Success and challenges with the use of graph theory in brain disorder studies: Seeking answers

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Alberta-Montana Combinatorics and Algorithms Days
BIRS Meeting, Banff, Alberta
June 3-5, 2022

UNIVERSITY OF CALGARY

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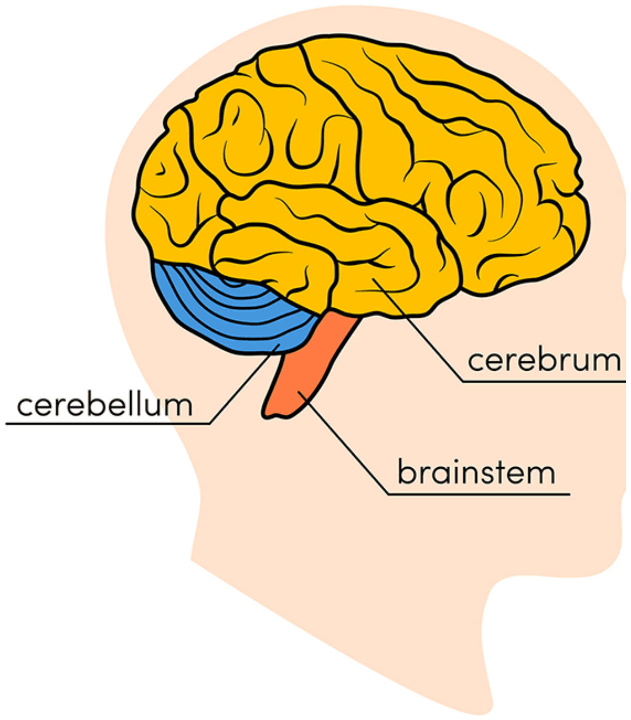
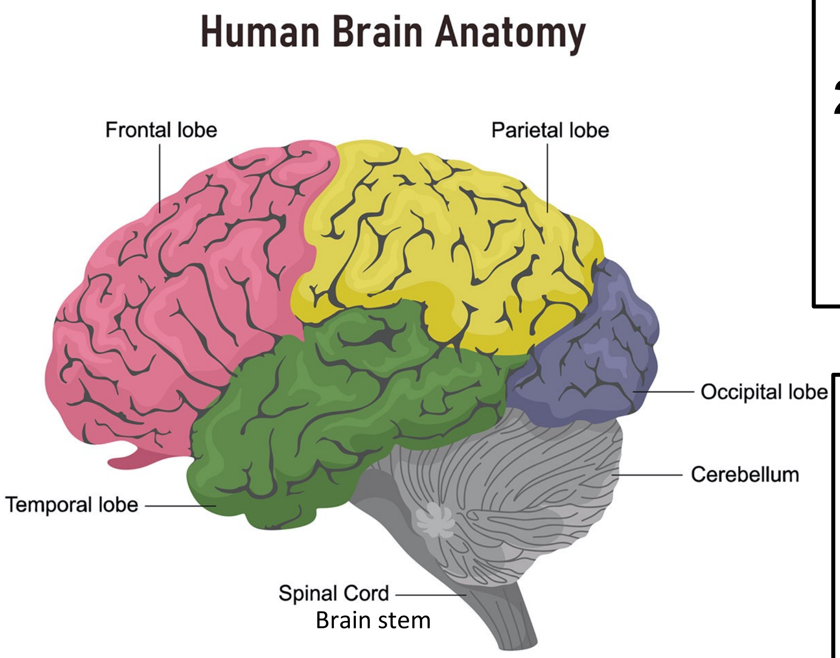
Preamble





2a. Blood oxygen levels in the brain

Cerebral circulation (15% of the cardiac output)

2b. Electrical behaviour of neurons

Excitatory and inhibitory neurons, Neuronal oscillations

3. Experiments exploiting the magnetic and electrical properties of the cerebral circulation and neurons

BOLD fMRI, EEG, iEEG, MEG

1. Two prominent brain cells:

Glial cells (support role) and Neurons (lead role)

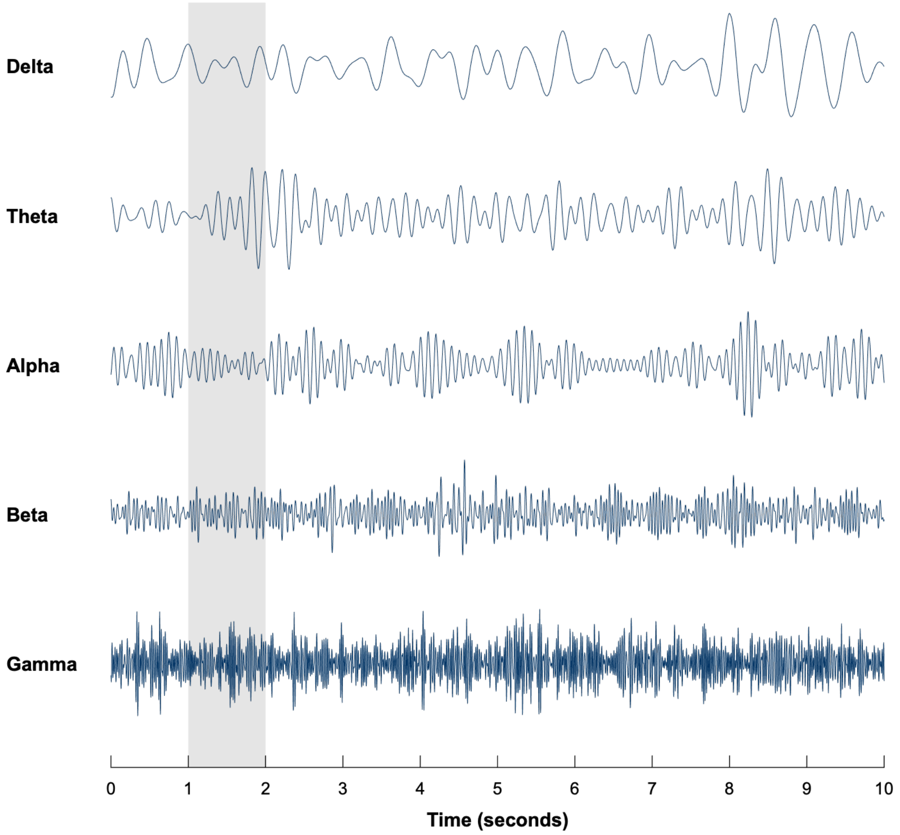
- ✓ **Functional connectivity in BOLD fMRI data**
- ✓ **Functional connectivity in EEG, iEEG data**
- **Functional connectivity in MEG data**

Courtesy: John Hopkins University

Preamble

4. Neural oscillations, or **brainwaves:** (1) Rhythmic or repetitive patterns of neural activity in the central nervous system (2) Oscillatory activity within individual neurons or by interactions between neurons (3) Synchronized activity of large numbers of neurons leading to macroscopic oscillations.

Phylogenetically preserved and functionally relevant frequency bands of interacting neuronal oscillations of the human brain:



Name	Band frequency in Hz
Delta	1-4
Theta	4-8
Alpha	8-12
Beta	13-30
Low Gamma	30-70
High Gamma	70-150

5. Cross-frequency coupling effects: Phase-amplitude coupling, amplitude-amplitude coupling

Preamble

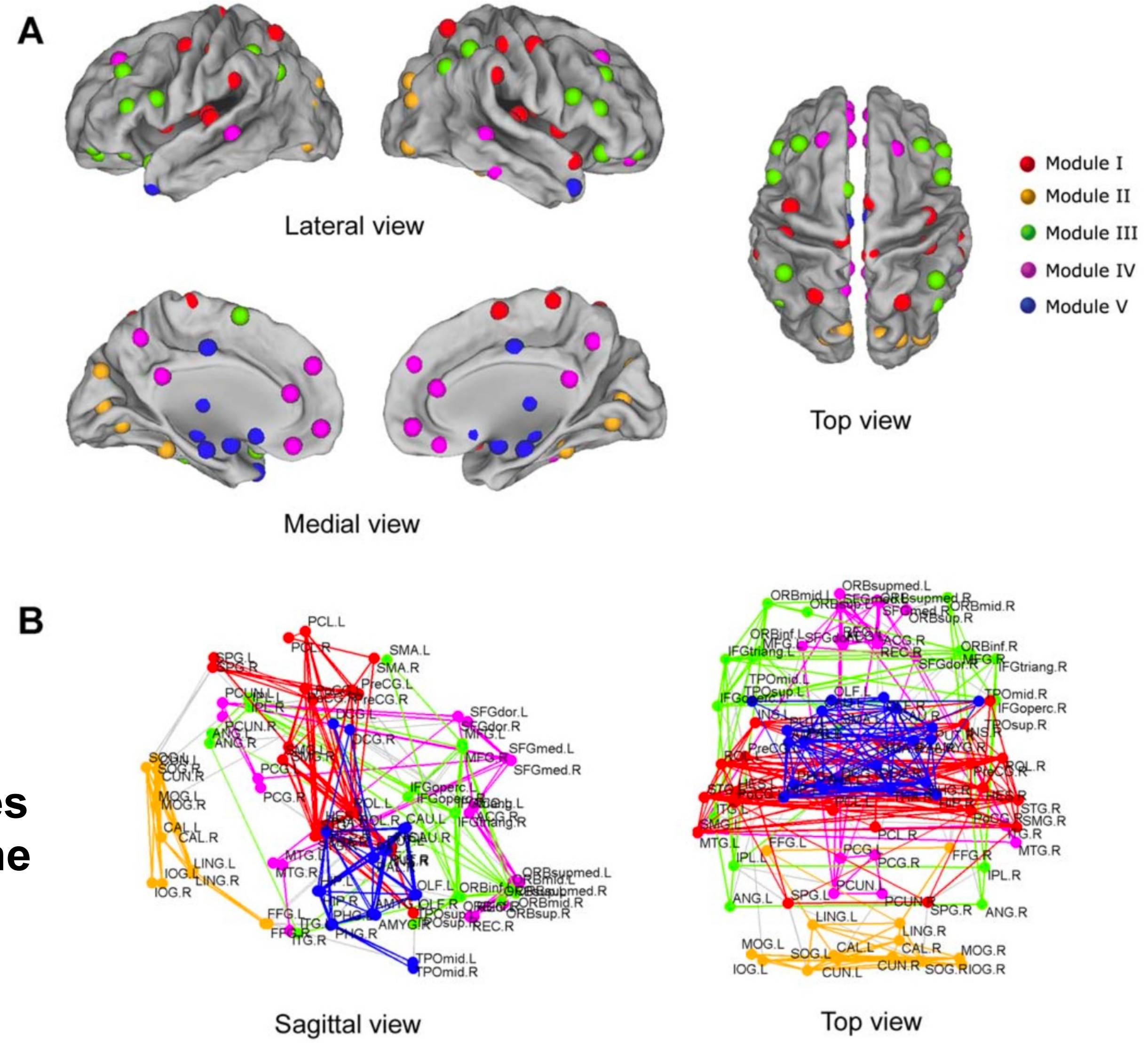
An example

Surface and anatomical representation of modular architecture of the human brain functional network

Anatomical regions of the brain studied: 90*

***This number is dependent on the method used to establish the number of optimal parcellations of the brain.**

All of 90 regions are placed in 5 modules identified by different colours. The nodes and edges are marked in one single colour. The inter-module connections are shown in gray lines.



