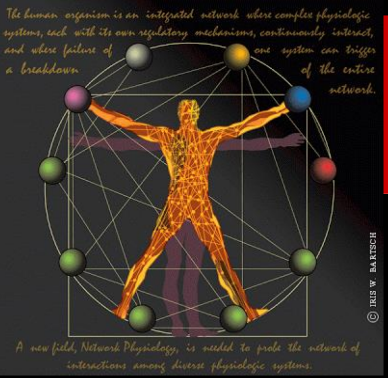
The human organism is an integrated network where complex physiologic systems, each with its own regulatory mechanisms, continuously interact, and where failure of one system can trigger a breakdown of the entire network.

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

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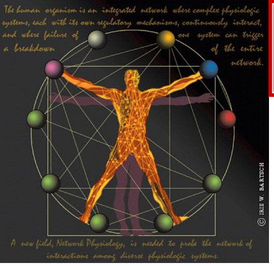
FONDAZIONE ALESSANDRO VOLTA
CULTURA EDUCAZIONE CIVITAS

Network Physiology of Cortico–Muscular Interactions: Reorganization with Sleep Stages Transitions & Neurodegenerative Disorders

Dr Rossella Rizzo

dipartimento di ingegneria unipa
Università degli Studi di Palermo

Third International Summer Institute on Network Physiology (ISINP)
Lake Como School of Advanced Studies – 24-29 July 2022



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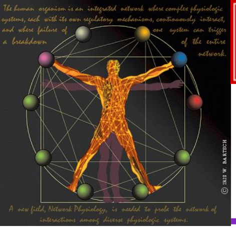
- Introduction
- Research hypothesis
- Part I: Network Physiology of Cortico-Muscular Interactions
- Part II: Dynamic Networks of Cortico-Muscular Interactions: Breakdown with Parkinson's during Sleep
- Frontiers Research Topic: Cortico-Muscular Networks



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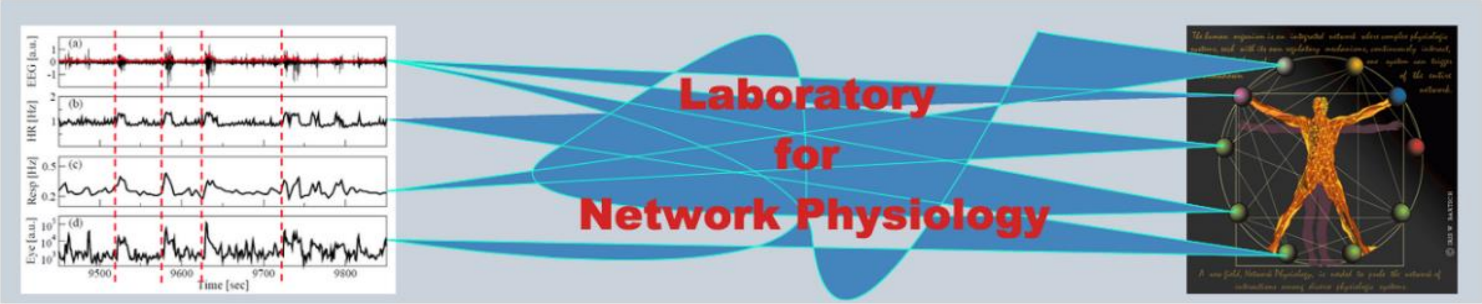
Introduction

NETWORK PHYSIOLOGY



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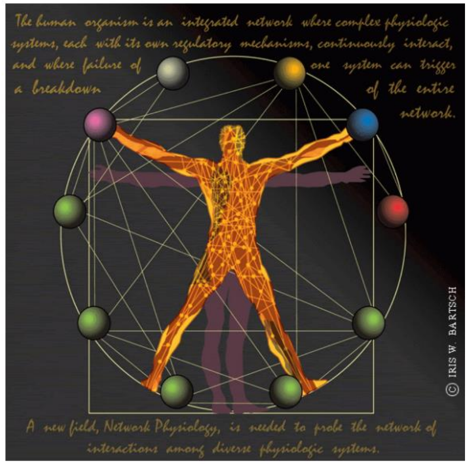
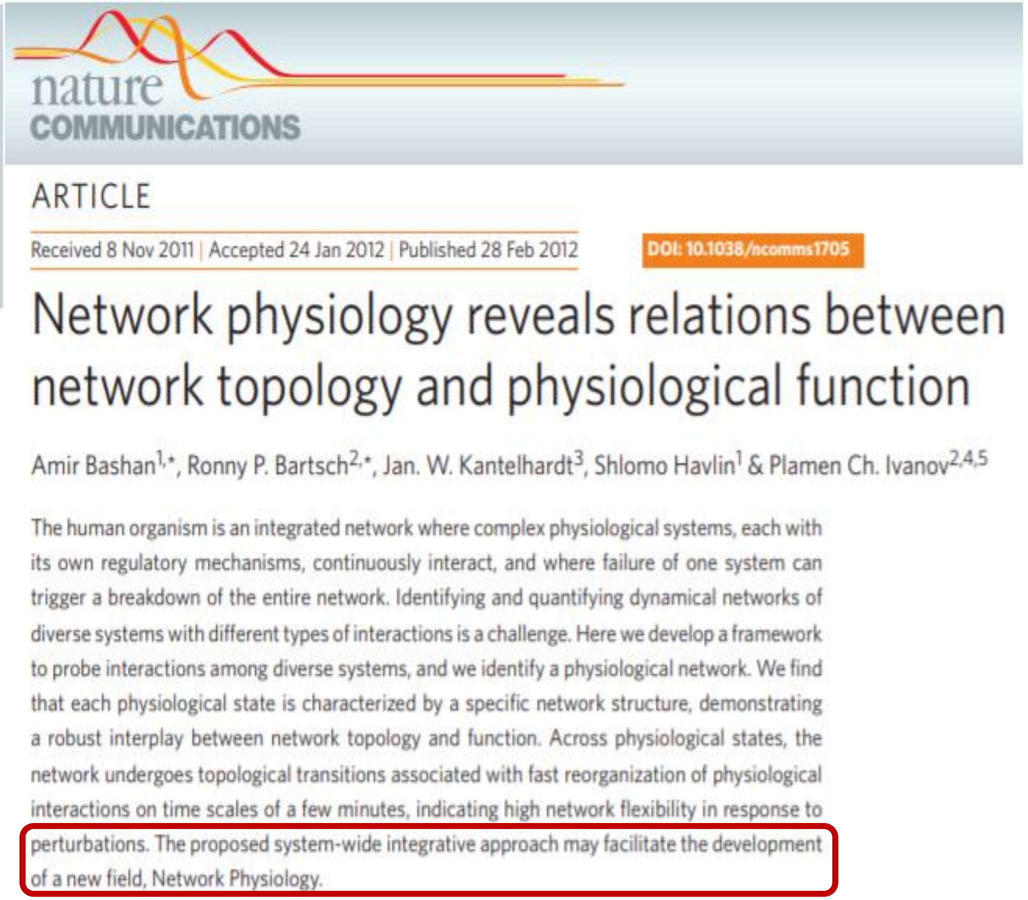
BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Welcome to the Keck Laboratory for Network Physiology

Director: Prof. Plamen Ch. Ivanov





nature COMMUNICATIONS

ARTICLE

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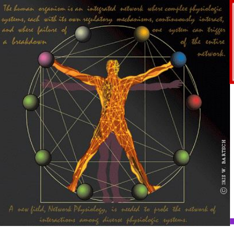
DOI: 10.1038/ncomms1705

Network physiology reveals relations between network topology and physiological function

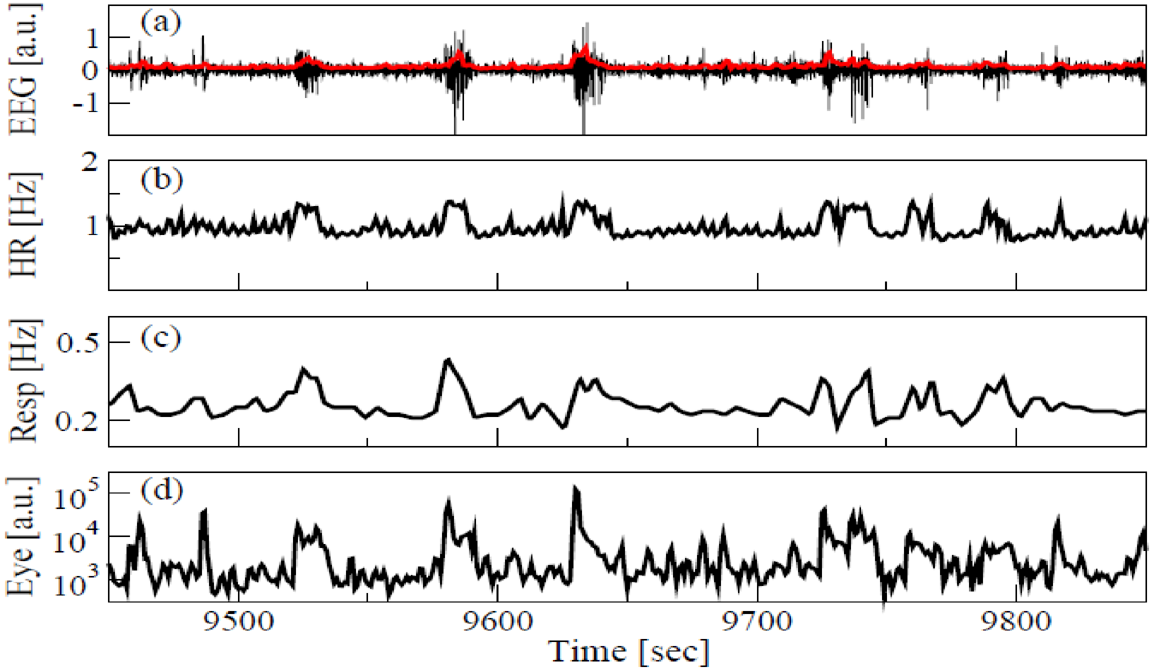
Amir Bashan[1,*], Ronny P. Bartsch[2,*], Jan. W. Kantelhardt[3], Shlomo Havlin[1] & Plamen Ch. Ivanov[2,4,5]

The human organism is an integrated network where complex physiological systems, each with its own regulatory mechanisms, continuously interact, and where failure of one system can trigger a breakdown of the entire network. Identifying and quantifying dynamical networks of diverse systems with different types of interactions is a challenge. Here we develop a framework to probe interactions among diverse systems, and we identify a physiological network. We find that each physiological state is characterized by a specific network structure, demonstrating a robust interplay between network topology and function. Across physiological states, the network undergoes topological transitions associated with fast reorganization of physiological interactions on time scales of a few minutes, indicating high network flexibility in response to perturbations. The proposed system-wide integrative approach may facilitate the development of a new field, Network Physiology.



Introduction

NETWORK PHYSIOLOGY [1,2]

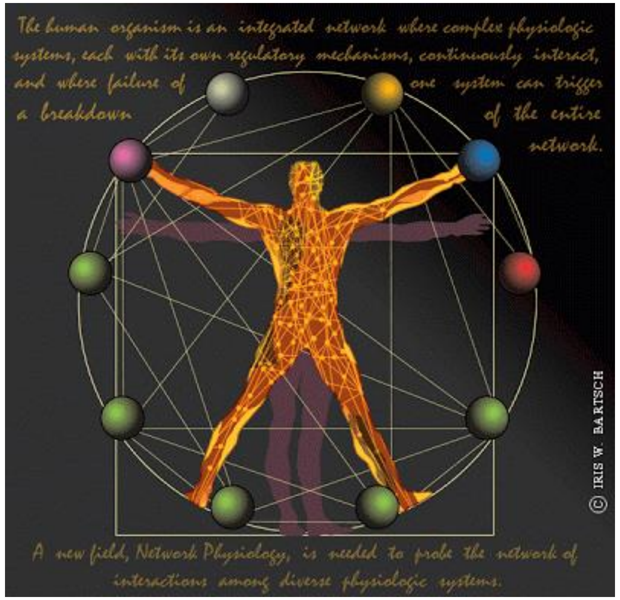


Brain EEG

Heart rate

Respiratory rate

Eye movements



Keck Laboratory for Network Physiology
Department of Physics, Boston University

How organ systems dynamically interact?

- Define the organ systems interactions
- Determinate and descriminate physiologic from pathologic conditions

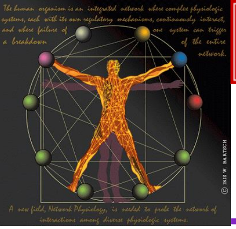
---

[1] **Bashan, A., Bartsch, R. P., Kantelhardt, J. W., Havlin, S., & Ivanov, P. C. (2012). Network physiology reveals relations between network topology and physiological function. Nature communications, 3(1), 1-9.**

[2] **Bartsch, R. P., Liu, K. K., Bashan, A., and Ivanov, P. Ch. (2015). Network physiology: how organ systems dynamically interact. PloS ONE 10, e0142143. doi:10.1371/journal.pone.0142143**

Part I

Network Physiology of Cortico–Muscular Interactions



Past literature

Movements → **Particular cortical rhythms firing (EEG)** [3,4]
at particular cortical locations [5]

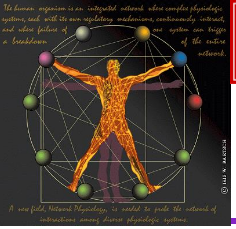
Cortico-muscular direct coupling ?

What happens at rest ?

→ **" Default" Brain-Muscle Network Communication**

---

[3] Ball, T., Demandt, E., Mutschler, I., Neitzel, E., Mehring, C., Vogt, K., et al.(2008).Movement related activity in the high gamma range of the human EEG. Neuroimage 41, 302–310. doi: 10.1016/j.neuroimage.2008.02.032
[4] Omlor, W., Patino, L., Hepp-Reymond, M. C., and Kristeva, R. (2007). Gammarange corticomuscular coherence during dynamic force output. Neuroimage 34, 1191–1198. doi: 10.1016/j.neuroimage.2006.10.018
[5] Rendeiro, C., and Rhodes, J. S. (2018). A new perspective of the hippocampus in the origin of exercise brain interactions. Brain Struct. Funct. 223:25272545. doi: 10.1007/s00429-018-1665-6



Research Hypothesis

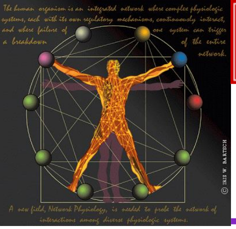
1 **Network Interactions** → **Changes in physiologic regulation across physiologic states.**

2 **Interaction Channels** → **Physiologically relevant EEG and EMG frequency bands**

Brain control on Locomotor system during SLEEP

---

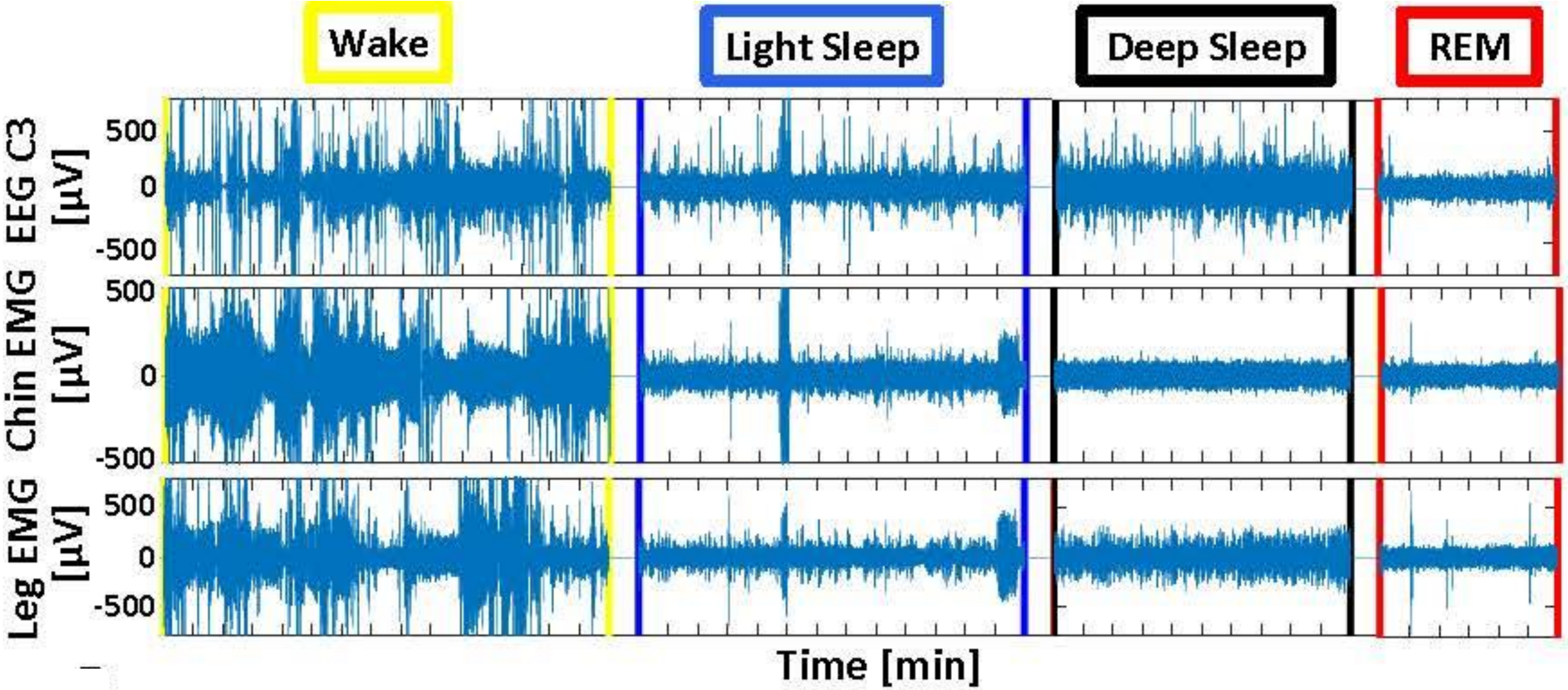
[6] Lin, A., Liu, K. K., Bartsch, R. P., and Ivanov, P. C. (2020). Dynamic network interactions among distinct brain rhythms as a hallmark of physiologic state and function. Commun. Biol. 3, 1–11



Data

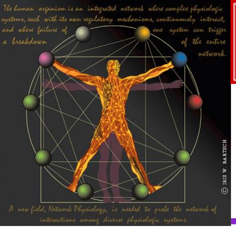
- EEG data from six brain locations (Fp1, Fp2, C3, C4, O1, O2)
- chin (*mentalis*) and leg (*tibialis anterioris*) muscle tone EMG data
- from 36 healthy subjects (mean age = 29 years)
- 4 major, well defined physiologic states: Wake, REM, Light Sleep (LS), deep sleep (DS)
- 7 cortical rhythms : δ (0.5–3.5 Hz), θ (4–7.5 Hz), α (8–11.5 Hz), σ (12–15.5 Hz), β (16–19.5Hz), γ1 (20–33.5 Hz), and γ2 (34–98.5 Hz)
- 7 EMG frequency bands : δ (0.5–3.5 Hz), θ (4–7.5 Hz), α (8–11.5 Hz), σ (12–15.5 Hz), β (16–19.5Hz), γ1 (20–33.5 Hz), and γ2 (34–98.5 Hz)

