

From Network Neuroscience to Network Neurology:

25 years of development and innovation

*Anastasios (Tassos) Bezerianos Barrow Neurological Institute, Phoenix, AZ, USA, and
Andrei Dragomir The N.1 Institute for Health, NUS, Singapore SG*

The seminar will begin with an overview of the historical development of network neuroscience, which emerged from the mathematical formulation of network models using graph theory and its applications to the neural networks of the brain already known from anatomy and physiology. The results of mathematical analyses based on experimental data derived from modern brain imaging techniques helped to understand the importance of not only the existence of neurons in the brain, but also that the communication between them. In this way, we can monitor rapid phenomena such as cognition or the brain's response to external stimuli, and slow phenomena such as the progression of Alzheimer's disease, schizophrenia, depression, etc. In the second part, the speaker will present the important discoveries made with the application of connectivity analysis in the healthy brain and mental disorders. To name a few, (1) the discovery that brain plasticity is a matter of hours, not days, (2) the visualization of brain conditioning to perform repetitive tasks, (3) advances in the study of fatigue mechanisms, and (4) the brain response in autonomous driving.

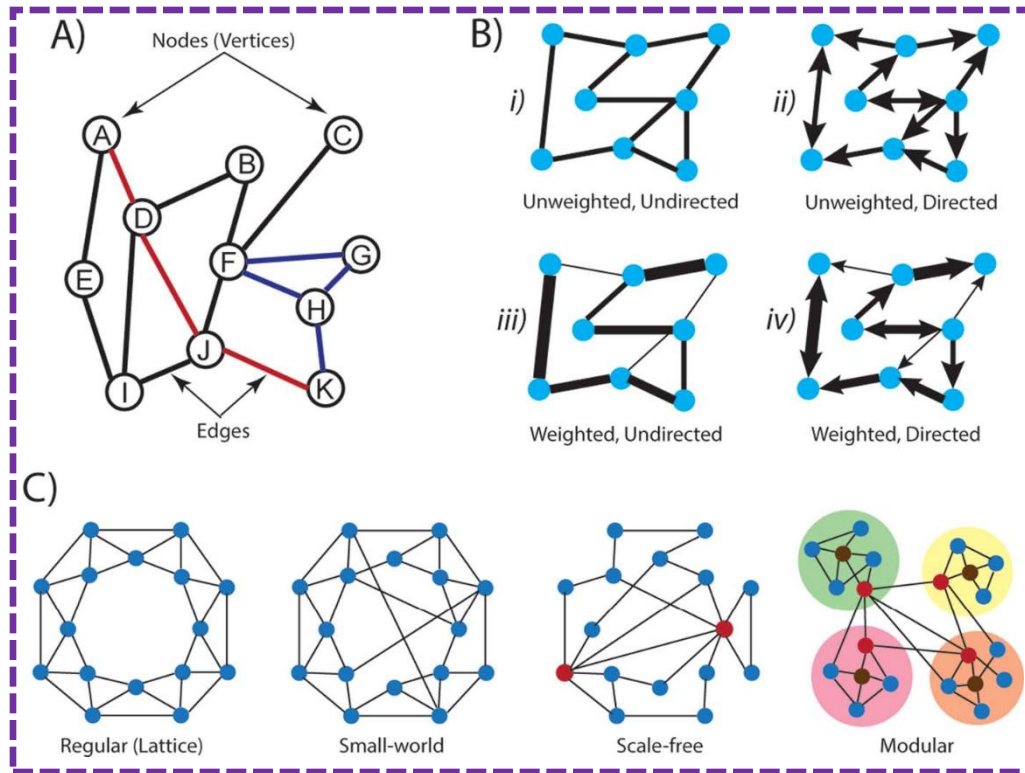
Summer School and Conference on Dynamical Systems and Complexity

AUTh camping of Kalandra Chalkidiki, 28/8 – 6/9/2024

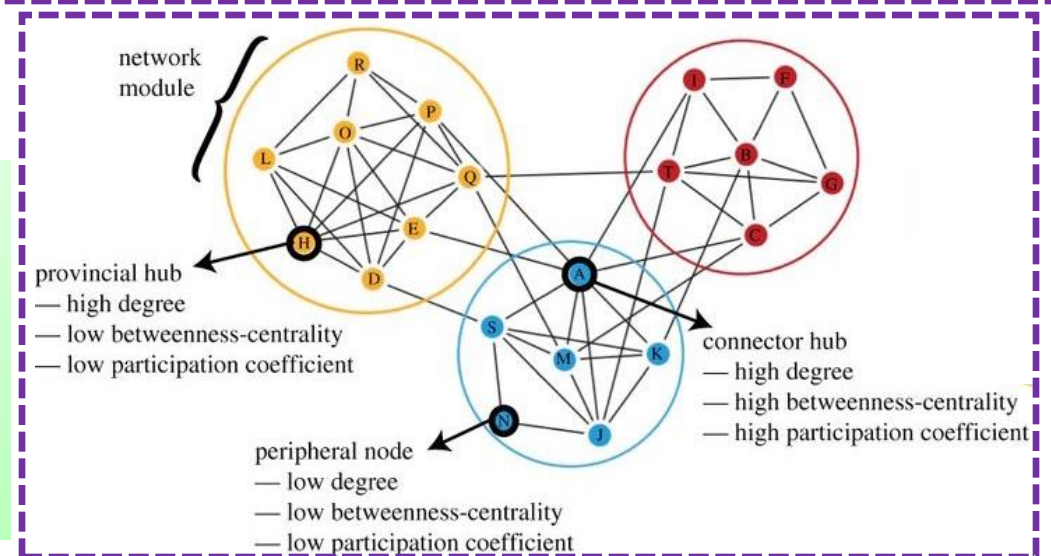
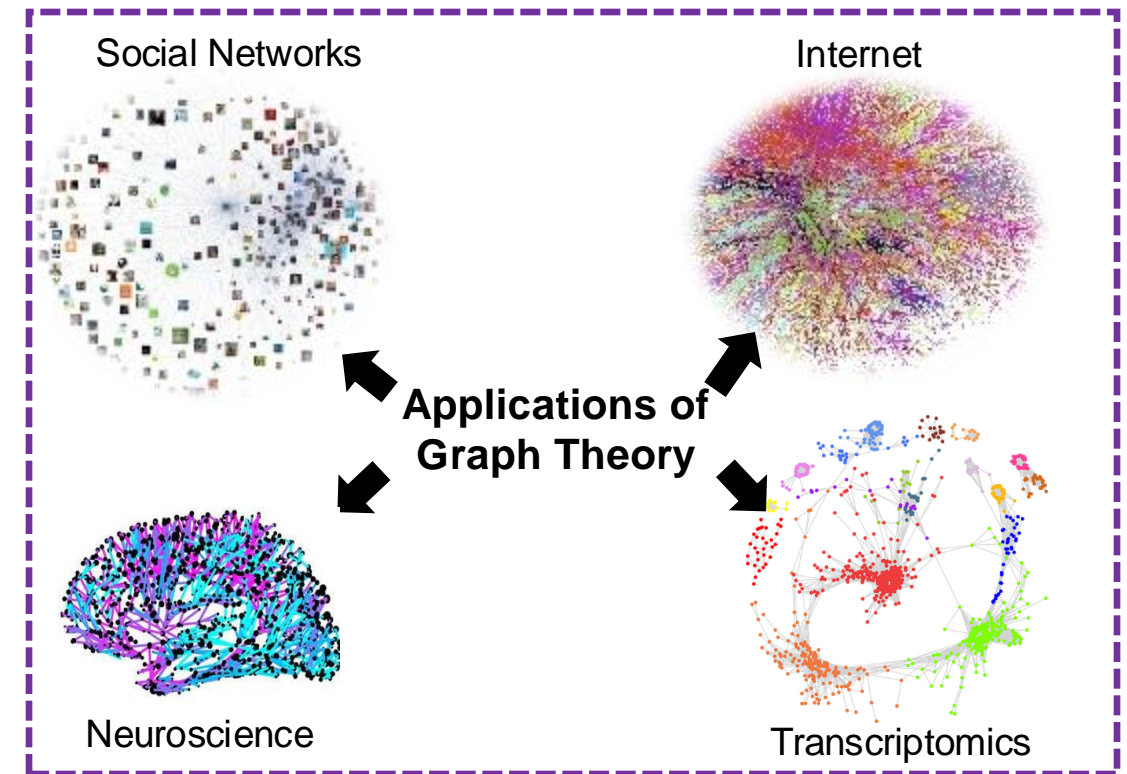
Part I

Graph Theory and Applications to the Brain

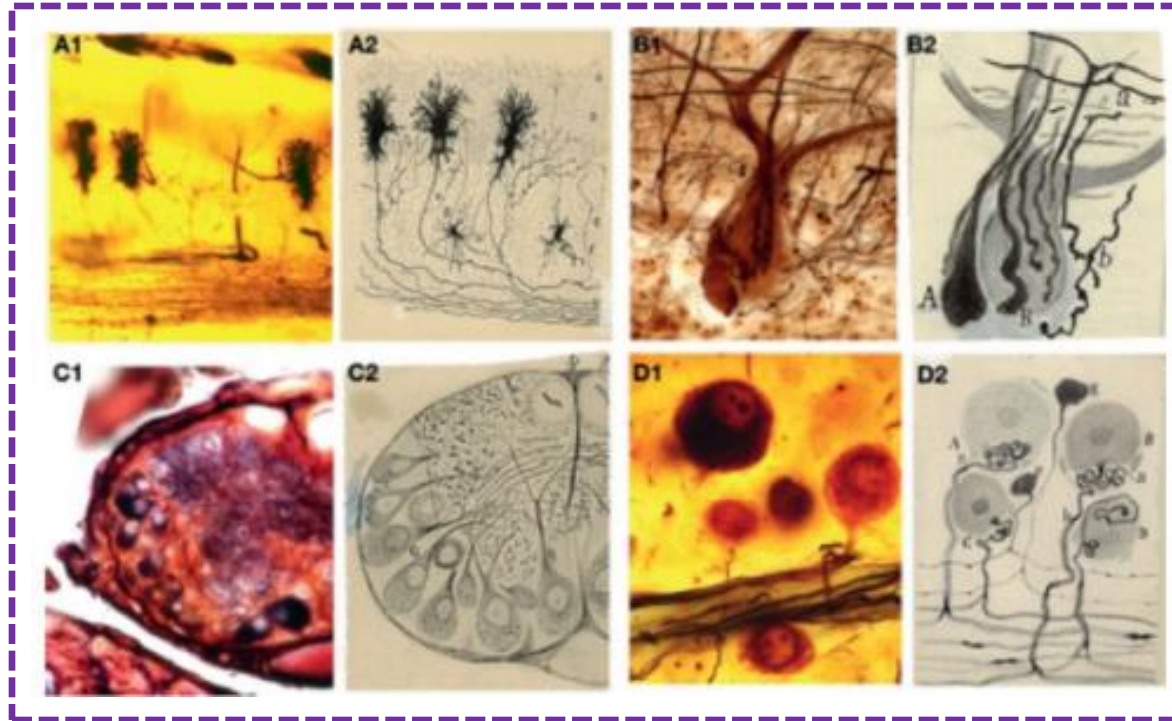
Introduction to Graph Theory



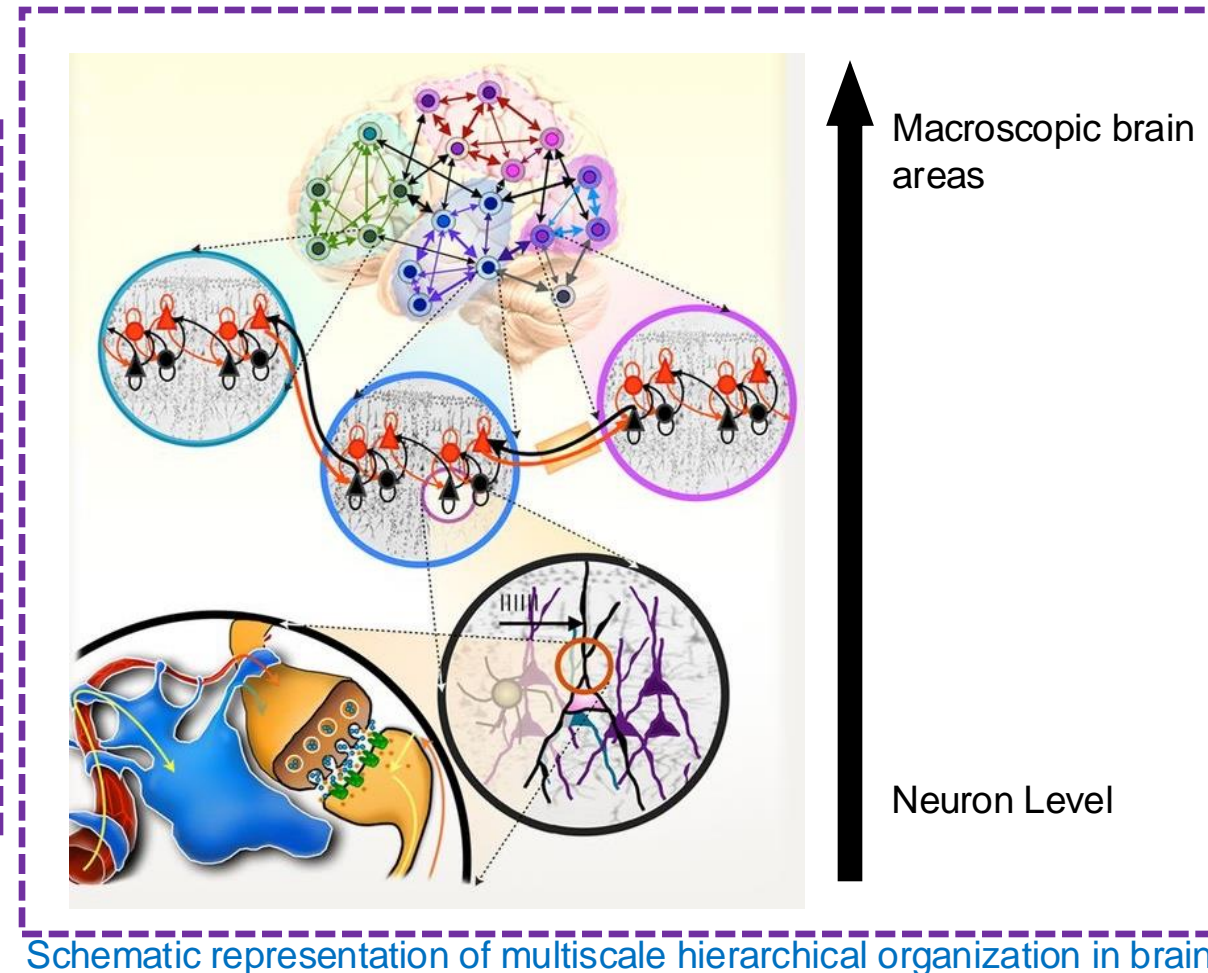
- Graph theory is a tool used to study complex networks (also known as Network Science), where the nodes represent distinct elements and the edges represent the connection between the elements
- Graphs can be weighted, unweighted, directed and undirected
- Graph theory has been widely applied in biological, social, telecommunication and computer networks
- Network analysis includes centrality measures, finding hubs, small worldness, motif analysis and community structures



Introduction to Brain Networks



First microscopic study by Ramon that evolved neuron theory



Schematic representation of multiscale hierarchical organization in brain

- Seminal neuron theory, established by Ramon y Cajal's microscopic studies first showed the complex branching process in neurons and set the scene for graph theory analysis in neuroscience
- The microscale analysis was extended to the macroscopic level where the white matter connections and functional interactions were analyzed between the cortical brain regions
- Network theory provides techniques for analyzing these structural and functional interaction in the brain, along with their associated dynamics

Complex Networks (Mathematics Applied Sciences) for Brain Networks (Neuroscience and Neurology)

