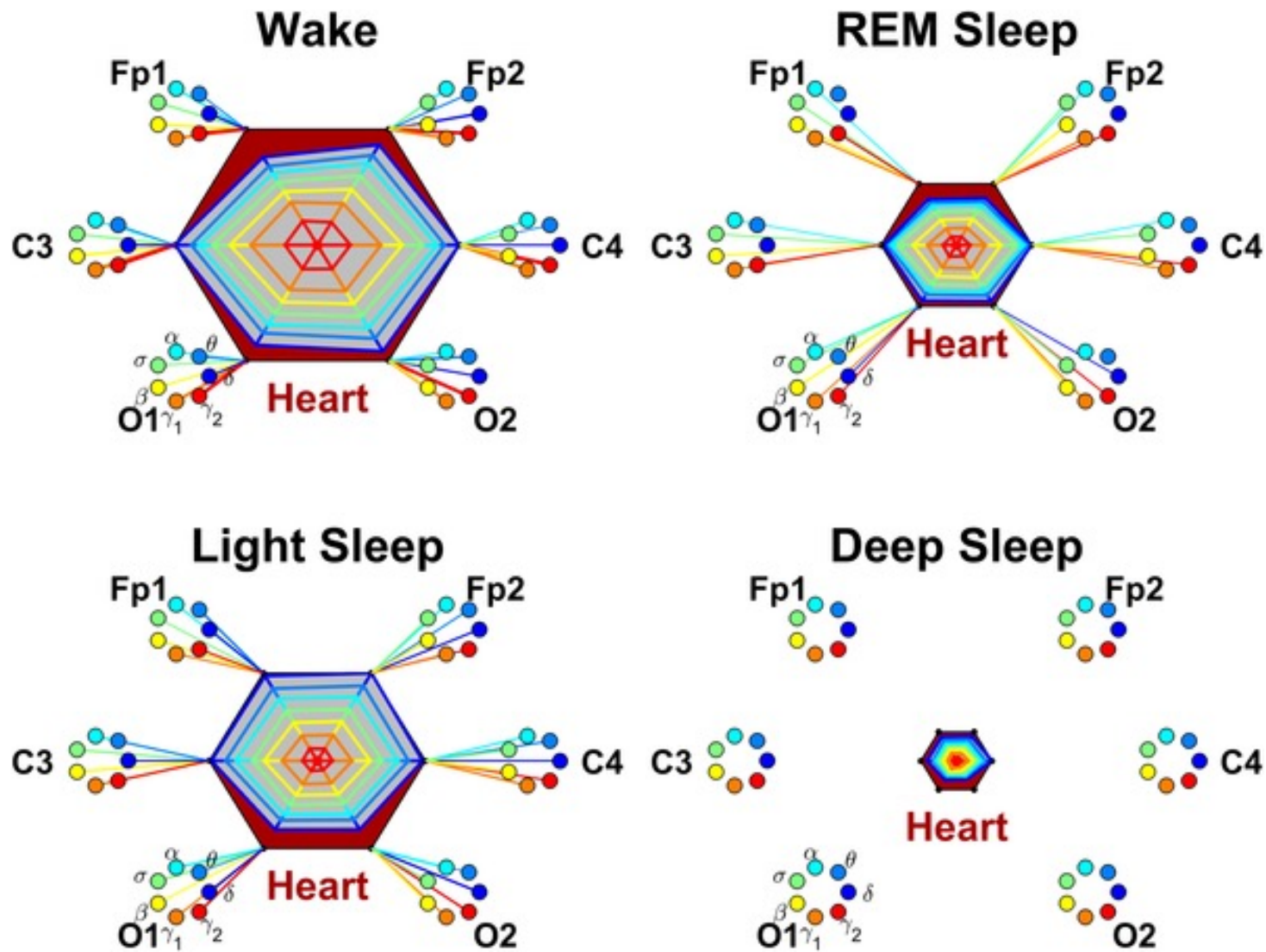
Network communications and topological clustering of brain rhythm interactions at different cortical locations uniquely represent physiological states.

Chen B, Ciria L, Hu C, and Ivanov PCh.

Ensemble of coupling forms and networks among brain rhythms as function of states and cognition.

*Communications Biology*, 2022;53: 82.

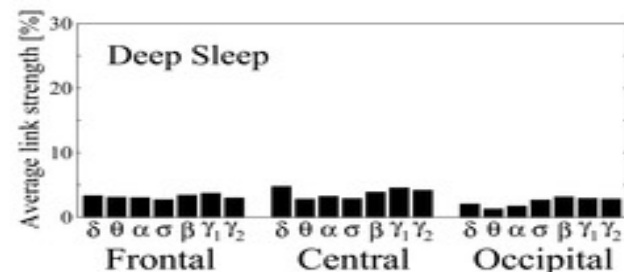
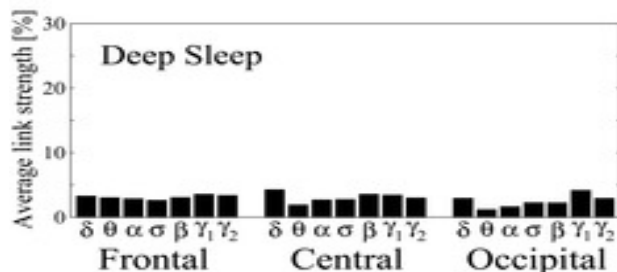
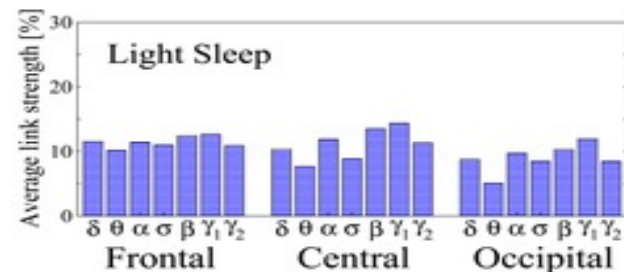
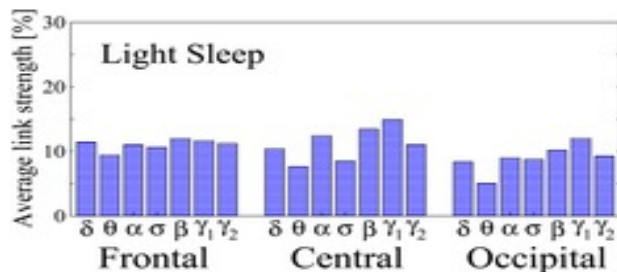
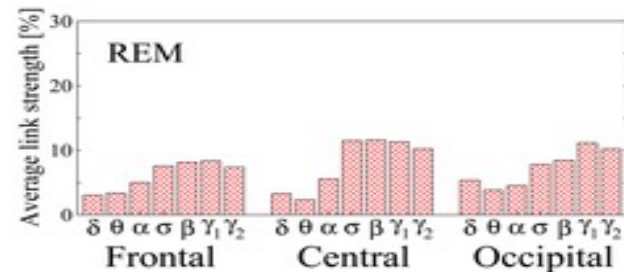
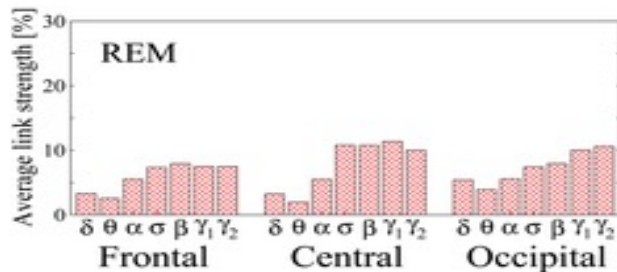
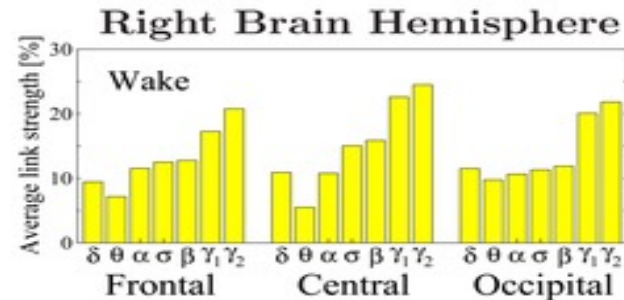
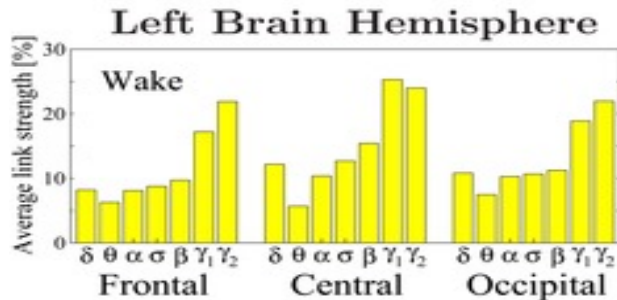
# Visualization: different physiologic states