Methods



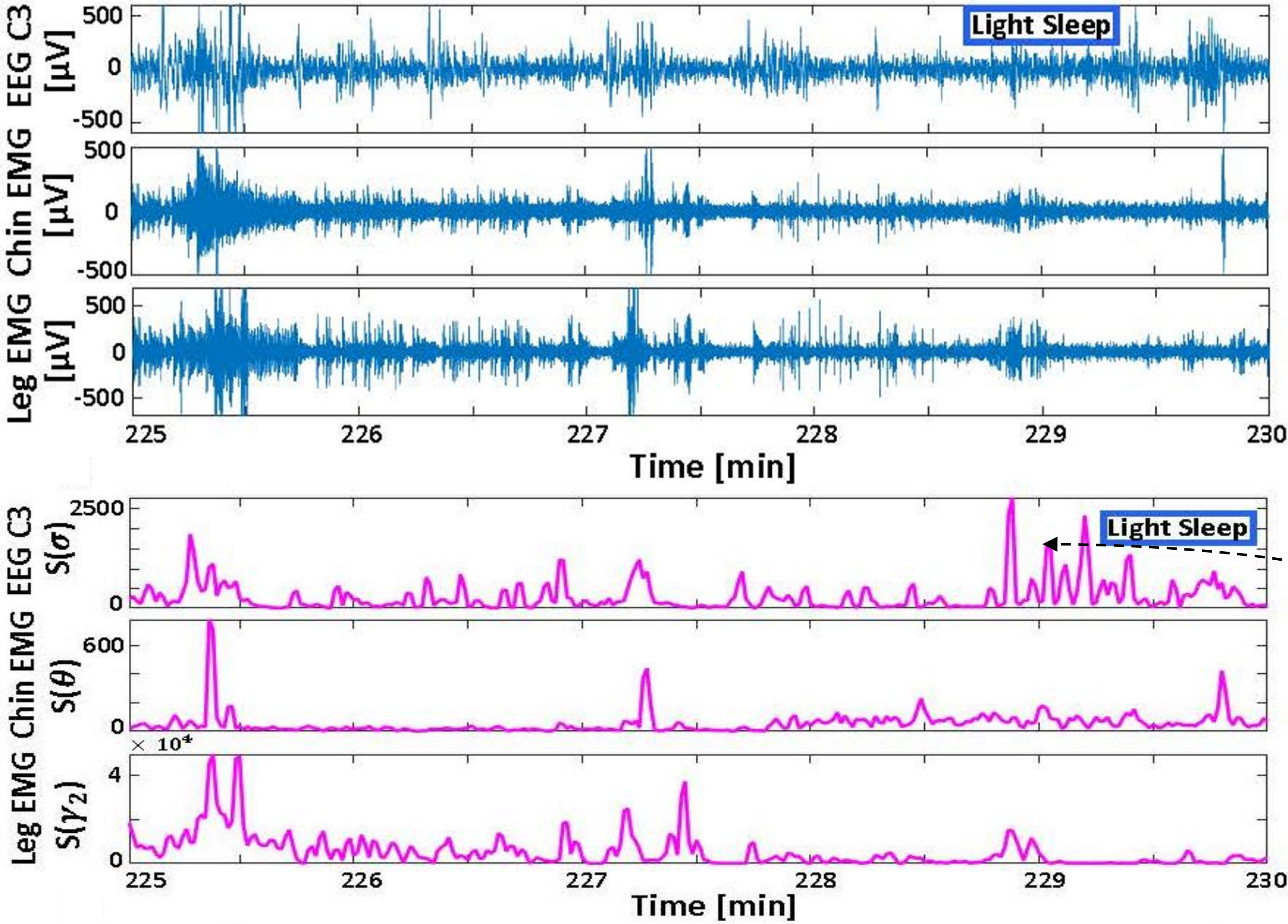
Cleaning procedure:

- Manually removed beginning/end
- 50 Hz notch filter
- Band pass filter [0.5, 98.5] Hz



Methods

Bursting morphology for brain C3 and chin and leg muscle tone during Light Sleep [7]



Synchronized bursts

- Spectral power S(f)

$$S(f) = |F(f)|^2/(W \cdot Fs)$$

$F(f)$ the Fourier transform, W the window size, F_s the sampling frequency

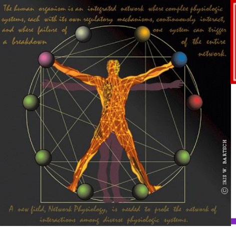
- Spectral power in a time window ν for a frequency band Δf

$$S^{\nu}(\Delta f) = \int_{f_1}^{f_2} S^{\nu}(f)\,df$$

$f1$ and $f2$ are the lower and upper bound of Δf (ν = 2 sec, 1 sec overlap)

Synchronized bursts

[7] Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070



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Methods

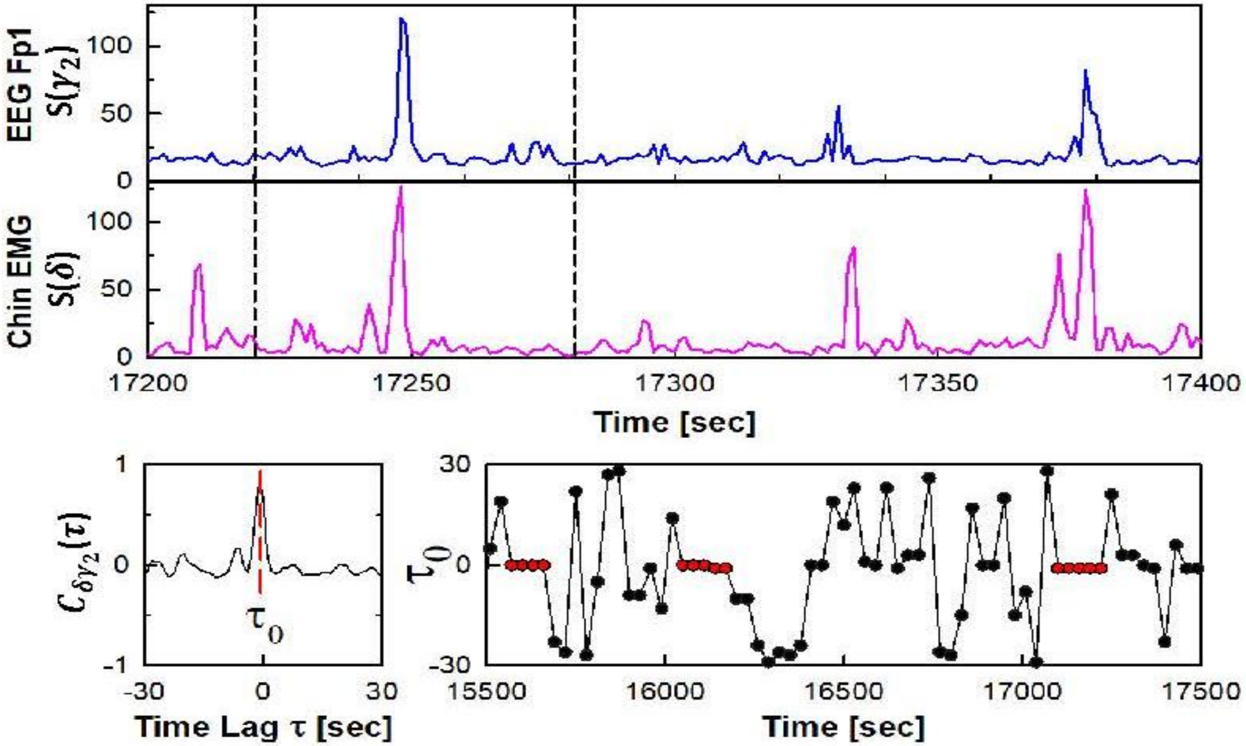
Physics Concept: Time Delay

→

New Concept:

Time Delay Stability (TDS) [1,8]

Novel Measure of Coupling Strength



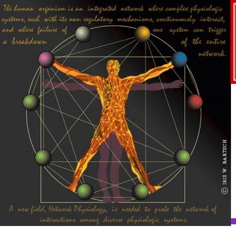
Higher percentage of TDS

↓

Stronger link

[1] Bashan, A., Bartsch, R. P., Kantelhardt, J. W., Havlin, S., & Ivanov, P. C. (2012). Network physiology reveals relations between network topology and physiological function. Nature communications, 3(1), 1-9.

[8] Bartsch R.P., Ivanov P.C. (2014) Coexisting Forms of Coupling and Phase-Transitions in Physiological Networks. In: Mladenov V.M., Ivanov P.C. (eds) Nonlinear Dynamics of Electronic Systems. NDES 2014. Communications in Computer and Information Science, vol 438. Springer, Cham.



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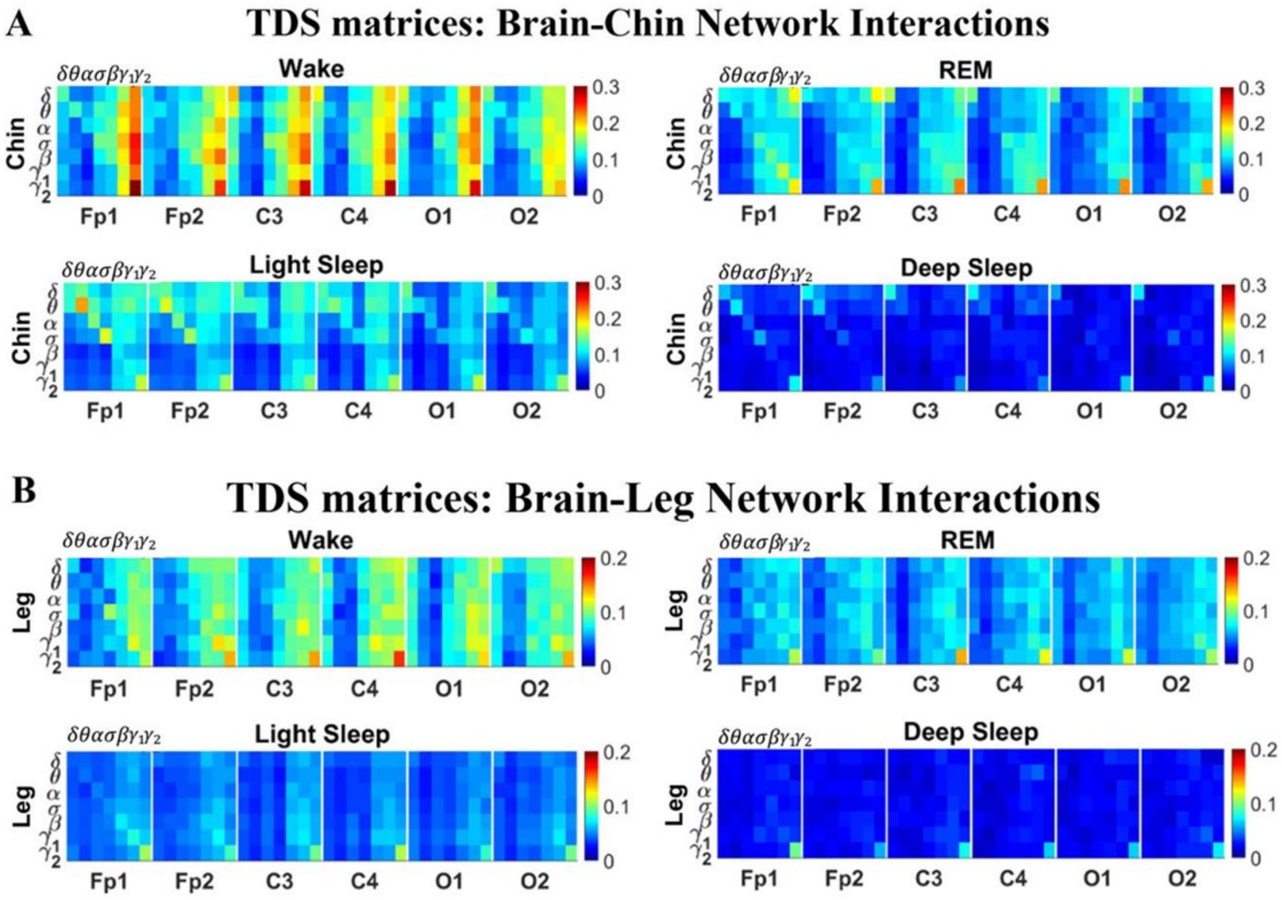
Results

TDS matrix representation of brain-muscle network connectivity across physiologic states [7]



- Cortical rhythms: $\delta, \vartheta, \alpha, \sigma, \beta, \gamma_1, \gamma_2$
- Cortical locations: Fp1, Fp2, C3, C4, O1, O2

Sleep-stage stratification pattern

↑

Coupling network interactions

↓

Strong links with γ_1 and γ_2 brain waves

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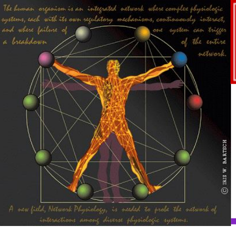
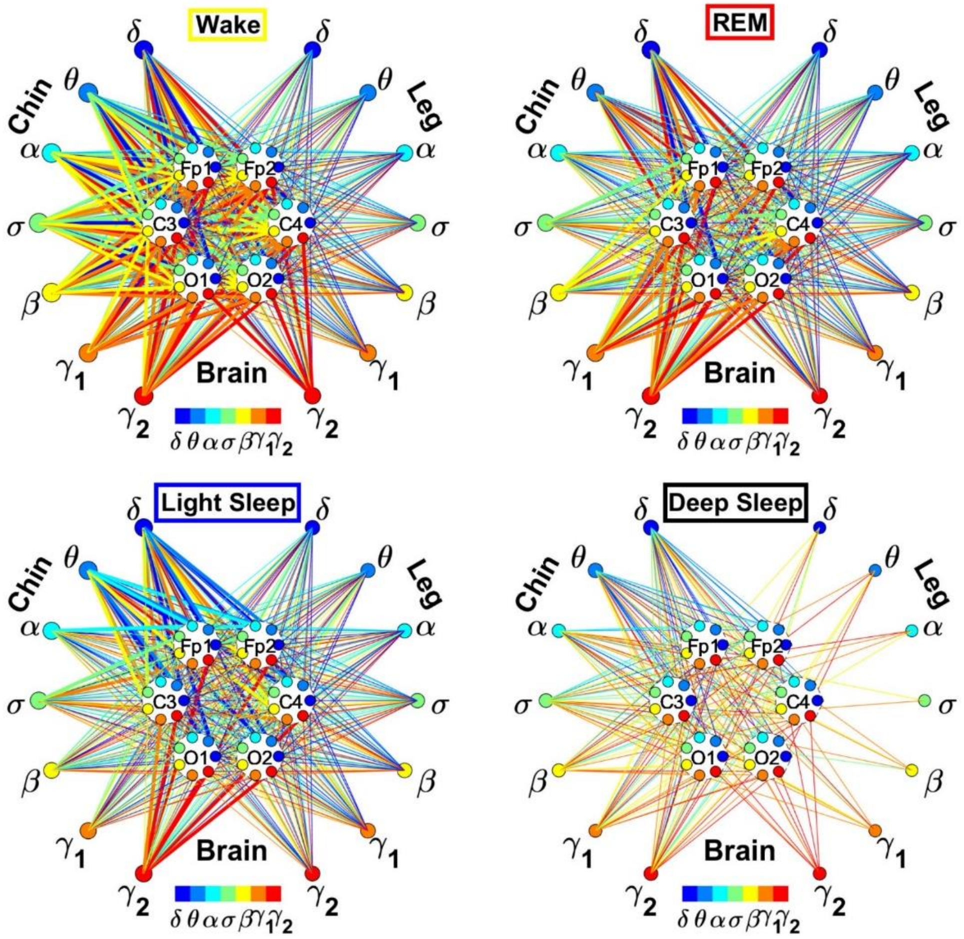
[7] **Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070**

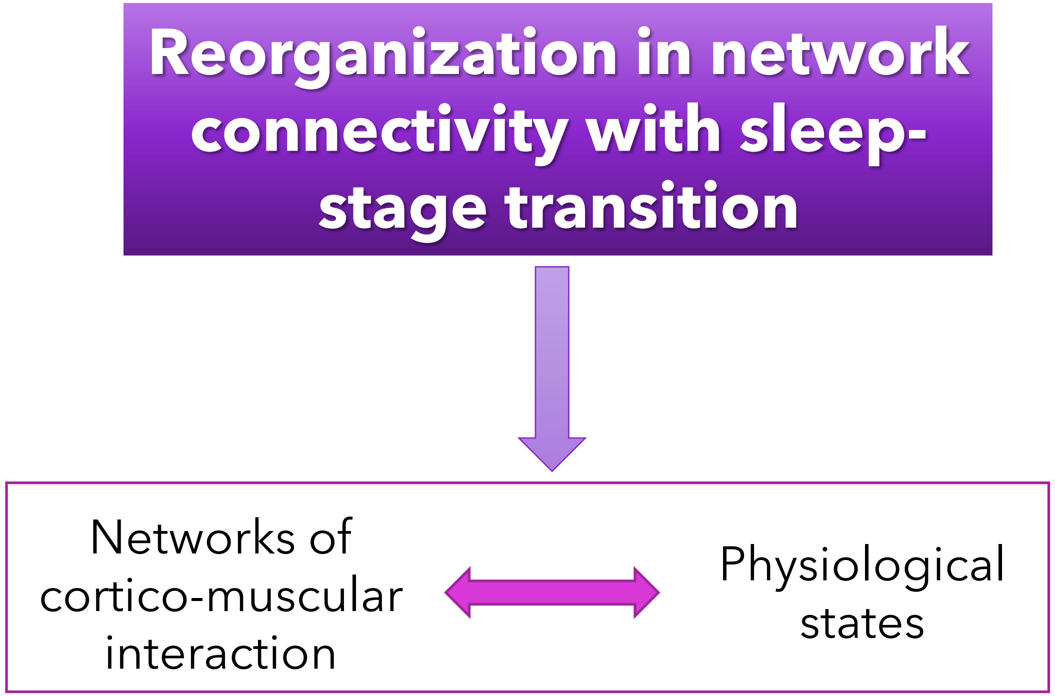


Results

Dynamic networks of cortico-muscular interactions across physiological states



Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070

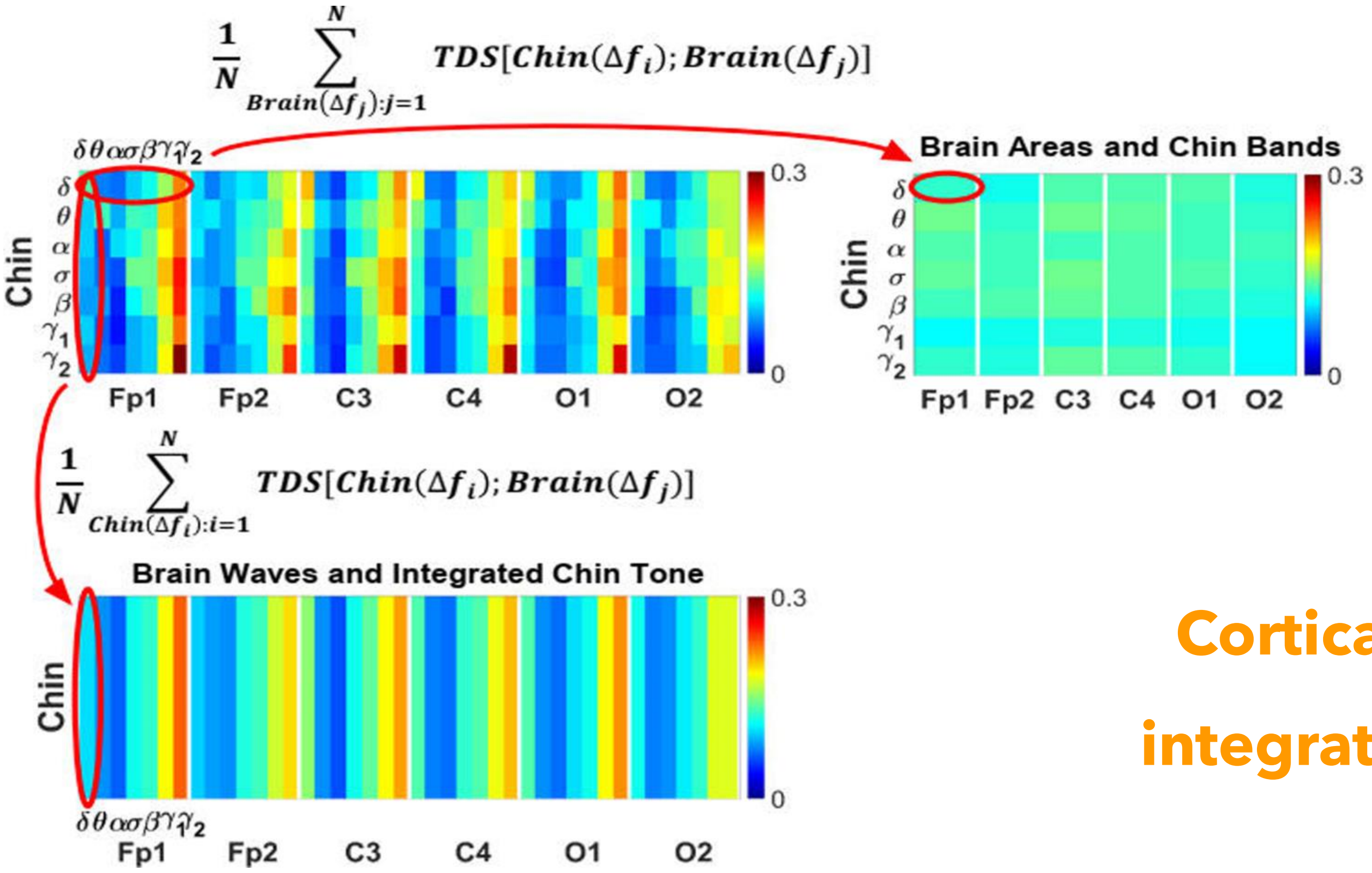


Reorganization in network connectivity with sleep-stage transition

Networks of cortico-muscular interaction ⟷ Physiological states

Results

Coarse-graining procedure



$$\frac{1}{N}\sum_{Brain(\Delta f_j):j=1}^{N} TDS[Chin(\Delta f_i);Brain(\Delta f_j)]$$

$$\frac{1}{N}\sum_{Chin(\Delta f_i):i=1}^{N} TDS[Chin(\Delta f_i);Brain(\Delta f_j)]$$

