Characterizing task-related interactions between brain regions with fMRI

Functional and effective connectivity approaches

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Mapping brain function with fMRI:
Traditional univariate GLM approach to functional localization

\[ y = \beta X + \varepsilon \]
But brain regions do not act in isolation...

Felleman & Van Essen, 1991
Mapping brain function with fMRI: 
*Functional connectivity approach*

- Early functional connectivity analyses examined temporal correlations during the resting state (e.g., Biswal et al., 1995)
  - This approach continues to an extremely useful assay of inter-regional coupling

- Later studies began to examine *task-dependent* modulation of inter-regional coupling
  - Attending to motion vs. not attending to motion (Friston et al., 1997)
  - 2-back vs. 0-back working memory task (Lowe et al., 2000)
  - Listening to continuous speech vs. resting (Hampson et al., 2002)

- A growing collection of methods have been developed to extract information about functional interactions from fMRI data
Types of connectivity

**Documenting the correlation between spatially remote neurophysiological events**

- Data-driven / exploratory
  - Bivariate approaches (seed-based or ROI-based)
    - Timeseries correlations
    - Beta series correlations
  - Multivariate approaches
    - PCA, ICA, PLS

**Characterizing the influence that one neuronal system exerts over another**

- Hypothesis-driven / model-based
  - Psychophysiological interactions (PPI)
  - Structural equation modeling (SEM)
  - Dynamic causal modeling (DCM)
  - Granger causality

[figures adapted from Sporns (2007), Scholarpedia]
Functional connectivity

*Time series correlations*

- Similar to resting state analyses, except that correlations are computed on data collected during task performance
  - Requires that experiment utilizes a block design

Honey et al. (2002), *NeuroImage*
Functional connectivity

Time series correlations

Functional Connectivity Map - Reference Voxel in BA44/45 (-50 28 16)

Color Legend:
- words, pseudowords & letter-strings
- words & pseudowords
- words & letter-strings
- pseudowords & letter-strings

Bodke et al. (2001), Neuron
Measuring functional connectivity during distinct task stages: 
**Beta series correlation analysis**

Rissman, Gazzaley, and D'Esposito (2004), *NeuroImage*
• Beta series correlation analysis method applied to simple bimanual motor task.

• In the **Right-then-Left** condition, subjects played a sequence of 4 keystrokes with their right hand and then played a different sequence with their left.

• In the **Interleaved** condition, subjects played 8 keystrokes alternating between hands – a task requiring increased bimanual coordination.

• **Hypothesis:** The Interleaved condition should induce more inter-hemispheric cross-talk between motor regions.
Beta series correlations:
A meaningful metric of inter-regional coupling?

Bimanual coordination

One hand at a time

Univariate

Correlation

Rissman, Gazzaley, and D’Esposito (2004), *NeuroImage*
Beta series correlations: 
*A meaningful metric of inter-regional coupling?*

Rissman, Gazzaley, and D'Esposito (2004), *NeuroImage*
Beta series correlation analysis applied to a basic visual working memory task

- **Hypothesis**: Frontoparietal regions interact with neural ensembles in inferotemporal cortex to keep behaviorally-relevant visual representations active

- Analysis performed on fMRI data from 17 subjects

- **Task**: maintain a single face across a 7-8 sec delay period

- Which brain regions are most strongly correlated with this seed region during face maintenance?
Gazzaley, Rissman, and D'Esposito (2004), *Cognitive, Affective, and Behavioral Neuroscience*
Gazzaley, Rissman, and D'Esposito (2004), *Cognitive, Affective, and Behavioral Neuroscience*
Another example:
Age-related changes in prefrontal coupling

3 task conditions:
- Interrupting stimulus (IS): make judgment about face (male over 40?)
- Distracting stimulus (DS): ignore face; no decision required
- No interference (NI): no face stimulus presented

Older adults failed to reestablish connectivity following interruptions!
Pros & cons of beta series correlation method

