Dynamic Functional Connectivity: Methods, Applications, and Issues

fMRI Seminar
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Outline

• Static versus Dynamic Functional Connectivity
• Sliding Window Correlation
• Dynamic Conditional Correlation
• Characterization of States from DFC estimates
• Characterization of States from Direct Data Modeling.
• Dependence on Wakefulness
• Nuisance Regression
Resting-State BOLD Connectivity

Static Functional Connectivity (FC):
Correlations computed over the duration of the scan (e.g. 5 to 10 minutes)

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Static FC Correlation Matrix

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Dynamic Functional Connectivity (DFC)
Sliding Window Correlation Analysis

ROI time courses (based on parcellation of choice, e.g. anatomic, HCP, ICA)

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Hutchison et al, NIMG 2013
Dynamic Functional Connectivity in Bipolar Disorder Is Associated With Executive Function and Processing Speed: A Preliminary Study
Tanya T. Nguyen, Sanja Kovacevic, Sheena I. Dev, Kun Lu, Thomas T. Liu, and Lisa T. Eyler
Online First Publication, October 24, 2016. http://dx.doi.org/10.1037/neu0000317

Underconnected, But Not Broken? Dynamic Functional Connectivity MRI Shows Underconnectivity in Autism Is Linked to Increased Intra-Individual Variability Across Time
Falahpour et al, Brain Conn. 2016

MPFC
DMN
Spurious DFC Fluctuations when the Window Length is too Short

95% confidence interval for null data is approximately \( \pm \frac{2}{\sqrt{\text{window length}}} \)

Because of the sliding window, neighboring estimates are highly correlated

Lindquist et al, NIMG 2014
Spurious DFC Fluctuations when the Window Length is too Short

\[ f = 0.025 \text{ Hz} \]
\[ T = 40 \text{ s} \]

**Recommendations:**
Use high pass filtering
Window Length \( > \frac{1}{(\text{Minimum Frequency})} \)
Example: if \( f_{\text{min}} = 0.01 \text{ Hz} \) \( \rightarrow W > 100s \)

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Leonardi and Van De Ville, NIMG 2015
Windowing low pass filters the DFC estimates.

Picking too long of a window can filter out fluctuations of interest.

In the literature, window lengths lie primarily in the range of 30s to 60s.

Most common window length is about 20 TRs.

Handwerker et al, NIMG 2012; Preti et al, NIMG 2017
Sliding Window DFC Issues

- Rectangular versus tapered windows: tapered windows can improve the low pass filtering properties, but can also be less sensitive to state transitions.

- Choice of window offset (or step size): Most common step sizes are (a) step size = window size and (b) step size = 1 TR. Lack of consensus.

Allen et al Cereb Cortex 2012; Shakli et al NIMG 2016; Preti et al NIMG 2017

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Dynamic Conditional Correlation (DCC)
Dynamic Conditional Correlation (DCC)

**Basic Idea:** At each time \( t \), DCC computes a time-varying covariance matrix \( Q_t \) as the weighted average of the past estimate \( Q_{t-1} \) and an update based on the current data \( e_t \).

\[
\begin{align*}
\sigma^2_{i,t} &= \omega_i + \alpha_i y^2_{i,t-1} + \beta_i \sigma^2_{i,t-1} \quad \text{for } i = 1, 2 \\
D_t &= \text{diag}\{\sigma_{1,t}, \sigma_{2,t}\} \\
\epsilon_t &= D_t^{-1} e_t \\
Q_t &= (1-\theta_1-\theta_2)\bar{Q} + \theta_1 \epsilon_{t-1} \epsilon'_{t-1} + \theta_2 Q_{t-1} \\
R_t &= \text{diag}\{Q_t\}^{-1/2} Q_t \text{diag}\{Q_t\}^{-1/2} \\
\Sigma_t' &= D_t R_t D_t.
\end{align*}
\]

GARCH model that allows for time-varying variance.

[Diagram showing a time series with annotations relating to DCC formulas]

http://sfb649.wiwi.hu-berlin.de/fedc_homepage/xplore/tutorials/sfehtmlnode66.html

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Lindquist et al, NIMG 2014
Dynamic Conditional Correlation (DCC)
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• Static versus Dynamic Functional Connectivity
• Sliding Window Correlation
• Dynamic Conditional Correlation
• **Characterization of States from DFC estimates**
• Characterization of States from Direct Data Modeling.
• Dependence on Wakefulness
• Global Signal and Nuisance Regression
A

- group ICA components
- subject time courses
- windowed correlation matrices
- aggregate across subjects
- k-means clustering

B

Hutchison et al, NIMG 2013; Allen et al Cerb. Cortex 2012;
http://www.optimaldesign.com/ArrayMiner/AMAlgorithms.html

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At each time point, the correlation matrix is assigned to the cluster that has the most similar DFC state.
The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery; Calhoun et al, Neuron 2014

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At each time point, the correlation matrix is represented as a linear combination of orthogonal principal FC components.
Principal Components of Dynamic Functional Connectivity

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Leonardi et al (2014) argued that the PCA representation may be a better representation of resting-state data.
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Cluster averages are used to form the co-activation patterns (CAPS). 4 out of 30 are shown here.
Hidden Markov Models

Hidden Markov Modeling: assume that the FMRI time series data can be described using a hidden sequence of a finite number of states, where each state has a mean activation and connectivity pattern.