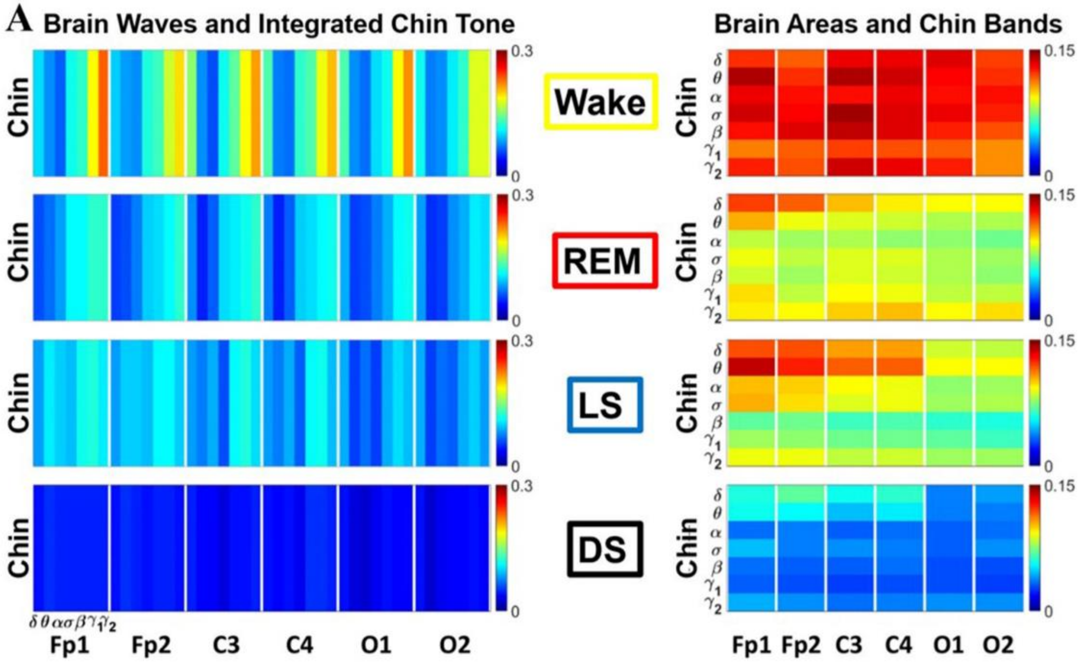
Integrated brain areas and chin EMG frequency bands

Cortical rhythms and integrated muscle tone

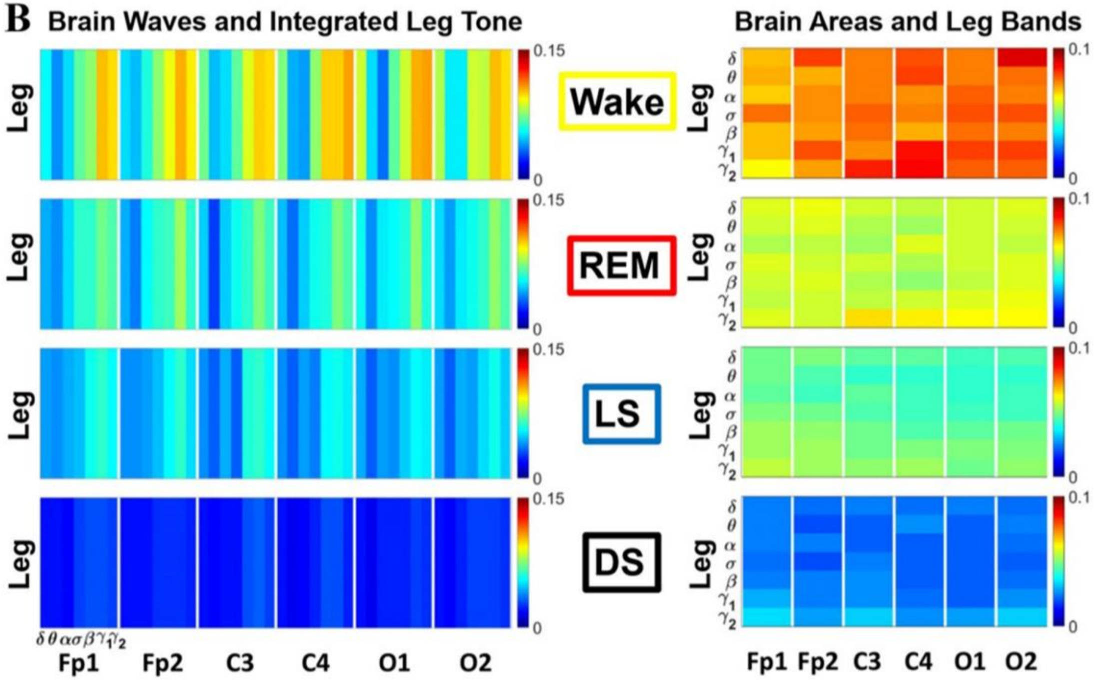
Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070

Results

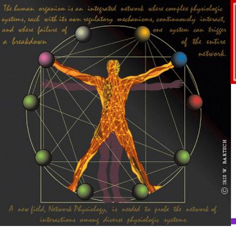
Brain rhythms and chin muscle tone interactions



Brain rhythms and leg muscle tone interactions

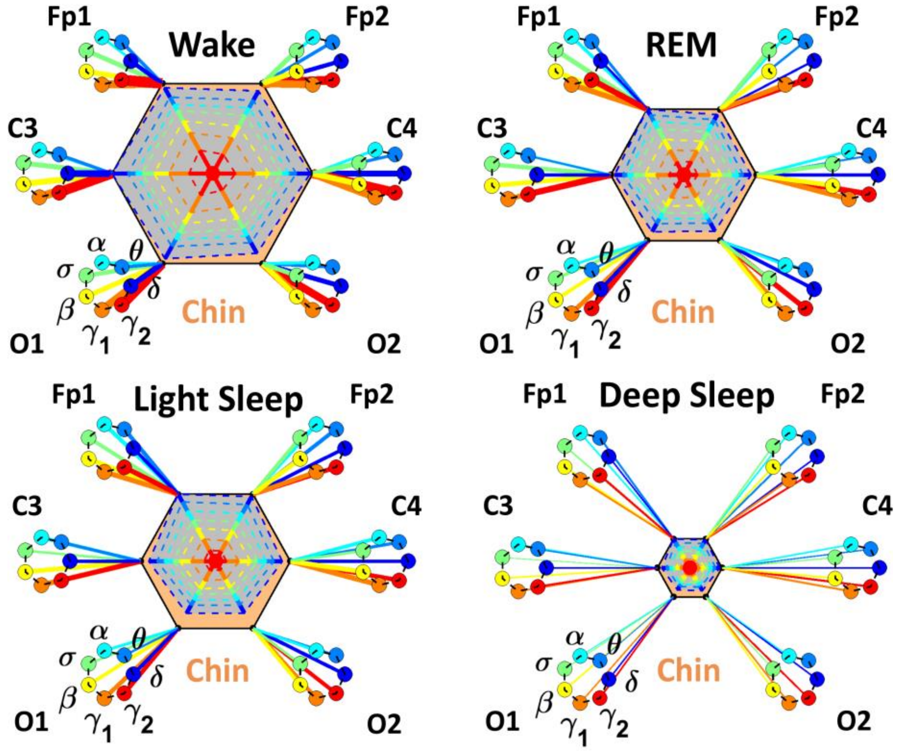


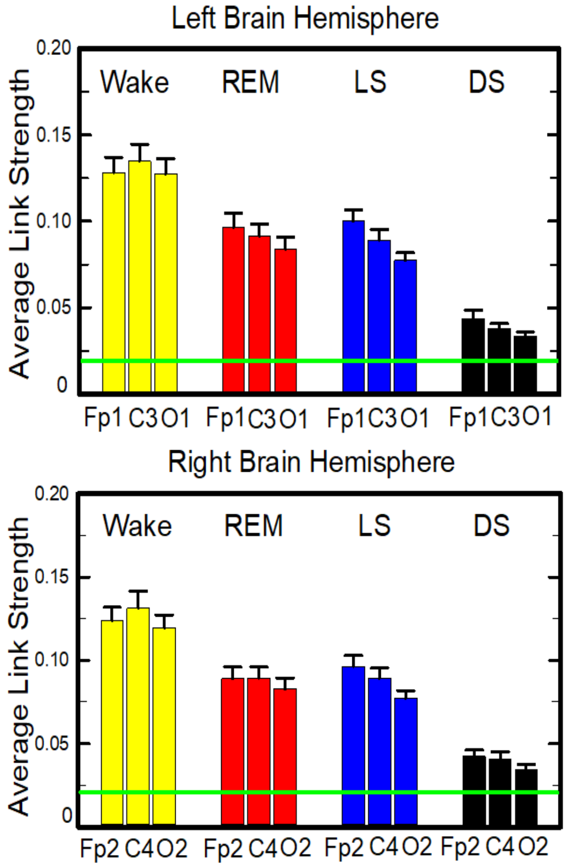
Interaction is mediated through specific rhythms



Results

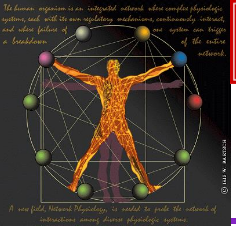
Dynamic networks Brain rhythms and integrated Chin-Muscle tone



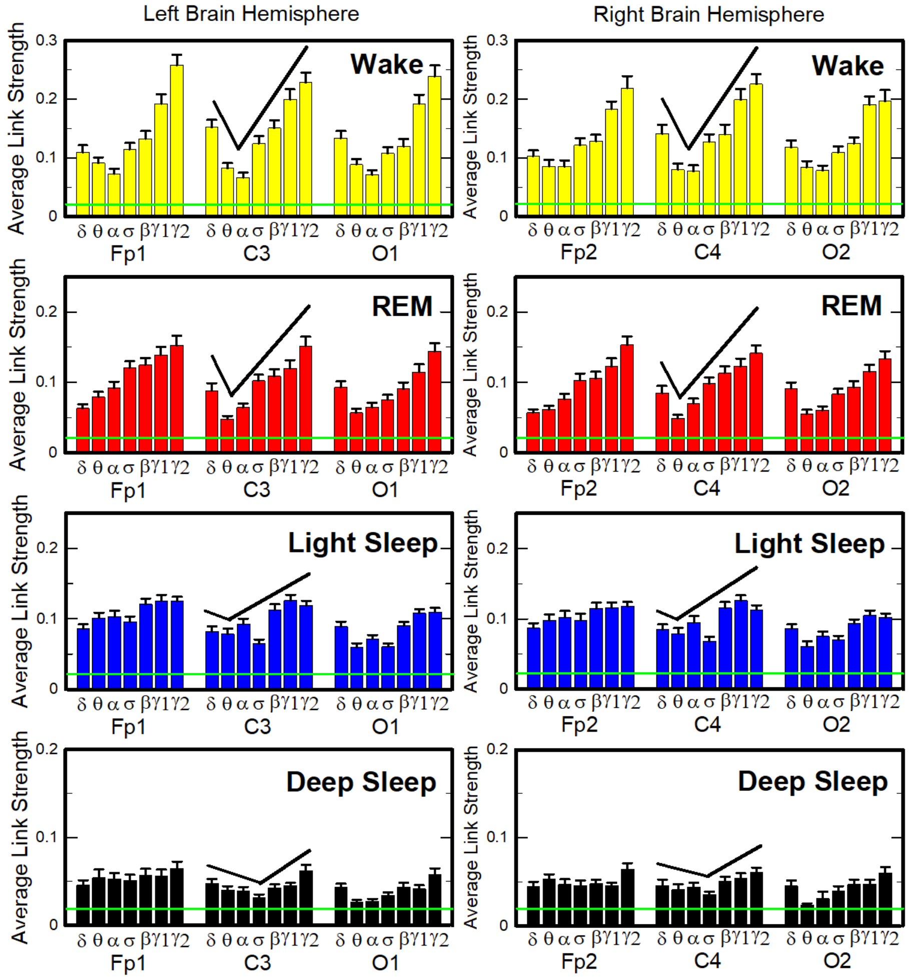


- **Universality**
- **Network Reorganization**
- **Sleep-stage Stratification**

Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070



Results



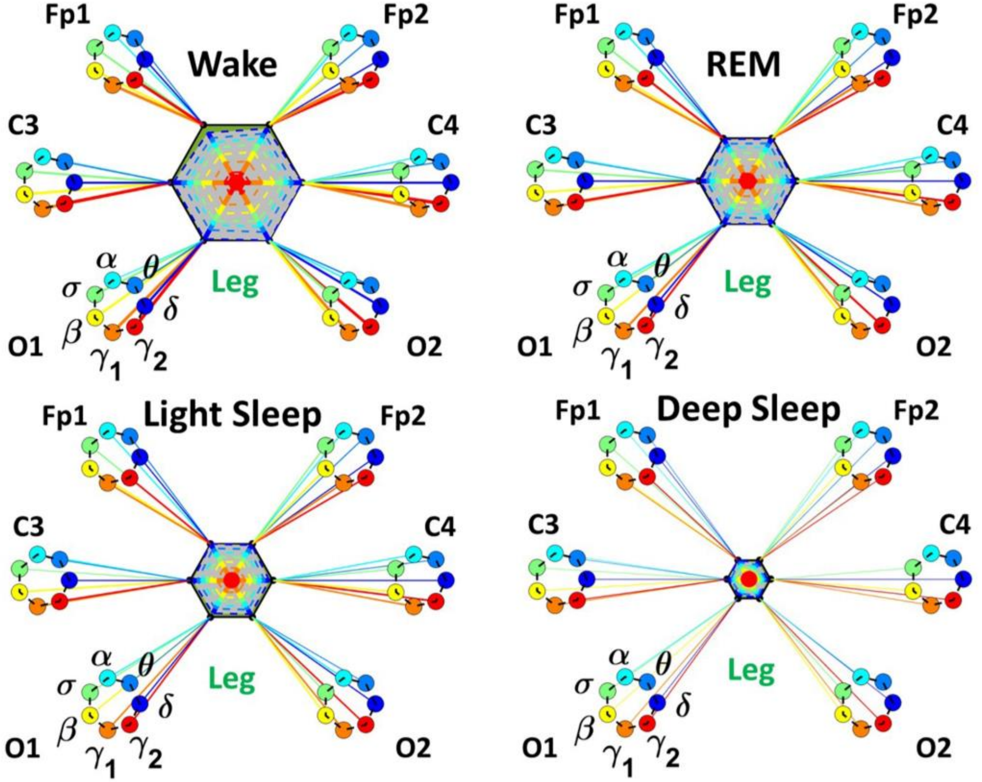
Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070

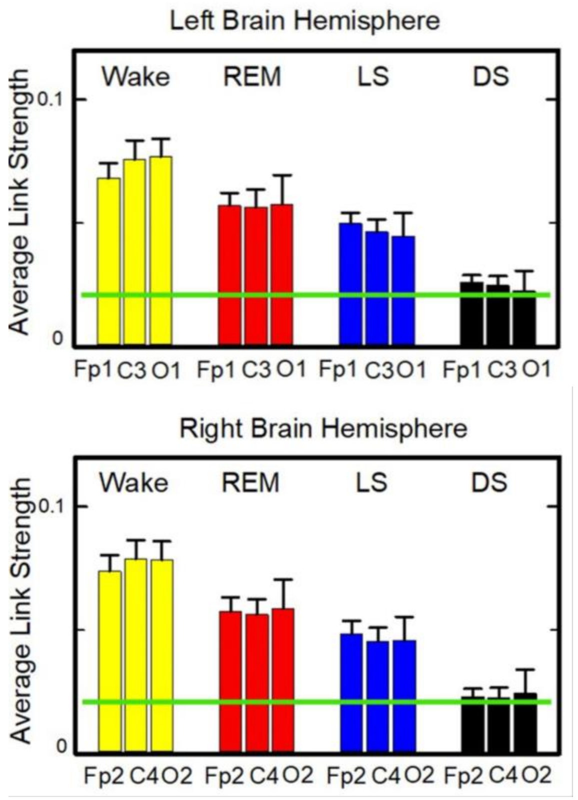
Interaction Profiles of Network Links Strength Brain waves with integrated Chin-Muscle tone

- **Gradual decline in link strength connectivty from Wake to Deep Sleep**
- **Characteristic profile for each physiologic state**
- **Universality of coupling profiles across brain locations at a given state**
- **Right and Left Brain Hemisphere symmetry**

Results

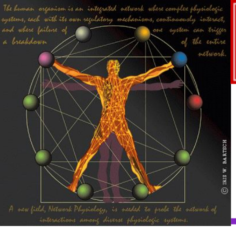
Dynamic networks Brain rhythms and integrated Leg-Muscle tone



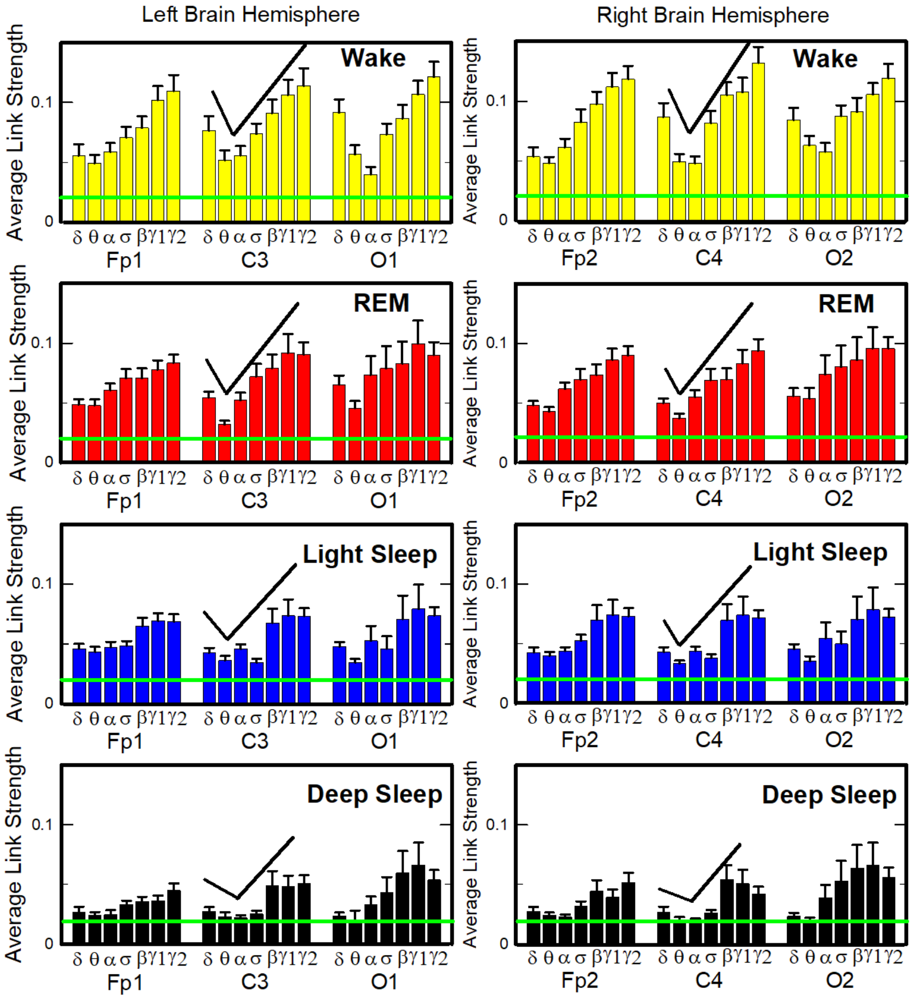


- ❖ **Universality**
- ❖ **Network Reorganization**
- ❖ **Sleep-stage Stratification**

Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070



Results



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Interaction Profiles of Network Links Strength Brain waves with integrated Leg-Muscle tone

