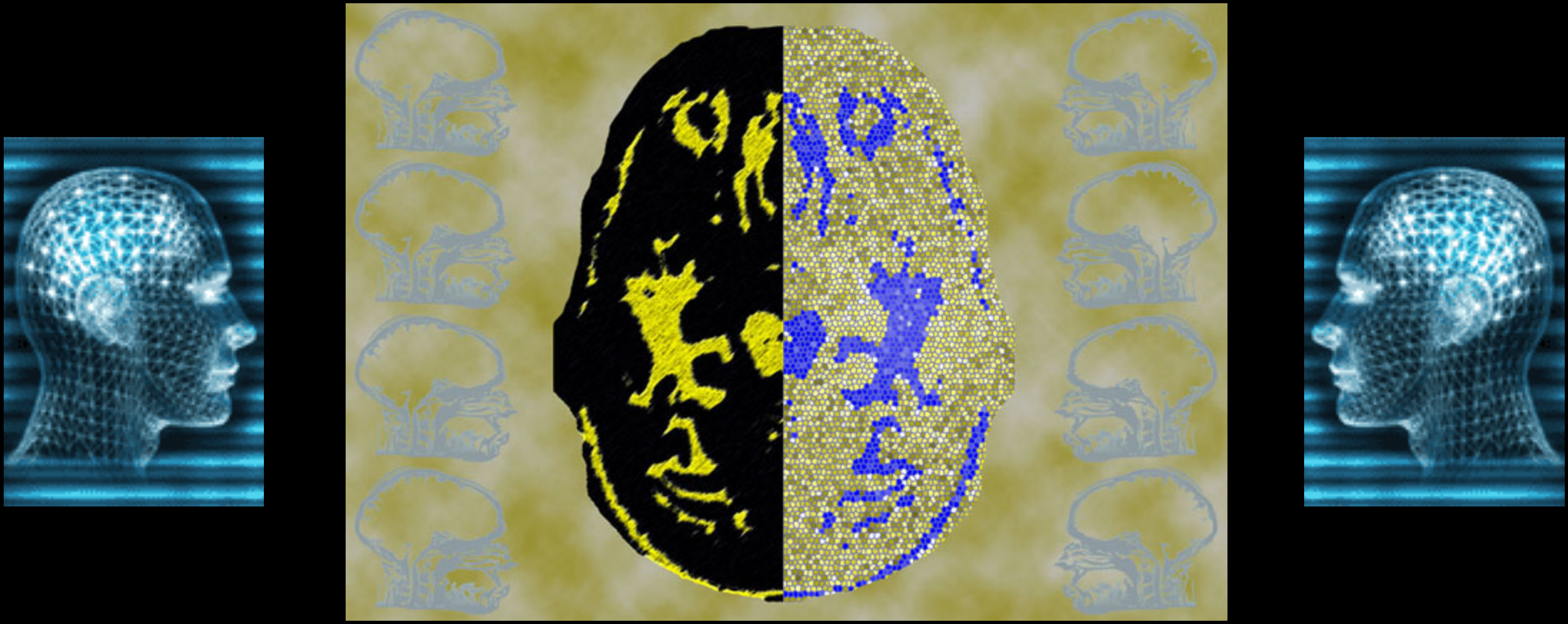
Characterizing task-related interactions between brain regions with fMRI

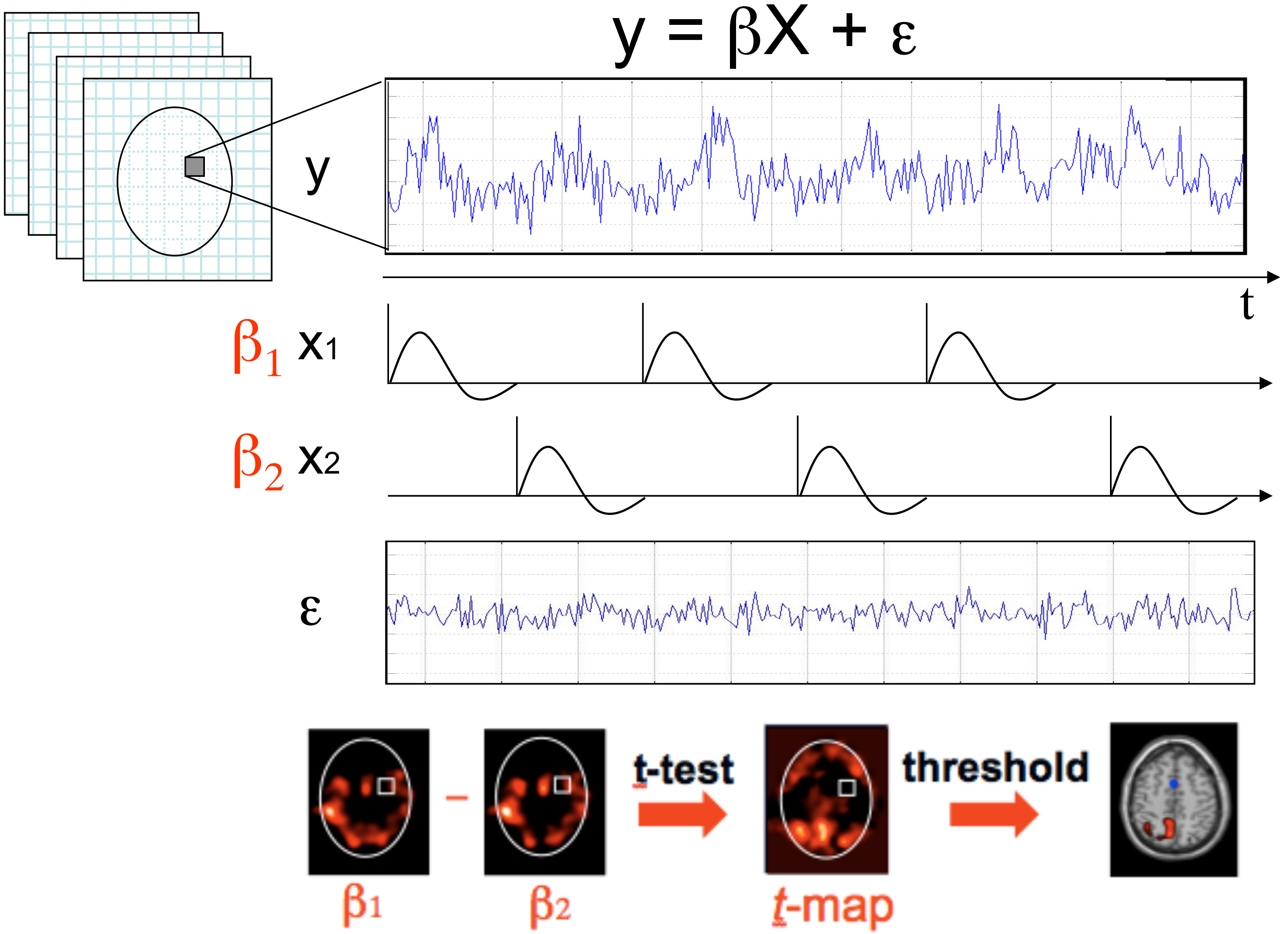
Functional and effective connectivity approaches



Jesse Rissman, Ph.D.
Dept. of Psychology
UCLA

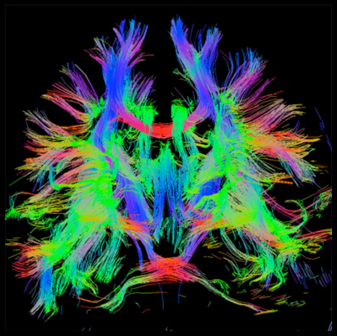
Mapping brain function with fMRI:

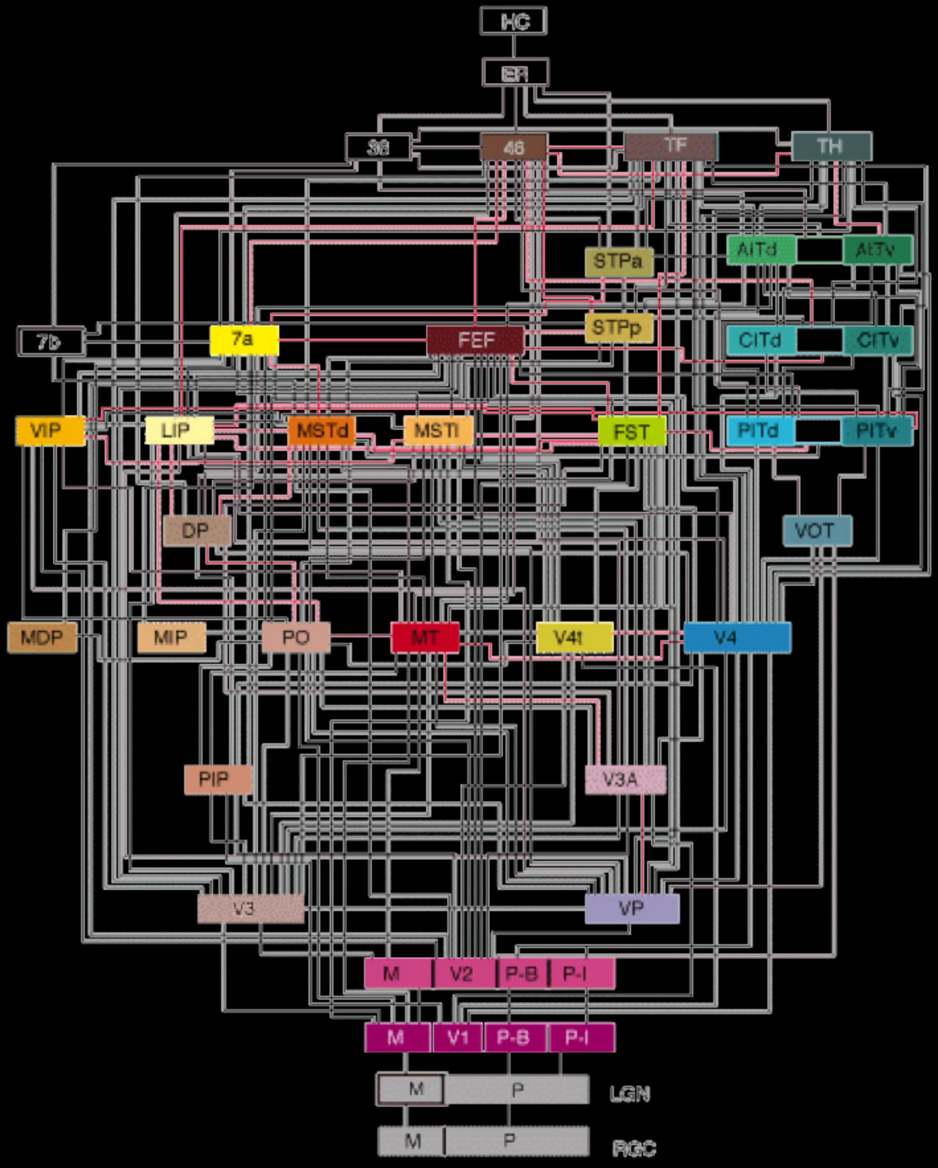
Traditional univariate GLM approach to functional localization



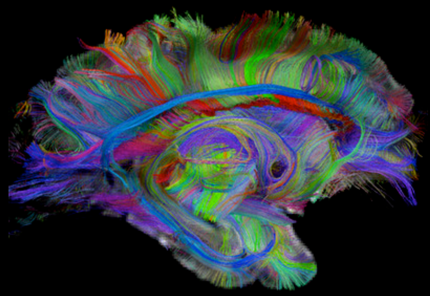
$$y = \beta X + \varepsilon$$

But brain regions do not act in isolation...



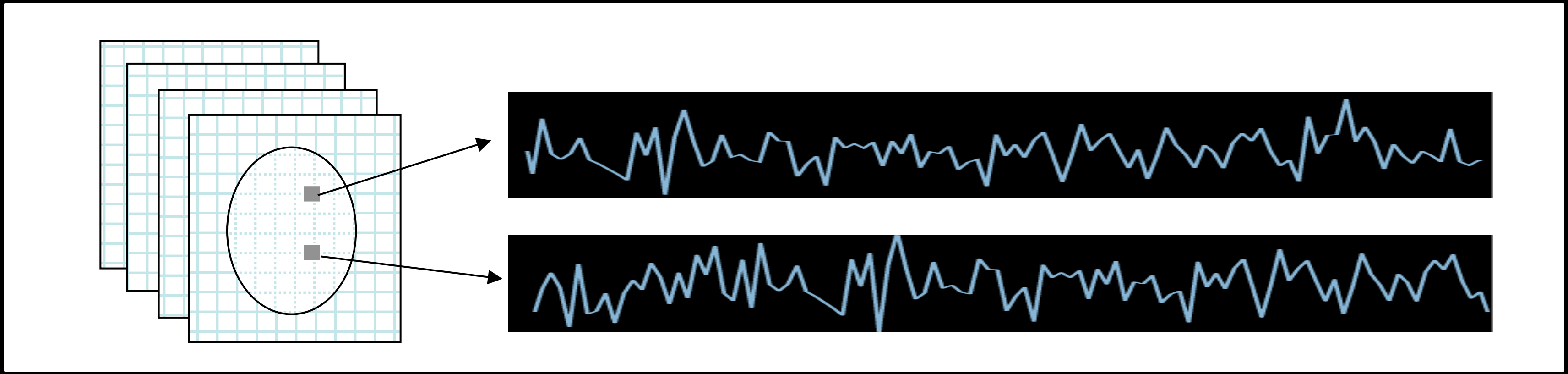


Felleman & Van Essen, 1991



Mapping brain function with fMRI:

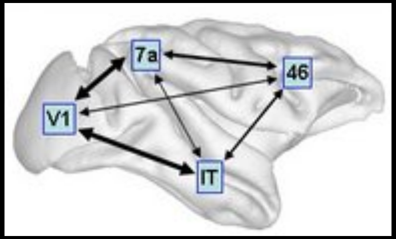
Functional connectivity approach



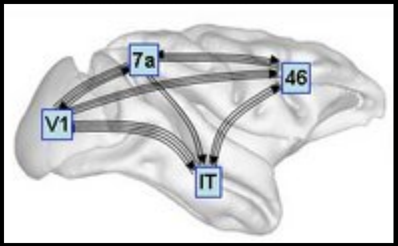
- Early functional connectivity analyses examined temporal correlations during the resting state (e.g., Biswal et al., 1995)
  - This approach continues to an extremely useful assay of inter-regional coupling
- Later studies began to examine task-dependent modulation of inter-regional coupling
  - Attending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

