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Functional Connectivity with fNIRS: from basic to integrated approaches

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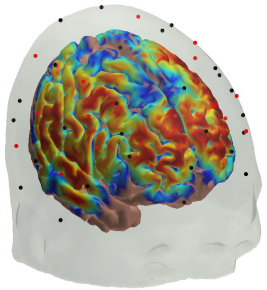
CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

FAPESP

Introduction to the Mini-Course

Intro to functional connectivity



Pipeline for data preprocessing

Motion correction, filtering, and removal of autocorrelation

Removal of systemic physiology

- Short channels
- Extra physiological measurements
- Short channels + Extra physiological measurements
- Principle component analysis

Extracting functional networks

- Seed-based analysis
- Graph Theory

Introduction to the Mini-Course

Logistics & Information

- This course consists at an *introductory* overview of functional connectivity approaches with fNIRS
- The course will mix discussion/fundamental information and hands-on components
- The hands-on should be primarily performed in pairs
- The codes for the hands-on sessions can be downloaded from:
  - https://github.com/FC-training-course-fNIRS-2022/codes
- Inform Rickson, Sergio, or Androu if you need any assistance throughout the hands-on activities
- The slides for this presentation will be available after the course for all attendees.
- You are welcome to use and/or adapt parts of the codes shared during this course for your own research. In this case, please cite the original publications that originated the part of the code used (you can check them on these slides).

What is Functional Connectivity?

Functional Neuroimaging at a glance

fNIRS

Ideas about how the brain works ⟷ Biophysical/statistical model

Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

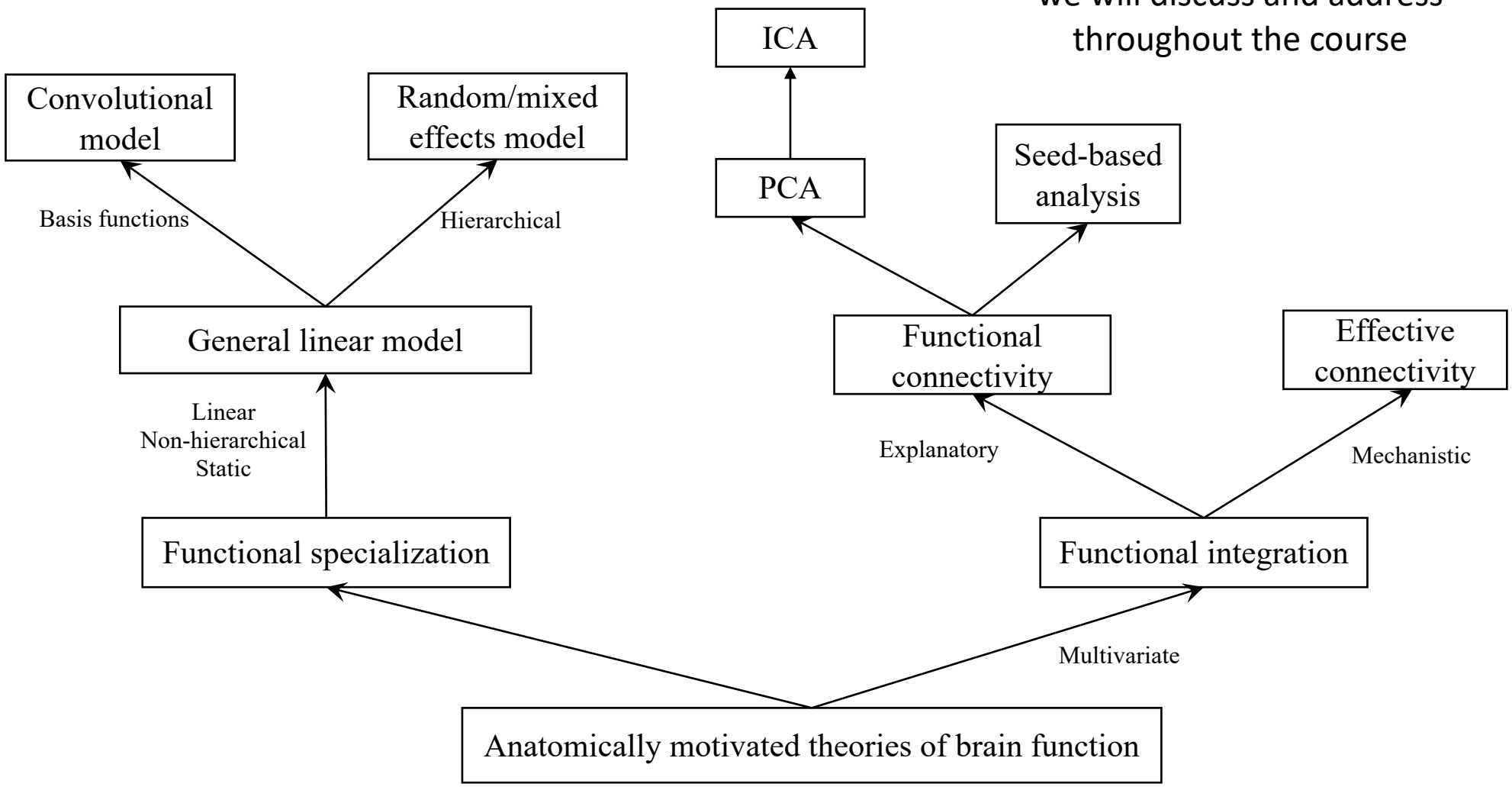
1. *Where* evoked brain responses are expressed → Functional *specialization*
2. *How* neuronal responses are caused → Functional *integration*

Models in functional neuroimaging

It also has limitations that we will discuss and address throughout the course

It assumes a brain process should lead to activity changes in specialized areas.

Ignores that the functional role of any brain unit is defined largely by its connections.



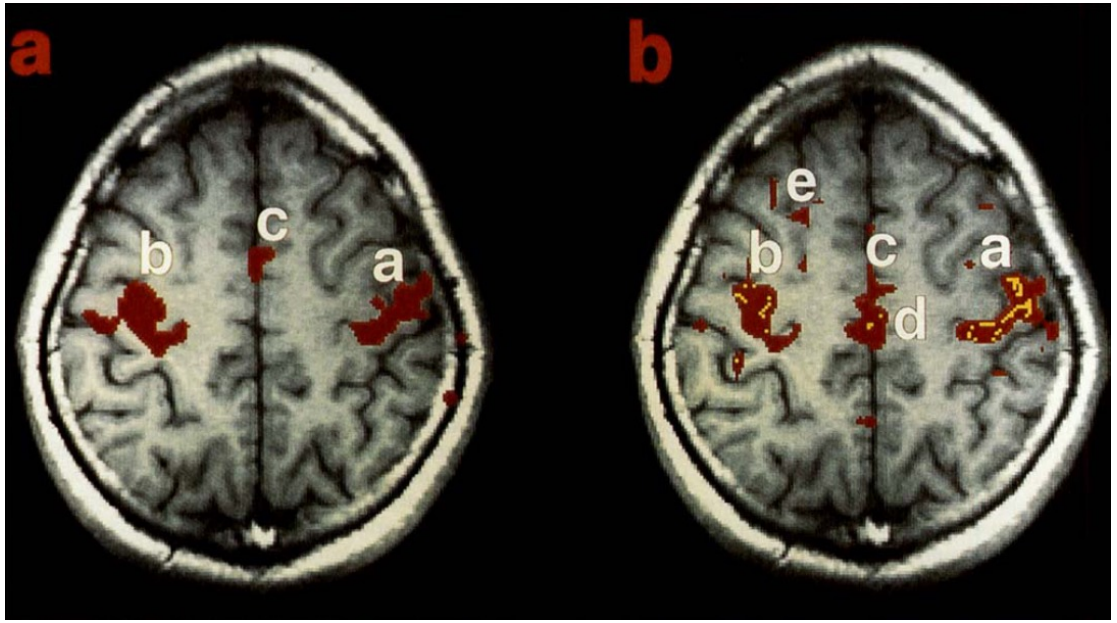
Adapted from Stephan et al., Current Medical Imaging Reviews (2006)

What is Functional Connectivity?

Seed-Based Analysis

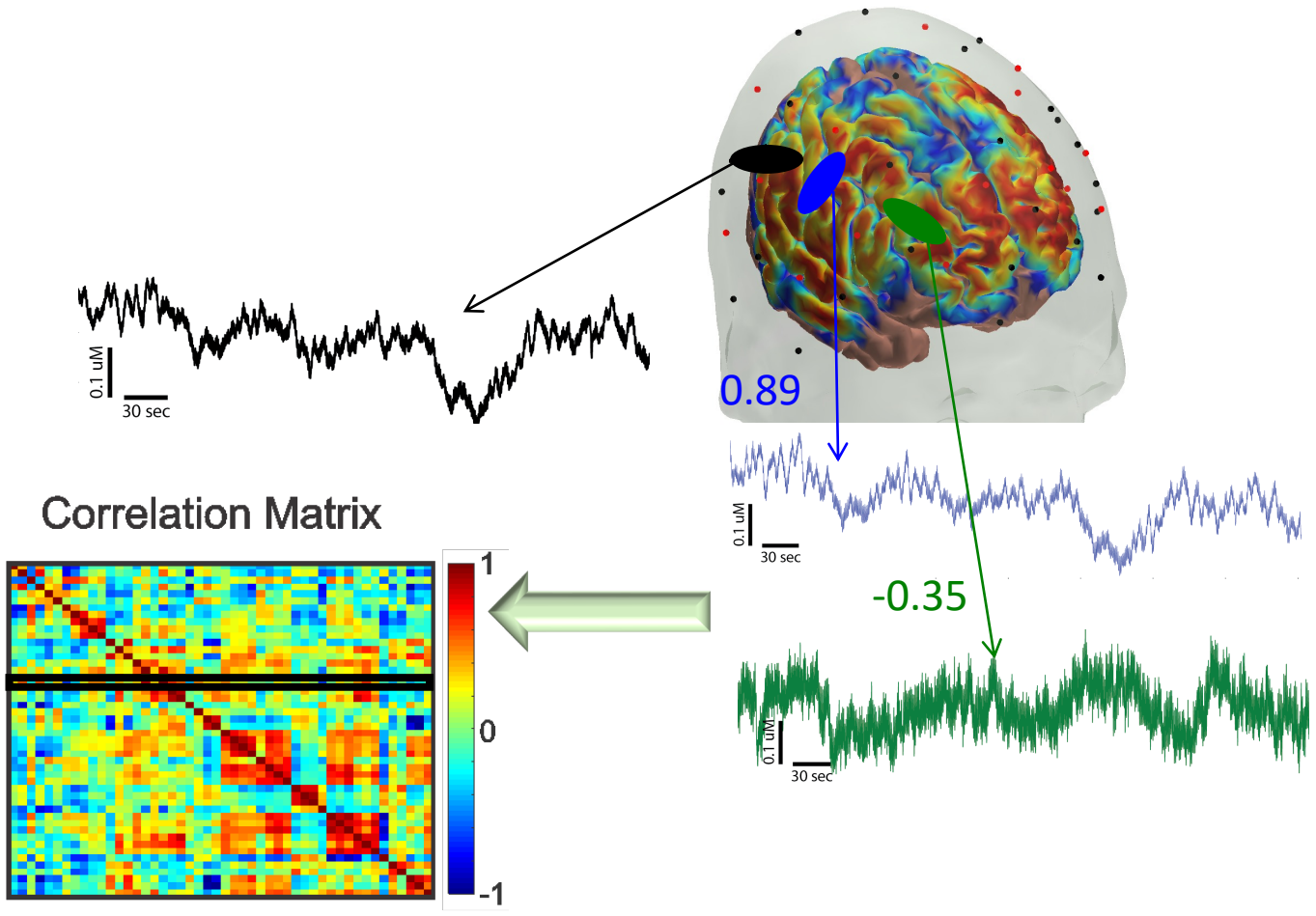
fMRI task-activation response to bilateral left+right finger movement

Low-frequency (< 0.1 Hz) fluctuations in resting brain from regions of the primary sensory motor cortex



Z-squared transformation (for math manipulation)

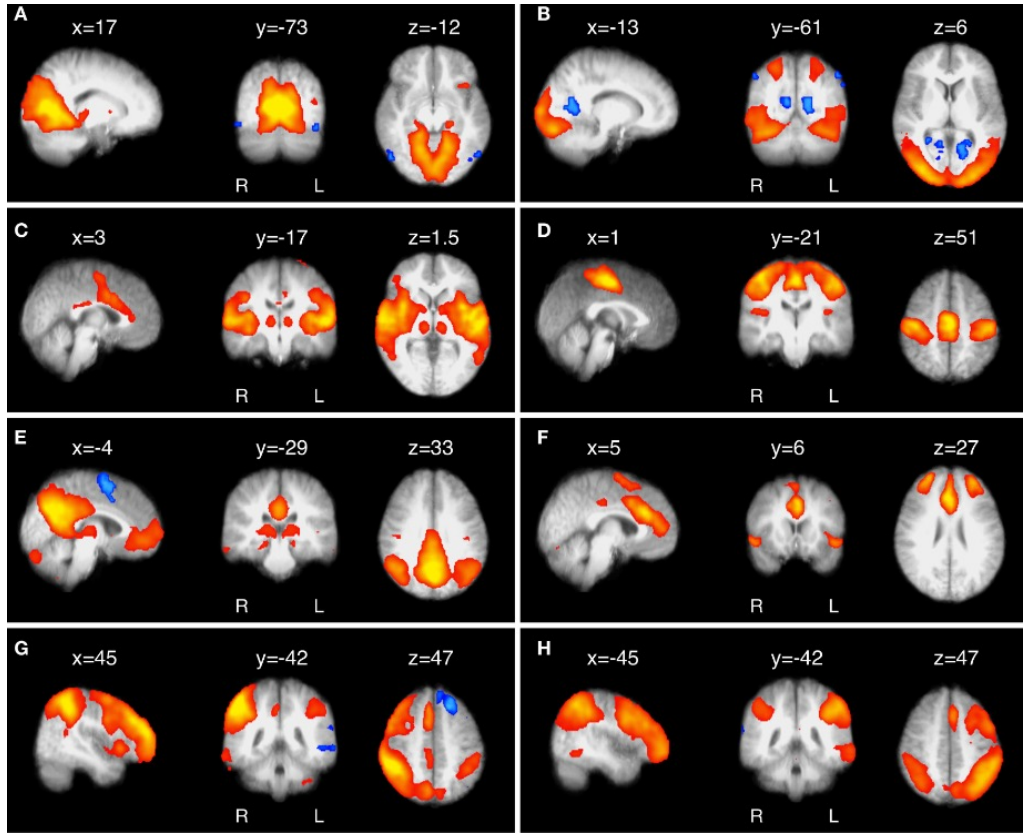
Observed neuronal or hemodynamic signal

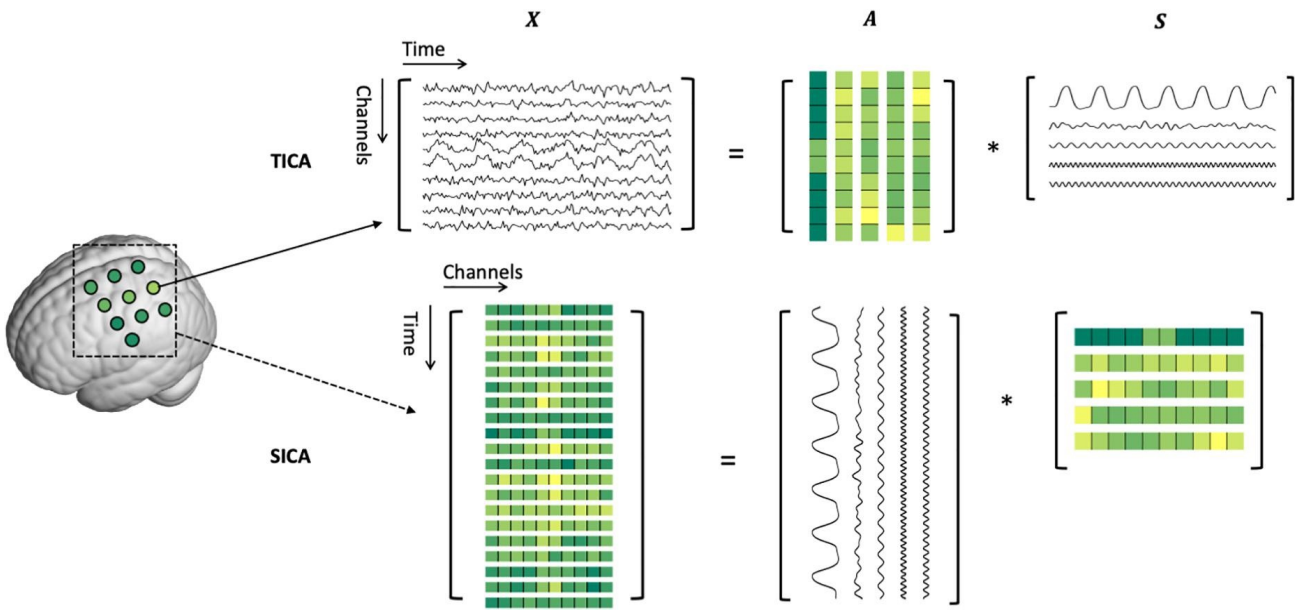


Biswal et al., Magn. Res. Med. (1995)

What is Functional Connectivity?

