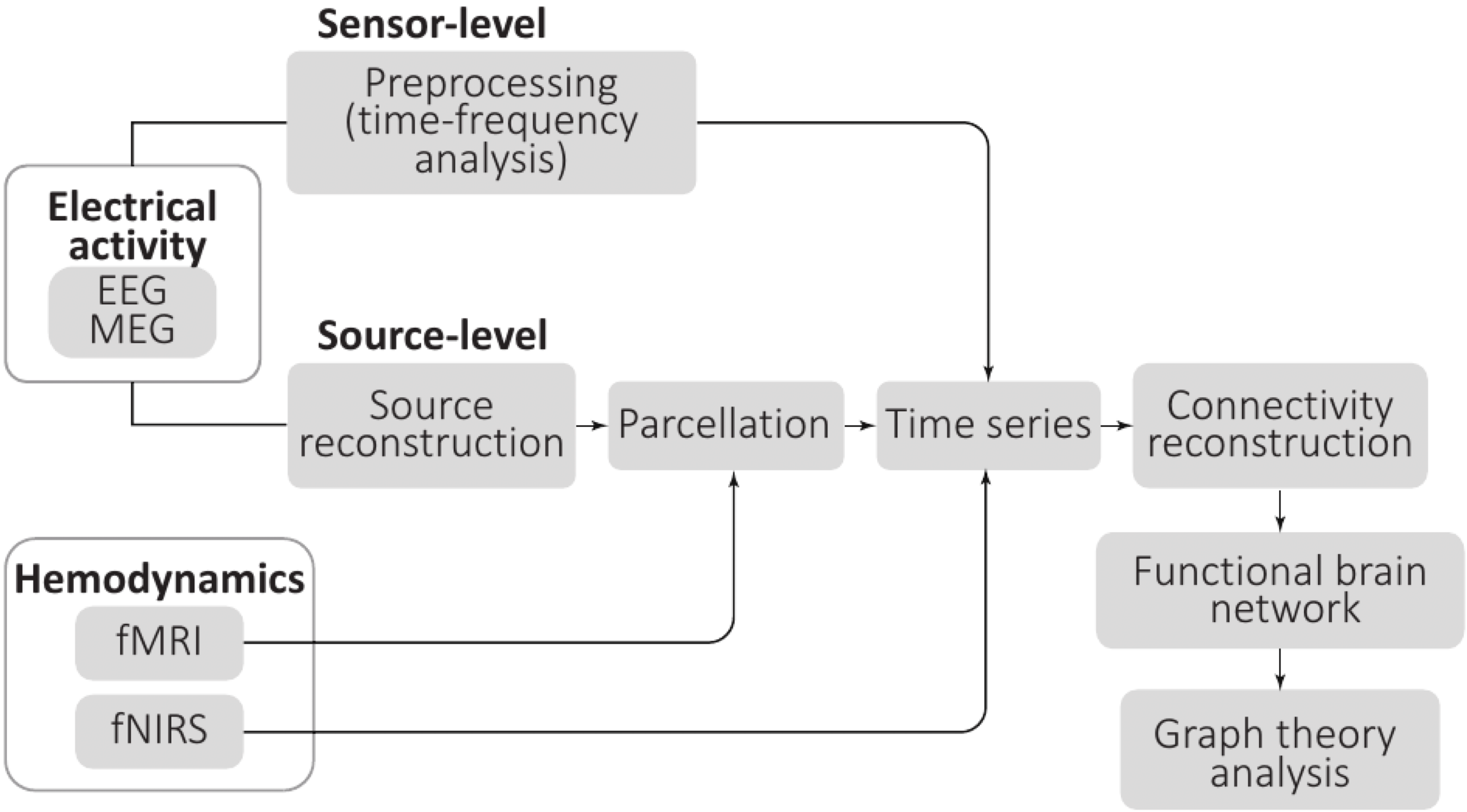
Methods for functional brain connectivity detection

Lecture 8

Outline

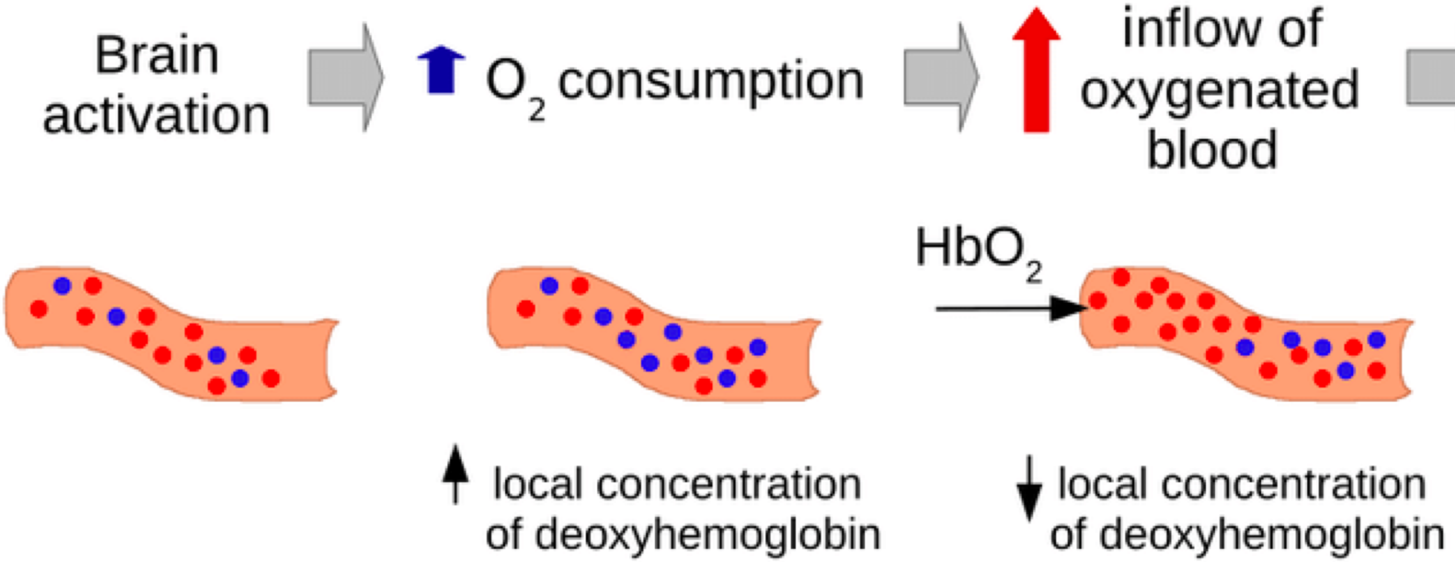
- A taxonomy of methods for functional connectivity detection
- Model-based and model-free methods
- Non-directed and directed methods
- Granger causality
- Phase locking method
- Recurrence-based measure

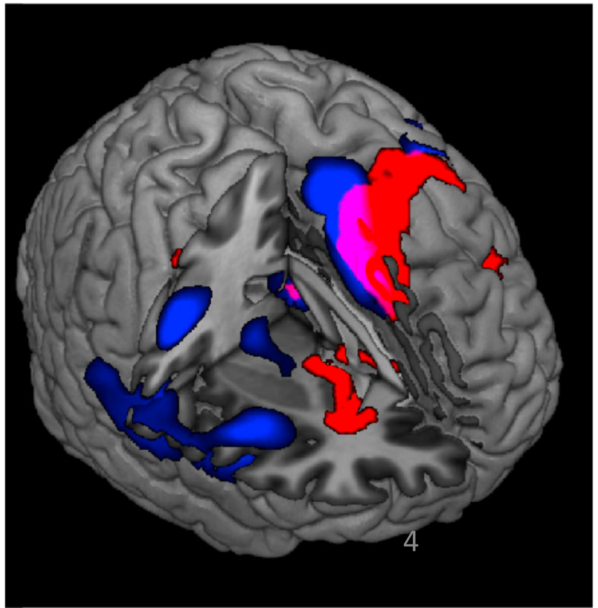
Restoration and analysis of functional brain networks



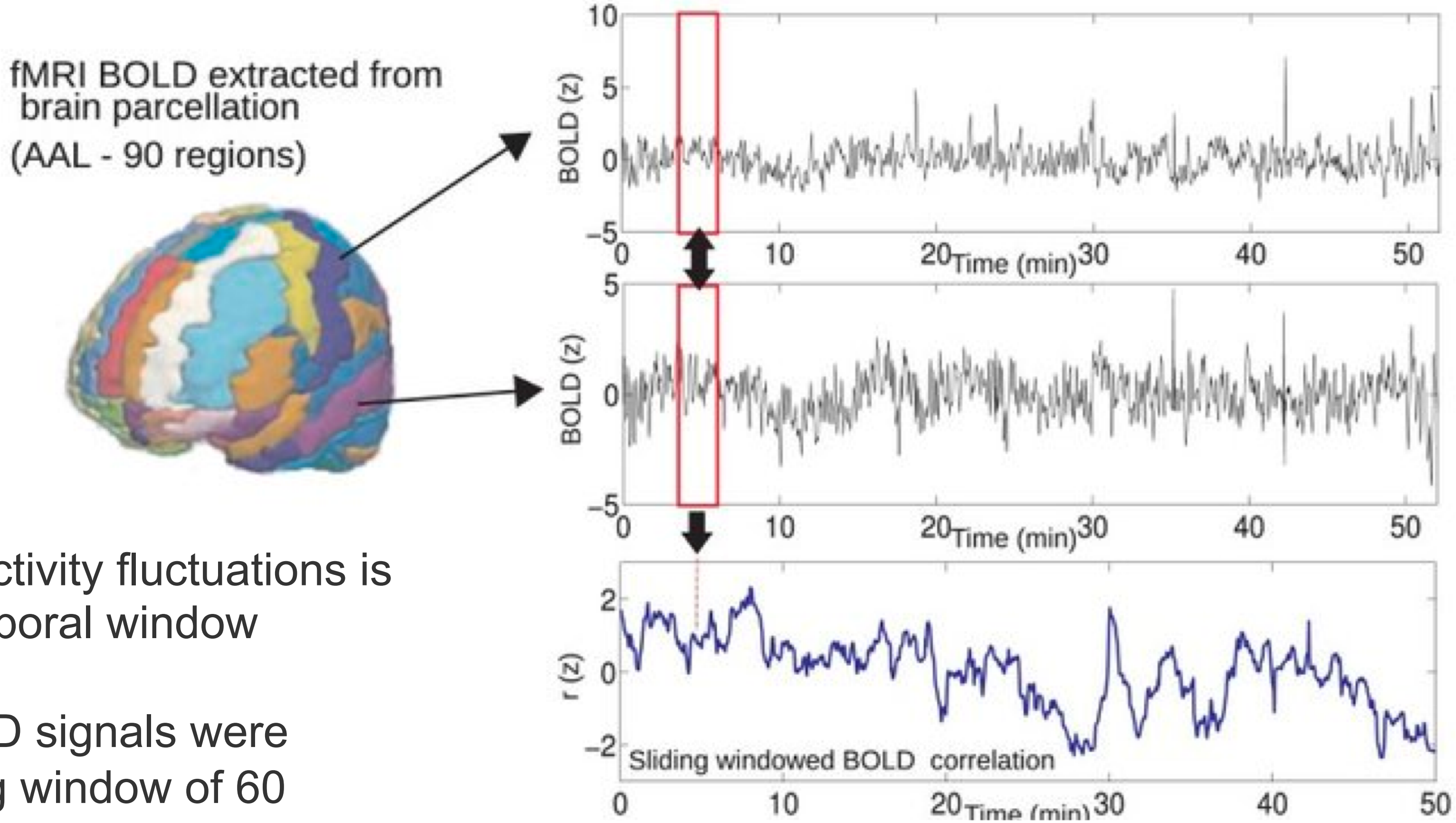
EXAMPLE:
Blood oxygenation level–dependent (BOLD) imaging