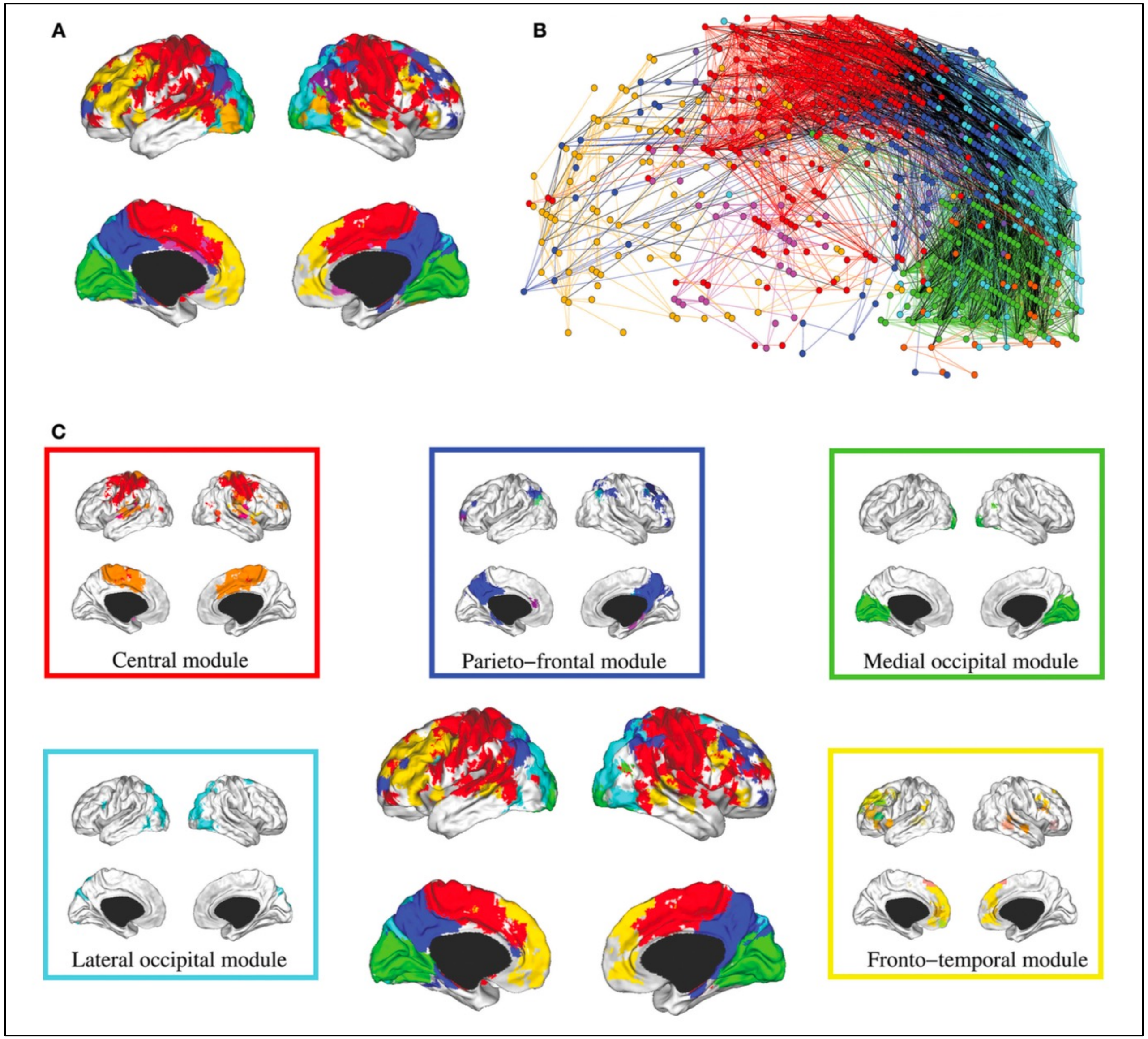
Functional connectivity

Y. He, J. Wang, L. Wang, Z. J. Chen, C. Yan, H. Yang, H. Tang, C. Zhu, Q. Gong, Y. Zang and A. C. Evans, PLoS One (2009)

Preamble

Hierarchical modularity of a human brain functional network

"modules-within-modules"



A. Cortical surface mapping of the community structure

B. Anatomical representation of the connectivity between nodes

C. Sub-modular decomposition of the five largest modules

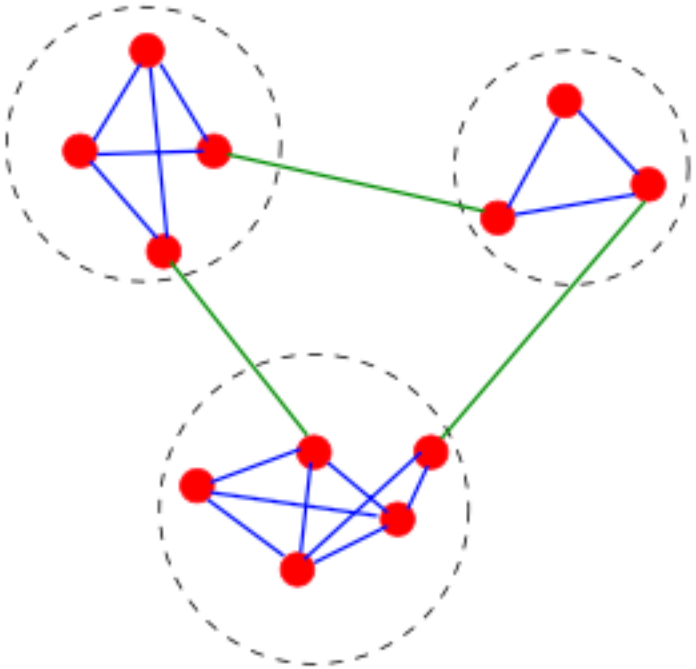
The largest five modules at the highest level of the hierarchy here are medial occipital, lateral occipital, central, parieto-frontal, and fronto-temporal systems.

D. Meunier, R. Lambiotte, A. Fornito, K.D. Ersche and E. T. Bullmore, Front. Neuroinf. (2009)

Preamble

◆ Brain networks in terms of the mathematics of graph theory

A simple graph with three communities



Modularity in the brain

Structural connectivity deals with clusters of brain areas that are more highly connected to each other than the rest of the brain. i.e. physical connections in the brain.

Functional connectivity refers to the functionally integrated relationship between spatially separated brain regions.

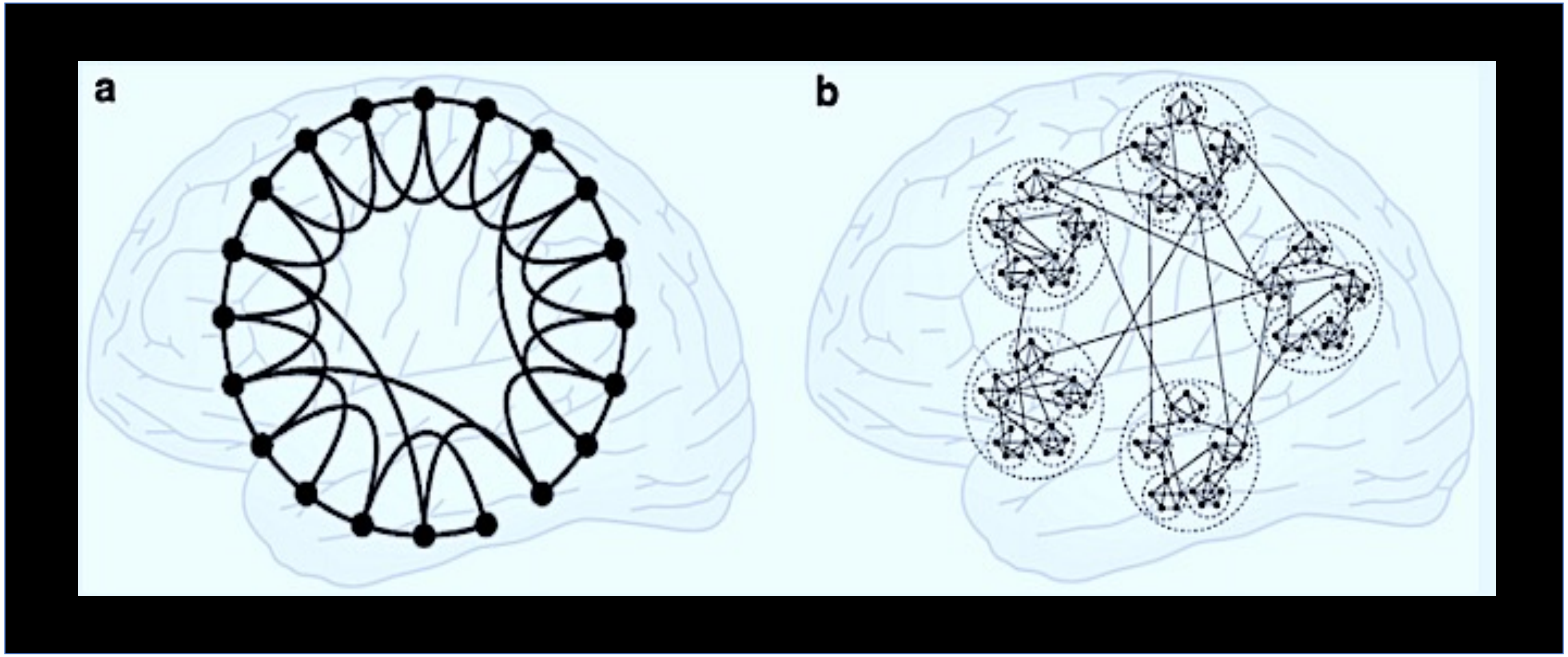
Vertex, a single neuron or a collection of neurons