# Level 3: Networked Interactions

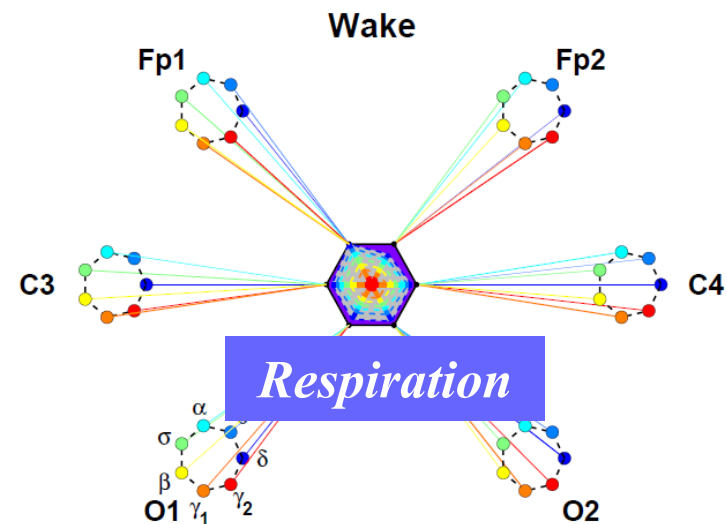
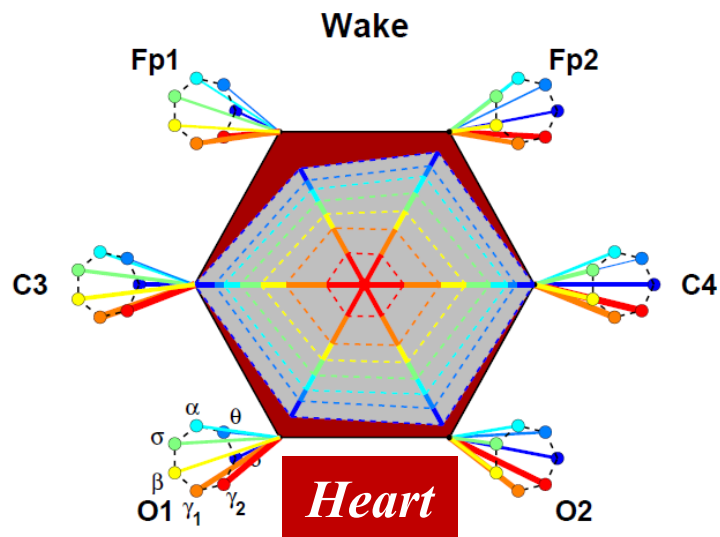
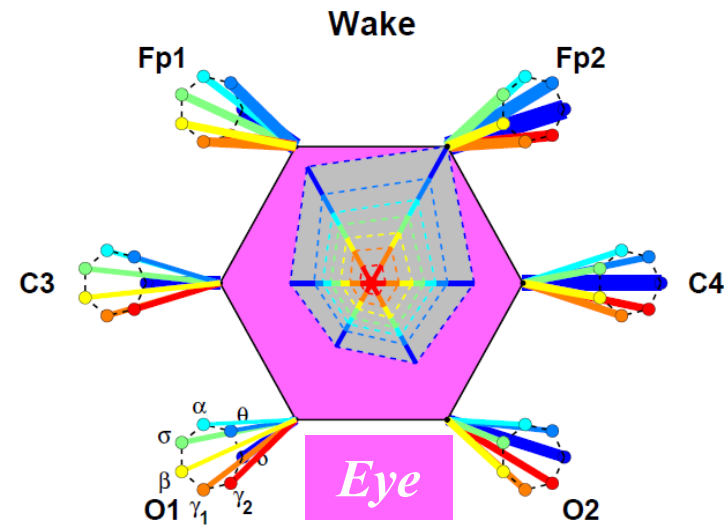
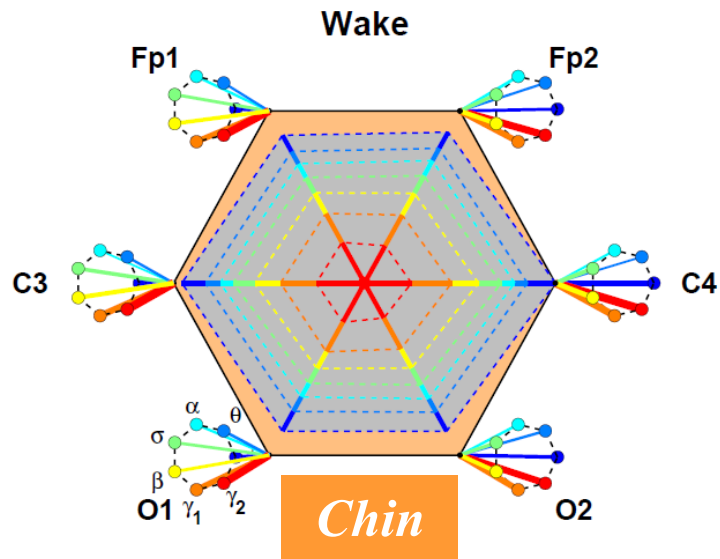
# Brain-organ interactions

## Brain-Heart Interaction



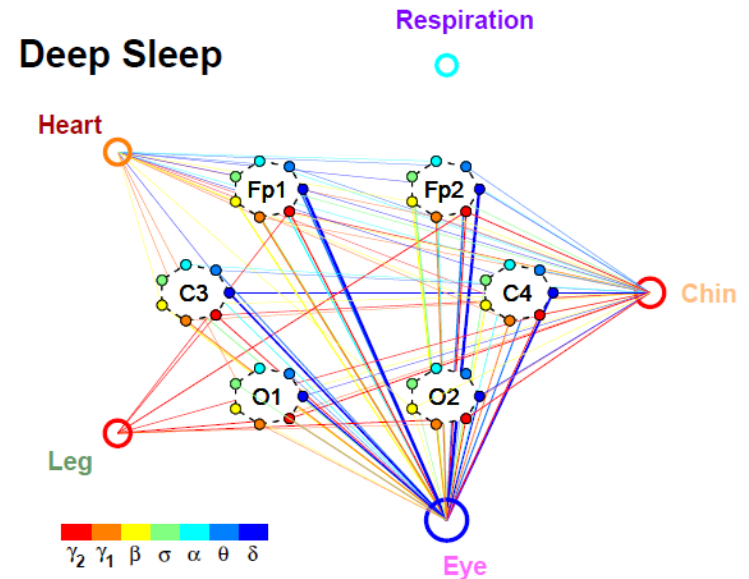
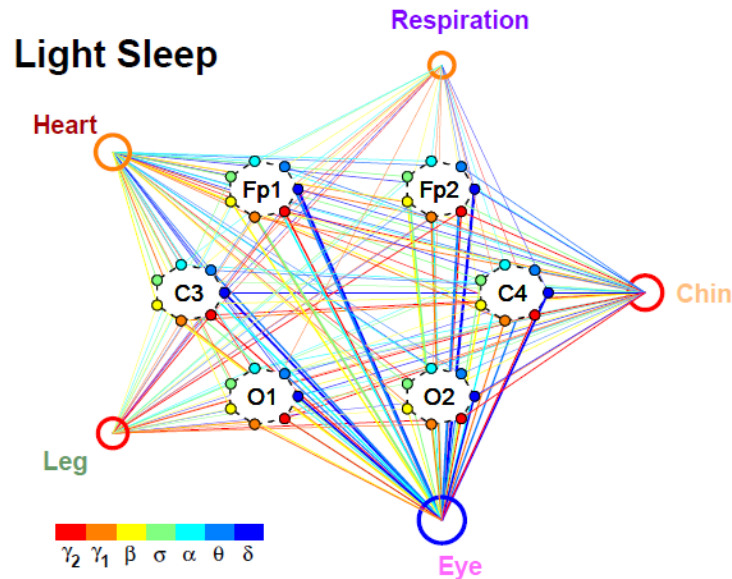
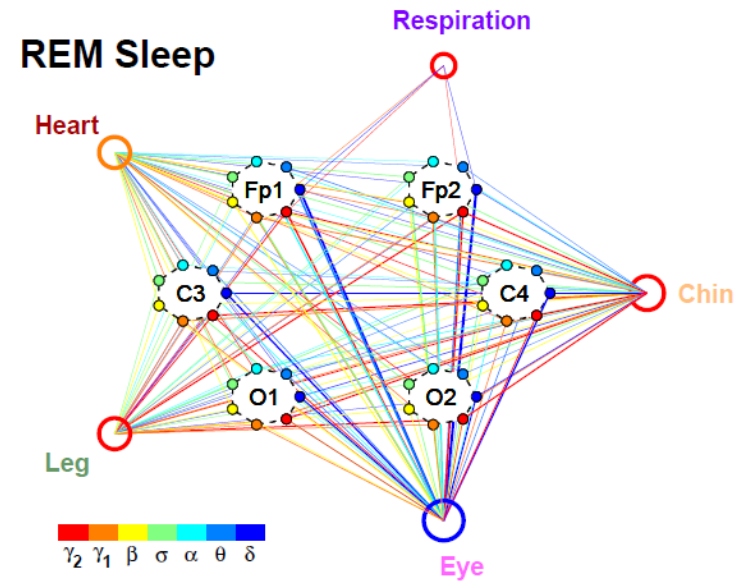
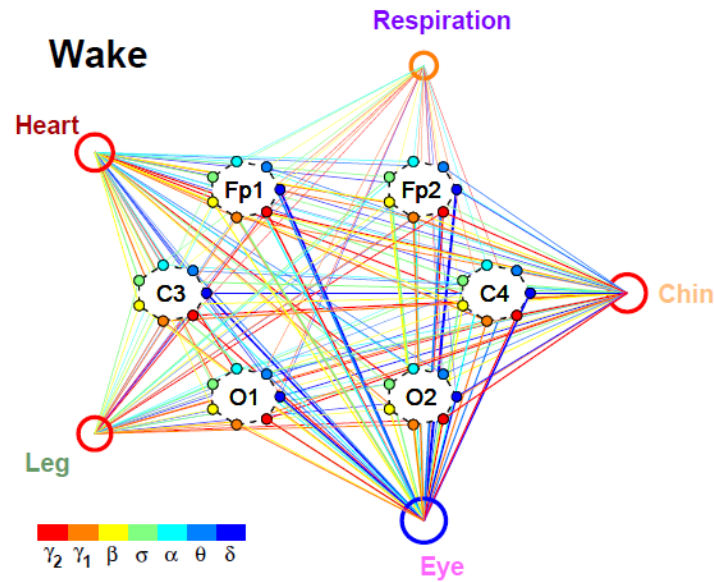
mediated by  
different  
frequency bands