The BOLD signal measures the local changes in blood oxygenation ocurring during brain activity:



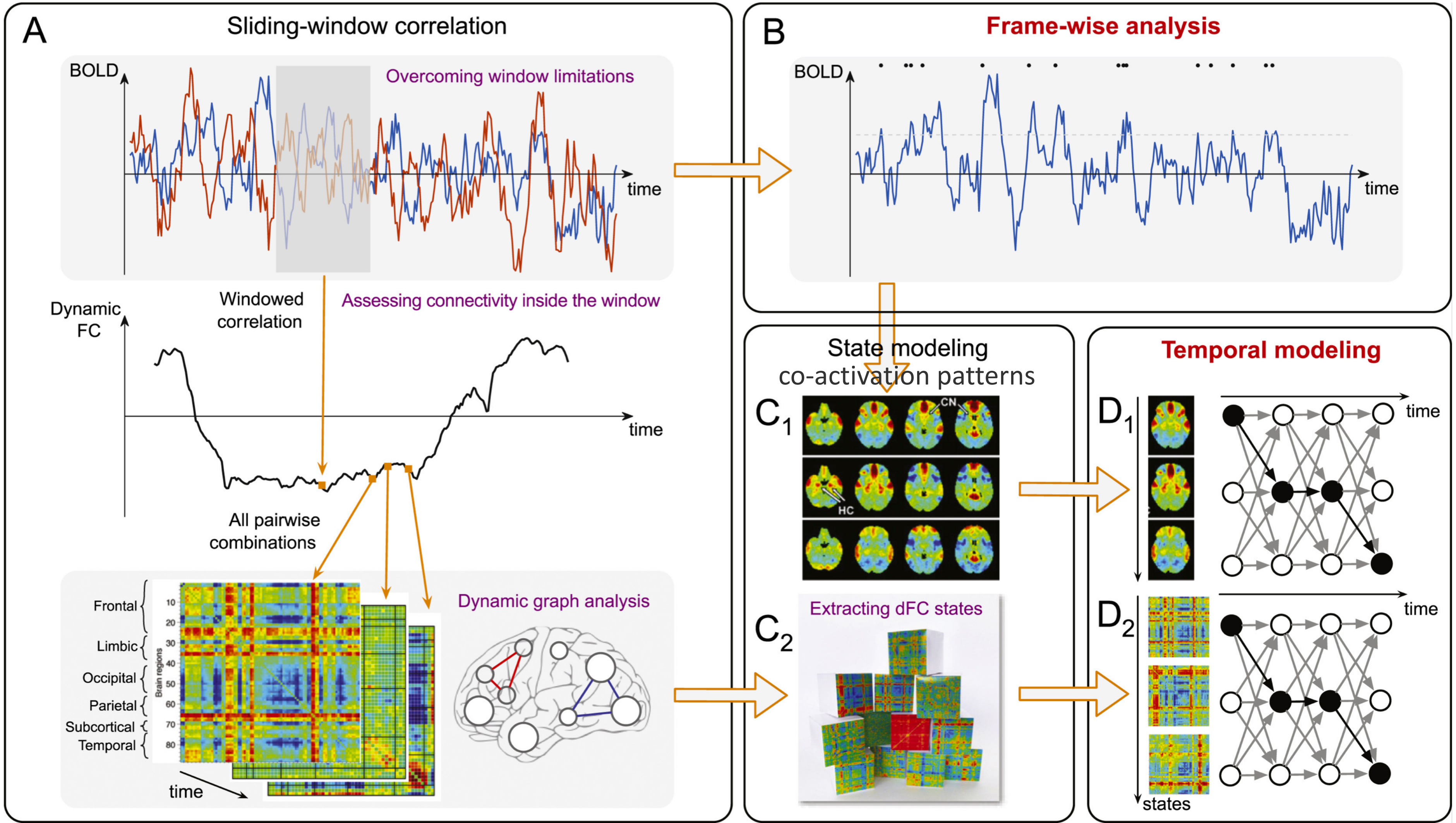


BOLD connectivity restoration



Method used to compute BOLD connectivity fluctuations is based on analysis of correlation in temporal window
.
For each pair of regions, average BOLD signals were extracted and correlated using a sliding window of 60 volumes (≈2 min). This resulted in a connectivity estimate over time.

BOLD connectivity restoration strategy

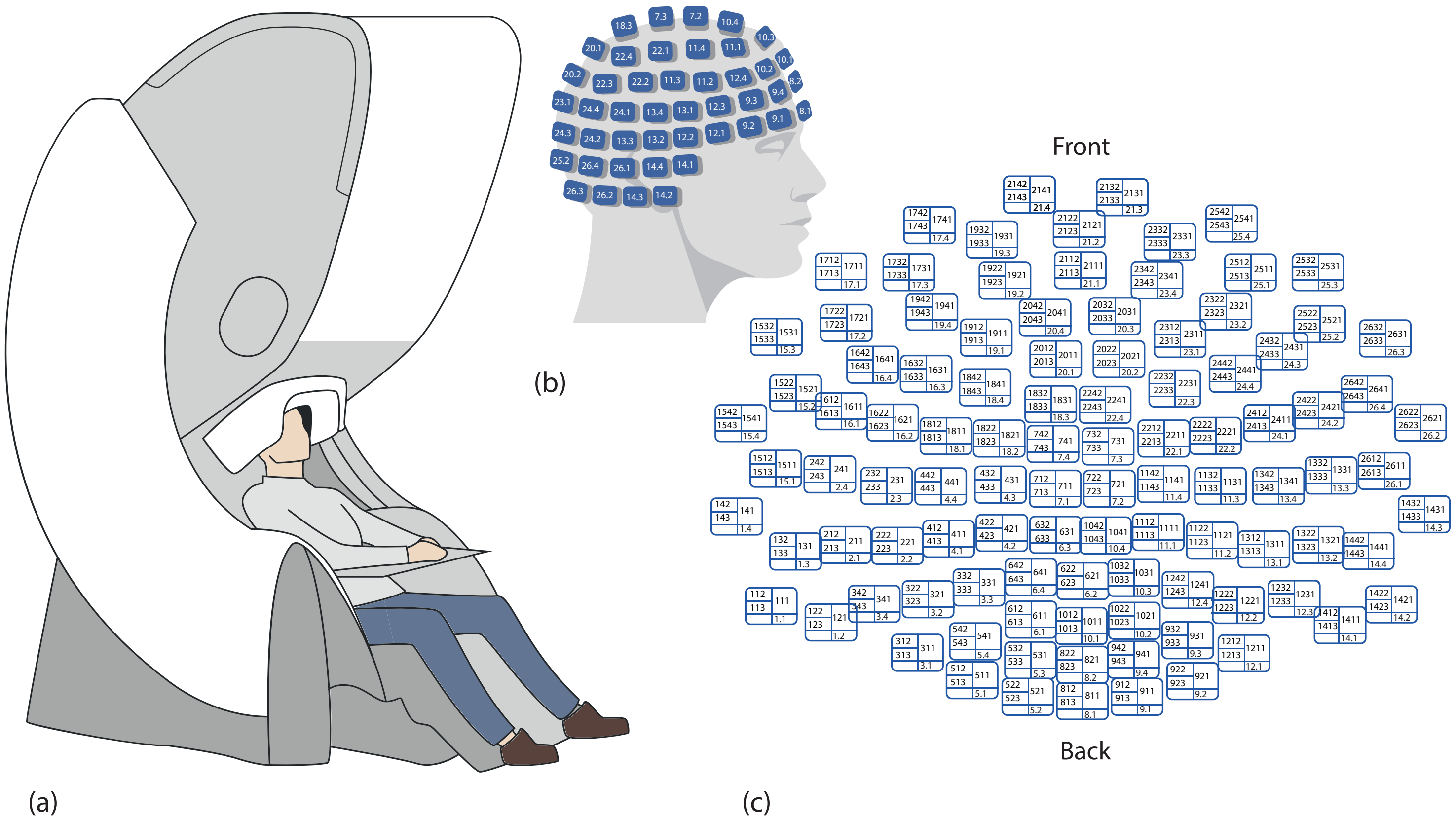


Traditional sliding window methodology, where the connectivity between brain regions is computed as Pearson correlation between pairs of BOLD time series, over a temporal interval spanned by a rectangular window

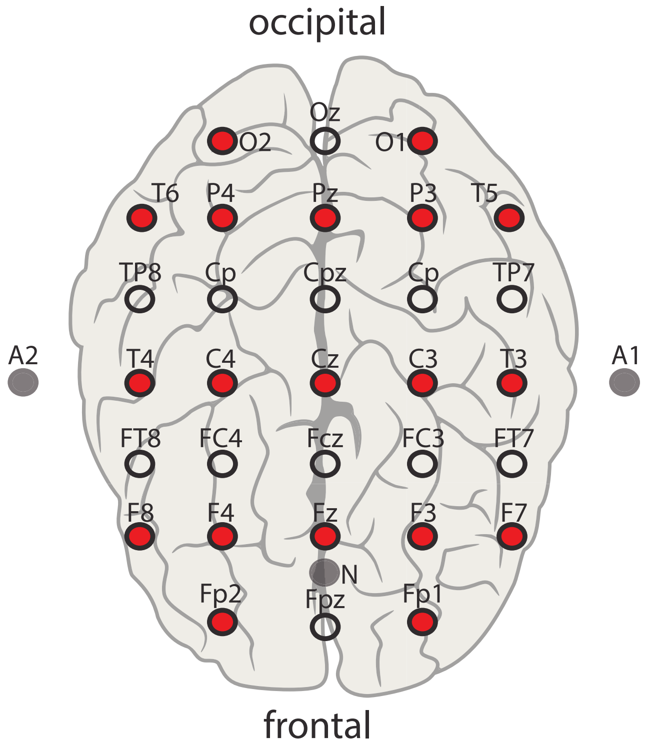
Frame-wise description, where only moments when the BOLD signal exceeds a threshold are retained for the analysis