Edge, synapses between neurons (intra-edges)

Edge, synapses between neurons (inter-edges)

Preamble

(1) Hierarchical modular networks as a model for the brain network and neuronal dynamics



Small-world Network — Hierarchical Modular Network

Hilgetag and Goulas, 2015

Preamble

(2) Anticorrelation across various spatial and temporal scales

Differing correlation strengths, Differing signs, Undetermined directions

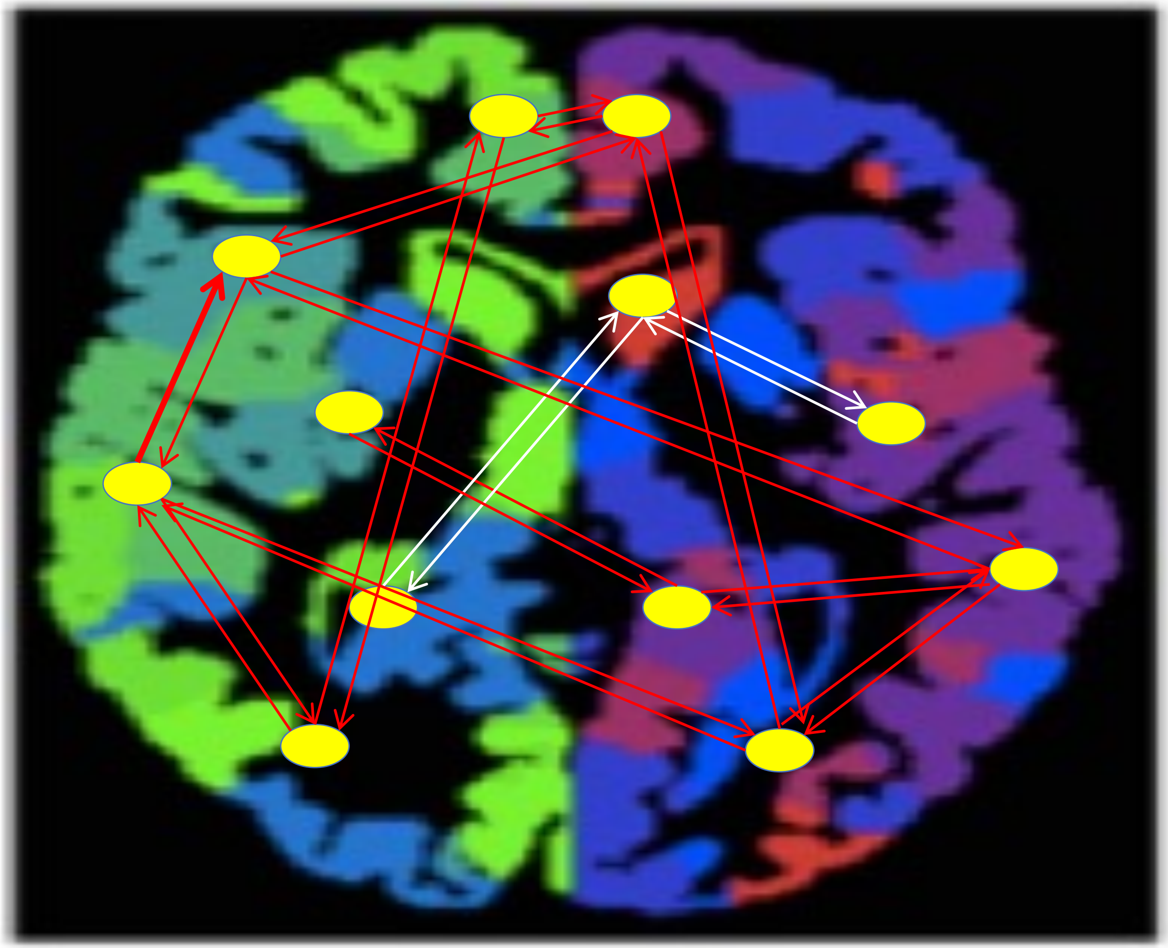
Nodes:

Neuronal subpopulations

Some functional connections of the resting state

Edges:

Correlation coefficients



 # Parcellations in different colours (Method dependent)

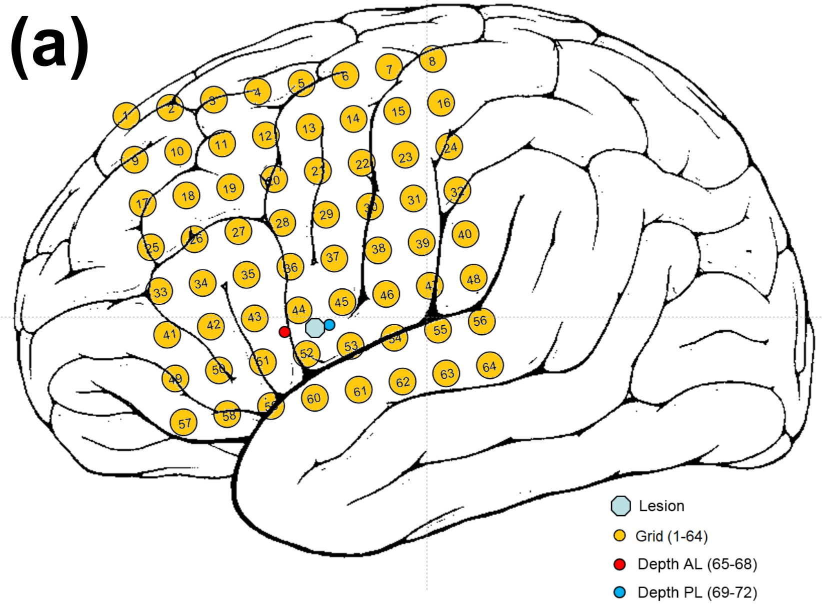
Positive correlation coefficient

Negative correlation coefficient

What do anticorrelations mean?

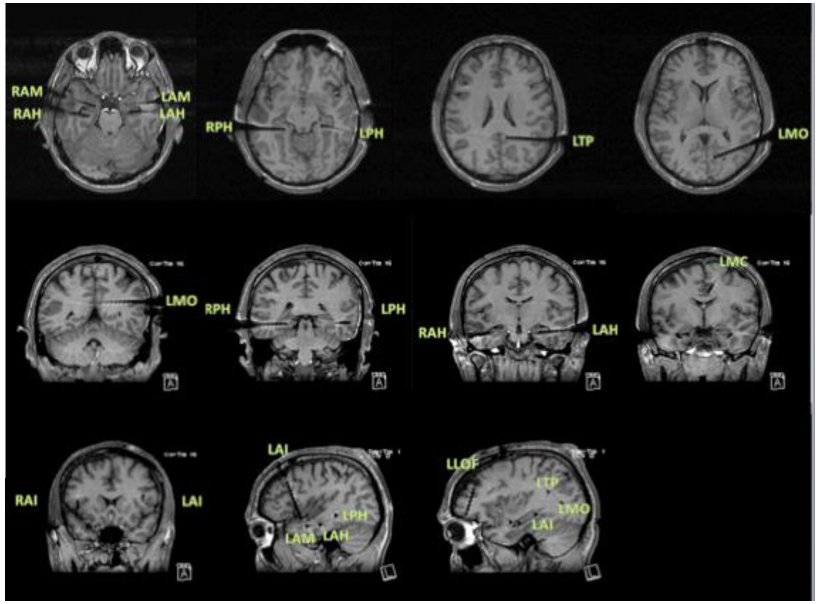
Intracranial EEG experiments in brain disorder studies: Epileptic seizures

(a)



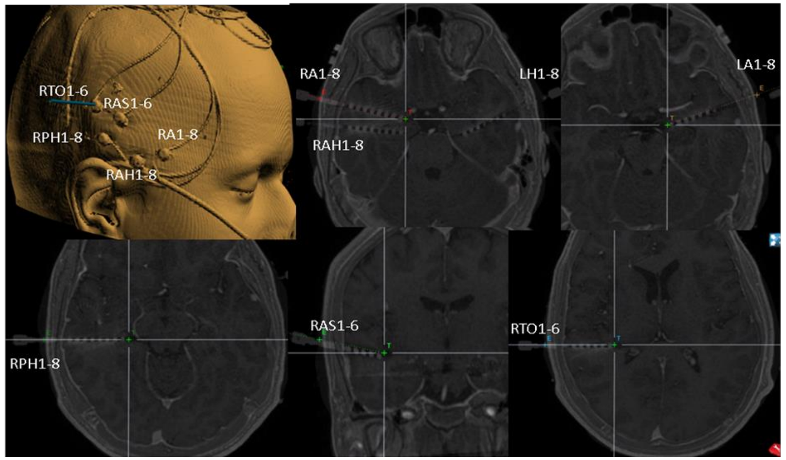
(b)

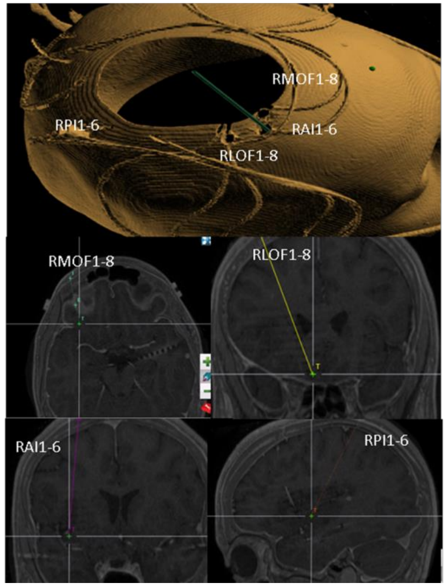
Channels	Brain Region (Abbreviation)
1-10	Left Anterior Insula (LAI)
11-20	Left Lateral Orbitofrontal (LLOF)
21-28	Left Mid Cingulate (LMC)
29-38	Left Amygdala (LAm)
39-46	Left Anterior Hippocampus (LAH)
47-54	Left Posterior Hippocampus (LPH)
55-64	Left Medial Occipital (LMOc)
65-74	Left Temporoparietal (LTP)
75-84	Right Anterior Insula (RAI)
85-92	Right Amygdala (RAm)
93-100	Right Anterior Hippocampus (RAH)
101-108	Right Posterior Hippocampus (RPH)