# Maps for different organ systems



# Level 3: Networked Interactions

# Network Physiology: Networks of brain activity and other physiologic systems across sleep stages



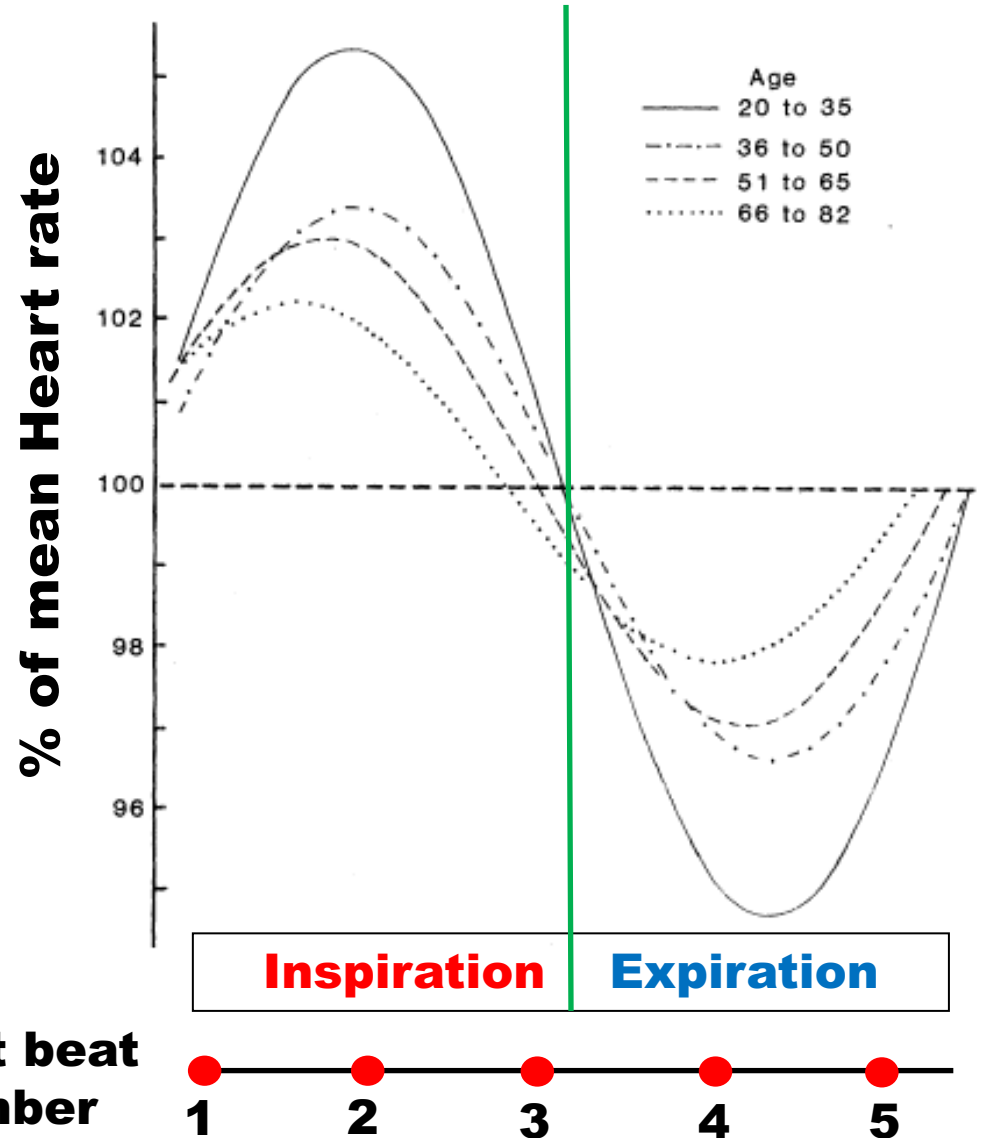
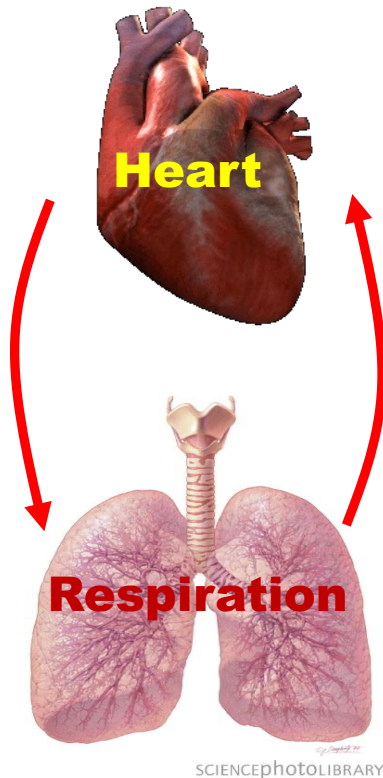
Level 2:  
Pair-wise Coupling

# Cardio-respiratory Interaction

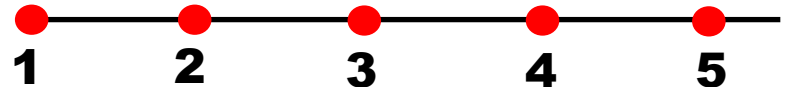
## Respiratory Sinus Arrhythmia (RSA)

Inspiration → Heart rate ↑

Expiration → Heart rate ↓



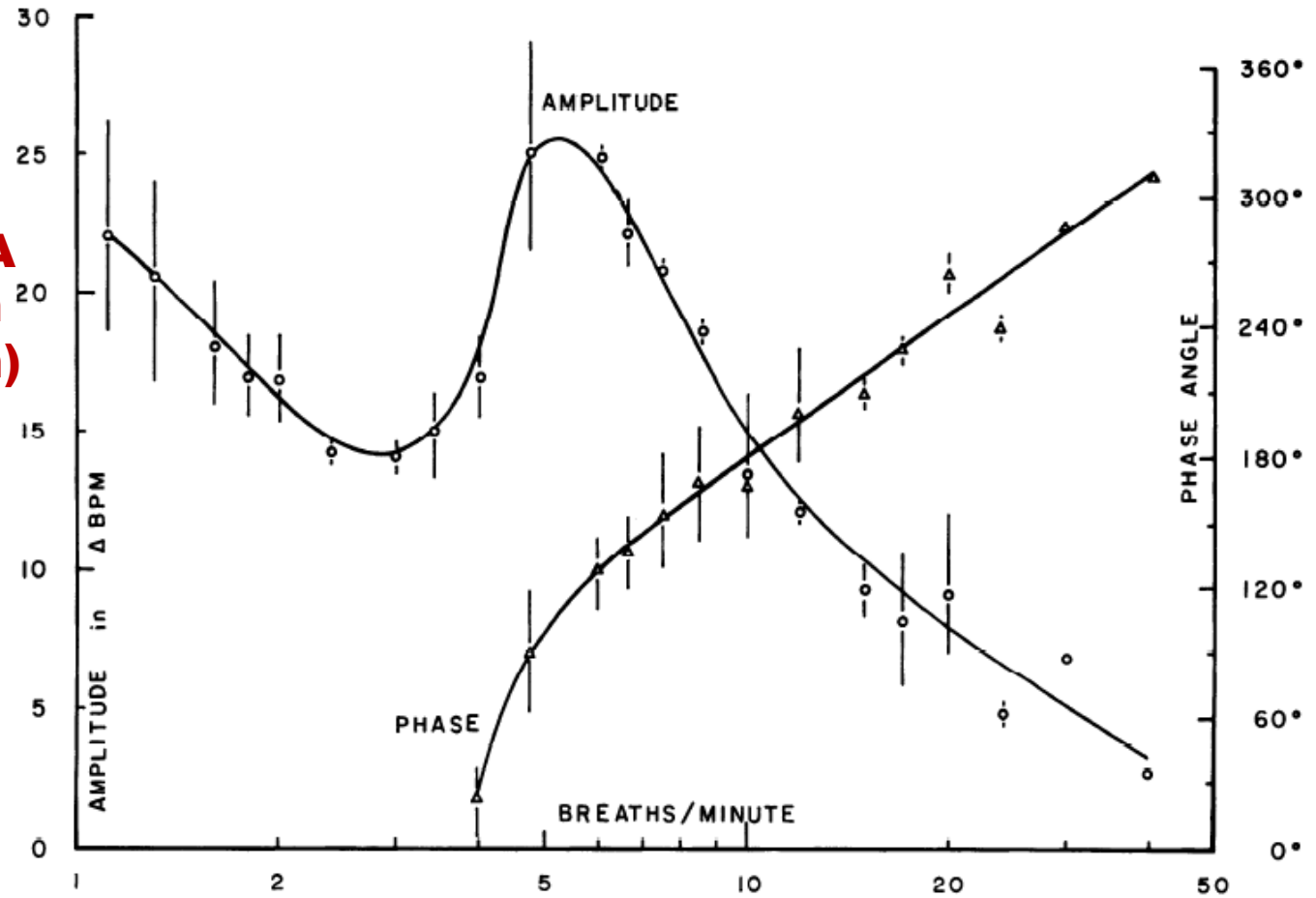
Heart beat  
number



Level 2:  
Pair-wise Coupling

# Cardio-respiratory Interaction Respiratory Sinus Arrhythmia (RSA)

**Strength of RSA  
(deviation from  
mean beats/min)**



**Breathing Rate (breaths per min)**

Angelone & Coulter, *J Appl Physiol* **19**, 479 (1964)

Level 2:  
Pair-wise Coupling

# How do systems interact? Synchronization: Definition

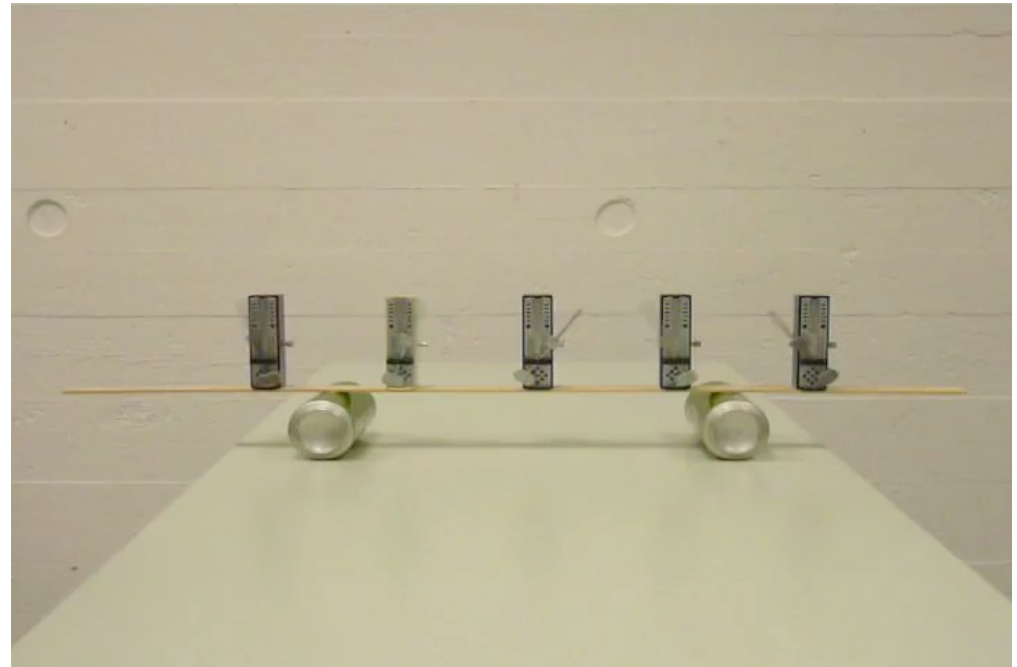
**“Synchronization is an adjustment of rhythms of **self-sustained** oscillators due to their weak interaction.”**