EEG/MEG connectivity restoration: sensor-level

MEG

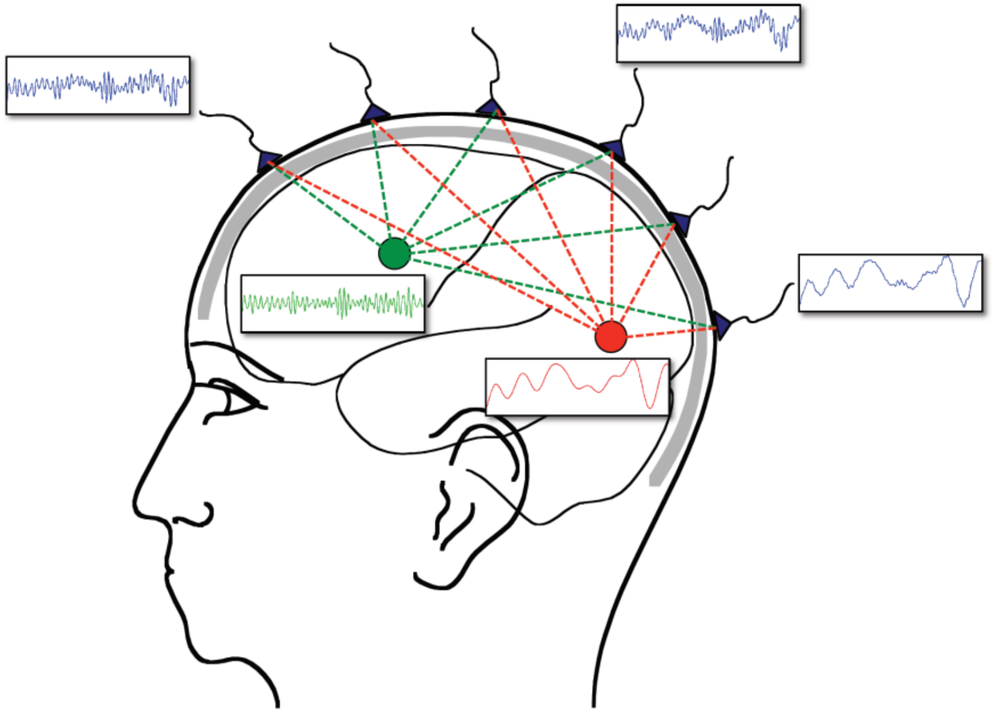


EEG

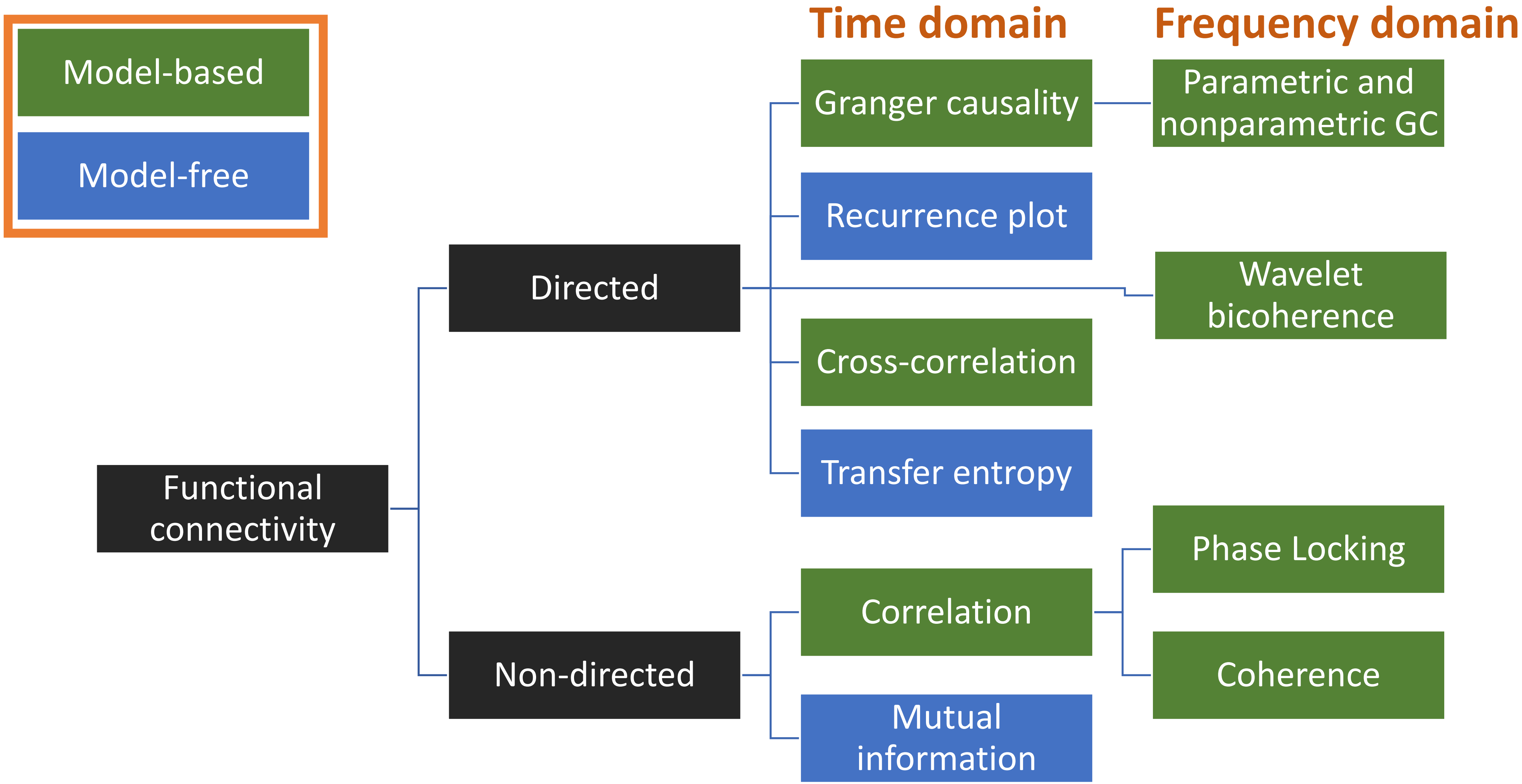


EEG/MEG connectivity restoration: source-level

- “Location” requires interpretation
- Sensor-level → Source-level
- Forward and inverse modeling helps to interpret location
- Inverse problem
- Forward and inverse modeling helps to disentangle overlapping source timeseries



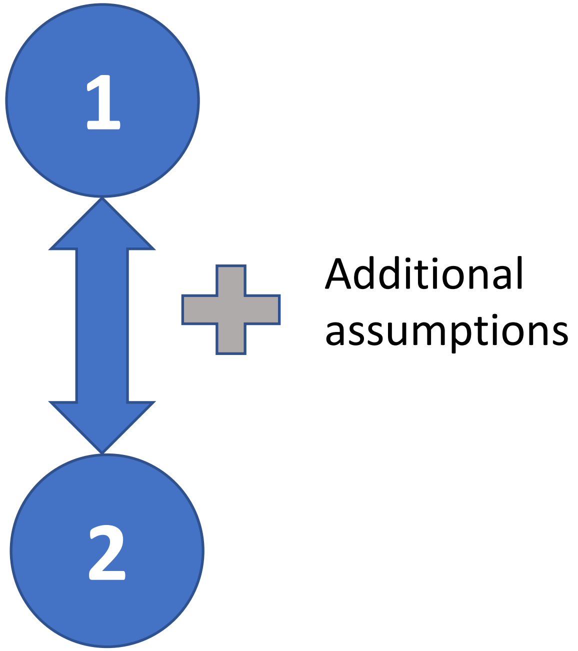
A taxonomy of popular methods for quantifying functional connectivity



Model-based and model-free approaches

- The model-based approaches make an assumption of character of interactions that may take place between two signals. **EXAMPLE:** The simplest measure for non-directed model-based interactions is the Pearson correlation coefficient, which measures the linear relationship between two random variables. In the general linear modeling framework the squared correlation coefficient (R^2) represents the fraction of the variance of one of the signals that can be explained by the other, and vice versa.

- A more generalized approach that does not assume a linear relationship is mutual information, which measures the generalized interdependence between two or more time series using concepts from information theory.



Pierson correlation coefficient

$$X = \{X_1, X_2, ..., X_N\}$$

$$Y = \{Y_1, Y_2, ..., Y_N\}$$

$$\mathbf{r}_{XY} = \frac{\mathbf{cov}XY}{\sigma_X \sigma_Y}$$

$$\mathbf{cov}XY = \frac{1}{N} \sum_{t=1}^{N} (X_t - \overline{X})(Y_t - \overline{Y})$$

σ_X, σ_Y is standard deviation

$\overline{X}$, $\overline{Y}$ is mean values

Non-directed methods for FBC detection

Measures of Synchronization and Coherence

To determine neuronal oscillations at similar frequencies in brain areas A and B engage in oscillatory coupling with a preferred phase difference, linear measures such as coherence or PLV will capture this interaction.
Advantages: clear interpretation, big speed of numerical processing
Disadvantages: assumption of linear coupling.

Mutual information (MI)

MI measures the generalized (linear and non-linear) interdependence between two or more variables (or time series) using concepts from information theory.
Advantages: model-free
Disadvantages: results difficult to interpret.

Measures of Synchronization

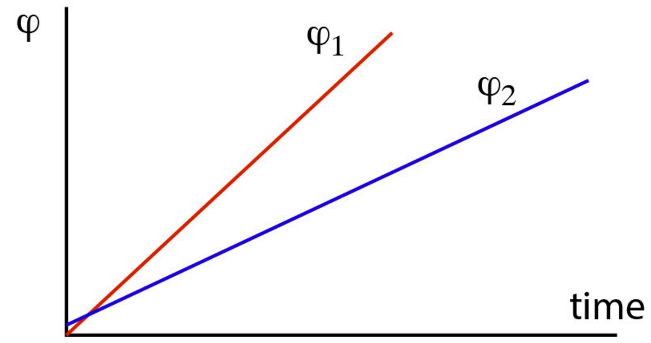
$x(t) = A \cos \varphi(t)$, $\varphi(t) = 2\pi f t + \varphi_0$

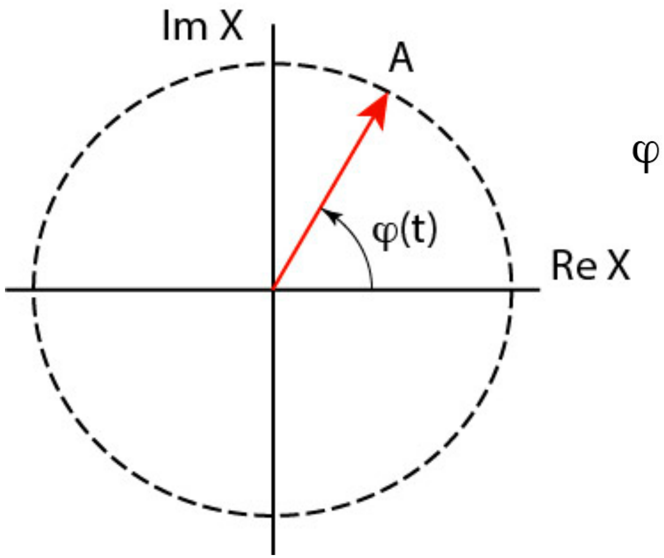
$X(t) = A \exp[-i\varphi(t)]$

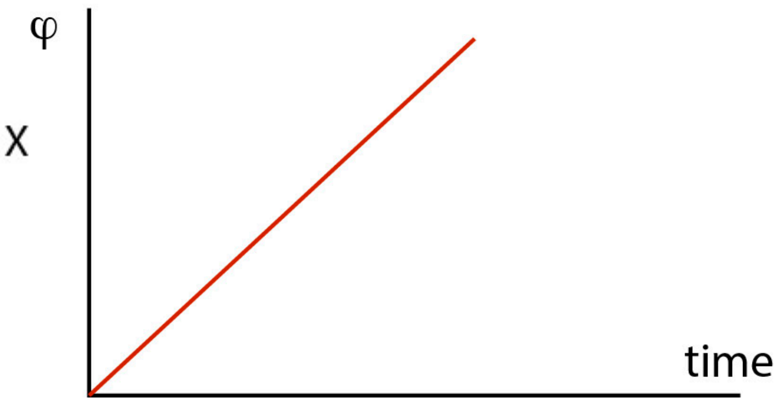
$\varphi_1(t) = 2\pi f_1 t + \varphi_{01}$