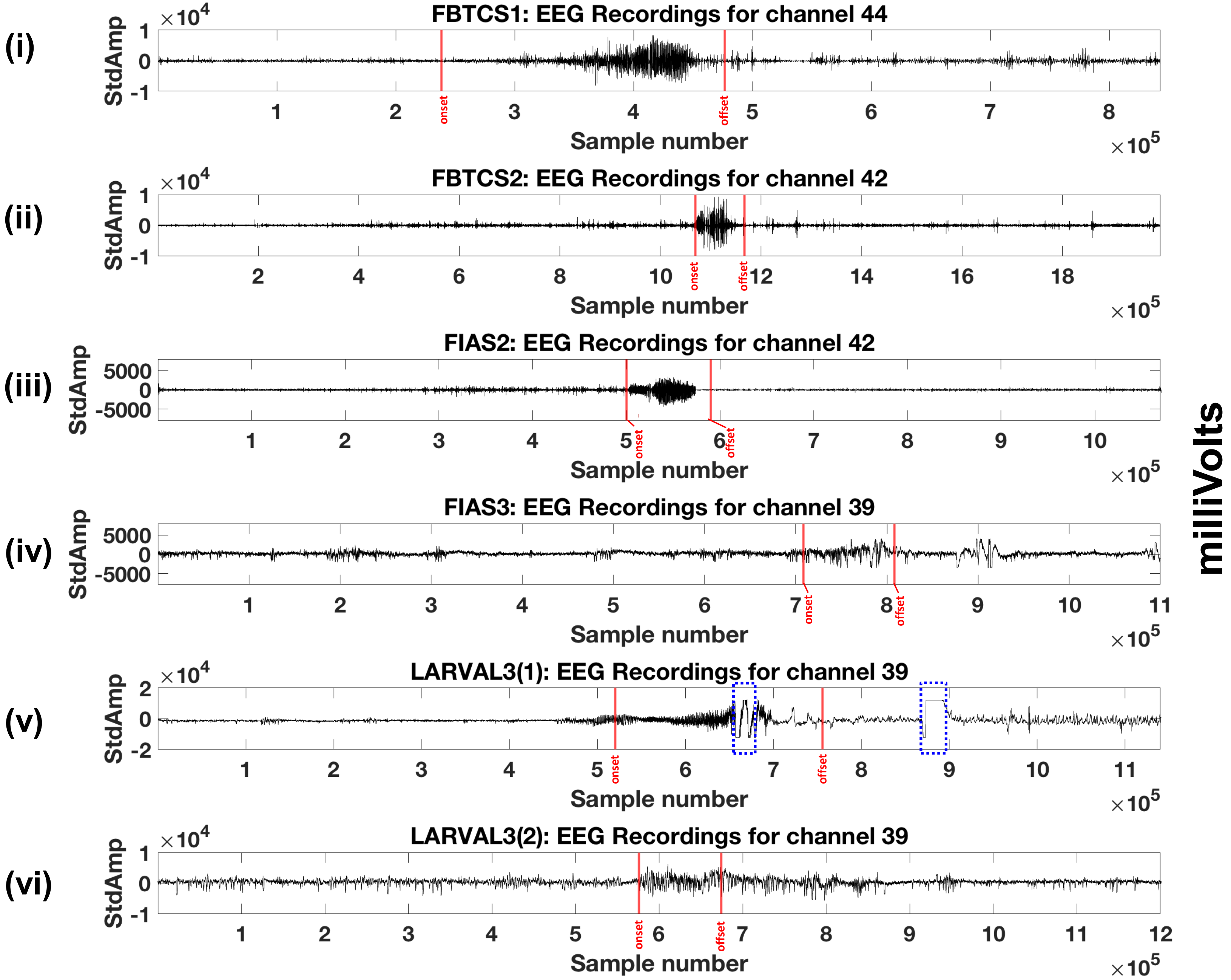
(c)

Channels	Brain Region (Abbreviation)
1-8	Right Amygdala (RA)
9-16	Right Anterior Hippocampus (RAH)
17-24	Right Posterior Hippocampus (RPH)
25-30	Right Anterior Insula (RAI)
31-36	Right Posterior Insula (RPI)
37-44	Right Medial Orbitofrontal (RMOF)
45-52	Right Lateral Orbitofrontal (RLOF)
53-60	Left Amygdala (LA)
61-68	Left Anterior Hippocampus (LH)
69-74	Right Posterior Temporal Operculum
75-80	Right Anterior Superior Temporal (RAS)

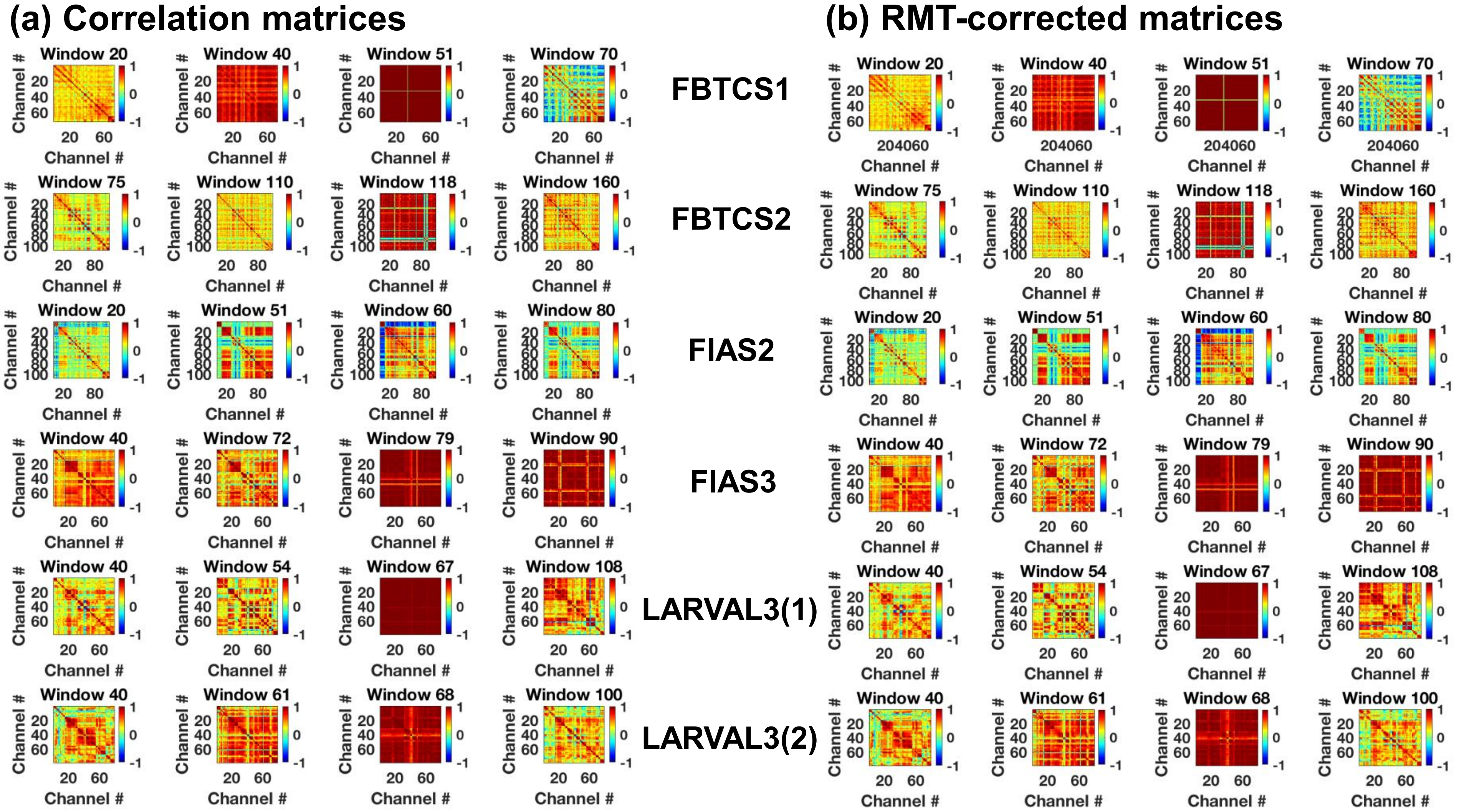




Examples of iEEG data: Epilepstic seizures



Correlation matrices and random matrix theory-corrected matrices



FBTCS, Focal bilateral tonic-clonic seizure
FIAS, Focal impaired awareness seizure
LAEVAL, Electrographic seizure

Functional networks and graph theory

1. The brain is a natural fit for graph theory approaches as it is readily represented as a network (a graph) of elements and their pairwise interconnections, also called nodes and edges.

2. Structural and functional graph. Nodal measure (local): Node degree or strength. Global measures (network-wide): Path length or efficiency.

3. Modularity: Modularity maximization which aims to divide a given network into a set of nonoverlapping communities by maximizing a global objective function, the modularity metric.

4. Centrality measures to chart the global architecture of a brain network.

5. Future directions: Generative models, dynamic networks, multilayer networks, algebraic topology

Olaf Sporns, Graph theory methods: applications in brain networks, Dialogues in Clinical Neuroscience (2018)

Community structure determination

Definition of modularity, Q_0

Adjacency matrix

Standard resolution parameter for module

Community i

$$\boxed{Q_0 = \sum_{ij} [A_{ij} - \gamma P_{ij}] \delta(g_i, g_j)}$$

Null model adjacency matrix

Community j

Standard Null Model $P_{ij} = \dfrac{k_i k_j}{2m}$

Standard Resolution parameter $\gamma = 1$

Many graph partitioning methods as well !

Newman, PNAS, 2006; Fortunato, Phys. Reps., 2010, Bassett et al., Chaos, 2013; Monfared et al., ArXiv (2018)

Signed modularity[a]

$$\boldsymbol{Q_S = (m^+Q^+ - m^-Q^-)/(m^+ + m^-)}$$

Q^+ is the modularity of the graph G where all the negative edges are removed.
Q^- is the modularity of the graph G where all the positive edges are removed.
m^+ is the number of positive edges and m^- is the number of negative edges.

=> Look for the maximum signed modularity.

Simulated annealing method to maximize signed modularity[b]

[a]Gomez et al., Phys. Rev. E. (2009)
[b]Monfared et al., ArXiv (2018)

Eigenvector centrality, *EVC*, for the i^{th} node for the k^{th} window:

$$EVC_k(i) = \frac{1}{\lambda(k)} \sum_j B_{ij}(k) EVC_k(j)$$

where EVC_k is a dominant positive unit eigenvector for the largest eigenvalue λ of $B(k)$ and $B(k) = A(k) + J$ with J denoting a square matrix with order matching $A(k)$ and every entry equal to one.