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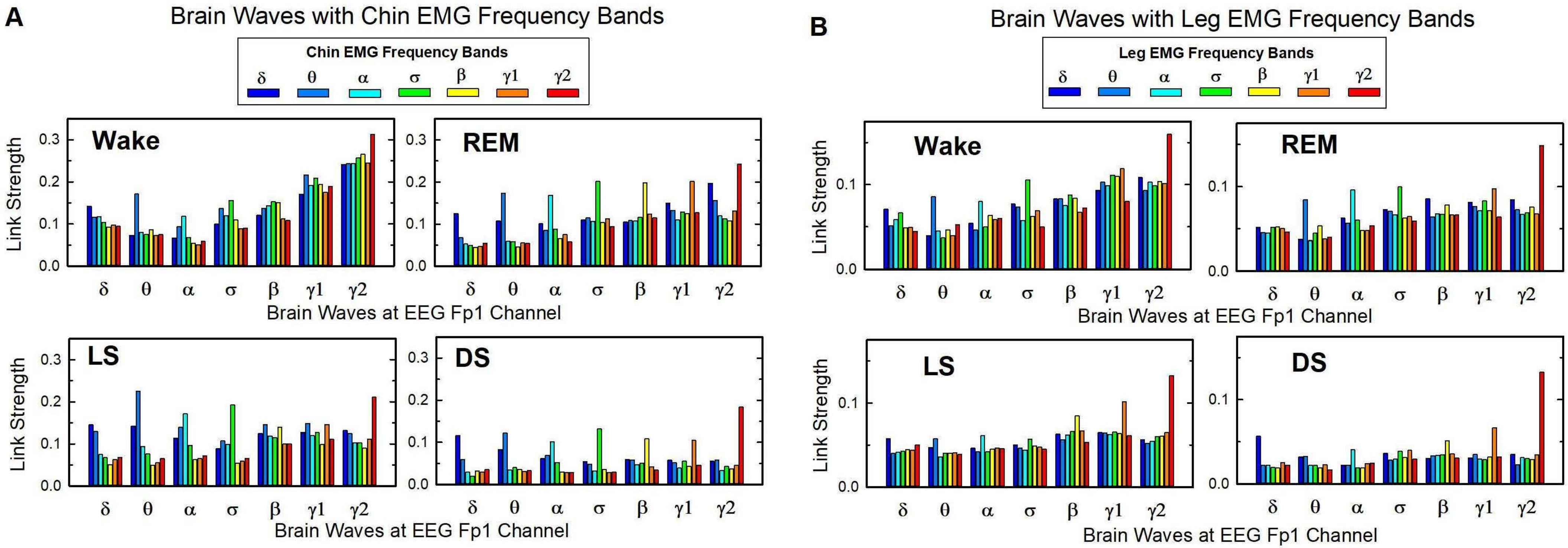
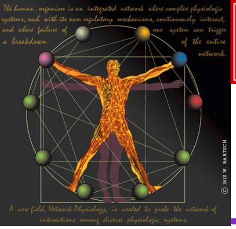
Results

Brain-muscle interaction profiles



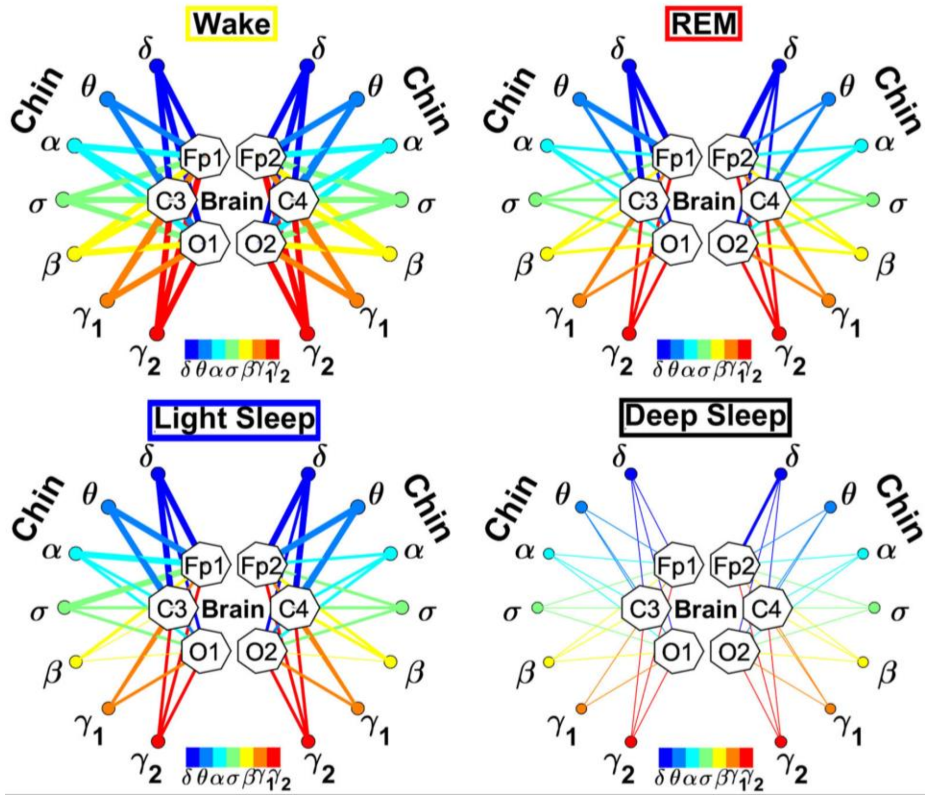
Stronger links between same frequency cortical rhythms and EMG frequency bands

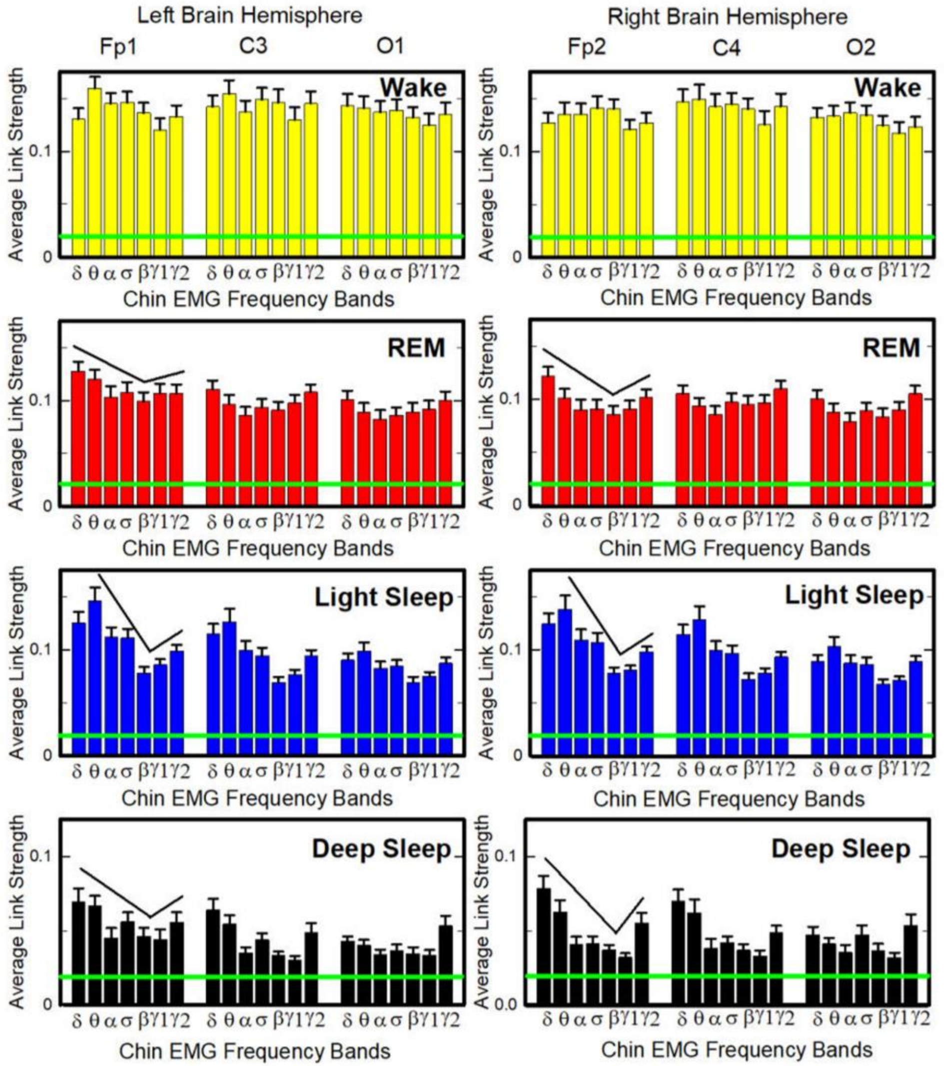
Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070



Results

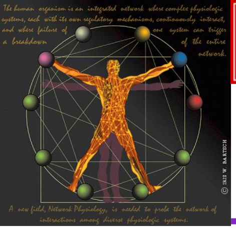
Integrated Brain Areas and Chin EMG Frequency Bands





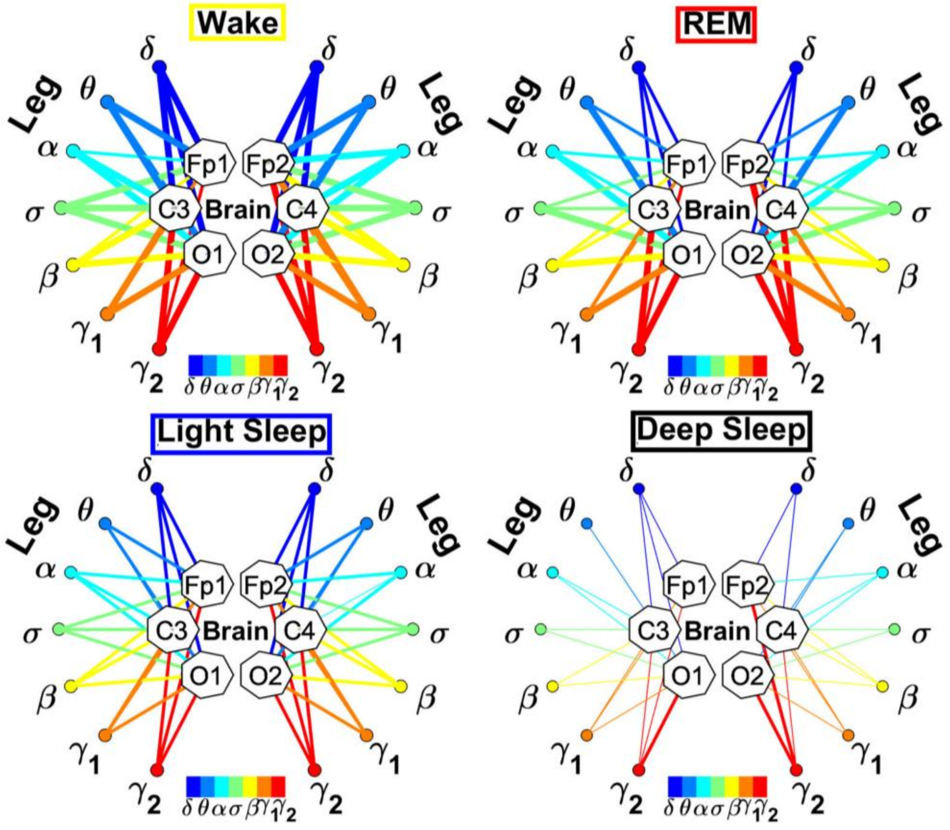
Network structure and Interaction Profiles → Uniquely Define Each Physiologic State

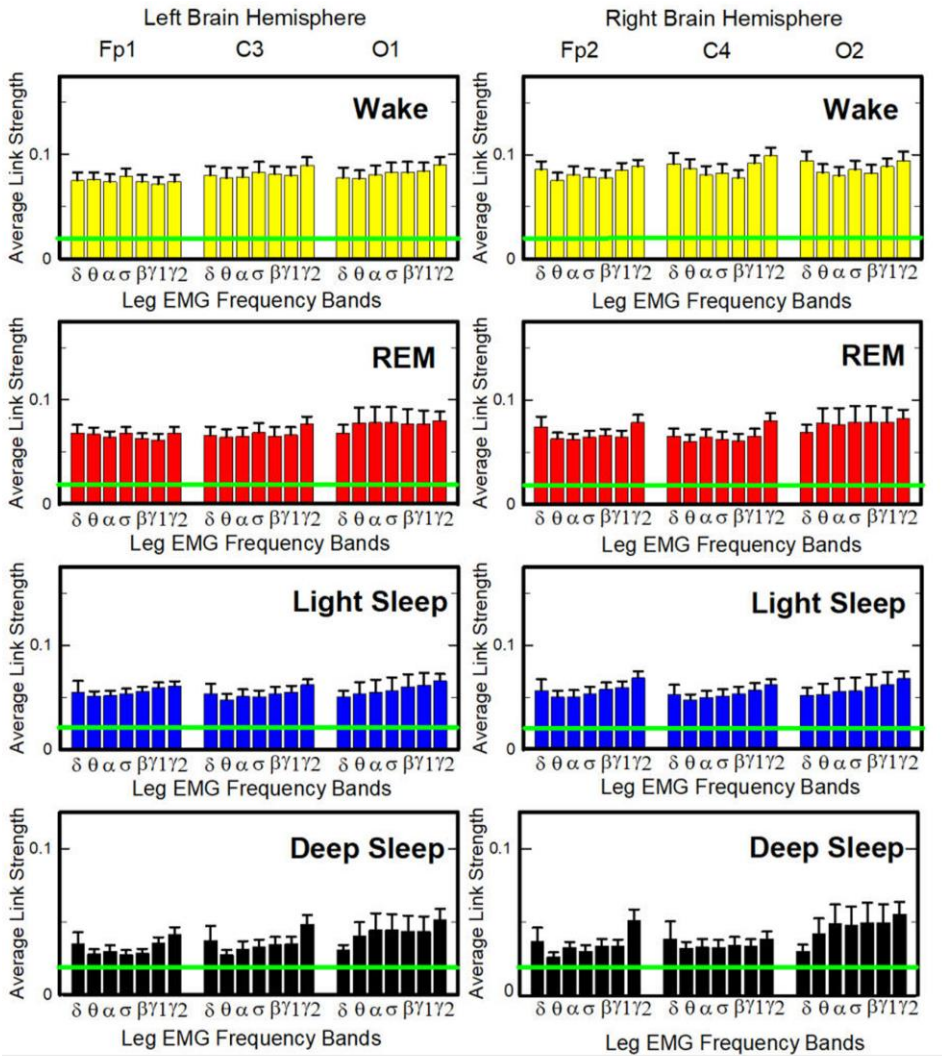
Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070



Results

Integrated Brain Areas and Leg EMG Frequency Bands





Network structure → Uniquely Define Each Physiologic State

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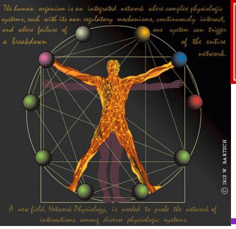
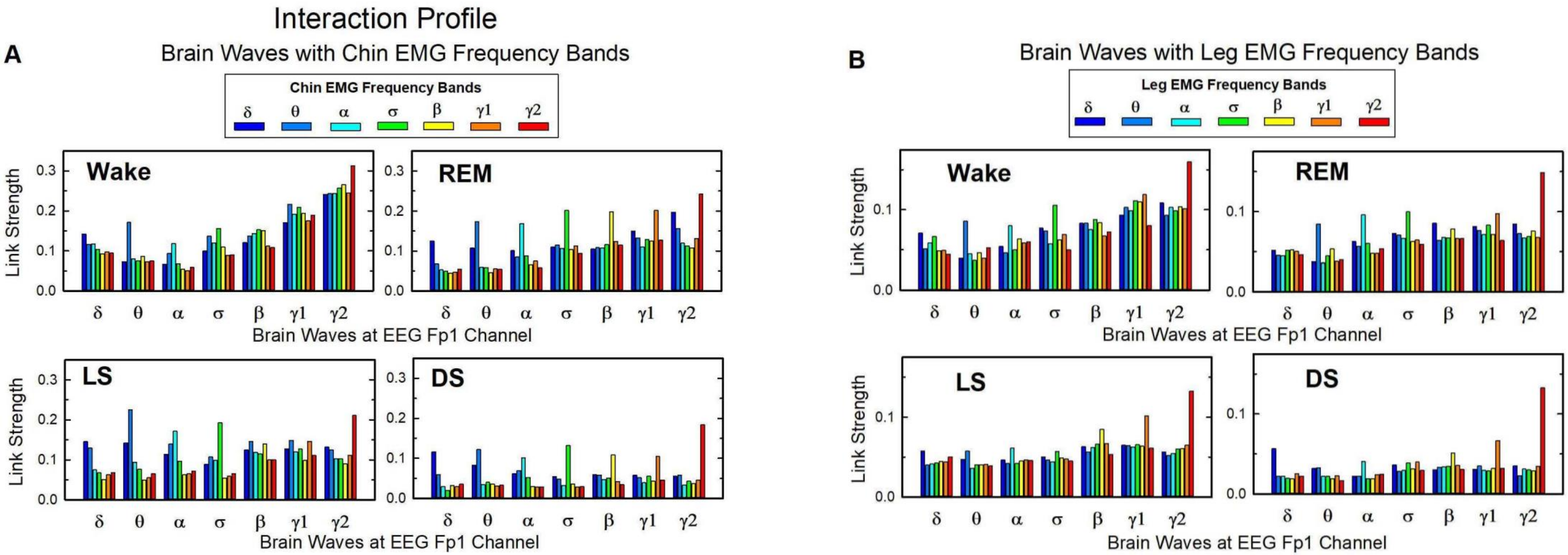


Results

Brain-muscle interaction profiles

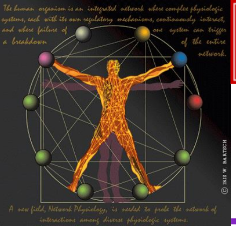


Stronger links between same frequency cortical rhythms and EMG frequency bands

Rizzo R, Zhang X, Wang JWJL, Lombardi F, and Ivanov PCh. Network Physiology of Cortico–Muscular Interactions. *Frontiers in Physiology*. 2020; 11:558070

Part II

Dynamic Networks of Cortico–Muscular Interactions: Breakdown with Parkinson’s during Sleep



Past literature

Parkinson's Disease (PD) → the second most common progressive neurodegenerative disorder affecting older adults.

Well known symptoms →

- ✓ resting tremors
- ✓ slow movement
- ✓ rigid muscles
- ✓ unsteady gait

Recently found symptoms →

- ✓ changes in sleep regulation [9]
- ✓ difficulty in maintaining sleep / fragmented sleep [9]
- ✓ reduced REM sleep and deep sleep
- ✓ REM sleep behavior disorder (RBD)

absence of normal muscle atonia during REM sleep stage [10,11]

↓

dream enacting behavior

in the early stage of disease and even prior to the onset of motor symptoms of 12 years [10,11]

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[9] Cochen De Cock, V. and Arnulf, I. (2008). Rem sleep behavior disorders and their characteristics in parkinson's disease. Revue Neurologique 164, 683-691

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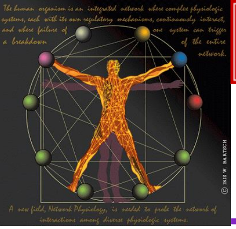
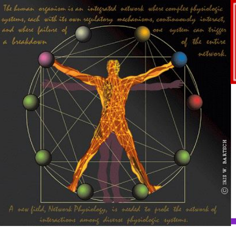
[11] Postuma, R., Gagnon, J., Vendette, M., Fantini, M., Massicotte-Marquez, J., and Montplaisir, J. (2009). Quantifying the risk of neurodegenerative disease in idiopathic rem sleep behavior disorder. Neurology 72



Research Goal

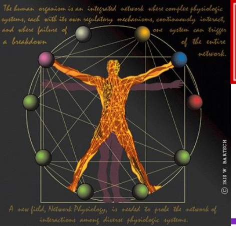
To map the cortico-muscular networks and their transition across physiologic states in both healthy and PD subjects

To develop useful biomarkers and provide a deeper understanding on the impact of PD on human organism networks.