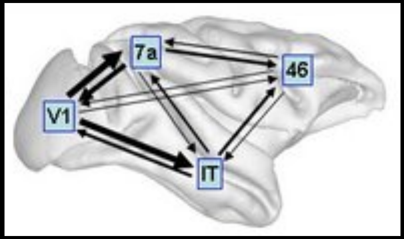
Functional Connectivity



Structural Connectivity



Effective 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

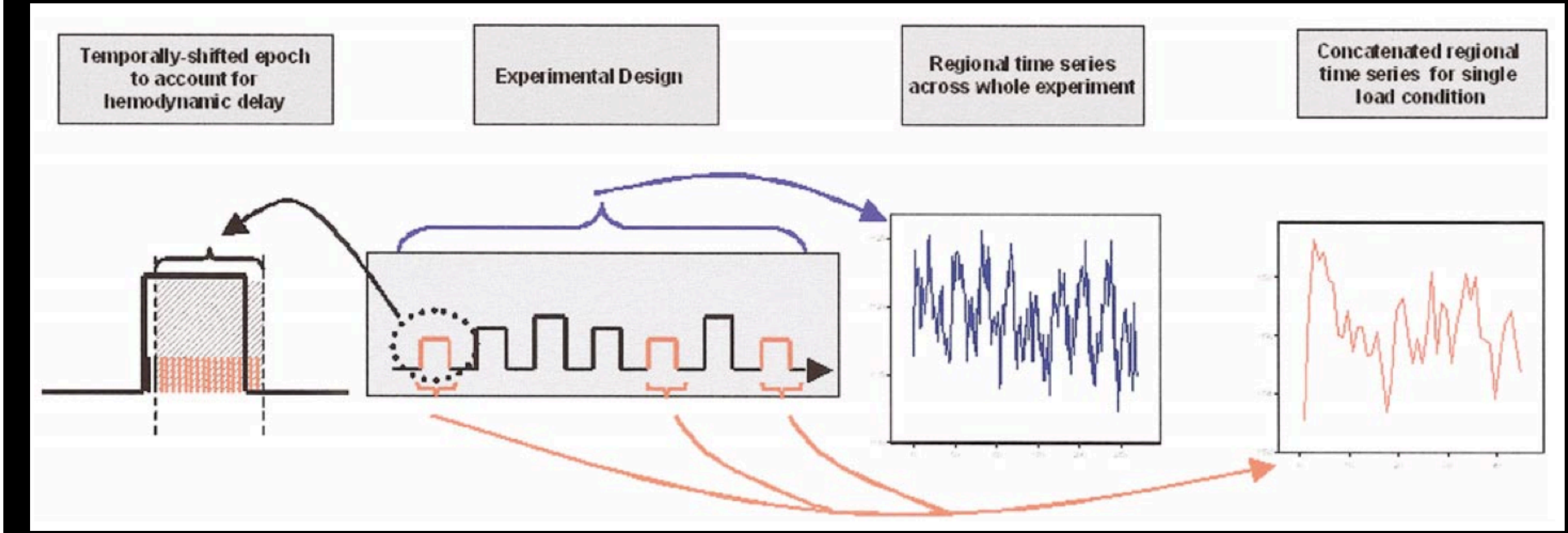
- Hypothesis-driven / model-based
  - Psychophysiological interactions (PPI)
  - Structural equation modeling (SEM)
  - Dynamic causal modeling (DCM)
  - Granger causality

[figures adapted from Sporns (2007), *Scholarpedia*]

Functional connectivity

Time series correlations

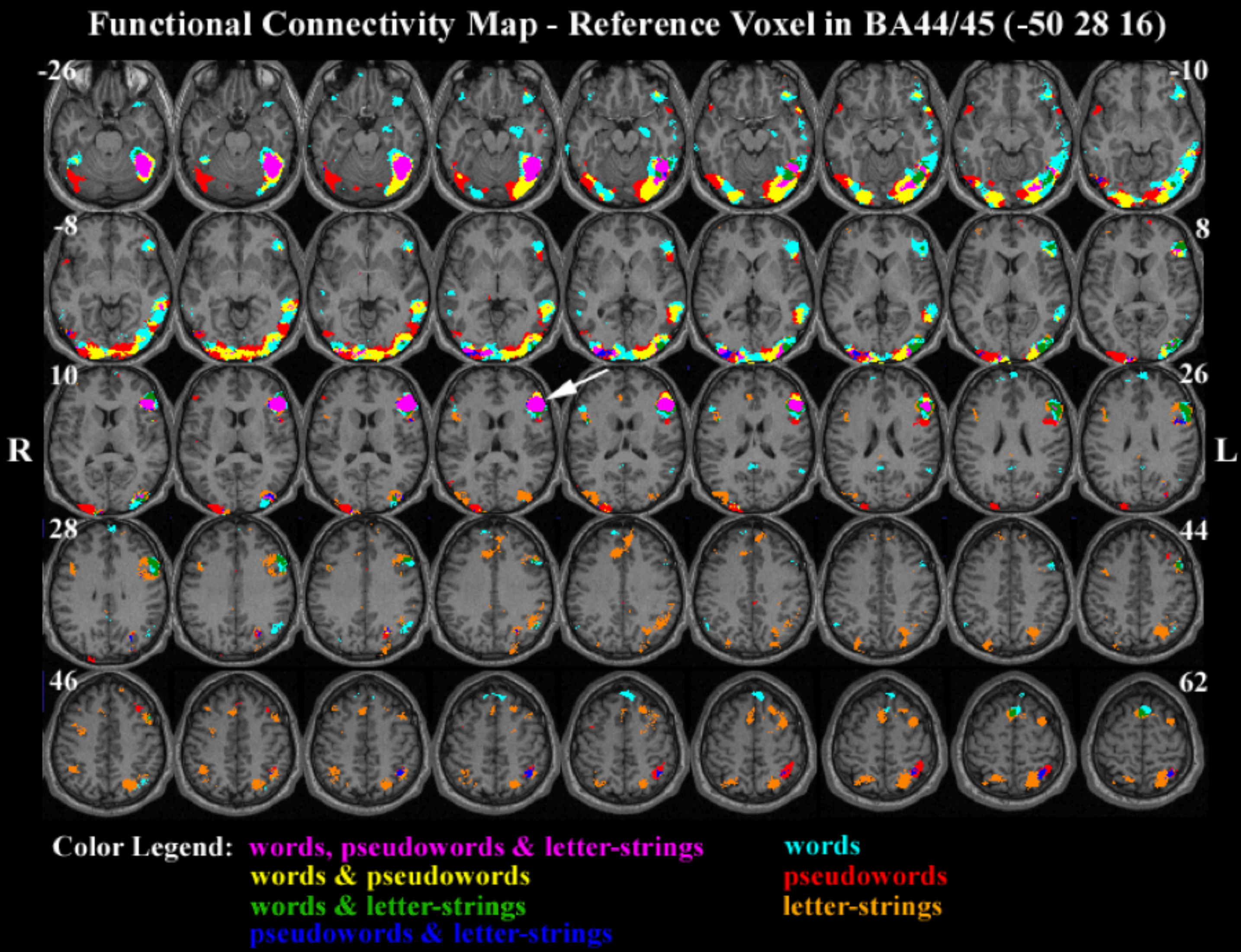
- Similar to resting state analyses, except that correlations are computed on data collected during task performance
  - *Requires that experiment utilizes a block design*



