Novel time delay stability approach to infer coupling in systems with bursting dynamics and to identify networks of organ interactions

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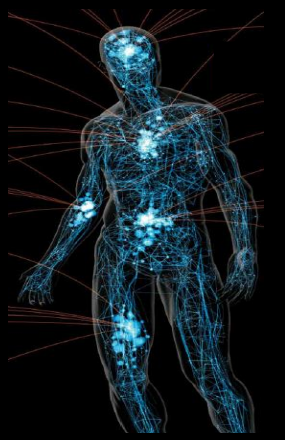


Phase transitions in physiolgic coupling. ***PNAS 109(26)*** *(2012).*

Network Physiology reveals relations between network topology and physiological function. ***Nature Communications*** *3:702 (2012).*

Network Physiology: How organ systems dynamically interact . ***PLoS ONE*** *10(11): e0142143 (2015).*.

ISINP, Como 7/26/17

Multiple Organ Failure

• leading cause of death in most intensive care units
(Deitch EA. *Ann. Surg.*1992;216:117–134;
Buchman TG. *Complex Systems Science in BioMedicine* 2006; 631–640.)

• autopsy findings in patients show that:
→ organs are intact
→ tissue architecture is preserved
→ cells do not appear abnormal
(Lizana FG et al. *Med. Clin.* 2000;114:99–103)

What went wrong?

Multiple Organ Failure

• Multiple Organ Failure = Uncoupled Oscillators?!
(Buchman TG. Ibid)

• critical care medicine offers support for specific organ systems but also need to support (”fix”) the links between organ systems

→ Important to identify and quantify interactions between organ systems, and how these interactions change under different conditions and with medical treatment.

• prior to our work, there was no systematic method to quantify these interactions

Network of physiological interactions

Despite its importance to physiology and medicine the network of interactions between organ systems in the human body is *not known*

Need a map of real-time communications between organ systems

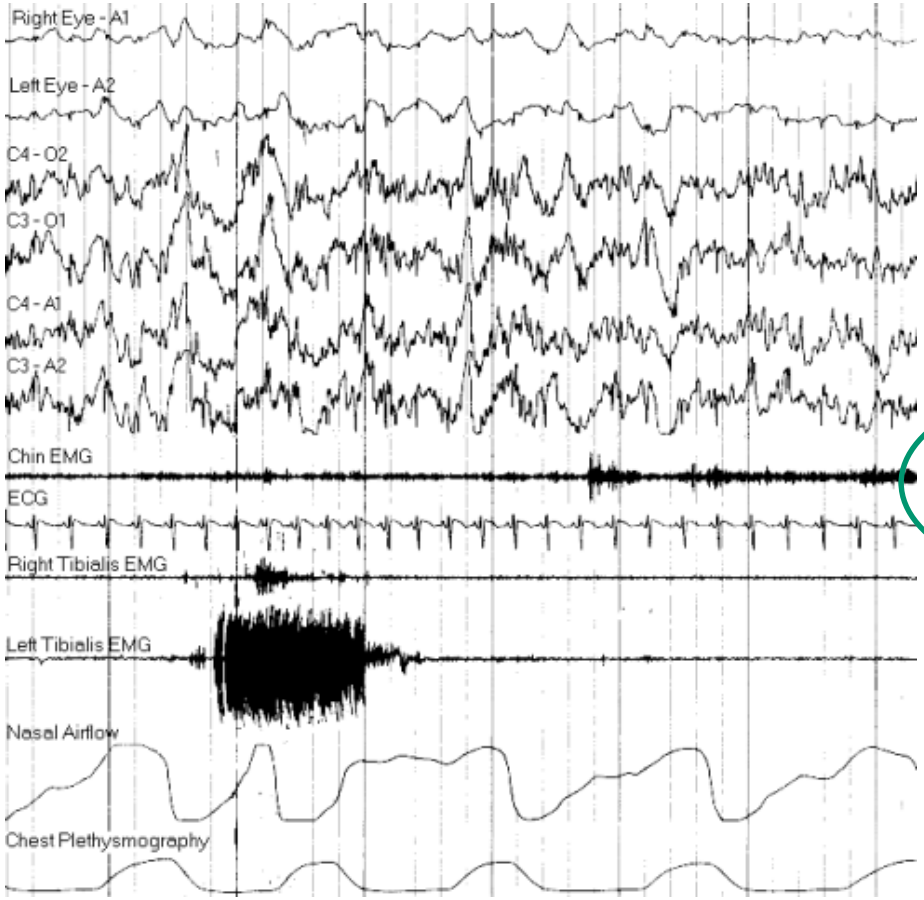
Challenges:

- Network nodes are not simple units but *complex dynamical systems*
- Network nodes are *diverse systems* working on different time scales
- Network nodes are involved in *multiple simultaneous interactions*
- Network nodes have *output characteristics* that *change in time*
- Network links/strength of *coupling* between systems *varies in time*

Physiological data

Muscle tone
EMG

Respiration



Eye movements
EOG

Brain activity
EEG

Heart dynamics
ECG

→ Network of dynamical interactions; study the evolution of multiple physiologic interactions across different physiologic states

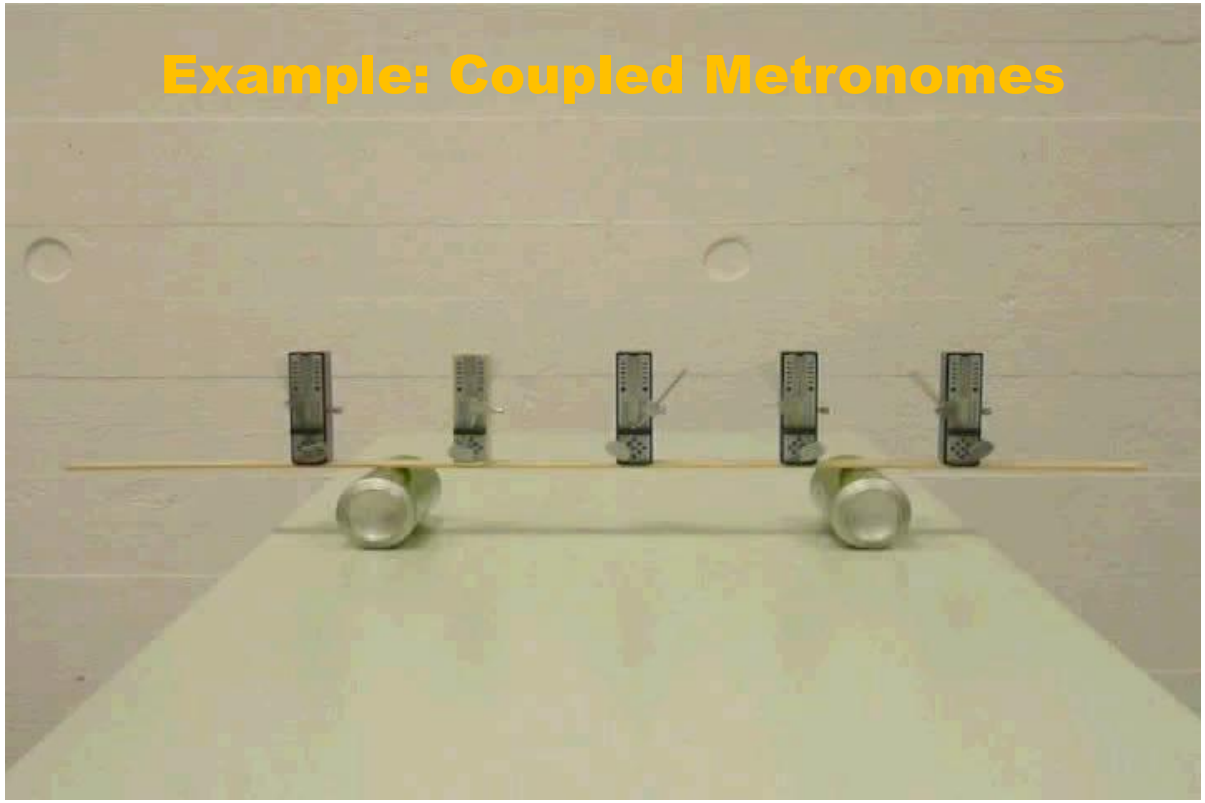
Synchronization: Definition

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

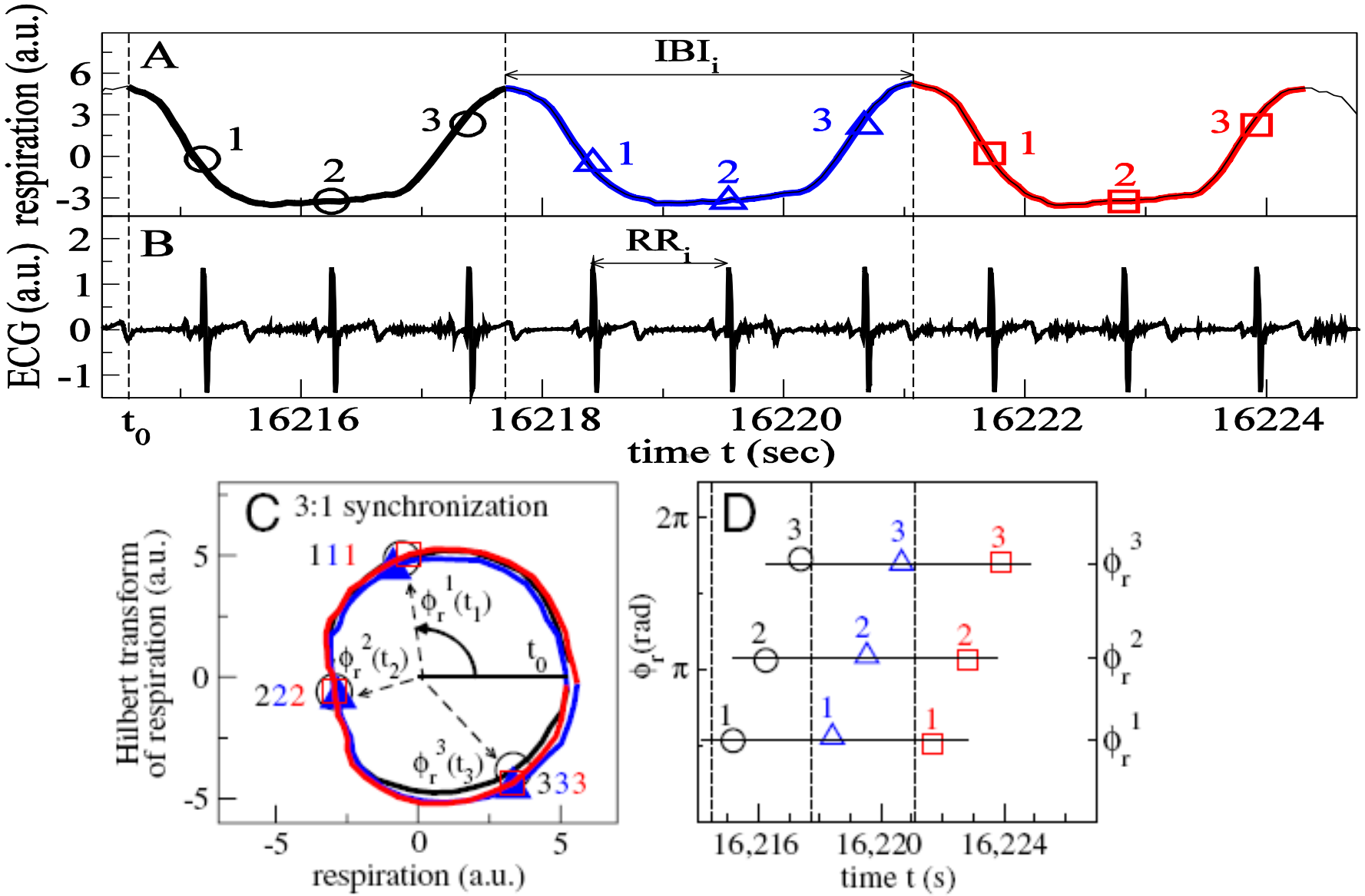
Pikovsky, Rosenblum, Kurths.
Synchronization: a universal concept in nonlinear sciences
Oxford University Press, 2001