Independent Component Analysis (ICA)





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Cole, Smith & Beckmann, Front. Sys. Neurosci. (2010)
Kiviniemi et al., NeuroImage (2003)

Zhao et al., Frontiers in Neuroinformatics (2021)

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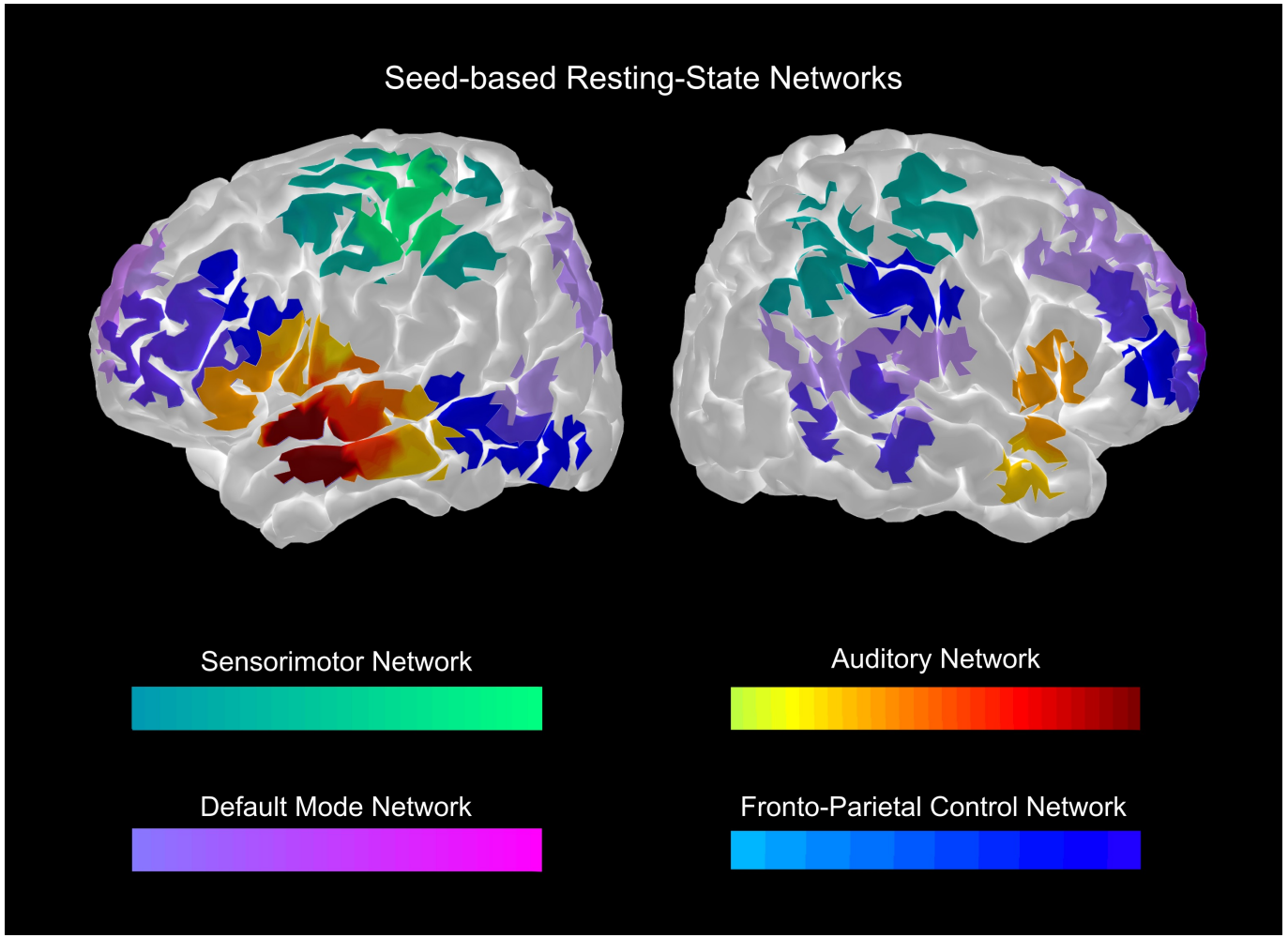
Resting-State Functional Connectivity Networks

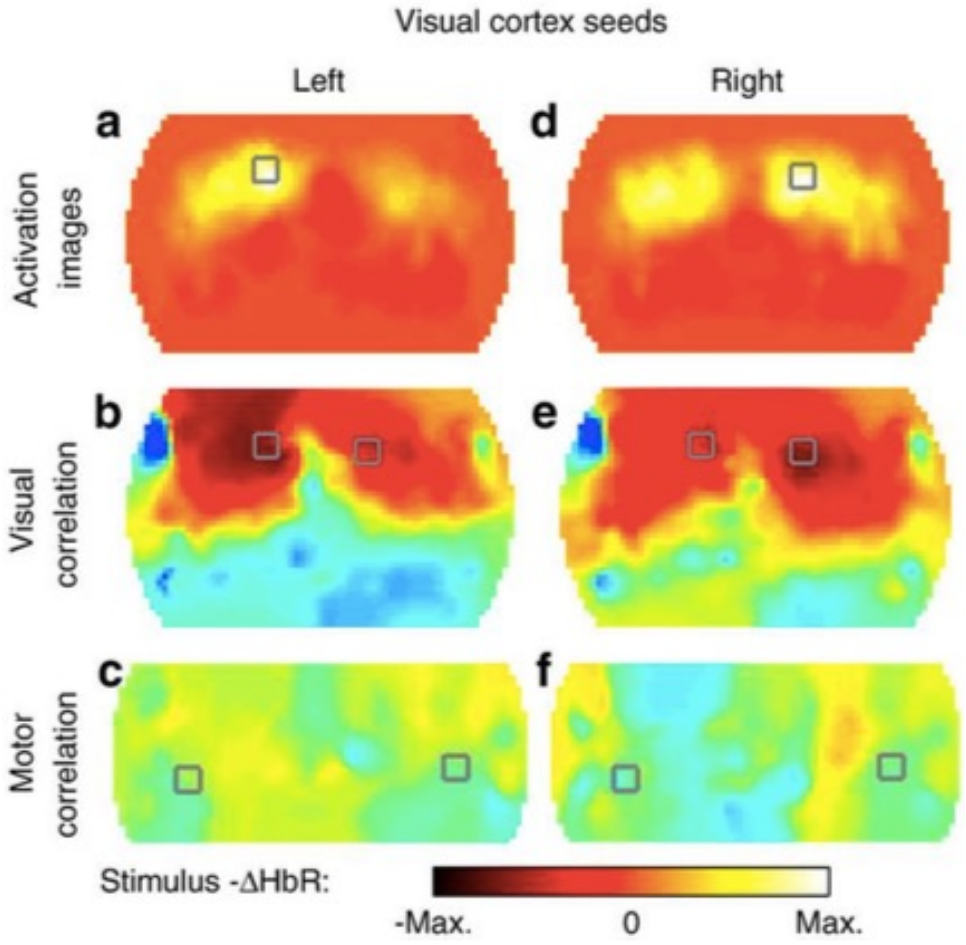


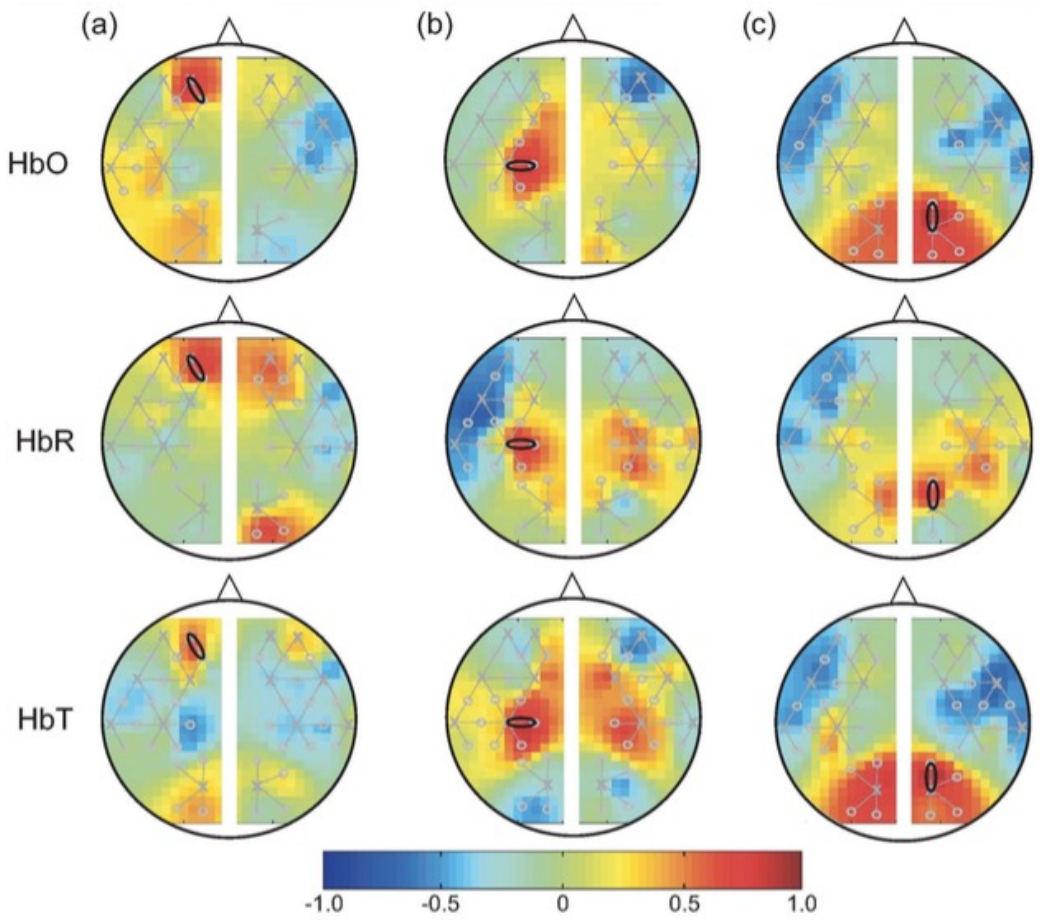
- No need for tasks
- Hemodynamics association (not necessarily neural-origin)
- Sensitive to brain disorders/injuries
  - Detect residual awareness in patients with disorders of consciousness
  - Understand differences between healthy controls and stroke patients

- Association studies not clear

Stephan et al., Current Medical Imaging Reviews (2006)
Li et al., Neural Regeneration Research (2014)
Luppi et al., Nature Communications (2019)

Functional Connectivity with fNIRS techniques

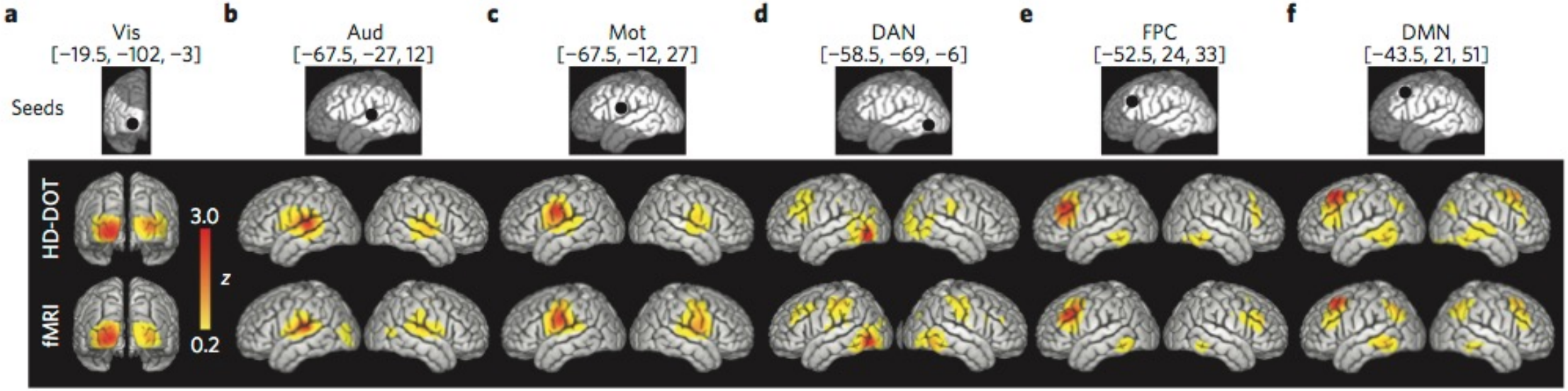


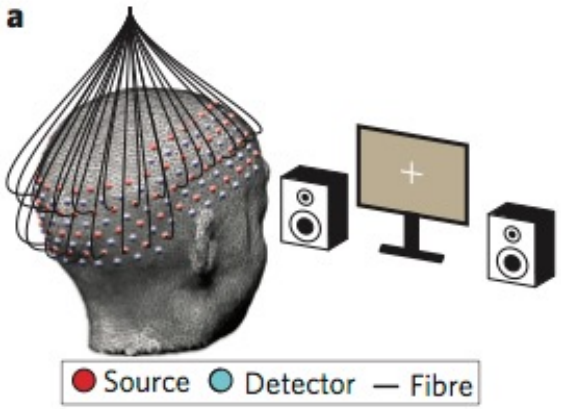


White et al., NeuroImage (2009)

Mesquita et al., Biomed. Opt. Express (2010)

Functional Connectivity with HD-DOT





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Eggebrecht et al., Nature Photonics (2014)

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Data Pipeline in fNIRS-based FC

Workflow for extracting fNIRS-based resting state networks

Probe Design & Experimental Protocol

fNIRS

Ideas about how the brain works ⟷ Functional Connectivity

Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

Design considerations for fNIRS-based rs-FC

Intrinsic fNIRS

- Lack of standard spatial coordinates
  - fNIRS vs. HD-DOT
  - Neuronavigation vs. Probe registration
- Effects of Channel Prunning to group average

Experimental Protocol

- What is “do nothing”?
- Eyes closed vs. Opened
- Sitting vs. Lying

Probe Design & Experimental Protocol

fNIRS

Ideas about how the brain works ⟷ Functional Connectivity

Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

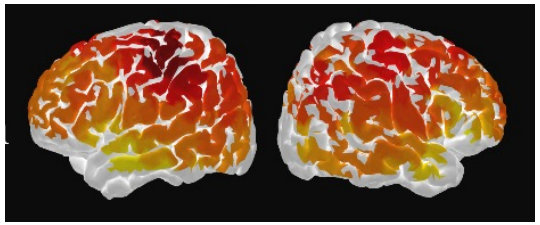
Workflow for extracting fNIRS-based resting state networks

Remove autocorrelation

Band-pass filtering [0.009, 0.08 Hz]

Estimation of Hemoglobin Concentration Changes

Pearson Correlation



Probe Design & Experimental Protocol

fNIRS

Ideas about how the brain works

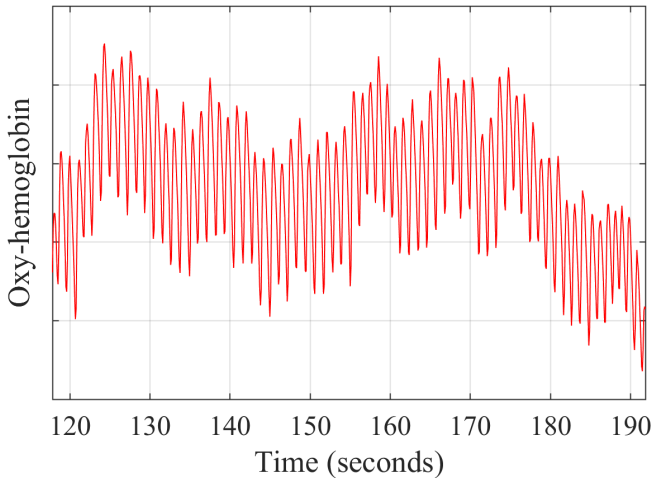
Functional Connectivity

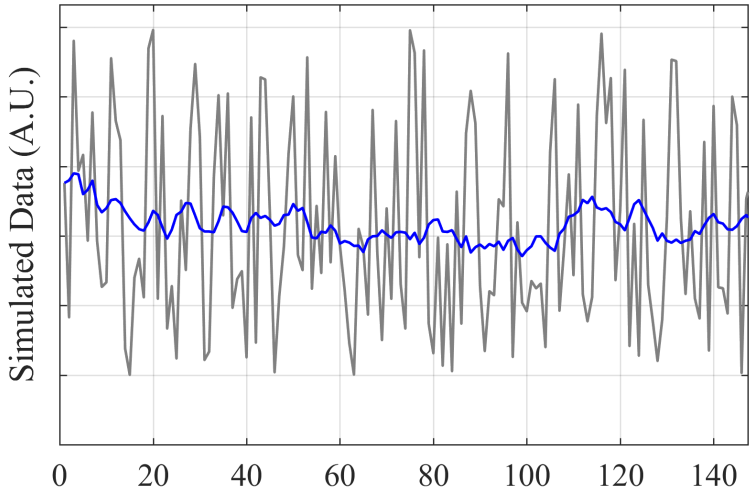
Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