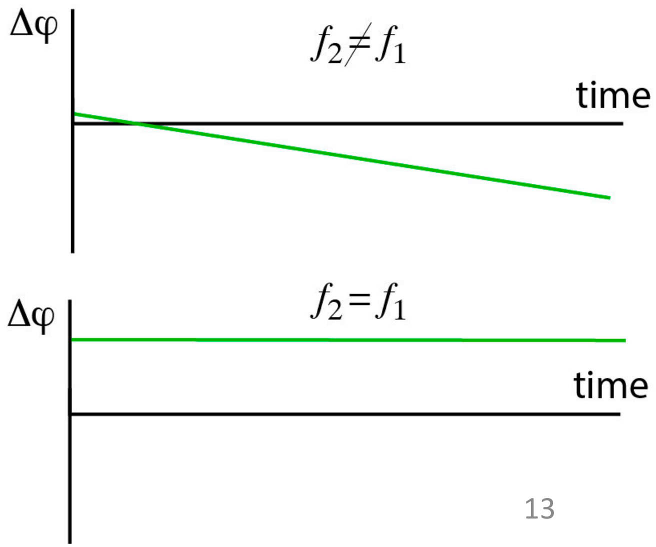
$\varphi_2(t) = 2\pi f_2 t + \varphi_{02}$

$\Delta\varphi_{21}(t) = \varphi_2(t) - \varphi_1(t)$

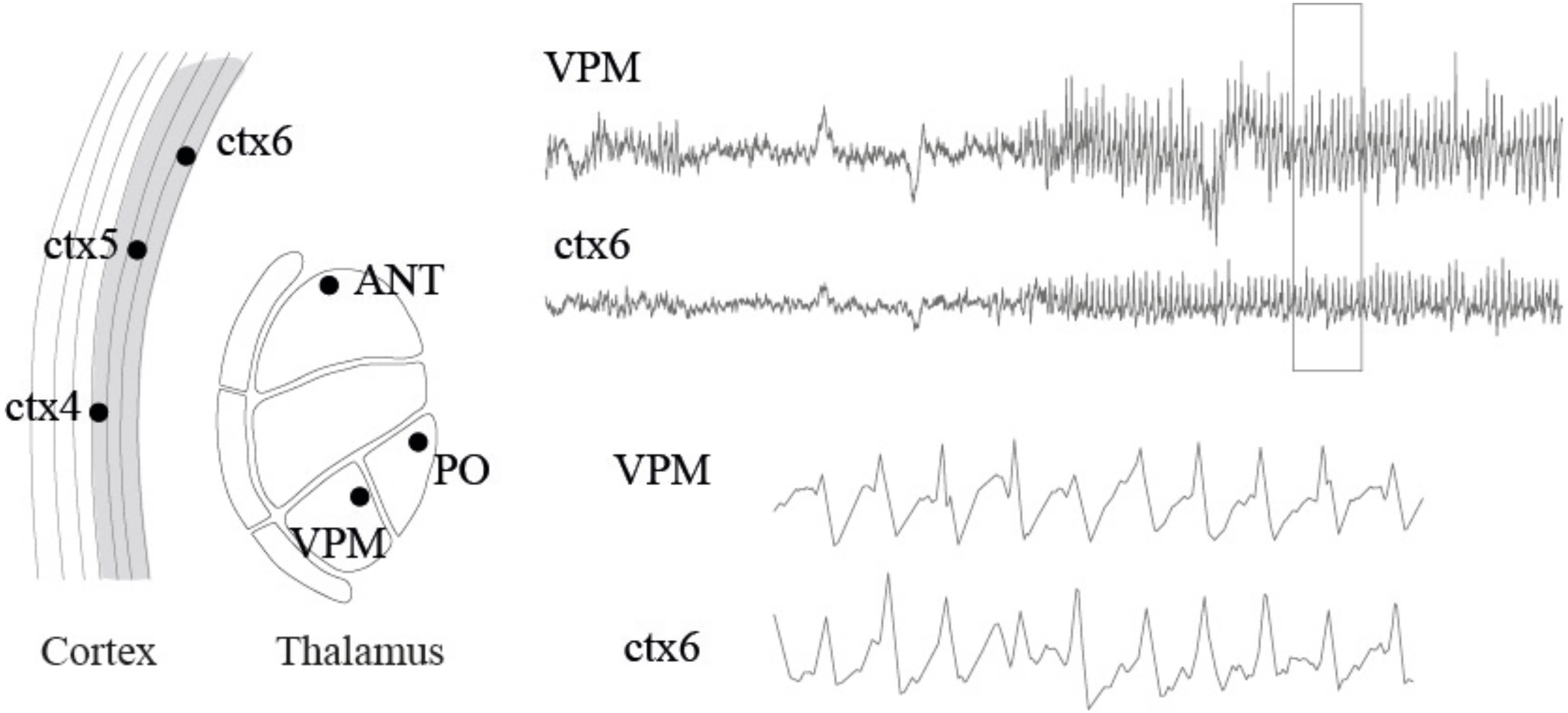








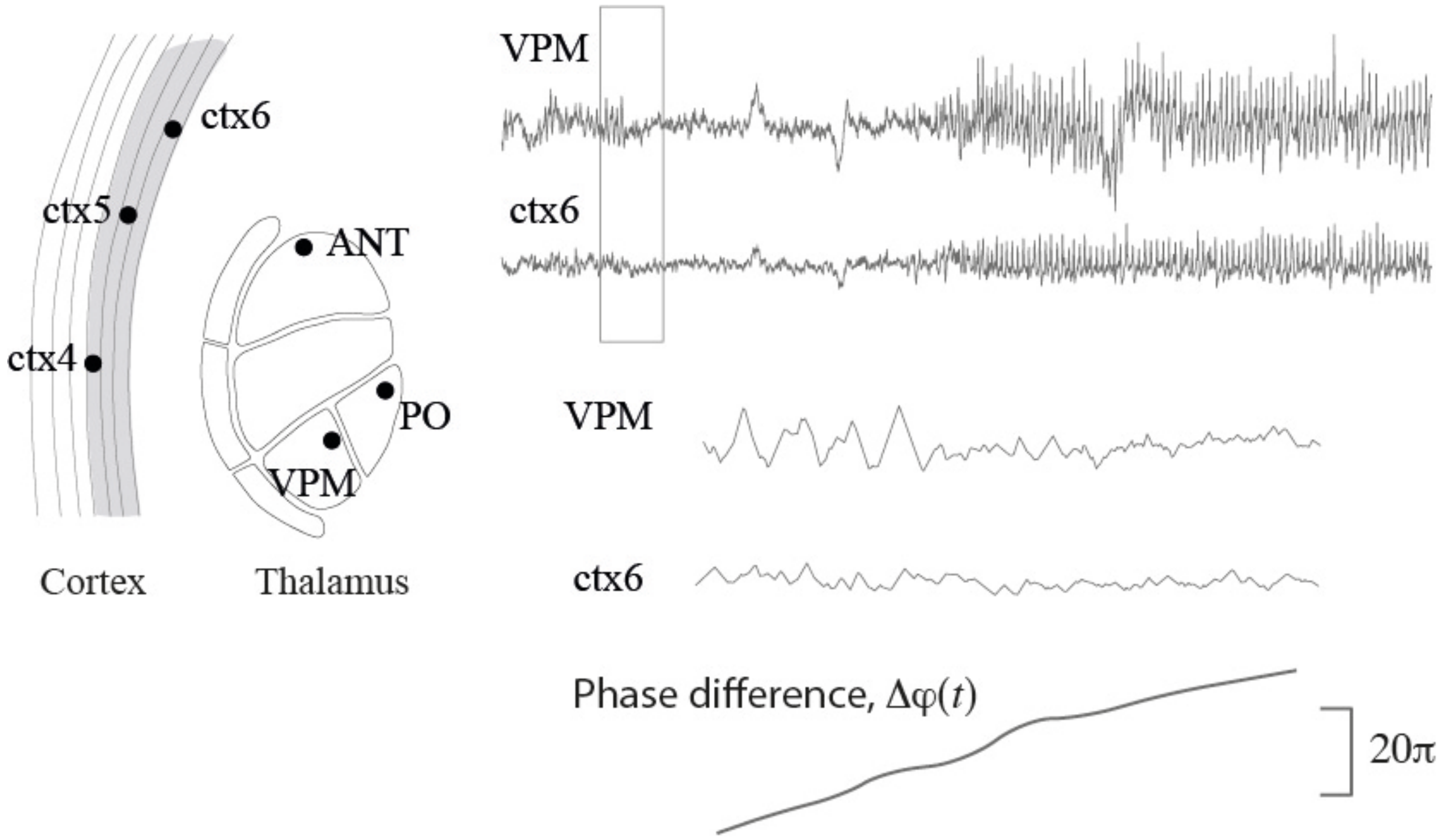
Measures of Synchronization



Main hypothesis: the oscillatory phase coupling or frequency locking governs neuronal interactions.

EXAMPLE: if we are interested in determining whether neuronal oscillations at similar frequencies in brain areas **ctx6** and **VPM** engage in oscillatory coupling with a preferred phase difference, non-linear measures such as coherence or phase locking index will capture this interaction.

Measures of Synchronization



Main hypothesis: the oscillatory phase coupling or frequency locking governs neuronal interactions.

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Coherence coefficient

Fourier transform

$$X(t) = \sum_{\omega=-\infty}^{\infty} A_X(\omega, t) e^{i\varphi_X(\omega,t)},$$

$$Y(t) = \sum_{\omega=-\infty}^{\infty} A_Y(\omega, t) e^{i\varphi_Y(\omega,t)},$$

Coherence coefficient

$$coh_{xy}(\omega) = \frac{\left| \frac{1}{n} \sum_{k=1}^{n} A_x(\omega,k) A_y(\omega,k) e^{i\left(\varphi_x(\omega,k) - \varphi_y(\omega,k)\right)} \right|}{\sqrt{\left(\frac{1}{n} \sum_{k=1}^{n} A_x^2(\omega,k)\right)\left(\frac{1}{n} \sum_{k=1}^{n} A_y^2(\omega,k)\right)}}$$

The numerator term represents the length of the vector average of the individual trial cross-spectral densities between signal *x* and *y* at frequency ω. The denominator represents the square root of the product of the average of the individual trial power estimates of signals *x* and *y* at frequency ω.