Start:
different frequencies,
different phases
→ No synchronization

End:
same frequencies,
same phase difference
("phase locked")
→ Synchronization

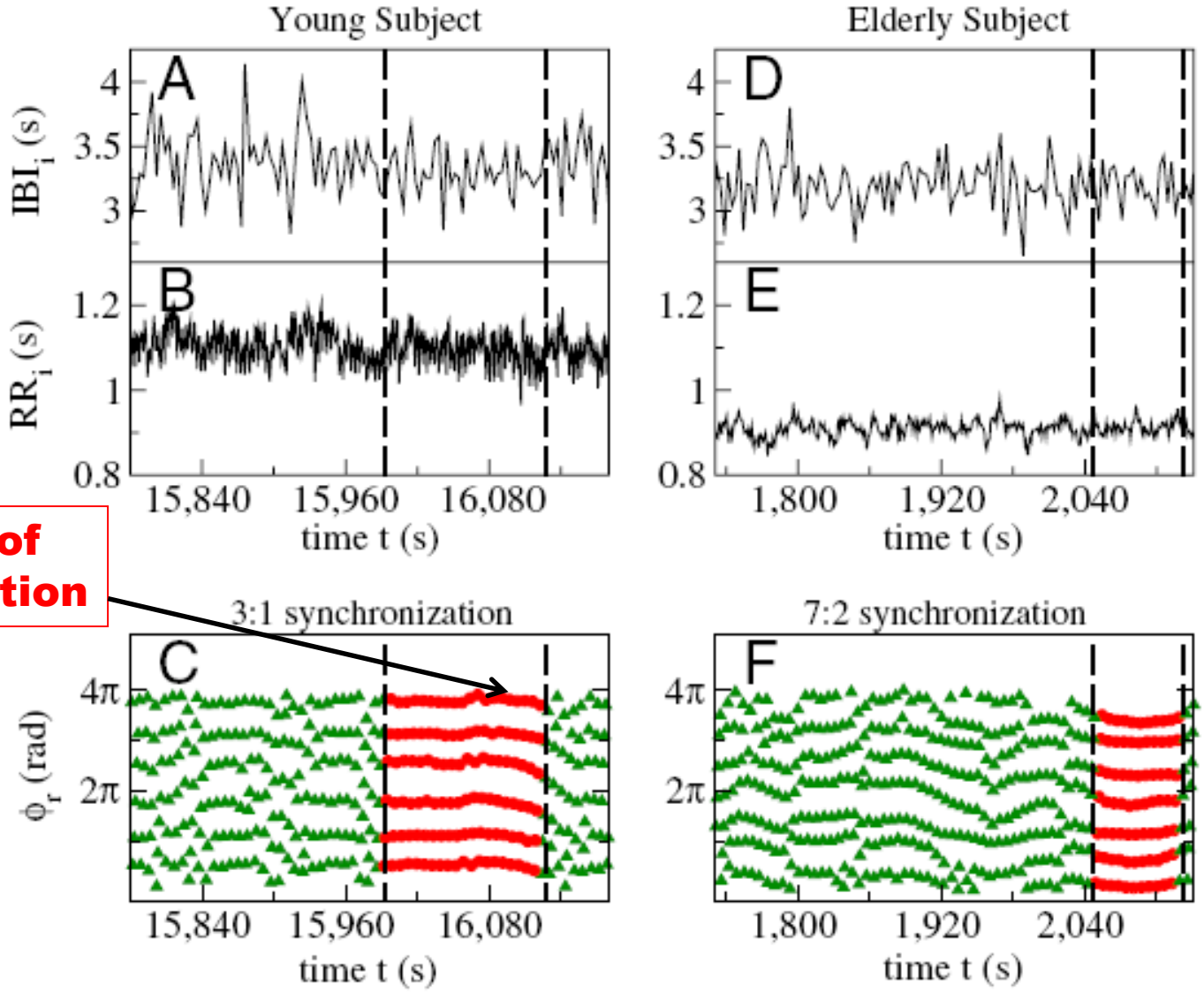


Cardio-respiratory phase synchronization



Cardio-respiratory phase synchronization

despite continuous fluctuations



Segments of Synchronization

Cardio-respiratory phase synchronization
during full-night sleep

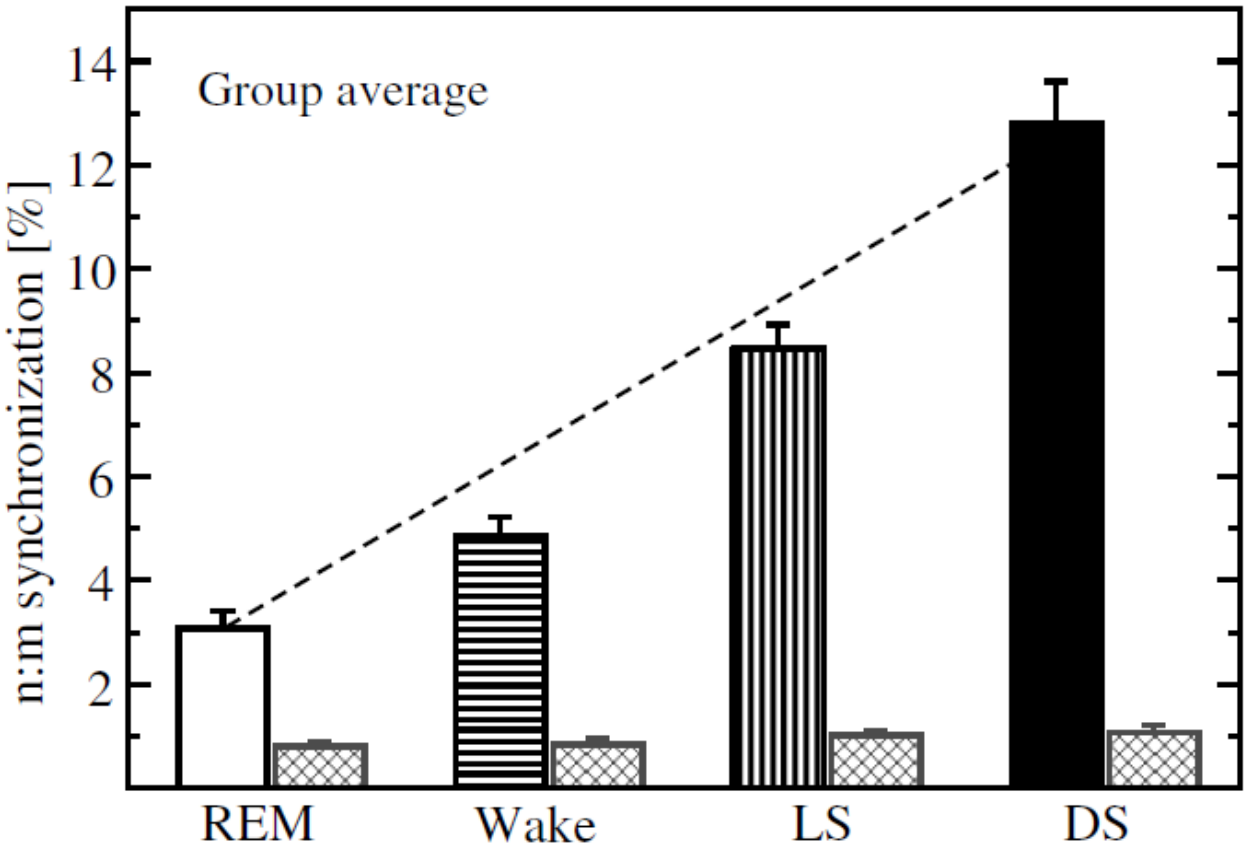
Polysomnographic Database:

- **simultaneous recordings of heartbeat, respiration and sleep stages of 200 healthy subjects during sleep (EU-Project SIESTA)**
- **all age groups from 20-90 years**
- **data length 8 hours**