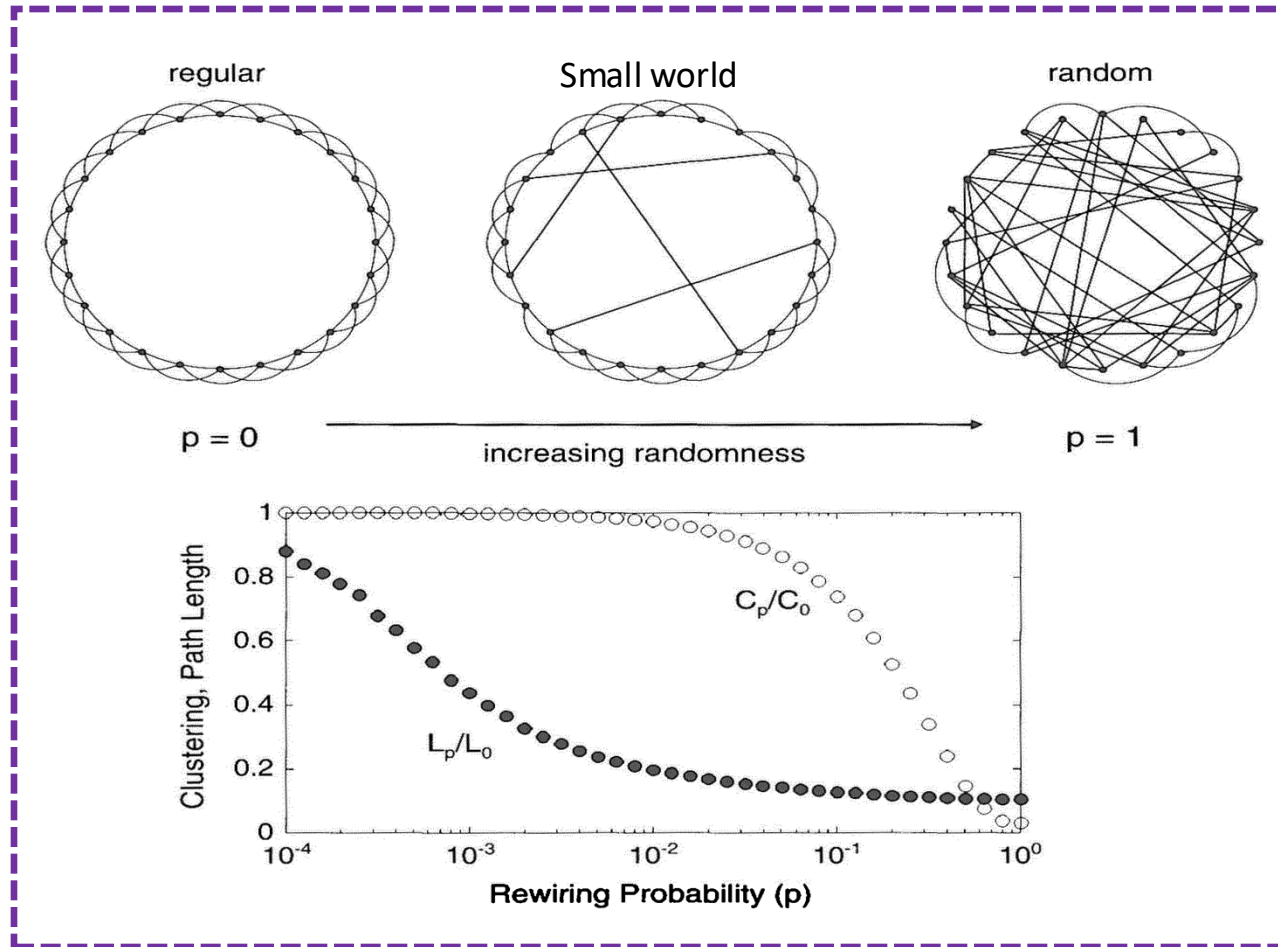
The Challenge: *A system of Billions of Nodes (~200 cells) with Trillions (~100) of edges (synapses) (the Brain) must be formulated as system of limited number of equations and degrees of freedom.*

Biological Innovations by The Dimensionality Reduction: *(1) Synchrony of oscillation (2) Spatiotemporal processes*

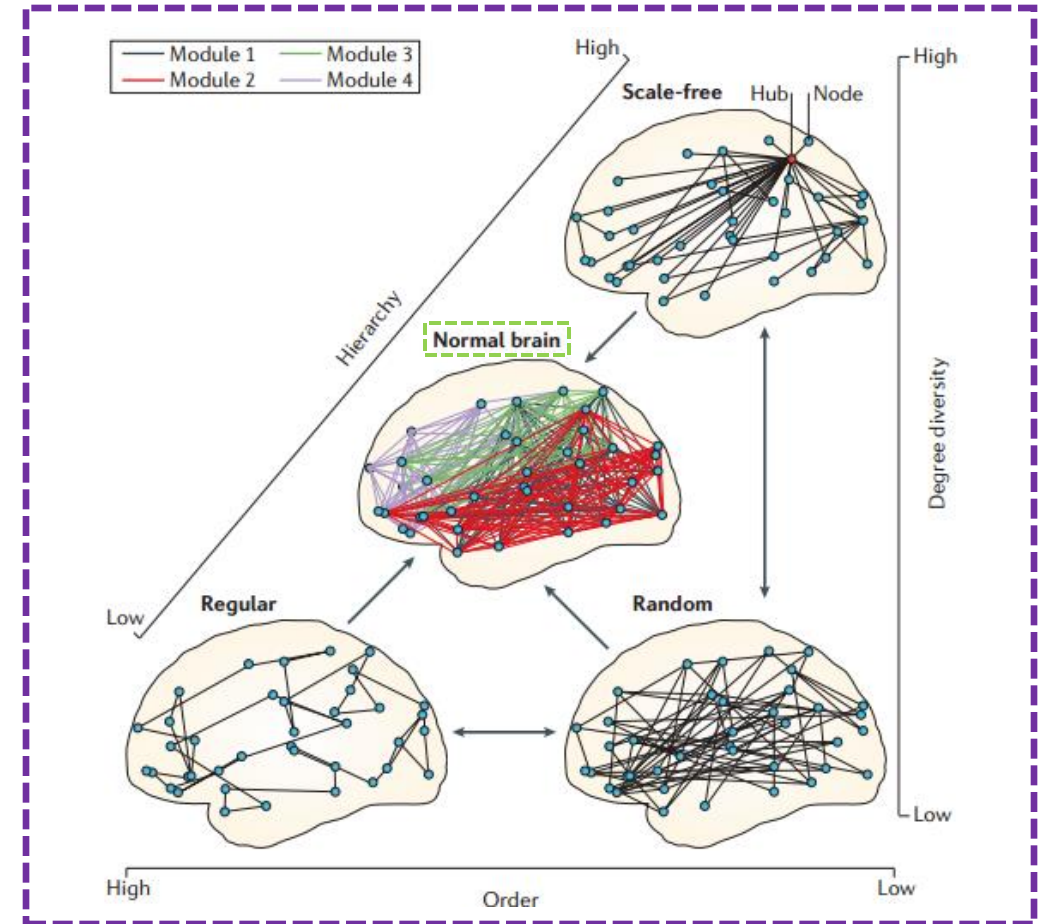
Scientific Innovations by Graph Theory and Signal Processing

Technological Innovations: *New Imaging Techniques (MRI, fMRI, LFP, and High Density EEG)*

Brain at Multiple Scales

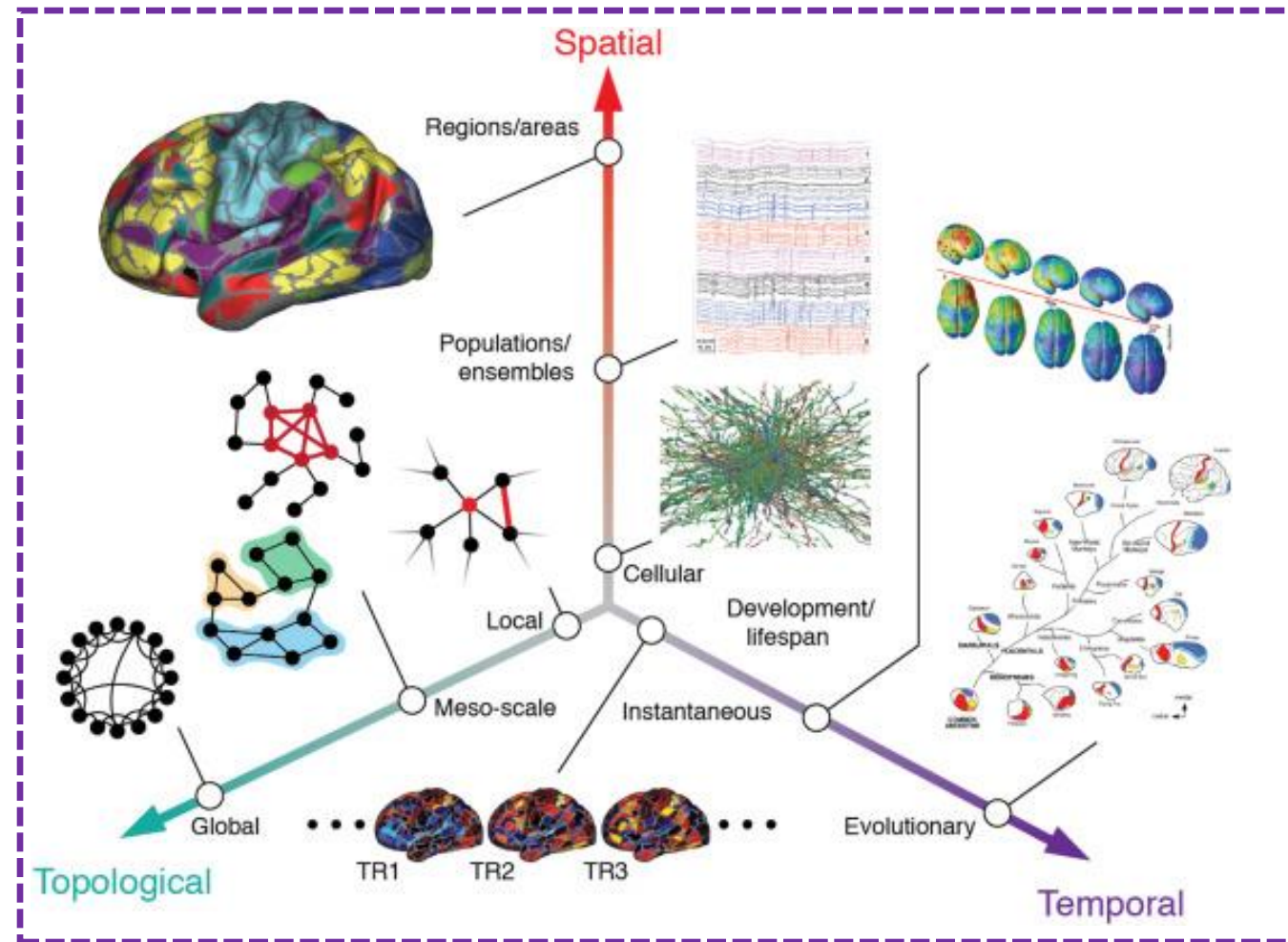


Intermediate structure organization of normal brain network



- The need of graph theory is due to a paradigm shift in brain function, which has been observed from localized populations of neurons to the importance of connectivity between the brain regions (Bassett et al., 2006; Park et al., 2013)
- The brain networks is also a composite mixture of 'random', 'regular' and 'scale-free' networks

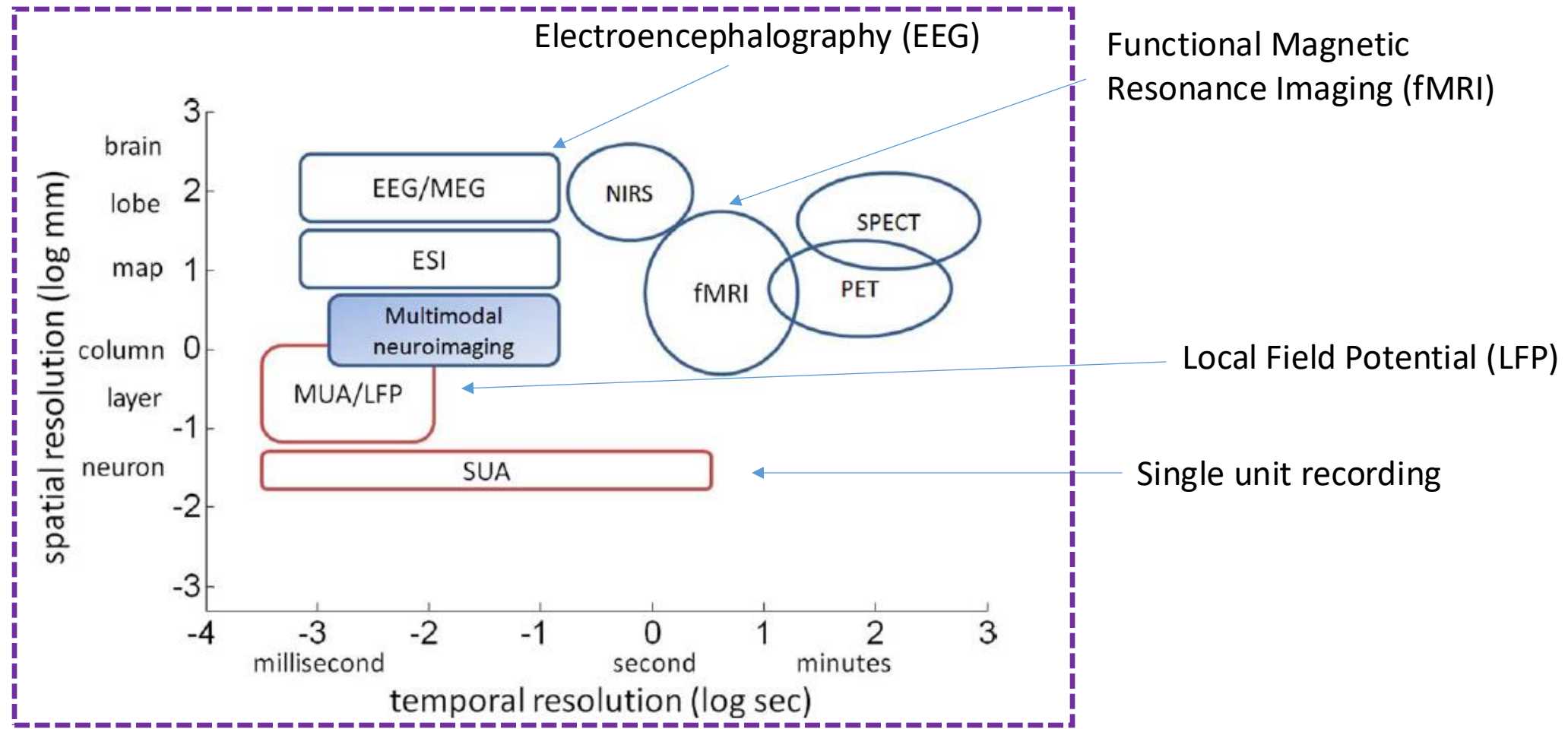
Brain at Multiple Scales



Organization of brain networks in Spatial, Topological and Temporal scales

- The brain networks are fundamentally based on multiple scales: Spatial, Topological and Temporal scales (Betzel et al., 2017)
- Hence, for real-time effective tracking of cognitive states, an advanced framework incorporating multiple scales of brain network is essential

Brain Signals



Schematic illustration of the ranges of spatial and temporal resolution of various **noninvasive** imaging techniques and **invasive** experimental techniques