Window size: 10,000 samples

Weighted clustering coefficient for the i^{th} node for a signed network, A_k

$$WCC_k(i) = \frac{\sum_{j,q} A_{j,i}(k) A_{i,q}(k) A_{j,q}(k)}{\sum_{j \neq q} |A_{j,i}(k) A_{i,q}(k)|}.$$

FBTCS, Focal bilateral tonic-clonic seizure
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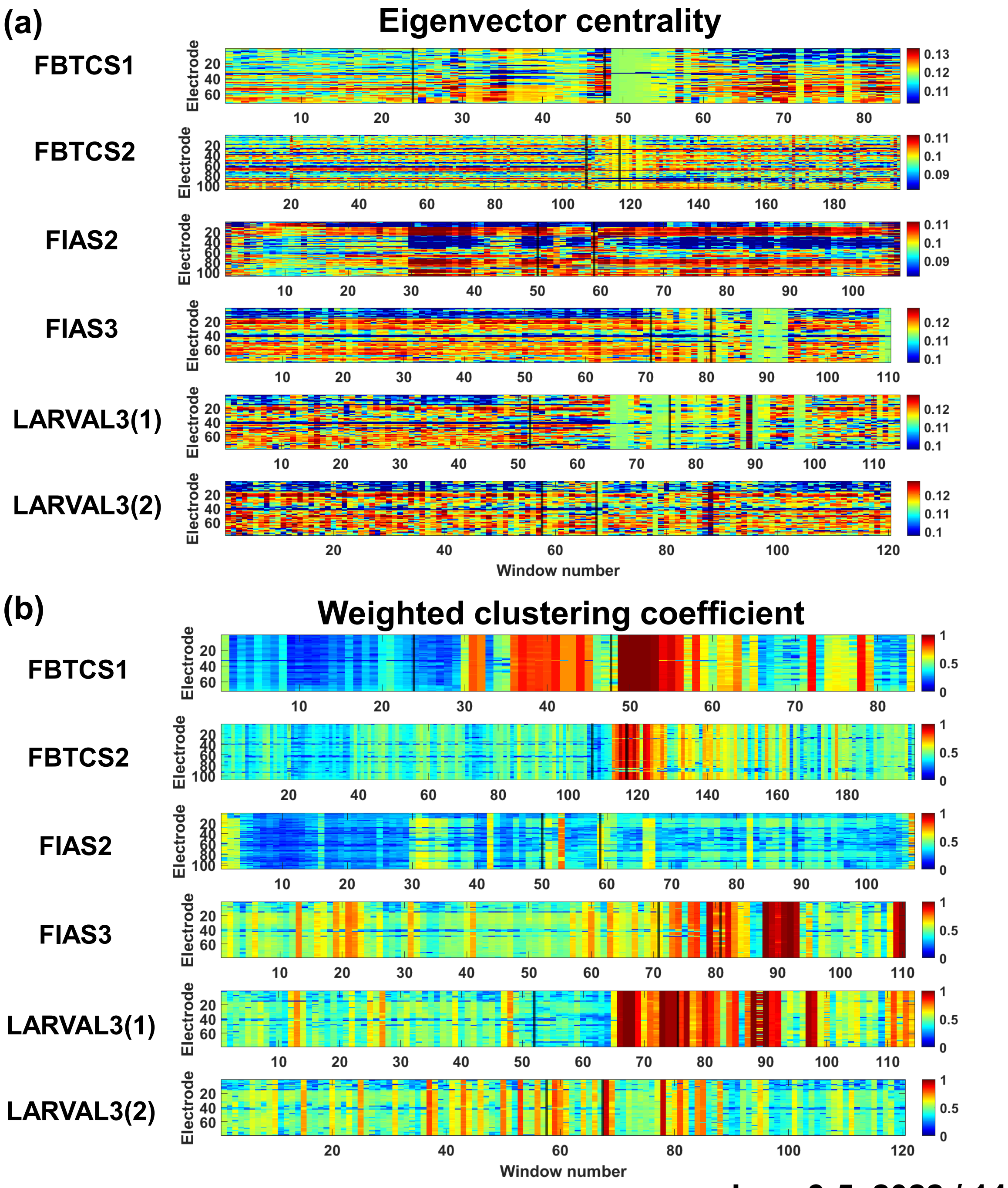
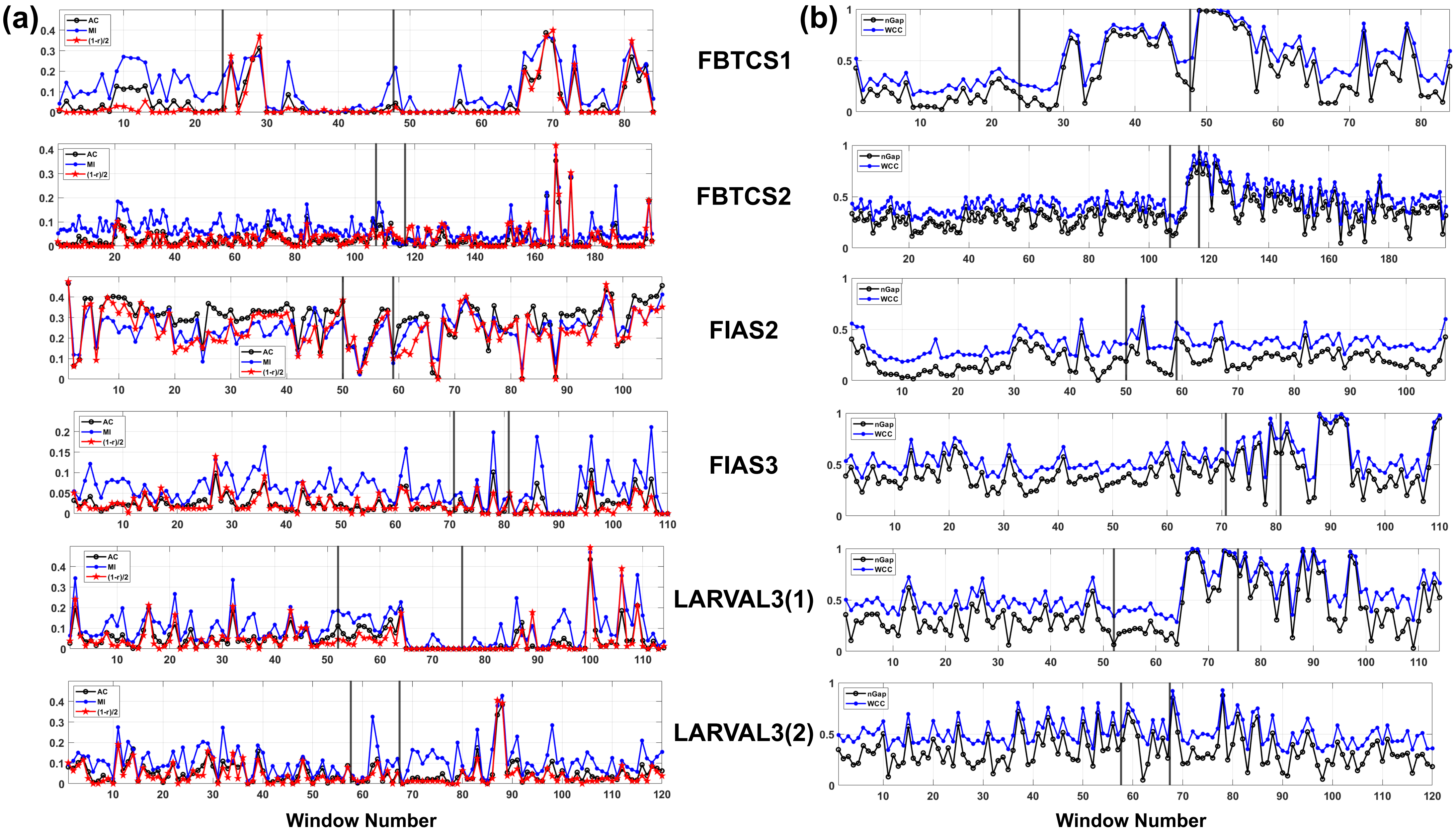


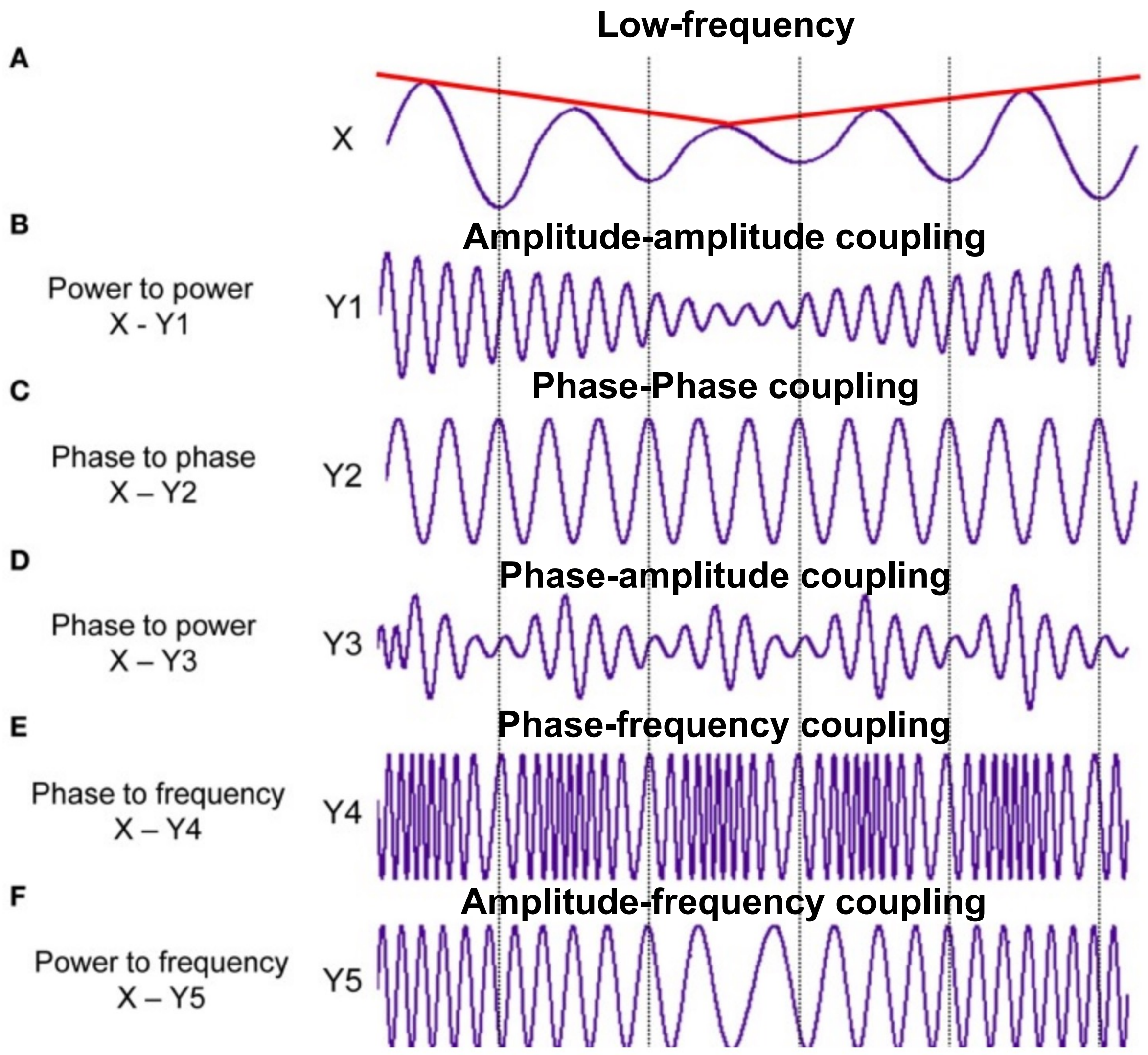
Anticorrelation index, modulation index

Spectral gap, WCC



What is cross-frequency coupling and why is it important?