**Pikovsky, Rosenblum, Kurths. Synchronization: a universal concept in nonlinear sciences (Cambridge University Press 2001)**

**Start:**  
different frequencies,  
different phases  
→ **No synchronization**

**End:**  
same frequencies,  
same phase difference  
(“phase locked”)  
→ **Synchronization**

## Coupled Metronomes





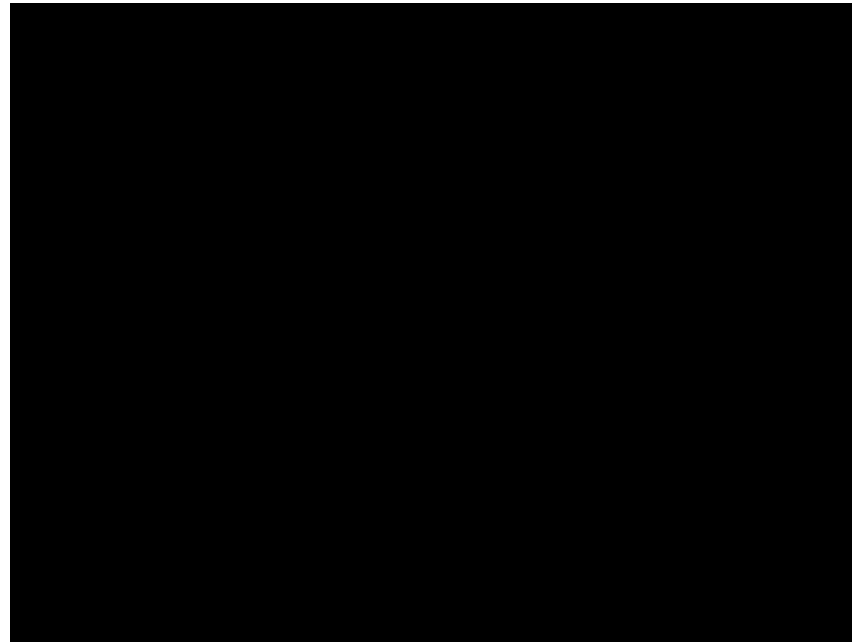
Level 2:  
Pair-wise Coupling

# The Synchronization Phenomenon

- **London: Millennium (“Wobbly”) bridge opening day June 10, 2000**



- **London: Millennium (“Wobbly”) bridge opening day June 10, 2000**

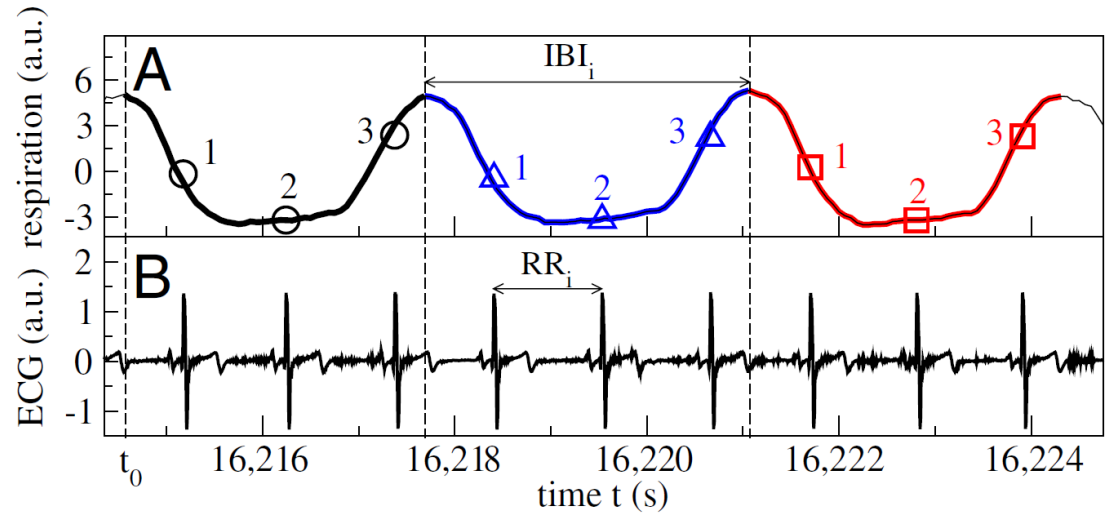
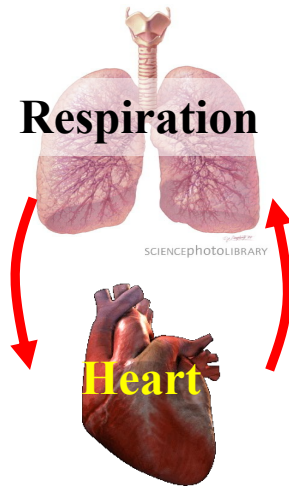


**Millenium bridge reopened in February 2002:**

- **after 5 Million £ spent on bridge modifications**
- **research based on work by S. Strogatz et al. Nature 438, 43 (2005)**

Level 2:  
Pair-wise Coupling

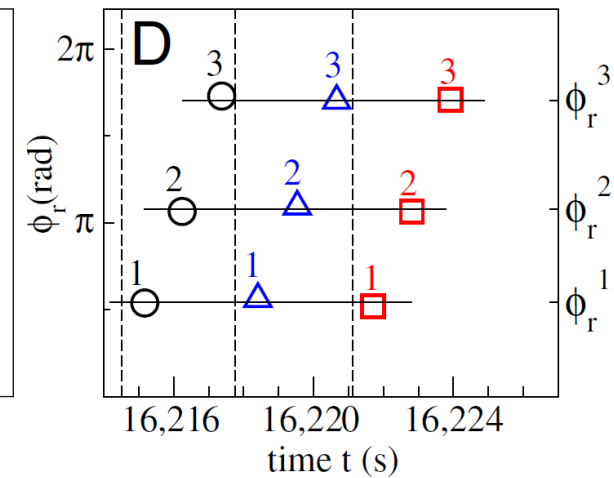
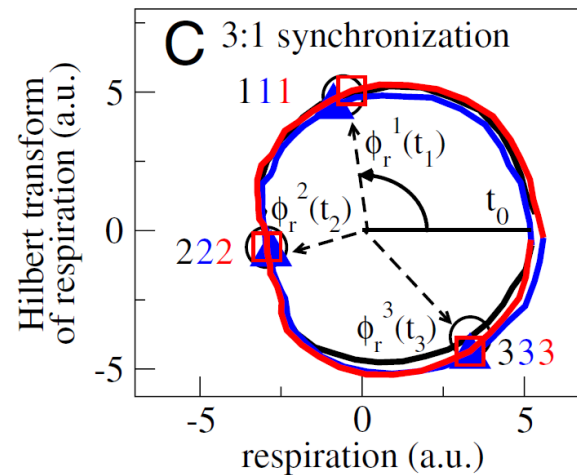
# Cardio-respiratory Interaction Phase Synchronization