Bin He et al., 2008

Types of Imaging Machines

Structural Network



Functional Network

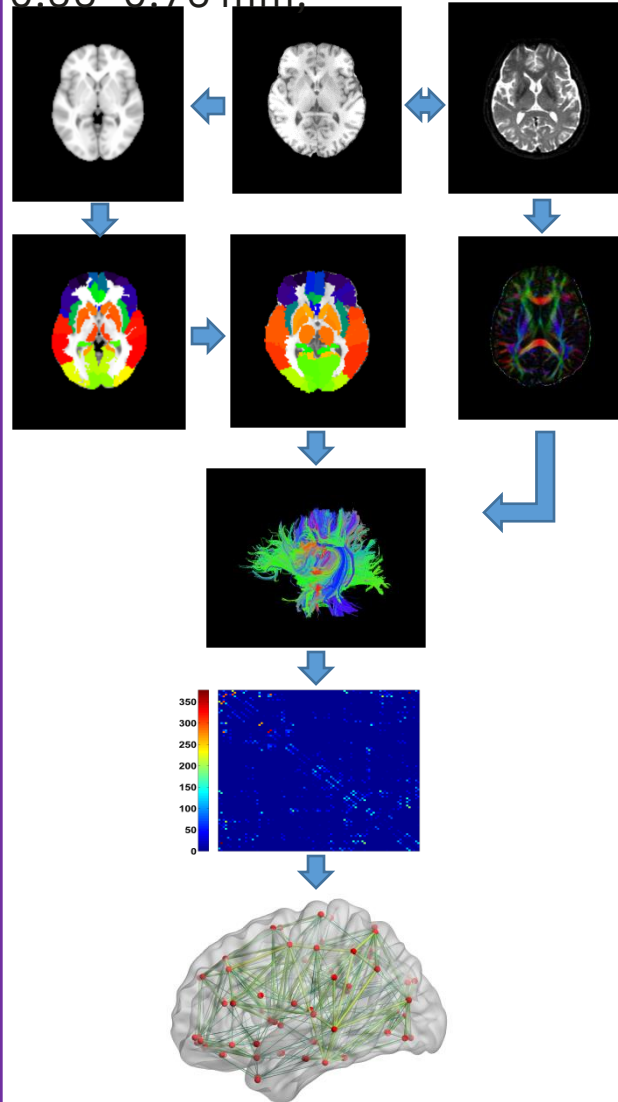
Effective Network



Types of Connectivity Network

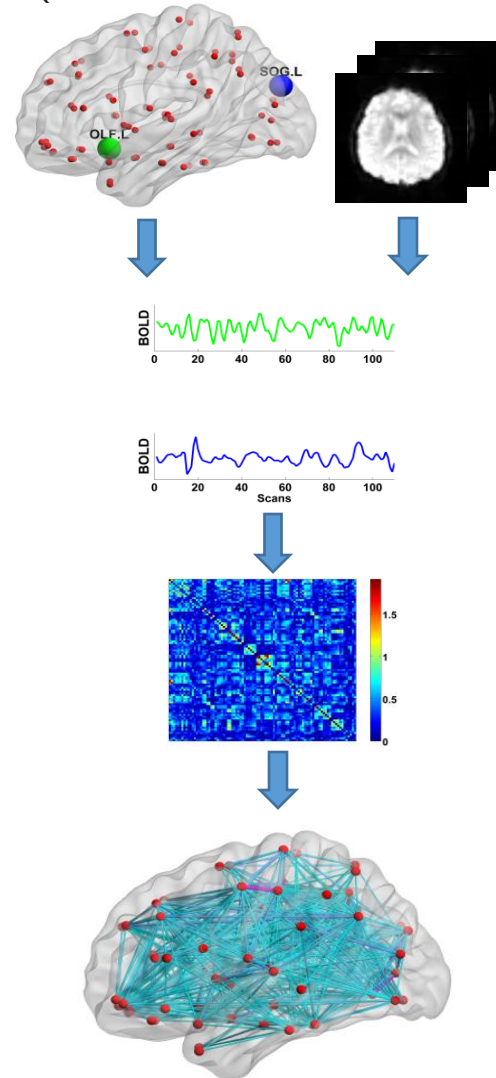
Structural Network

Isotropic resolutions as fine as 0.66–0.76 mm.



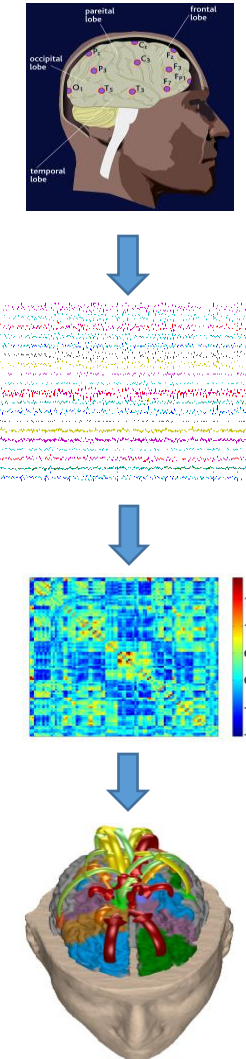
Functional Network

voxel 1 mm³ to 3 mm³
(300 - 500Kneurons)



Effective Network

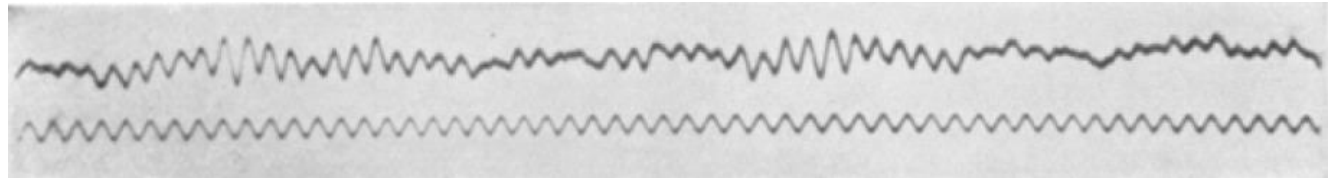
Few mm (HREEG) to
several cm (16-32sensors)



Electroencephalography (EEG)

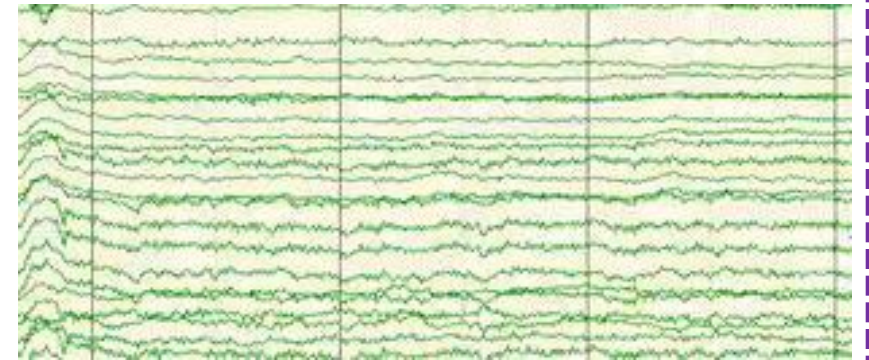
- High Temporal Resolution
(sampling rate 250 Hz - 4 KHz)
- Multichannel
(usually 32- 64 and up to 512)

From paper to digital signal recording



First human EEG by Hans Berger, 1924.

Upper: EEG signal, lower: 10 Hz timing signal



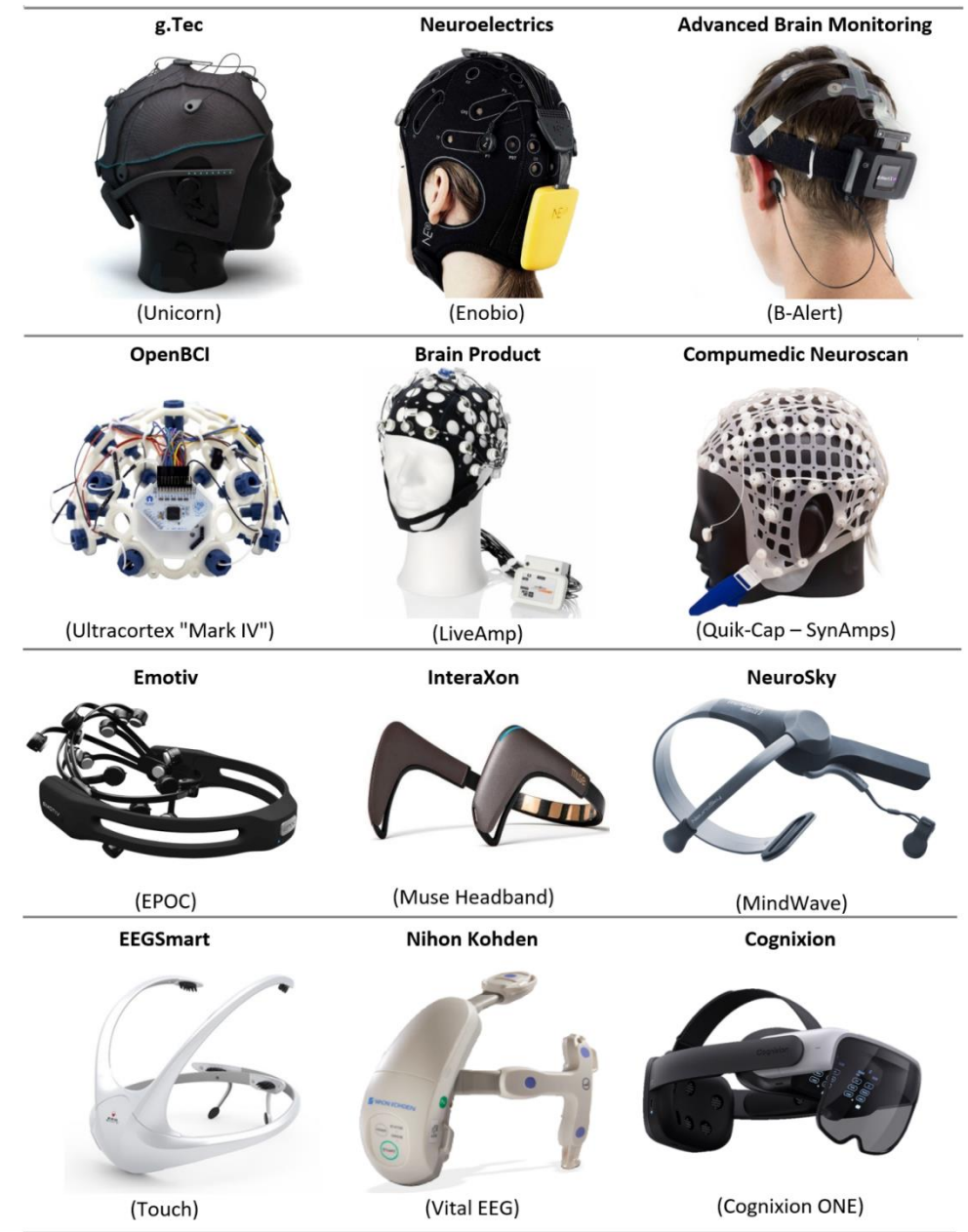
EEG Devices

From Lab to real applications:

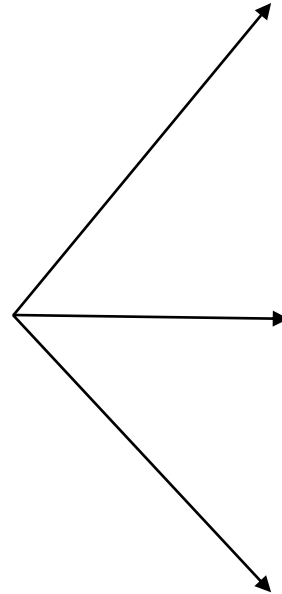
Wired → wireless (Bluetooth) devices

Wet (with gel) → dry electrodes

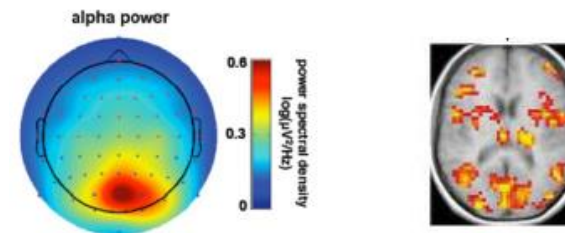
Many → few electrodes at specific locations



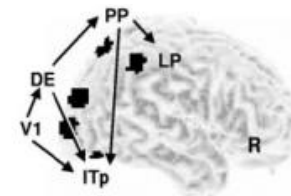
EEG signal analysis



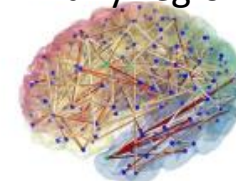
Univariate Measures –
Magnitude, Power, etc –
Single regions



Bivariate Measures –
Functional Connectivity –
Two regions



Multivariate Measures –
Network Analysis –
Many regions

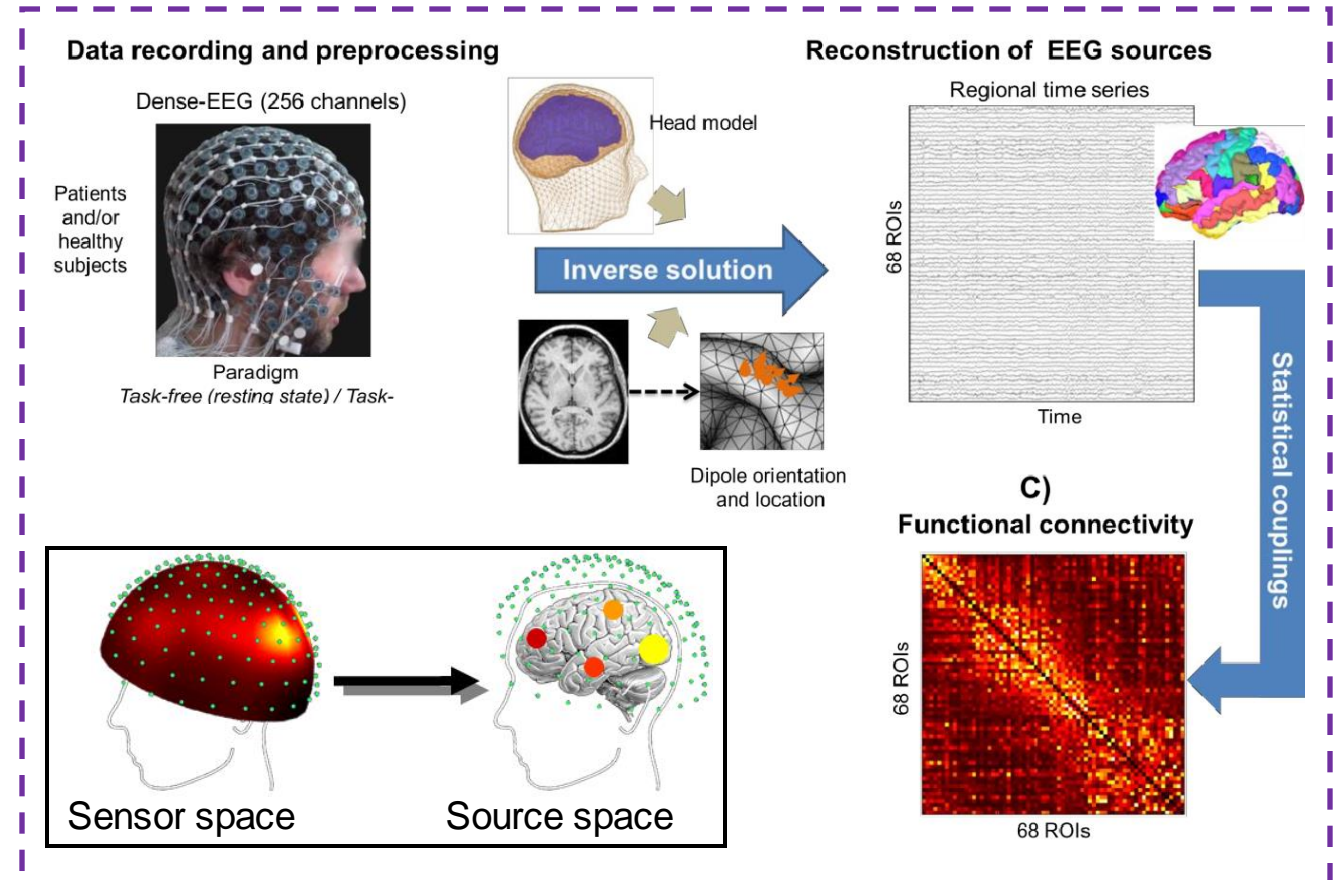
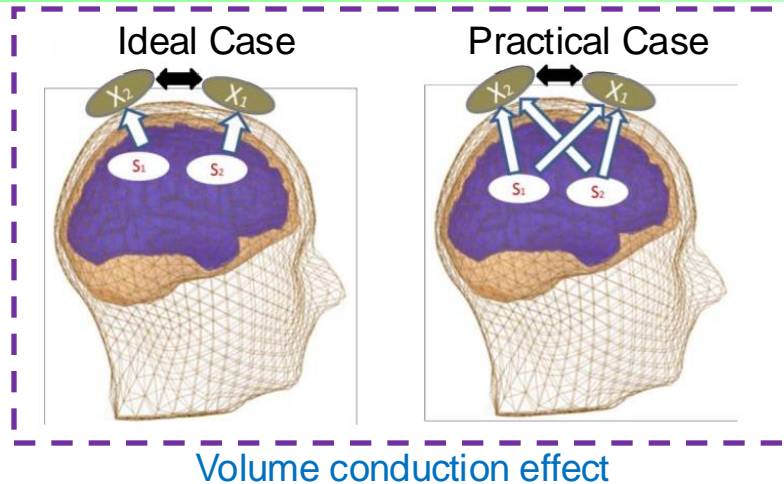