"Canolty et al. (2006) acquired data from five human subjects who had had subdural electrodes implanted intra-cranially as part of neurosurgical treatment for epilepsy. The authors found that the power (or amplitude) of the fast gamma oscillations was systematically modulated during the course of a theta cycle. In other words, there was a cross-frequency coupling observed as a strong correlation between theta phase and gamma power." O. Jensen and L. L. Colgin, Trends in Cognitive Neuroscience (2007)



Jirsa and Mueller, Frontiers in Neuroscience (2013)

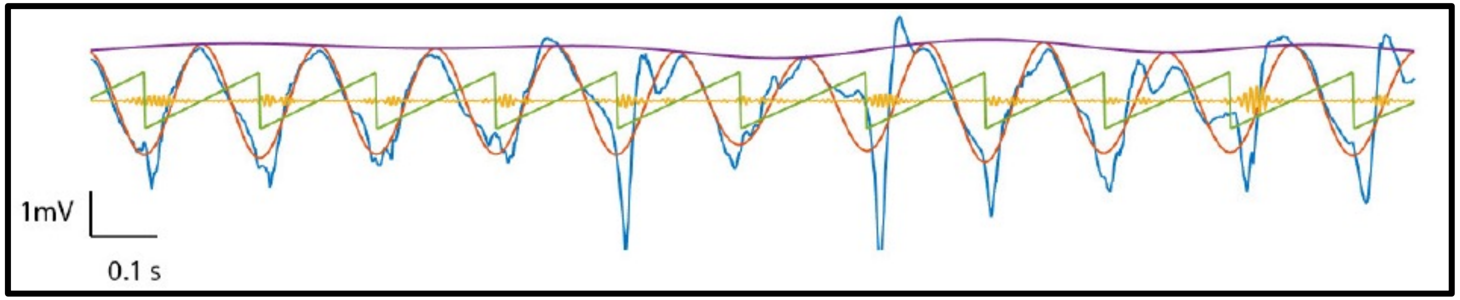
Cross-frequency coupling (CFC) metrics

Metrics defined: Moving Vector Length (MVL), Modulation Index (MI), Phase-locking value(PLV), **Generalized Linear Model (GLM) CFC metrics**

Required quantities: Phase of the low frequency signal, Φ_{low}, Amplitude envelope of the high frequency, A_{high}, Amplitude envelope of the low frequency, A_{low}.

GLM-CFC approach: Model the distribution of A_{high} as a function of different predictors such as Φ_{low}, A_{low} and their combinations and use the modelled curves or surfaces to estimate the distances between them . We use the works of Kramer and Eden (2013), Nadalin et al. (2019) to compute the distance-based metrics for both the phase-amplitude coupling and the amplitude-amplitude coupling.

A snippet of a human seizure data



Nadalin et al., eLIFE, 2019

Cross-frequency coupling (CFC) metrics

Modulation Index (MP)

The Kullbach-Leibler distance measuring how much an empirical distribution over phase bins deviate from the uniform distribution.
Source: Tort ABL, Komorowski R, Eichenbaum H, and Kopell N, J. Neurophysiol. 2010

GLM-CFC (*KER*$_{\mathbf{PAC}}$)
A statistical model to fit A_{high} as a function of ϕ_{low}. One computes the maximum absolute fractional change between the spline and null models. ***KER***$_{\mathbf{PAC}}$ is the metric defined by the previous statement. A large value of ***KER***$_{\mathbf{PAC}}$ is indicative of CFC.
Source: Kramer MA and Eden UT, J. Neurosci Methods, 2013.

GLM-CFC (*R*$_{\mathbf{PAC}}$ and *R*$_{\mathbf{AAC}}$)
A statistical model to fit A_{high} as a function of ϕ_{low}, A_{low}, and their combinations. For a good fit, one estimates distances between the modelled surfaces.
Source: Nadalin JK et al., eLIFE, 2019.