Cardio-respiratory phase synchronization

across sleep stages

Pronounced stratification of synchronization

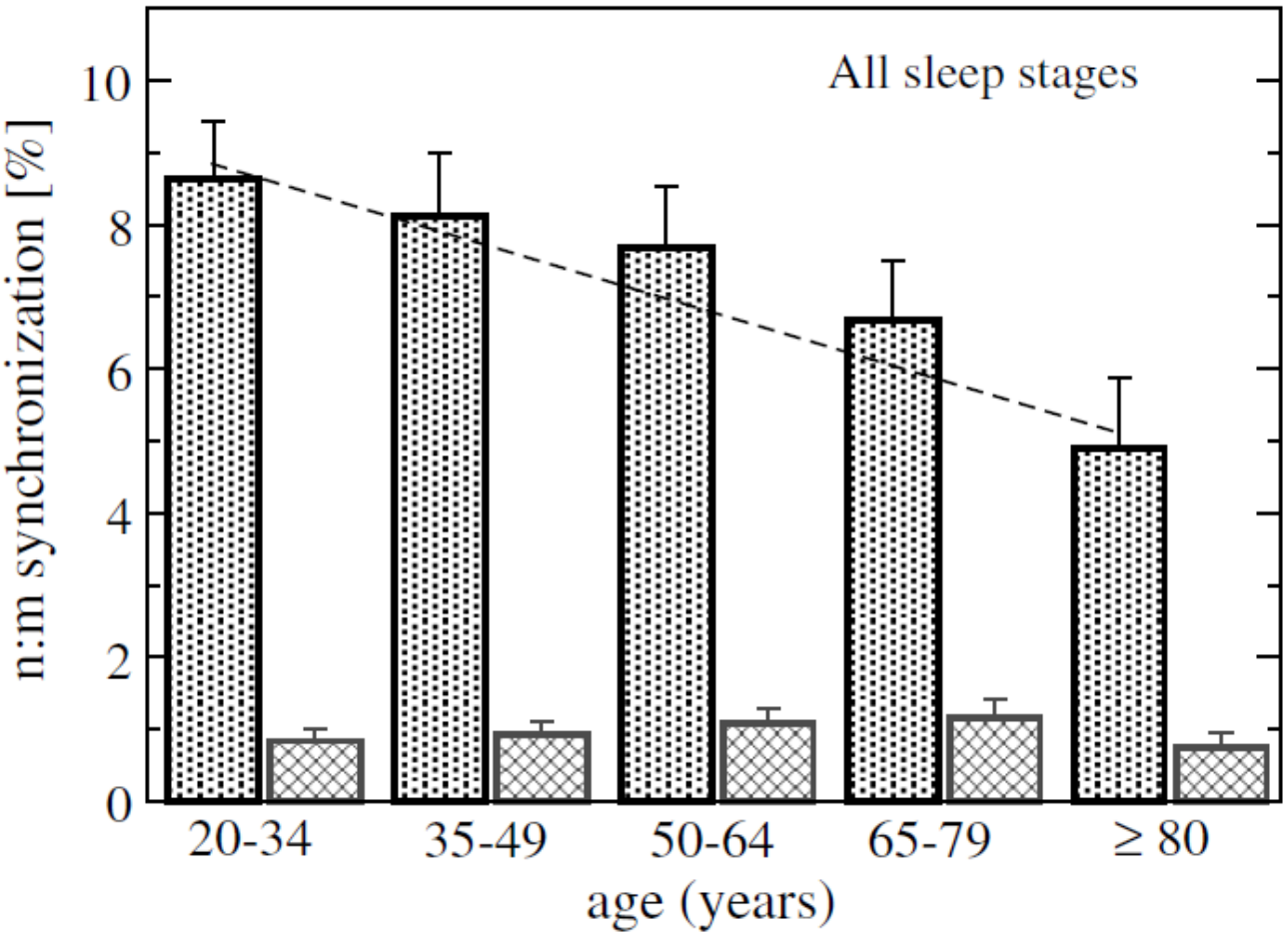


400% increase in synchronization from REM to deep sleep

Phase transitions in cardio-respiratory coupling

Cardio-respiratory phase synchronization

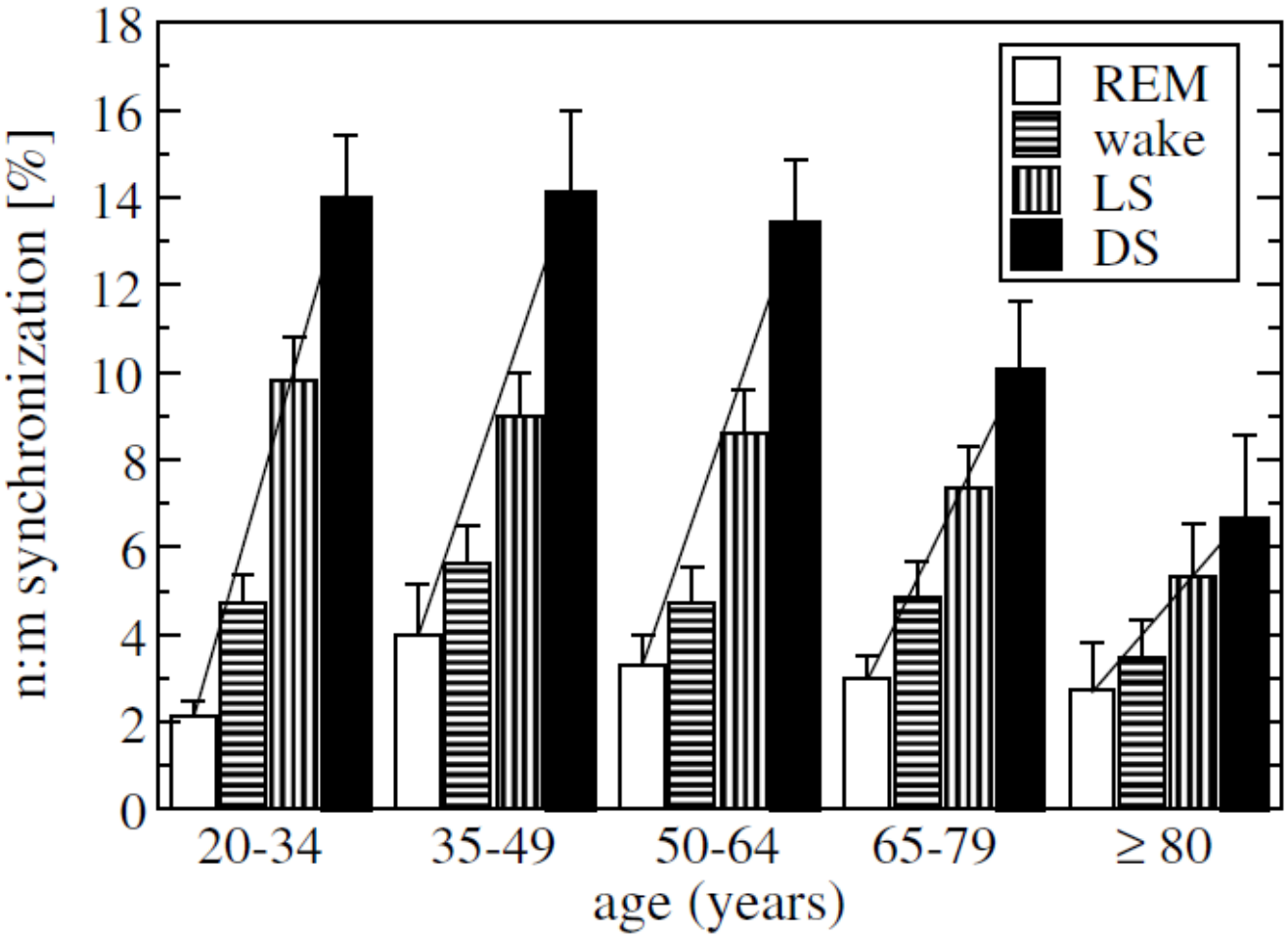
across age groups



50% reduction with advanced age

Cardio-respiratory phase synchronization

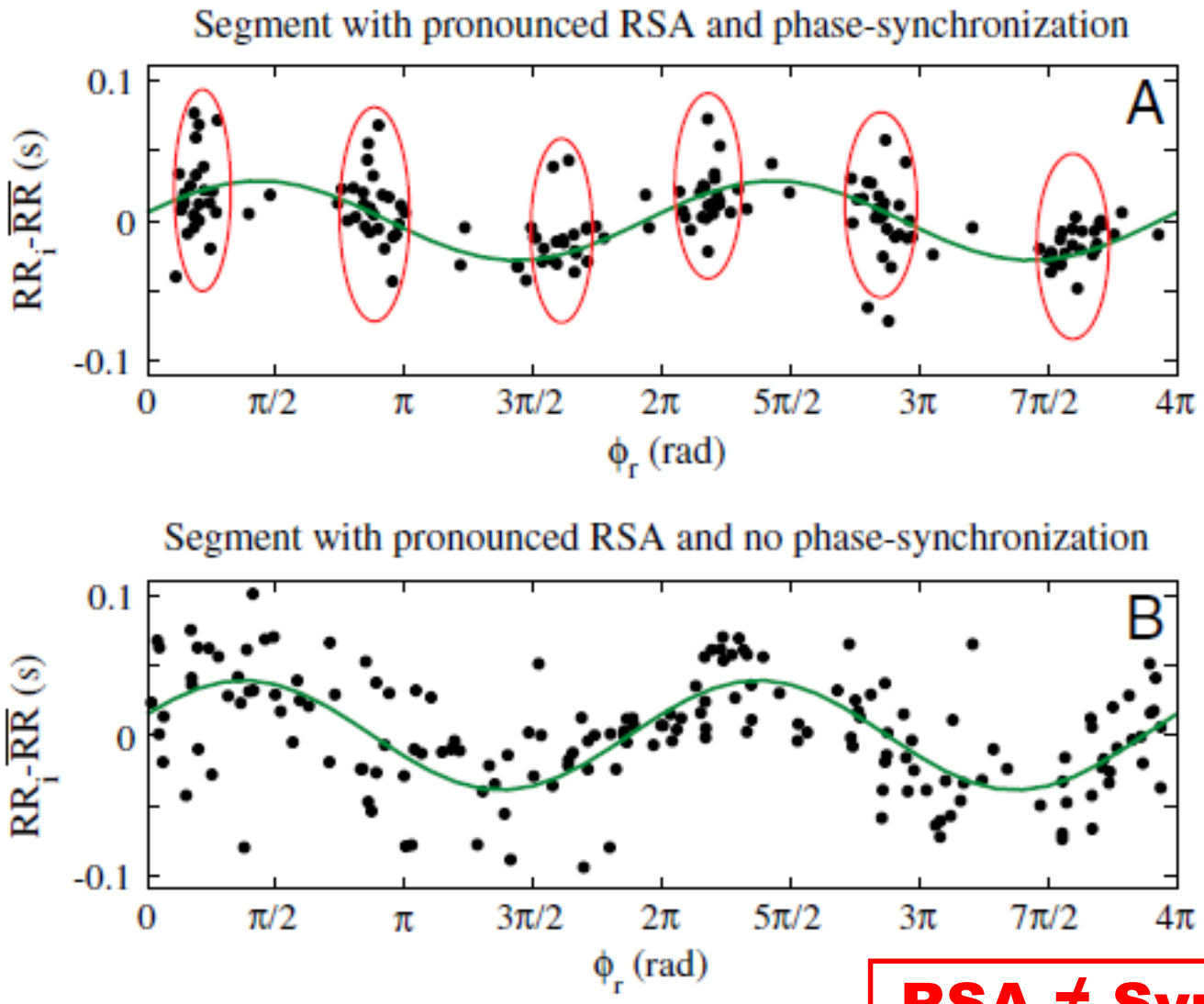
Stratification pattern across all age groups