Source Localization

- Source localization provides brain functional connectivity at the cortical source level from the sensor level
- Provides higher spatial resolution to the EEG data and reduces the volume conduction effect
- Additional advantage from fMRI is the higher time resolution present in EEG

Data required for Source localization (e-LORETTA)

- The scalp-recorded EEG signals
- 3-D position of the electrodes
- The head model, containing electrical and geometrical characteristics of the head
- The source model containing location and orientation of dipole sources



Steps involved in reconstruction of EEG sources from the sensor level

EEG – Frequency Analysis

Important information about brain signals is encoded in frequency domain

Common frequency bands:

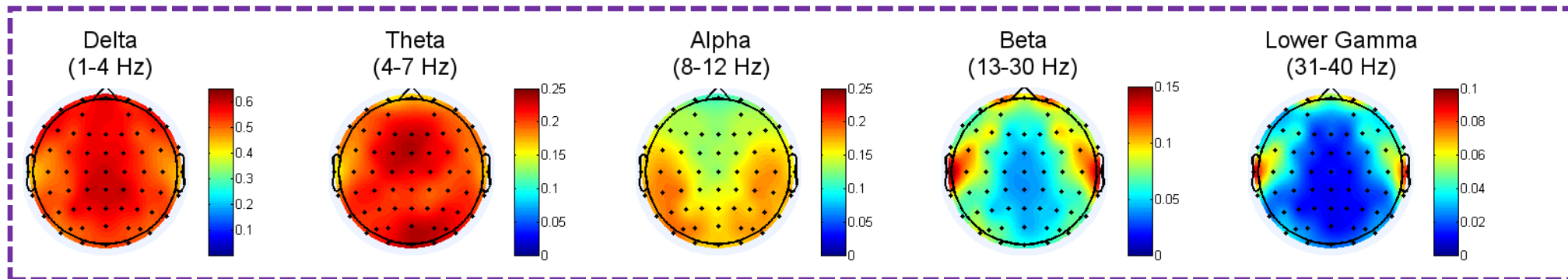
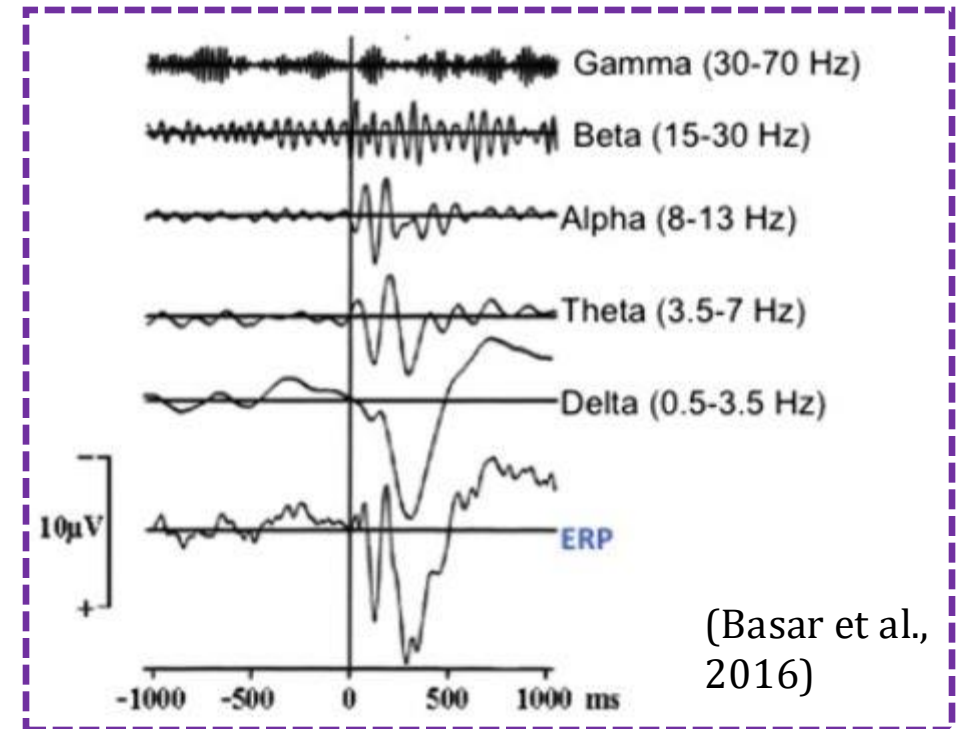
Delta (δ): 0.5 - 4 Hz

Theta (θ): 4 -7 Hz

Alpha (α): 8 -12 Hz

Beta (β): 13 - 30 Hz

Gamma (γ): 30 -70 Hz

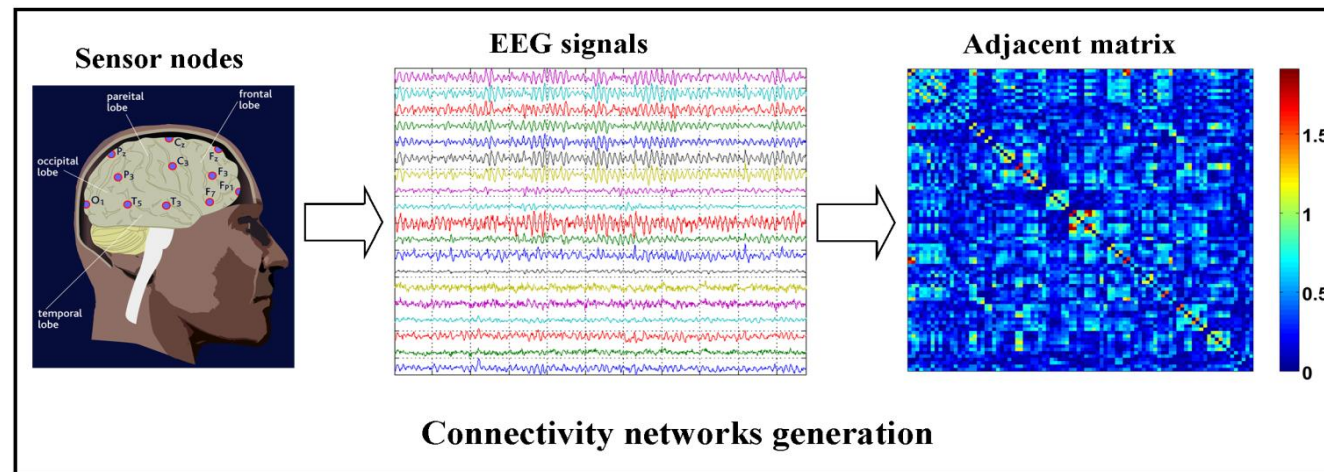


Graph theoretical analysis

Graph Theoretical Analysis

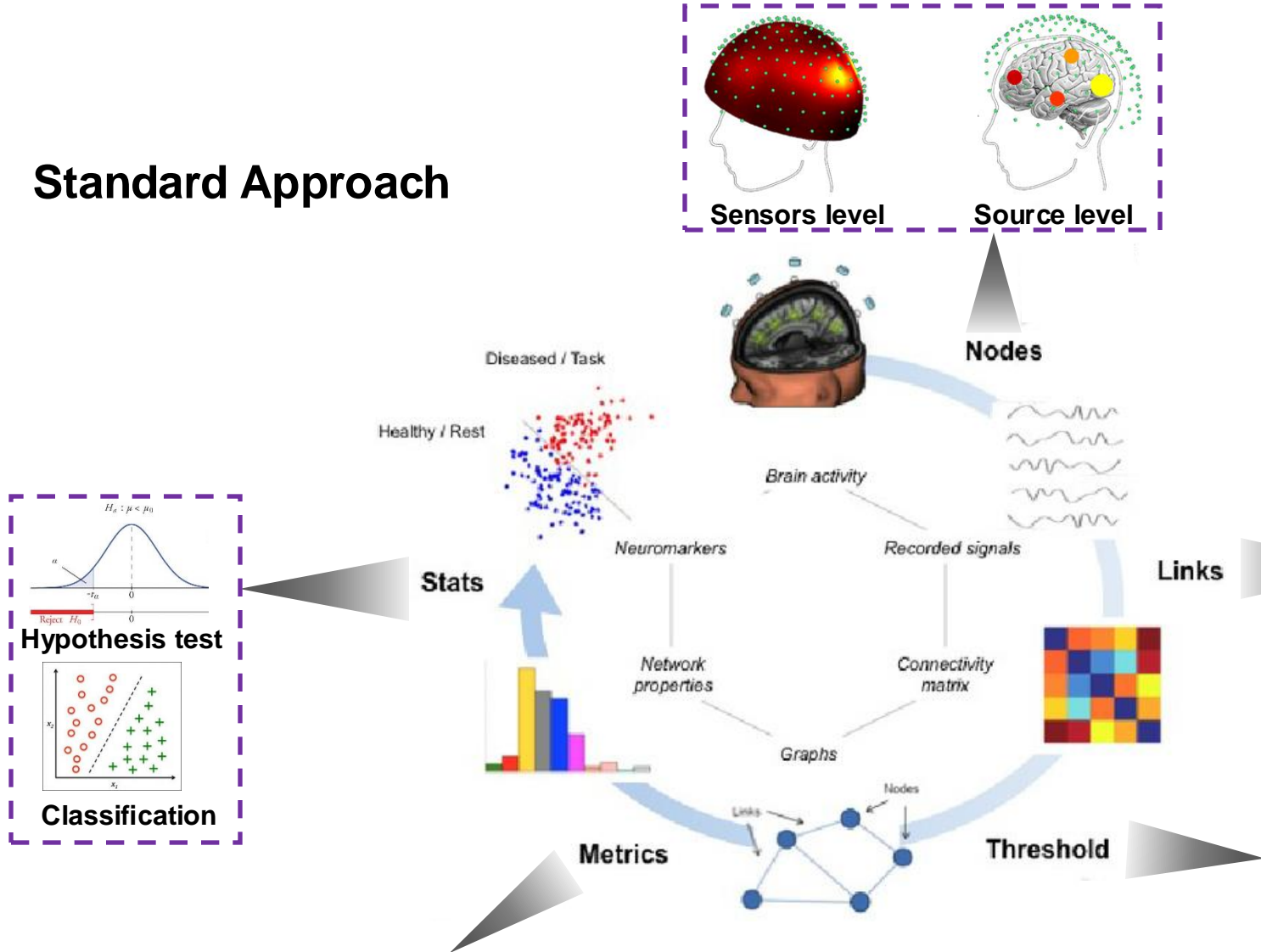


Multivariate analysis involves interactions among brain areas



- Interactions which hold the direction and strength of the information flow between brain areas (nodes).
- Usually via estimation of temporal covariance/correlation between different spatial sites.
- Better understanding of the organized behavior of cortical regions.

Standard Approach



Cosine

Similarity

$$\frac{x_i^T x_j}{\sqrt{x_i^T x_i} \sqrt{x_j^T x_j}}$$

Pearson's

Correlation

$$\frac{(x_i - \bar{x}_i)^T (x_j - \bar{x}_j)}{\sqrt{(x_i - \bar{x}_i)^T (x_i - \bar{x}_i)} \sqrt{(x_j - \bar{x}_j)^T (x_j - \bar{x}_j)}}$$

Partial

Correlation

$$\rho_{ij \cdot V \setminus \{i, j\}} = -\theta_{ij} / \sqrt{\theta_{ii} \theta_{jj}}$$

where $(\theta_{ij})_{d \times d} = \Theta = \Sigma^{-1}$ is the inverse covariance matrix (or precision matrix).

Jaccard

Index

$$\sum_{k=1}^d \min(x_{ik}, x_{jk}) / \sum_{k=1}^d \max(x_{ik}, x_{jk})$$

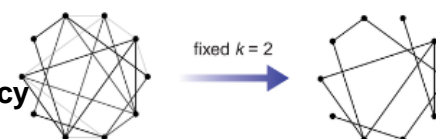
Sparsity

Absolute thresholding

Maximize cost-efficiency

Shortest Path Length

Minimum Spanning Tree



Characteristic Path Length

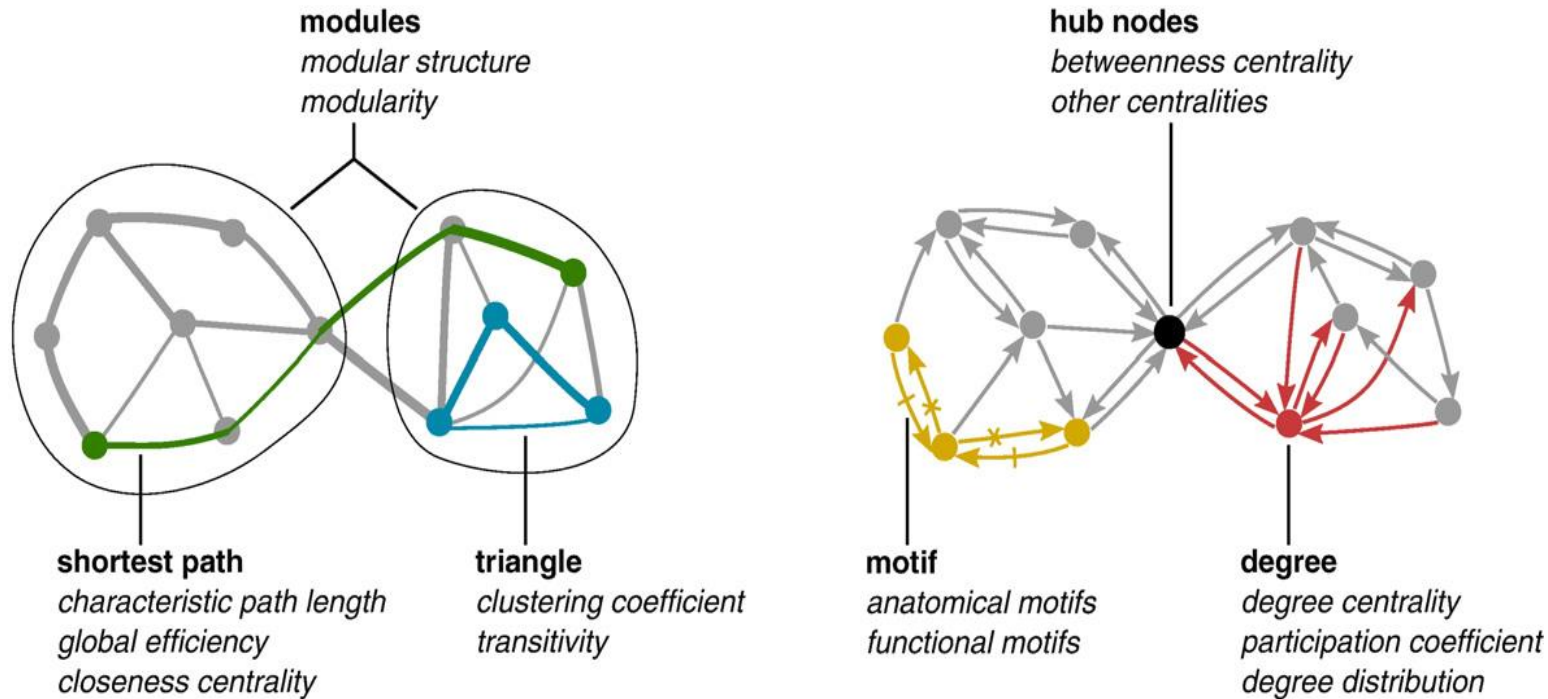
Clustering coefficient

Efficiency

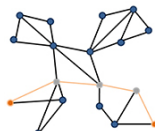

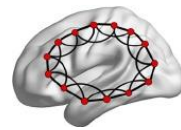
Small worldness

Network metrics

An individual network measure may characterize one or several aspects of global and local brain connectivity.



Schematic paradigm of graph theoretical measurements (key complex network measures in *Italics*). These measures are typically based on basic properties of network connectivity (in **bold type**) (Rubinov, 2010).