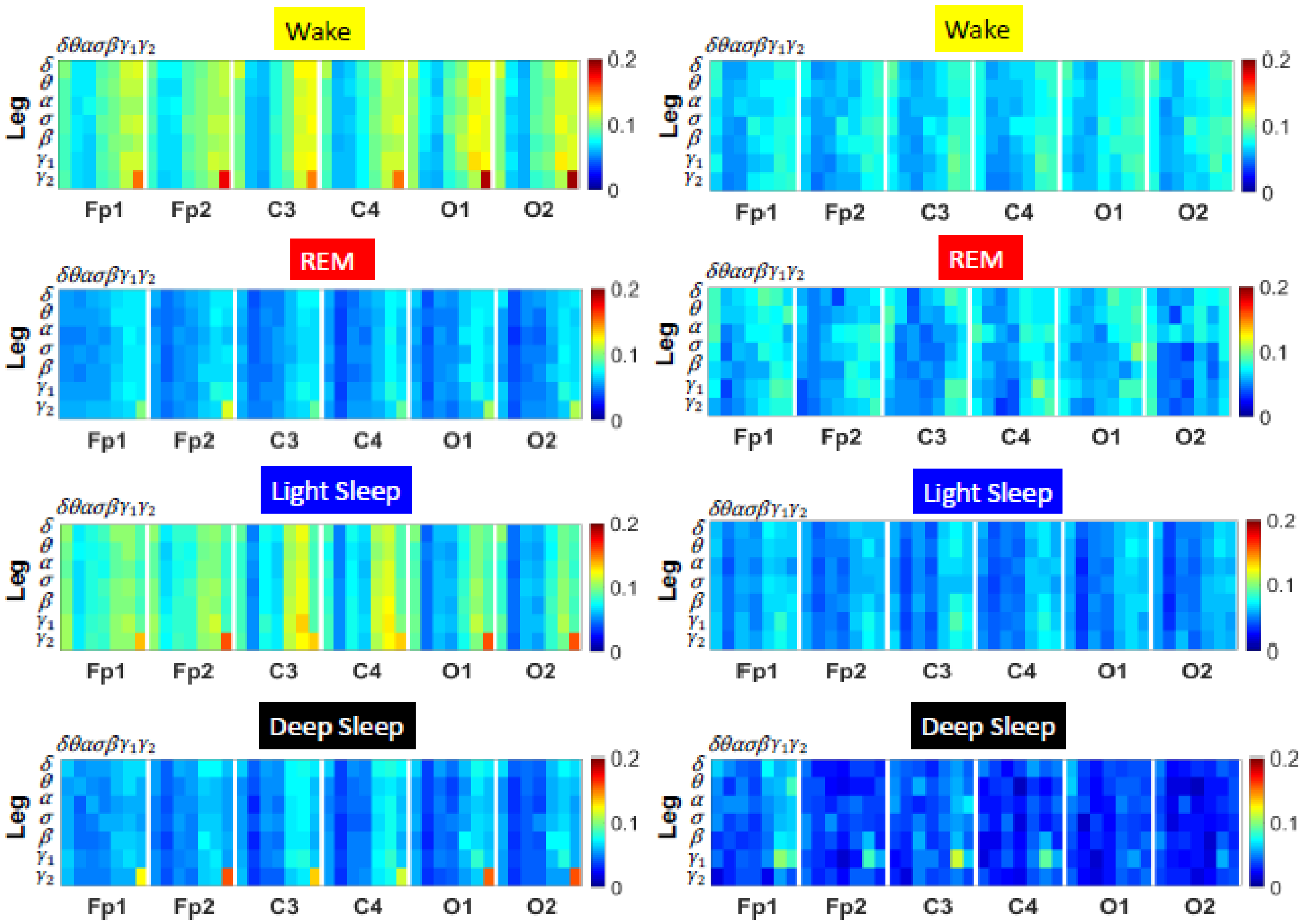
Data

- EEG data from six brain locations (Fp1, Fp2, C3, C4, O1, O2)
- chin (*mentalis*) and leg (*tibialis anterioris*) muscle tone EMG data
- from 97 healthy subjects (mean age = 67.4 years) and 33 PD subjects (mean age = 72.6 years)
- 4 major, well defined physiologic states: Wake, REM, Light Sleep (LS), deep sleep (DS)
- 7 cortical rhythms : δ (0.5–3.5 Hz), θ (4–7.5 Hz), α (8–11.5 Hz), σ (12–15.5 Hz), β (16–19.5Hz), γ1 (20–33.5 Hz), and γ2 (34–98.5 Hz)
- 7 EMG frequency bands : δ (0.5–3.5 Hz), θ (4–7.5 Hz), α (8–11.5 Hz), σ (12–15.5 Hz), β (16–19.5Hz), γ1 (20–33.5 Hz), and γ2 (34–98.5 Hz)



Results

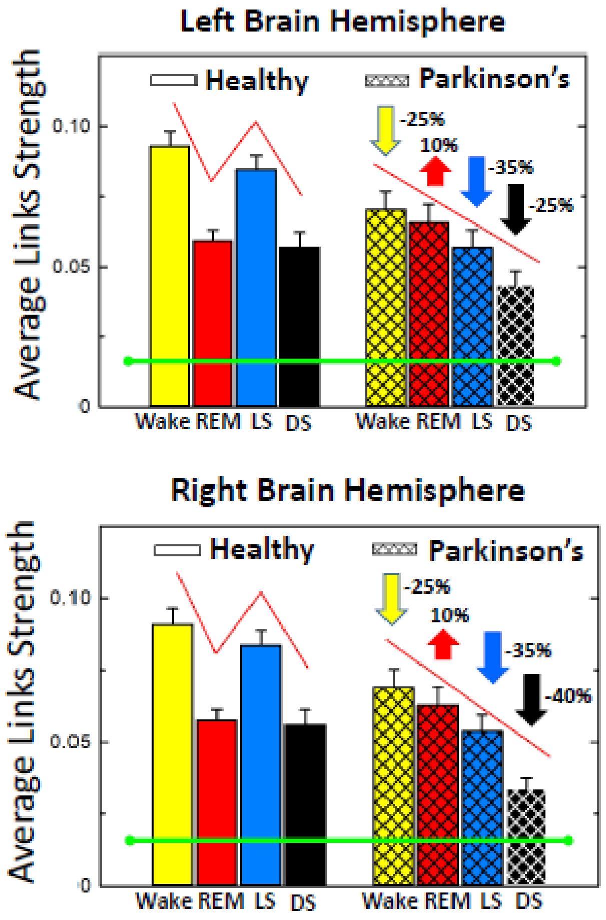
A TDS matrices of Cortical Rhythms and Leg-Muscle Network Interactions



Healthy Group

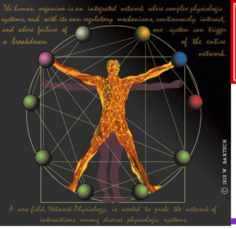
Parkinson's Group

B Stratification of Brain-Leg Network Links Strength across Sleep Stages

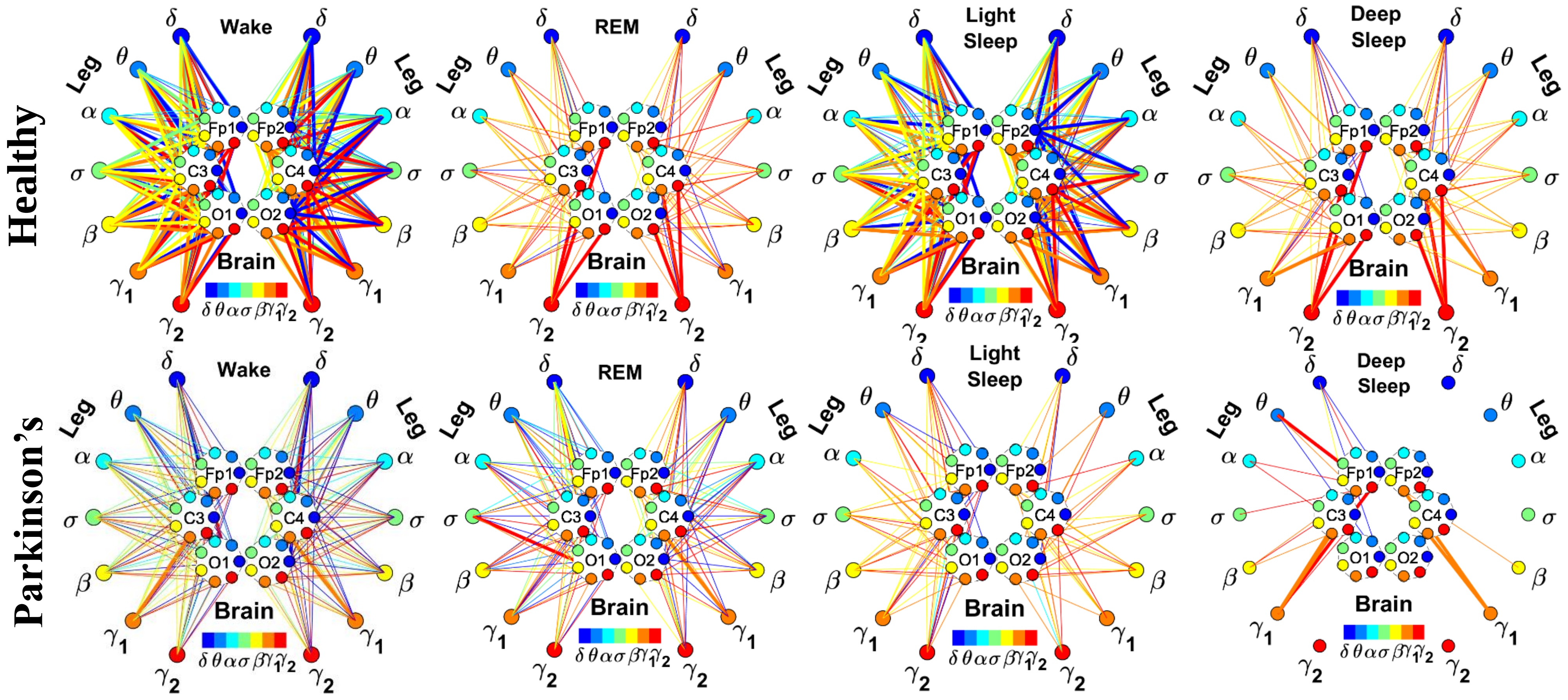


Left Brain Hemisphere

Right Brain Hemisphere



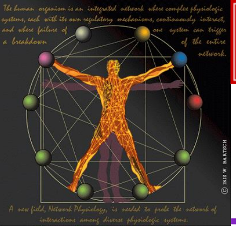
Results



Network Reorganization with states

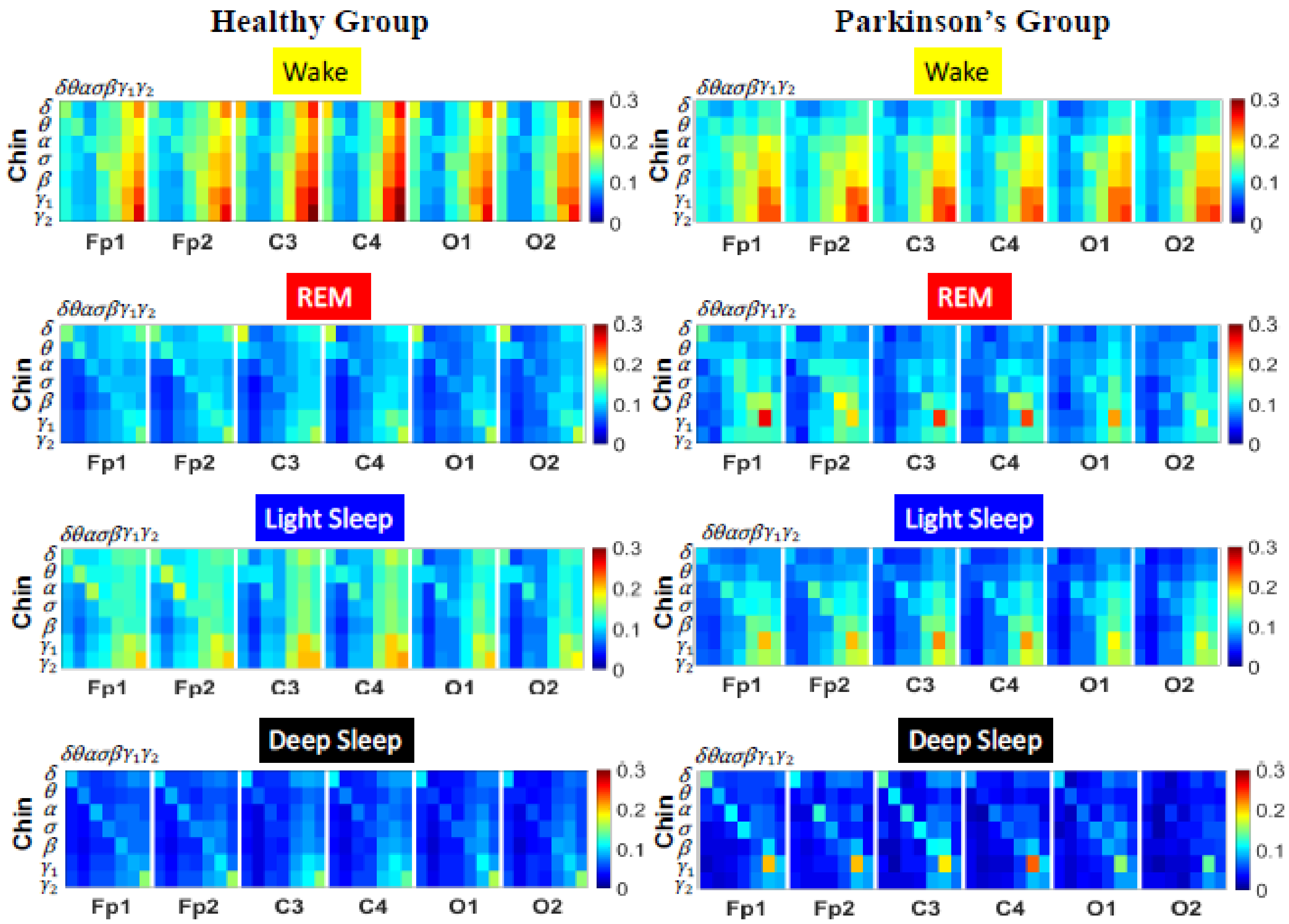
Network Connectivity ↓

Network Link Strength ↓

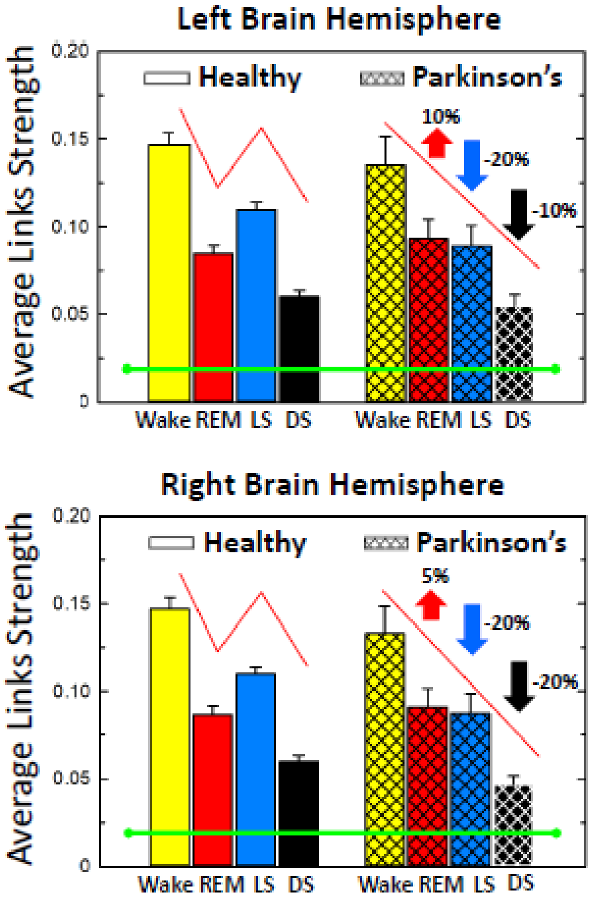


Results

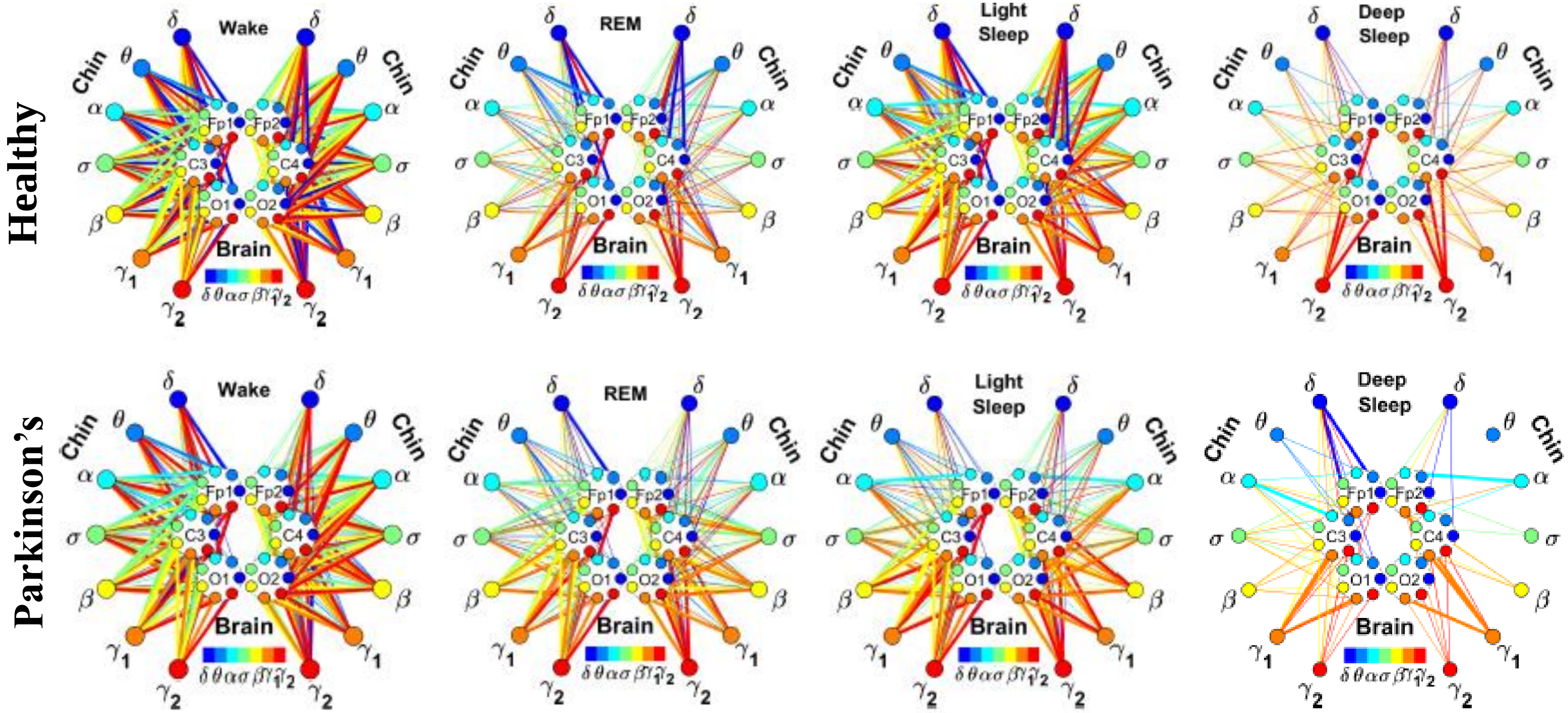
A TDS matrices of Cortical Rhythms and Chin-Muscle Network Interactions