sleep-stage stratification pattern is *stable* for all age groups

RSA versus Phase Synchronization

two distinct forms of cardio-respiratory coupling

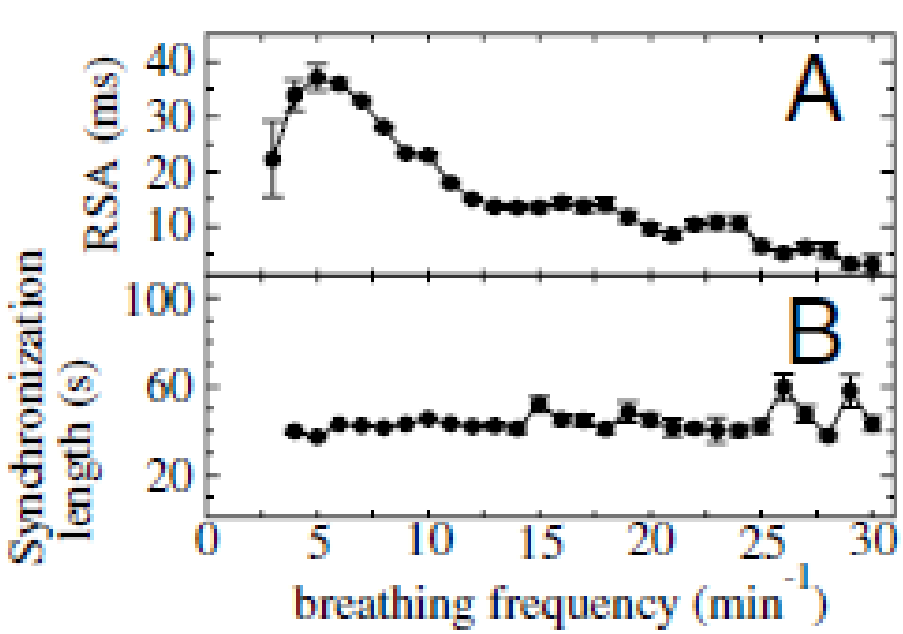


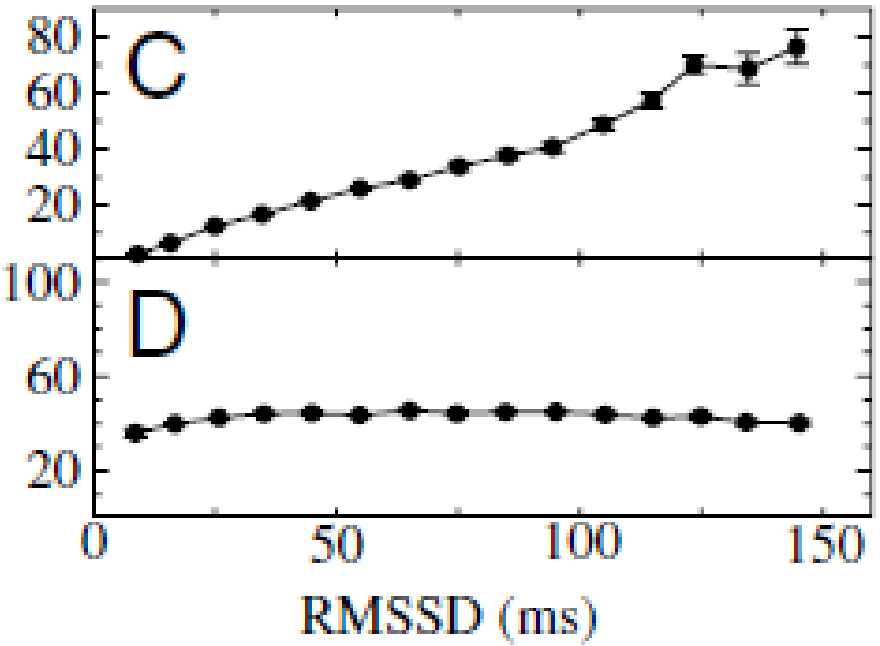
Same subject, same sleep stage episode

RSA ≠ Synchronization

RSA versus Phase synchronization

Dependence on key physiologic variables

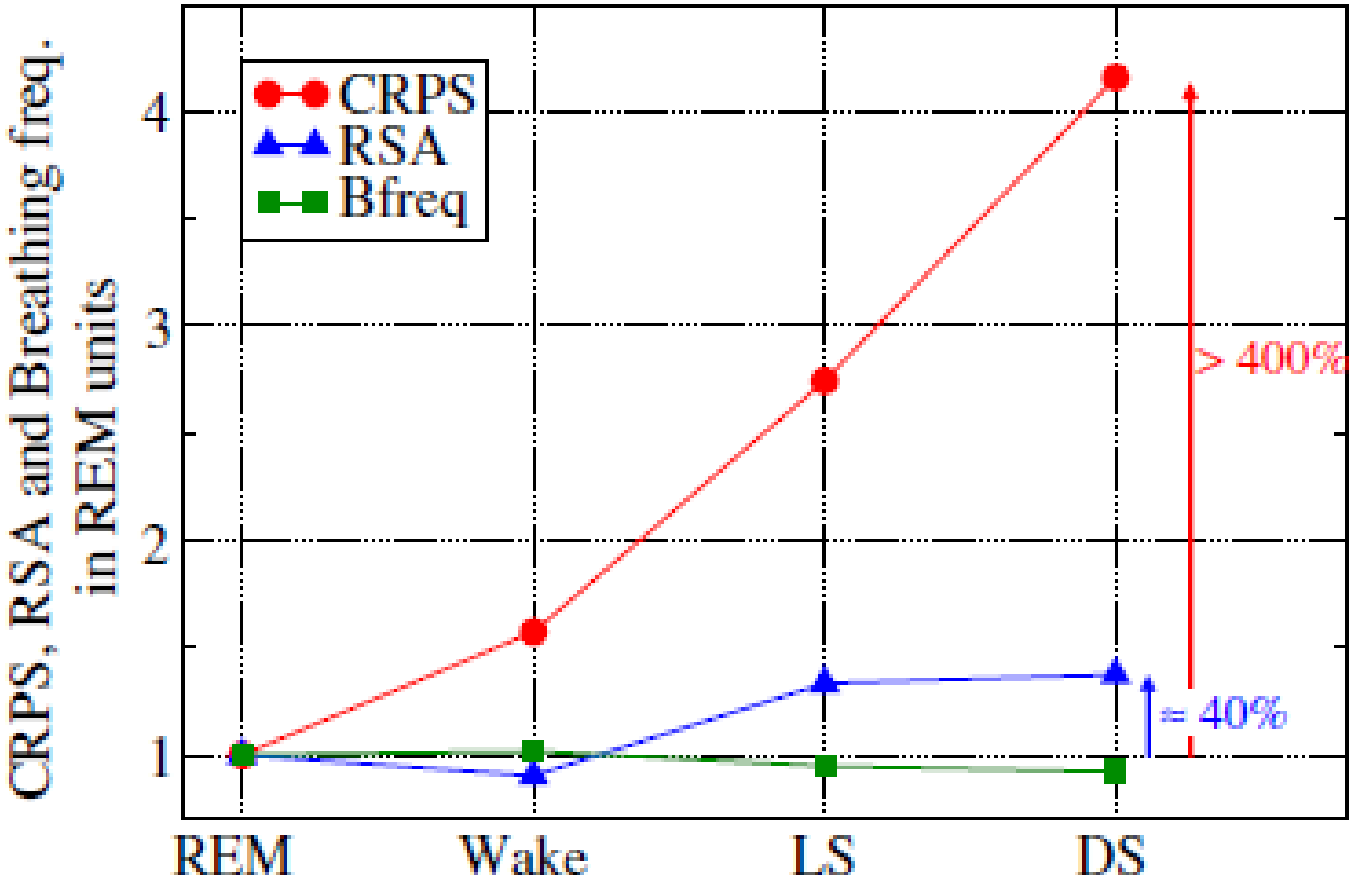




Measure of parasympathetic tone

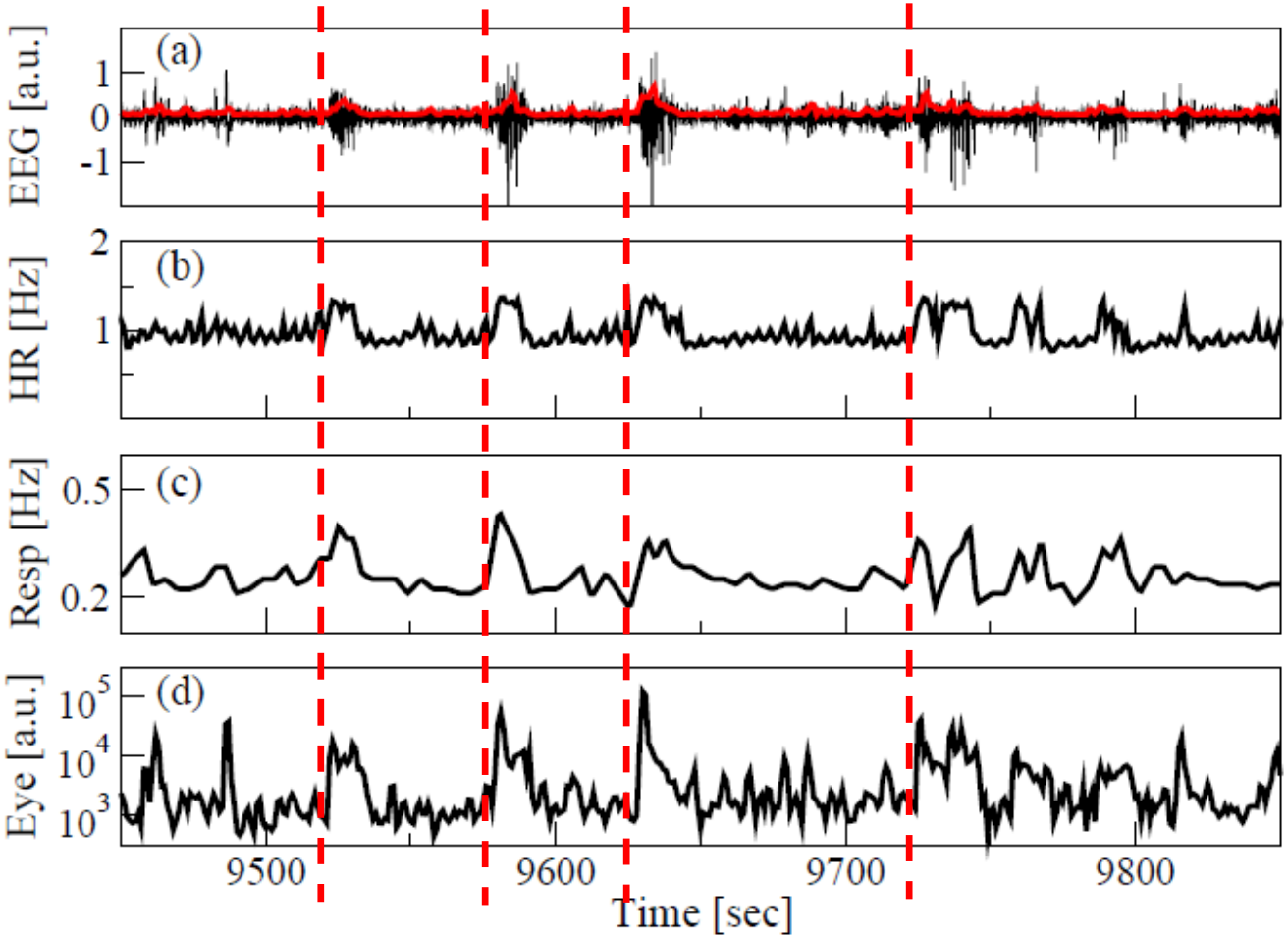
→ different mechanisms underlie these two forms of cardio-repiratory interaction

