Introduction to Connectivity: resting-state and PPI

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Types of Brain Connectivity

- **Anatomical/ Structural connectivity** refers to the physical presence of an axonal projection from one brain area to another.

- **Functional connectivity** refers to the correlation structure (or more generally: any order of statistical dependency) in the data such that brain areas can be grouped into interacting networks.

- **Effective connectivity** modeling moves beyond statistical dependency to measures of directed influence and causality within the networks constrained by further assumptions.

Connectivity - From a historical perspective, the distinction between functional segregation and functional integration relates to the dialectic between localizationism and connectionism that dominated ideas about brain function in the 19th century.

The default mode network, shown here in resting-state fMRI scans (Upper), includes the posterior cingulate cortex, hippocampus, and the medial prefrontal cortex. (Lower) Diffusion tensor imaging, an MRI technique that highlights the brain's white matter, reveals nerve fibers connecting these brain regions (posterior cingulate cortex in red; medial prefrontal cortex in yellow; hippocampus in green and pink).
FUNCTIONAL CONNECTIVITY

• Resting State Connectivity - Different regions of the brain’s sensorimotor system fluctuated slowly and synchronously in the absence of any explicit task. It was the first step toward the study of “resting-state connectivity,” (Biswal, 1995).

• Advantages
  • Resting-brain networks
  • Clinical Studies

• Disadvantages
  • Experimental Control
Resting state fMRI

- **Spatiotemporal Characteristics**
  - ‘task-positive’ or ‘task-negative’
  - cortico-cerebellar and cortico-subcortical connectivity associations
  - functional connectivity
- **Spectral Characteristics**
  - **Then**: Low Frequency ranges (0.01–0.08 Hz), separable from respiratory (0.1–0.5 Hz) and cardiovascular (0.6–1.2 Hz)
  - **Now**: Filtering RSN signals haemodynamic response function ‘flattens’ (0.01 Hz up to 0.15 Hz)
  - RSN ‘neural’ dynamics may be more ‘broadband’ than previously thought
- **RSNs and Electrophysiological Recordings**
  - fMRI - low-frequency oscillations
  - EEG - higher frequency neuronal oscillatory activity
Summarizing time series data

1. Time Frequency Analysis
2. Correlation (Functional Connectivity)
3. Cross Spectral Density – Frequency
4. Graph theory measures

EEG/ fMRI data

Choosing brain regions

- Task – based studies
  - General Linear Model (GLM)
  - Psychophysiological Interaction (PPI)

- Resting State
  - Independent Component Analysis (ICA)
  - Seed Based Correlation Analysis (SCA)
Independent component Analysis (ICA)

- Decomposes a two-dimensional data matrix into the time courses and associated spatial maps of the underlying 'hidden' signal sources
- **Advantage**: identify networks of spontaneous coherence comparable to known sensory and cognitive processing systems
- **Disadvantage**: decomposition is obtained by means of iterative optimization - run-to-run variability

Source: Tharwat, A., 2020
SEED Based correlation Analysis (SCA)

- *a priori* selection of a voxel, cluster or atlas region
- Time Series Data – Regressor – GLM = *univariate*
- **Advantage**: network of regions most strongly functionally connected with the seed voxel or ROI
- **Disadvantage**: influence of structured spatial confounds, such as *other* RSNs or structured noise

Source: Fox, M. & Raichle, M. 2007
Network properties - I

Source: Sporns O., 2013
Network properties - II

Source: Sporns O., 2013
Useful concepts?