Phase Locking Value

$$|\varphi_X(t) - \varphi_Y(t)| = \mathrm{const}$$

$$plv_{xy}(\omega) = \frac{\left|\frac{1}{n}\sum_{k=1}^{n} 1_x(\omega,k) 1_y(\omega,k) e^{i(\varphi_x(\omega,k)-\varphi_y(\omega,k))}\right|}{\sqrt{\left(\frac{1}{n}\sum_{k=1}^{n} 1_x^2(\omega,k)\right)\left(\frac{1}{n}\sum_{k=1}^{n} 1_y^2(\omega,k)\right)}} = \left|\frac{1}{n}\sum_{k=1}^{n} e^{i(\varphi_x(\omega,k)-\varphi_y(\omega,k))}\right|$$

In motivating the use of PLV, as opposed to coherence, it is often claimed that the former reflects more strictly phase synchronization than coherence, because the latter confounds the consistency of phase difference with amplitude correlation.

Phase dynamics definition: analytical signal

$$H(t) = X(t) + i\tilde{X}(t),$$

Here X(t) is the original signal, and X(t) is its Hilbert transform, which is defined in the sense of the principal value of the Cauchy integral

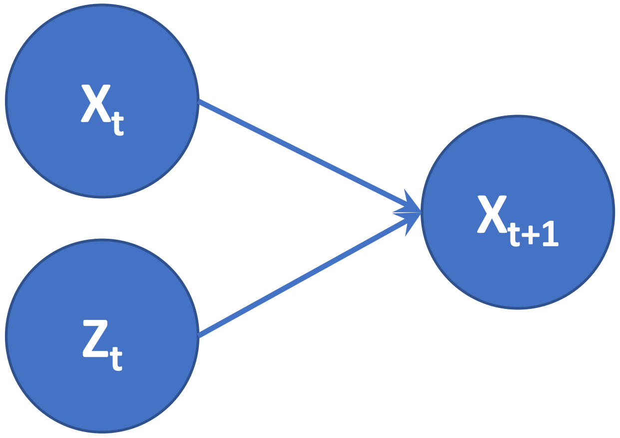
$$\tilde{X}(t) = \frac{1}{\pi}\mathrm{PV}\int_{-\infty}^{\infty} \frac{X(t')}{t - t'}dt'.$$

The phase of the analytical signal is defined as

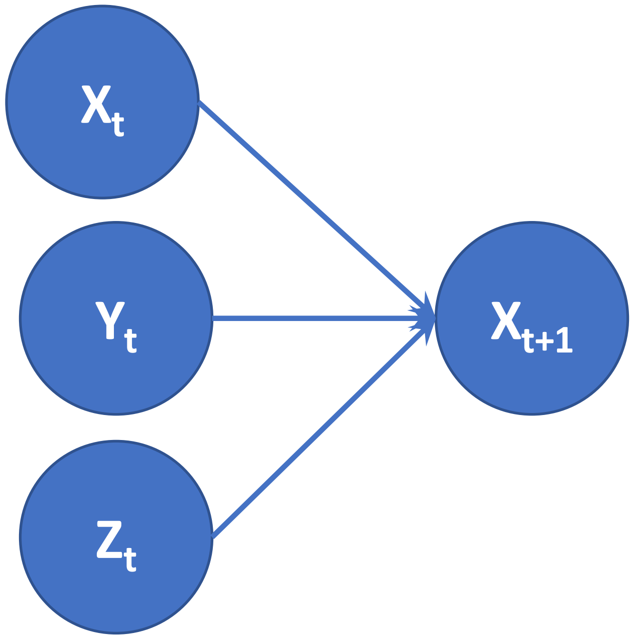
$$\varphi_X(t) = \arctan\frac{\tilde{X}(t)}{X(t)},$$

$$\mathrm{PLV}_{XY}(t) = \left|\frac{1}{N}\sum_{t=1}^{N} e^{i(\varphi_X(t)-\varphi_Y(t))}\right|$$

Granger Causality



There are three terms, X_t, Y_t , and Z_t. We first attempt to forecast X_{t+1} using past terms of X_t and Z_t

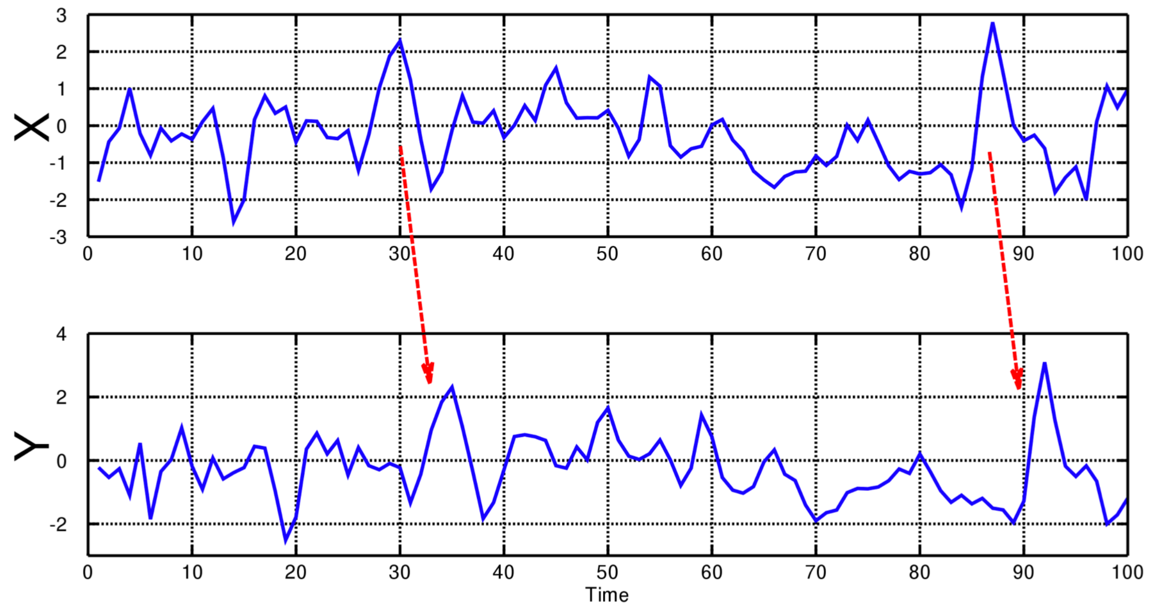


We then try to forecast X_{t+1} using past terms of X_t, Y_t, and Z_t

If the second forecast is found to be more successful, according to standard cost functions, then the past of Y appears to contain information helping in forecasting X_{t+1} that is not in past X_t or Z_t.

Thus, Y_t would ***Granger cause*** X_{t+1} if
(a) Y_t occurs before X_{t+1};
(b) it contains information useful in forecasting X_{t+1} that is not found in a group of other appropriate variables.

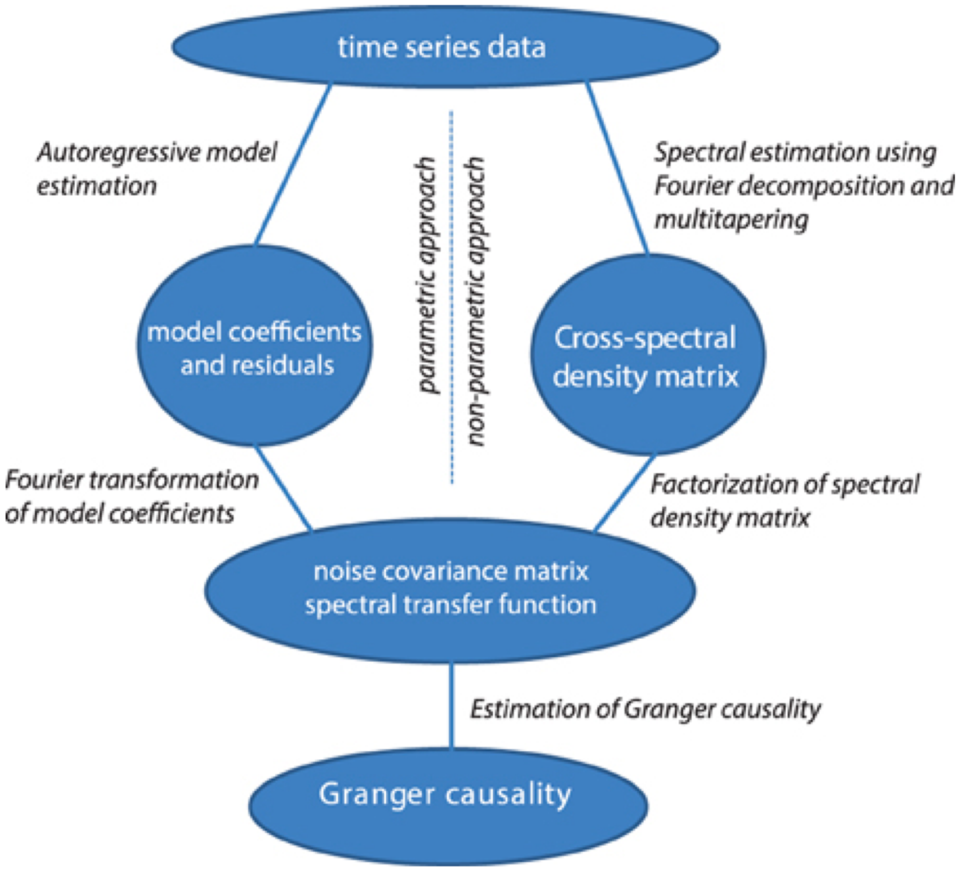
Granger Causality



When time series *X* Granger-causes time series *Y*, the patterns in *X* are approximately repeated in *Y* after some time.
Thus, past values of *X* can be used for the prediction of future values of *Y*.

Granger Causality

Granger causality represents the result of a model comparison.



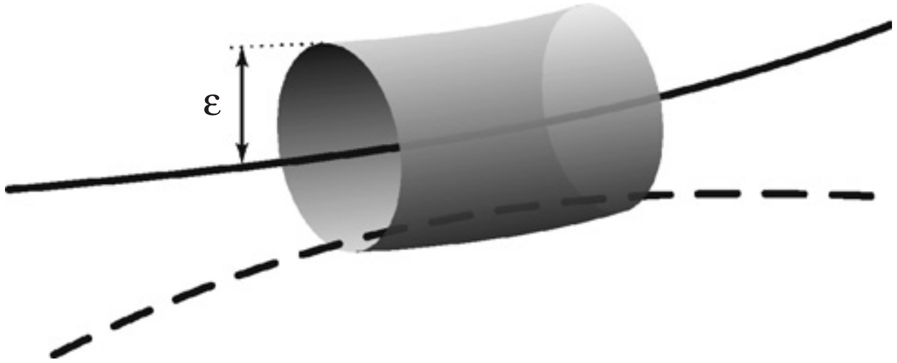
What is reccurence plots (RP)?