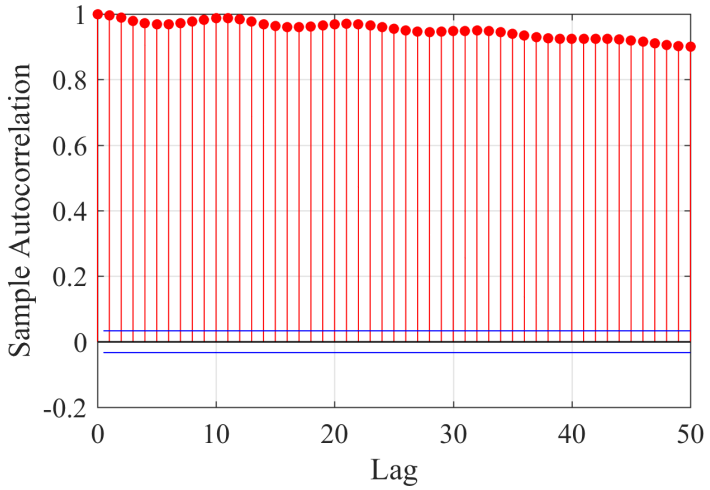
High fNIRS temporal resolution leads to significant autocorrelation

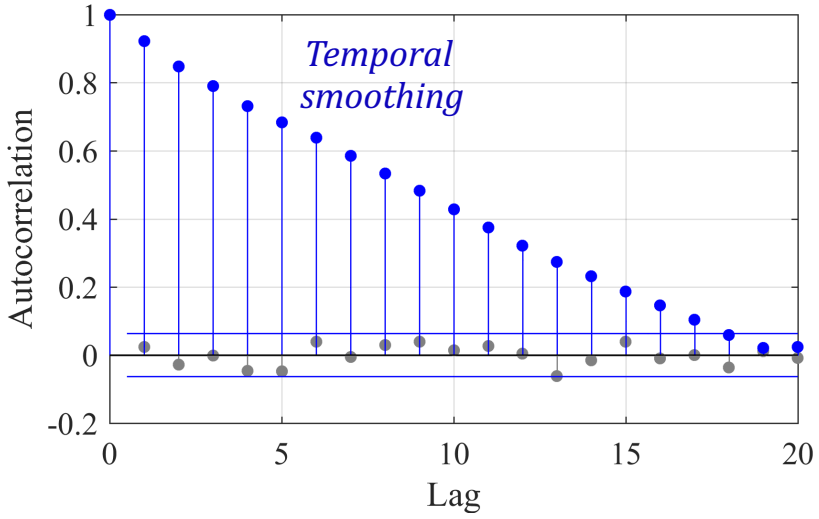
Typical fNIRS time series

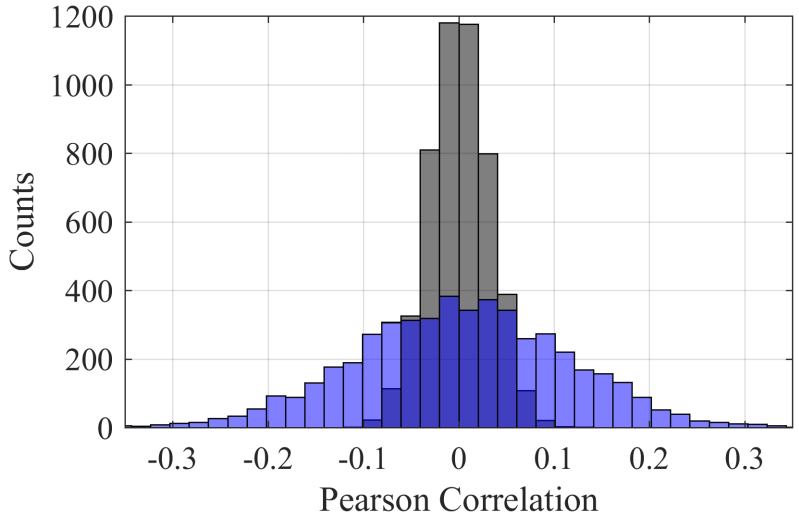




High autocorrelation leads to spurious Pearson correlation coefficients!







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Santosa et al., Neurophotonics (2017)
Baker et al., Biomedical Optics Express (2013)

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Pre-whitening as an autocorrelation filter

Autoregressive model

Order of the Model (can be determined empirically)

$$Y_t = \sum_{i=1}^{P} a_i Y_{t-i} + \nu_t$$

fNIRS Channel (HbO or HbR)

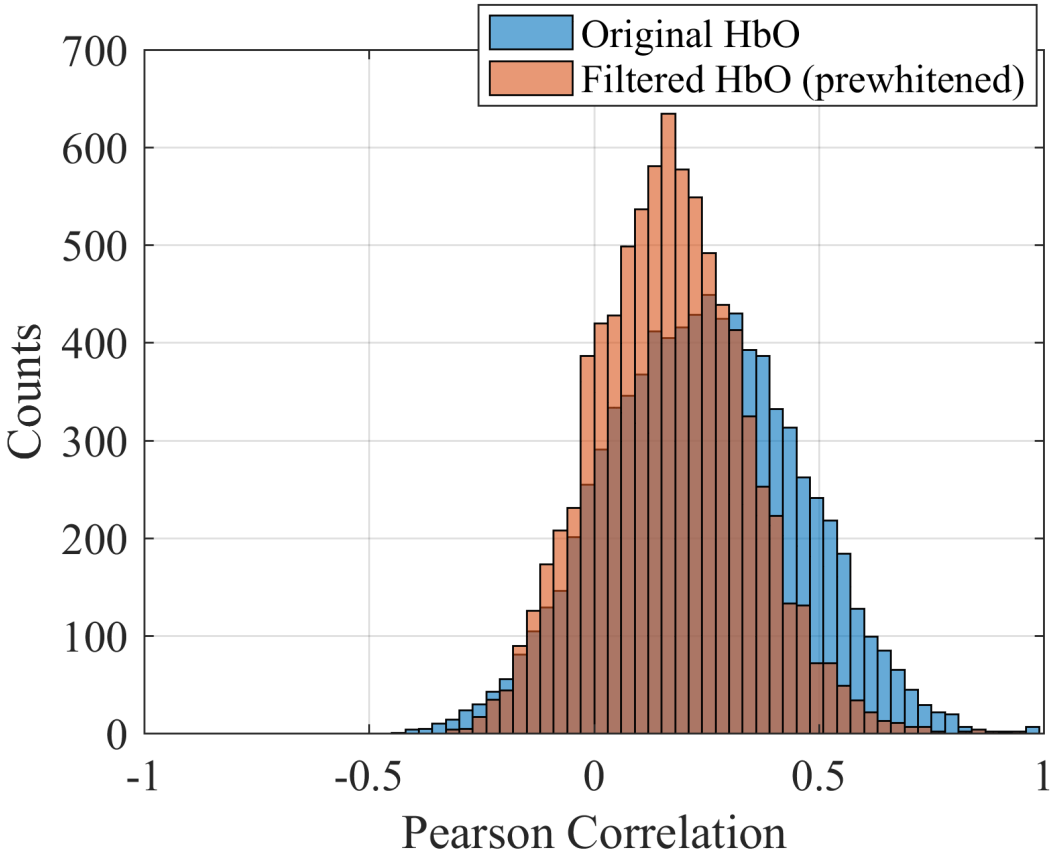
Filtering Coefficients

Innovation at time t

As an example, suppose a filter of order 3:

$$\begin{bmatrix} Y_4 \\ \vdots \\ Y_{t-1} \\ Y_t \end{bmatrix} = \begin{bmatrix} Y_3 & Y_2 & Y_1 \\ \vdots & \vdots & \vdots \\ Y_{t-2} & Y_{t-3} & Y_{t-4} \\ Y_{t-1} & Y_{t-2} & Y_{t-3} \end{bmatrix} \times \begin{bmatrix} a_1 \\ a_2 \\ a_3 \end{bmatrix} + \begin{bmatrix} \nu_4 \\ \vdots \\ \nu_{t-1} \\ \nu_t \end{bmatrix}$$

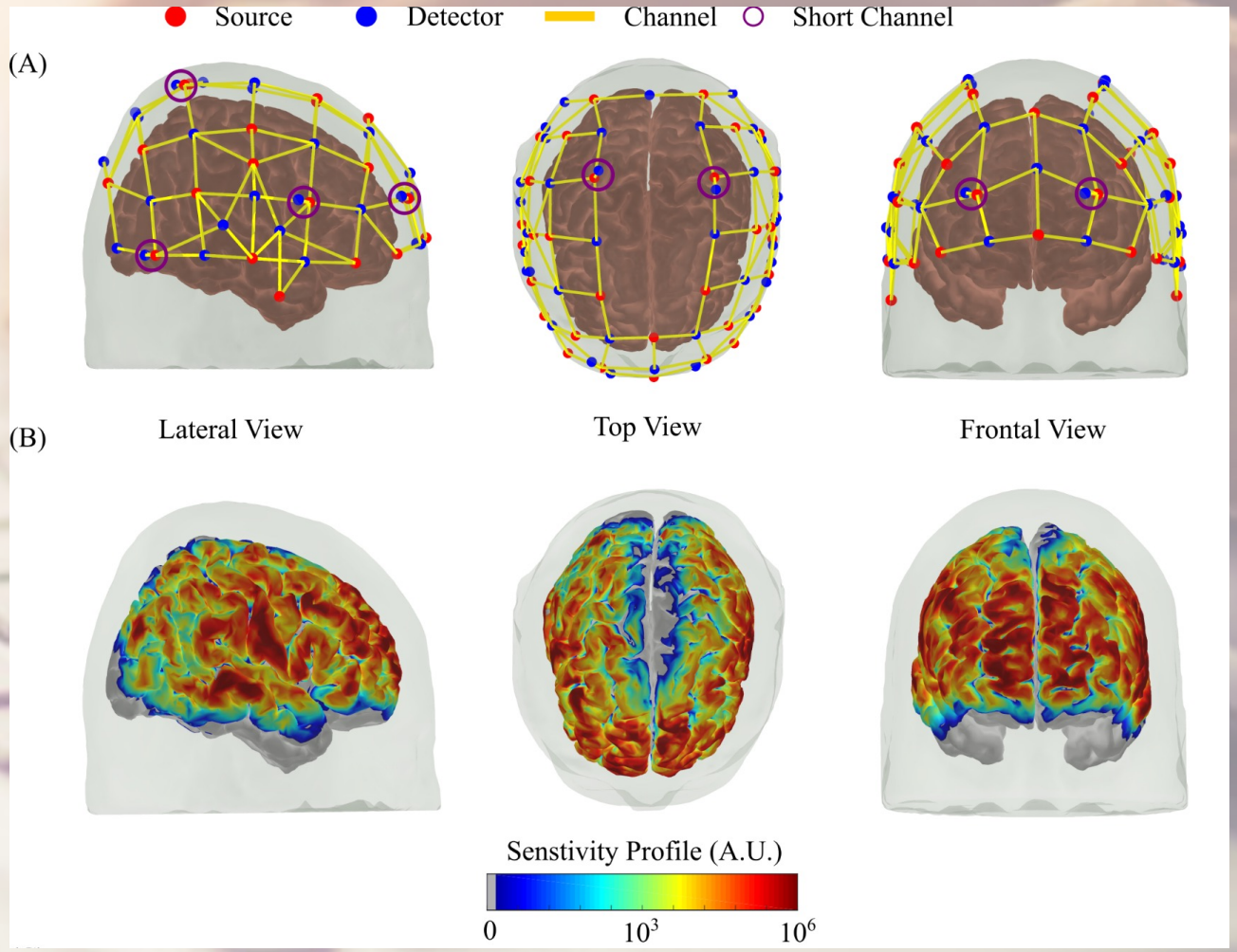
Effects of pre-whitening on HbO time-series during rs-FC



Santosa et al., Neurophotonics (2017)
Baker et al., Biomedical Optics Express (2013)

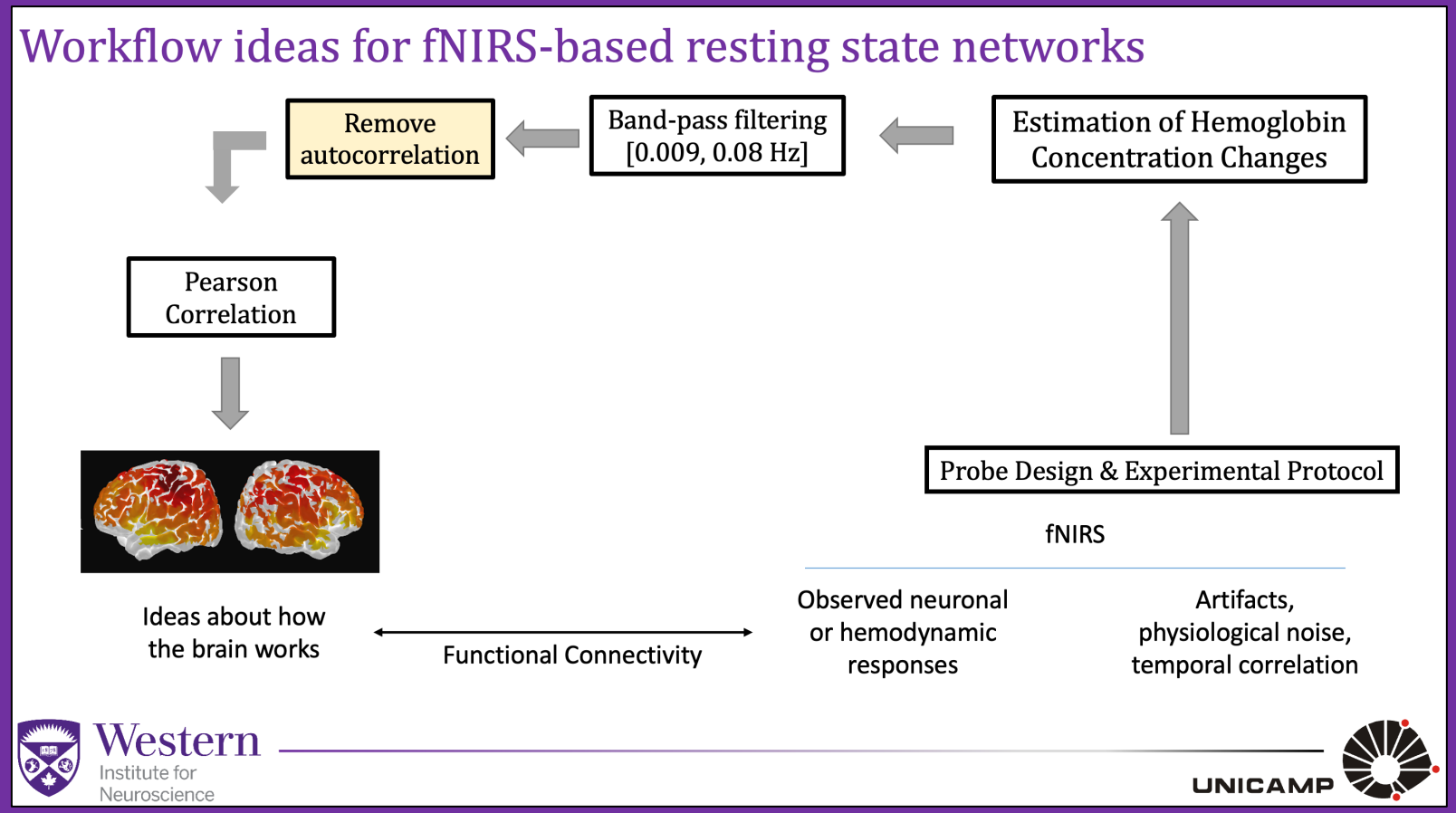
It's Your Turn Now!