- **Anti-correlated Networks**
  - task-negative DMN and task-positive attentional/cognitive control RSNs
- **Networks within-networks**
  - distinct patterns of functional connectivity exist, which share some spatial overlap in their foci, but underlie different aspects of cognitive control
- **Reciprocal Task – Rest Interactions**
  - Influence exerted by task-related activity and performance over network activity in resting periods, and *vice versa*.
- **Correlation is not Causality**
  - Is this due to incidental network-activity or noise?
Psychophysiological Interaction (PPI)
Functional connectivity

Effective connectivity

Sporns (2007)
Psychophysiological Interaction

Question:
Is the correlation in activity between two distant brain areas different in different psychological contexts?
Measures effective connectivity: how psychological variables or external manipulations change the coupling between regions

A. How contribution of one region to another is influenced by the experimental context

B. How an area’s response to an experimental context is modulated by input from another region

Zhan & Yu (2014)
Mathematically

From PowerPoint: Annamaria Balogh and Karel Kieslich
Expert: Dr Sarah Gregory
Practical Example

**Stimuli:**
SM = Radially moving dots  
SS = Stationary dots

**Task:**
TA = Attention  
TN = No attention

Francuzz (2014)

Büchel & Friston (1997)
How can brain activity in V5 (motion detection area) be explained by the interaction between attention to visual motion & V1/V2 (primary visual cortex) activity?
Practical Example

Remember the GLM equation for fMRI data?

\[ Y = X_1 \cdot \beta_1 + X_2 \cdot \beta_2 + \ldots + \beta_0 + \varepsilon \]

<table>
<thead>
<tr>
<th>Observed BOLD response</th>
<th>Regressor 1</th>
<th>Coefficient 1</th>
<th>Regressor 2</th>
<th>Coefficient 2</th>
<th>Constant</th>
<th>Error</th>
</tr>
</thead>
</table>

\[ Y = (V_1) \beta_1 + (\text{Att-NoAtt}) \beta_2 + [(\text{Att-NoAtt}) \cdot V_1] \beta_3 + \beta_0 + \varepsilon \]

**Physiological Variable:** V1 Activity  
**Psychological Variable:** Attention – Non-attention  
**Interaction:** the effect of attention vs no attention on V1 activity
Y = (V_1) \beta_1 + (\text{Att-NoAtt}) \beta_2 + [(\text{Att-NoAtt}) \times V_1] \beta_3 + \beta_0 + \varepsilon
**PPI: Analysis**

I. Standard GLM analysis (same preprocessing, first and second level analyses)

II. Extracting BOLD signal from a source region identified in the GLM and for which we want to investigate connectivity

III. Create interaction term

IV. Performing a second GLM including the interaction term, the source region’s extracted term and the experimental vector in the design
**PPI: Analysis**

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Standard GLM analysis

Determine regions of interest and interactions:

Adapted from: SPM12 Manualx
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Define Source Region and extract BOLD SIGNAL time series

Adapted from: SPM12 Manual
PPI: Analysis

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Second GLM

Green: task condition plot
Blue: convolved task conditions

Blue: Original BOLD signal
Red: Neuronal signal
Green: Deconvolved signal

PPI interaction term

All figures: adapted from: SPM12 Manual
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Second GLM

PPI GLM:

\[ Y = V_1 \beta_1 + (\text{Att-NoAtt}) \beta_2 + (\text{Att-NoAtt}) \cdot V_1 \beta_3 + \beta_i X_i + e \]

\( H_0: \beta_3 = 0 \)

Interaction effect

Adapted from: SPM12 Manual
Second GLM

PPI plot results:

```matlab
% Load PPIs
v2noatt = load( 'PPI_V2xNoAttention.mat' );
v2att = load( 'PPI_V2xAttention.mat' );
v5noatt = load( 'PPI_V5xNoAttention.mat' );
v5att = load( 'PPI_V5xAttention.mat' );

% Plot PPI data points
figure
d2noatt = PPI.ppi(v2noatt.PPI.ppi,
v5noatt.PPI.ppi, k');
hold on
plot(v2att.PPI.ppi,v5att.PPI.ppi, r');

% Plot the best fit for NoAttention
x = v2noatt.PPI.ppi(:,);
x = [x, ones(size(x))];
y = v5noatt.PPI.ppi(:,);
B = x\y;
y1 = B(1)*x(:,1)+B(2);
plot(x(:,1),y1, k-);
```

% For attention
Second GLM

PPI plot results:

Adapted from: SPM12 Manual
Questions?

End of Presentation

ANY QUESTIONS?
References

• Fox, M., Raichle, M. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8, 700–711 (2007). https://doi.org/10.1038/nrn2201