Honey et al. (2002), *NeuroImage*

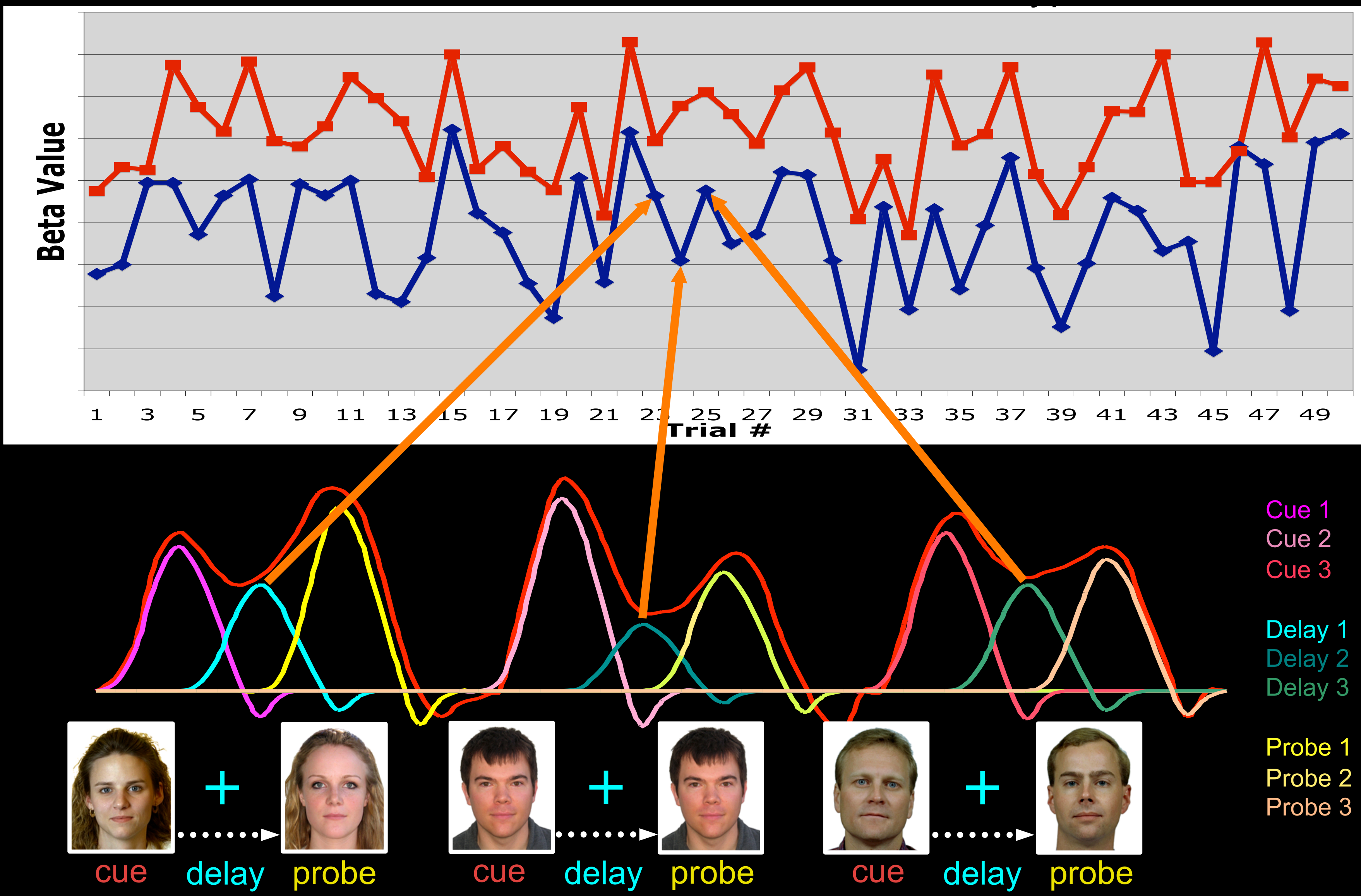
Functional connectivity

Time series correlations



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 correlations:

Methodological validation

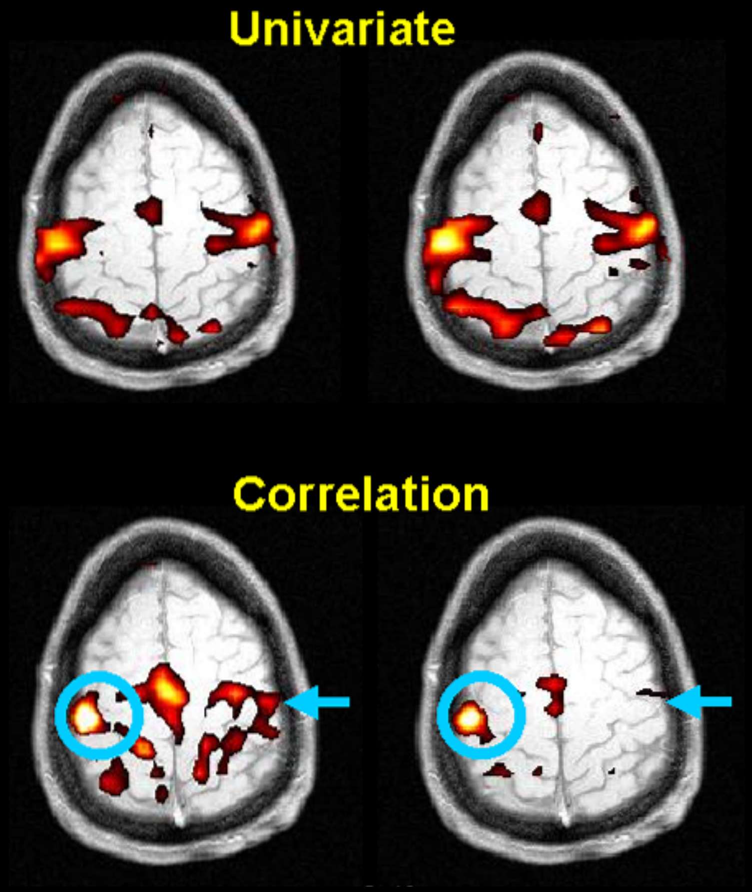
- Beta series correlation analysis method applied to simple bimanual motor task.
- In the **Right-then-Left** condition, subjects played a sequence of 4 keystrokes with their right hand and then played a different sequence with their left.
- In the **Interleaved** condition, subjects played 8 keystrokes 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