- **One healthy subject, 12 min resting-state, sitting**
- **32 sources, 32 detectors**
- **Whole head, 121 regular and 8 short channels**
- **Mean arterial pressure, heart rate, and end-tidal CO_2 were also collected**



Hands-on #1

- Let's generate a very basic rs-FC matrix using the pipeline presented so far
- Run code: Part_1_fNIRS_course_2022_RestingState.m
- Investigate the difference of pre-whitened in these data



Workflow for extracting fNIRS-based resting state networks

Estimation of Hemoglobin Concentration Changes

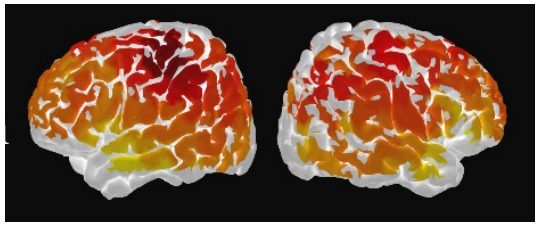
Band-pass filtering [0.009, 0.08 Hz]

Remove autocorrelation

Pearson Correlation

Motion Artifact Correction

Probe Design & Experimental Protocol



fNIRS

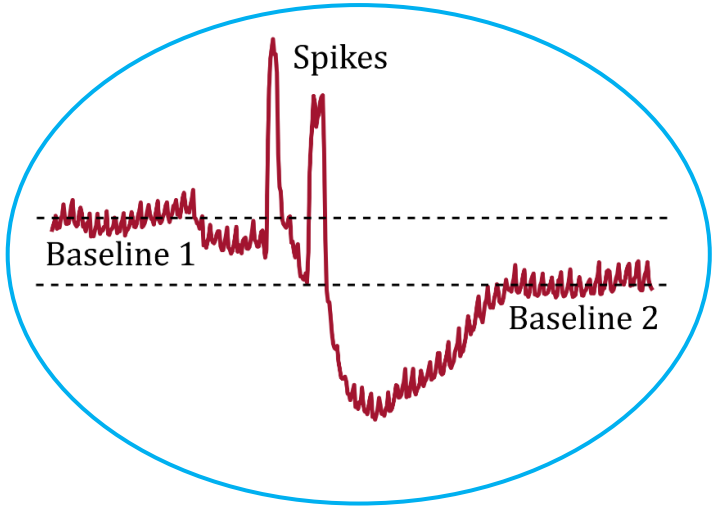
Ideas about how the brain works

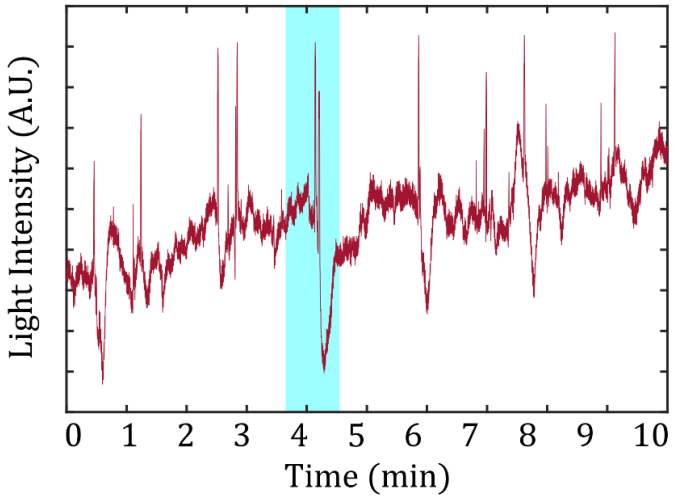
Functional Connectivity

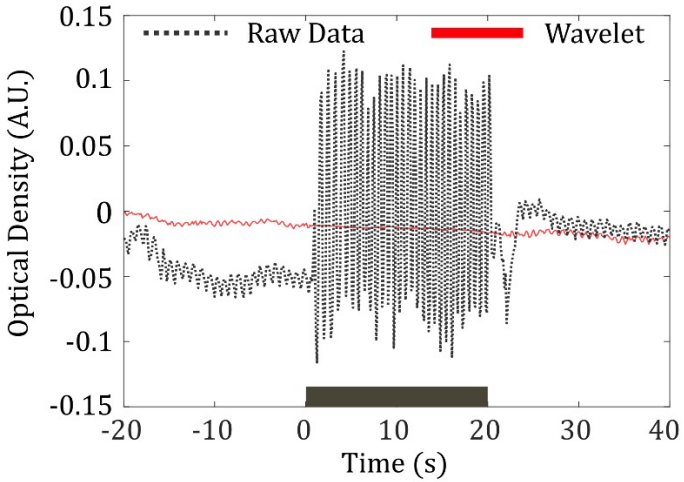
Observed neuronal or hemodynamic responses

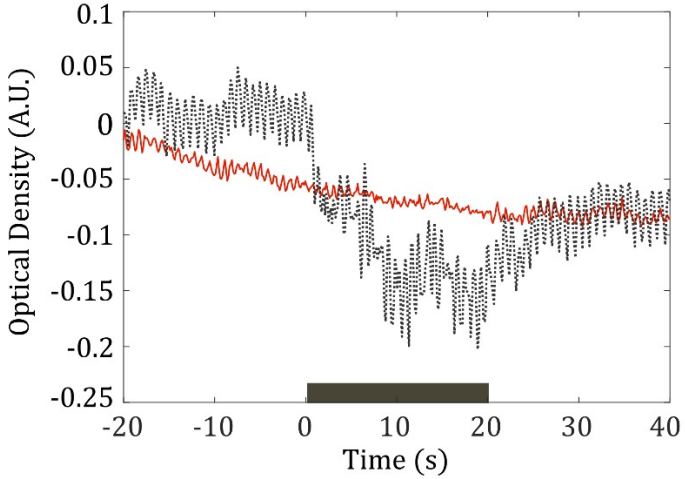
Artifacts, physiological noise, temporal correlation

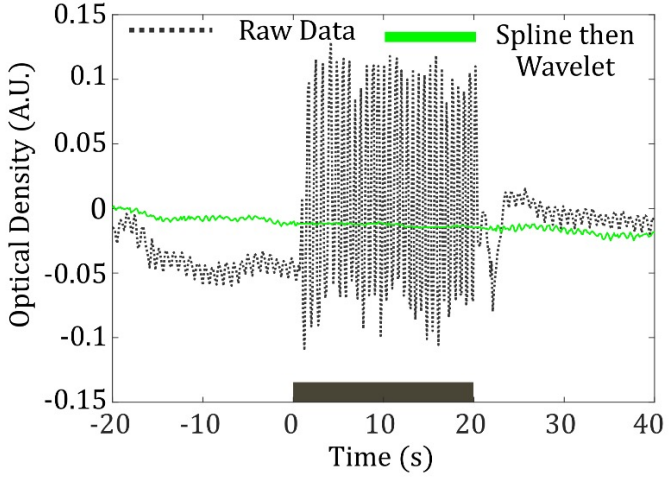
Motion artifacts in fNIRS data inflate correlation coefficients

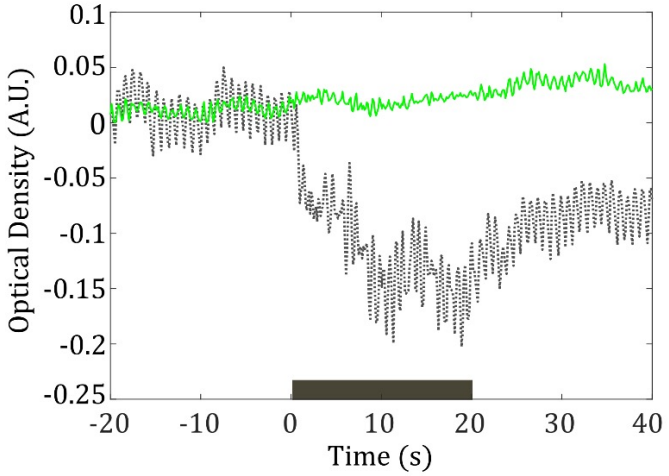












Novi et al., Neurophotonics (2020)

Hands-on #2

- Generate a basic rs-FC matrix using general pre-processing pipeline
- Run code: Part_1_fNIRS_course_2022_RestingState.m
- Uncomment motion correction section (line 40) and see the difference

```
dOD = Hybrid_motion_correction(dOD,SD);
```

Workflow for extracting fNIRS-based resting state networks

Estimation of Hemoglobin Concentration Changes

Band-pass filtering [0.009, 0.08 Hz]

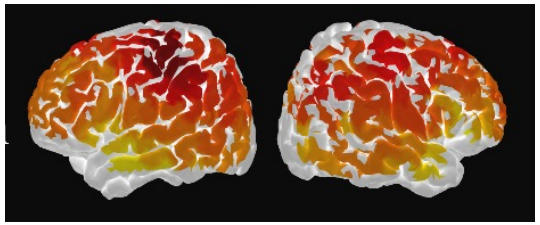
Remove autocorrelation

Pearson Correlation

Removal of systemic physiology

Motion Artifact Correction

Probe Design & Experimental Protocol



fNIRS

Ideas about how the brain works

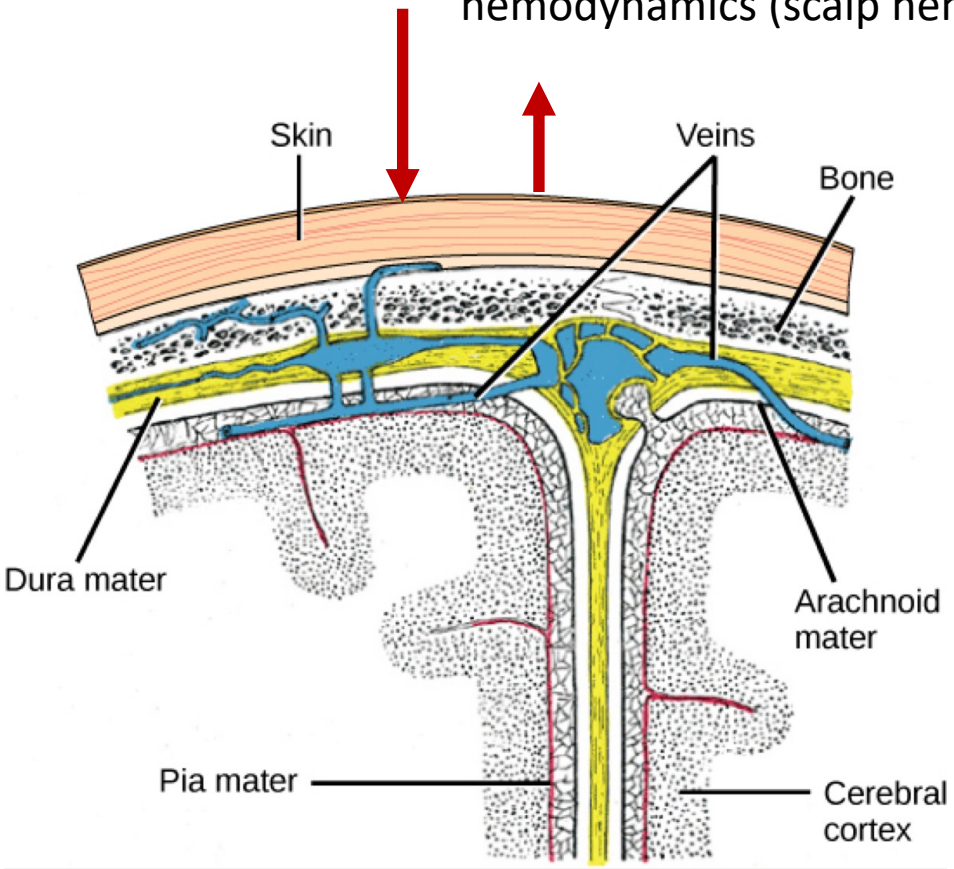
Functional Connectivity

Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

Extra-cortical Hemodynamics: The problem

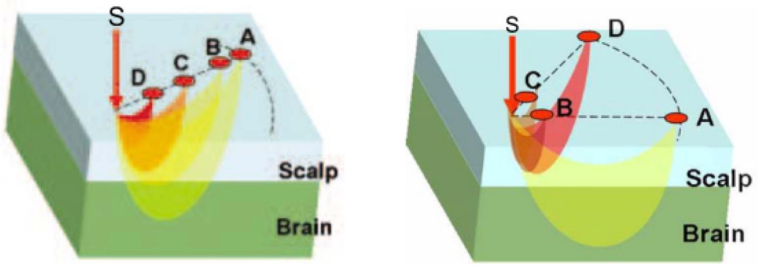
Intensity detected carries information about extra-cerebral hemodynamics (scalp hemodynamics, systemic physiology, etc.)



Source: Wikimedia Commons

Different approaches to deal with physiological "noise"

1. Use of short channels to measure extra-cerebral hemodynamics & regress it out from the "regular" fNIRS data



Saager & Berger, J. Biomed. Opt. (2008)

2. Use of independent physiological measurements (arterial pressure, EtCO2, etc.) : assumes all extra-cerebral hemodynamics is from global systemic physiology

3. Common Factor Analysis (e.g., PCA) : attempts to remove global signals based on the assumption that they exclusively reflect global systemic physiology

Solution 1: Short-Channel Regression within the GLM framework

Design Matrix

Residue

$$Y = \boldsymbol{X} \times \beta + \varepsilon$$

fNIRS Channel
(HbO or HbR)

Predicted signal
by SCs

$$Y_{filtered} = Y - \overbrace{\boldsymbol{X} \times \hat{\beta}}$$

Design Matrix for Short-Channel Regression:

1. Closest short channel;
2. Highest Correlation with the long channel;
3. First N (usually 2) Principal Components computed with all short channels;
4. Every short channel for both HbO and HbR.

$$\boldsymbol{X}_{Short} = [\underbrace{SC_1^{HbO}\ SC_2^{HbO}\ \dots\ SC_8^{HbO}}_{\textbf{HbO}}\ \underbrace{SC_1^{HbR}\ SC_2^{HbR}\ \dots\ SC_8^{HbR}}_{\textbf{HbR}}]$$

Solution 1: Short-Channel Regression

Model:

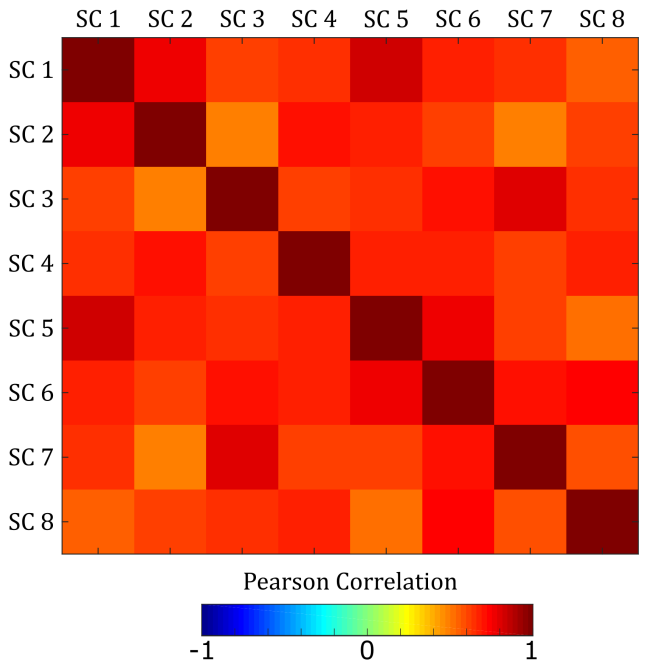
$$Y_{HbO} = [\boldsymbol{X}_C\ \boldsymbol{X}_{short}]\times\beta + \varepsilon$$

$$Y_{HbR} = [\boldsymbol{X}_C\ \boldsymbol{X}_{short}]\times\beta + \varepsilon$$

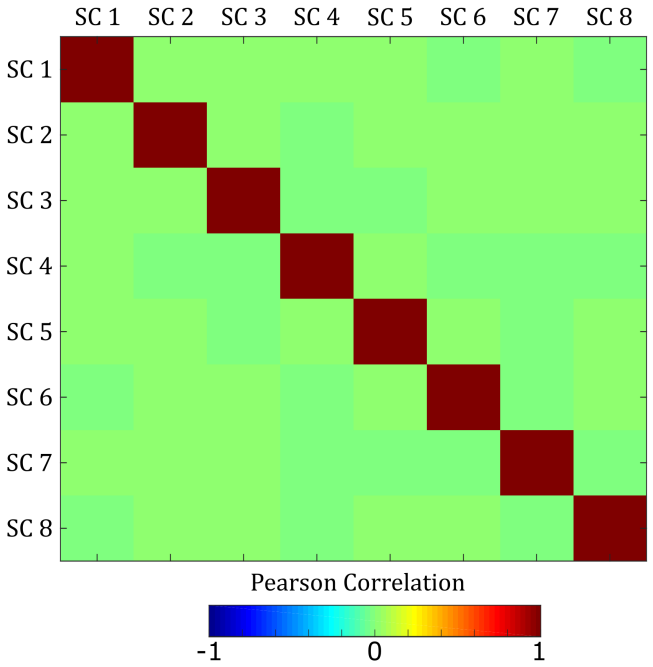
$$\boldsymbol{X}_{Short} = [\underbrace{SC_1^{HbO}\ SC_2^{HbO}\ \ldots\ SC_1^{HbR}\ SC_2^{HbR}\ \ldots SC_8^{HbR}}_{\text{only GOOD short channels}}]$$

Collinearity across short channels!

Oxy-hemoglobin



PCA in $\boldsymbol{X}_{Short}$



Santosa et al., Neurophotonics (2020)
Mumford et al., PloS One (2015)

Hands-on #3

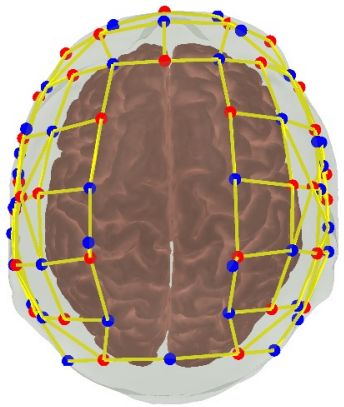
- Generate a basic rs-FC matrix using general pre-processing pipeline with short-channel regression
- Run code: Part_2_fNIRS_course_2022_RestingState.m
  - Use solution 1 (short channel regression)
  - Uncomment lines (16-18)

```
AdditionalRegressors = [];

[dc_only_SC,~] = PhysiologyRegression_GLM_fnirs_course...

   (dc,SD,SSlist,AdditionalRegressors);
```

Solution 2: Independent Physiological Measurements



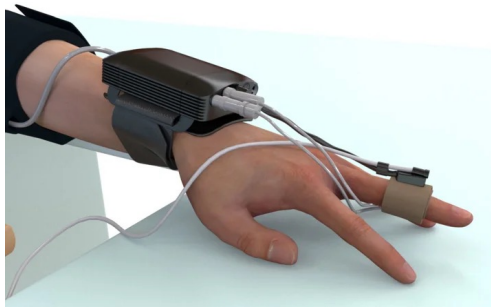
Sources

Detectors

Channels

- fNIRS measurements;
- 3.9 Hz.