**Phases collapse**



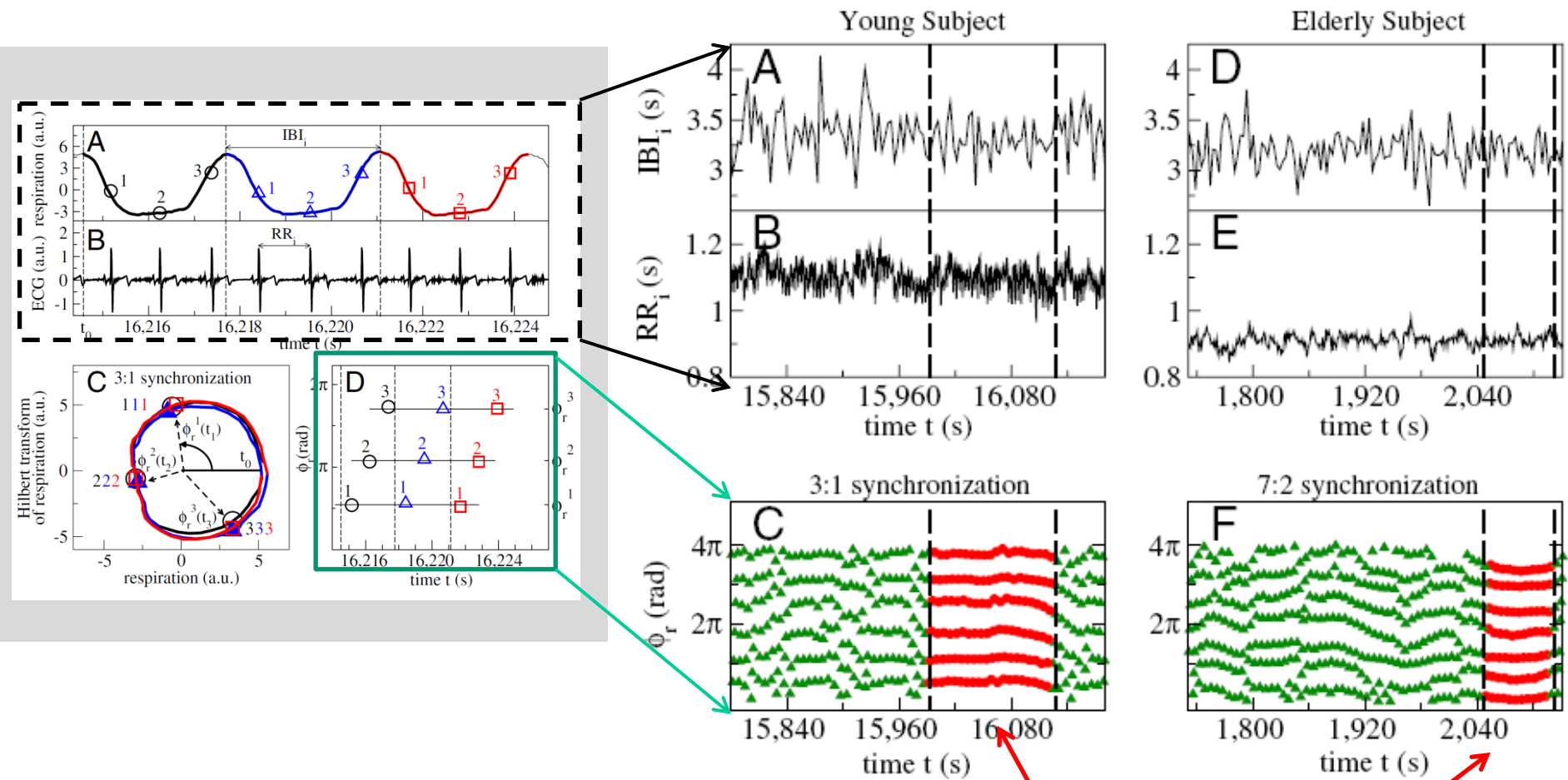
**Phase synchronization**



**Level 2:  
Pair-wise  
Coupling**

# Cardio-respiratory Interaction

## Phase Synchronization despite continuous fluctuations

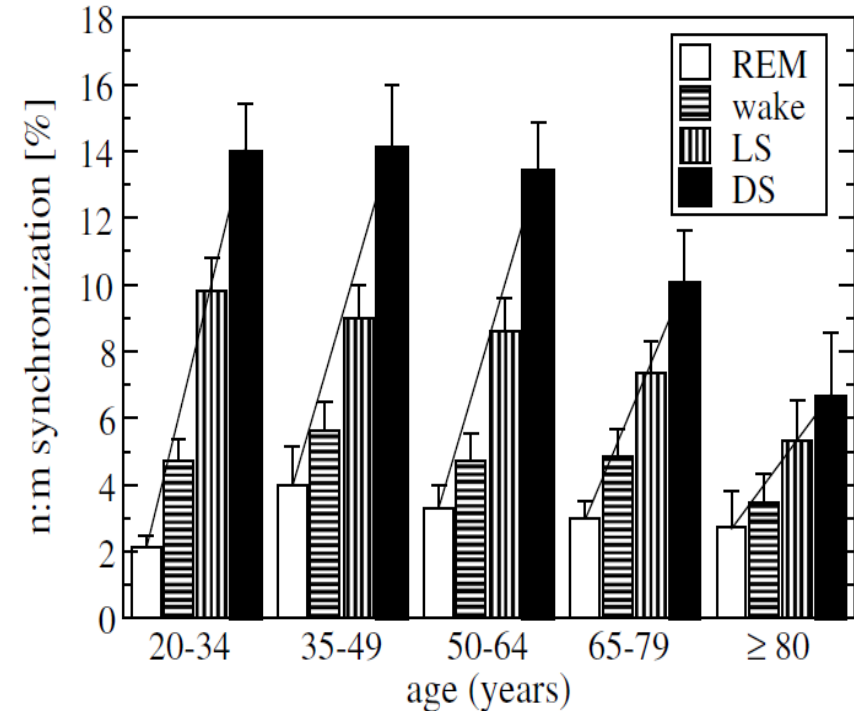
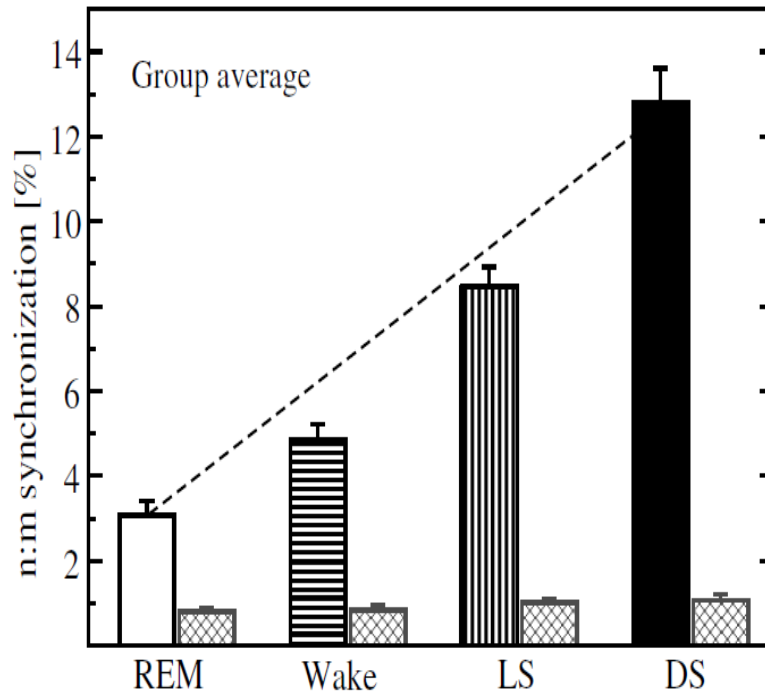


**Segments of Synchronization**

## Level 2: Pair-wise Coupling

# Cardio-respiratory Interaction Phase Synchronization

Pronounced stratification of synchronization is stable for all age groups



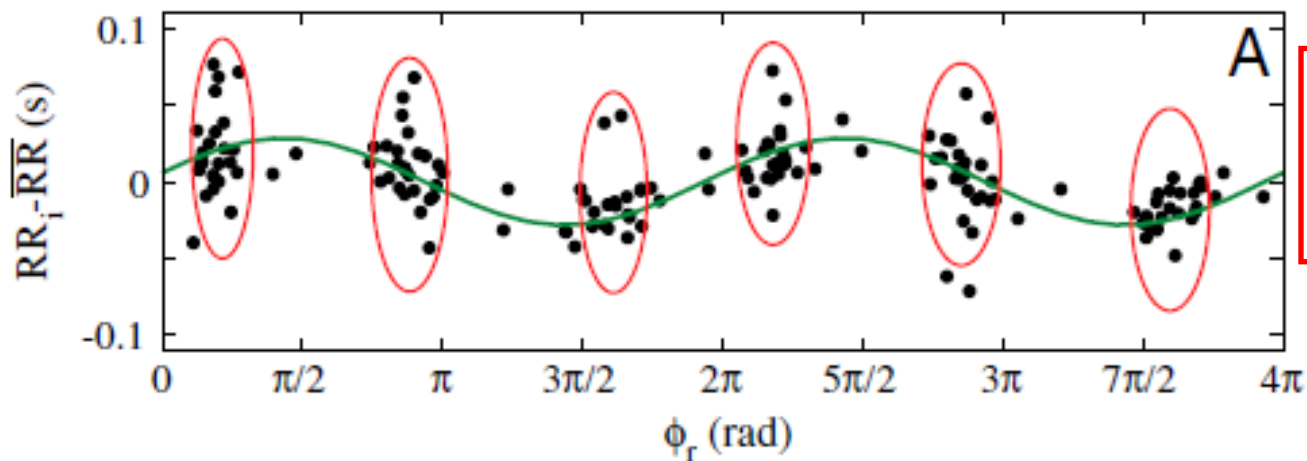
**400% increase in  
synchronization from  
REM to deep sleep**

**Discovery:  
Phase transitions in  
cardio-respiratory coupling**

Level 2:  
Pair-wise Coupling

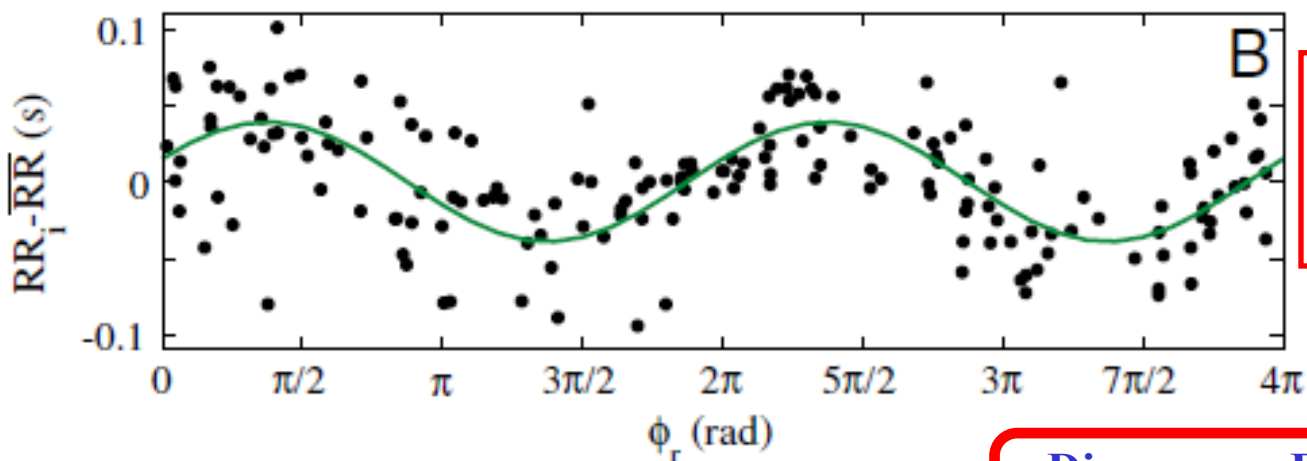
# Coexisting forms of physiologic coupling Cardio-Respiratory interaction