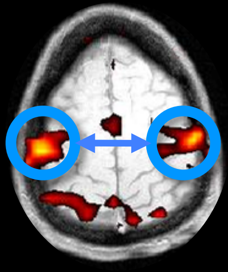
One hand at a time

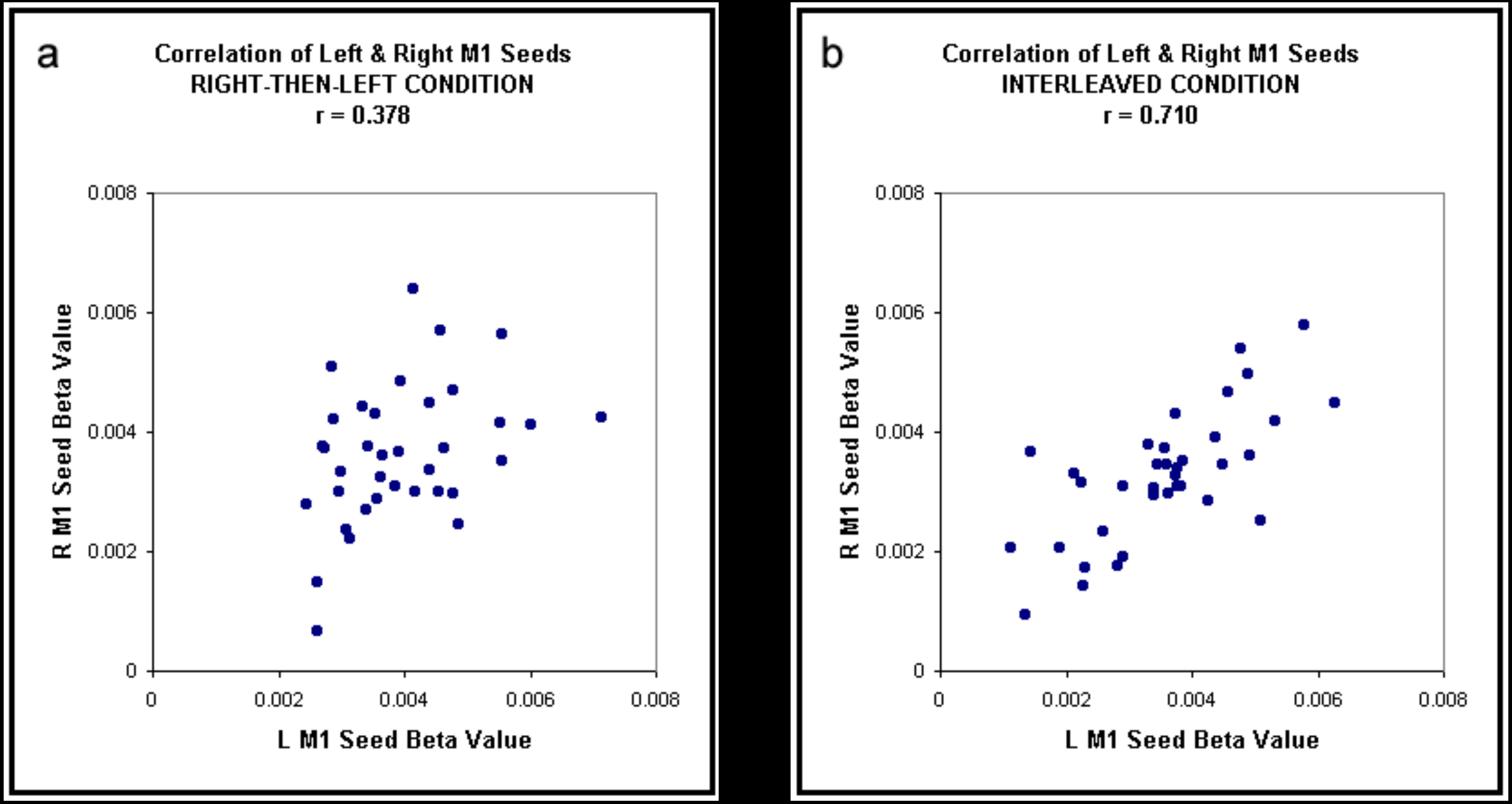


Rissman, Gazzaley, and D’Esposito (2004), *NeuroImage*

Beta series correlations:

A meaningful metric of inter-regional coupling?





a Correlation of Left & Right M1 Seeds
RIGHT-THEN-LEFT CONDITION
r = 0.378

b Correlation of Left & Right M1 Seeds
INTERLEAVED CONDITION
r = 0.710

Rissman, Gazzaley, and D’Esposito (2004), *NeuroImage*

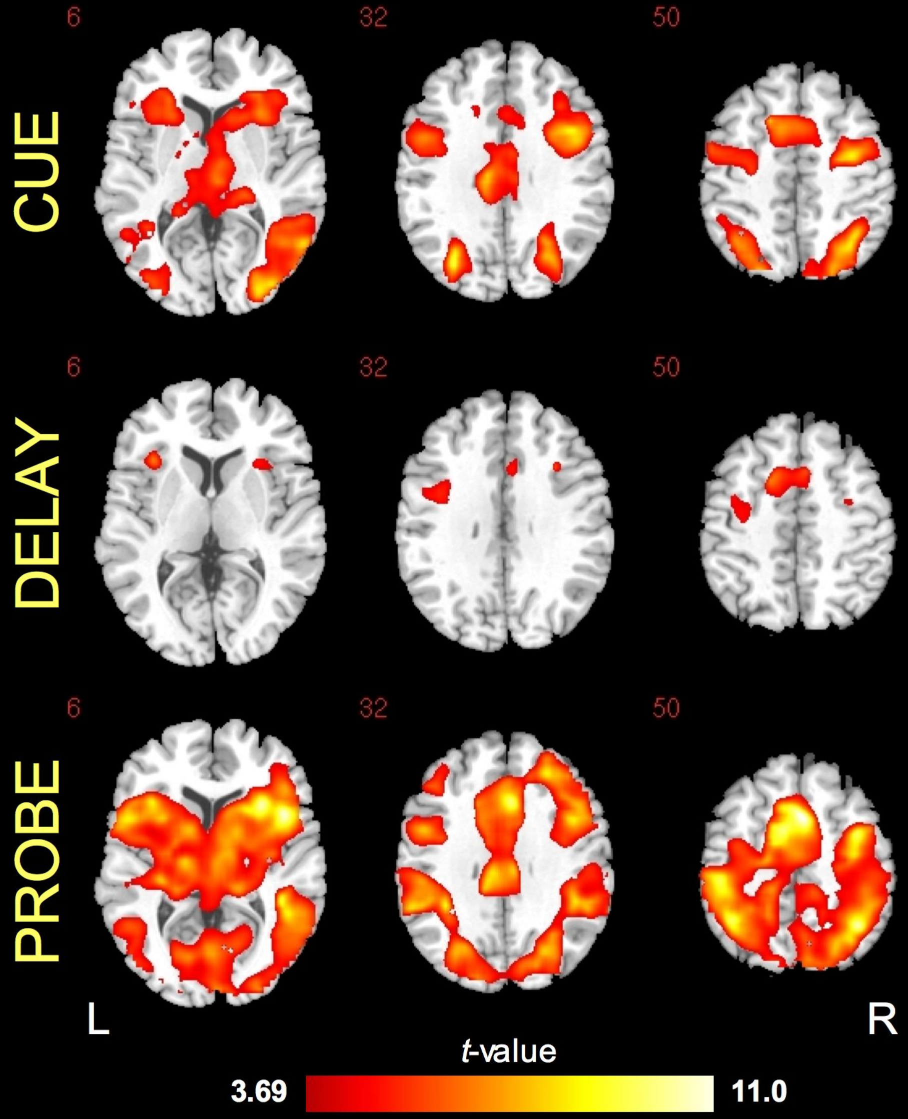
Beta series correlation analysis applied to a basic visual working memory task