Finapress



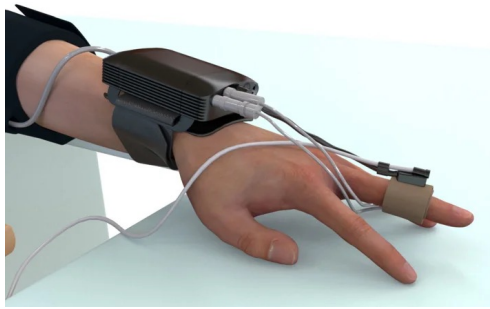
- Mean Arterial Pressure (MAP);
- Heart rate (HR);
- 200 Hz.

Capnograph

- End-tidal CO2;
- 4 Hz.

Phys Regression: $Y_{HbX} = [\boldsymbol{X}_C\ \boldsymbol{X}_{Phys}] \times \beta + \varepsilon$ $\boldsymbol{X}_{Phys}: [MAP, HR, CO_2]$

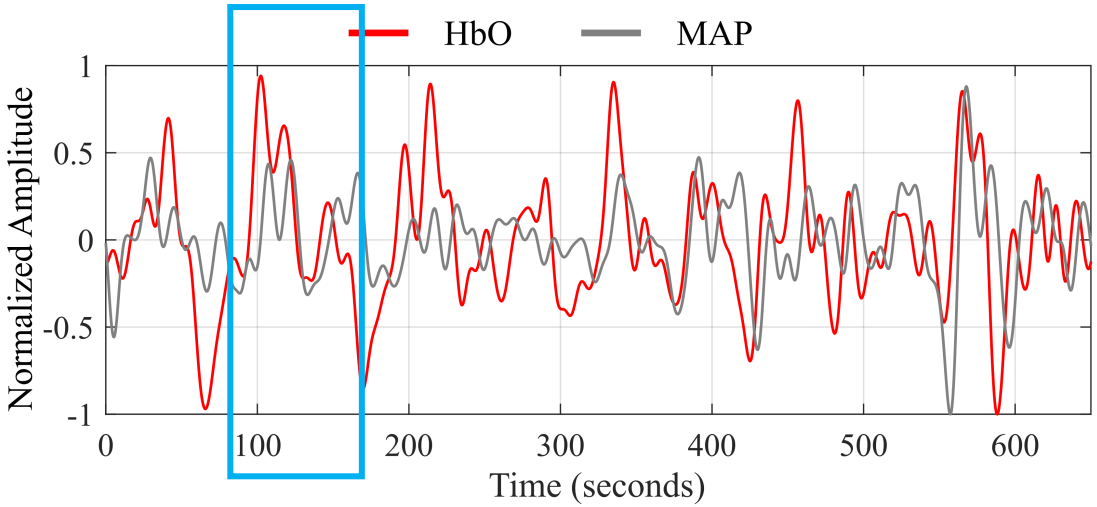
Solution 2: Correcting for different transit times

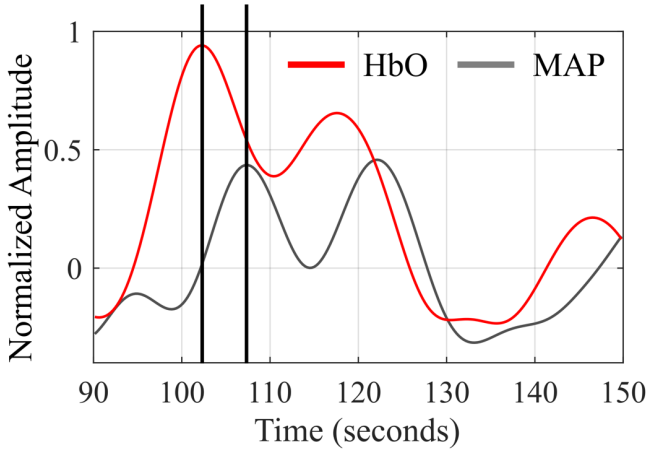


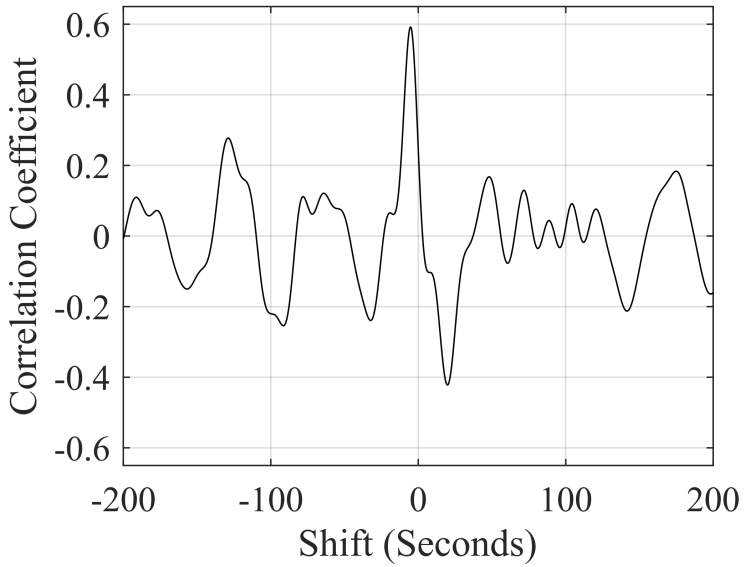
MAP and HR

CO2

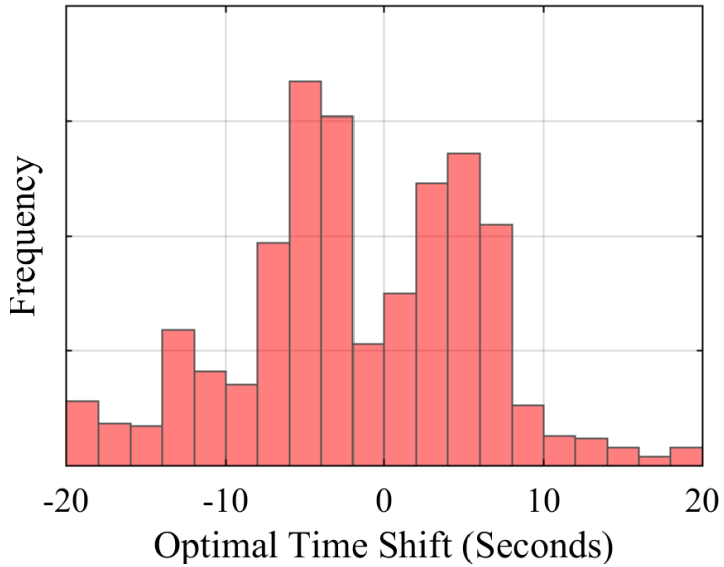
MATLAB function:
"xcorr"







HbO *vs* MAP



Mesquita et al., Biomedical Optics Express (2010)
Tong et al., Journal of Biomedical Optics (2012)

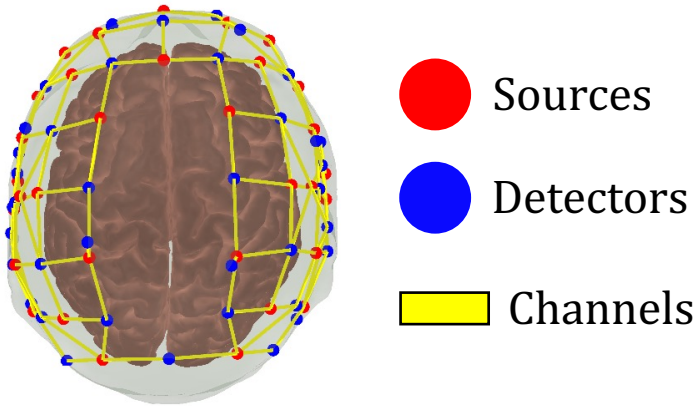
Hands-on #4

- Generate a basic rs-FC matrix using general pre-processing pipeline plus regressing independent physiological measurements

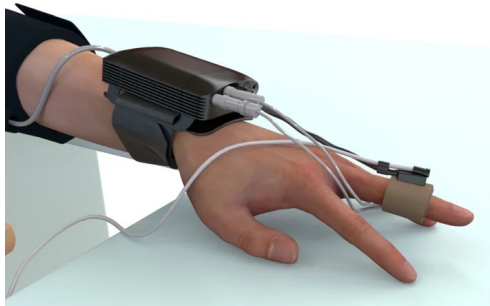
- Run code: Part_2_fNIRS_course_2022_RestingState.m
  - Uncomment solution 2 (independent physiological measurements)
  - Lines 21-23

```
AdditionalRegressors = Phys_data;
[dc_only_Phys,~] = PhysiologyRegression_GLM_fnirs_course...
   (dc,SD,[],AdditionalRegressors);
```

If you have SCs and independent physiological information, you can combine both approaches



Finapress



Capnograph

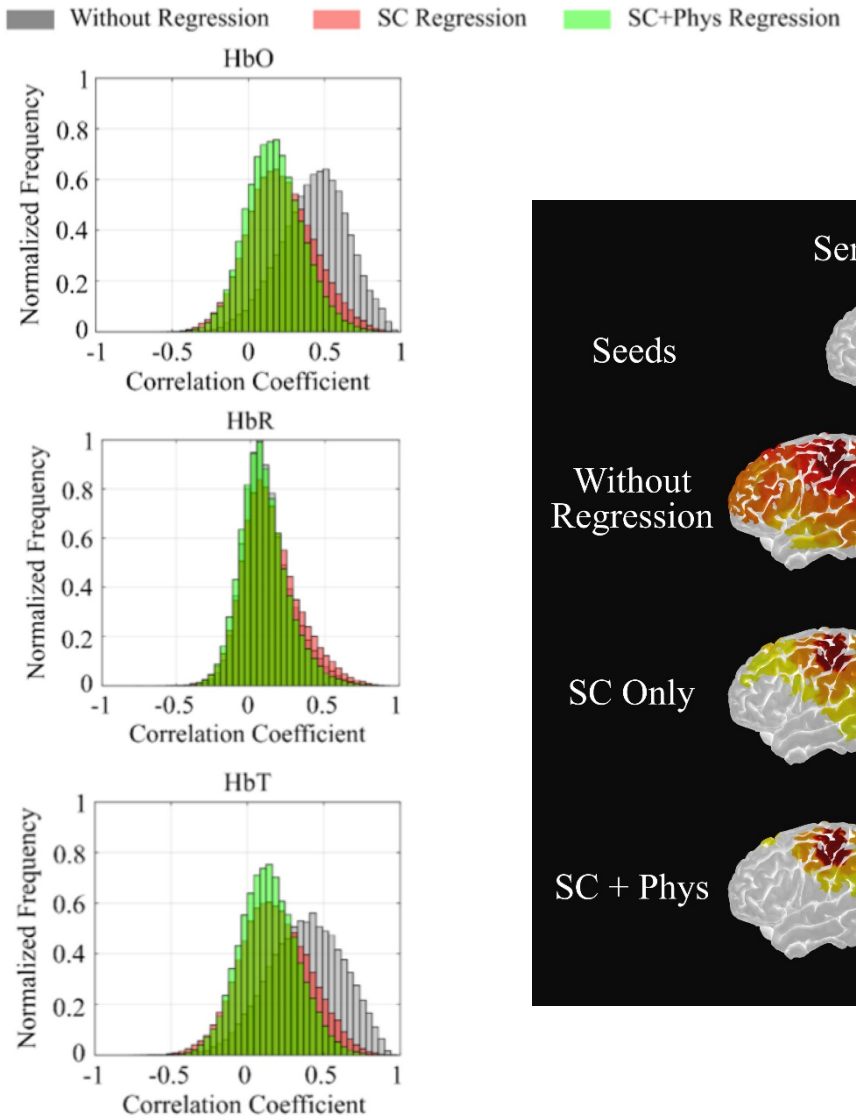
SC + Phys Regression: $Y_{HbX} = [\boldsymbol{X}_C\ \boldsymbol{X}_{Short}\ \boldsymbol{X}_{Phys}] \times \beta + \varepsilon$

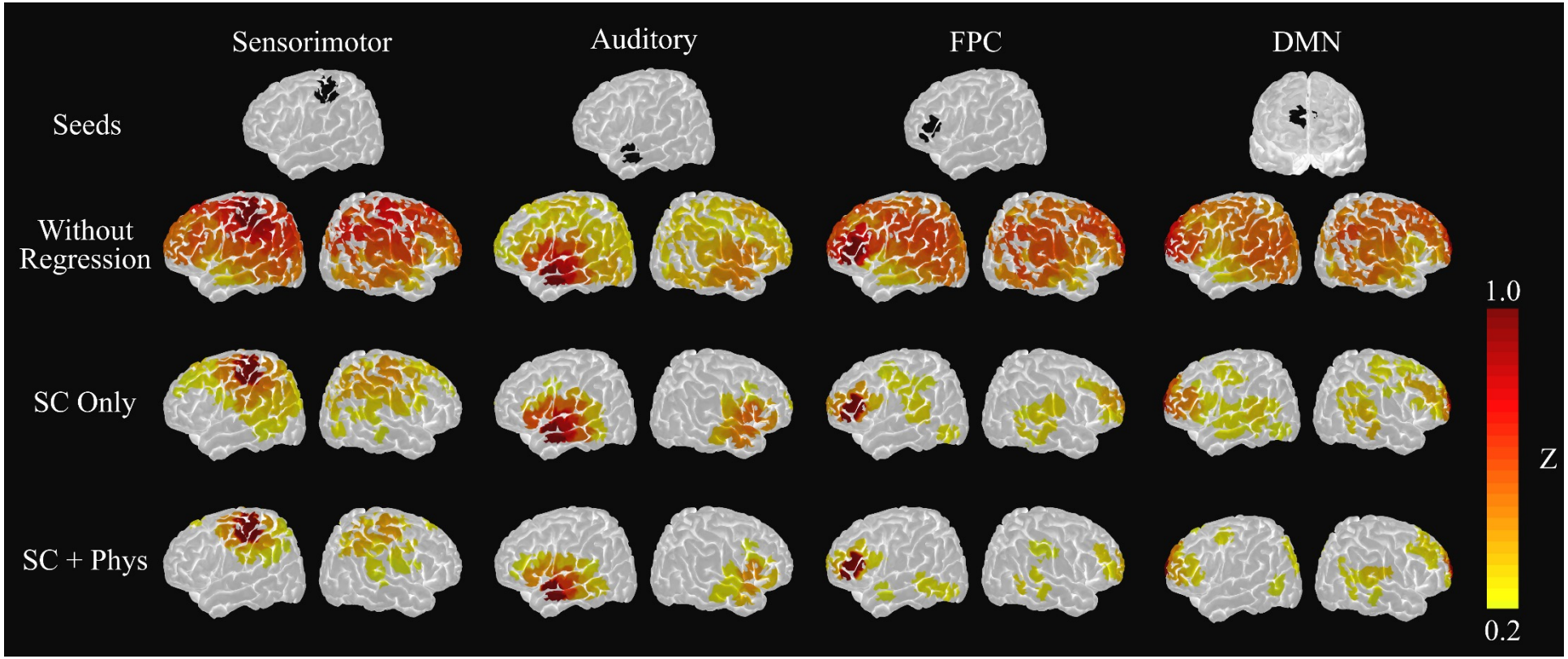
$\boldsymbol{X}_{Phys}$: $[MAP, HR, CO_2]$

$$\boldsymbol{X}_{Short} = [\underbrace{SC_1^{HbO}\ SC_2^{HbO} \ldots SC_1^{HbR}\ SC_2^{HbR} \ldots SC_8^{HbR}}_{\text{Include HbO and HbR short channels}}]$$

Abdalmalak & Novi et al., Frontiers in Neuroscience (2022)

Solution 3: Short channels + Additional Physiological Measurements





Abdalmalak & Novi et al., Front. Neuroscience (2022)

Solution 4: Principal Component Analysis (PCA) as proxy of global systemic noise

$$Y_{HbX} = [\boldsymbol{X}_C\ \boldsymbol{X}_{Sh}\ \boldsymbol{X}_{Phys}]\times\beta + \varepsilon$$

What can we do if additional measurements are not available?

1. Global Signal Regression:

$$\boldsymbol{X}_{globalSignal}(t) = \frac{1}{N}\sum_{i=1}^{N} Y_i\,(t)$$

$$Y_{HbX} = [\boldsymbol{X}_C\ \boldsymbol{X}_{globalSignal}]\times\beta + \varepsilon$$

2. Principal Component Analysis:

$$PC_1 = \alpha_1 Y_1 + \alpha_2 Y_2 + \alpha_3 Y_3 \ldots \alpha_N Y_N = \sum_{i=1}^{N} \alpha_i Y_i$$

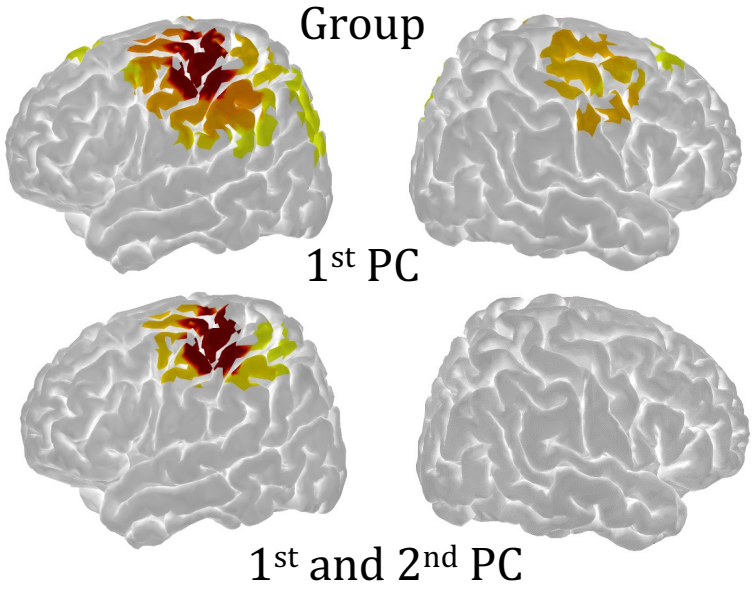
Linear Combination of each channel that maximizes the variance across channels.

$$PC_2 = \beta_1 Y_1 + \beta_2 Y_2 + \beta_3 Y_3 \ldots \beta_N Y_N = \sum_{i=1}^{N} \beta_i Y_i$$

Santosa et al., 2020 Neuroph.
Carbonell et al., 2011 Brain Connect.