• **Pros:**
  – Can examine how functional interactions between regions evolve over the course of a multi-stage trial
  – Relatively simple to implement (demo this afternoon)

• **Cons:**
  – Single trial activity estimates can be quite noisy
  – Serially-positioned HRF-convolved regressors may not provide ideal fit to data
  – Not ideal for rapid, jittered event-related designs
  – Cannot determine whether inter-regional correlations reflect direct or indirect communication
Psychophysiologically interaction (PPI)

• Bilinear model of how a psychological context $A$ changes the influence of area $B$ on area $C$:

$B \times A \rightarrow C$

• A PPI corresponds to a difference in regression slopes for different contexts

• Seed-based approach
  • PPI effects computed voxel-by-voxel across entire brain

Friston et al. (1997), *NeuroImage* [slide adapted from K.E. Stephan]
Psychophysiological interaction (PPI)

GLM of a 2x2 factorial design:

\[ y = (T_A - T_B) \beta_1 + (S_1 - S_2) \beta_2 + (T_A - T_B)(S_1 - S_2) \beta_3 + e \]

- Replace one main effect in the GLM by the time series of an area that shows this main effect
- e.g., swap out the main effect of stimulus type with the time series of area V1

Friston et al. (1997), *Neuroimage*

[slide adapted from K.E. Stephan]
Psychophysiological interaction (PPI)

PSY main effect (task variable)

PHYS main effect (time series from seed region)

PPI = PSY.*PHYS

Overlay:
Psychophysiologica\al interaction (PPI)

Friston et al. (1997), *NeuroImage*
Psychophysiological interaction (PPI)

\[ y = (T_A - T_B) \beta_1 + V1 \beta_2 + (T_A - T_B) V1 \beta_3 + e \]

Two possible interpretations of the PPI term:

[slide adapted from K.E. Stephan]
PPI on event-related fMRI data

The importance of hemodynamic deconvolution

\[(A \otimes \text{HRF}) \times (B \otimes \text{HRF}) \neq (A \times B) \otimes \text{HRF}\]

Gitelman et al. (2004), NeuroImage
Pros & cons of PPI analysis

• Pros:
  – Provides useful exploratory assay of how a given region’s connectivity with the rest of the brain is modulated by task context
  – Easy to implement (FSL demo this afternoon)

• Cons:
  – Can only model contributions from a single area
  – PPI regressor may be highly correlated with psychological task regressor, reducing power
    • Factorial designs help avoid this problem!
  – Limited causal interpretability
Inferring causality from fMRI data

• How can we determine whether the apparent relationship between activity fluctuations in two regions is due to their *direct* communication or the *indirect* influence of another region?
Structural Equation Modeling (SEM)

• A technique for characterizing the causal relationship between variables based on their covariance structure
  – Widely used in the social sciences; Also referred to as “path analysis”
  – First applied to PET data (McIntosh & Gonzalez-Lima, 1992, 1994) and later extended to fMRI data (Büchel & Friston, 1997)

• Requires specification of anatomical graph model indicating hypothesized connections between brain regions
  – Connection paths are unidirectional (reciprocal connections allowed)
  – Model should be motivated by anatomical data (tracer studies / DTI)

• Parameters of the model are estimated by minimizing the difference between the observed covariances and the covariances implied by the structural model
  – Compare goodness of fits across models
Assessing effects of task context

- Let’s revisit the Attention-to-Motion data set
- How does attention influence connectivity of these nodes?
- Null model: constrain path coefficients to be identical
- Alternative model: allow path coefficients to vary across conditions
- Allowing V1→V5 path to vary significantly improves goodness of fit

Penny et al. (2004), *NeuroImage*
Comparing path coefficients across populations

Schlösser et al. (2003), *NeuroImage*
Pros and cons of SEM

Pros:
• Can examine the functional interplay of many brain areas at once
• Allows inferences about the causal structure within a network

Cons:
• Need to partition time series data to calculate condition-specific covariances
• No explicit inputs to system
  – use primary sensory regions and/or estimate residual influences
• Some models are not identifiable
  – especially when lots of reciprocal connections are allowed
• Searching for the best model can be unreliable
  – adding connections vs. pruning connections?
  – constrain model to the be the same across subjects?
From static to dynamic models...