B Stratification of Brain-Chin Network Links Strength across Sleep Stages



Results



Network Reorganization with states

Network Connectivity ↓

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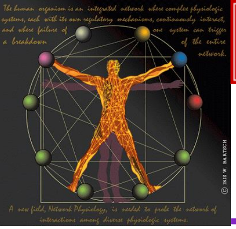
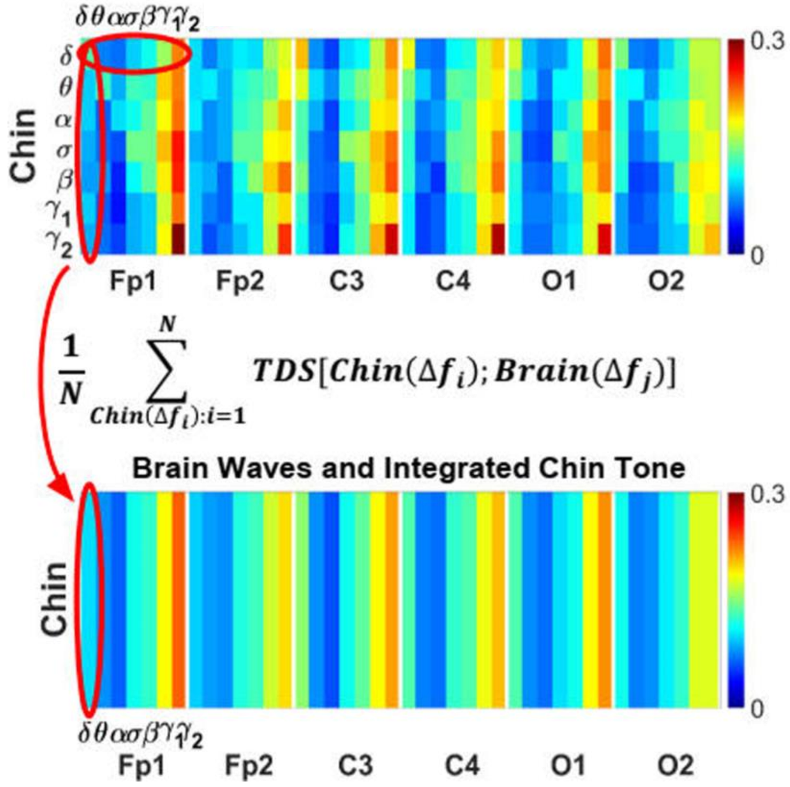
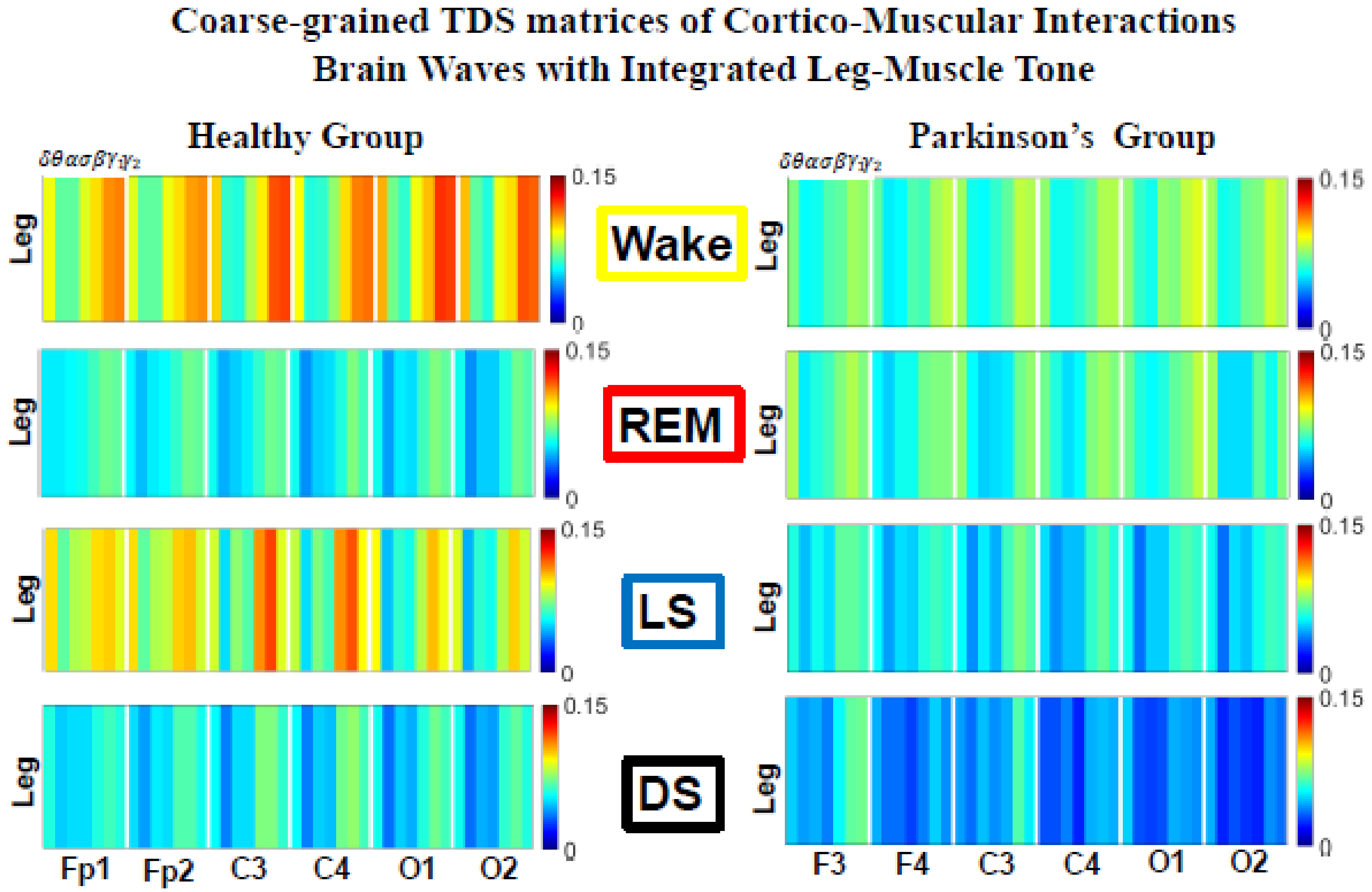


Results



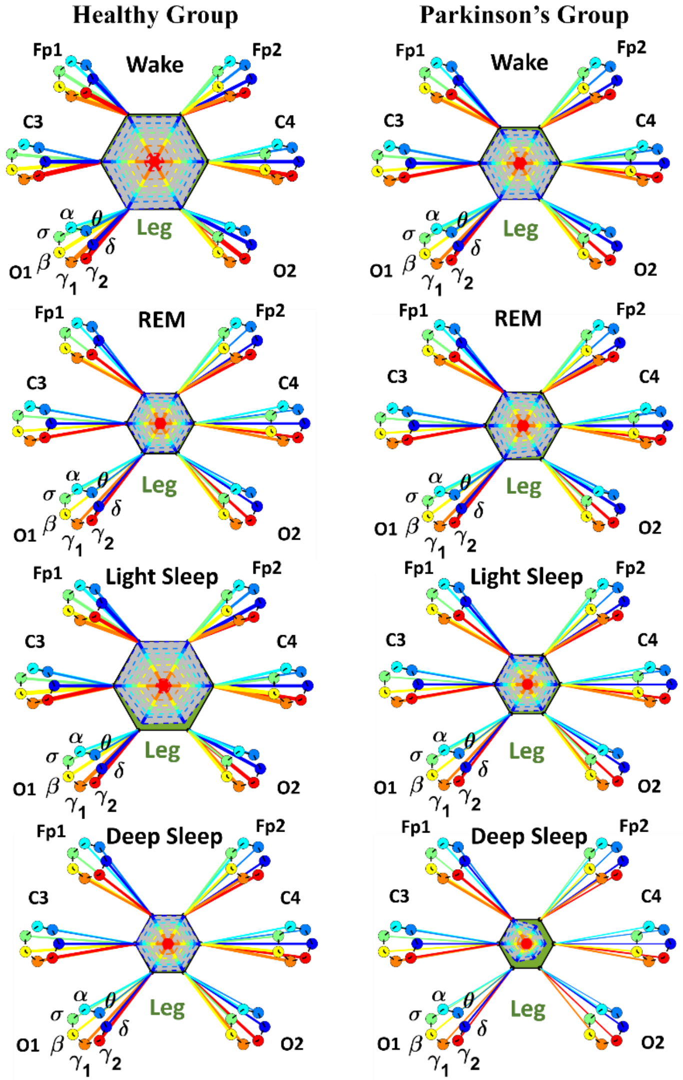
$$\frac{1}{N}\sum_{Chin(\Delta f_i):i=1}^{N} TDS[Chin(\Delta f_i); Brain(\Delta f_j)]$$

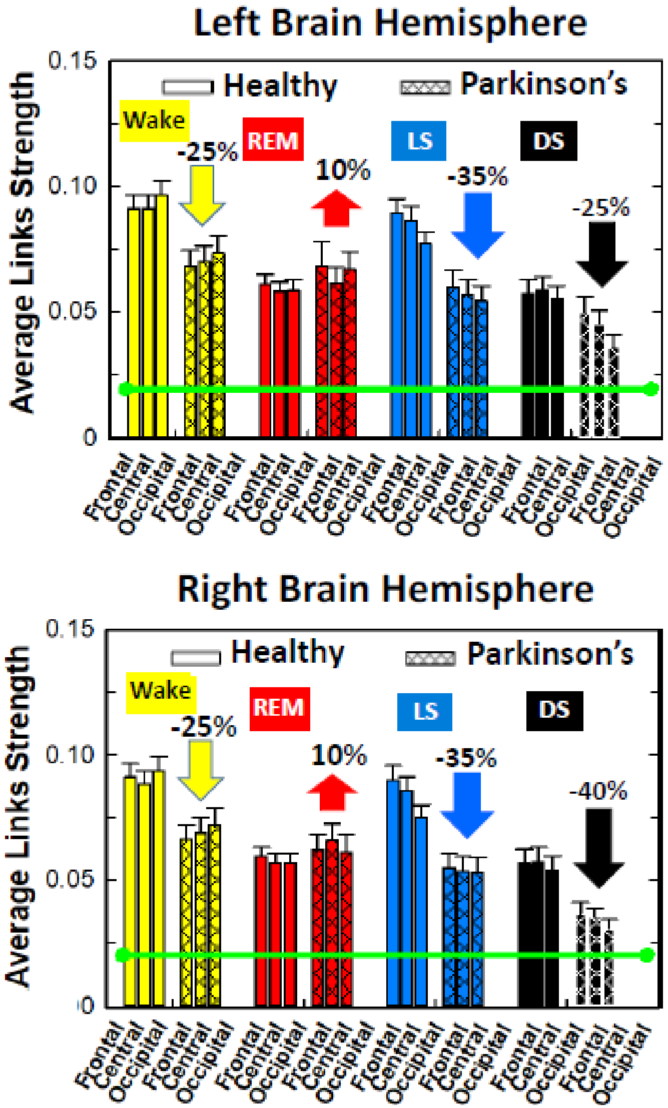
Brain Waves and Integrated Chin Tone



Coarse-grained TDS matrices of Cortico-Muscular Interactions
Brain Waves with Integrated Leg-Muscle Tone

Results





- Global decline with Parkinson
- Change in sleep-stage stratification pattern

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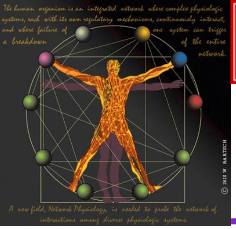
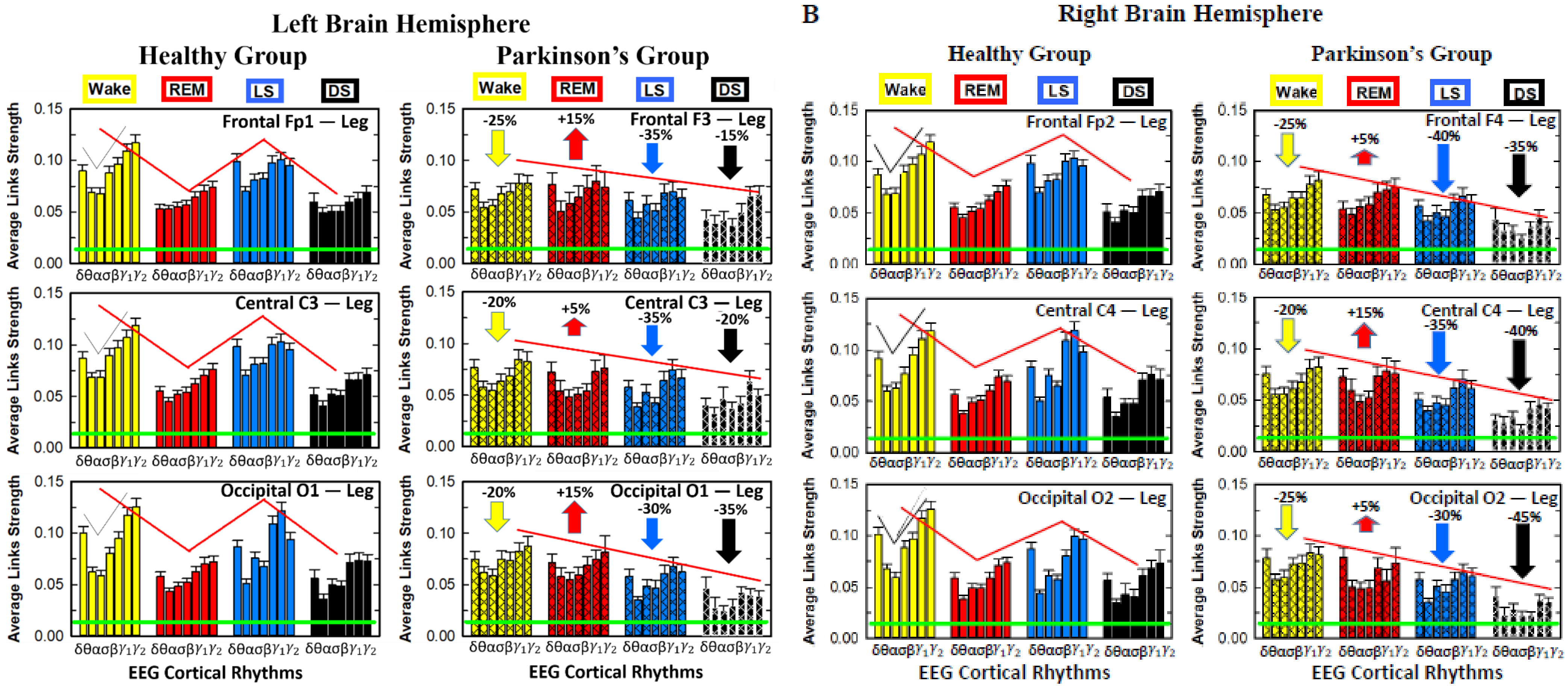
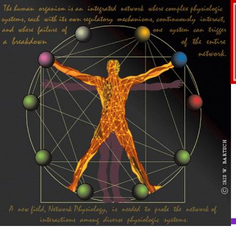


Results

Interaction Profiles: Brain Waves with Integrated Leg-Muscle Tone



- Global decline with Parkinson
- Change in sleep-stage stratification pattern
- Change in the frequency profile



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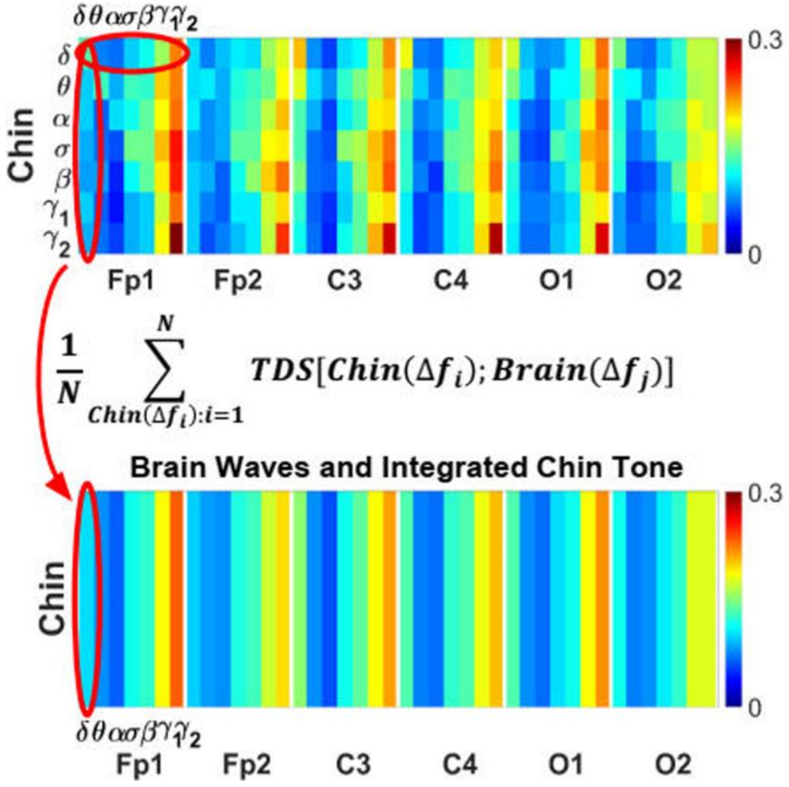
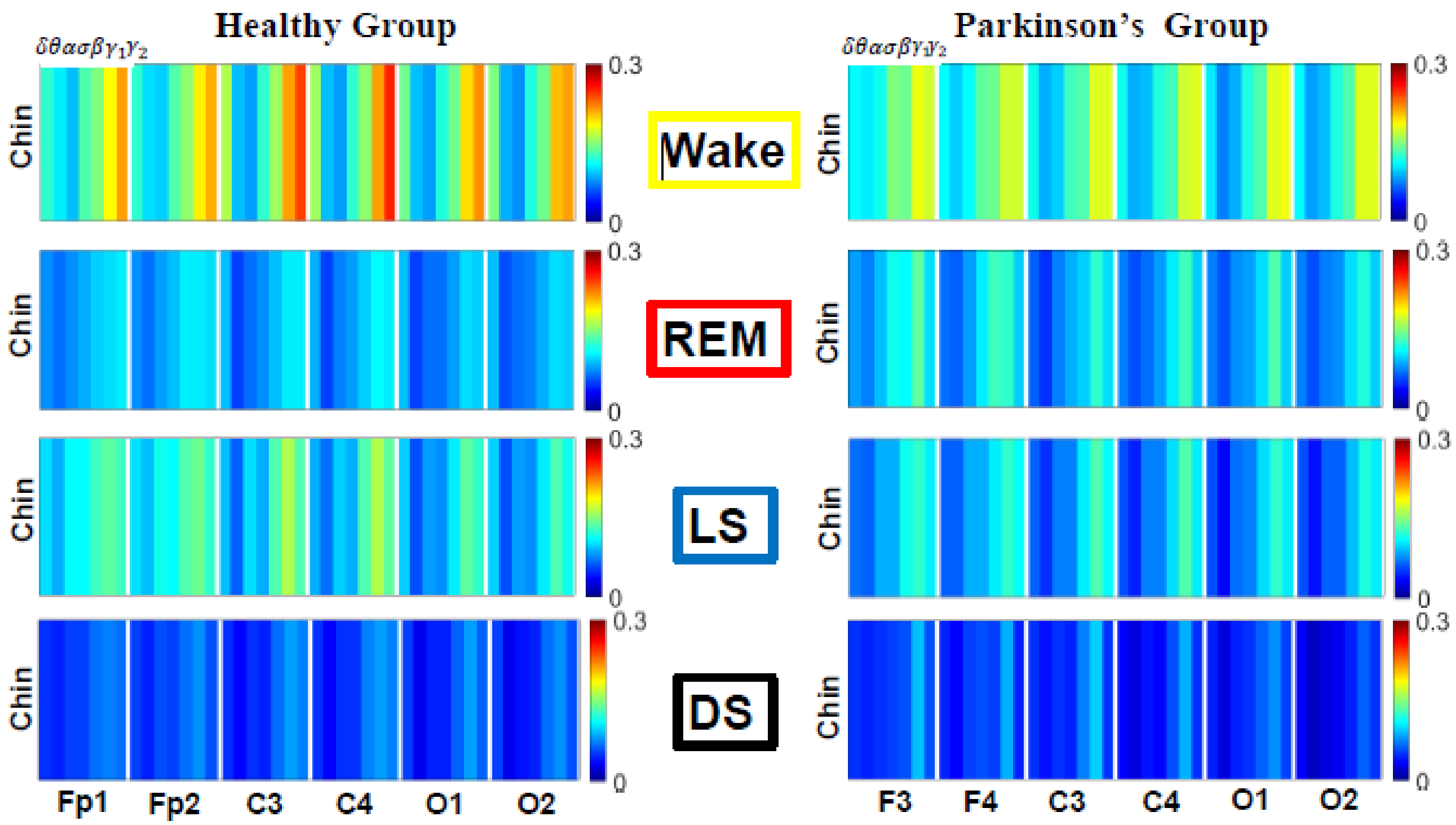