Recurrence is a fundamental property of system dynamics reflected fact of possibility of short-term prediction. A powerful tool for their visualisation and analysis is *recurrence plot* (RP)

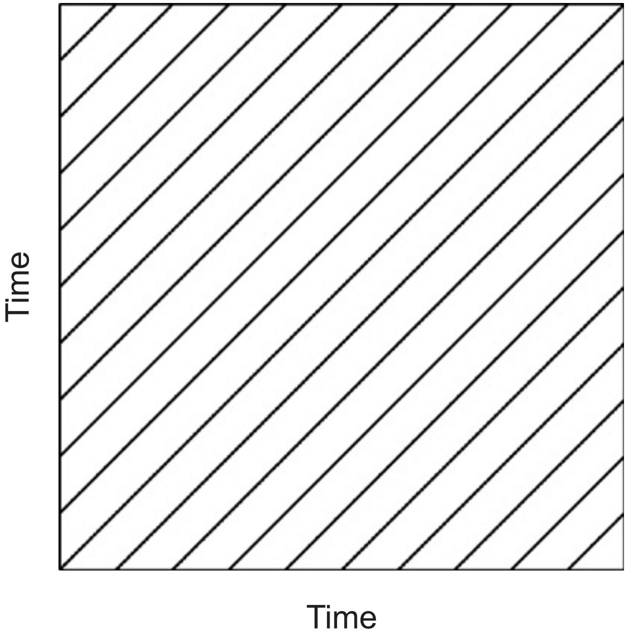
The corresponding RP is based on the following recurrence matrix:

$$\mathbf{R}_{i,j} = \begin{cases} 1: \vec{x}_i \approx \vec{x}_j, \\ 0: \vec{x}_i \not\approx \vec{x}_j, \end{cases} \qquad i, j = 1, \ldots, N,$$

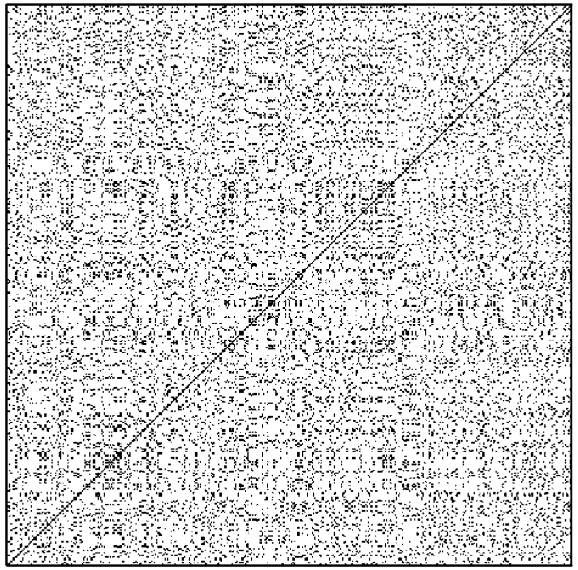
where *N* is the number of considered states and $x_i \approx x_j$ means equality up to an error (or distance) ε.
ε is essential as systems often do not recur exactly to a formerly visited state but just approximately.



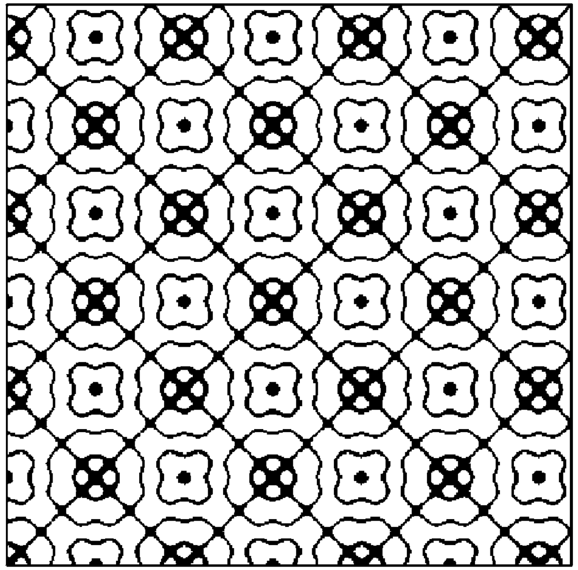
Examples of reccurence plots



Periodic oscillations with one frequency
The periodic motion is reflected by long and non-interrupted diagonals.



Uniformly distributed, independent noise
The RP consists of many single black points. The distribution of the points in this RP looks rather erratic



Multi-frequency signal
It leads *to* checkerboard structure formation.
The RP of a periodic system with two harmonic frequencies and with a frequency ratio of four (two and four short lines lie between the continuous diagonal lines)

Connectivity identification based on recurrence plots

Reccurence matrix for given discrete signal $\mathbf{x} = \{\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N\}$

$$\mathbf{R}_{i,j}^{X}(\varepsilon) = \Theta(\varepsilon - \parallel \mathbf{x}_i - \mathbf{x}_j \parallel), \quad i, j = 1, \ldots, N.$$

The probability that a point **x** visits the neighbourhood of $\mathbf{x}_i$ is equal to the column-sum of the recurrence matrix **R**

$$P(\mathbf{x}_i) = \frac{1}{N} \sum_{j=1}^{N} \mathbf{R}_{i,j}^{X}$$

To infer the influences that two processes **x** and **y** might have on each other the recurrence structures are compared and joint reccurence matrix are defined

$$\mathbf{JR}_{i,j}^{XY}(\varepsilon_x, \varepsilon_y) = \Theta(\varepsilon_x - \parallel \mathbf{x}_i - \mathbf{x}_j \parallel)\,\Theta(\varepsilon_y - \parallel \mathbf{y}_i - \mathbf{y}_j \parallel) \quad i, j = 1, \ldots, N,$$

Direct connectivity identification based on recurrence plots

The joint probability that two processes **x** and **y** recur in the neighbourhood of $\mathbf{x}_i$ and $\mathbf{y}_i$ simultaneously

$$P(\mathbf{x}_i, \mathbf{y}_i) = \frac{1}{N} \sum_{j=1}^{N} \mathbf{JR}_{i,j}^{XY}$$

In order to estimate how *non-independent* signals **x** and **y** are from each other, the quantity is calculated

$$RMD_i = \frac{P(\mathbf{x}_i, \mathbf{y}_i)}{P(\mathbf{x}_i) P(\mathbf{y}_i)}$$

Recurrence-based Measure of Dependence

lagged probabilities in RMDi

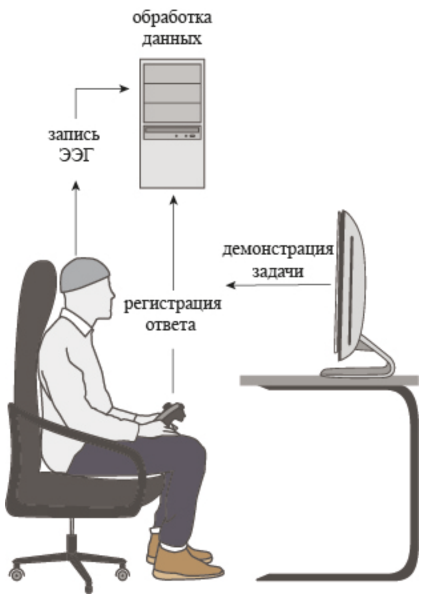
$$RMD(\tau) = \log_2 \left(\frac{1}{N'} \sum_{i=1}^{N'} RMD_i(\tau) \right)$$

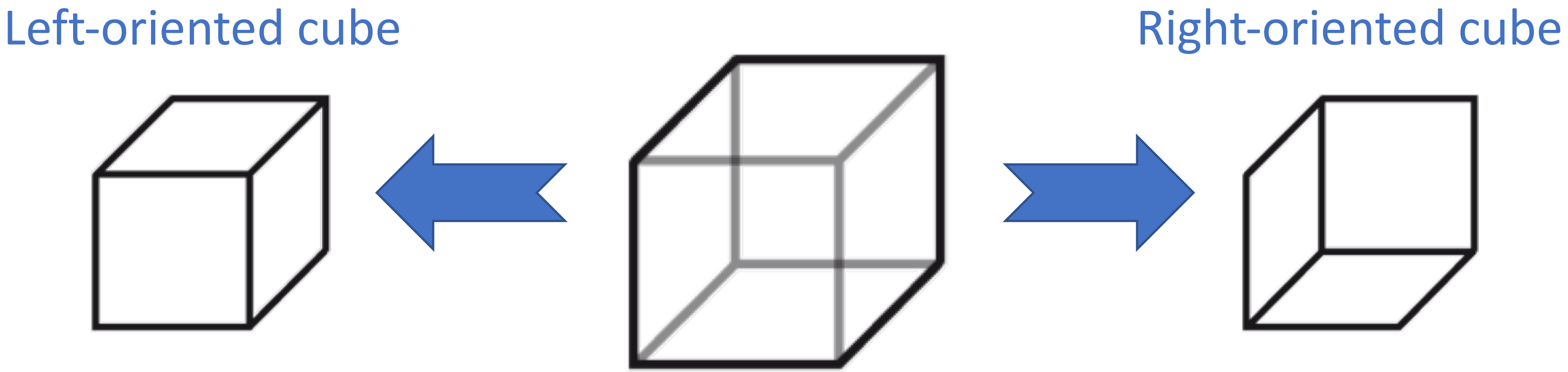
$$N' = N - \tau$$

$$RMD_i(\tau) = P(\mathbf{x}_i, \mathbf{y}_i(\tau)) / (P(\mathbf{x}_i) P(\mathbf{y}_i(\tau)))$$

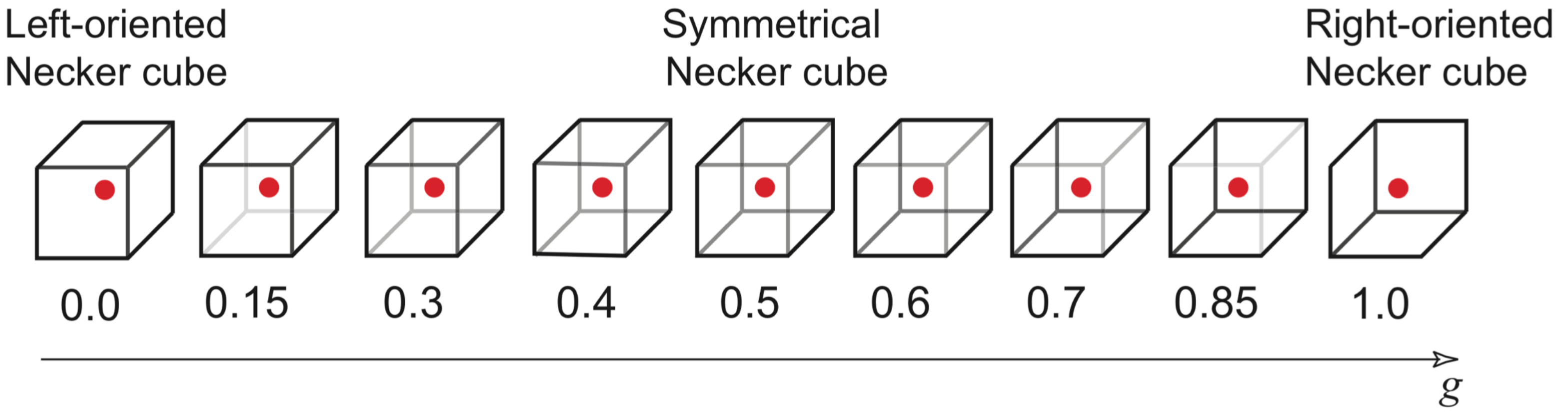
$$\tau \begin{cases} < 0 & \mathbf{x} \text{ is dependent on } \mathbf{y} \\ > 0 & \mathbf{y} \text{ is dependent on } \mathbf{x} \end{cases}$$

Experiment





- L. A. Necker, Observations on some remarkable phenomena seen in Switzerland; and an optical phenomenon which occurs on viewing of a crystal or geometrical solid. *Philos. Mag.* **3**, 329 (1832)



Each subject was instructed to fix his/her sight at the central red dot.