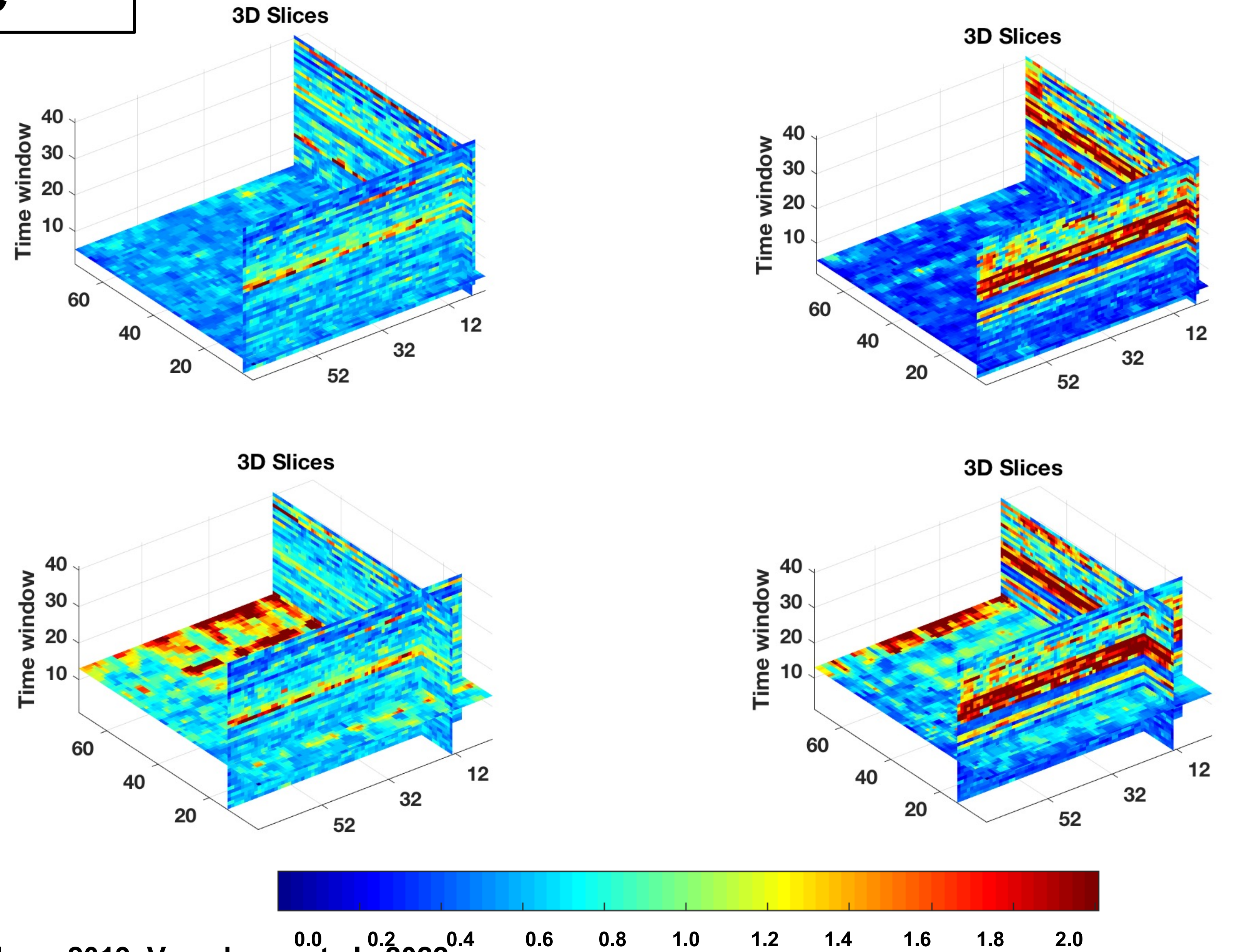
FBTCS1: Delta to Gamma CFC

A 3D scan

R_{PAC} R_{AAC}

Pre-ictal

Onset



Pre-ictal

Onset

Nadalin et al. methodology, 2019, Vasudevan et al., 2022

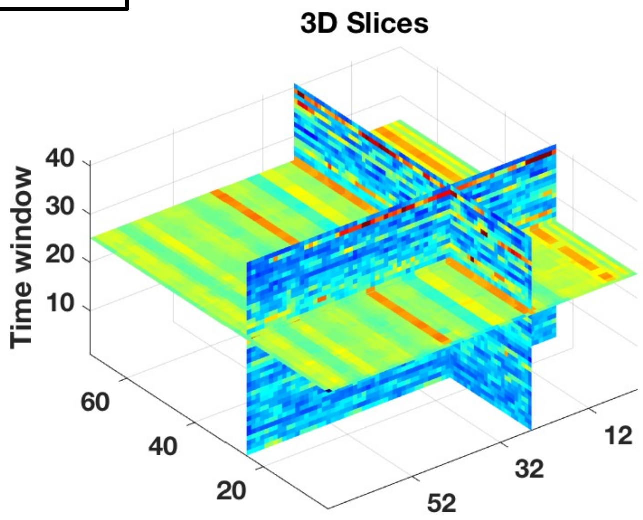
FBTCS1: Delta to Gamma CFC

A 3D scan

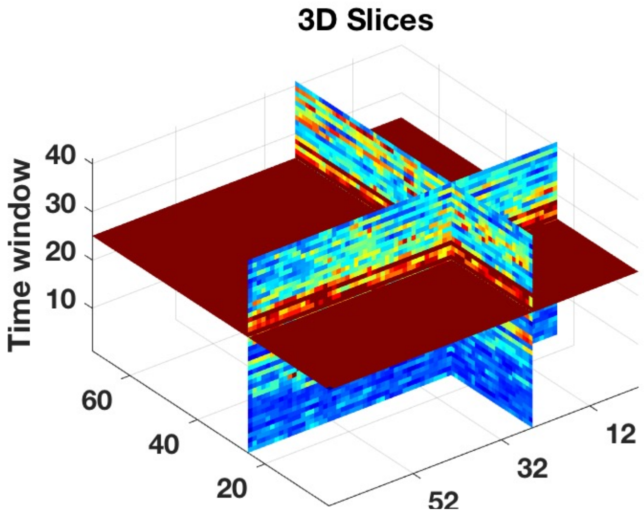
R_{PAC}

R_{AAC}

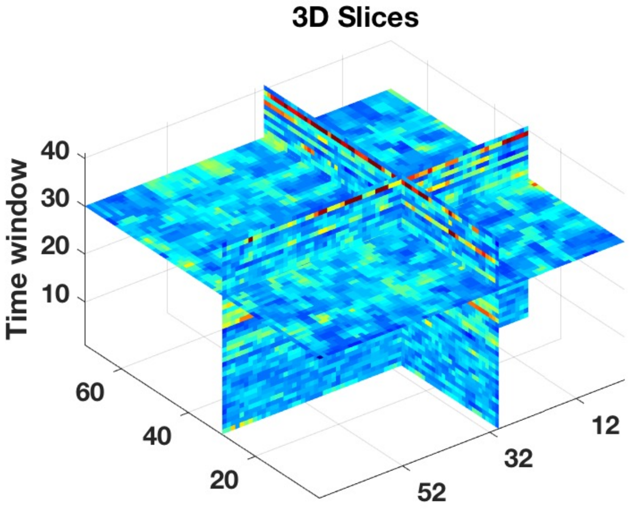
Offset



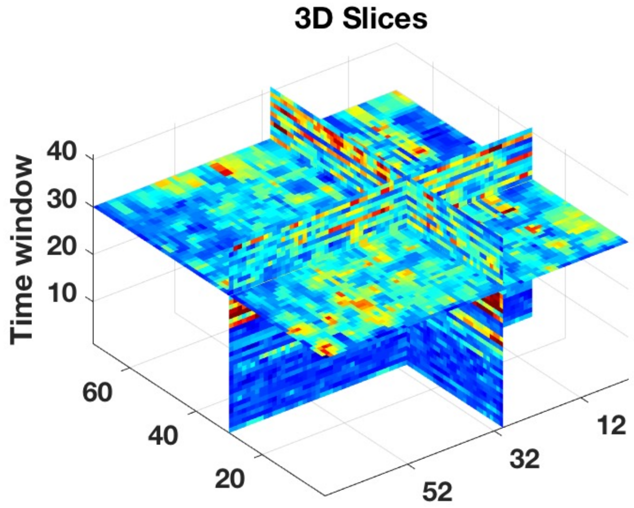
Offset

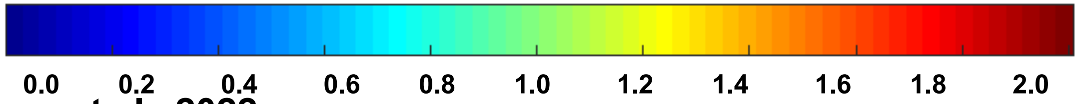


Post-ictal



Post-ictal





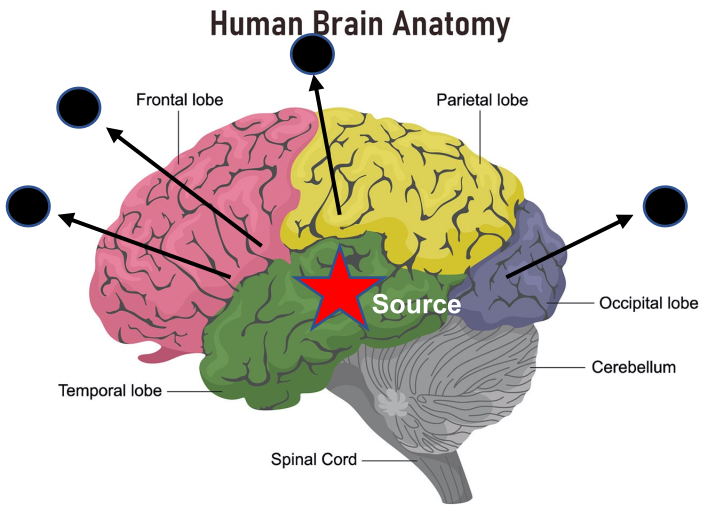
Nadalin et al. methodology, 2019, Vasudevan et al., 2022

Questions and seeking answers

(1) What is **volume conduction?** How does it affect traditional pair-wise interaction metrics such as correlation and coherency?

Volume conduction, a term used in **bioelectromagnetism**, can be defined as the transmission of electric or magnetic fields from an electric primary current source through biological tissue towards measurement sensors. A direct consequence is linear mixing of local field potentials from different brain regions where electrodes are placed. Volume conduction is instantaneous.

Correlation and coherency metrics are not robust metrics.



(2) What are the alternative robust metrics?

Imaginary coherency, weighted phase lag index, phase lag index

(3) Is considering a pair-wise interaction adequate?

No. Considering a many-body interaction would be an ideal thing. Also, venturing into simplicial complexes in the topological space would be an attractive option (**Giusti et al, J. Comp. Neuroscience, 2016**).

Essential metrics of phase synchronization

Cross-spectrum between two signals i and j : $S_{ij}(f) := \left\langle X_i(f)\ X_j^*(f) \right\rangle$

Coherency: $$\left|C_{ij}(f)\right| := \left| \frac{\left\langle A_i(f)\ A_j(f)\ e^{\iota\ \Delta\theta_{ij}(f)} \right\rangle}{\sqrt{\left\langle A_i^2(f) \right\rangle \left\langle A_j^2(f) \right\rangle}} \right|$$

Imaginary coherency: $\mathrm{ImCoh}_i j(f) := \Im\left(C_i j(f)\right)$

(Nolte et al., Clinical Neurophysiology, 2004)

Phase locking value, PLV:

(Lachaux et al, Human Brain Mapping, 1999)

Imaginary part of PLV: $\mathrm{iPLV}_{\mathrm{ij}}(f) := \left| \left\langle \Im\left(e^{\iota\ \Delta\theta_{ij}(f)}\right) \right\rangle \right|$

(Yoshinaga et al., Front. Neuroscience, 2020)

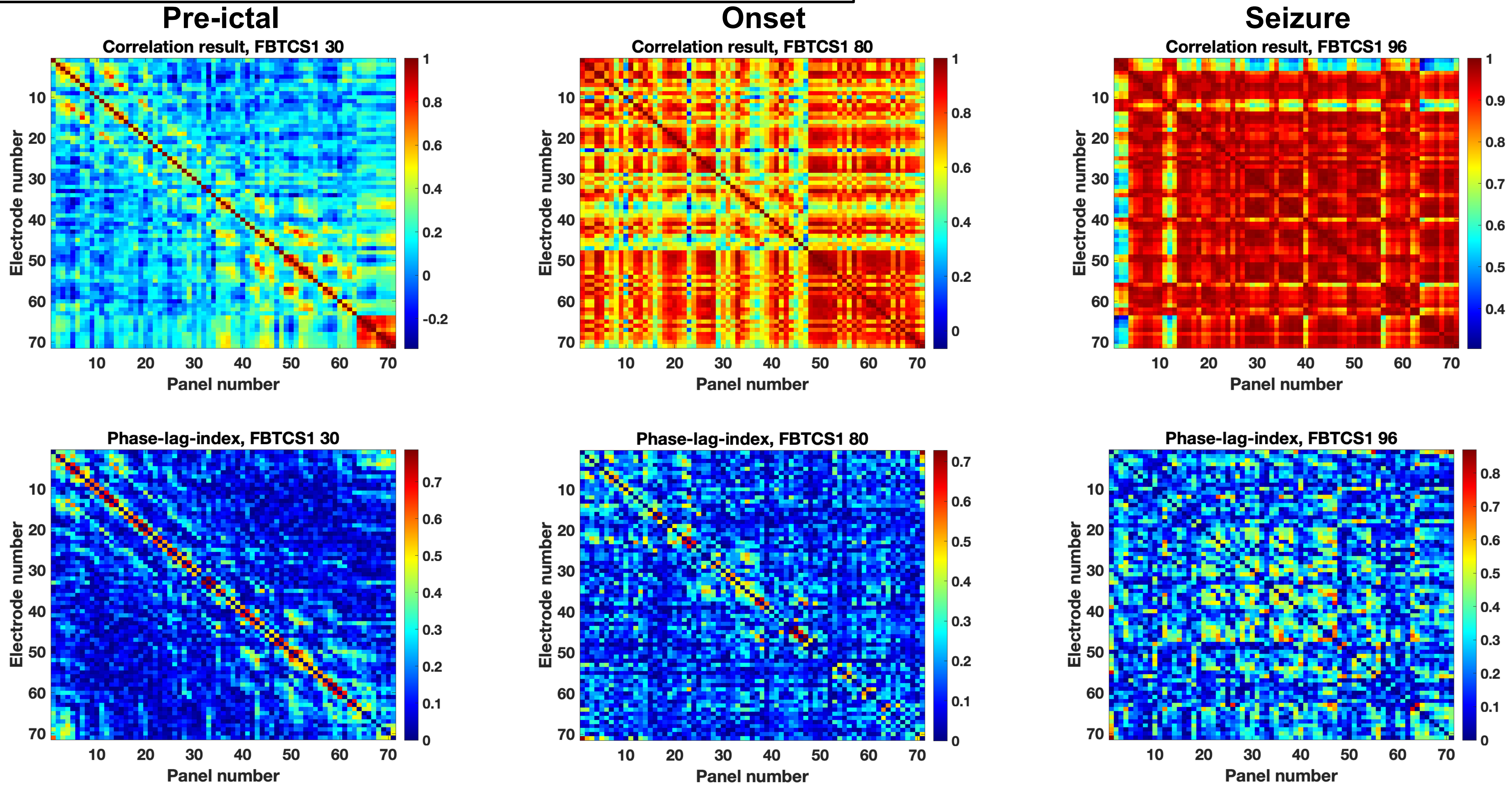
Phase-lag-index, PLI: $\mathrm{PLI}_{\mathrm{ij}}(f) := \left| \left\langle sign\left(\Delta\theta_{ij}(f)\right) \right\rangle \right|$