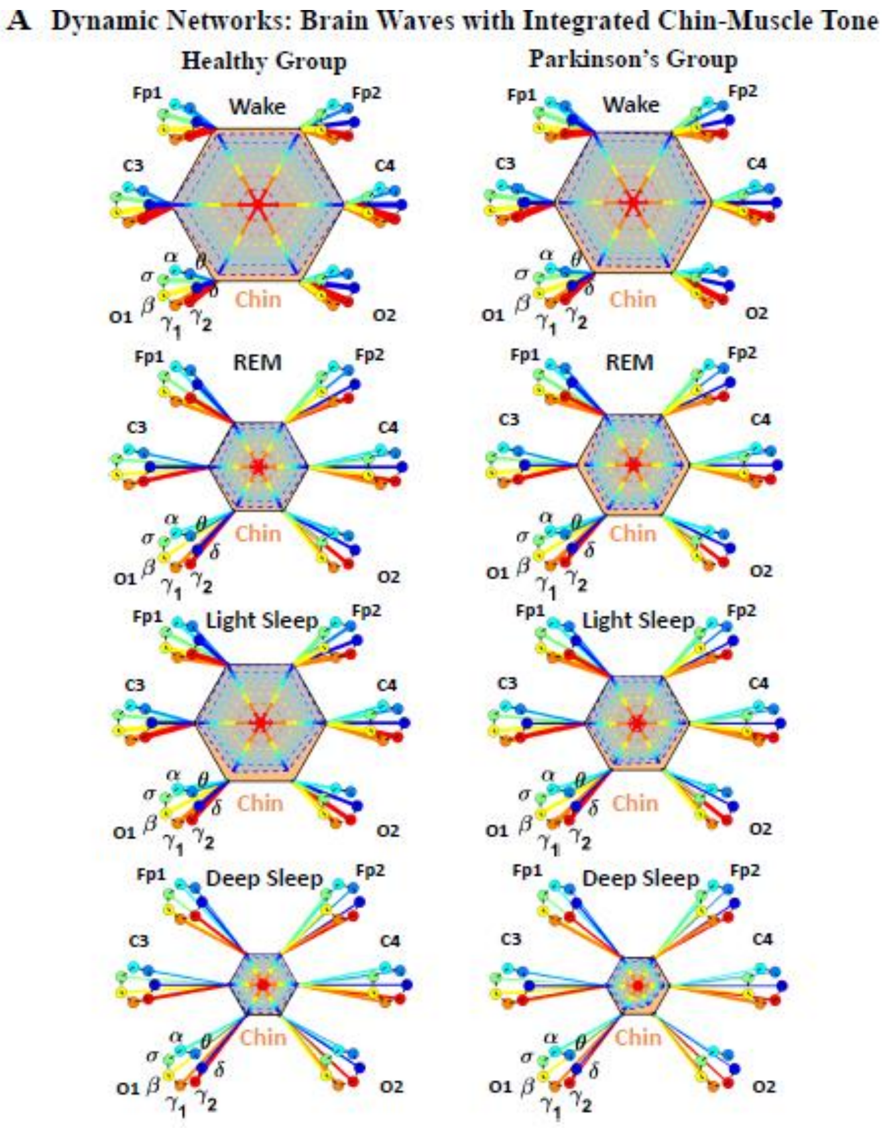
$$\frac{1}{N}\sum_{Chin(\Delta f_i):i=1}^{N} TDS[Chin(\Delta f_i); Brain(\Delta f_j)]$$

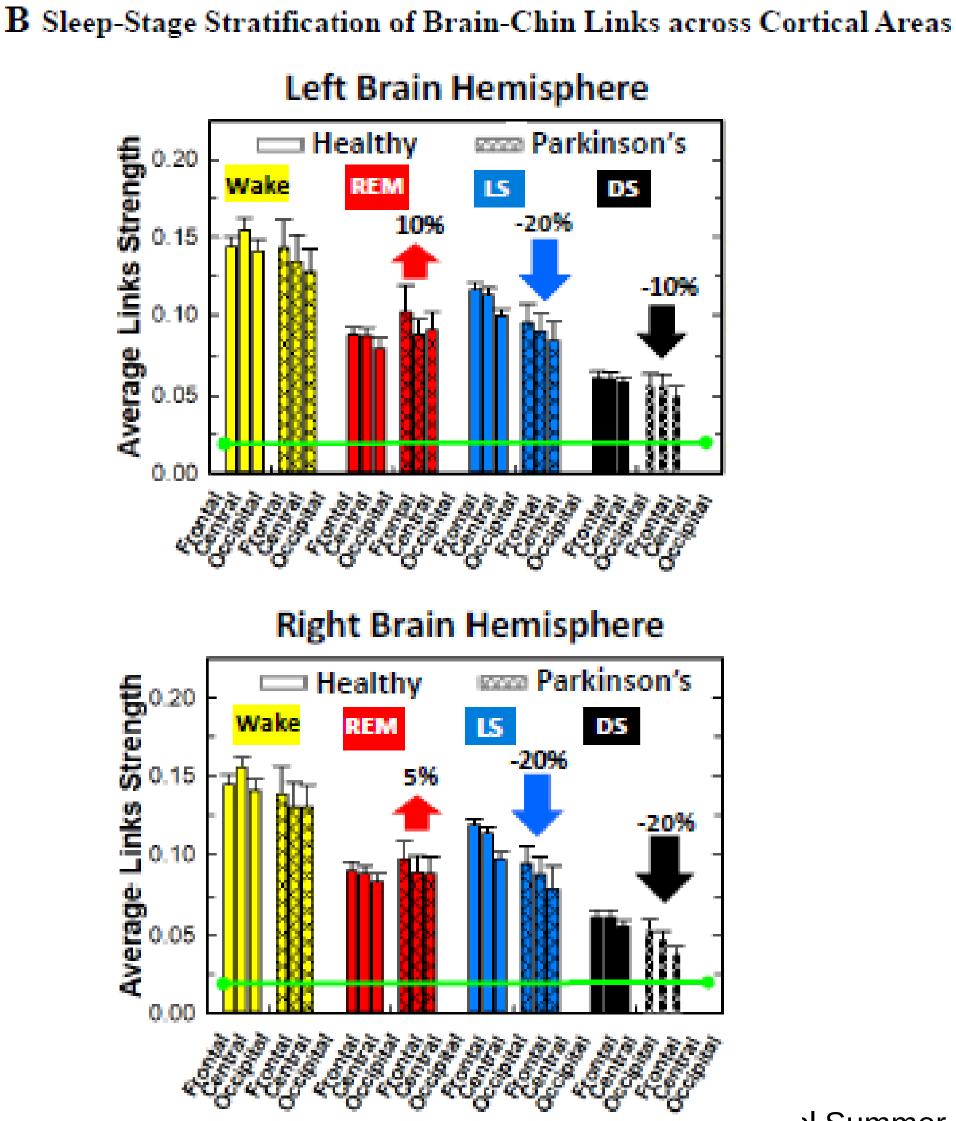
Brain Waves and Integrated Chin Tone

Coarse-grained TDS matrices of Cortico-Muscular Interactions
Brain Waves with Integrated Chin-Muscle Tone

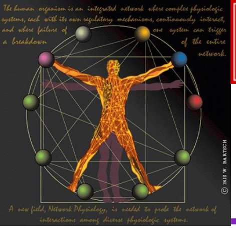


Results


A Dynamic Networks: Brain Waves with Integrated Chin-Muscle Tone

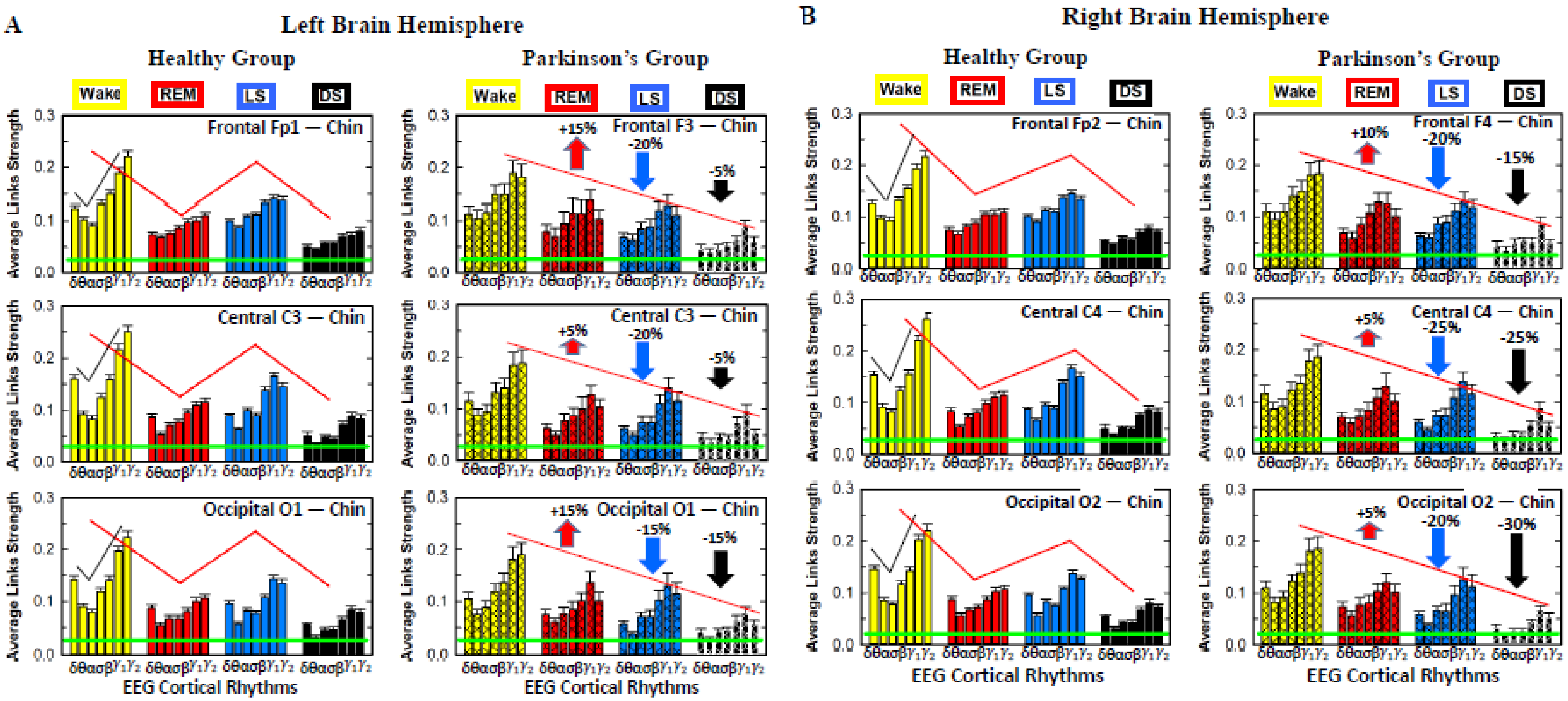

B Sleep-Stage Stratification of Brain-Chin Links across Cortical Areas

- Global decline with Parkinson
- Change in sleep-stage stratification pattern

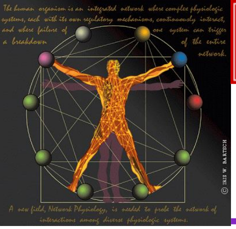


Results

Interaction Profiles: Brain Waves with Integrated Chin-Muscle Tone

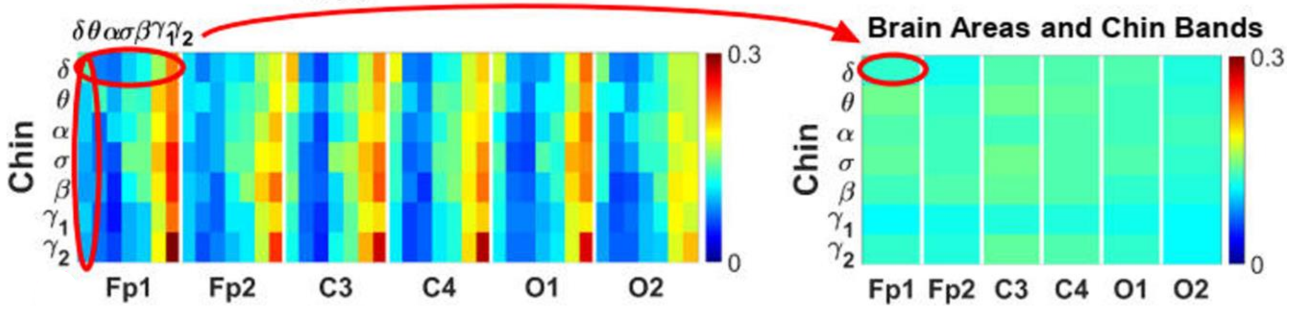


- Global decline with Parkinson
- Change in sleep-stage stratification pattern
- Change in the frequency profile

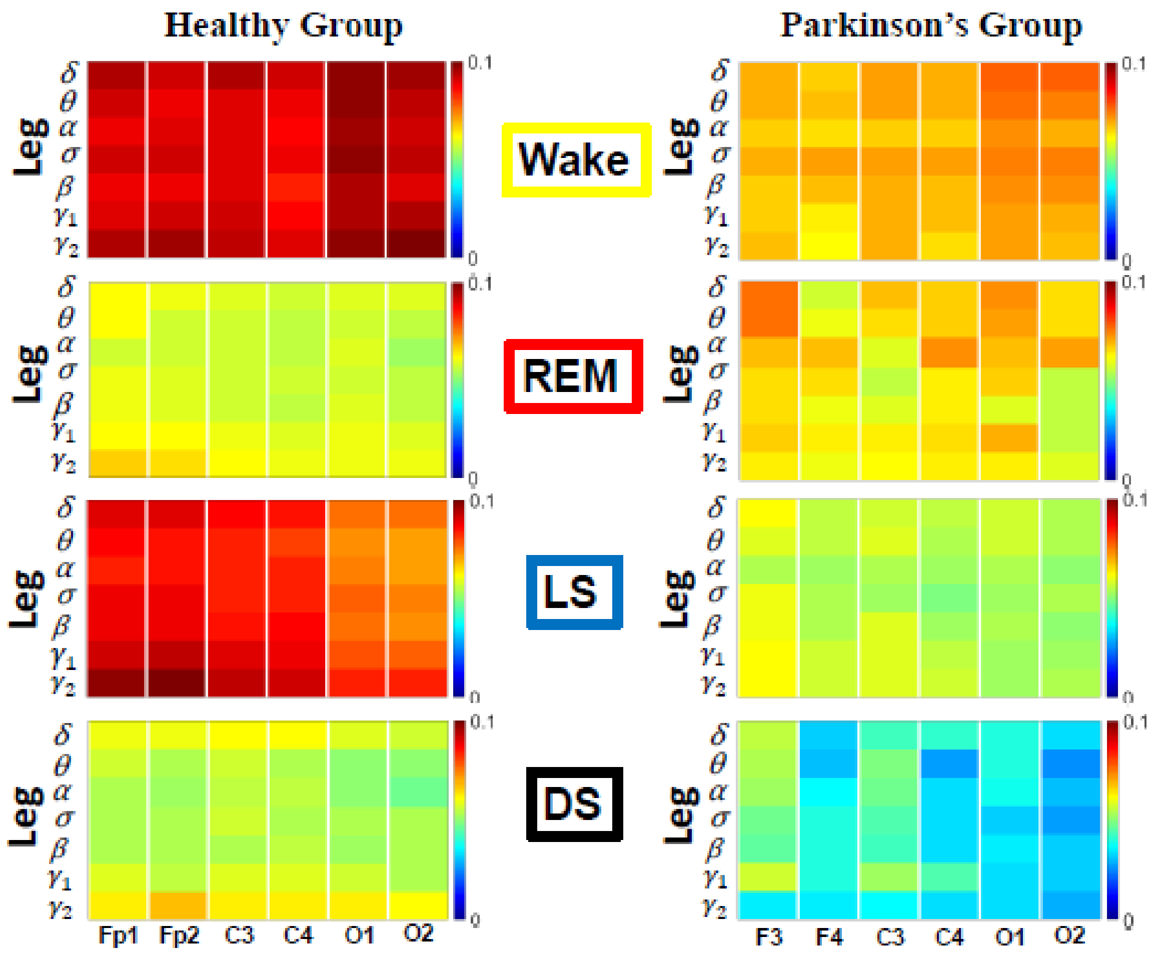


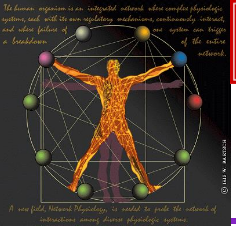
Results

$$\frac{1}{N}\sum_{Brain(\Delta f_j):j=1}^{N} TDS[Chin(\Delta f_i); Brain(\Delta f_j)]$$



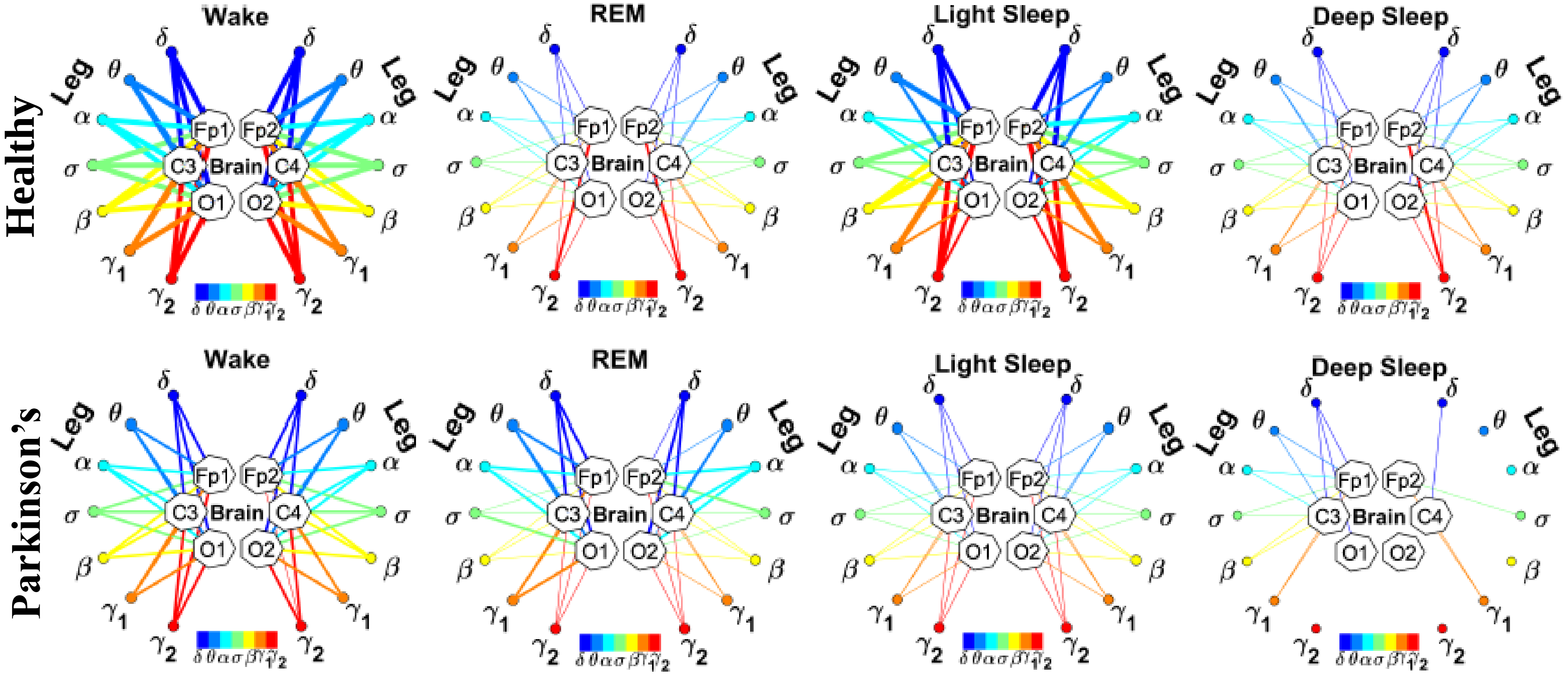
Coarse-grained TDS matrices of Cortico-Muscular Interactions
Integrated Brain Areas with Leg-Muscle Rhythms