RSA versus Phase synchronization



→ **cardio-respiratory phase synchroniztion: very sensitive marker of neuroautonomic control**

Synchronized activity across diverse systems



EEG-σ band: sleep spindles

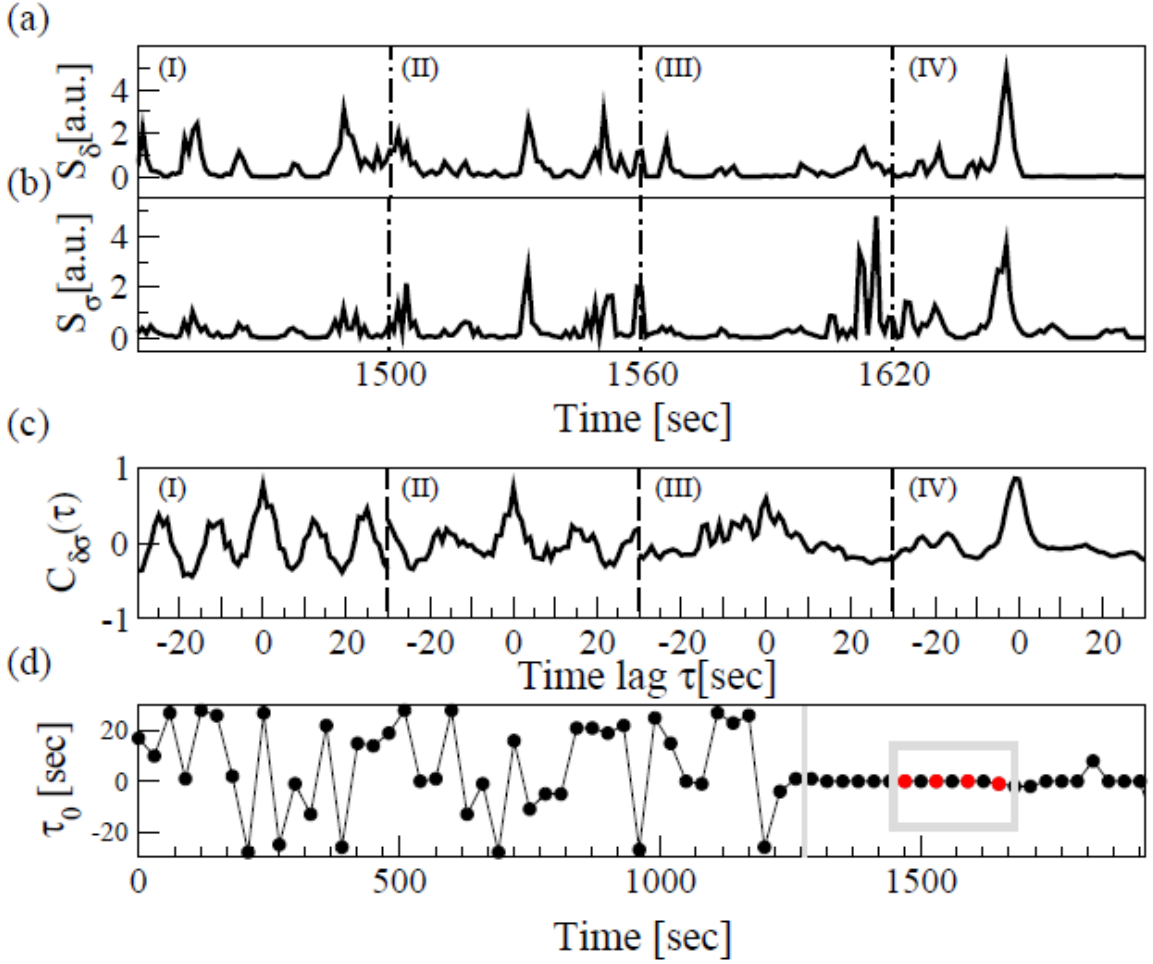
Heart rate

Respiratory rate

Eye movements

→ Bursts in the dynamics of one system are correlated with bursts in other systems

Quantifying interactions between diverse systems: concept of Time Delay Stability



normalized spectral power of EEG-δ band

normalized spectral power of EEG-σ band

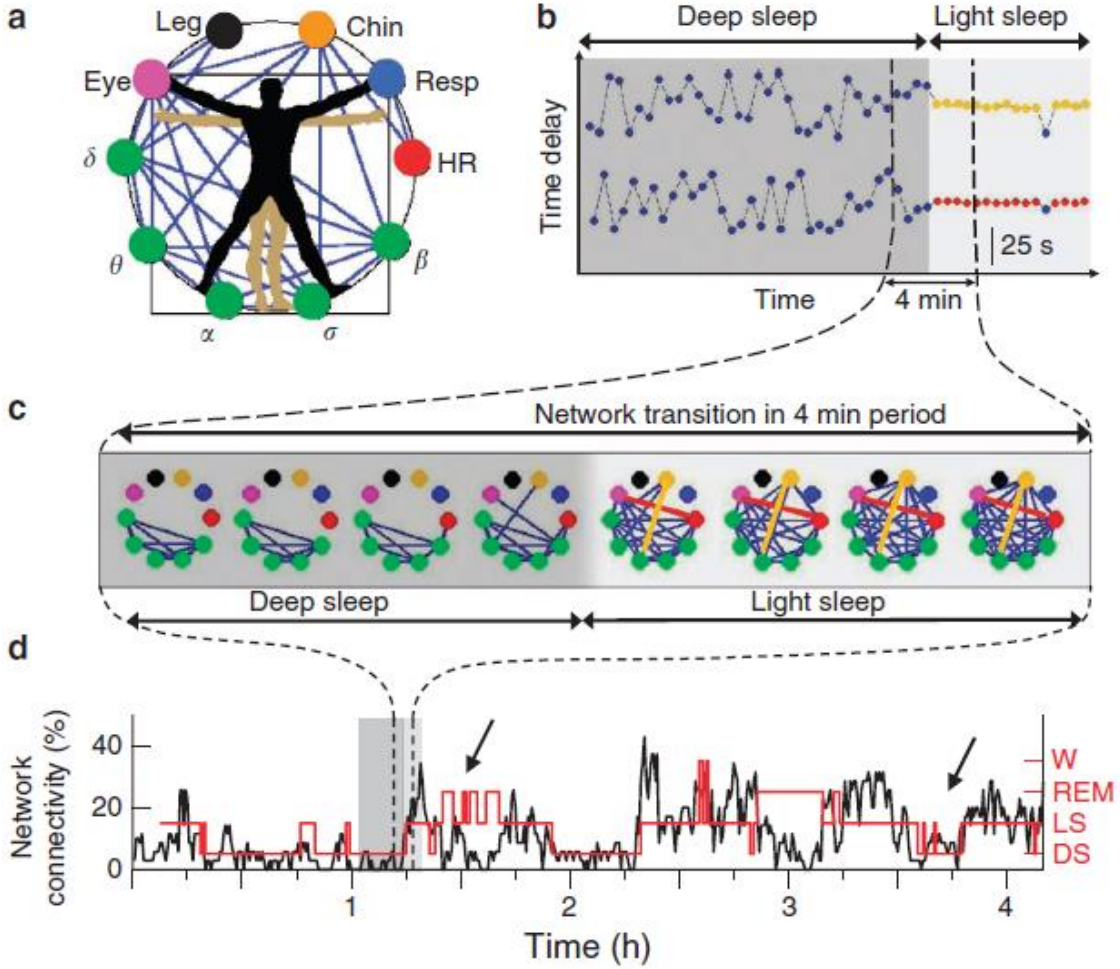
Cross-correlation function vs. time lag in 60 sec windows

Time delay vs. real time

$$\%TDS = \frac{stable\ time}{total\ time} \times 100$$

→ Time periods of constant time delay indicate stable interaction represented by network links

Transitions in the network of physiological interactions



α – Chin interaction

HR – Eye interaction

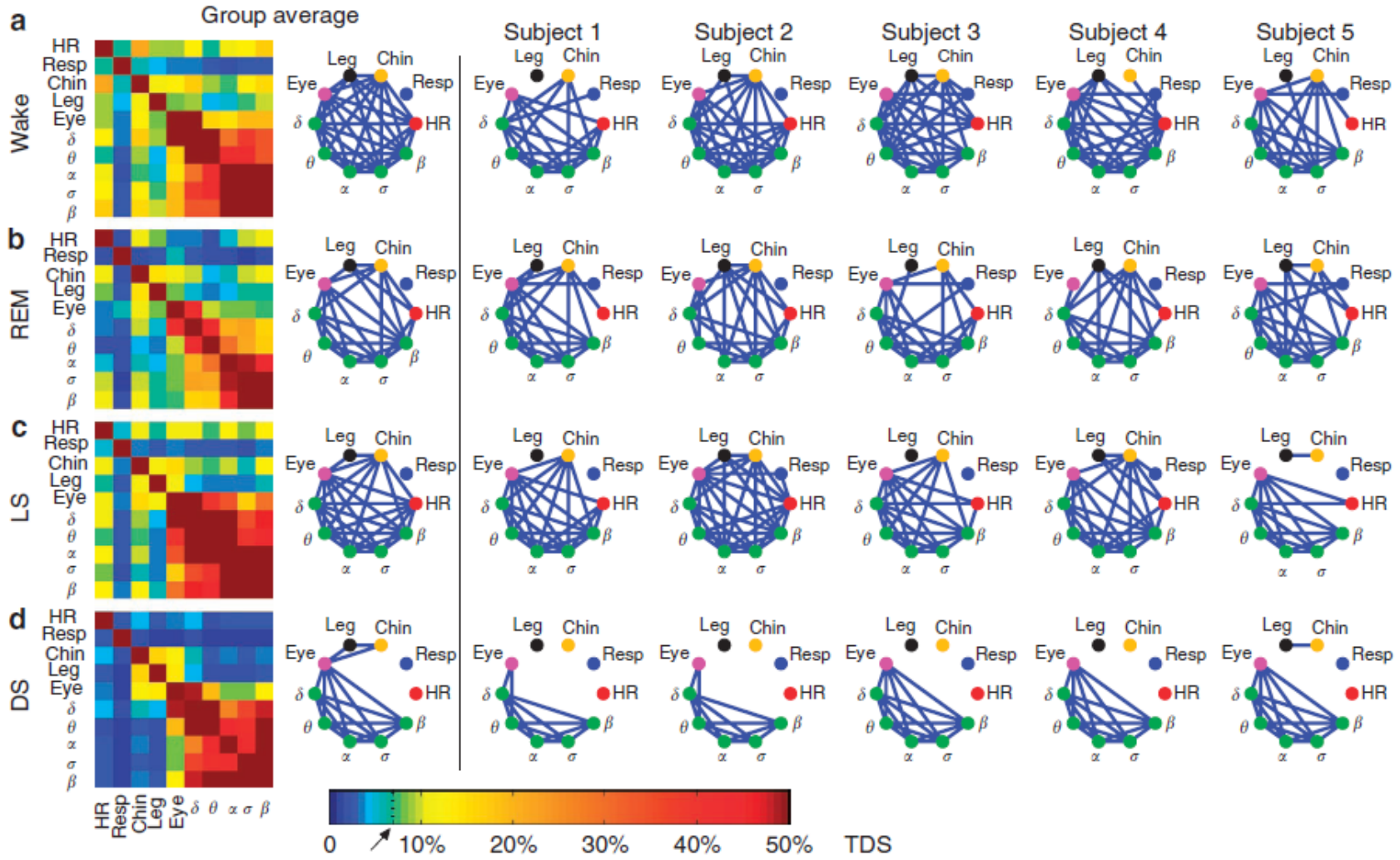
4 min snapshot

Dynamical Evolution

→ Fast reorganization of network connectivity with transitions across physiologic states