 $L = \frac{1}{n(n-1)} \sum_{i \in n} \sum_{j \neq i \in n} \min(L_{ij})$ <p>Shortest Path Length</p>	 $C = \frac{1}{n} \sum_{i \in n} \frac{2E_i}{k_i(k_i - 1)}$ <p>Clustering Coefficient</p>	 $\sigma = \frac{C_n}{L_n}$ <p>Small Worldness</p>	$E_g = \frac{1}{n(n-1)} \sum_{i \neq j \in n} \frac{1}{\min(L_{ij})}$ <p>Efficiency</p>
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Brain network construction methods

Frequency domain

- **Granger Causality (GC):** A time-series $X_1(t)$ is the cause of the second time-series $X_2(t)$ if the knowledge of the previous values of $X_1(t)$ significantly improves the prediction of $X_2(t)$.
- Two variables (bivariate) model of order p (number of previous time points):

$$X_1(t) = \sum_{j=1}^p A_{11}(j)X_1(t-j) + \sum_{j=1}^p A_{12}(j)X_2(t-j) + E_1(t)$$

$$X_2(t) = \sum_{j=1}^p A_{21}(j)X_1(t-j) + \sum_{j=1}^p A_{22}(j)X_2(t-j) + E_2(t)$$

- With Fourier transform, we obtain GC in frequency domain:

$$I_{1 \rightarrow 2}(f) = |H_{21}(f)|^2 = \frac{|A_{21}(f)|^2}{|A(f)|^2} \quad \text{where } H \text{ the transfer function} \quad H(f) = \left(\sum_{\tau=0}^p A_{\tau} e^{-i2\pi f \Delta t} \right)^{-1}$$

- GC is not symmetric, i.e., $X_1(t)$ can cause $X_2(t)$ without $X_2(t)$ causing $X_1(t)$.

Brain network construction methods

Frequency domain

- **Multivariate autoregressive model (MVAR)** of order p for multi-channel time-series $X(t) = [x_1(t) \dots x_N(t)]$:

$$X(t) = -\sum_{\tau=1}^p A_{\tau} X(t - \tau) + E(t)$$

- With Fourier transform:

$$X(f) = H(f)E(f)$$

- We can estimate matrix $S(f)$:

$$S(f) = H(f)\Sigma H^*(f)$$

where Σ the noise covariance matrix and $*$ notes the complex conjugate.

Brain network construction methods

Frequency domain

- **Directed Transfer Function (DTF)**: the ration between influx from channel j to channel i divided by the total influx to channel i :

$$DTF^2_{ij}(f) = \frac{|H_{ij}(f)|^2}{\sum_{m=1}^N |H_{im}(f)|^2}$$

- **Coherence** $C^2_{lk}(f) = \frac{S^2_{lk}(f)}{S_{ll}(f)S_{kk}(f)}$

- **Partial Directed Coherence (PDC)** $PDC_{ij}(f) = \frac{A_{ij}(f)}{\sqrt{a_j^*(f)a_j(f)}}$

- **Generalized Partial Directed Coherence (GPDC)** $GPDC_{ij}(f) = \frac{\frac{1}{\sigma_i} A_{ij}(f)}{\sqrt{\sum_{k=1}^N \frac{1}{\sigma_k^2} A_{kj}(f)A_{kj}^*(f)}}$

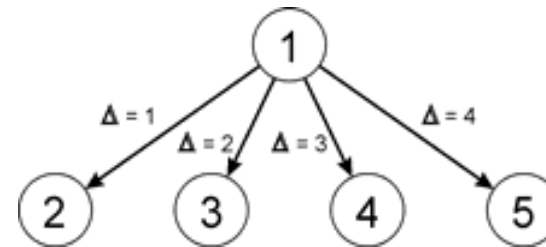
Bivariate vs multivariate models

Simulations showing difference between bi-variate and multi-variate estimates of directionality

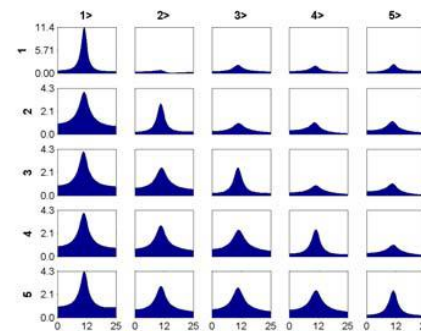
Bivariate and multivariate measures: In each small panel the causality measure is shown as the function of frequency.

the resulting patterns of causality relations (flows)
Red: indirect edges (false positive)

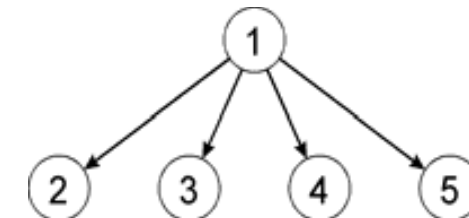
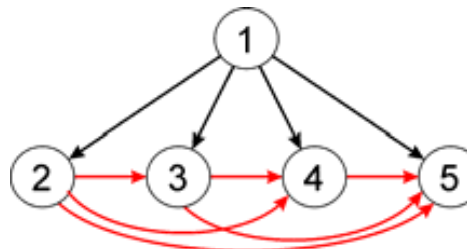
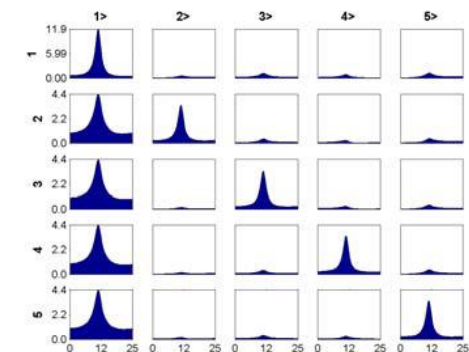
simulation scheme



bivariate

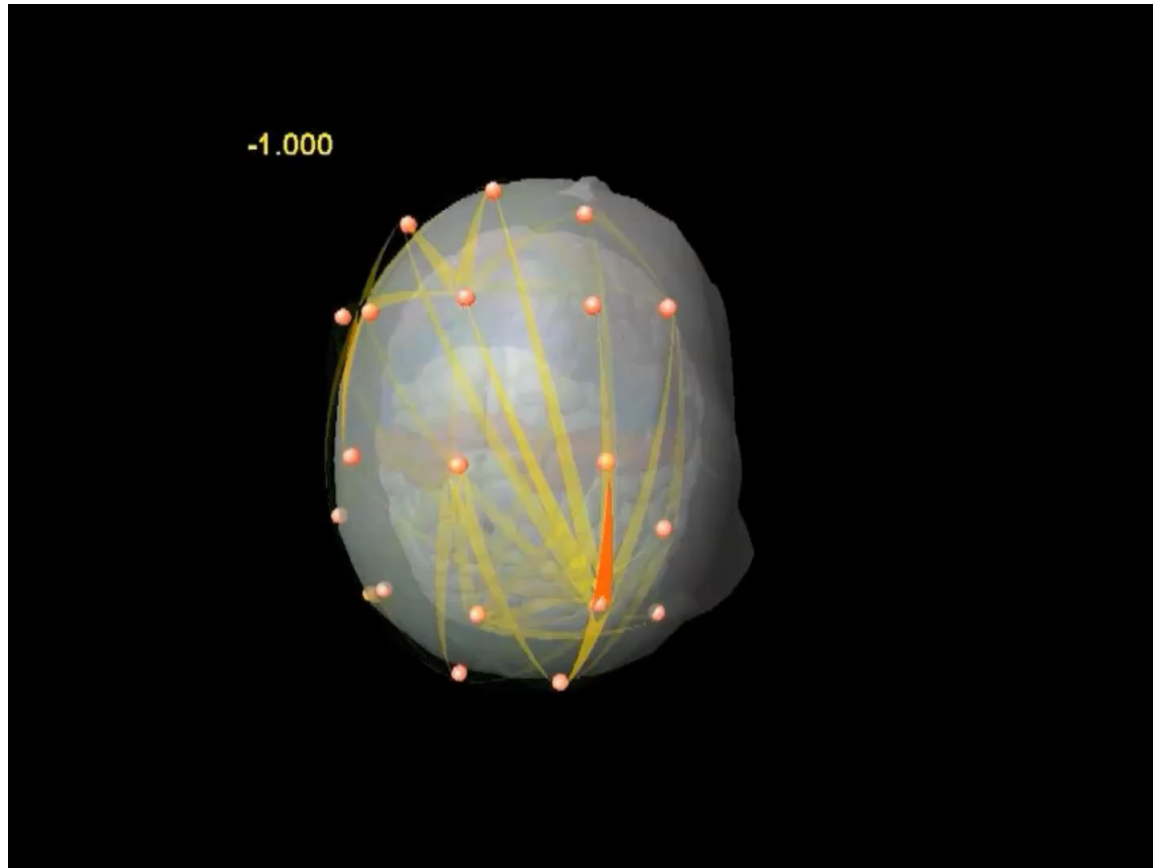


multivariate



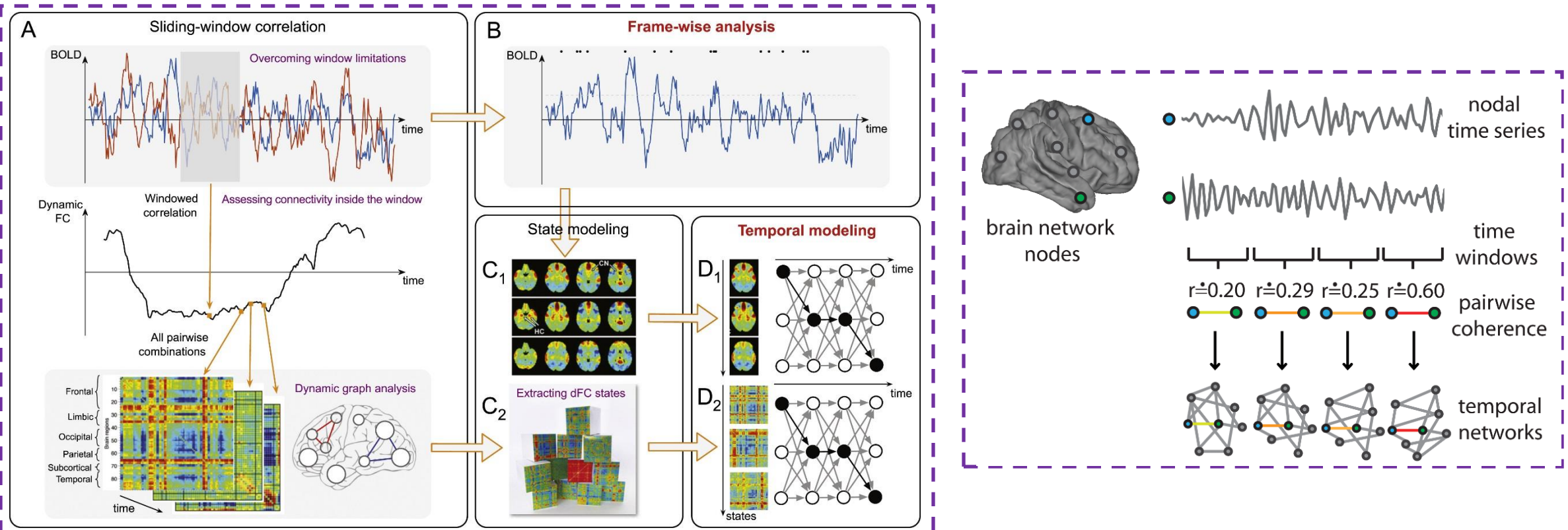
(K. Blinowska, 2008)

DTF: Dynamic patterns of EEG propagation



- In video: dynamic patterns of EEG propagation obtained by short time ffDTF during a Working Memory Task.
- Involvement of frontal and posterior parietal regions in working memory tasks is observed in accordance with imaging studies.
- Mostly neighboring electrodes are involved and occasionally long range connections.
- → Optimal organization of the brain networks for metabolic energy saving and efficient wiring includes modular structure with dense connectivity inside the modules and more sparse connections between modules

Dynamic Functional Connectivity



Current Challenges:

- Functional connections in human brain might **fluctuate over time**, which cannot be found from the standard approach that relies on a static graph to represent functional connectivity.

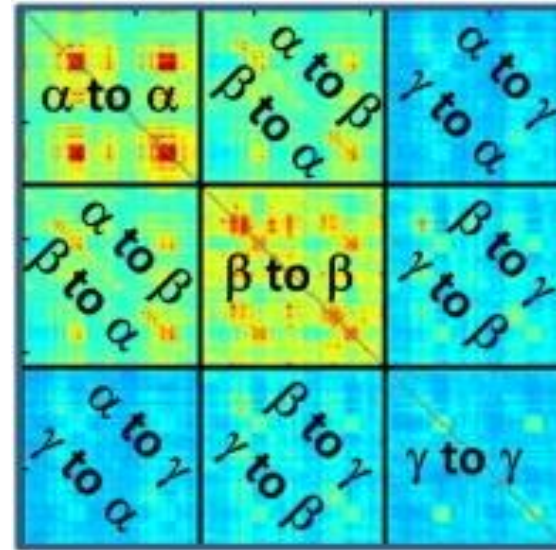
Solution:

Dynamic Functional Connectivity (DFC) provides the solution to observe the fluctuations and dynamic reorganization of the brain network over time. It allows to track the information flow and dynamic reconfiguration of the modular structure in the brain. This provides a better understanding of the neural mechanisms both during rest and task based conditions.

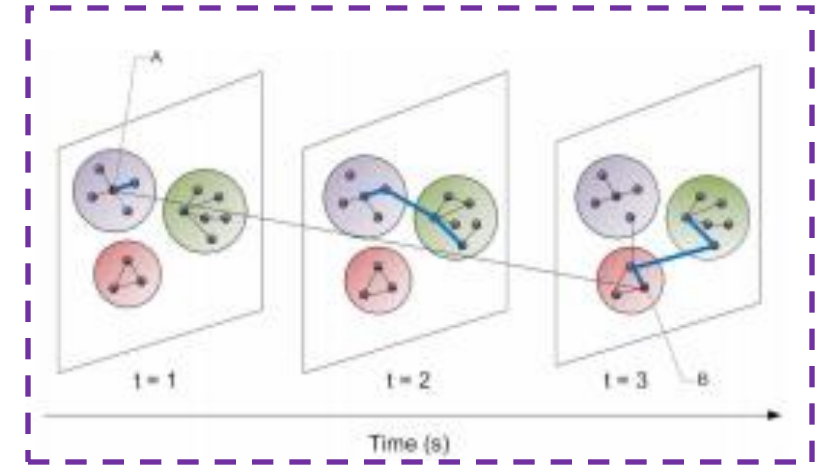
Multilayer Network

Multilayer network allows to model multiple domains like spatial, temporal and spectral, in an unified framework. Two representation of multilayer network are mostly studied:

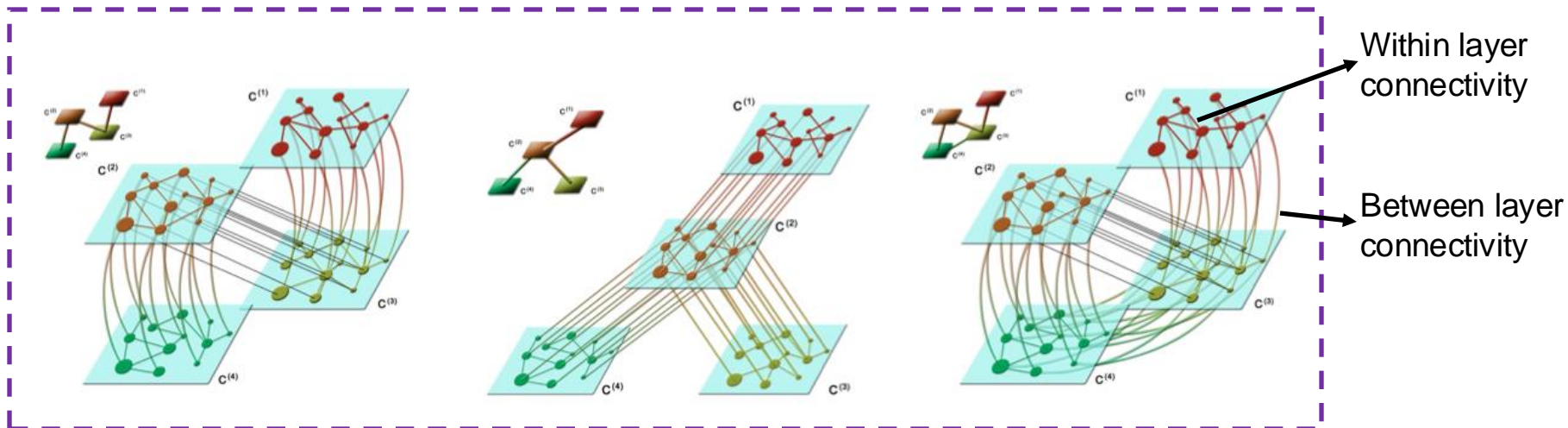
- Tensorial Representation- Layers are stacked and nodes are both connected at intra-layer and/or inter-layer. Mostly used for dynamic functional connectivity analysis.
- Supra-adjacency matrix- Flattened representation of multilayer network where individual adjacency matrix together forms the supra-adjacency matrix. It is mostly used for within and cross frequency coupling.