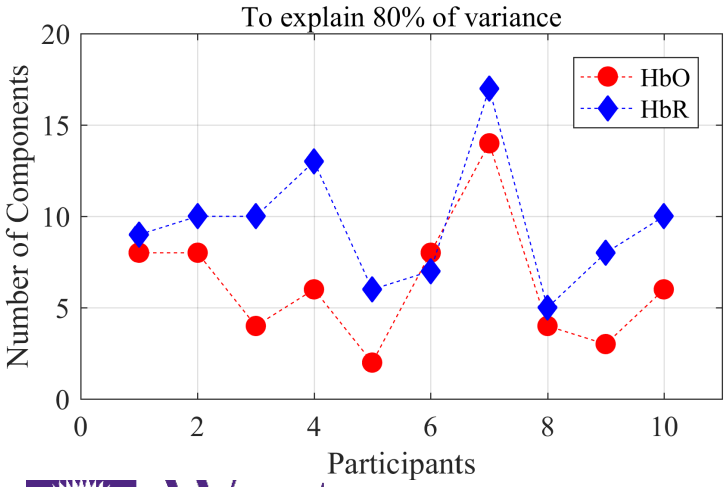
Zhang et al., 2005 J. Biom. Opt.

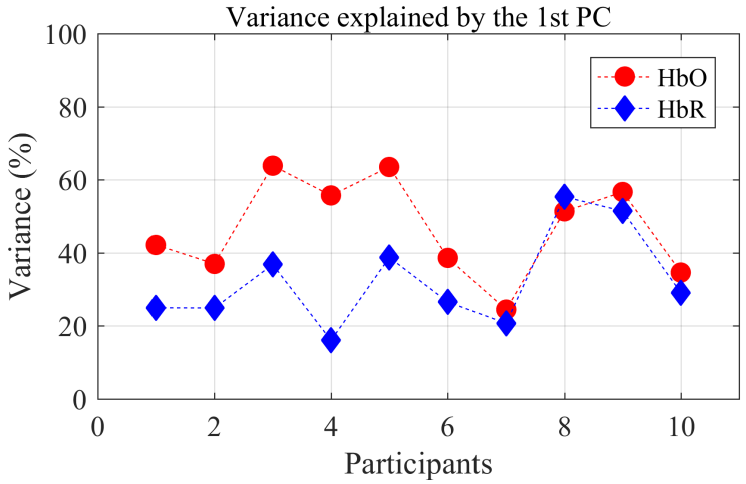
Solution 4: Principal Component Analysis (PCA) as proxy of global systemic noise

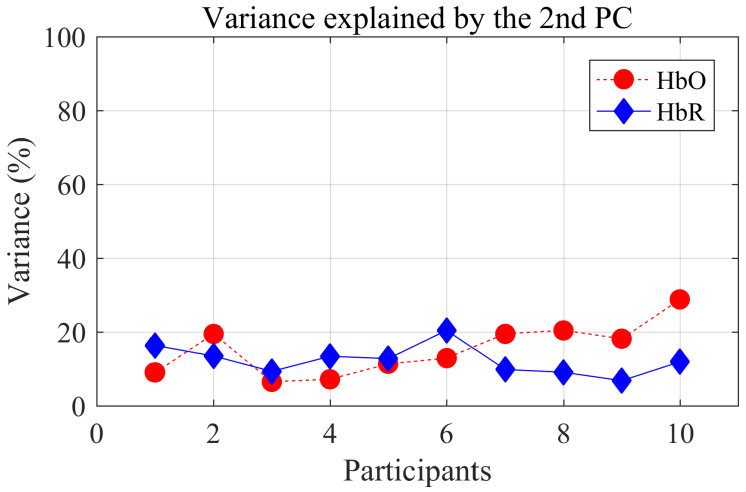


More details about PCA:

- PCA is applied separately for HbO and HbR;
- PCA is available at Homer2 package ("enPCAFilter").
- The user can define the **number of componets** directly or based on the **amount of variance** that the combined PCs represents.







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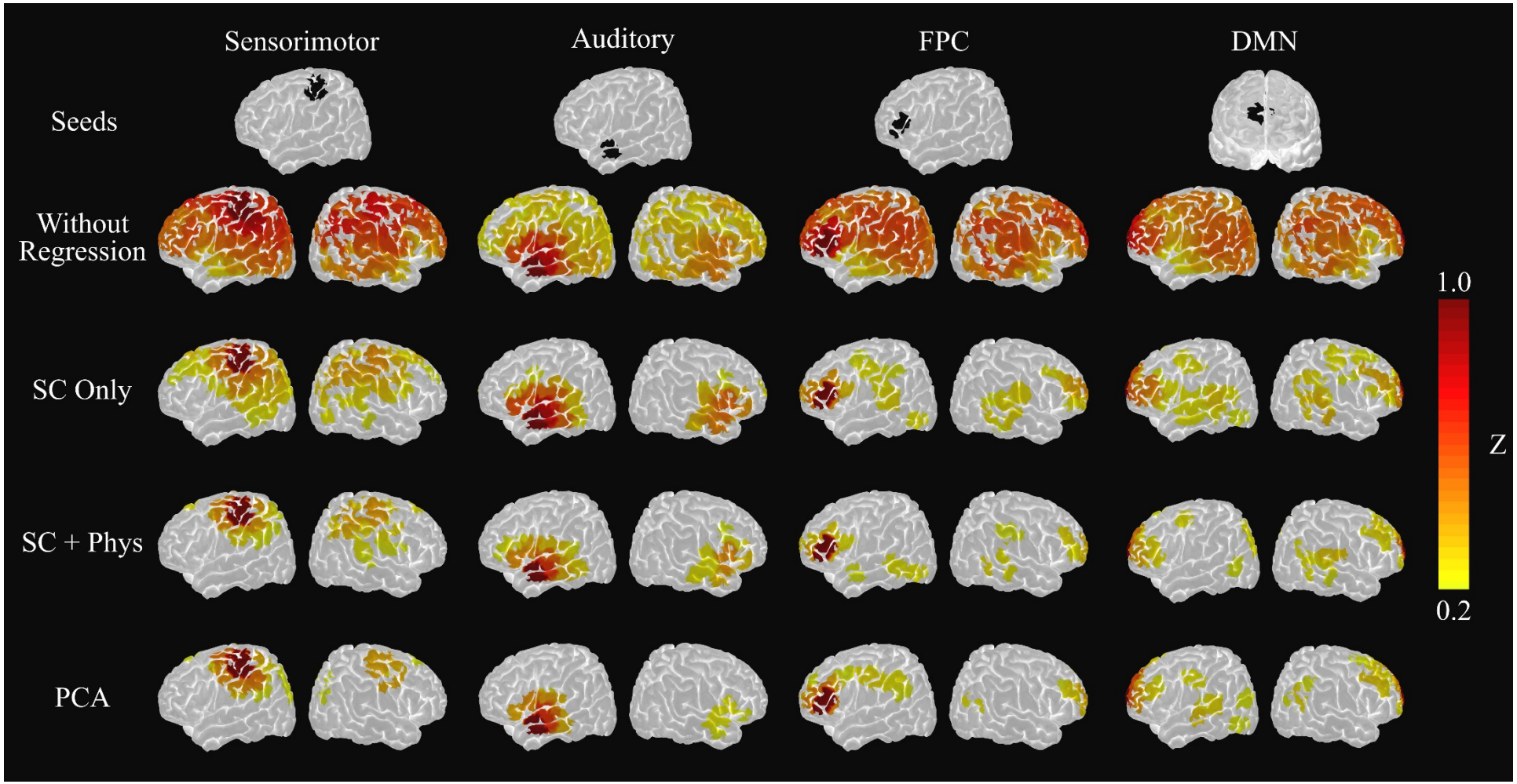
Hands-on #6

- Generate a basic rs-FC matrix using general pre-processing pipeline with PCA

- Run code: Part_2_fNIRS_course_2022_RestingState.m
  - Uncomment solution 4 (Employ PCA to remove the 1st component)
  - Lines 31-33

```
nSV = [1 1];
[dc_pca_one] = Perform_pca_regression_fnirs_course...
   (dc,SD,nSV,BadChannels);
```

Group Comparison with different approaches



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Abdalmalak & Novi et al., Front. Neuroscience (2022)

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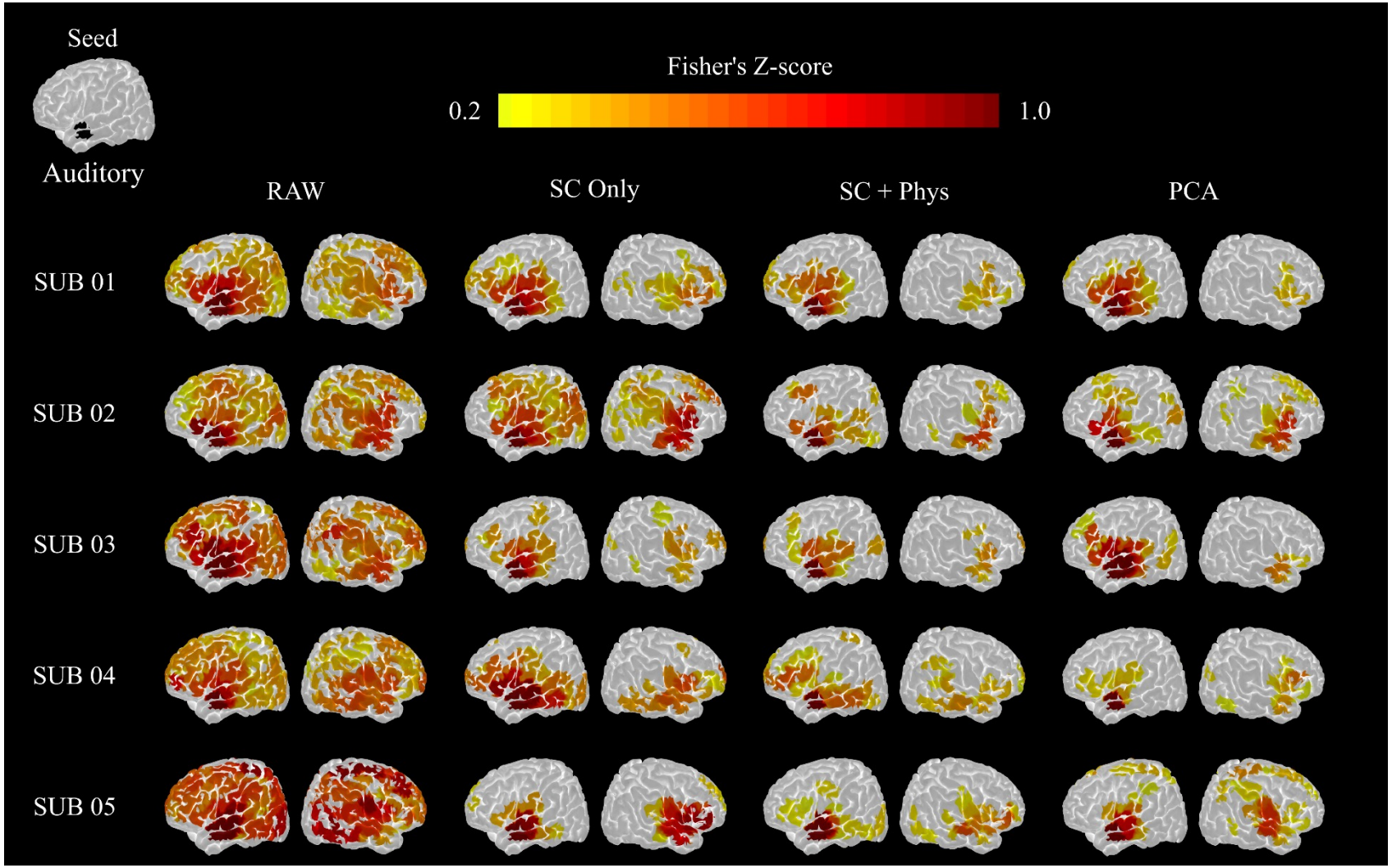
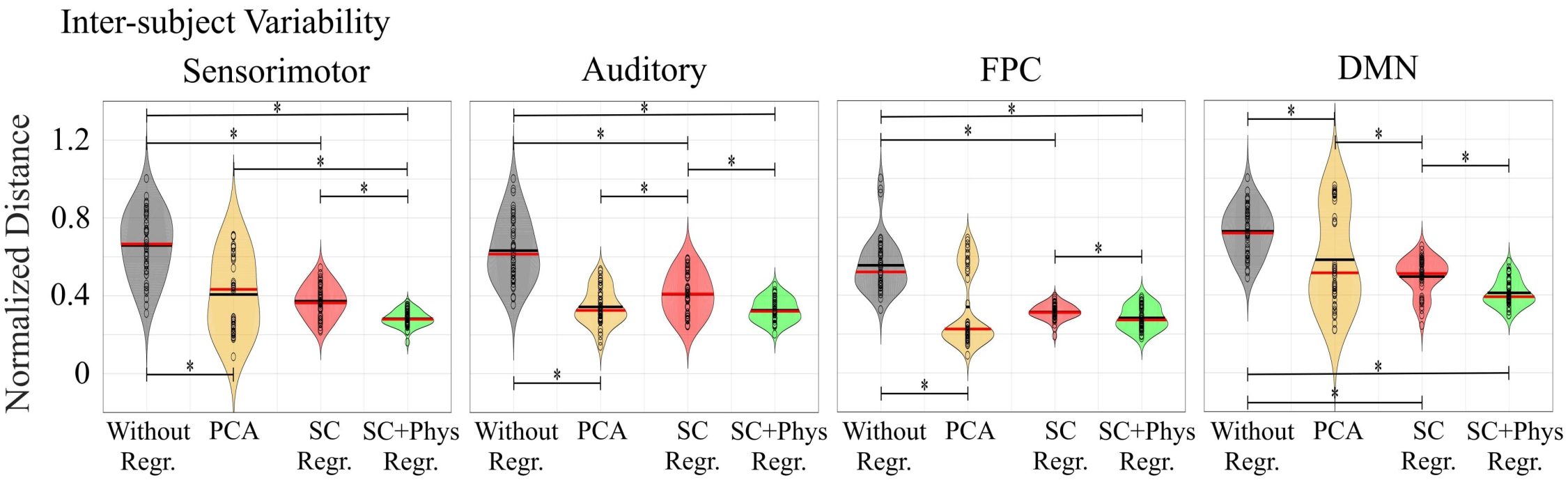
Networks tend to become localized for “better” approaches
PCA does not perform badly in group comparisons



Abdalmalak & Novi et al., Front. Neuroscience (2022)

Inter-subject variability for each approach



Abdalmalak & Novi et al., Front. Neuroscience (2022)

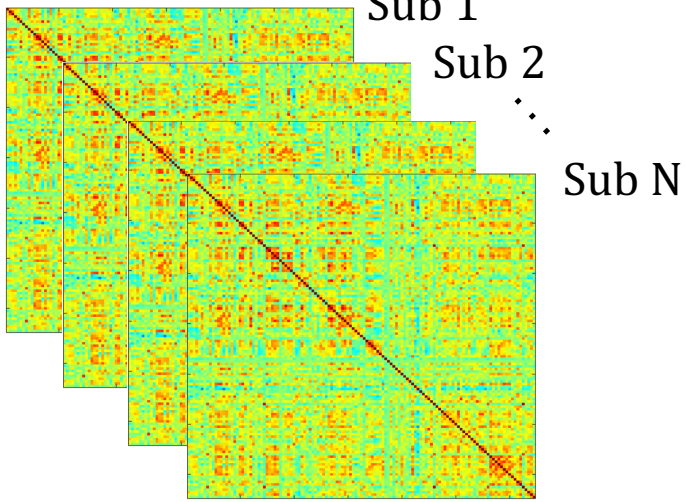
Group Analysis in Seed-based Resting State Networks

Individual Level (First Level Analysis)

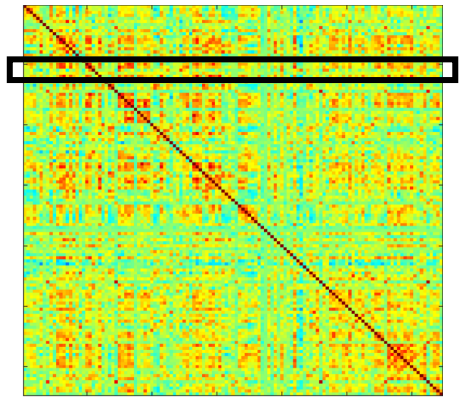
HbT = HbO + HbR (Prewhitenned)