- 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

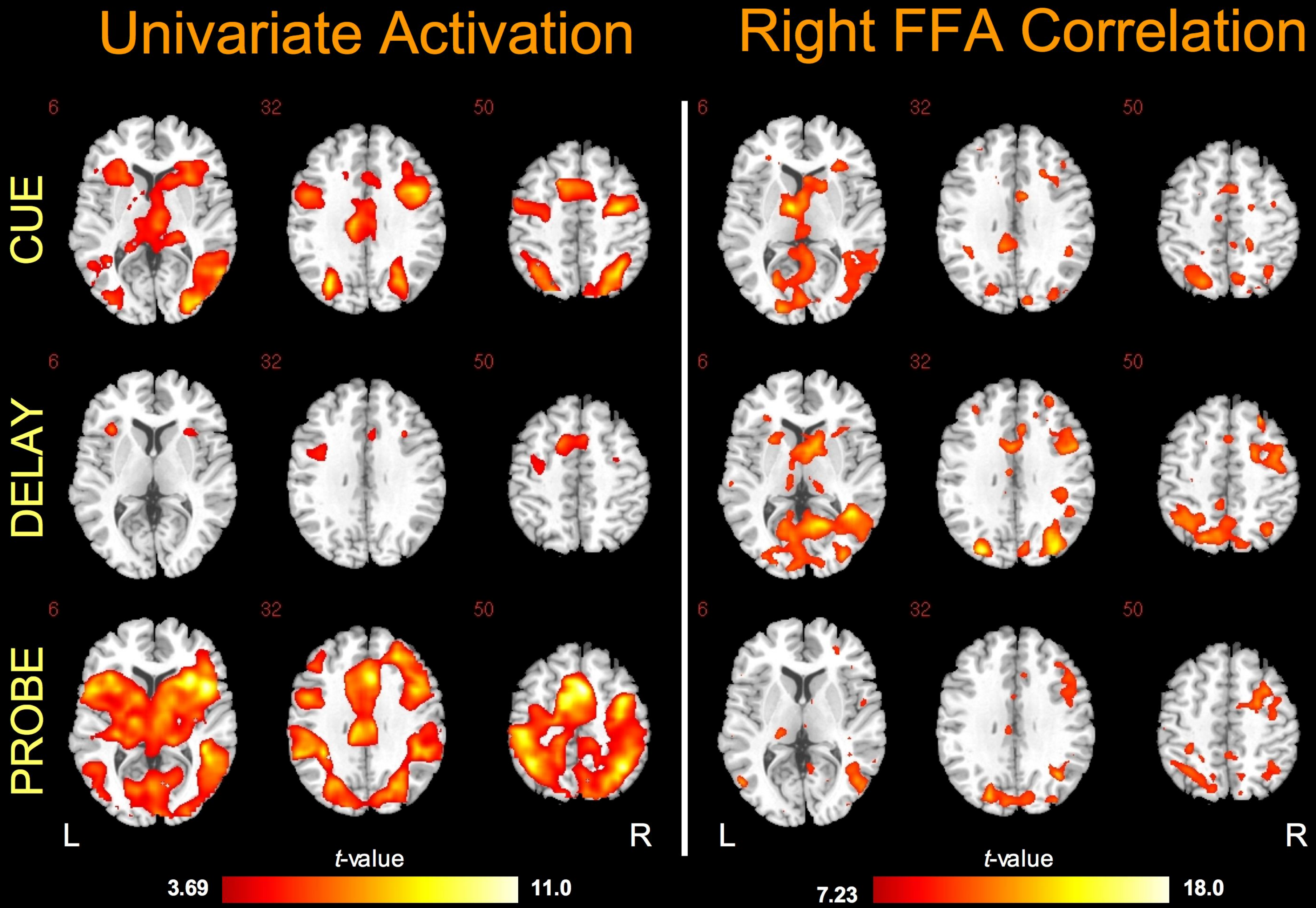
right fusiform face area (FFA) "seed"

Which brain regions are most strongly correlated with this seed region during face maintenance?

Univariate Activation



Gazzaley, Rissman, and D'Esposito (2004), *Cognitive, Affective, and Behavioral Neuroscience*



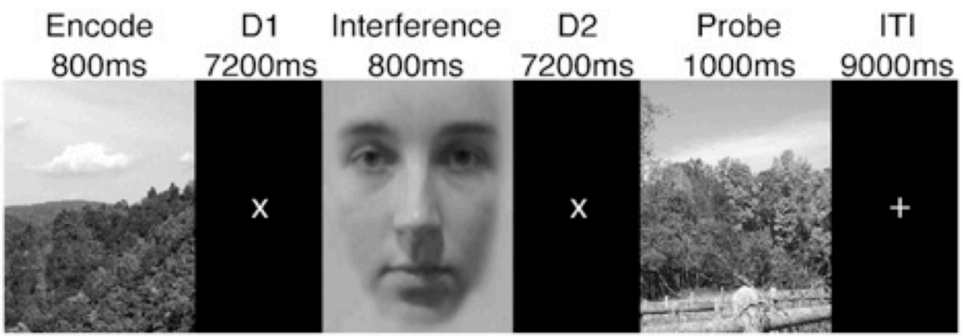
Univariate Activation

Right FFA Correlation

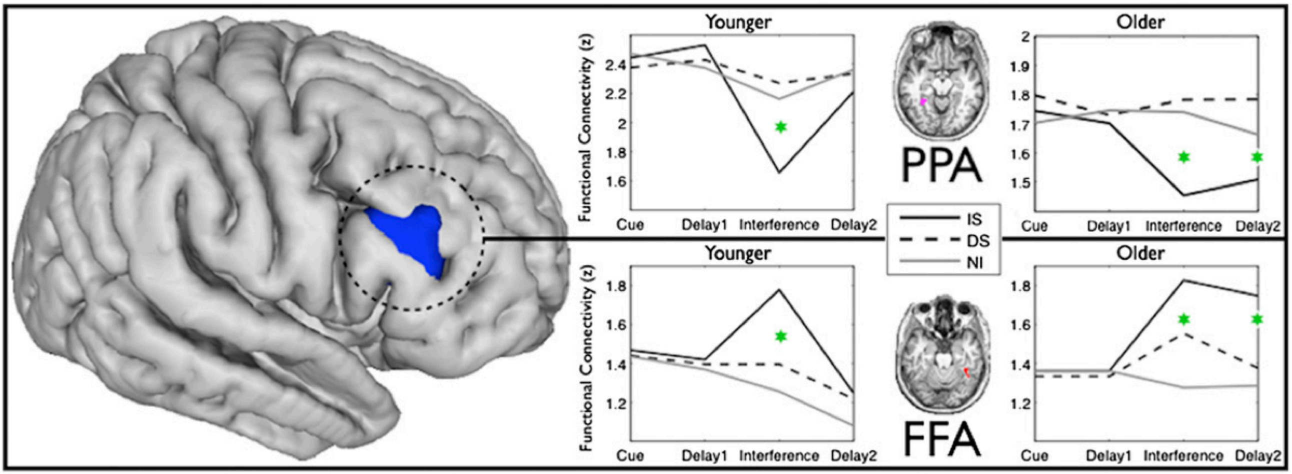
Gazzaley, Rissman, and D'Esposito (2004), *Cognitive, Affective, and Behavioral Neuroscience*

Another example:

Age-related changes in prefrontal coupling



<u>3 task conditions</u>:
- 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!

Clapp et al. (2011), *PNAS*

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

Psychophysiological interaction (PPI)

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

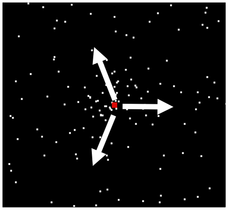
$$B \times A \rightarrow C$$

- 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)



		Task factor	
		Task A *NO ATTENTION*	Task B *ATTENTION*
Stimulus factor	Stim 1 *STATIC DOTS*	T_A/S_1	T_B/S_1
	Stim 2 *MOVING DOTS*	T_A/S_2	T_B/S_2

GLM of a 2x2 factorial design:

$$\begin{aligned} y = \; & (T_A - T_B)\,\beta_1 && \leftarrow \text{main effect of task} \\ & + (S_1 - S_2)\beta_2 && \leftarrow \text{main effect of stim. type} \\ & + (T_A - T_B)\,(S_1 - S_2)\beta_3 && \leftarrow \text{interaction} \\ & + e \end{aligned}$$