The transition matrix represents the probability of moving from one state to the next.

\[
p(y_t^s|S_t^s=i, \mu_i, \Sigma_i) = \frac{1}{(2\pi)^p/2|\Sigma_i|^{1/2}} \exp \left\{ -\frac{1}{2}(y_t^s - \mu_i)^T (\Sigma_i)^{-1} (y_t^s - \mu_i) \right\}
\]

data state mean covariance

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Eavani et al, Inf Proc. Med Imaging 2013
Hidden Markov Modeling: assume that the FMRI time series data can be described using a hidden sequence of a finite number of states, where each state has a mean activation and connectivity pattern. The transition matrix represents the probability of moving from one state to the next.
Windowed K-Means states

HMM States
Connectivity states based on sparse dictionary representation

State 1

State 2

State 3

State 4

State 5

Connectivity states based on sliding-window + K-means analysis

State 1

State 2

State 3

State 4

State 5

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Yaesoubi et al, HBM 2018
Recap: Sliding window versus data modeling approaches

(a) Sliding window analysis

(b) Hidden Markov model
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Simultaneous EEG/fMRI

Original data

MR gradient removed, filtered, and down-sampled to 250Hzs

Cardio-ballistic artifacts removed

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Tagliazucchi et al 2012
Figure 1. Subjects Quickly Fall Asleep during Resting-State fMRI Recordings

(A) Probability of subjects being continuously awake as a function of time. After 10 min, ~50% of the subjects had at least one epoch of sleep.

(B) Probability of subjects being awake and in the different NREM sleep stages (N1, N2, and N3 sleep) as a function of time.

(C) Total time spent by the subjects in wakefulness and all NREM sleep stages. Throughout ~40% of the experiment, subjects were asleep. The vertical dashed lines indicate that 10 min have elapsed since the experiment started.
DFC and Wakefulness Fluctuations

A. C1
C2
C3
C4

B. BOLD signal time series

C. EEG - Classification

Haimovici et al, Sci Rep 2017

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DFC and Wakefulness Fluctuations

Haimovici et al, Sci Rep 2017
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Nuisance Terms in fMRI

- Head motion
- Physiological traces: Peak amp., Heart rate, Global sig., Resp. belt
- fMRI signal

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Power et al 2016
Nuisance parameter regression

\[ Y = \beta_1 T_x + \beta_2 T_y + \beta_3 T_z + \beta_4 R_x + \beta_5 R_y + \beta_6 R_z + \beta_7 Y_{GS} + \beta_8 Y_{CSF} + \beta_9 Y_{WM} + \varepsilon \]

Head motions were regressed out to remove spin-history artefact.
Nuisance effects in DFC Estimates

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Nalci et al, NIMG 2019; ISMRM 2018 Abstract #2394
Nuisance effects in DFC Estimates

Percent Variance Explained (RMS) vs. Mean Orthogonal Nuisance Fraction

Linear Fit ($R^2=0.79$)

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Nalci et al, NIMG 2019; ISMRM 2018 Abstract #2394
$$|\Delta \text{DFC}| \leq 2 \left( \frac{1 - \sqrt{|n_o|^2/|n|^2}}{1 + \sqrt{|n_o|^2/|n|^2}} \right)$$
Nuisance effects in Static FC Estimates

Nalci et al, NIMG 2018
Nuisance effects in Static FC Estimates

(a) FC Estimates vs. IHMI Scan Norm
- Pre FC ($r_{TSN}=0.37, p=0.0019$)
- Post FC ($r_{TSN}=0.37, p=0.0017$)

(b) FC Estimates vs. Total IHM+WM+CSFI Scan Norm
- Pre FC ($r_{TSN}=0.53, p=3.8e-06$)
- Post FC ($r_{TSN}=0.31, p=0.0095$)

(c) FC Estimates vs. Total IGS+HM+WM+CSFI Scan Norm
- Pre FC ($r_{TSN}=0.63, p=1e-06$)
- Post FC ($r_{TSN}=0.3, p=0.013$)

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Summary

- Most DFC studies have been based on sliding window approaches.
- DFC states can be estimated from the sliding window estimates, and the properties of these states can be analyzed (e.g. transition probabilities, dwell times).
- Growing interest in direct data modeling to define DFC states. These approaches address some of the issues with the sliding window approach (e.g. fixed window length).
- Arousal and vigilance variations are a potential source of DFC fluctuations. Suggests the need for additional simultaneous measures of the subject’s state.
- Nuisance regression (including GSR) has an effect on DFC estimates, but more work is needed in this area.
Suggested Reading


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