Segment with pronounced RSA and phase-synchronization



**RSA  
&  
Synchronization**

Segment with pronounced RSA and no phase-synchronization



**RSA  
w/o  
Synchronization**

**Discovery: RSA and Synchronization**  
**Two coexisting forms of coupling**

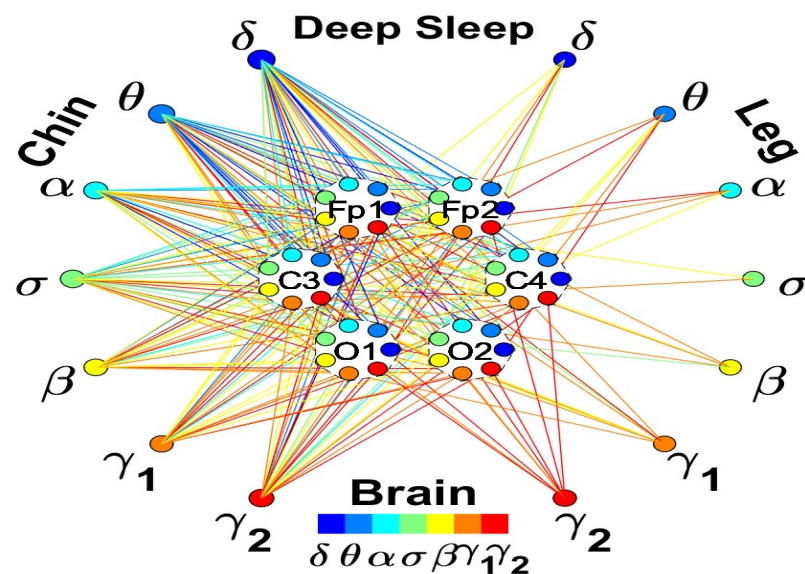
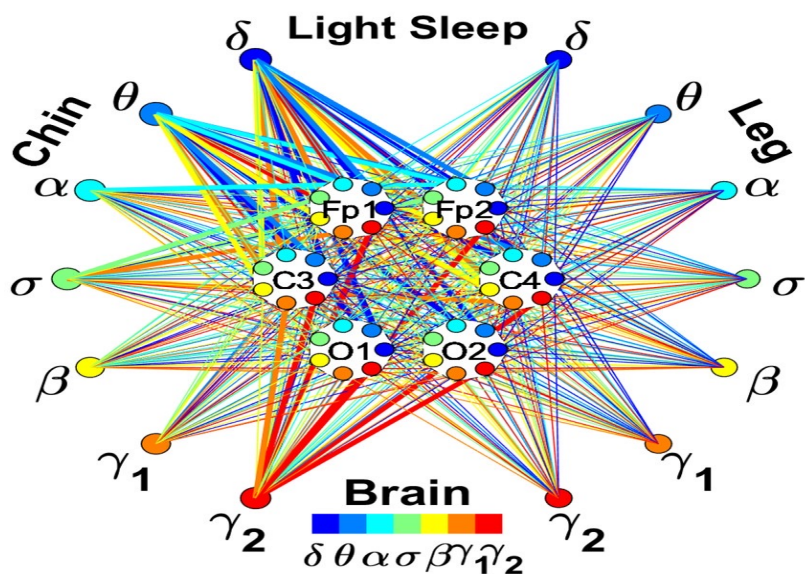
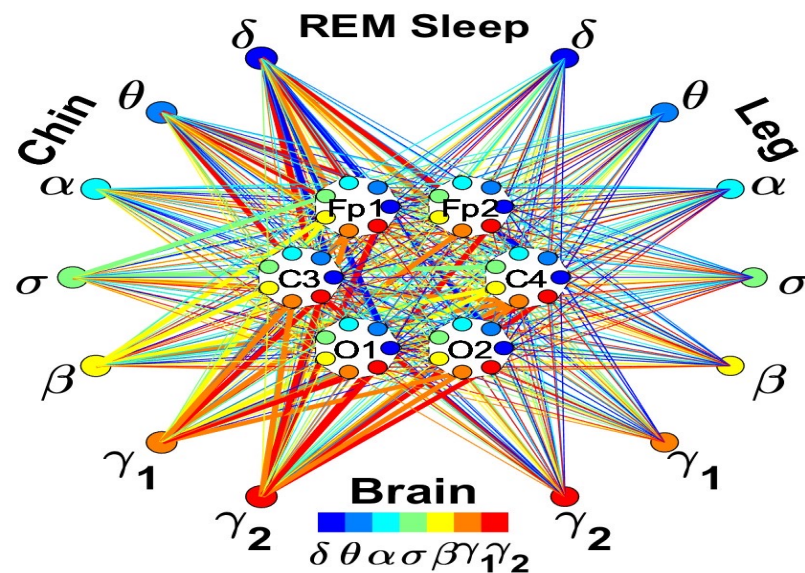
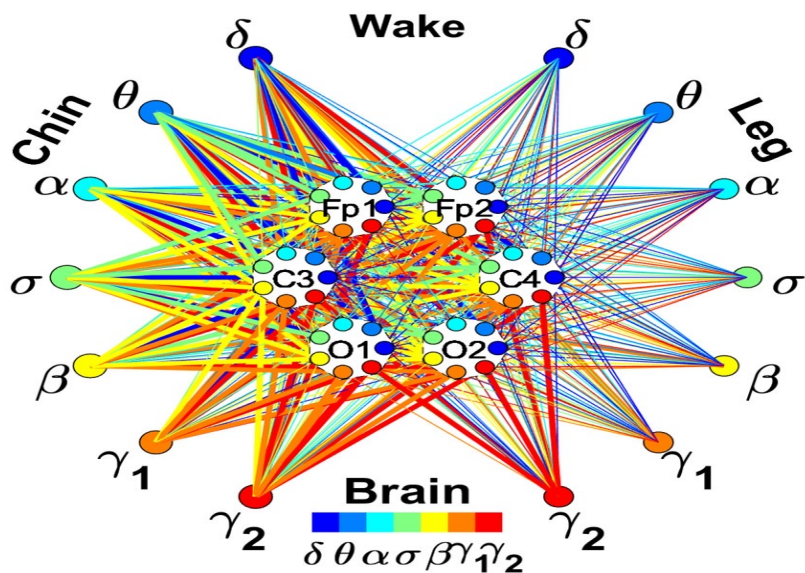
Bartsch RP, Liu KKL, Ma QDY, and Ivanov PCh.

Three independent forms of cardio-respiratory coupling: transitions across sleep stages. *Computing in Cardiology*, 2014; 41:781-784