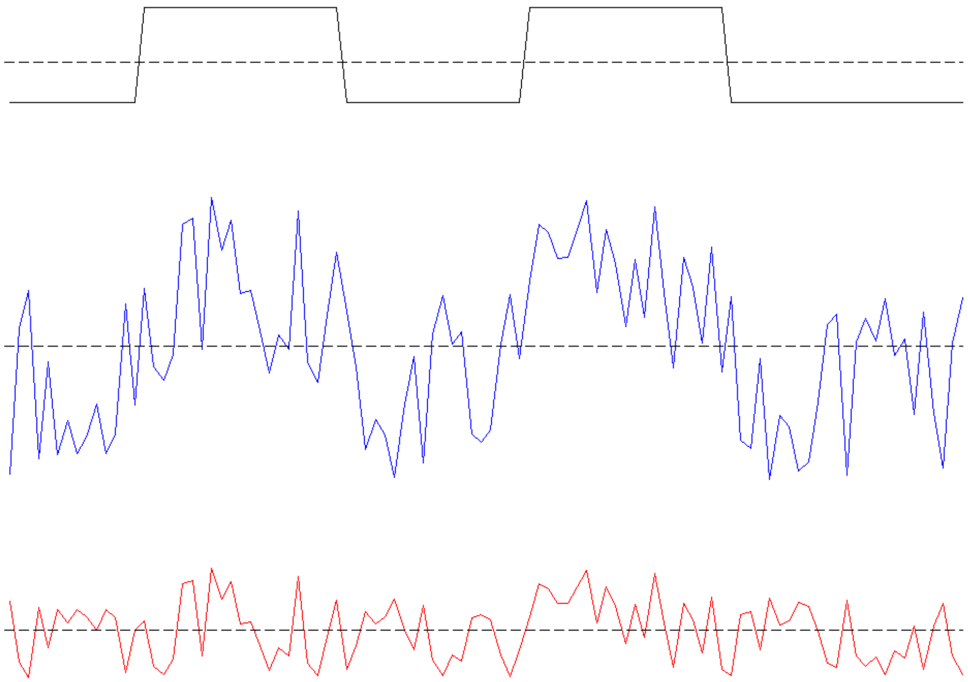
- Replace one main effect in the GLM by the time series of an area that shows this main effect
- e.g., swap out the main effect of stimulus type with the time series of area V1

$$\begin{aligned} y = \; & (T_A - T_B)\,\beta_1 && \leftarrow \text{main effect of task} \\ & + V1\beta_2 && \leftarrow \text{V1 time series} \approx \text{main effect of stim. type} \\ & + (T_A - T_B)\,V1\beta_3 && \leftarrow \text{psycho-physiological interaction} \\ & + e \end{aligned}$$

Friston et al. (1997), *NeuroImage*

[slide adapted from K.E. Stephan]

Psychophysiological interaction (PPI)



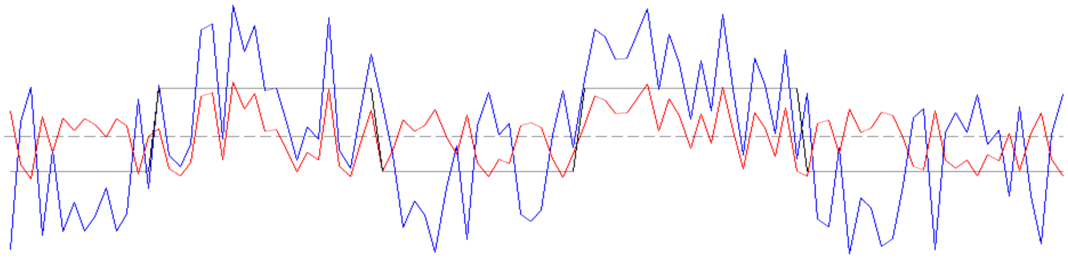
PSY main effect (task variable)

.*

PHYS main effect (time series from seed region)

PPI = PSY.*PHYS

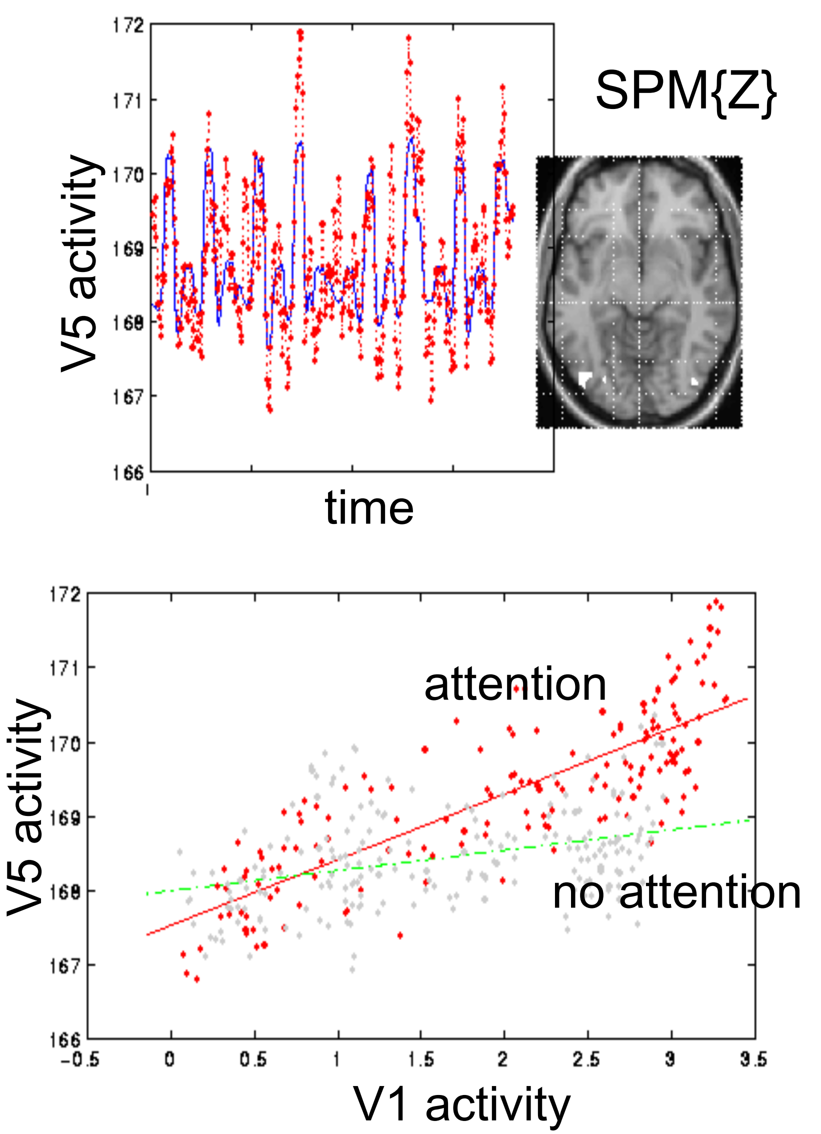
Overlay:



[slide adapted from J. O'Reilly]

Psychophysiological interaction (PPI)