Network connectivity across sleep stages

Wake, REM sleep, Light sleep (LS), Deep sleep (DS)

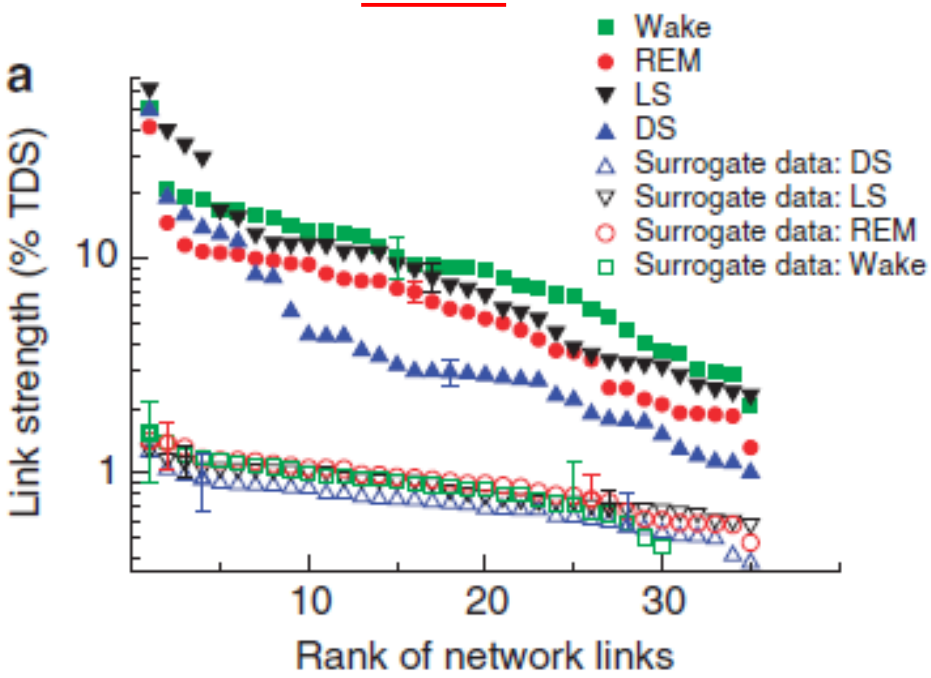


→ Network topology changes with sleep-stage transitions

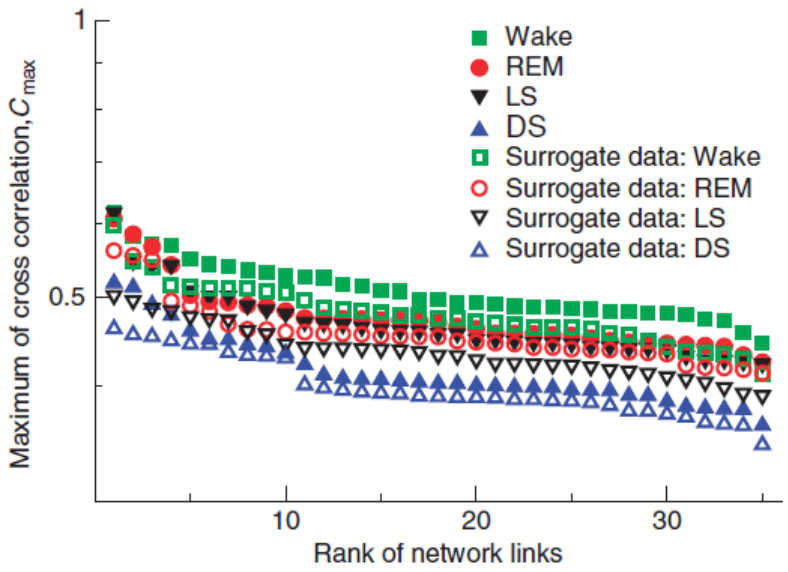
Rank distributions of the strength of network links

Group-averaged strength of individual links

TDS



Cross-Corr



Sleep-stage stratification pattern for most links

No difference between real and surrogate data

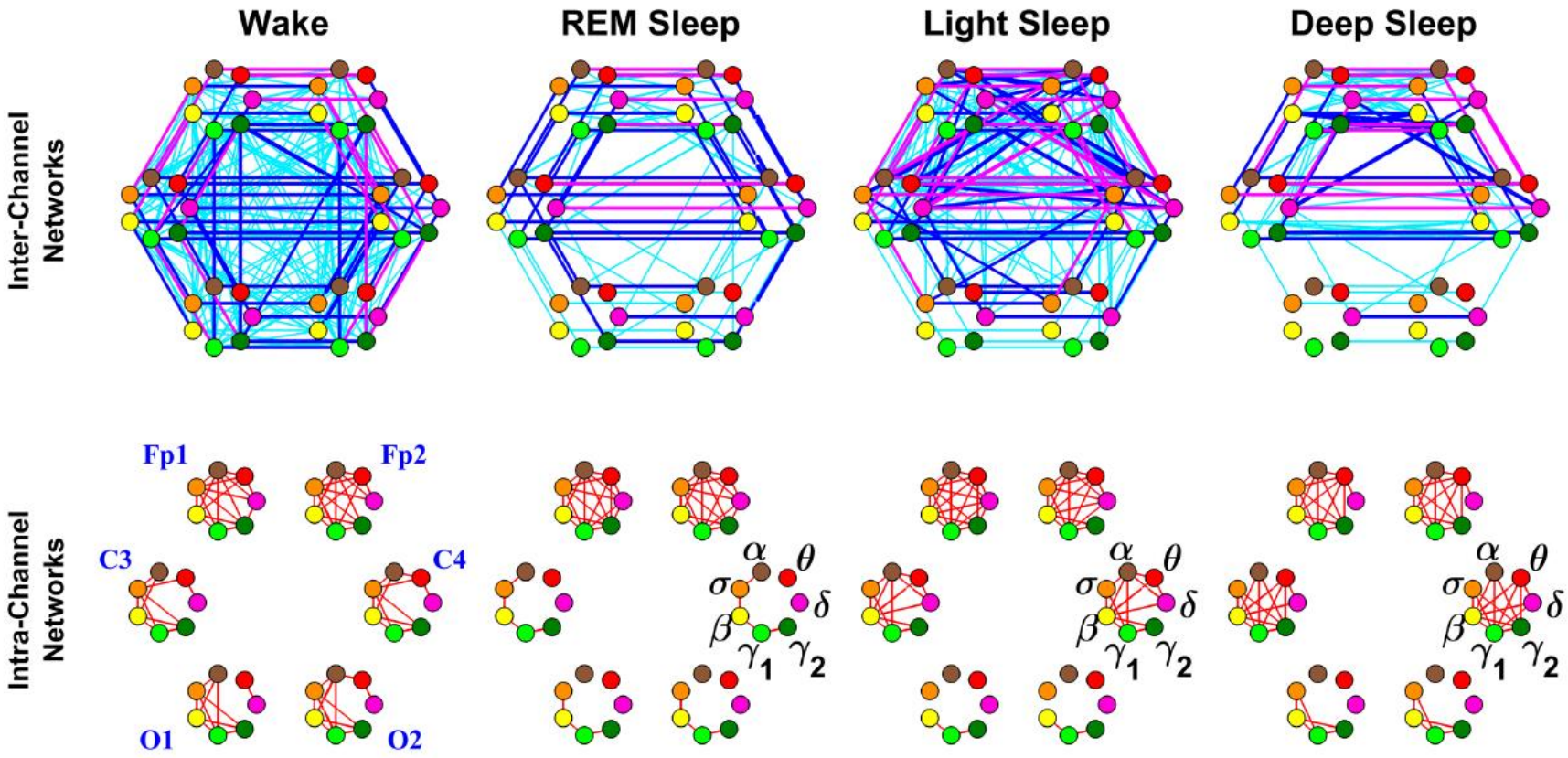
Time Delay Stability (TDS)

- **Suitable for heterogeneous and non-stationary signals**
- **Not affected by autocorrelations**
- **For systems with changing coupling strength**