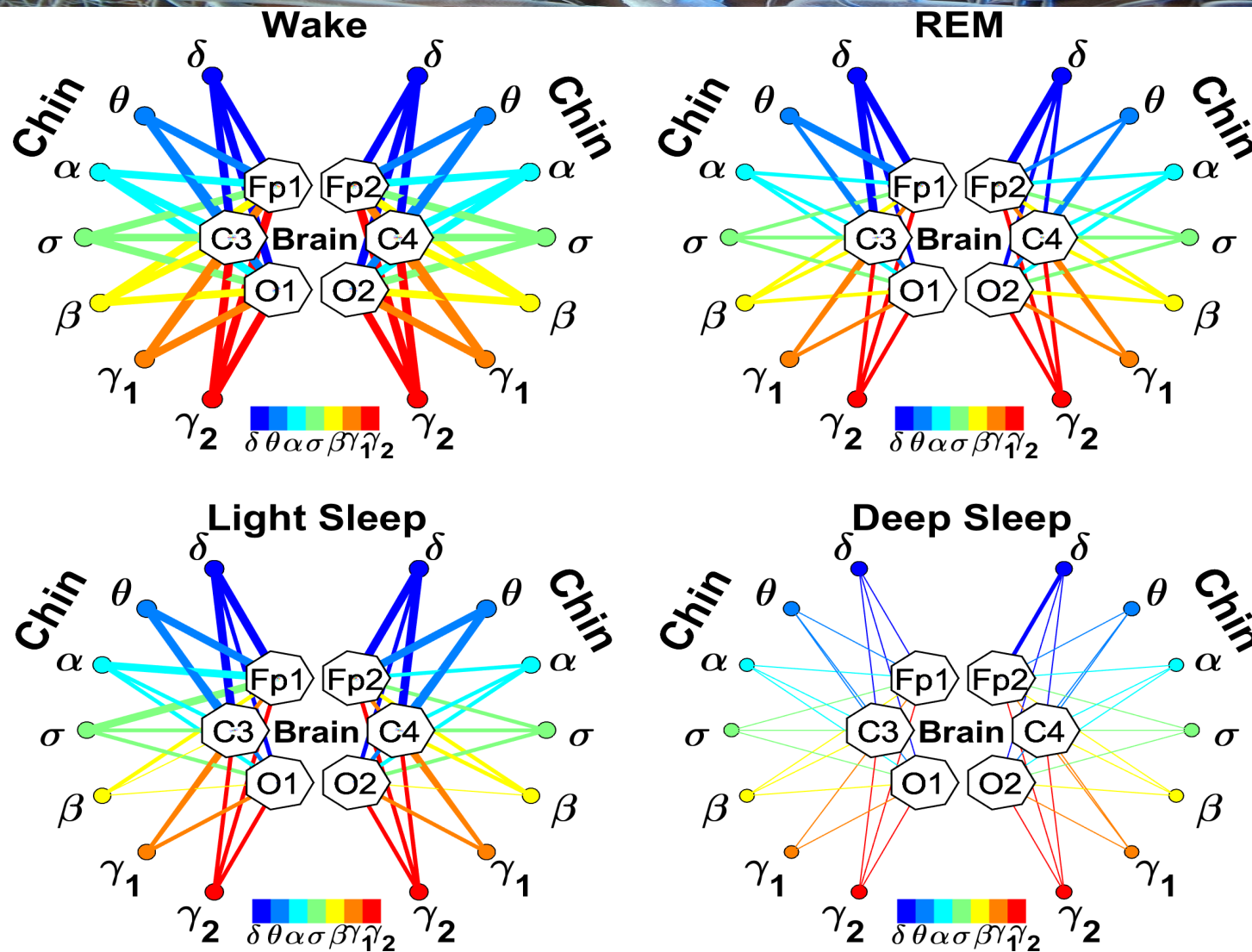
Level 3:  
Networked  
Interactions

# Functional Interaction Networks

## Brain waves vs EMG frequency bands

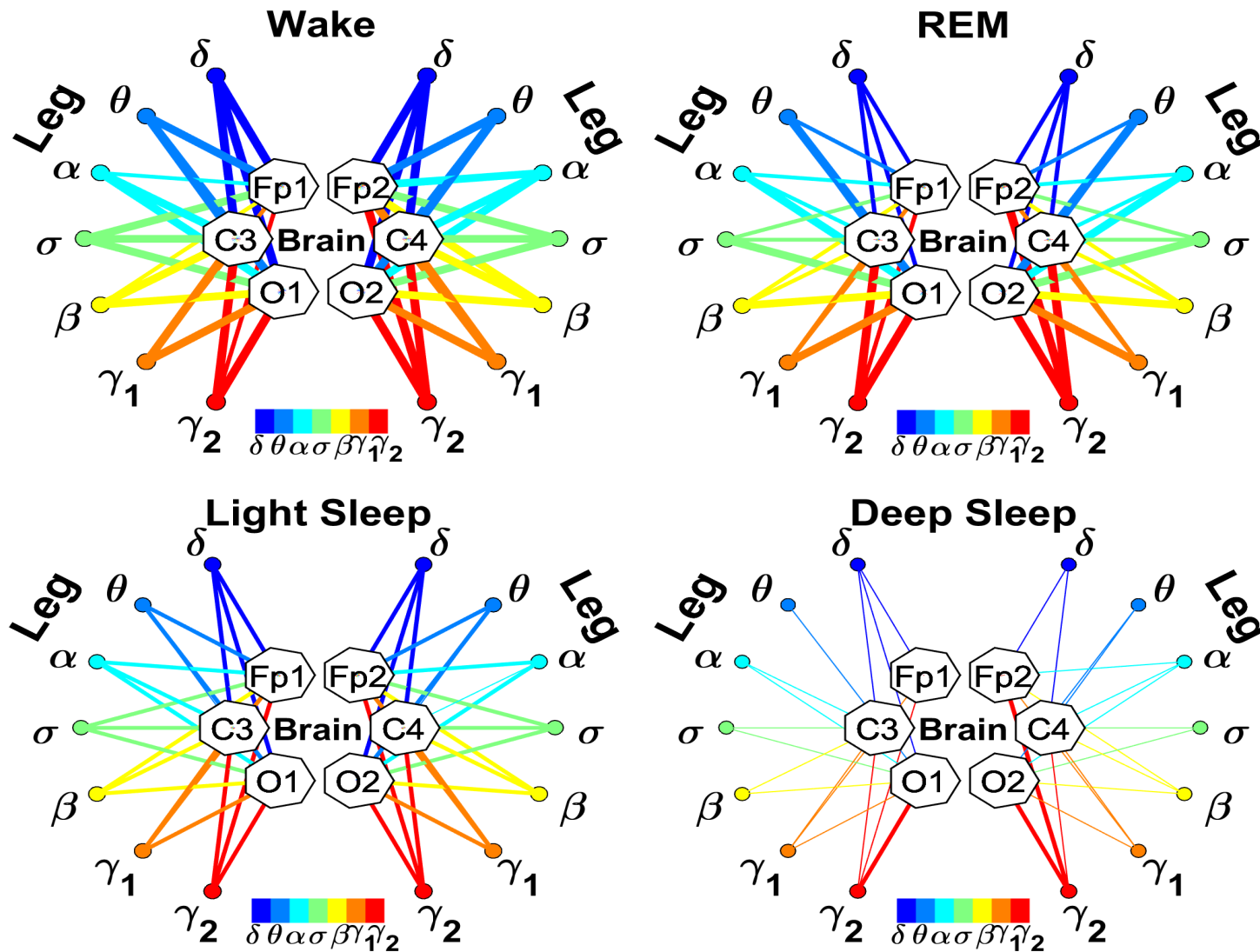


# Functional Interaction Networks Chin EMG Frequency Bands vs Brain Areas



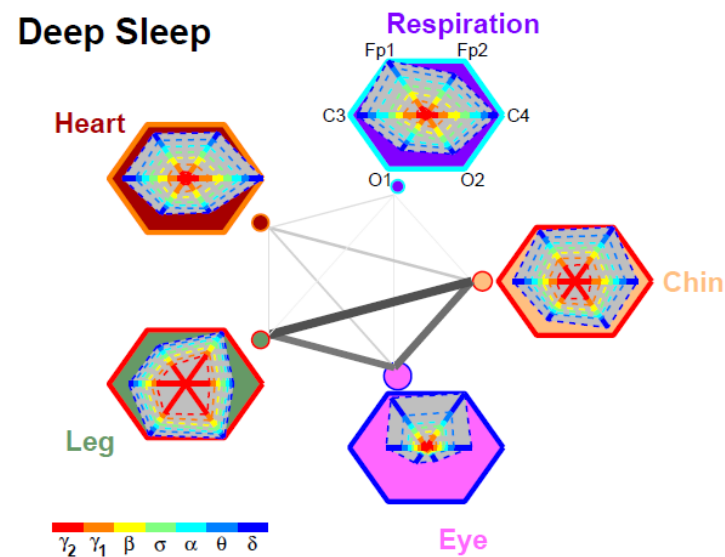
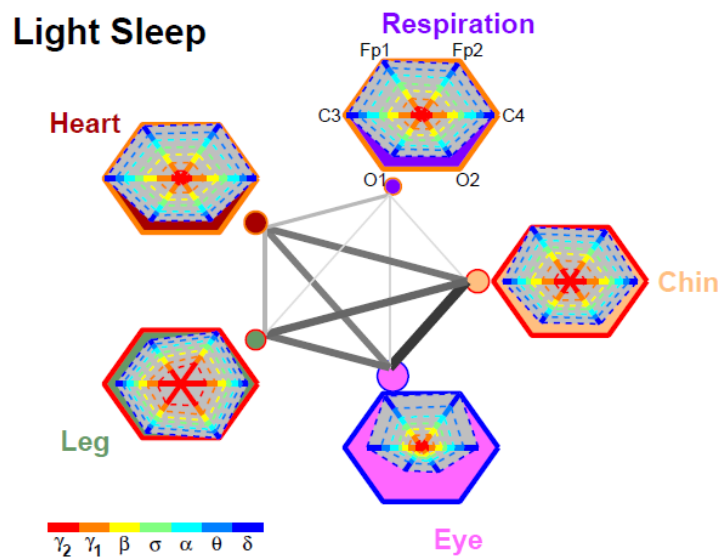
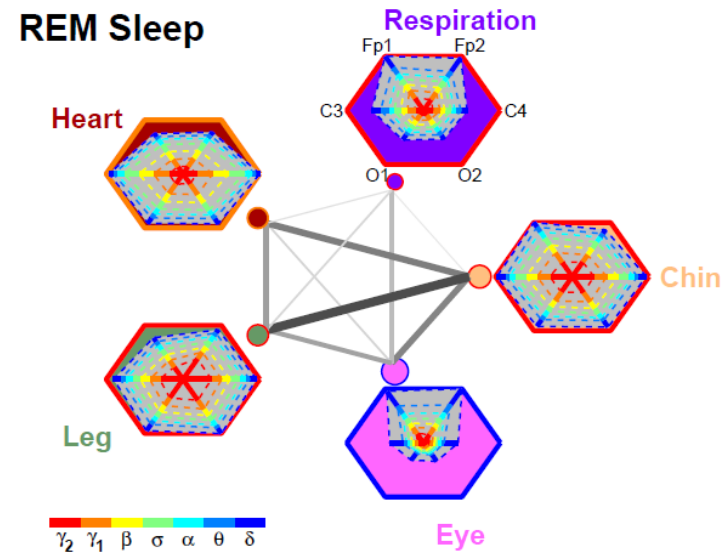
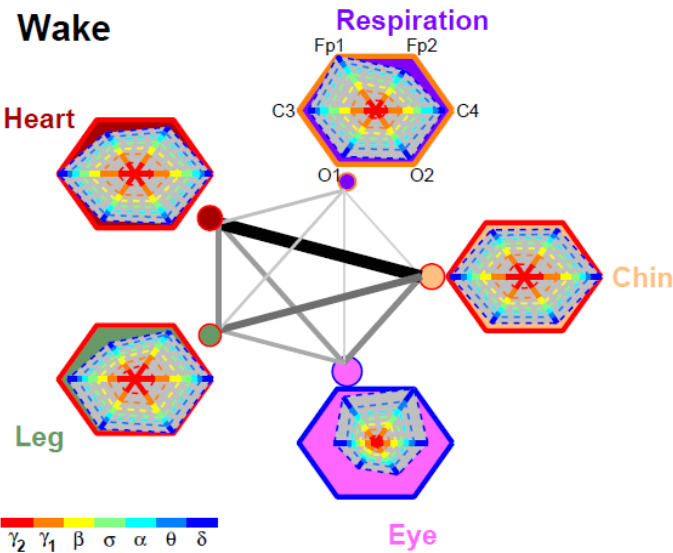