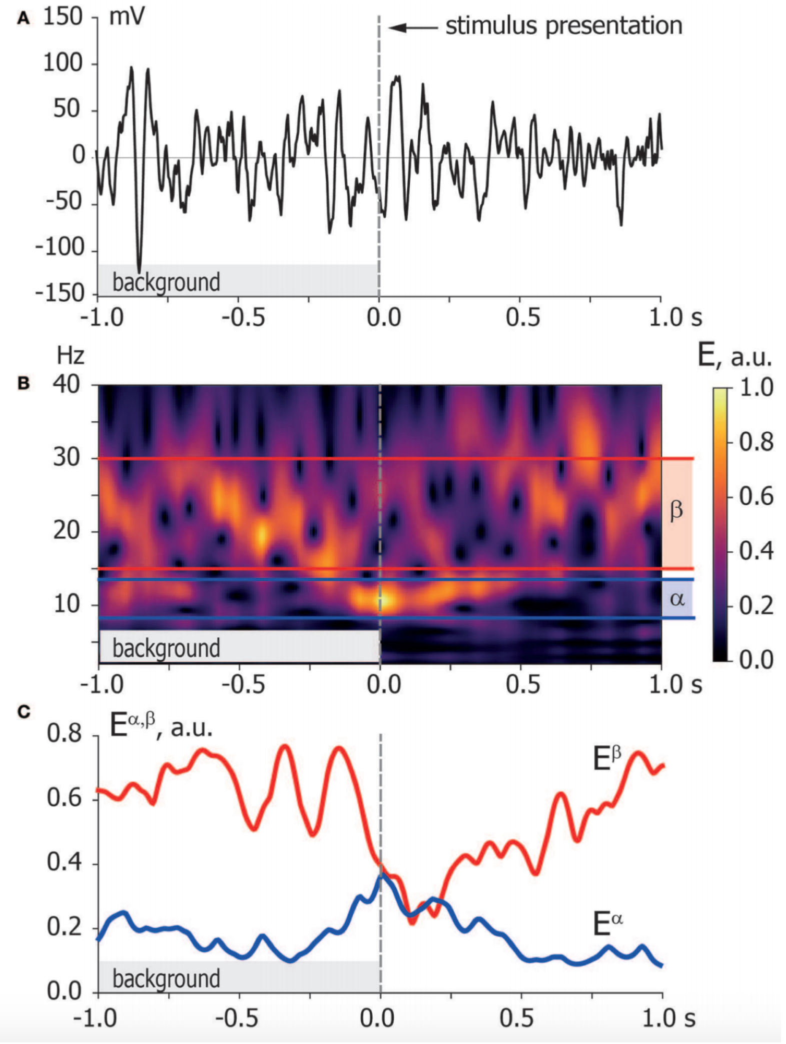
Time-frequency representation of EEG

$$W(f,t_0) = \sqrt{f}\int_{-\infty}^{+\infty} x(t)\psi^*(f(t-t_0))dt,$$

$$\psi(\eta) = \frac{1}{\sqrt[4]{\pi}} e^{j\omega_0\eta} e^{-\frac{\eta^2}{2}},$$

$$E^\alpha(t) = \int_{f\in f_\alpha} |W(f,t)|df,$$

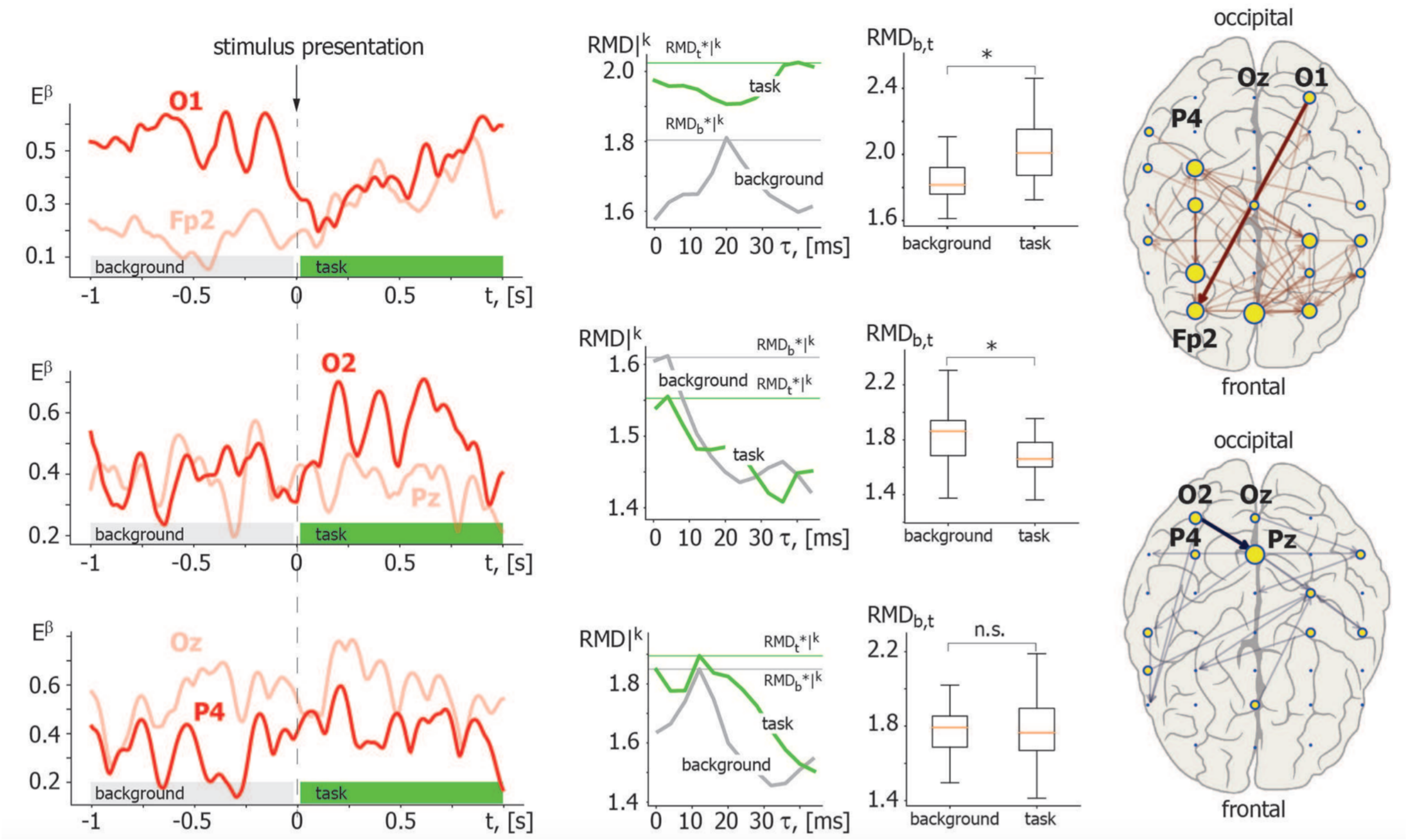
$$E^\beta(t) = \int_{f\in f_\beta} |W(f,t)|df$$

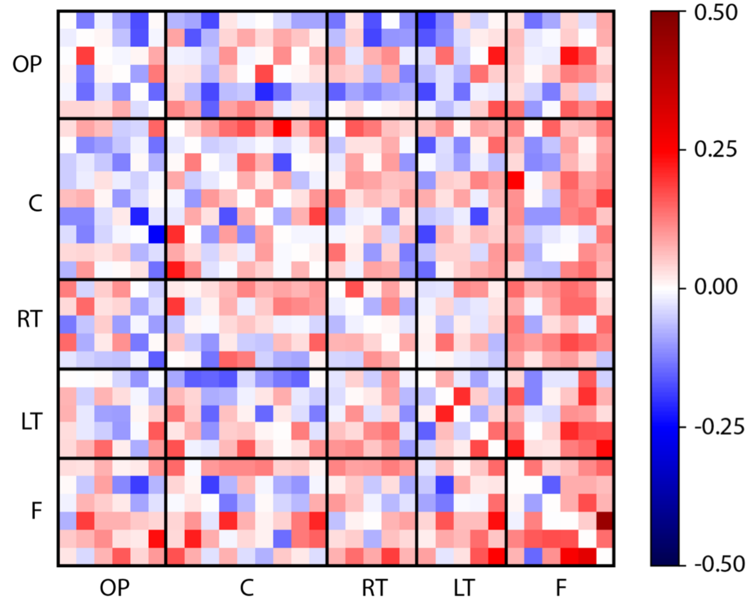


Illustrative example of functional link restoration

RMD dependence for considered pairs of $E^{\beta}(t)$ trials in background (gray) and visual perception (green) activity

results of pairwise comparison of maximal RMD values collected over K = 20 trials for background and task-related brain activity via t-test for related samples





Constructing weights matrix as

$$w(i,j) = median(RMDt(k,i,j)) - median(RMDb(k,i,j))$$

Artificial neuronal network based method

$$\mathbf{y}(t) = \mathbf{F}(\mathbf{x}(t))$$

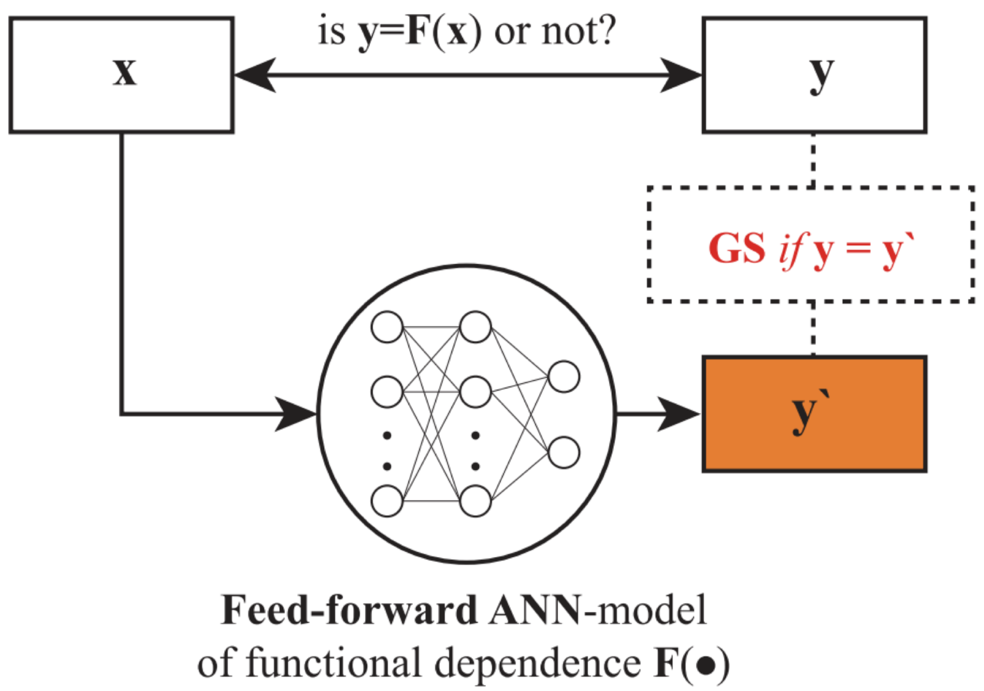


FIG. 1. Inference of functional connectivity using the proposed feed-forward ANN-based approach. Dependence of $\mathbf{y}$ on $\mathbf{x}$ is detected if the ANN-model of functional relation $F(\bullet)$ provides accurate prediction $\mathbf{y}'(t)$ of $\mathbf{y}(t)$-state by the $\mathbf{x}(t)$-state.