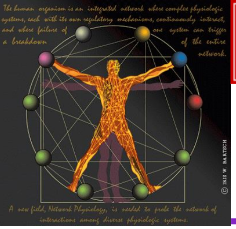
Results

Dynamic Networks: Integrated Brain Areas with Leg EMG Frequency Bands



Network Reorganization with states

Different sleep stages Reorganization pattern



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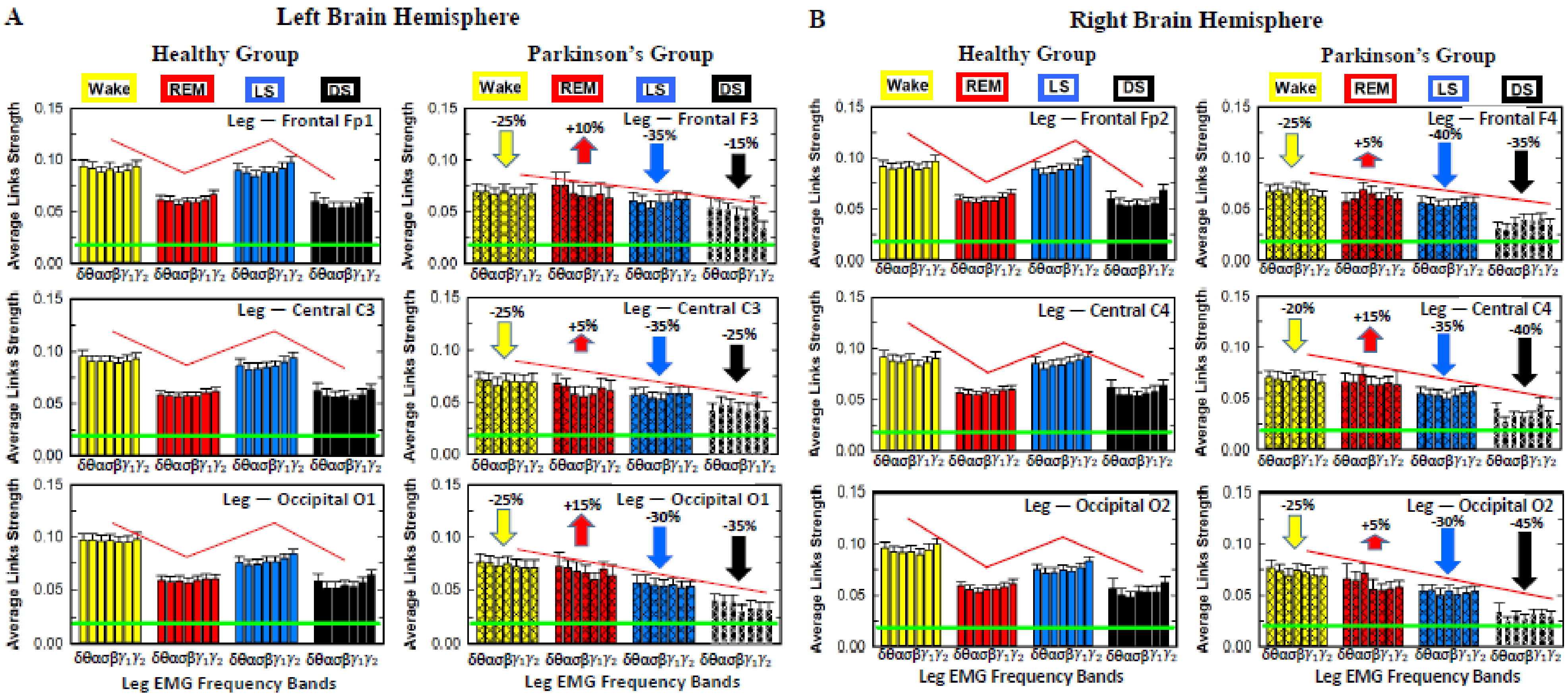

- Global decline with Parkinson
- Change in sleep-stage stratification pattern
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Results

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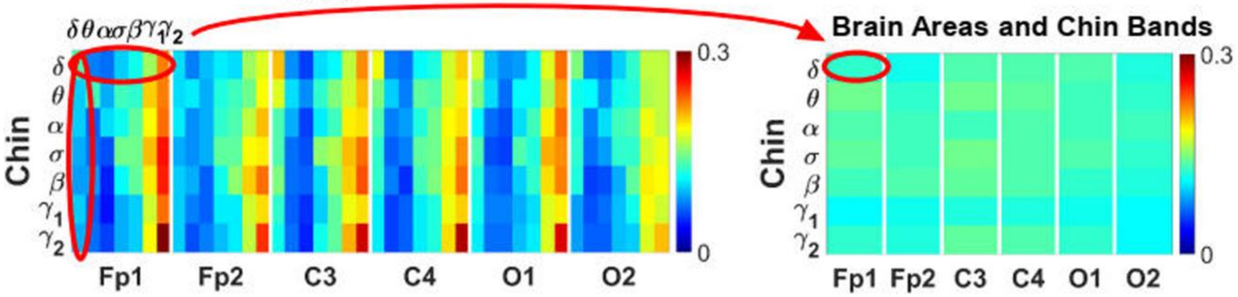
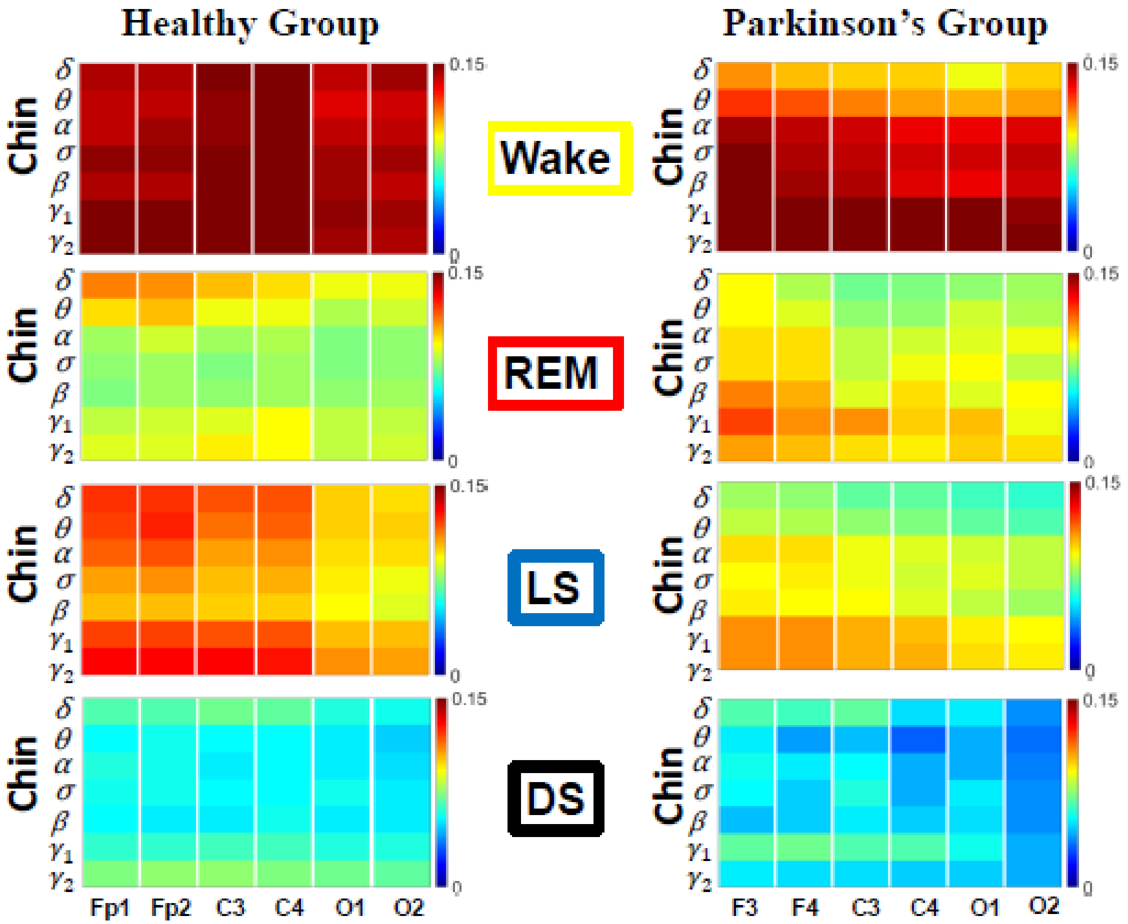


Coarse-grained TDS matrices of Cortico-Muscular Interactions Integrated Brain Areas with Chin-Muscle Rhythms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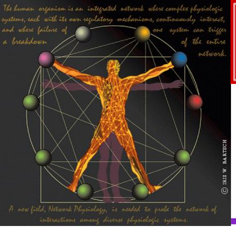
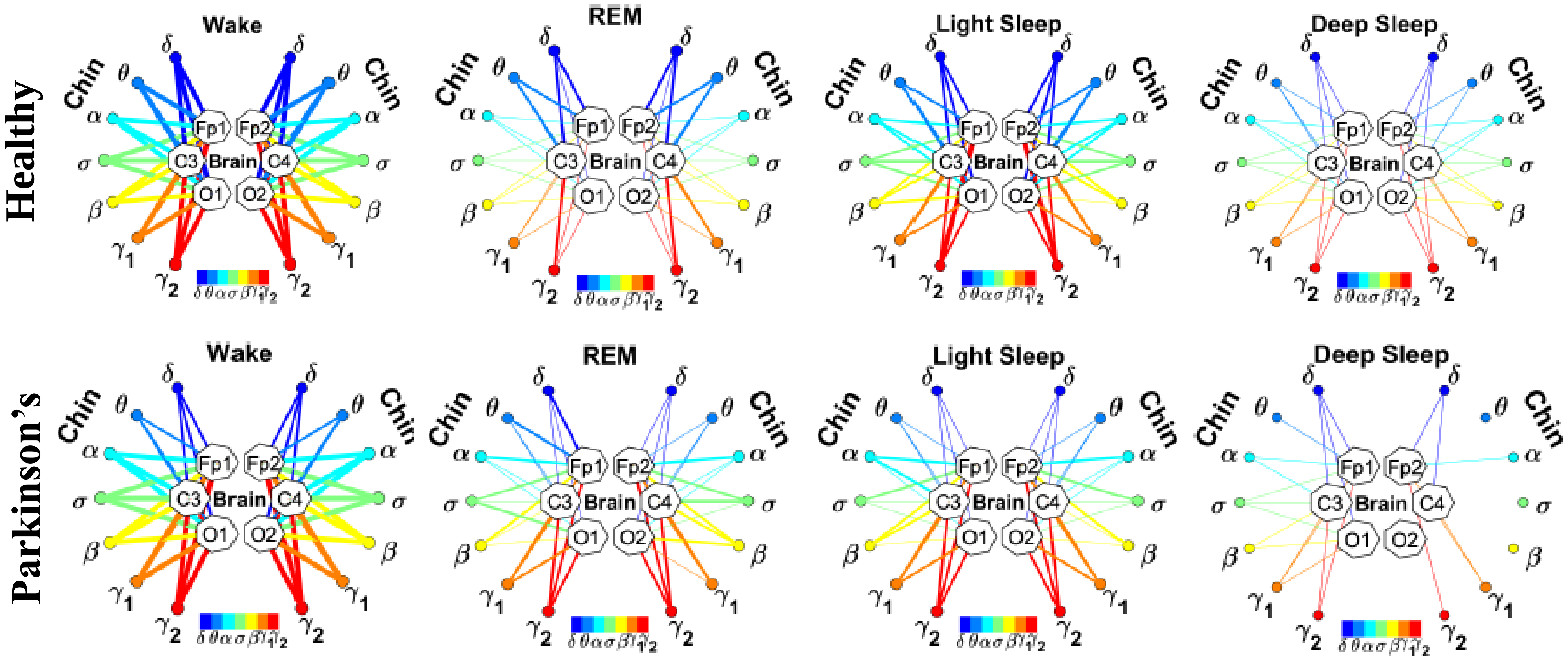


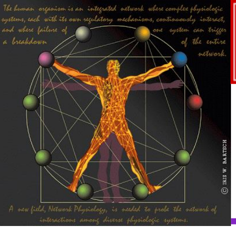
Results

Dynamic Networks: Integrated Brain Areas with Chin EMG Frequency Bands



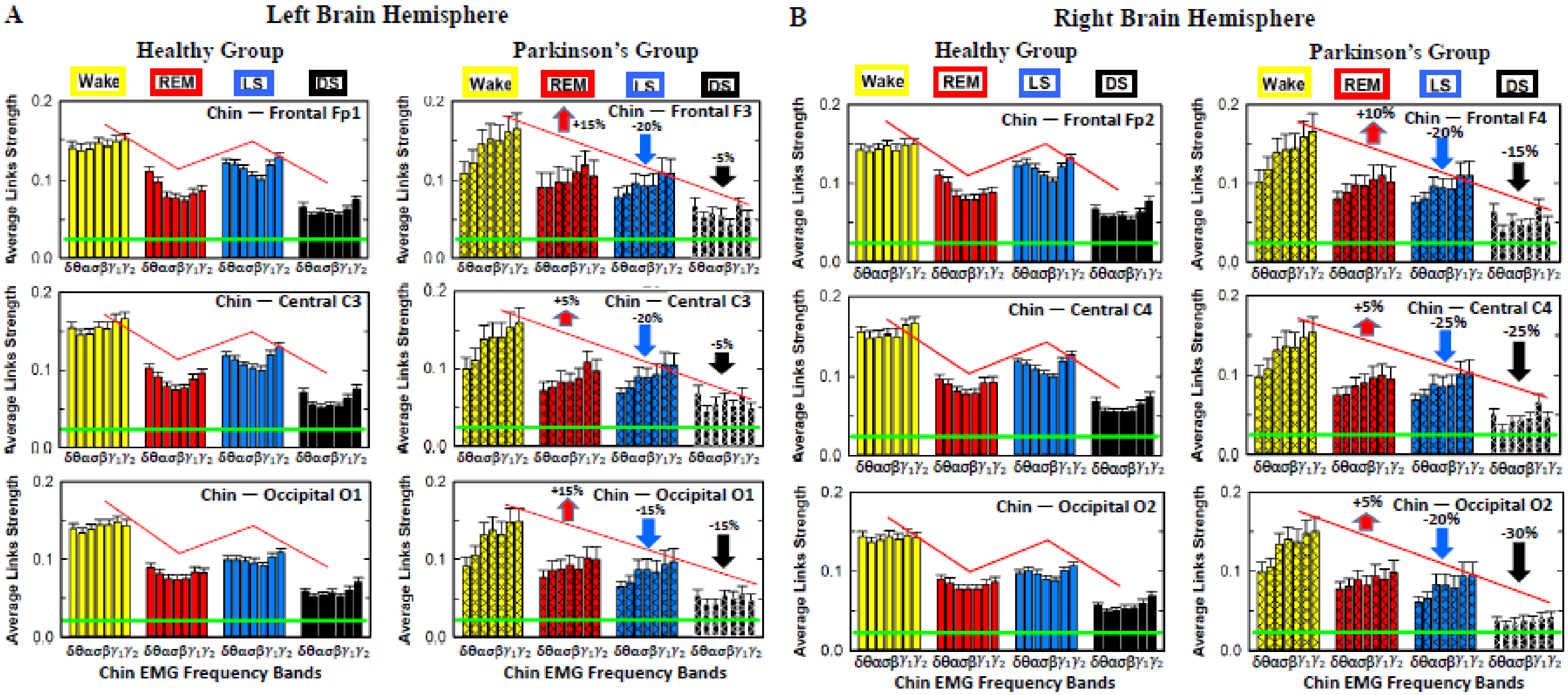
Network Reorganization with states

Different sleep stages Reorganization pattern



Results

Interaction Profiles: Integrated Brain Areas with Chin EMG Frequency Bands



- Global decline with Parkinson
- Change in sleep-stage stratification pattern
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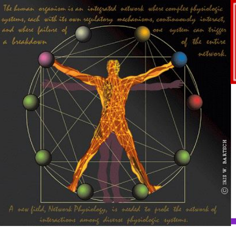
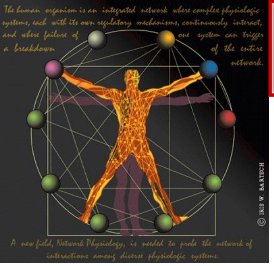


Summary

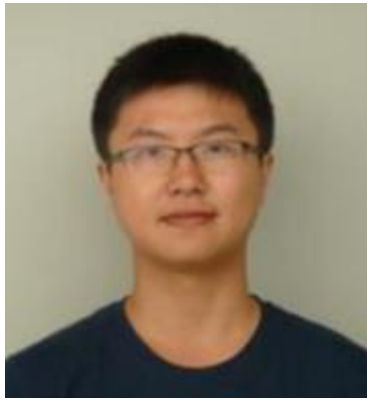
- **Structure and dynamic of brain-muscle networks**
- **Default brain-muscle interaction network**
- Identified cortico-muscular networks and how do they **respond to different sleep stages**
- Discriminate a physiologic situation from **pathologic conditions**
- Useful **biomarkers** for early **PD diagnosis**



Collaborators and friends

Plamen Ch Ivanov

Fabrizio Lombardi



Jilin JLW Wang

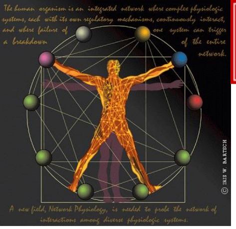
Xiyun Zhang

Sergi Garcia-Retortillo

James Holsapple

Okeanis Vaou

Anna Hohler


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.

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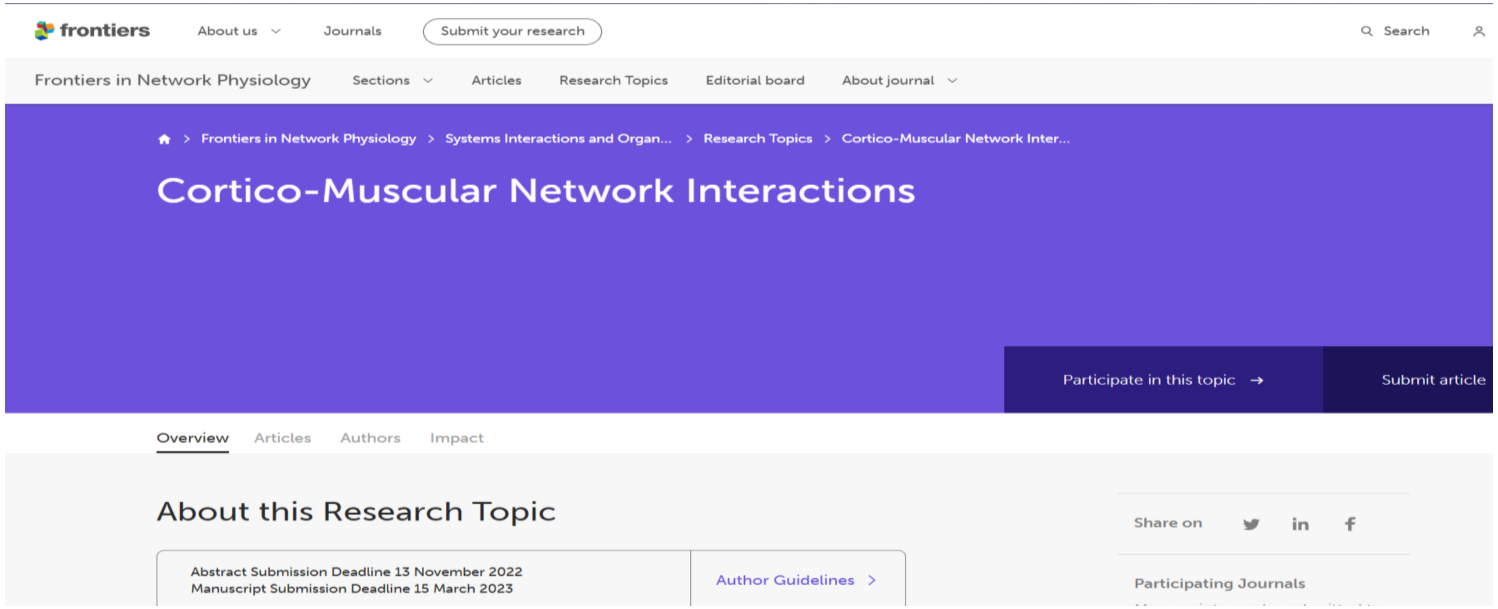
Research Topic in *Frontiers in Network Physiology*

Cortico-Muscular Network Interactions



Cortico-Muscular Network Interactions

About this Research Topic

Abstract Submission Deadline 13 November 2022
Manuscript Submission Deadline 15 March 2023

Topic Editors

- Franca Tecchio
- Rossella Rizzo
- Yuan Yang

Topic coordiantors

- Massimo Bertoli

Dr Rossella Rizzo

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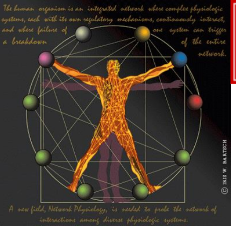
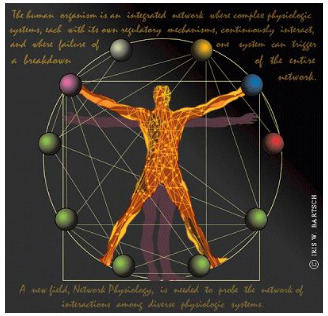


Thank you

Funders



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