(Stam et al., Human Brain Mapping, 2007))

Weighted PLI (wPLI): $$\mathrm{wPLI}_{\mathrm{ij}}(f) := \frac{\left| \left\langle \left| \Im\left(X_i(f)\ X_j^*(f)\right) \right| sign\left(\Delta\theta_{ij}(f)\right) \right\rangle \right|}{\left\langle \left| \Im\left(X_i(f)\ X_j^*(f)\right) \right| \right\rangle}$$

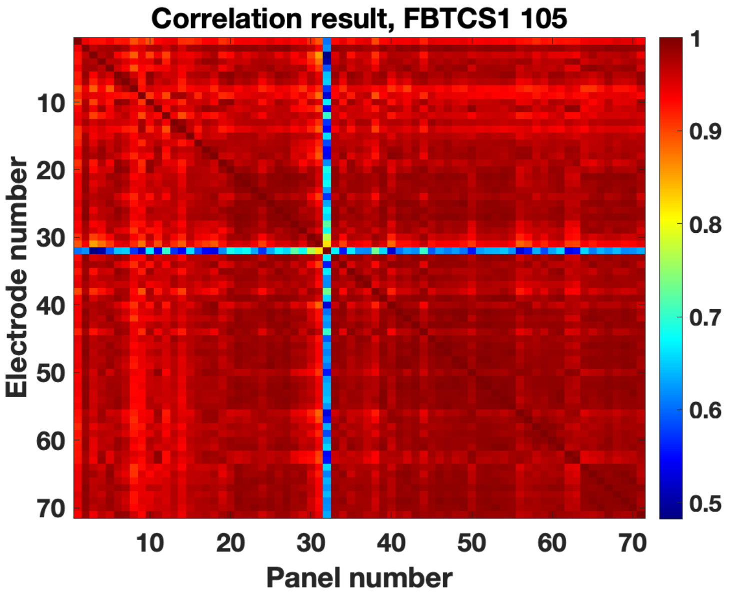
(Vinck et al., Neuroimage, 2011)

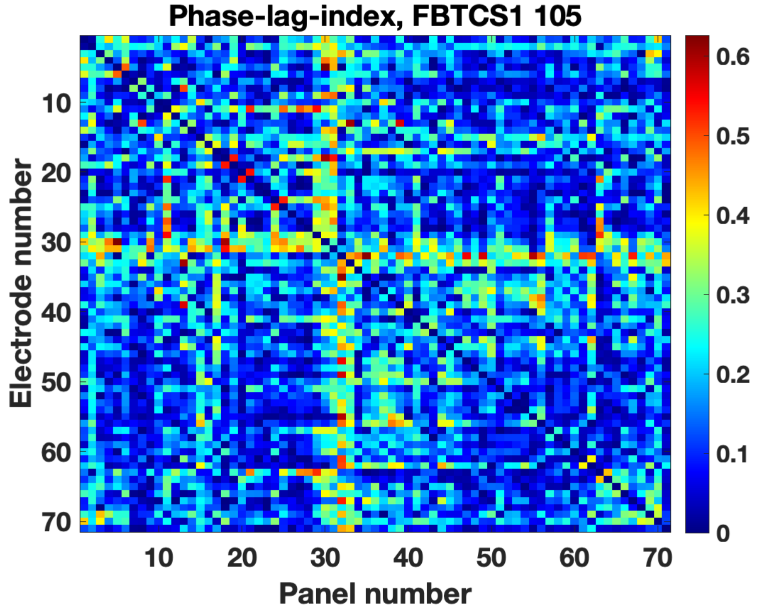
Correlation matrix vs phase-lag-index matrix



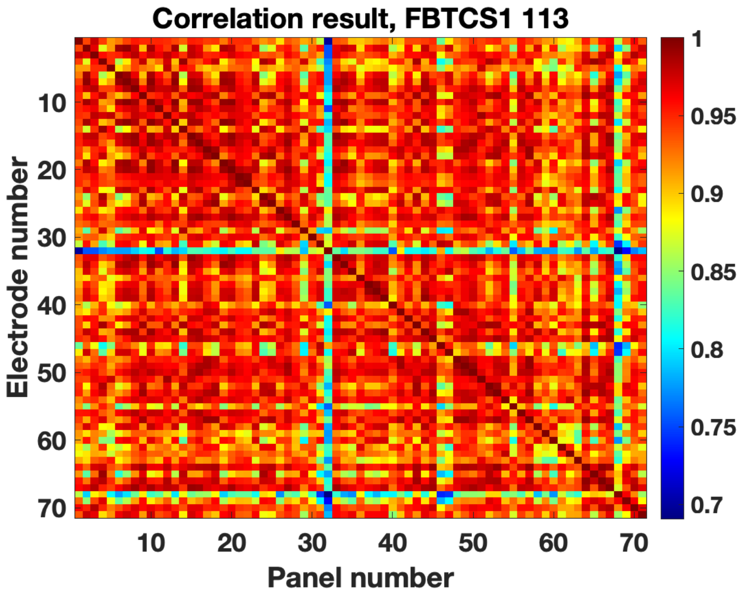
Correlation matrix vs phase-lag-index matrix

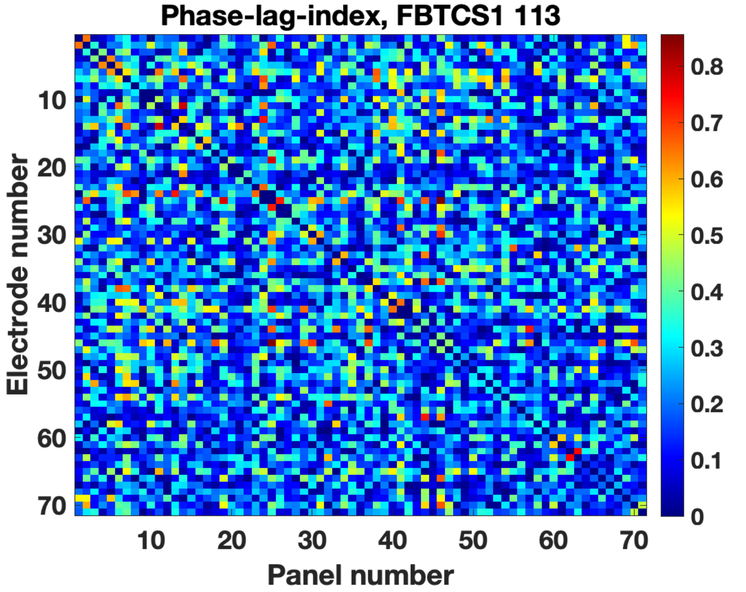
Offset





Post-ictal





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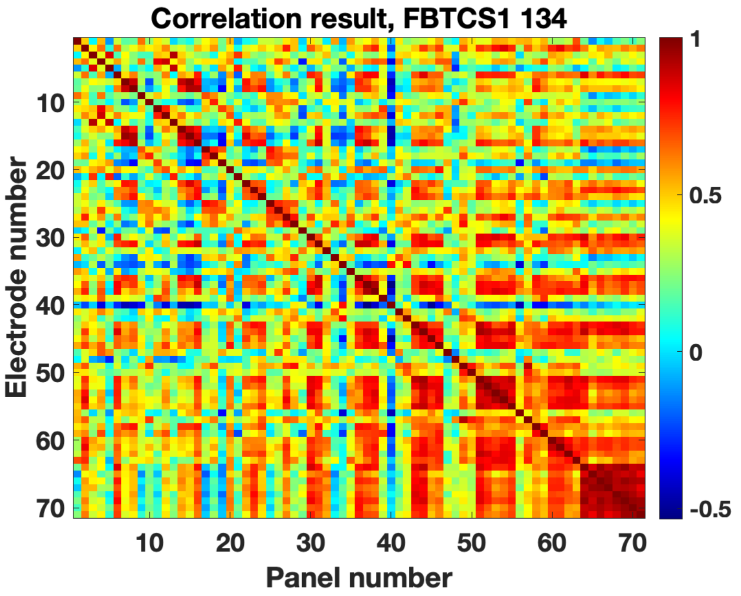

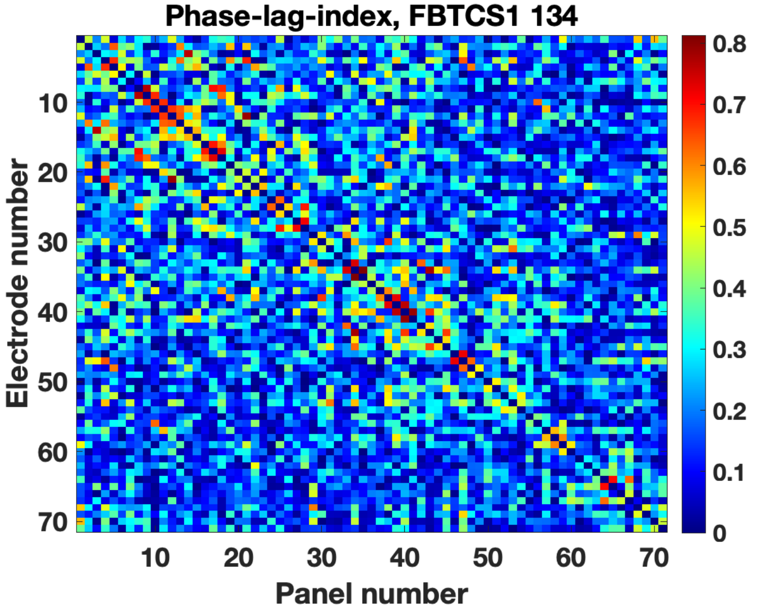

Observations and conclusions

(1) Correlation matrices at onset stage and in subsequent stages of seizure show higher correlation strengths, pointing to a high synchrony. Although we do not know the distribution exactly of what is factual and what is not factual, volume conduction because of its instantaneous responses at different electrodes (or brain regions) brings out the synchrony noticed.

(2) One robust measure such as phase-lag index which mitigates the volume conduction reveals certain characteristic changes during different stages of the ictal period. We are investigating these changes along with other phase synchronization metrics.

Future directions

(1) Functional connectivity based on the new robust metrics remains to be investigated for different seizure types.

(2) A comparison of the new results with the results from the old metrics will be made.

(3) Kuramoto-model dynamics will be investigated with the adjacency matrices built with the new metrics.

Acknowledgements: NSERC, Paolo Federico, Cam Teskey, Signe Bray, Hotchkiss Brain Institute, Department of Mathematics and Statistics, BIRS & the organizers.

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Thanks, Questions

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