Pearson Correlation for each Hemoglobin separately

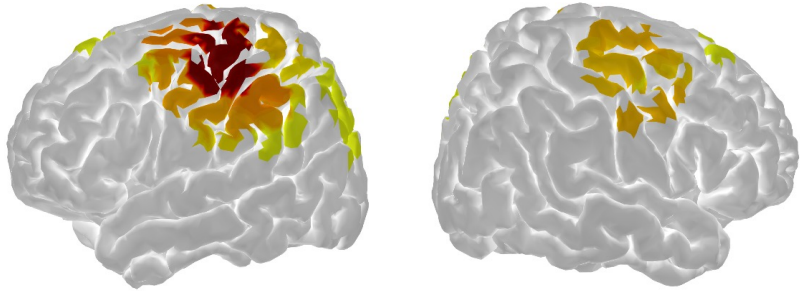
Compute Z-scores via Fisher's transformation



Z-scores Matrices for each Hemoglobin



Project in the brain



Graphs

Workflow for extracting fNIRS-based resting state networks

Removal of autocorrelation

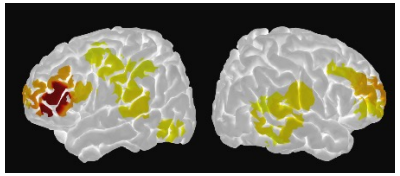
Band-pass filtering [0.009, 0.08 Hz]

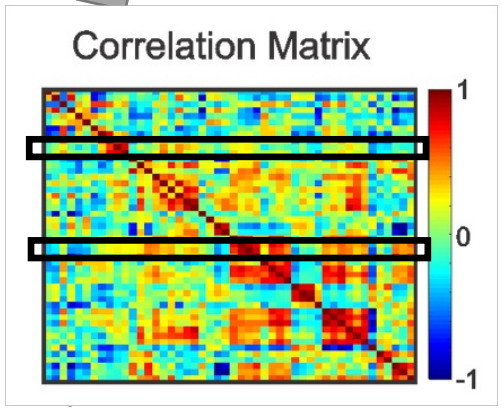
Estimation of Hemoglobin Concentration Changes

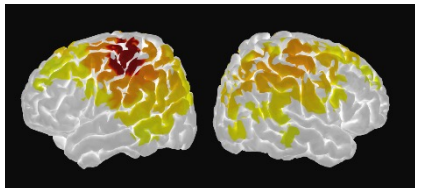
Pearson Correlation

Removal of systemic physiology

Motion Artifact Correction







Probe Design & Experimental Protocol

fNIRS

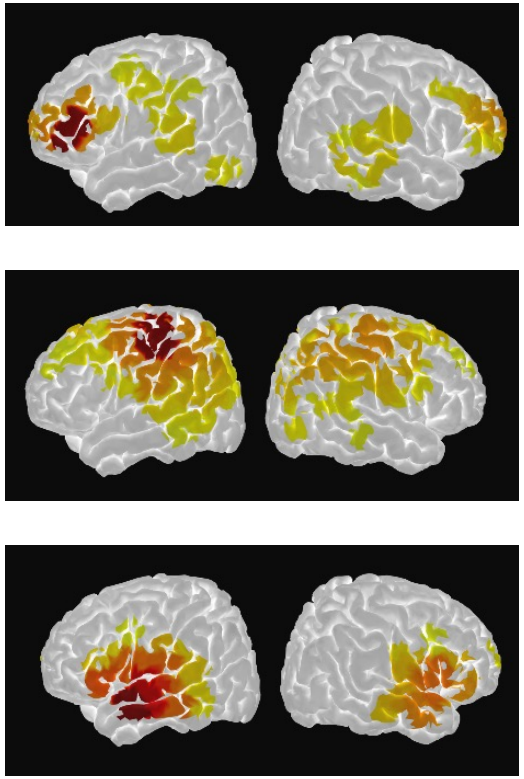
(separate) ideas about how the brain works

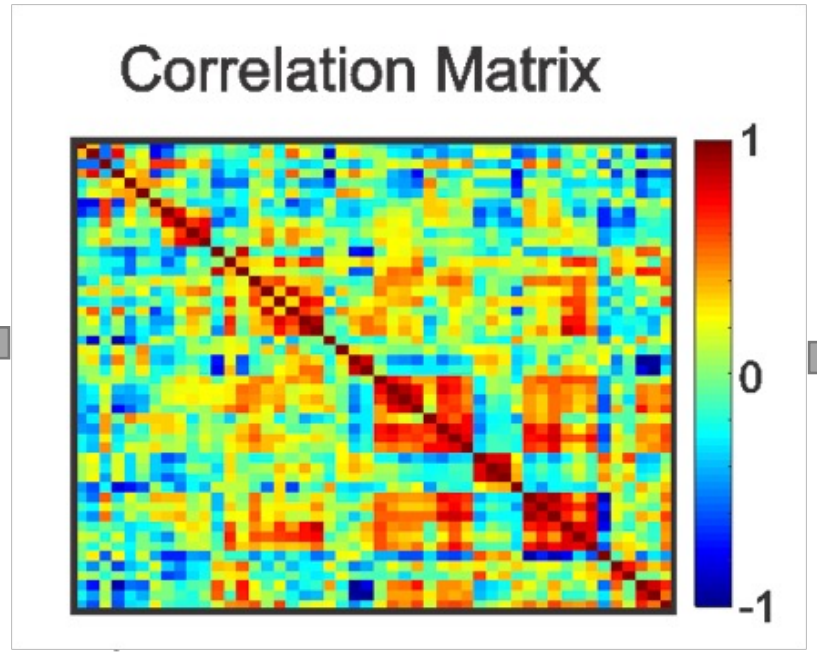
Functional Connectivity

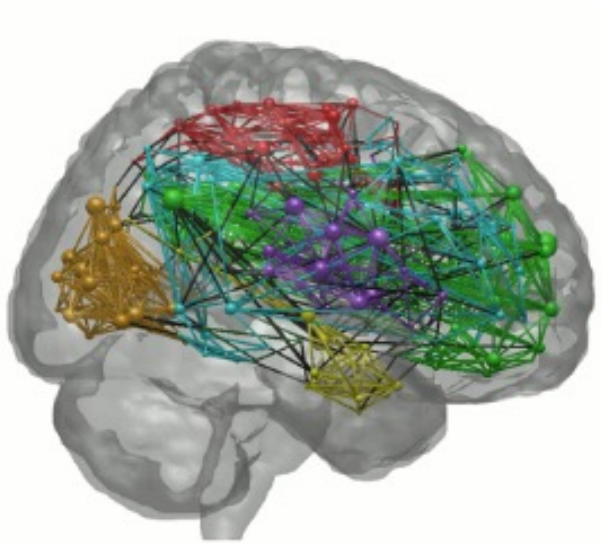
Observed neuronal or hemodynamic responses

Artifacts, physiological noise, temporal correlation

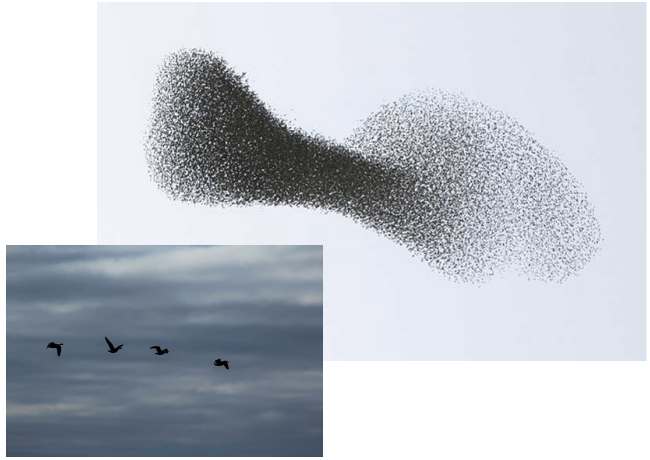
From functional connectivity to graphs







COMPLICATED

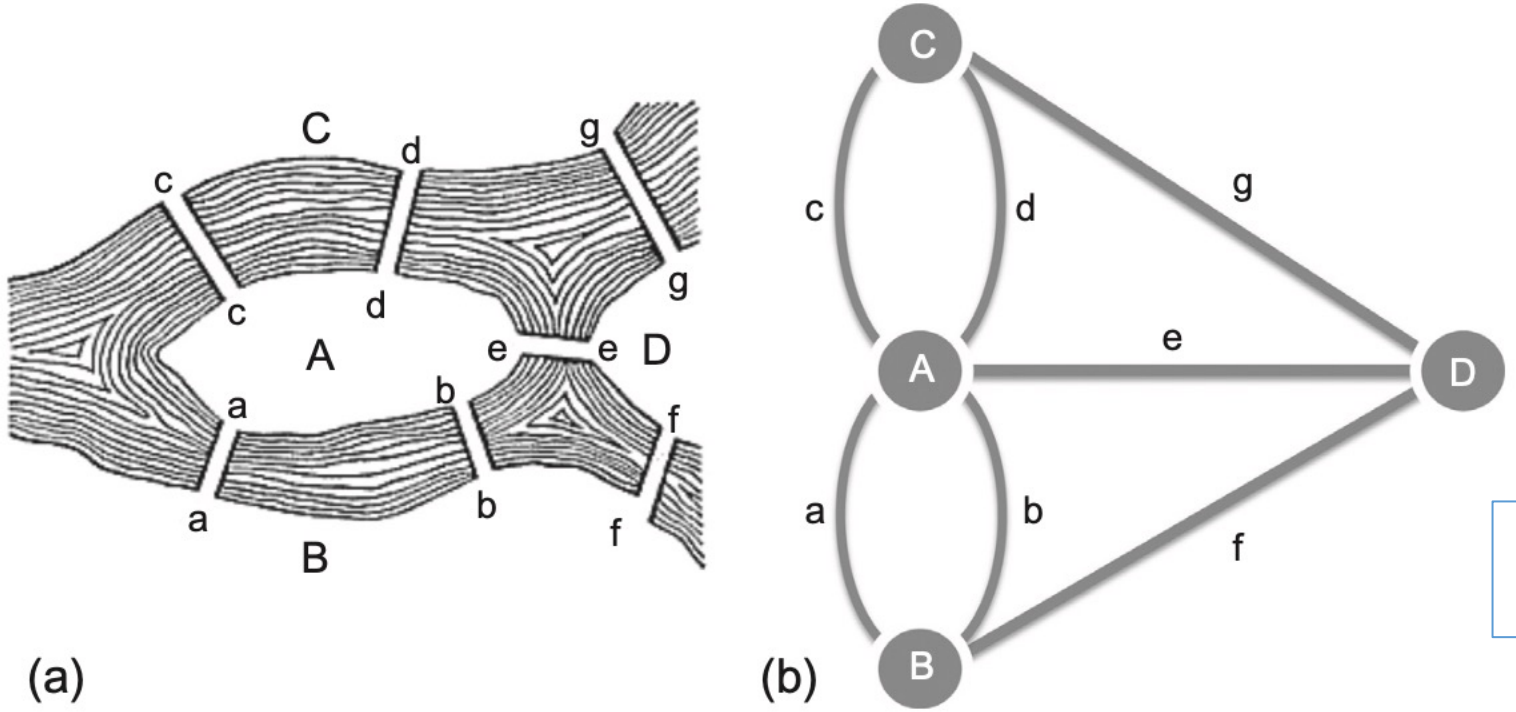


COMPLEX

What is a graph?

Euler's problem (1735)

Is it possible to walk around Königsberg (Kaliningrad) in a way that crossed each bridge once and only once?



Solution

- It is **NOT** on the details of the problem (length of the bridges, physical distance between them, etc.)
- It depends on the organization of the links between the nodes (*topology*)

Topological properties do not depend on any spatial transformation of the system

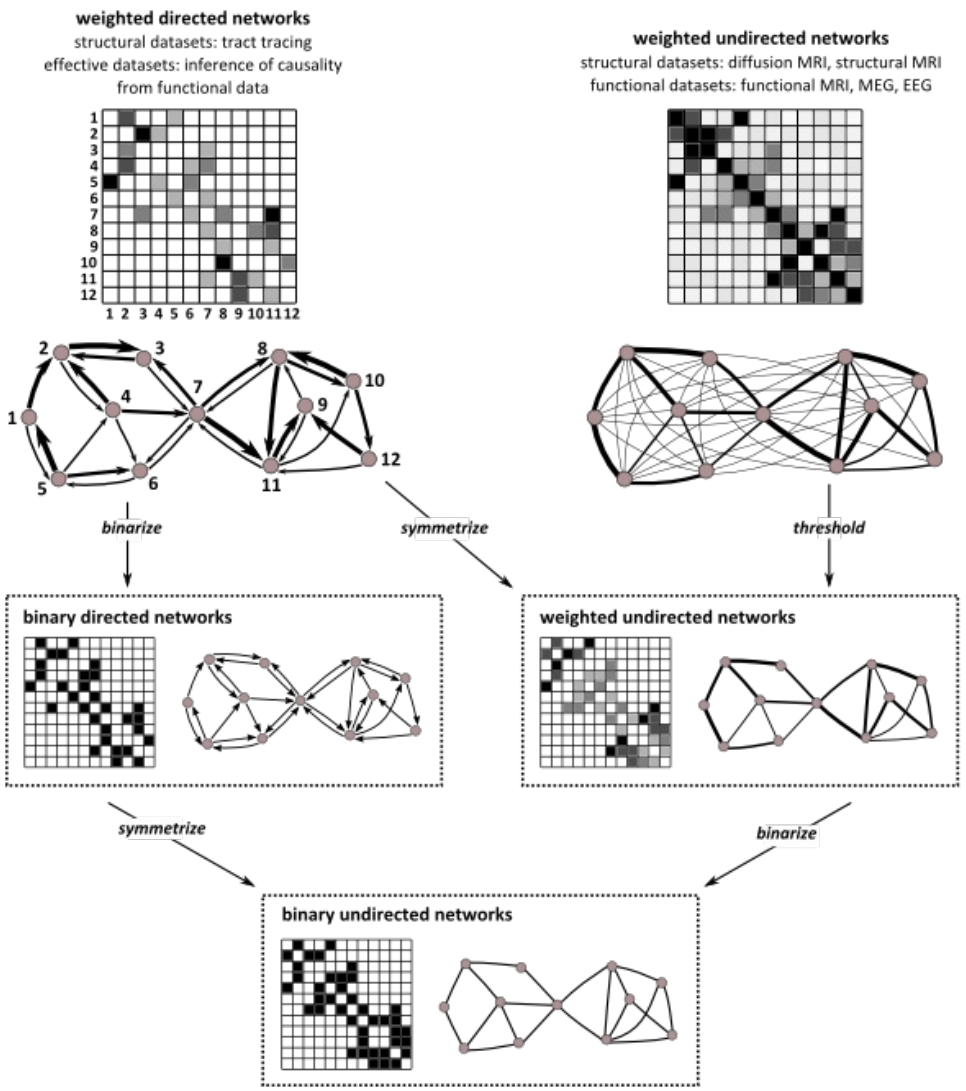
Graph Characteristics & Features

Graph Construction

- Link Strength: Binary vs. Weighted
- Directionality: Directed vs. Undirect
- Information: Homogeneous vs. Heterogeneous nodes/links

Topological Properties

- Connectiveness: How the nodes are connected
- Centrality: how connections are distributed in the graph
- Navigation: how information flows in the graph
- Wiring: are there wiring patterns?