→ Captures the dynamics of interactions

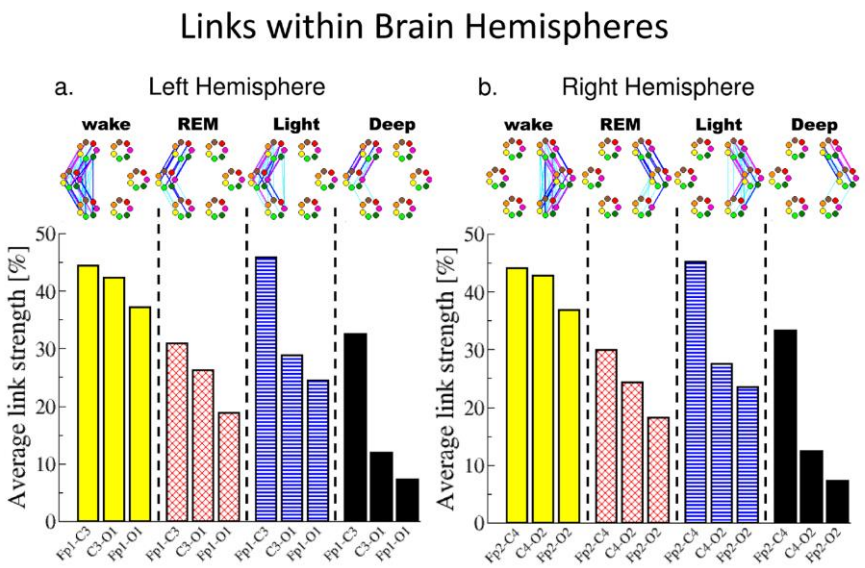
- **Can be applied to diverse systems**

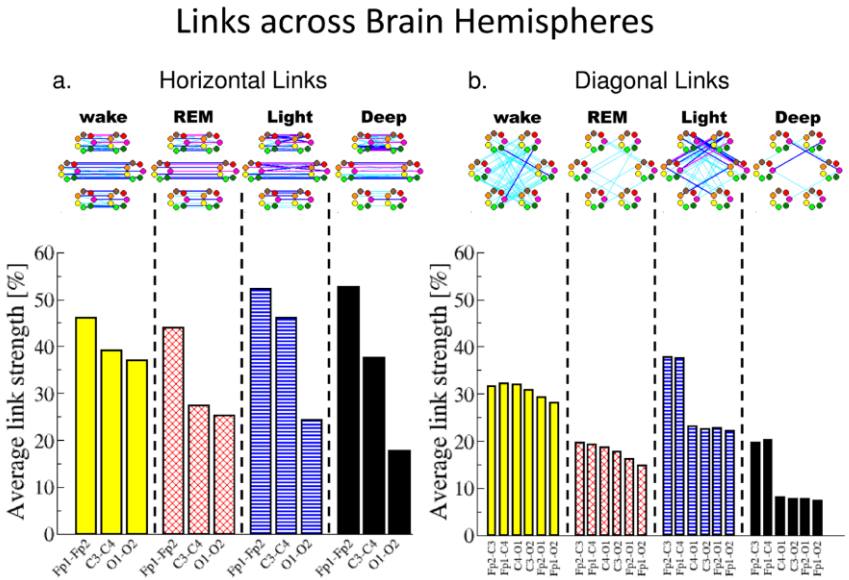
Network Physiology
Networks of brain activity across sleep stages



Phase transition in link strength and network topology

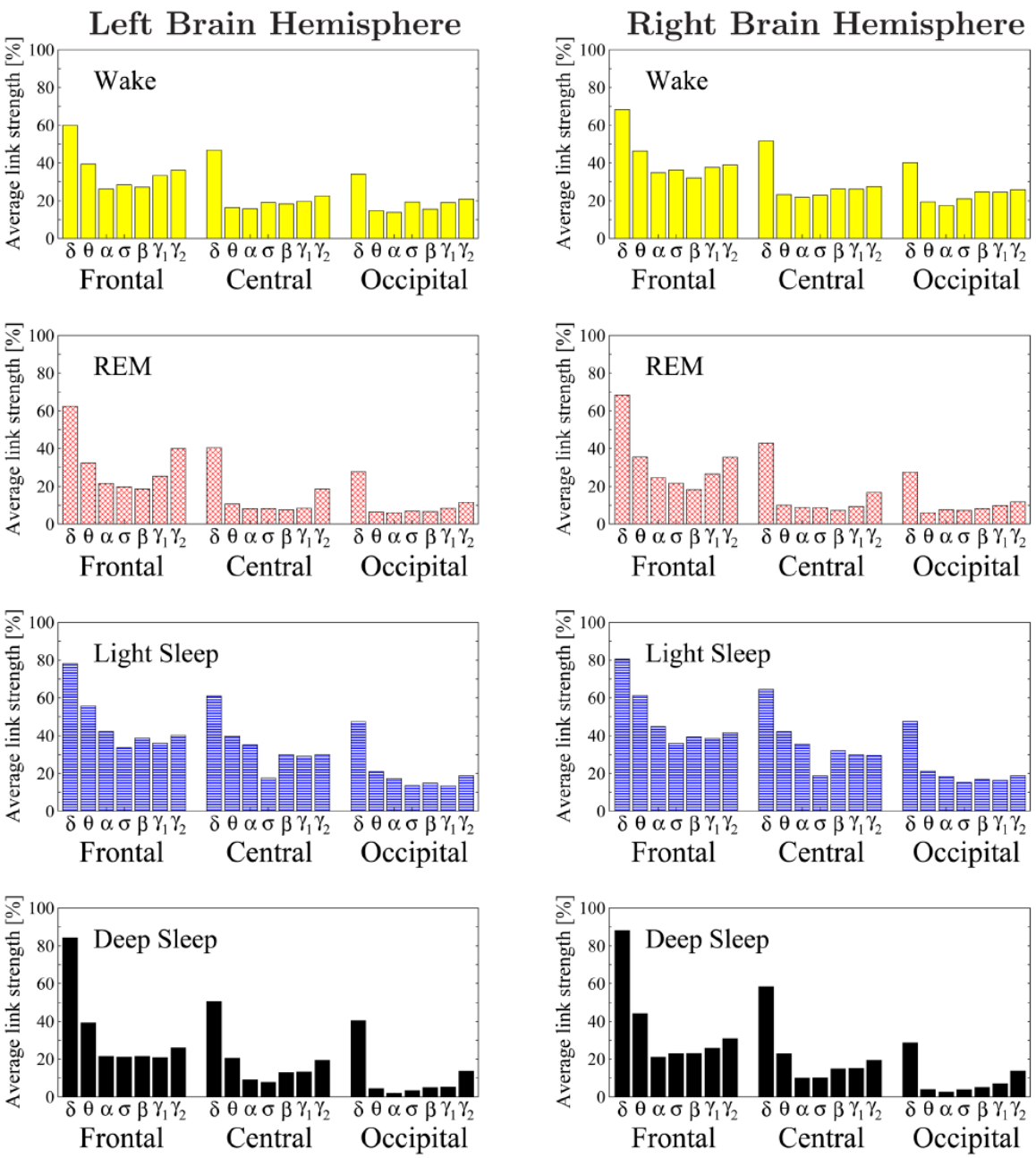
Network Physiology
Networks of brain activity across sleep stages