Seed voxel approach, PPI, SEM, etc.

Dynamic causal models

T₀  T₁  T₂  ...

T₀  T₁  T₂  ...

[slide adapted from Hanneke den Ouden; SPM Course]
Dynamic causal modeling (DCM)

- The dynamic state of a given neural circuit is modelled at its underlying **neuronal level** (not directly accessible with fMRI).
- The modeled neuronal dynamics (\(x\)) are transformed into area-specific ‘simulated’ BOLD signals (\(y\)) by a hemodynamic model (\(\lambda\)).
- The aim of DCM is to estimate parameters at the neuronal level such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.
  - Model parameters estimated using a Bayesian framework

[slide adapted from K.E. Stephan]
Dynamic causal modeling (DCM)

Schematic overview

**Intrinsic connections**
Based on prior data & concrete hypotheses
A Matrix

**BA39**

**STG**

**V4**

**BA37**

**V1**

**Contextual inputs**
Stimulus-free
{e.g., task set}
B Matrix

**Perturbing inputs**
Stimuli-bound
{e.g., visual words}
C Matrix

[slide adapted from Friston et al. (2003); J. Grace & H-M Boudrias]
The hemodynamic model

**activity** $x(t)$

**vasodilatory signal**

$$\dot{s} = x - ks - \gamma(f - 1)$$

**f low induction (rCBF)**

$$\dot{f} = s$$

**changes in volume**

$$\tau \dot{v} = f - v^{1/a}$$

**changes in dHb**

$$\tau \dot{q} = f E(f,E_0)/E_0 - v^{1/a}q/v$$

**BOLD signal**

$$y(t) = \lambda(v,q)$$

Hemodynamic parameters computed separately for each brain area

**Estimated BOLD response**

**stimulus functions**

$u$
Dynamic causal modeling (DCM)

Mathematical overview

Neural State Equation

\[ \dot{x} = \left( A + \sum_{j=1}^{m} u_j B^{(j)} \right) x + Cu \]

\[ \theta = \{ A, B, C \} \]

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\dot{x}_3 \\
\end{bmatrix} =
\begin{bmatrix}
a_{11} & a_{12} & 0 \\
a_{21} & a_{22} & a_{23} \\
0 & a_{31} & a_{33} \\
\end{bmatrix}
+ u_2
\begin{bmatrix}
0 & b^{(2)}_{21} & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
\end{bmatrix}
+ u_3
\begin{bmatrix}
0 & 0 & 0 \\
0 & b^{(3)}_{23} & 0 \\
0 & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
x_1 \\
x_2 \\
x_3 \\
\end{bmatrix}
+ \begin{bmatrix}
c_{11} & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
u_1 \\
u_2 \\
u_3 \\
\end{bmatrix}
\]

[slide adapted from Hanneke den Ouden; SPM Course]
The DCM processing stream
Model comparison

**Model 1:** attentional modulation of V1→V5

**Model 2:** attentional modulation of SPC→V5

**Model 3:** attentional modulation of V1→V5 and SPC→V5

Bayesian model selection: Model 1 better than model 2; model 1 and model 3 equal

Decide on Model 1 (since it is the simpler model):

*Attention primarily modulates V1→V5 pathway*
A recent DCM analysis example

Ballard (2011), J Neuroscience
Pros and cons of DCM

Pros:

• Like SEM, DCM examines the functional interplay of many brain areas at once
• Parameters estimated at the (inferred) neuronal level
• Stimulus-based and context-based perturbations of connectivity are explicitly coded into the model
  – Unlike SEM, where inputs are treated as unknowns and the path coefficients are separately computed for each condition
• Operates in the time series domain (dynamic)

Cons:

• Complex methodology with many built-in assumptions
• Requires a relatively small number of nodes to reduce model complexity
Thanks!