Supra-adjacency matrix



Tensorial Representation



Example of Multilayer Network Connectivity

Part II

Highlights of my research

- (1) the discovery that brain plasticity is a matter of hours, not days,
- (2) the visualization of brain conditioning to perform repetitive tasks,
- (3) advances in the study of fatigue mechanisms, and
- (4) the brain response in autonomous driving.

Evaluation of Cortical Connectivity During Real and Imagined Rhythmic Finger Tapping

Maria L. Stavrinou · Liviu Moraru · Laura Cimponeriu ·
Stefania Della Penna · Anastasios Bezerianos

TLDR: The results support the hypothesis that functional connectivity over the contralateral hemisphere during finger tapping is preserved in imagery and can be regarded as indicative evidences of a new strategy for recognizing imagined movements in EEG-based brain computer interface research

Fig. 1 Average stimulus locked time frequency maps of energy during motor task execution. Selected electrodes correspond to the contralateral hemisphere (C1, FC3) and of ipsilateral hemisphere (C2, FC4)

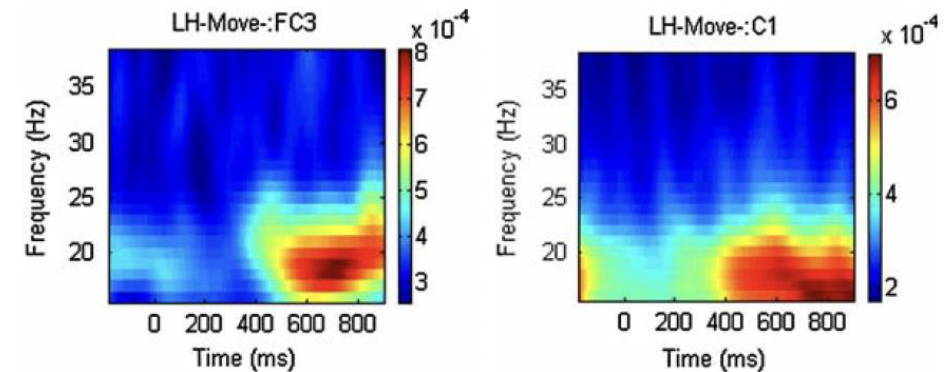
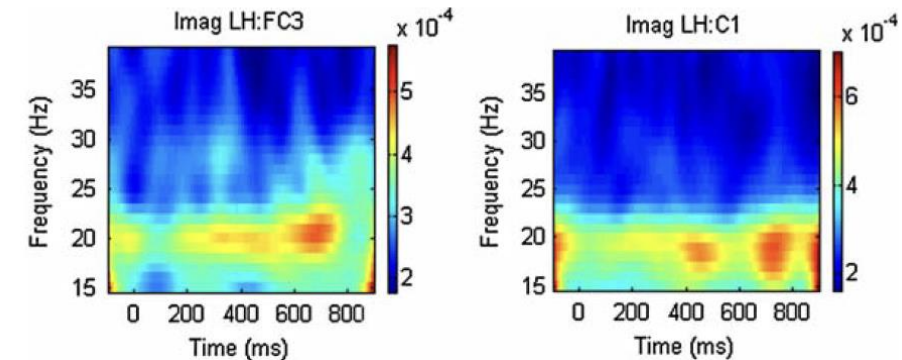


Fig. 2 Average stimulus locked time frequency maps of energy during imagery. Selected electrodes correspond to the contralateral hemisphere (C1, FC3) and of ipsilateral hemisphere (C2, FC4)



Evaluation of Cortical Connectivity During Real and Imagined Rhythmic Finger Tapping

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Remarkably, the matrices of phase synchronization indices are similar for both real and imagined movement. The significant synchronization values identify beta range synchronization between signals recorded at electrodes FCZ, C5, CPZ and C1. The topographic map of inferred functional connectivity is schematically displayed in Fig. 6.

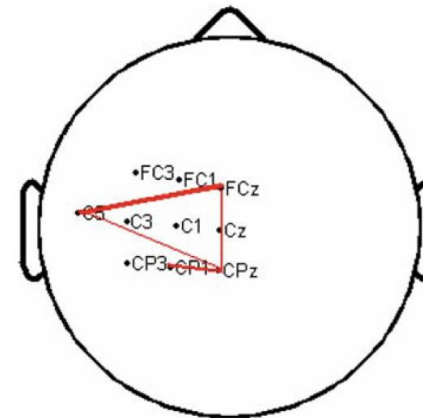
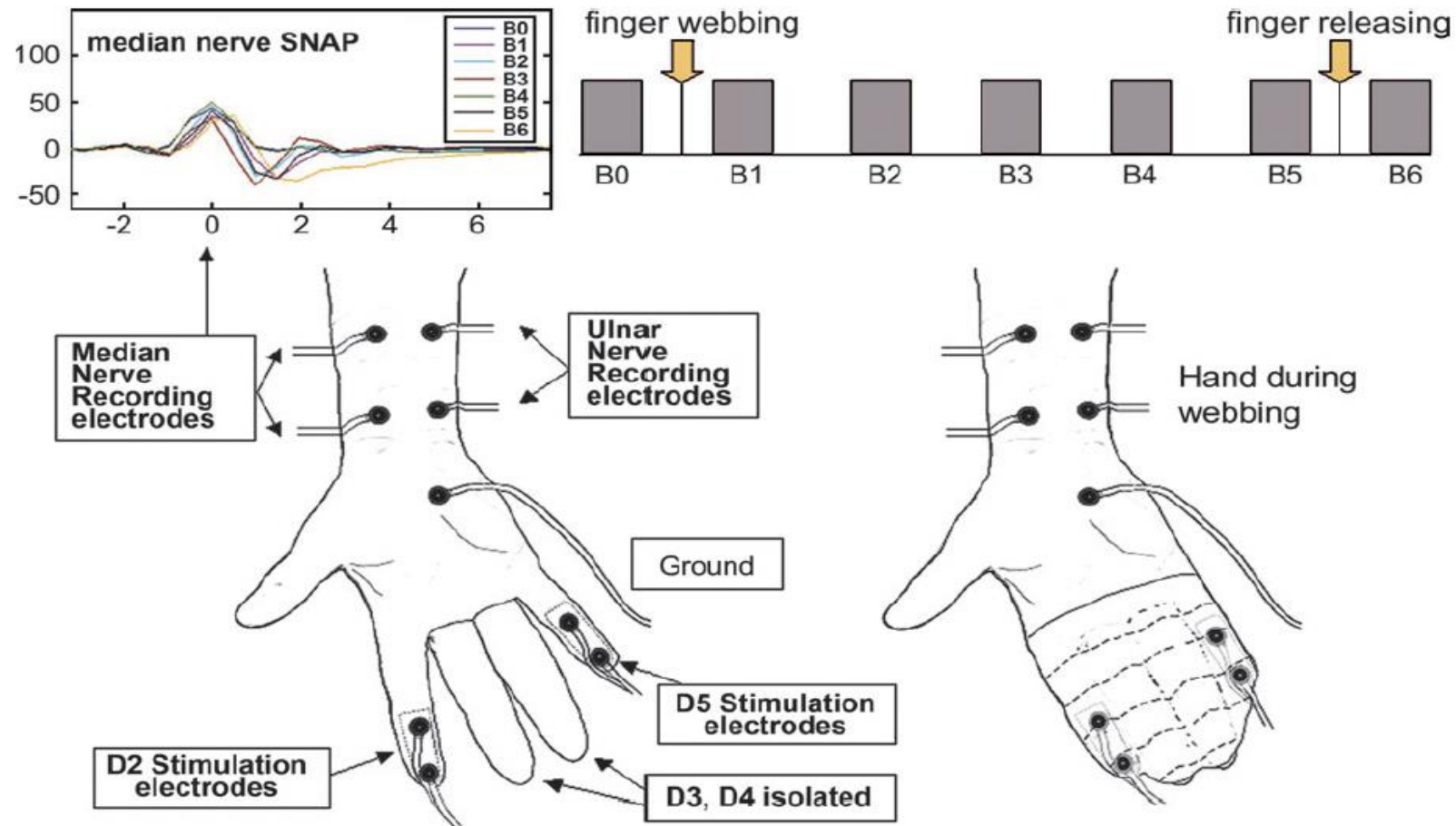


Fig. 6 Topographic map of inferred functional connectivity corresponding to statistical significant synchrony

Temporal Dynamics of Plastic Changes in Human Primary Somatosensory Cortex after Finger Webbing using MEG sensors

Maria L. Stavrinou^{1,2}, Stefania Della Penna^{1,3}, Vittorio Pizzella^{1,3}, Kathya Torquati^{1,3}, Francesco Cianflone^{1,3}, Raffaella Franciotti^{1,3}, Anastasios Bezerianos², Gian Luca Romani^{1,3} and Paolo Maria Rossini^{4,5,6}

- *TLDR: This study adapted the paradigm of finger webbing, in which 4 fingers are temporarily webbed together, hence modifying their sensory feedback, to provide a unique frame in which the different representational changes occur and shows how brain reorganization occurs over time*



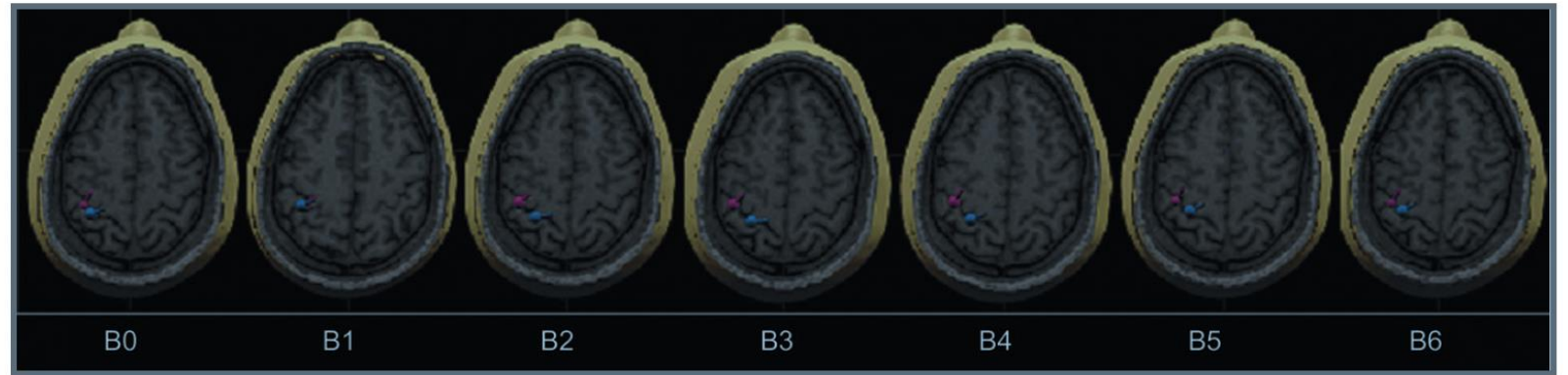
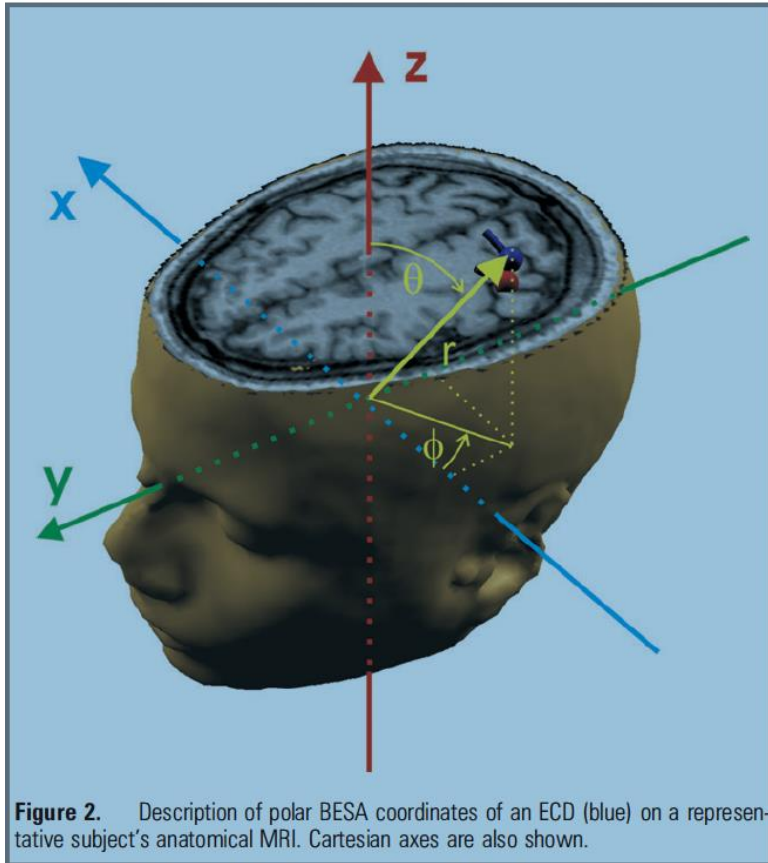


Figure 3. Dipole locations. ECD for D2 (red) and D5 (blue) projected onto the individual's anatomical MRI for a representative subject through the experimental blocks of B0–B6.

Our results showed brain that plasticity between cortical sources activated by electrical stimuli to the index and small finger **30 min after webbing**, followed by an increase lasting for about **2 h after webbing**, which was followed by a return toward baseline values.

Connectivity Analysis as a Novel Approach to Motor Decoding for Prosthesis Control

Heather L. Benz, Huaijian Zhang, Anastasios Bezerianos, *Senior Member, IEEE*, Soumyadipta Acharya, Nathan E. Crone, Xioaxiang Zheng, and Nitish V. Thakor, *Fellow, IEEE*

TLDR

This work introduces a new feature set based on connectivity and demonstrates its potential to improve ECoG BMI accuracy, and uses time-varying dynamic Bayesian networks (TV-DBN) to determine connectivity between ECoG channels in humans during a motor task

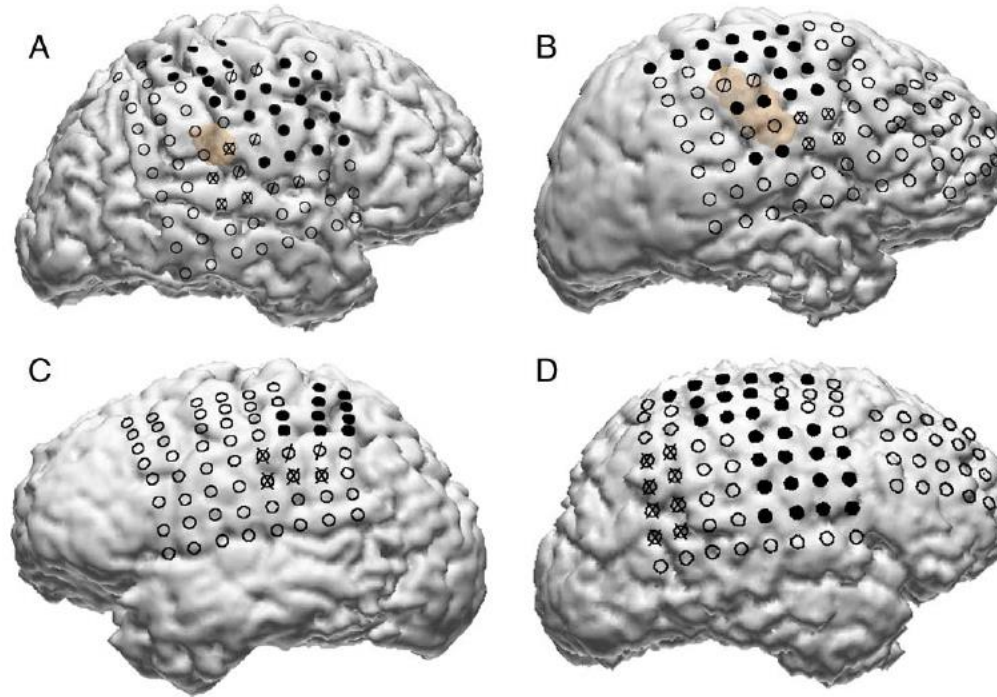


Fig. 1. Grid of ECoG electrode locations in each of the four studied subjects.