# Functional Interaction Networks Leg EMG Frequency Bands vs Brain Areas



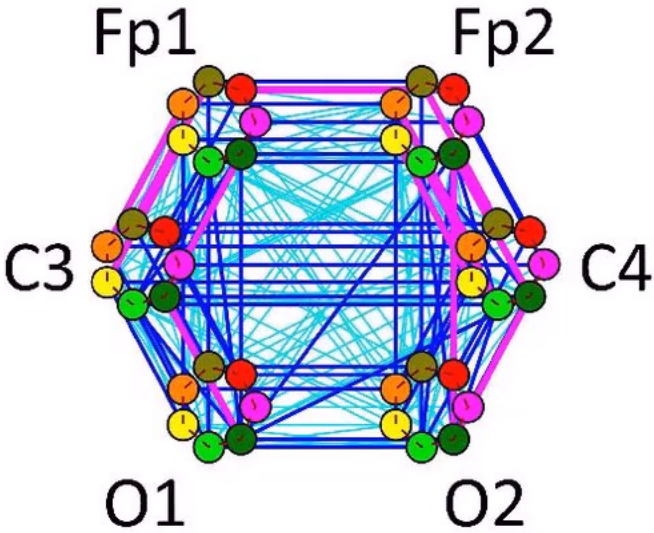
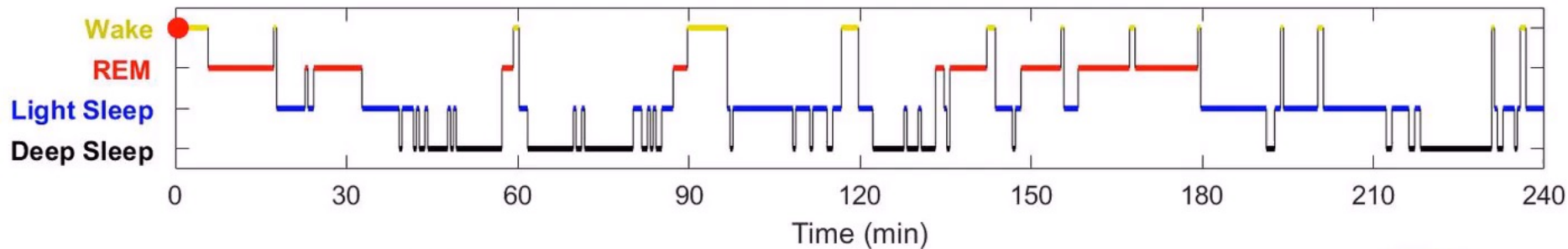
Level 3:  
Networked  
Interactions

# Network Physiology: Networks of brain activity and other physiologic systems across sleep stages

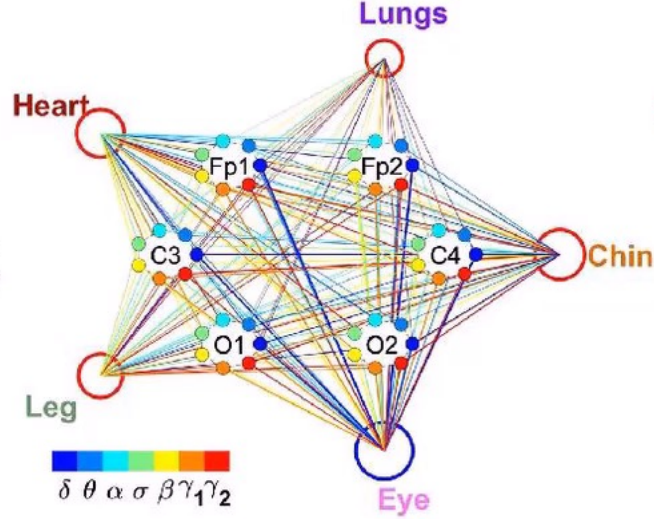
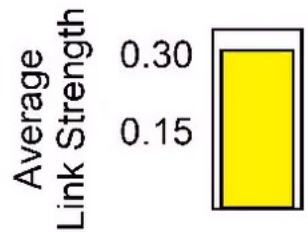


**Level 3:  
Networked  
Interactions**

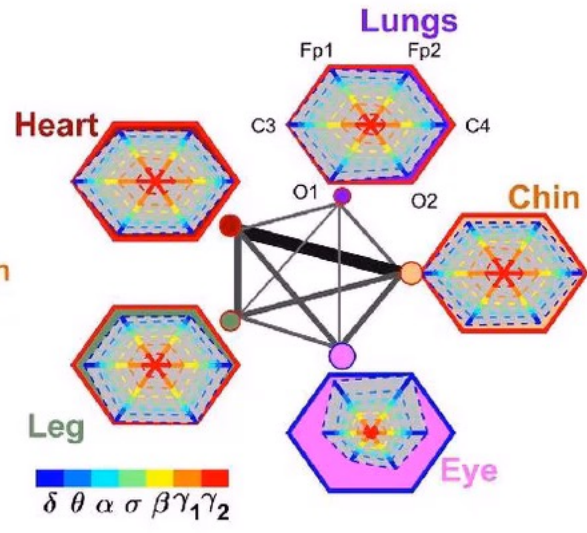
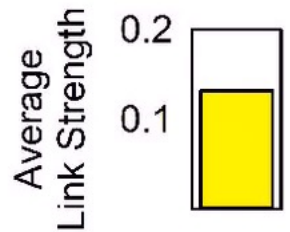
# Network Physiology: Networks of brain activity and other physiologic systems across sleep stages



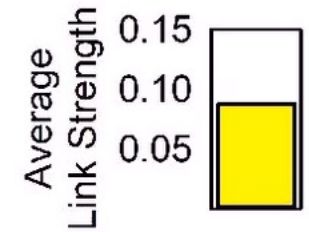
**Brain-Brain**



**Brain-Organ**



**Organ-Organ**



## Novel biomarkers



## New kind of Physicians



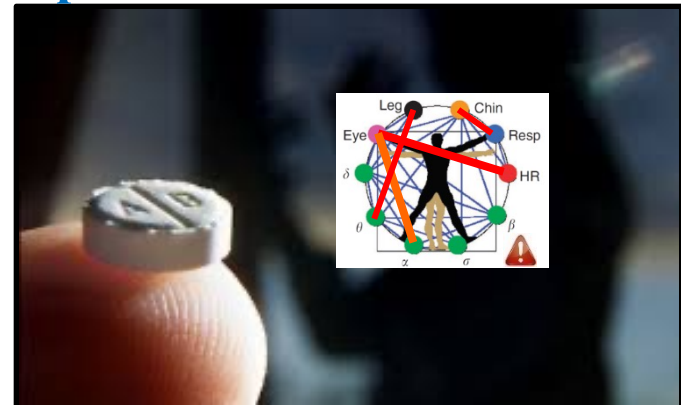
## Personalized health monitoring



## Next generation ICU monitoring devices and alert system

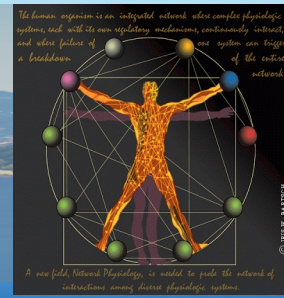


## Comprehensive assessment of drugs





**Third International Summer Institute  
on Network Physiology (ISINP)**  
Lake Como School of Advanced Studies,  
25 - 30 July 2022



## **New Journal: Frontiers in Network Physiology**



# **frontiers**

## **in Network Physiology**

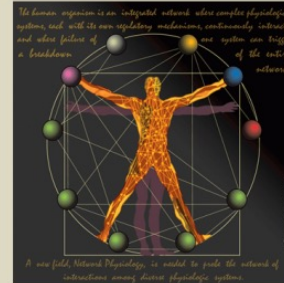
- **Ten journal sections**
- **Multiple focus issues**

Our Group:

<http://physics.bu.edu/labnetworkphysiology>



# Keck Laboratory for Network Physiology



*Openings:*

- **Research Scientists**
- **Visiting Researchers**

Support:

- *Atlas of Dynamic Interactions among Organ Systems*

W. M. KECK FOUNDATION

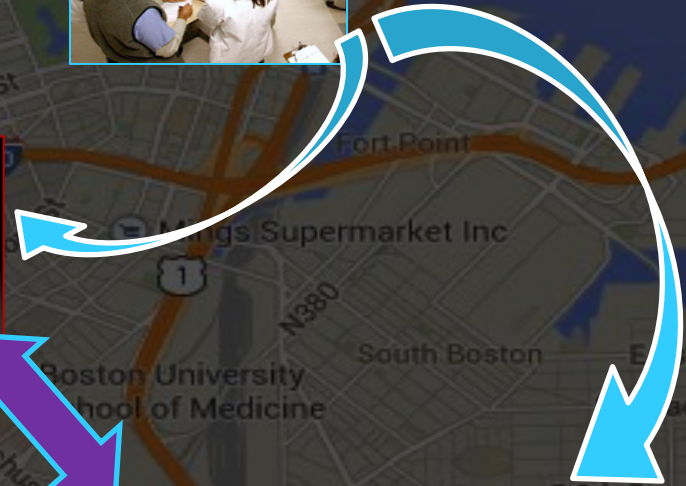
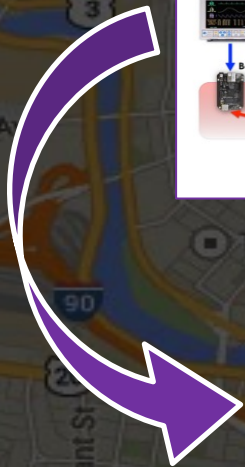
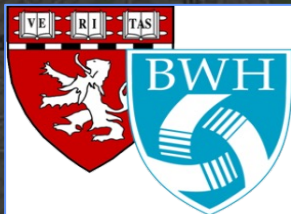
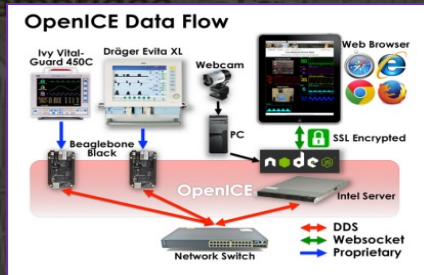


# Collaboration

# Ongoing Program: Interdisciplinary Collaboration



**Keck Support:** Catalyze a new field, *Network Physiology*; Leverage large-scale available resources





# Network Physiology

New BigData  
Dynamical Networks  
Sleep  
Network Analysis  
Lungs  
Human Physiome  
Multiple-Organ-Failure  
Nonlinear-Coupling  
Heart  
Brain  
Neuroanatomy  
Atlas-Organ-Interactions  
Synchronization  
Coordination-Emergence  
Medical-Device-platforms  
Physiologic-State-Function  
Statistical-Physics