From:
Frolov N., Maksimenko V., Lüttjohann A., Koronovskii A., Hramov A. **Feed-forward artificial neural network provides data-driven inference of functional connectivity.**
Chaos. 29 091101 (2019)
DOI: 10.1063/1.5117263

Artificial neuronal network

$$\mathbf{y}(t) = \mathbf{F}(\mathbf{x}(t))$$

$$R^2 = 1 - \frac{\sum_{d=1}^{D}\sum_{i=1}^{N}\left(y_d(t_i) - y'_d(t_i)\right)^2}{\sum_{d=1}^{D}\sum_{i=1}^{N}\left(y_d(t_i) - \bar{y}_d\right)^2},$$

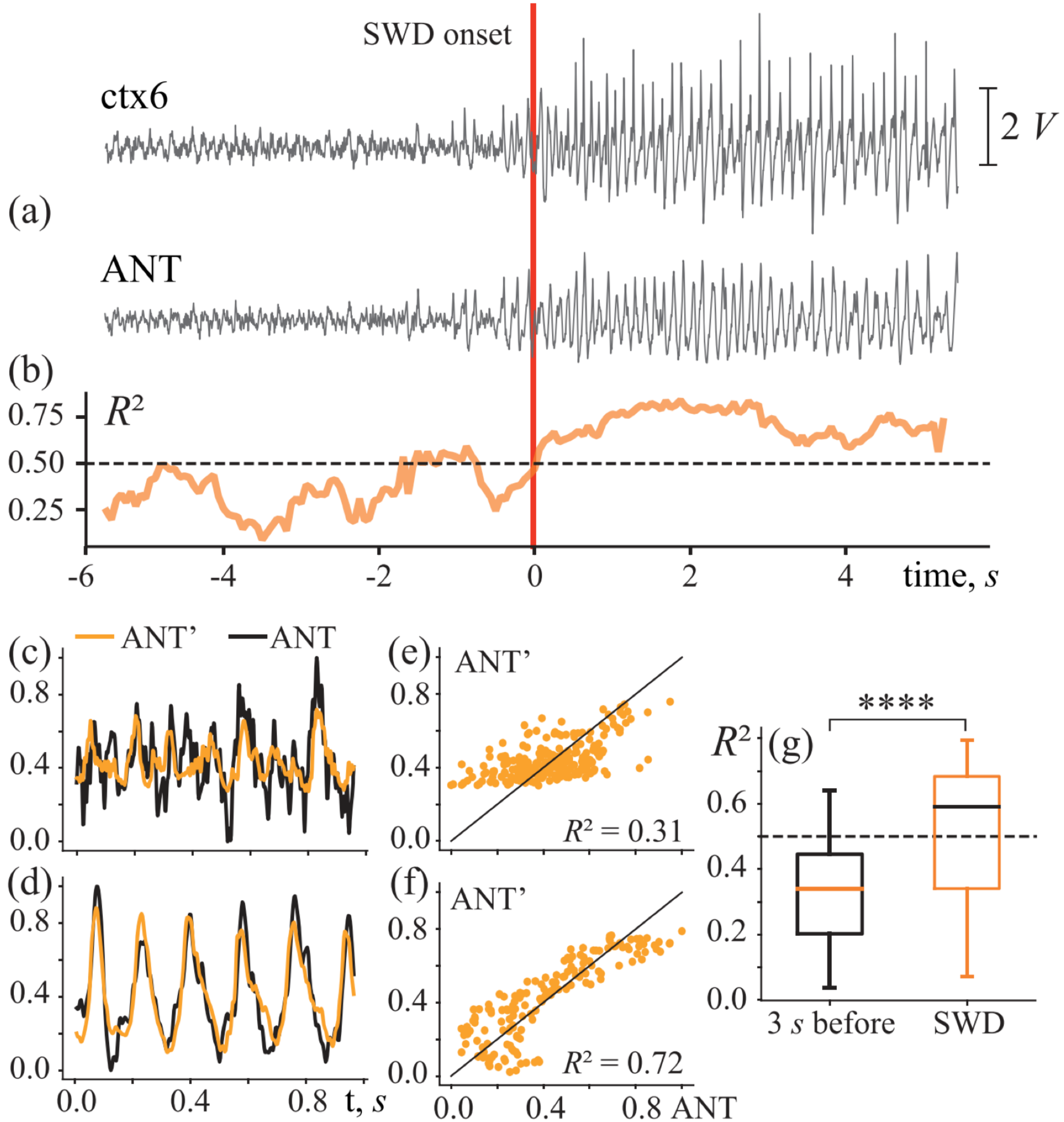
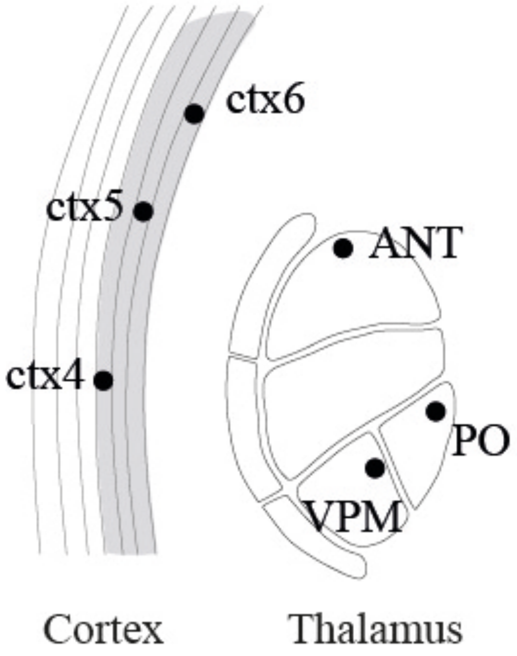
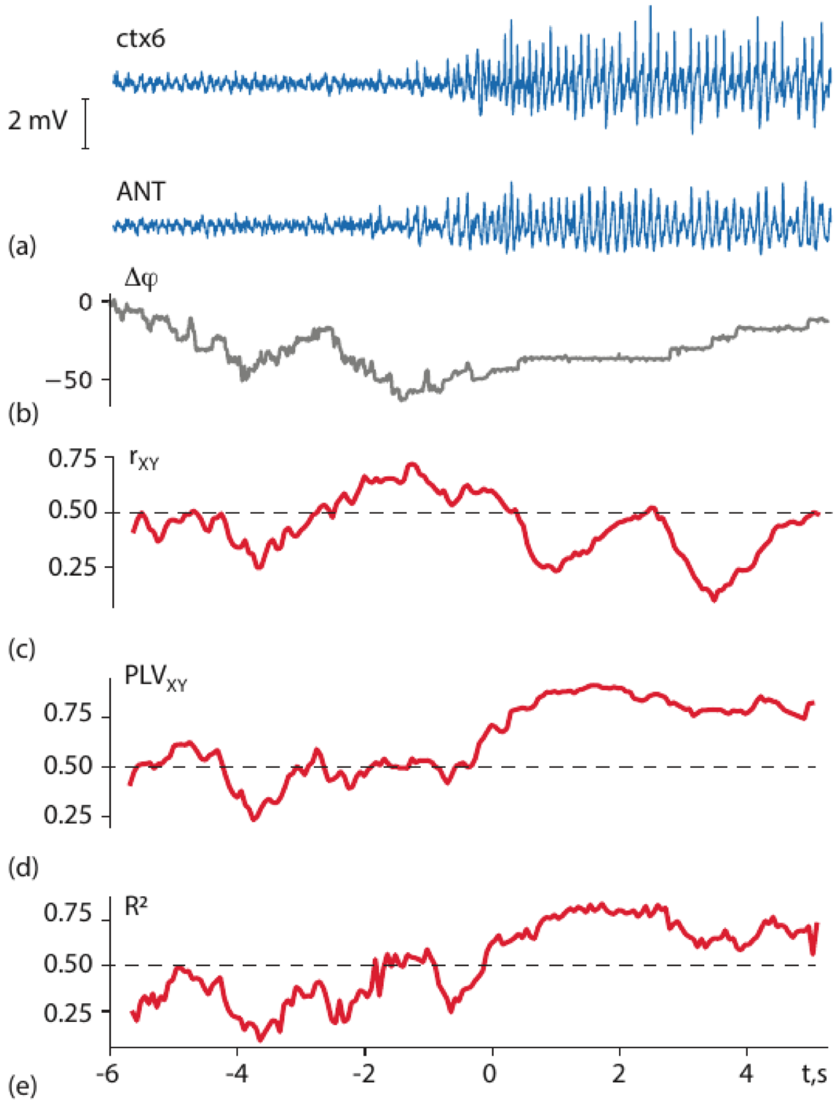


FIG. 5. (a) Typical ECoG signals recorded in cortical layer ctx6 and thalamic nucleus ANT of epileptic rat's brain including SWD beginning. (b) R^2-score computed in a floating 1-s window. Illustrations of ANT signal predictability 3 s before (c) and during SWD onset (d). Plots (e) and (f) present results of regression analysis for (c) and (d). (g) Comparison of R^2-scores computed 3 s before and during SWD onset over 20 seizure trials collected over 5 rats ($p < 0.0001$ via Wilcoxon signed-rank test for related samples). Dashed line in (b) and (e) defines R^2 threshold level of 0.5.

Comparative example





Phase difference

Pierson coefficient

Phase-locking index

Artificial neuronal network

Freeware software for FBC restoration

FieldTrip (MATLAB)

http://www.fieldtriptoolbox.org/

BrainStorm (MATLAB)
https://neuroimage.usc.edu/brainstorm/

CRP Toolbox
http://tocsy.pik-potsdam.de/CRPtoolbox