Connectivity Algorithm

Time-varying dynamic Bayesian networks:

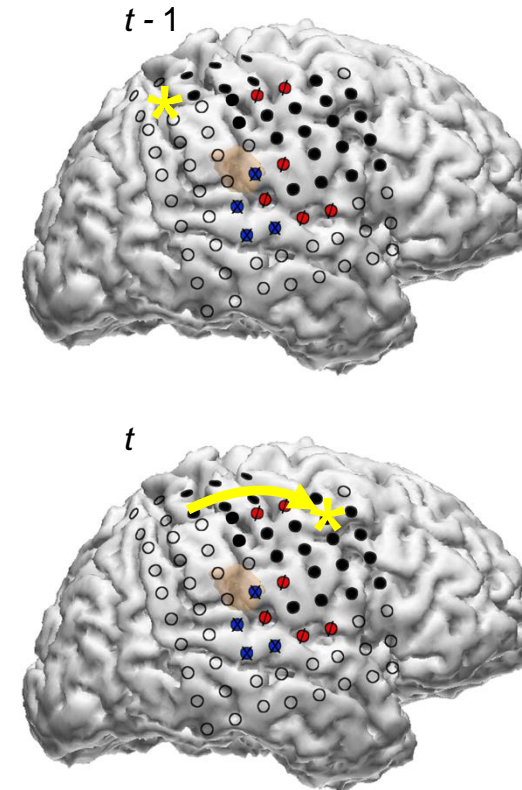
Based on determining conditional probability $P(X_t^j | X_{t-1}^k)$

Graph theory meets probability theory: efficient computing.

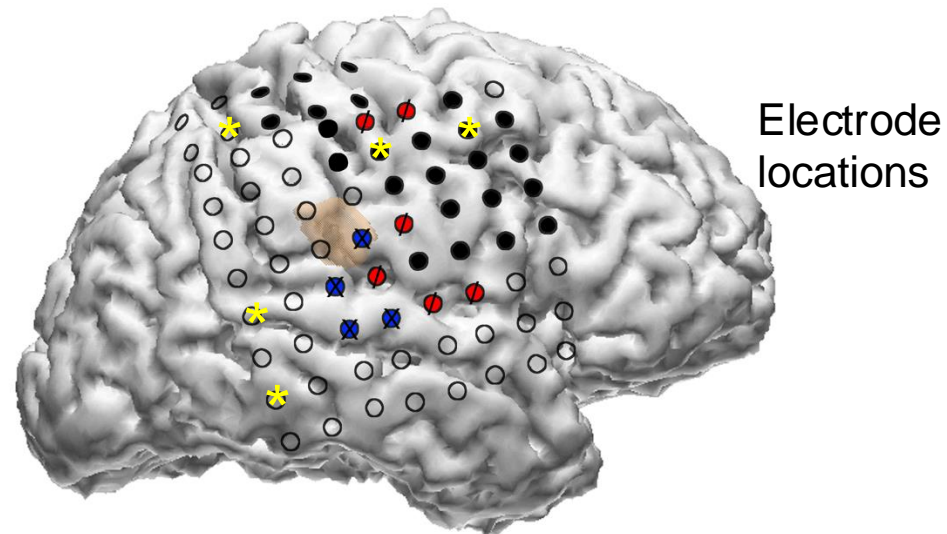
Describe distribution of temporal ECoG transitions as a linear model:

$$X_t = AX_{t-1} + e$$

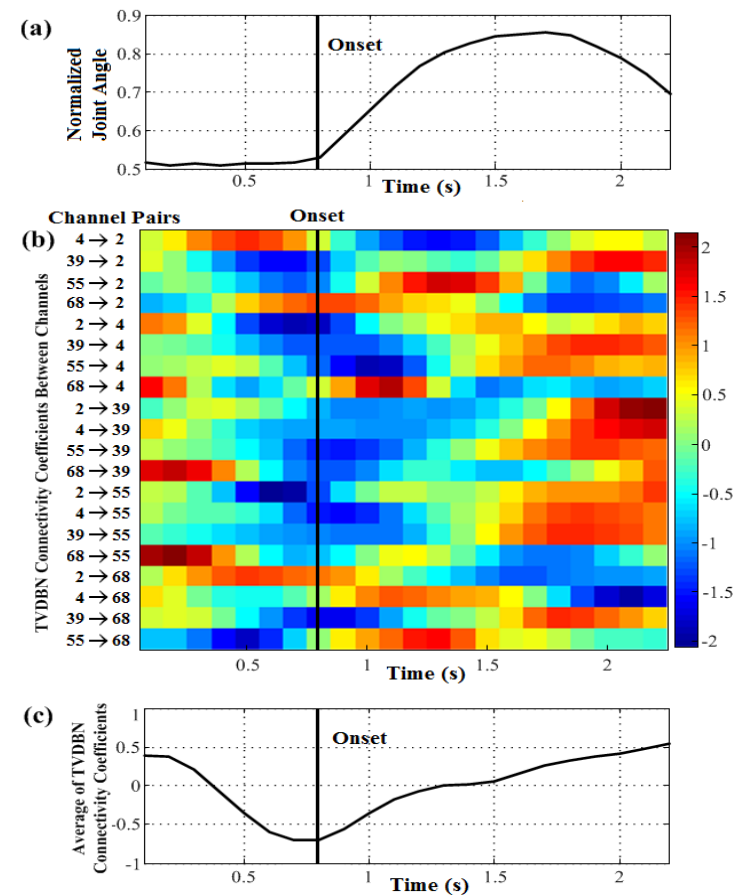
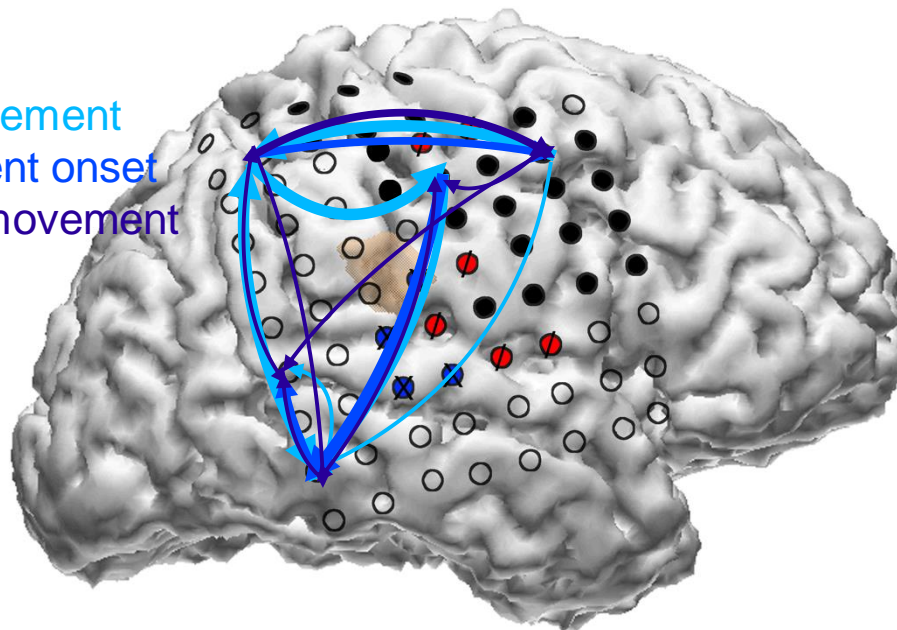
A is the connectivity coefficient matrix. A_{ij}^t is the connectivity weight from the i th to the j th channel from time $t - 1$ to time t .



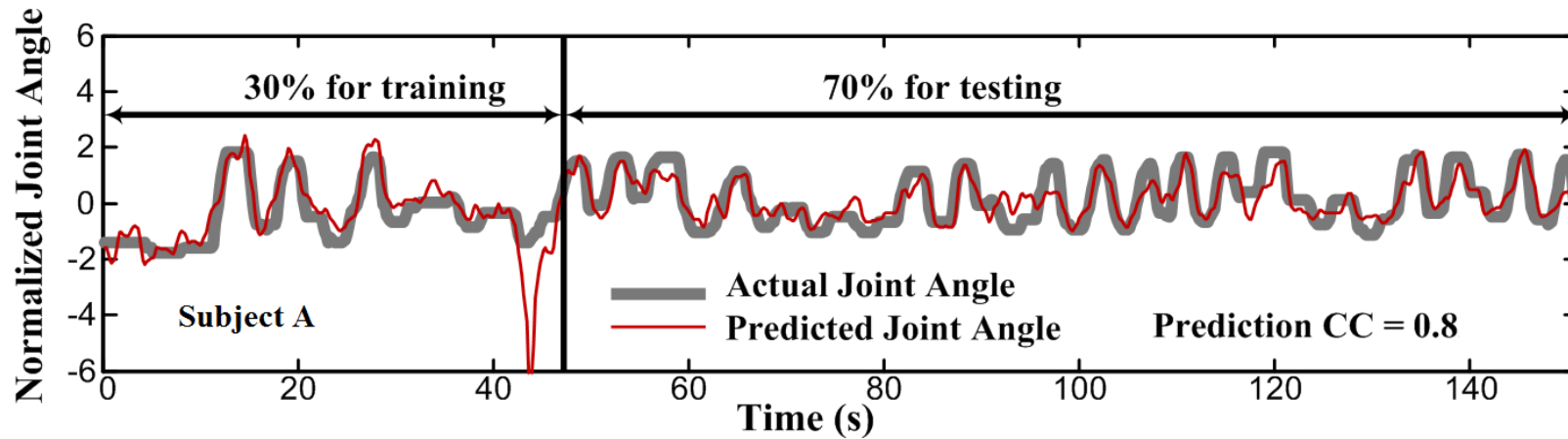
Connectivity



Pre-movement
Movement onset
During movement



Connectivity Decoding



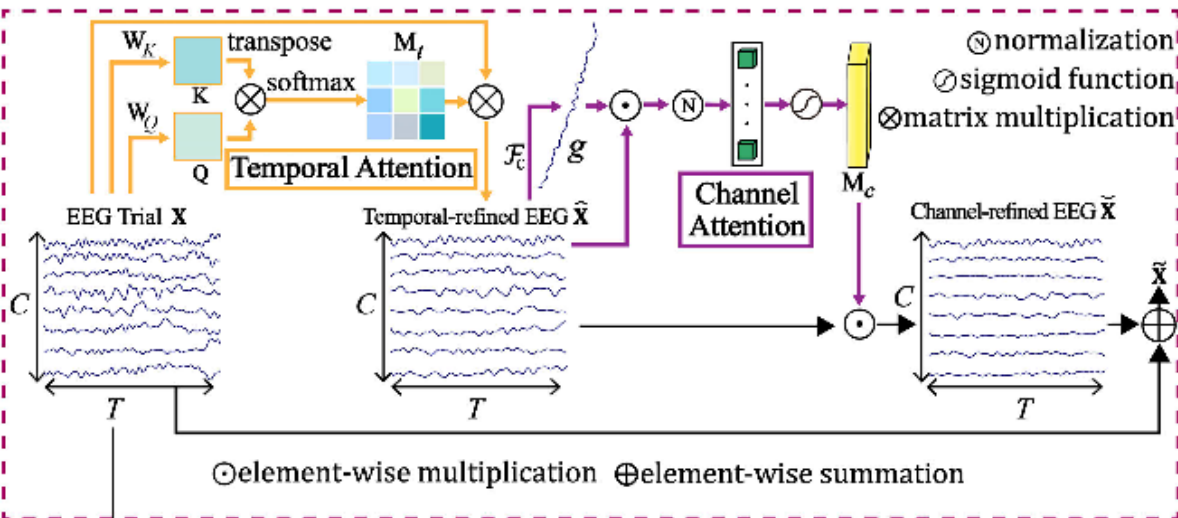
Average Maximum Decoding Accuracy by Subject (correlation coefficient, r)		
Subject	Spectral/LMP GRNN	TV-DBN GRNN
A	0.56	0.81
B	0.43	0.63
C	0	0.1
D	0.13	0.72

Self-Attentive Channel-Connectivity Capsule Network for EEG-Based Driving Fatigue Detection

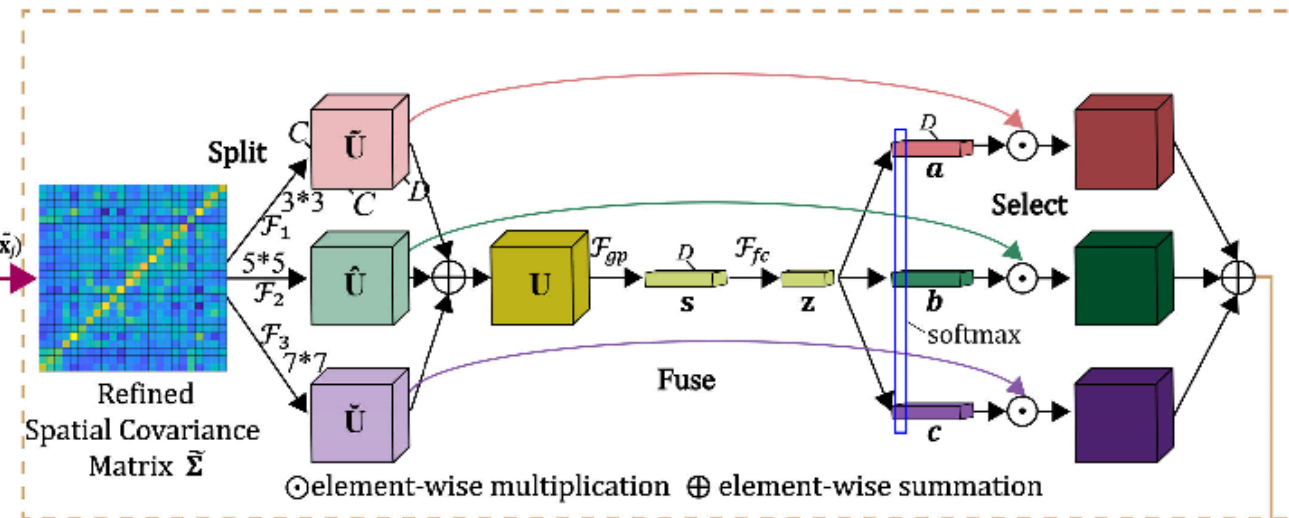
Chuangquan Chen, Zhouyu Ji, +3 authors Hongtao Wang • Published in IEEE transactions on neural... 26 July 2023 •