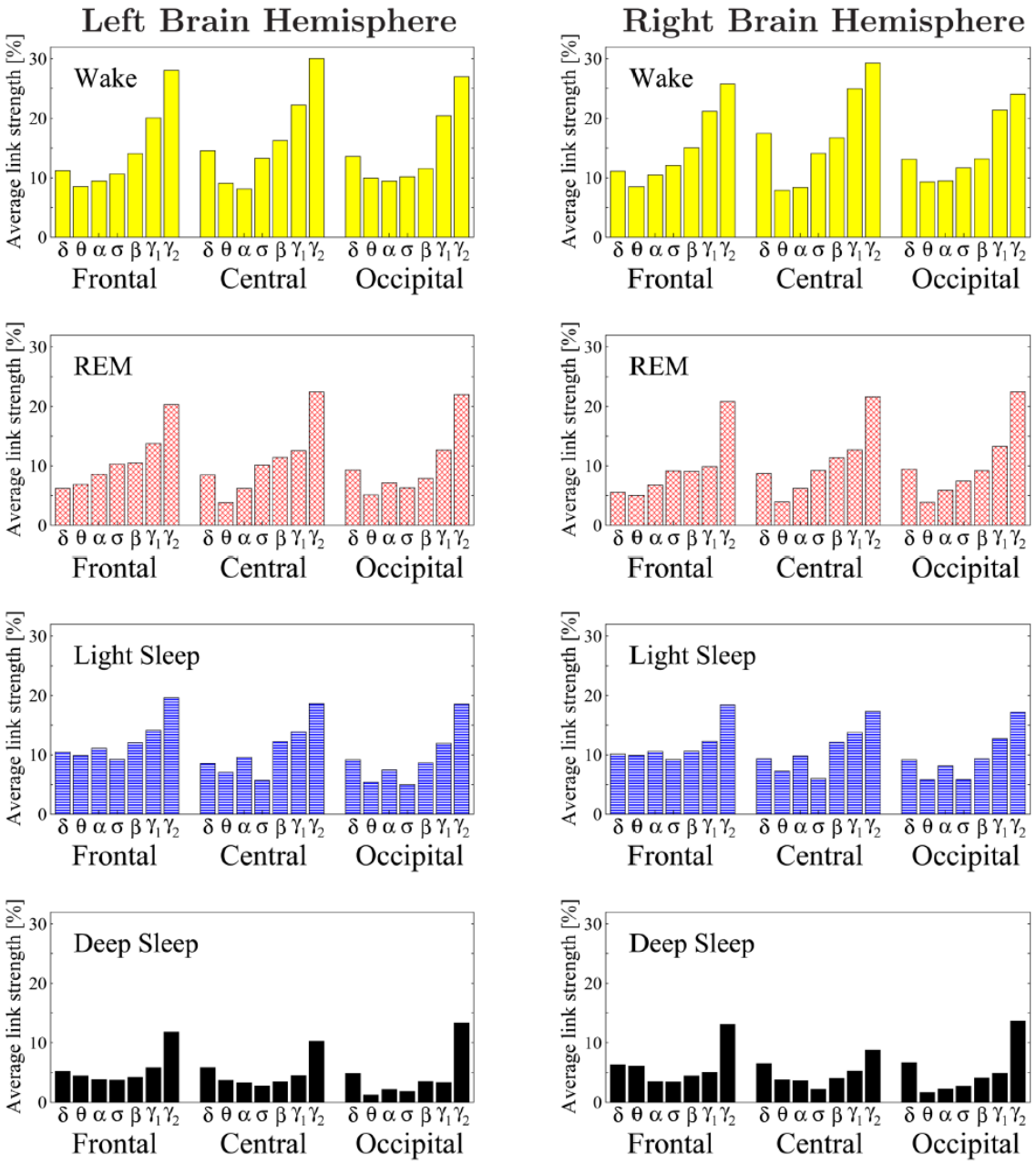


→ **Sleep-stage stratification pattern for physiologic interactions**

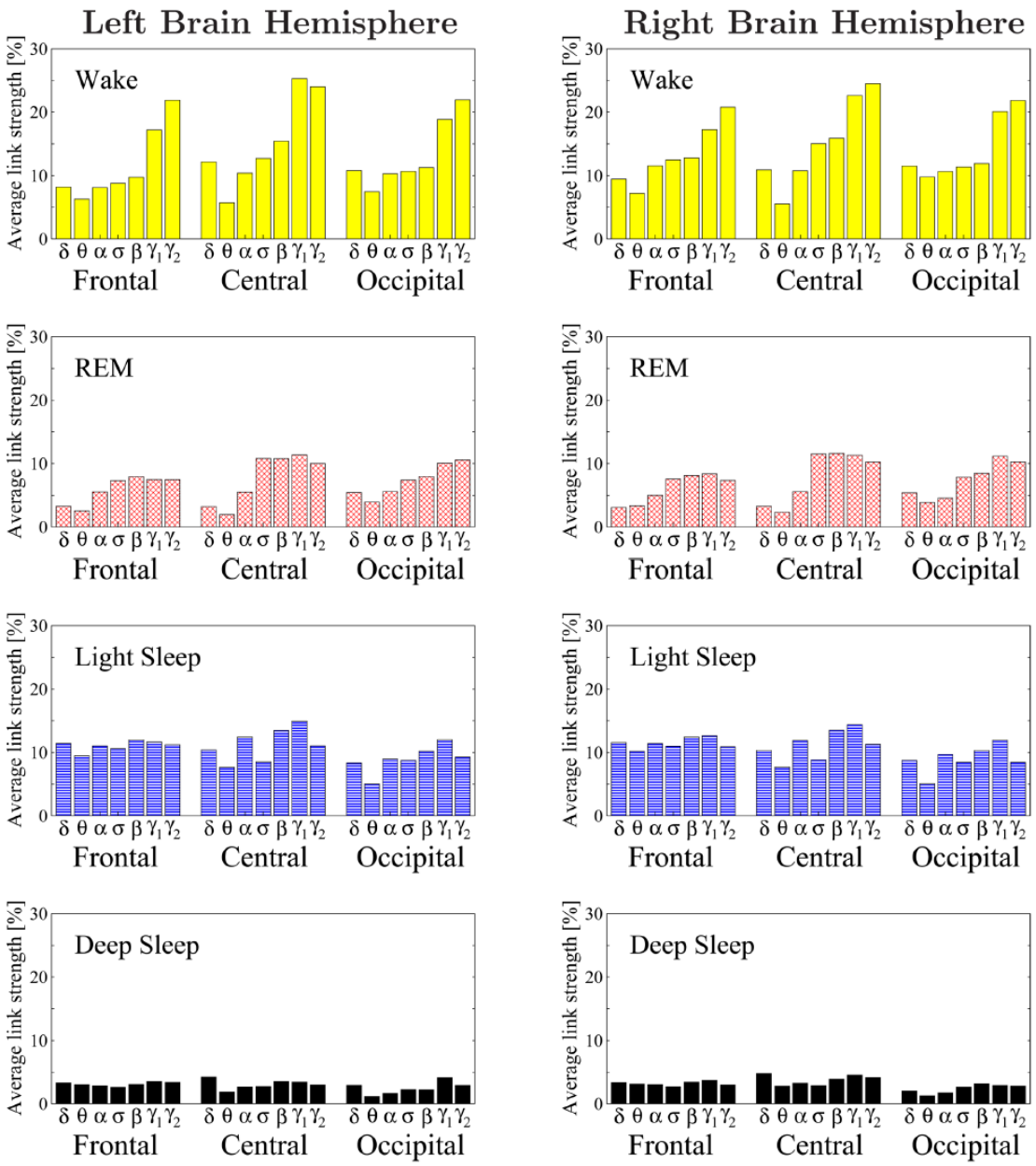
Brain-Eye Interaction



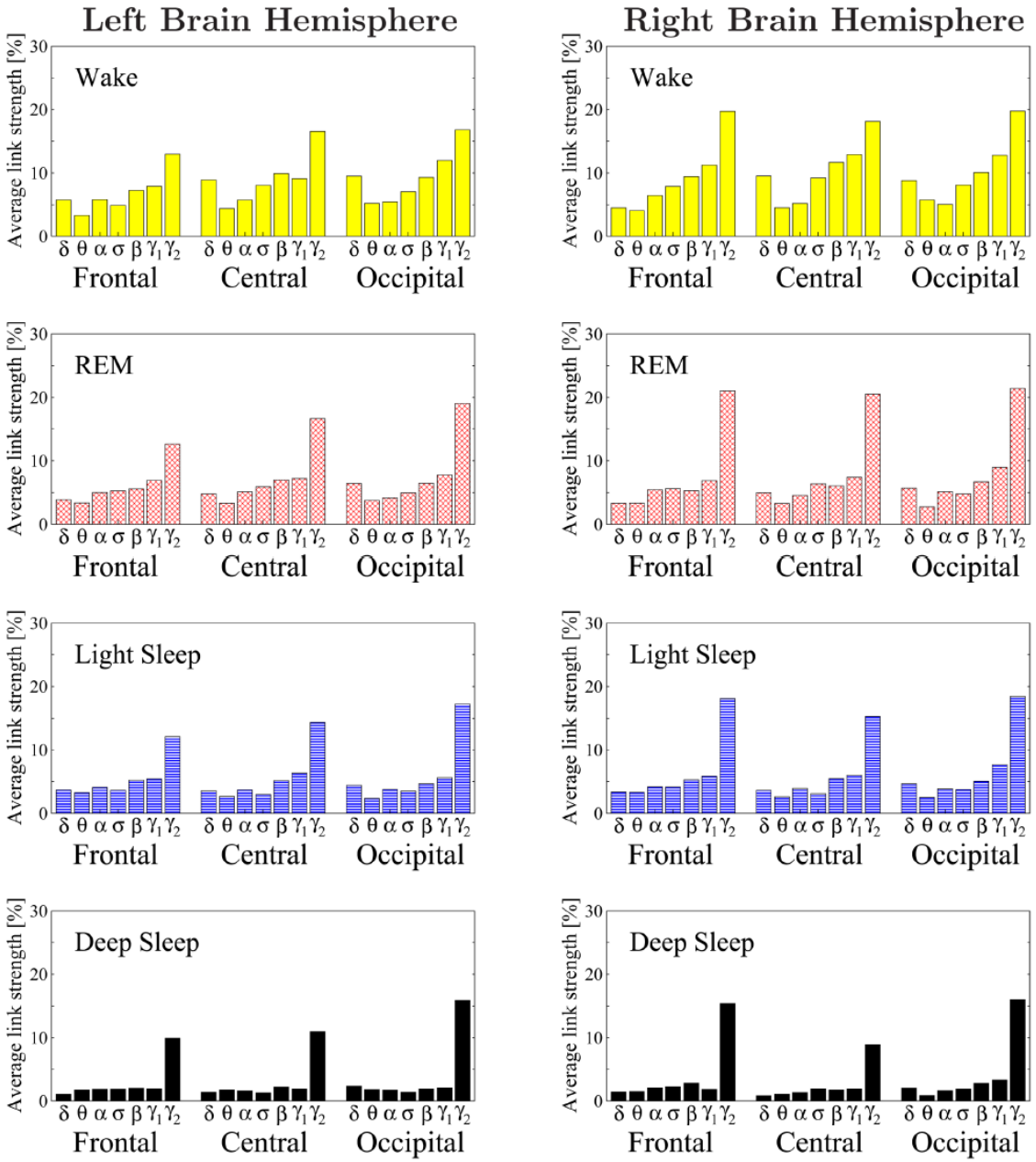
Brain-Chin Interaction



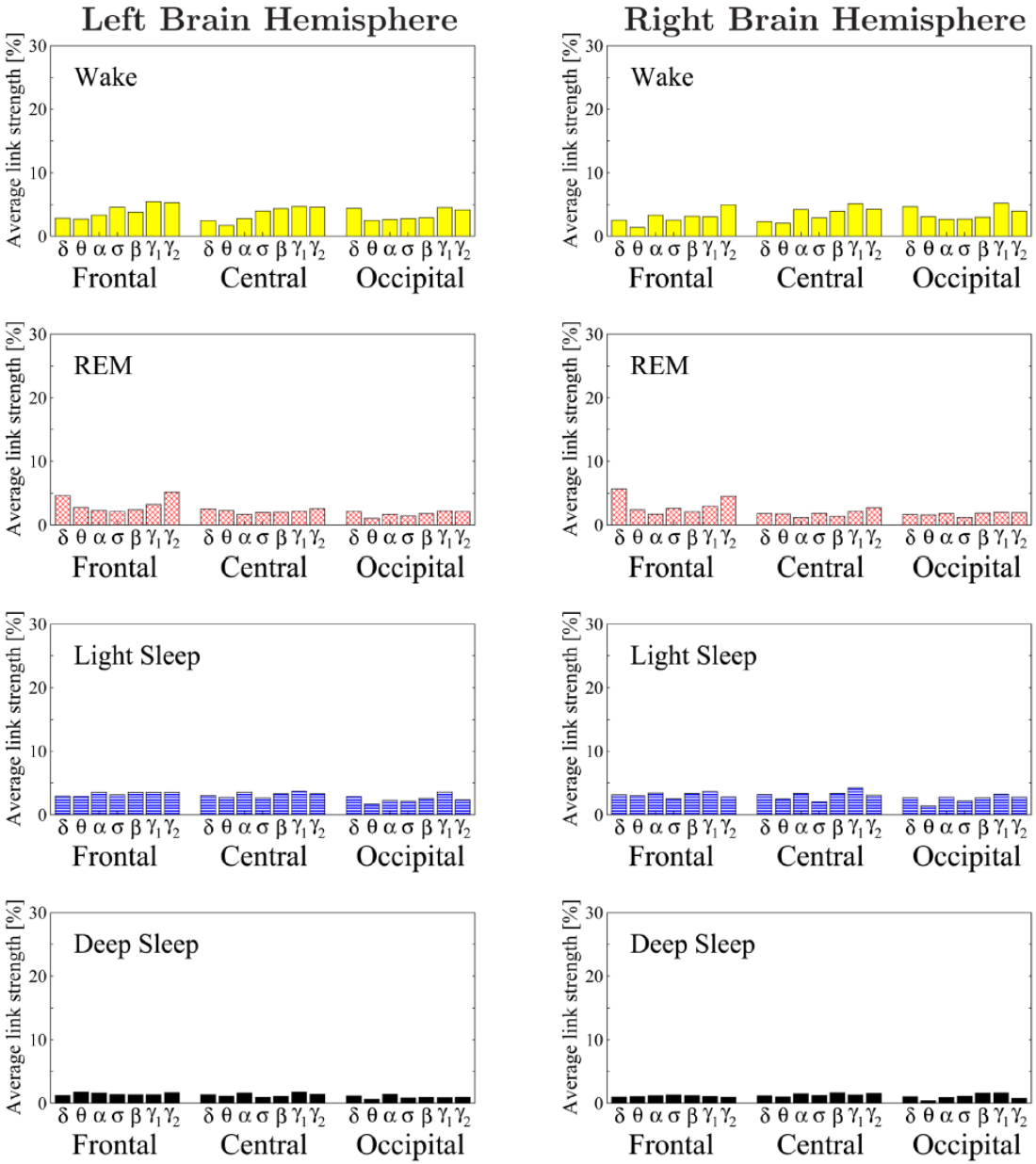
Brain-Heart Interaction



Brain-Leg Interaction



Brain-Respiration Interaction



Summary

- ✓ **First method/framework to quantify coupling between different organ systems → Constructed a network of physiologic interactions between different organs**
- ✓ **Dynamical evolution of the physiologic network during sleep → network topology changes with physiologic states**
- ✓ **Sleep-stage stratification pattern for physiologic interactions**
- ✓ **Example of coexisting forms of coupling: CRPS, RSA, TDS**

- ➢ **Next: Application to clinical medicine**
  → Multiple Organ Failure

THANK YOU!

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