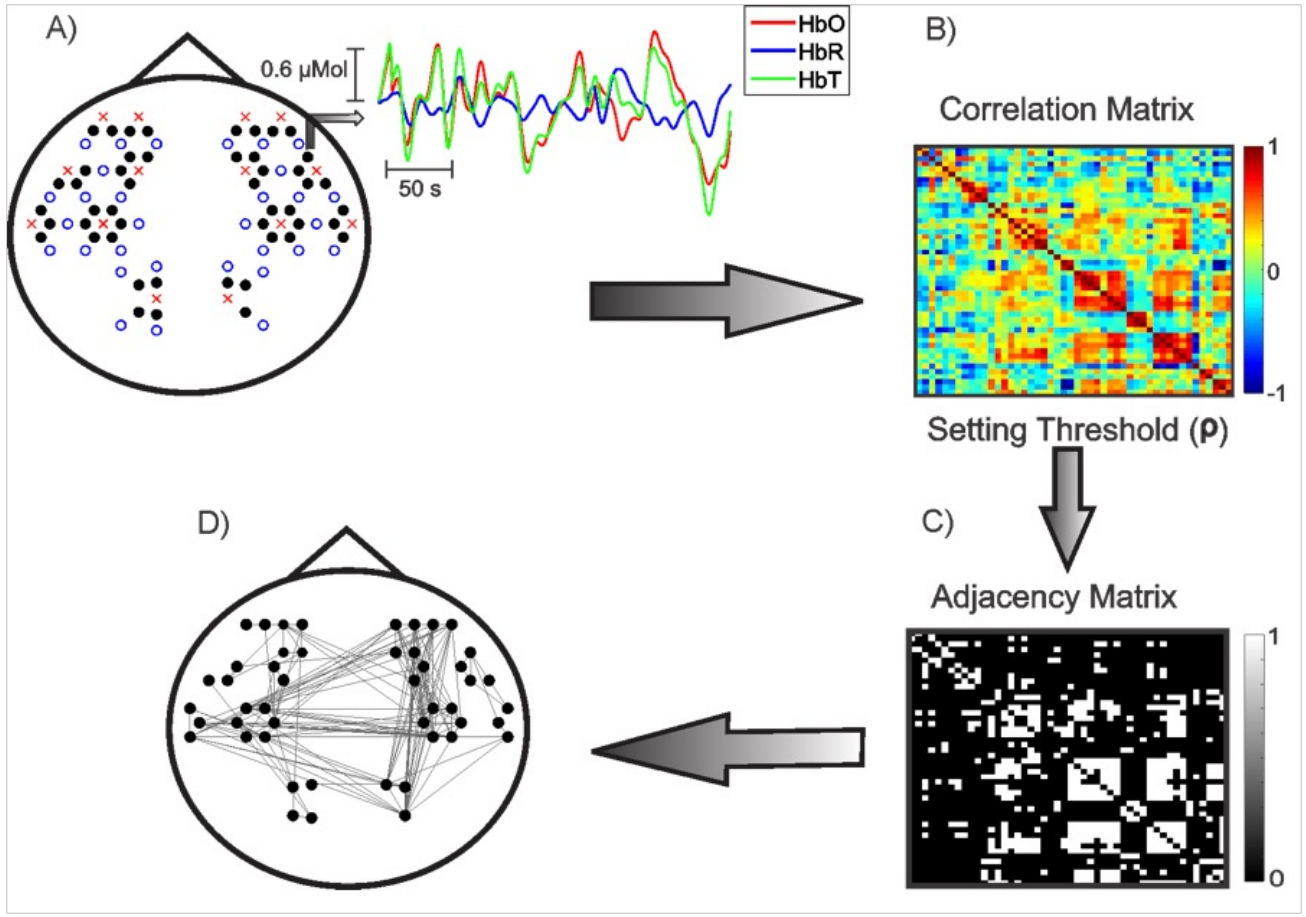


Rubinov & Sporns, NeuroImage (2010)

Resting-state Functional Connectivity Graphs with fNIRS

What do nodes & links represent in your data/technique/measurement?

- Hemodynamics
- Spatial Information



Nodes

Part of the system one has information from.

Links

Something that connects two nodes and represent their interaction in the system

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Novi, Rodrigues & Mesquita, Biomed. Opt. Express (2016)
H Niu et al., Plos One (2012)

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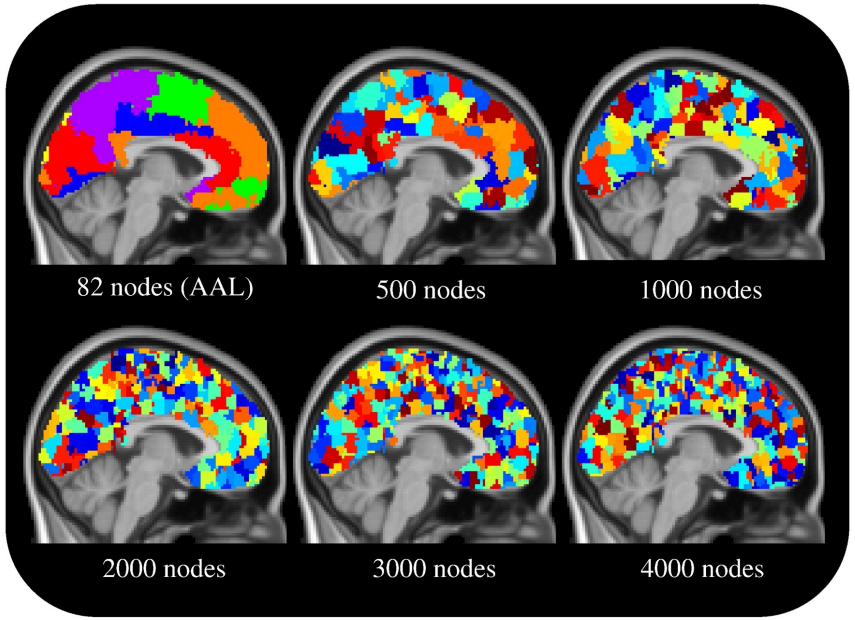
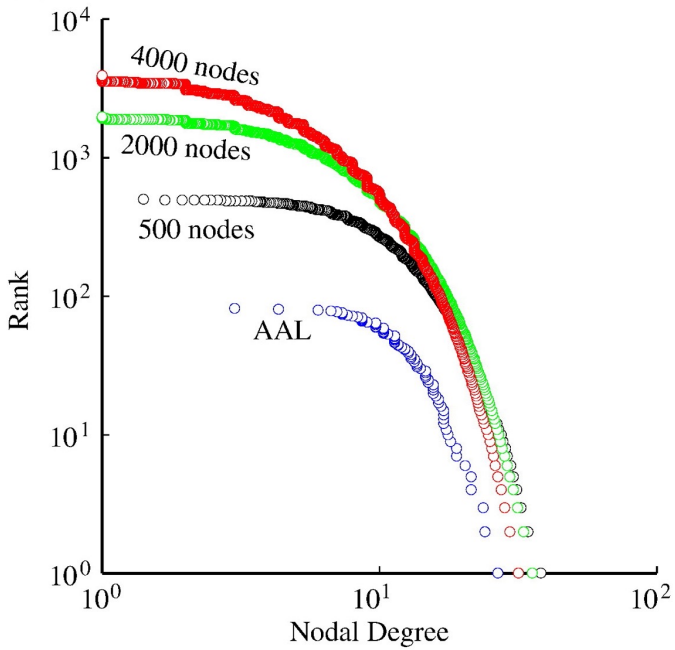
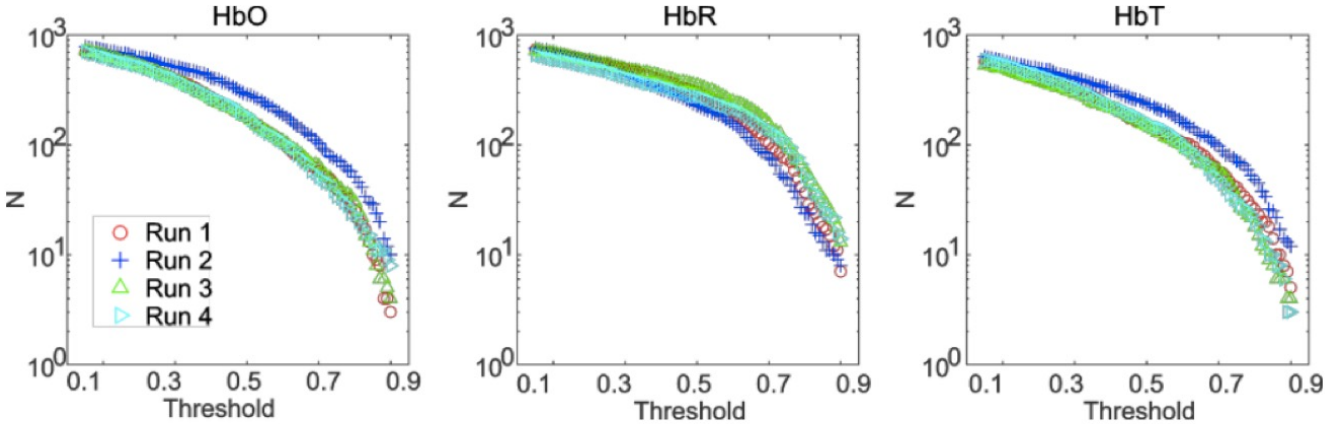
The influence of the nodes and links on the network

- Graphs with different number of nodes will yield different properties.
- Channel pruning may affect your graph!





Zalesky, NeuroImage (2010)



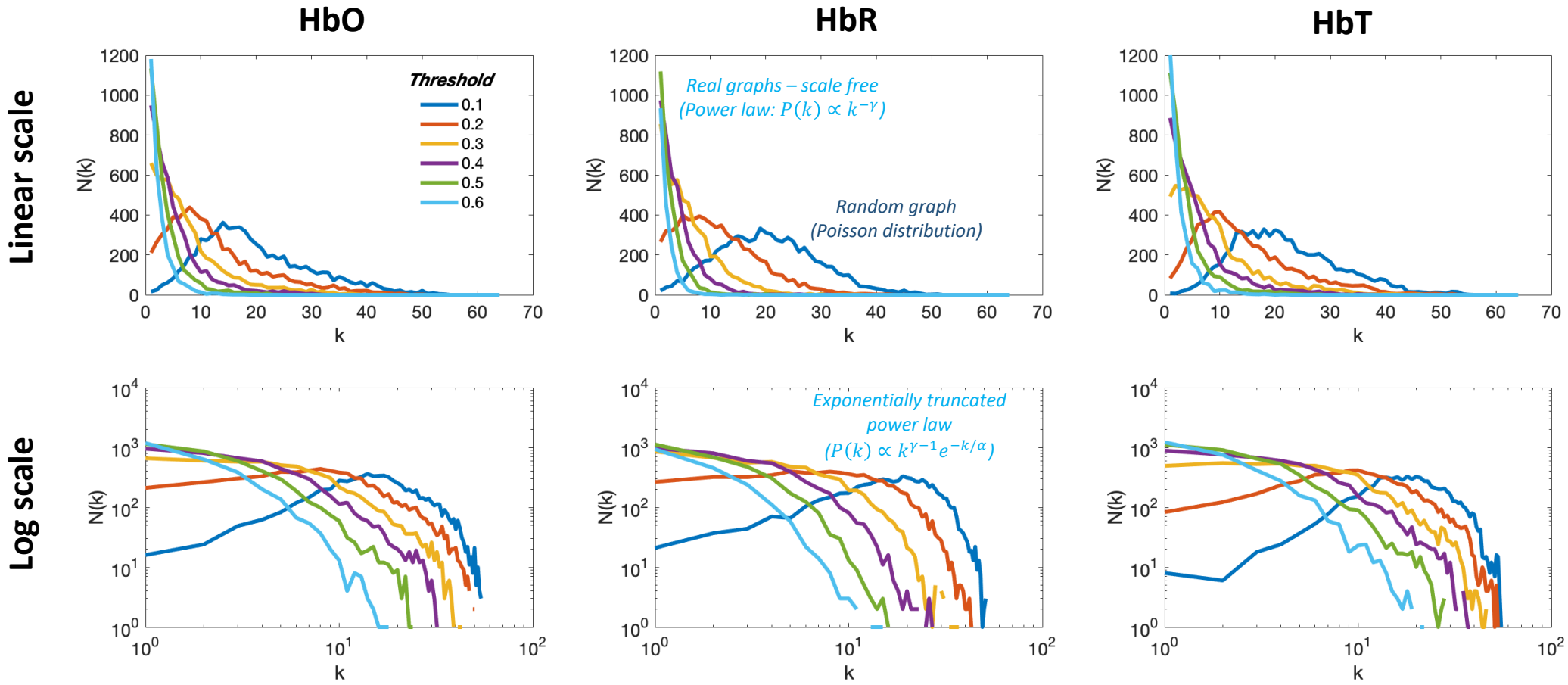
- Number of links is stable across runs & subjects

Novi, Rodrigues & Mesquita, Biomed. Opt. Express (2016)

In the end, it is all about how the links are distributed in the graph

Degree Number of links from a given node to other nodes in the graph

Degree Distribution



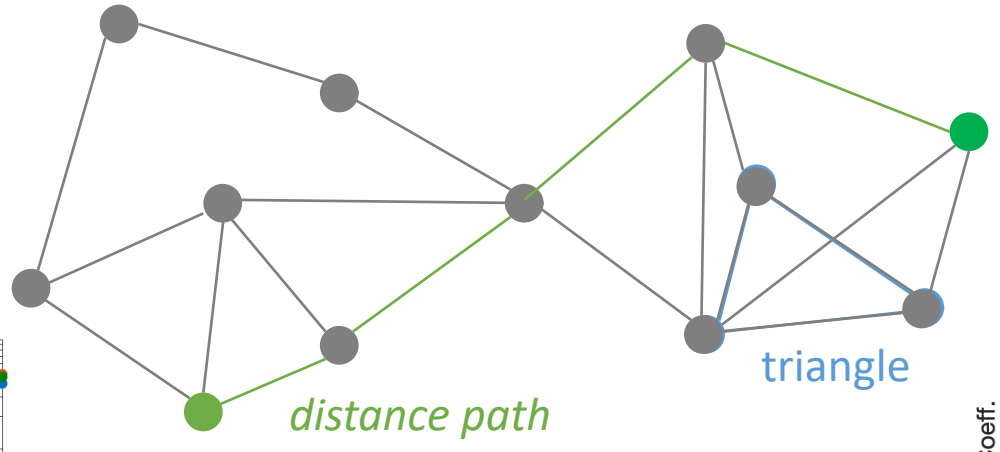
Sanchez et al., in prep.

In the end, it is all about how the links are distributed in the graph

Distance Path — Shortest distance between any two nodes
(characteristic pathlength, global efficiency, etc.)

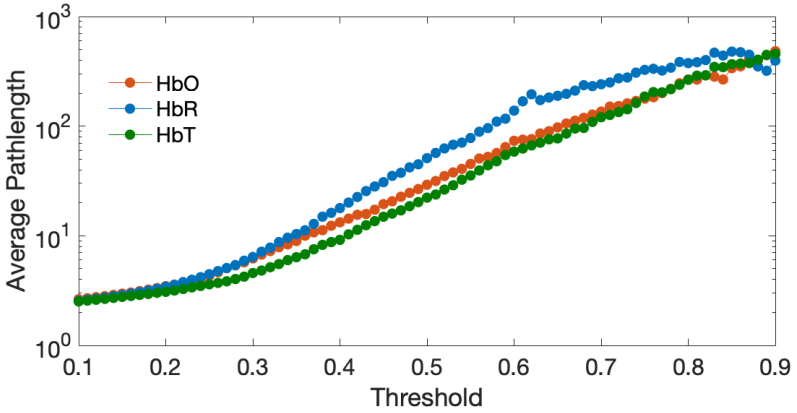
Triangulation — How node neighbors are connected among the three of them
(clustering coefficient, transitivity, etc.)

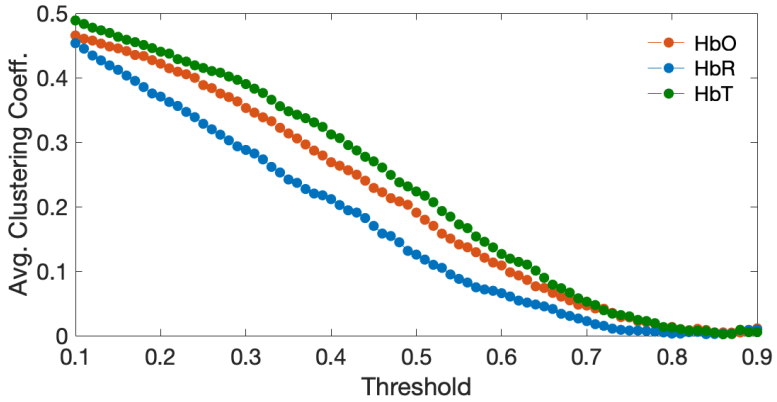
$$\langle d \rangle = \frac{2}{N(N-1)} \sum_{\substack{i,j=1 \\ i>j}}^{N} d_{ij}$$



 # links between k_i neighbors of node i

$$CC = \frac{2L_i}{k_i(k_i-1)}$$





Hands-on #7

- Calculate the average topological (macroscopic) properties of the rs-FC data
- Run code: Part_3_fNIRS_course_2022_RestingState.m

Highly connected nodes influence graph function

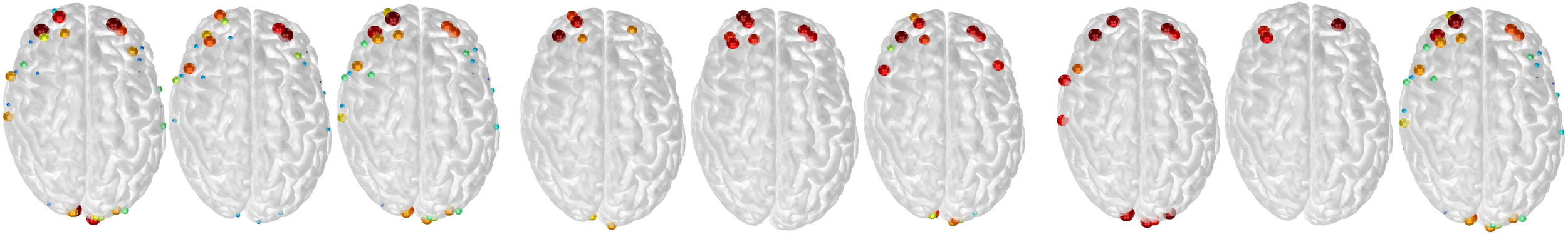
Centrality

Attempts to quantify the importance or influence of a node on graph function

Degree Centrality
Equivalent to node degree;
accounts for all connections equally

Eigenvector Centrality
Considers both the degree of the
node and the degree of its neighbors

Betweenness Centrality
Proportion of shortest paths
that pass through a given node



Thank you all!