Engineering, Computer Science

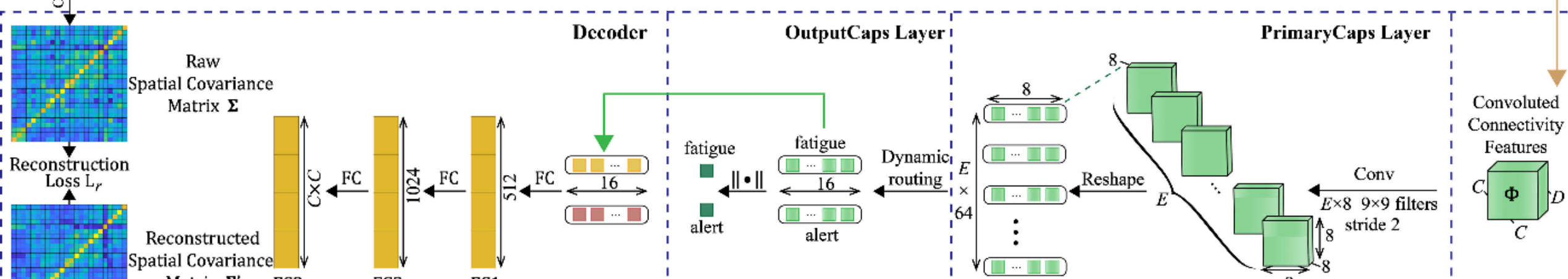
(a) Temporal-Channel Attention Module



(b) Channel-Connectivity Attention Module



(c) Capsule Network Module



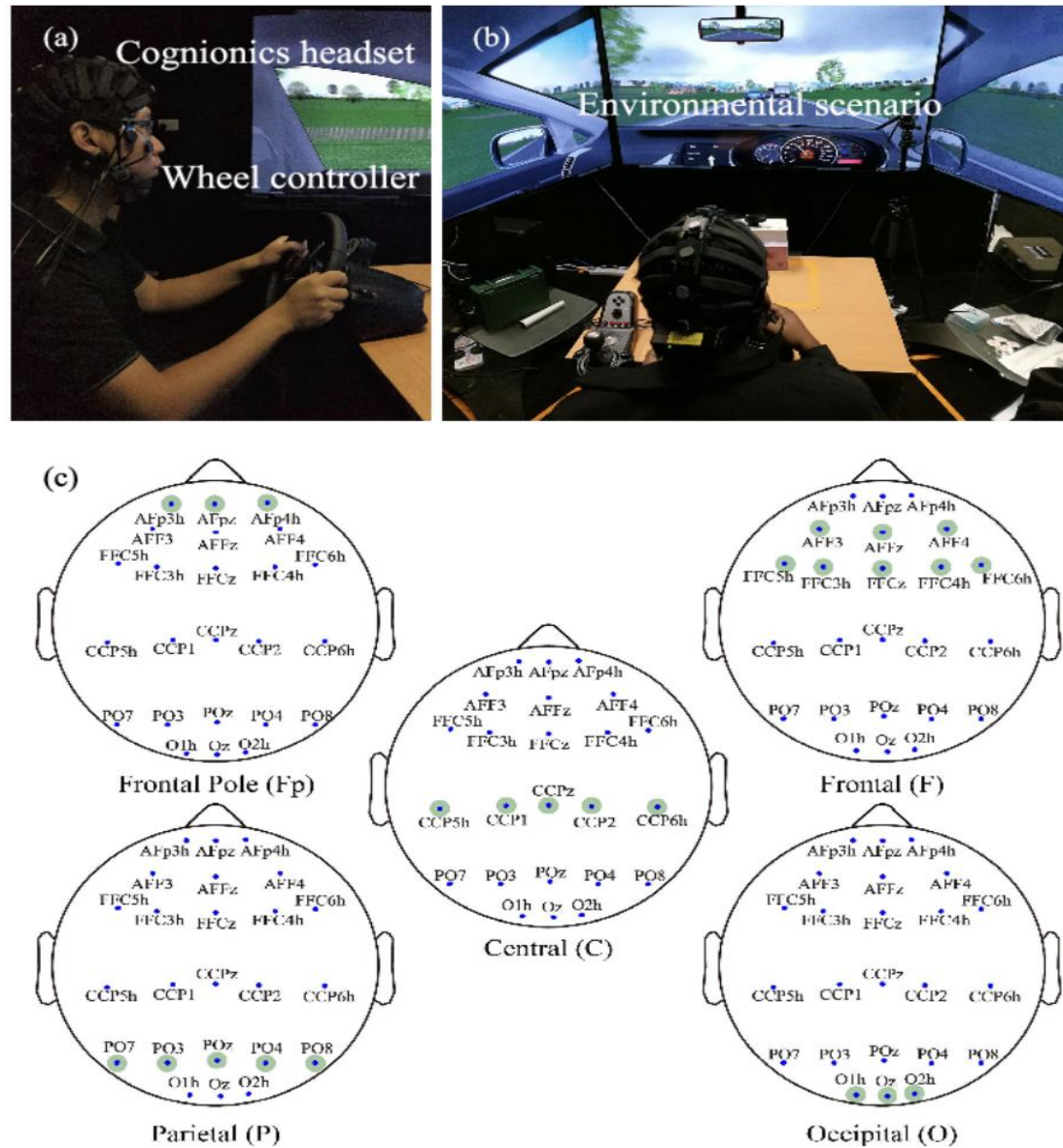


Fig. 2. Simulated driving system and the employed scalp for the experiment. (a) Simulated driving system. (b) Experimental scenario. (c) Distribution of the electrodes used for the experiment and the subdivisions based... [Expand](#)

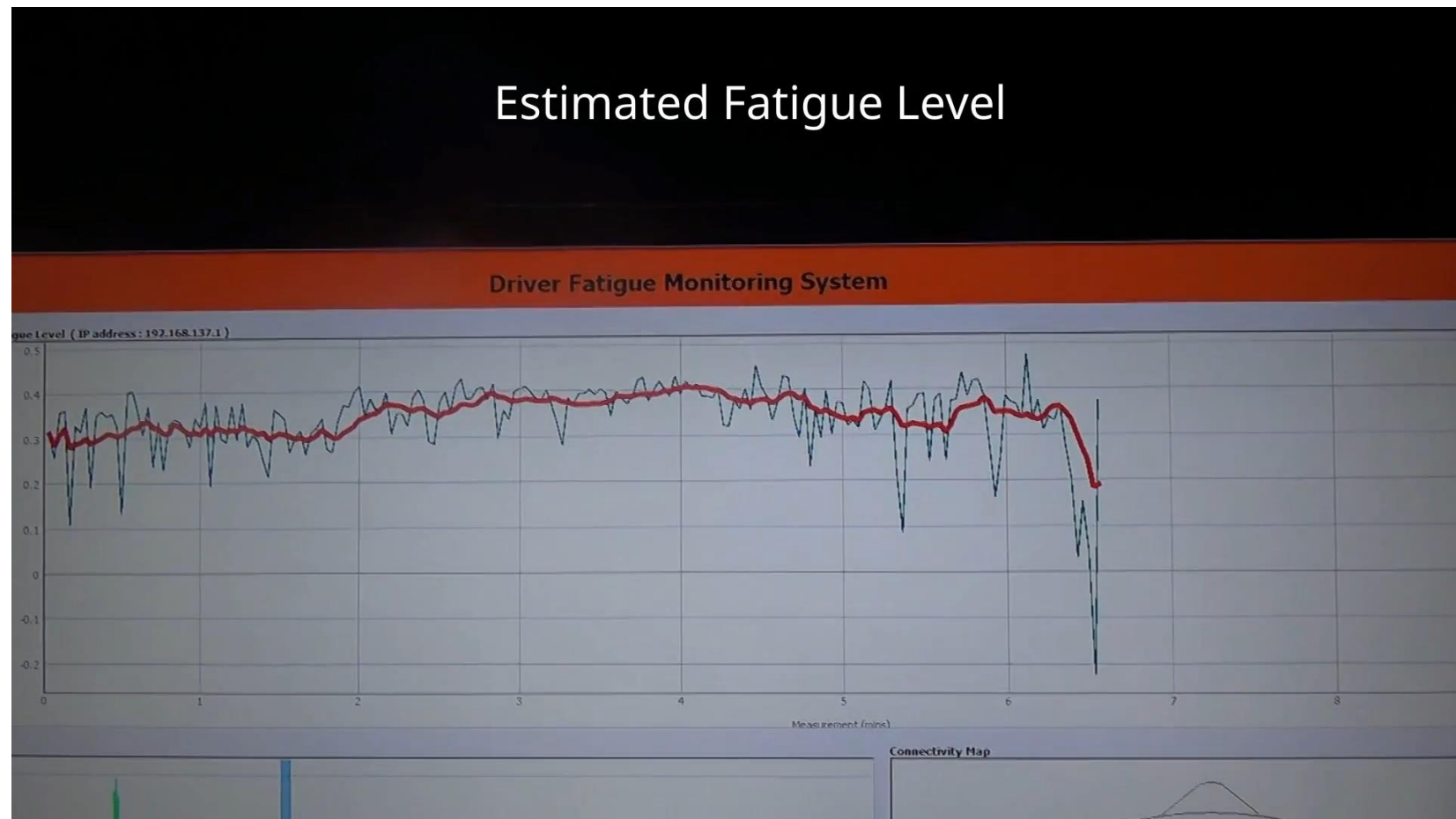
2A. Real-time Workload Assessment



Real-time Workload Assessment

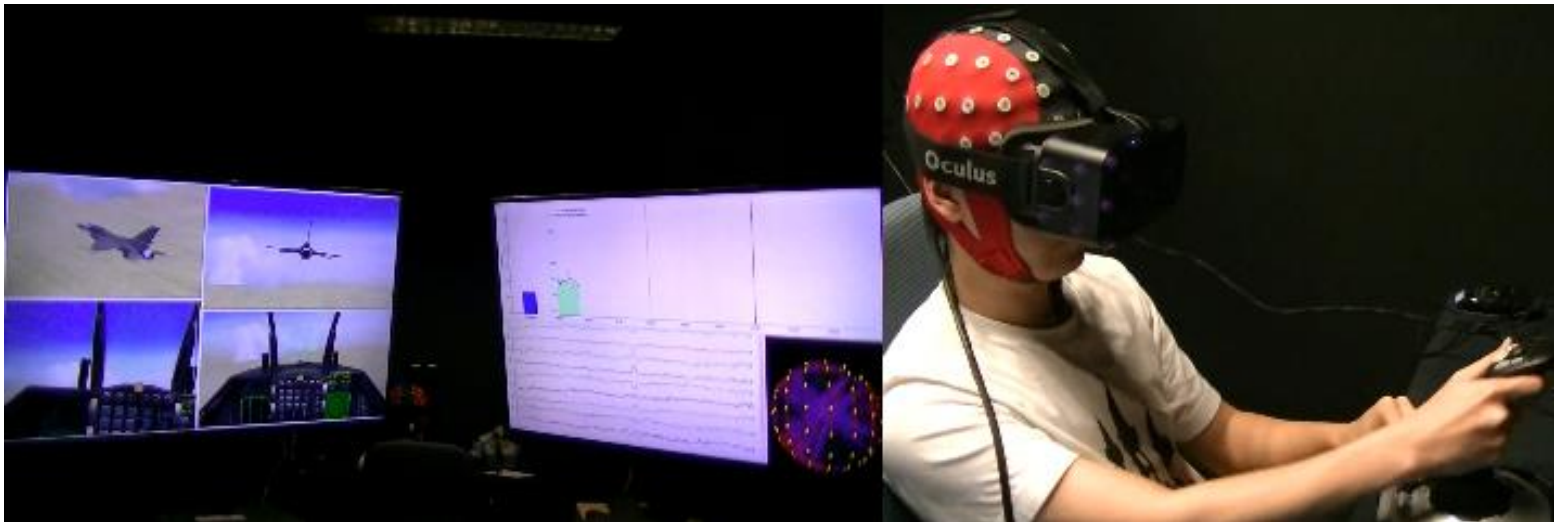


Real-time Smart Phone Workload Assessment



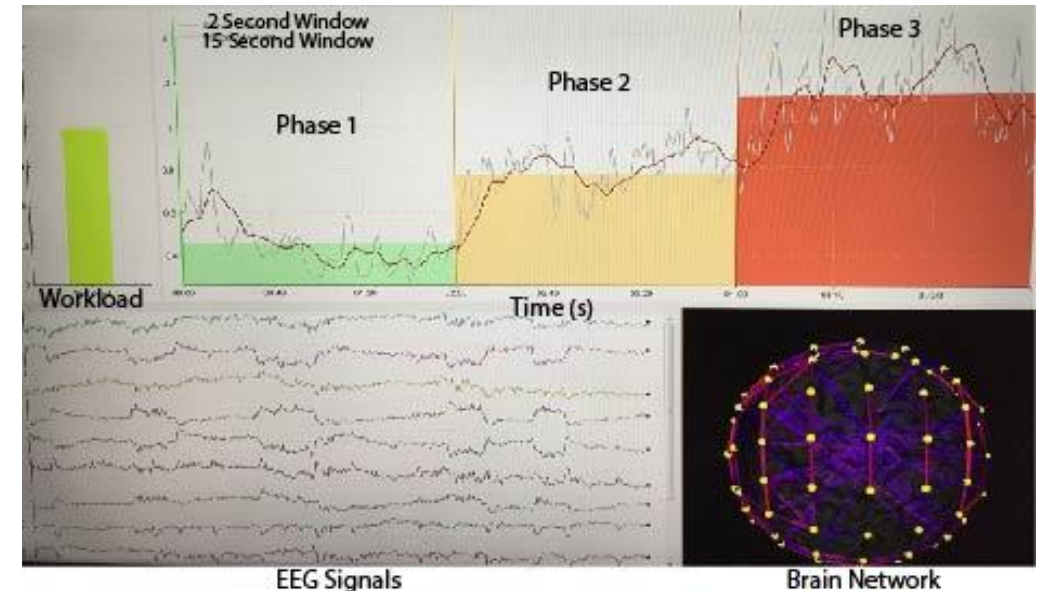
2. Mental Workload in flight simulation

- Studies of the mental workload are limited to well-controlled cognitive tasks using a 2D computer screen.
- We investigated functional brain network alterations in a **simulated flight** experiment
- In the experiment, we used **three mental workload levels** and we compared the reorganization pattern between **computer screen (2D)** and **virtual reality (3D)** interfaces (via the Oculus Rift headset).

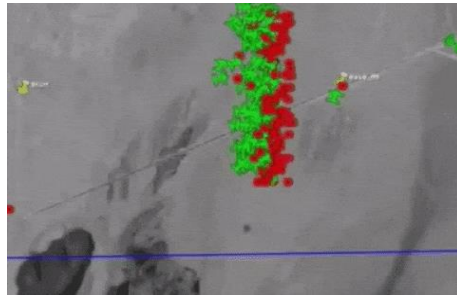


2A. Real-time Workload Assessment

- Simple and computationally efficient methods are required for real-time performance.
- We implemented a real-time workload monitoring system in a VR-based realistic flight simulator. The continuous flight scenario was designed to induce workload from low to high level in 3 phases.
- **Ratio of power** in theta band in 3 frontal channels to alpha band in 4 parietal-occipital channels is used as workload index.



Trusted Autonomous Systems (TAS)



US DoD – Perdix drone swarm
2017



Waymo – Google’s self driving car(2019)

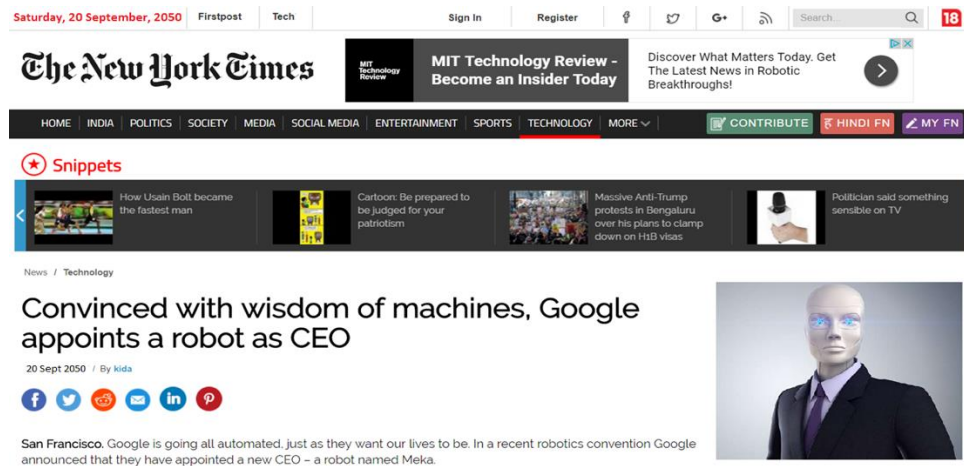
- ❑ Advanced robotics and autonomous systems = emerging disruptive technologies which will transform life, business and global economy (McKinsey Global Institute Report - 2013)

- ❑ TAS = projected market of US\$ 2tn by 2025



2050 ?

Human Machine Coexistence



WAYMO 2024

Acknowledgments

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- Collaborators and friends over the world ([Listed here](#))