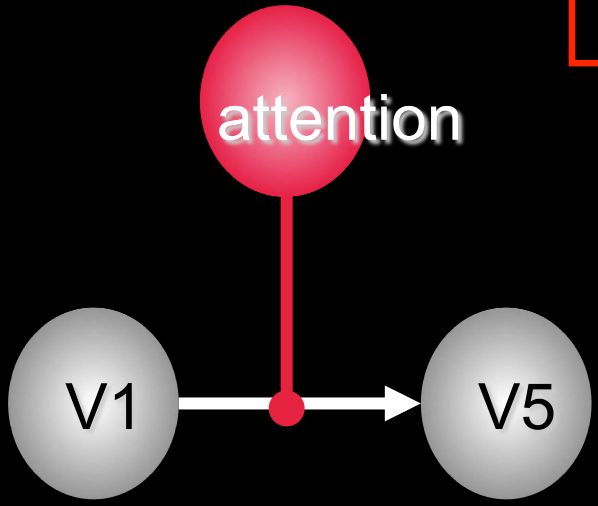
Friston et al. (1997), *NeuroImage*

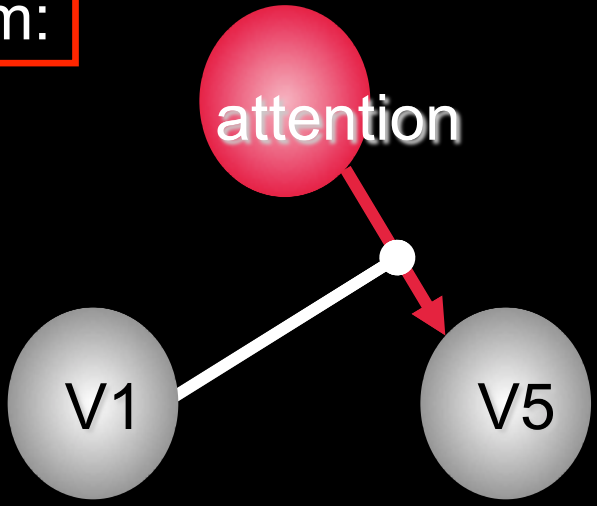


Psychophysiological interaction (PPI)

$$
\begin{aligned}
y = \; & (T_A - T_B)\,\beta_1 \\
& + V1\beta_2 \\
& + (T_A - T_B)\,V1\beta_3 \\
& + e
\end{aligned}
$$

Two possible interpretations of the PPI term:

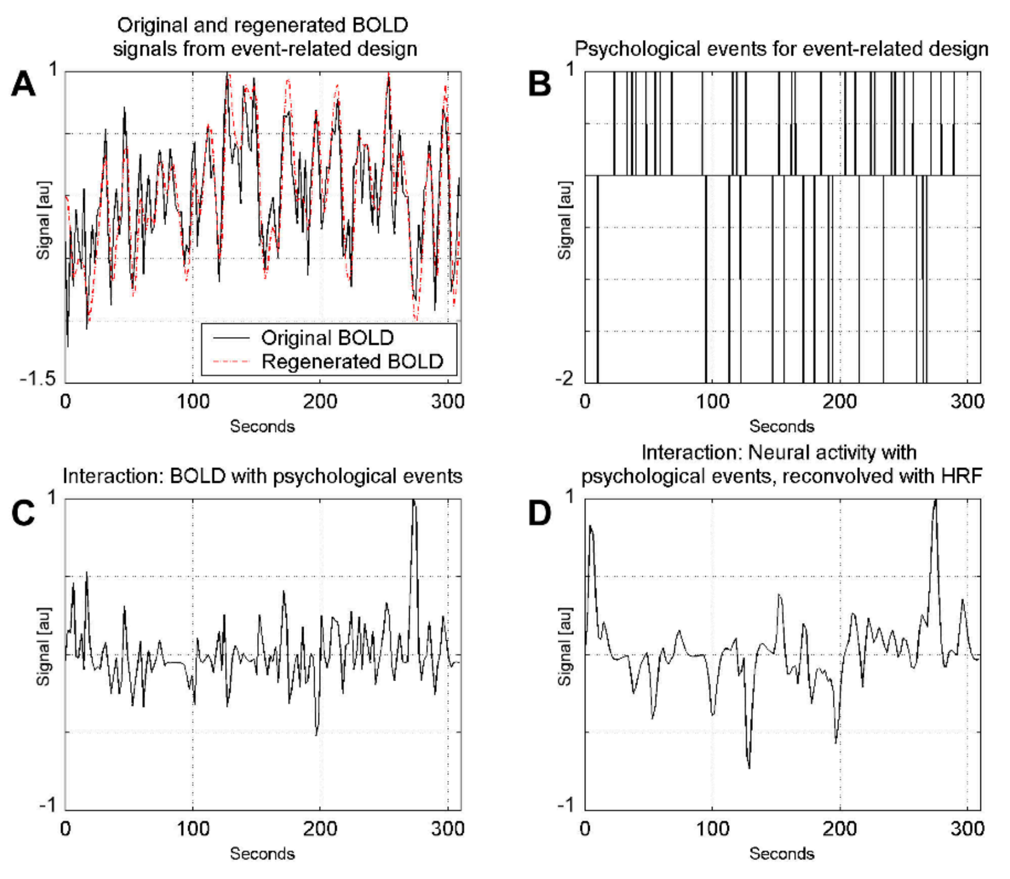




[slide adapted from K.E. Stephan]

PPI on event-related fMRI data

The importance of hemodynamic deconvolution



$$(A \otimes HRF) \times (B \otimes HRF) \neq (A \times B) \otimes HRF$$

Gitelman et al. (2004), *NeuroImage*

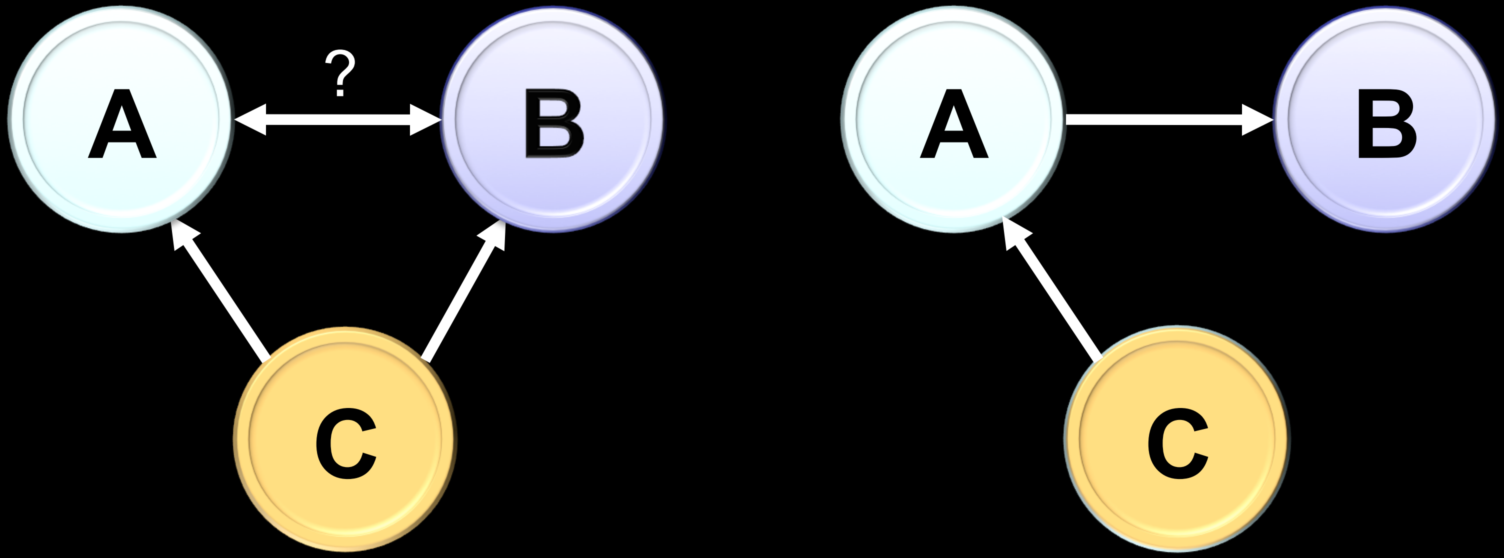
Pros & cons of PPI analysis

- 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?



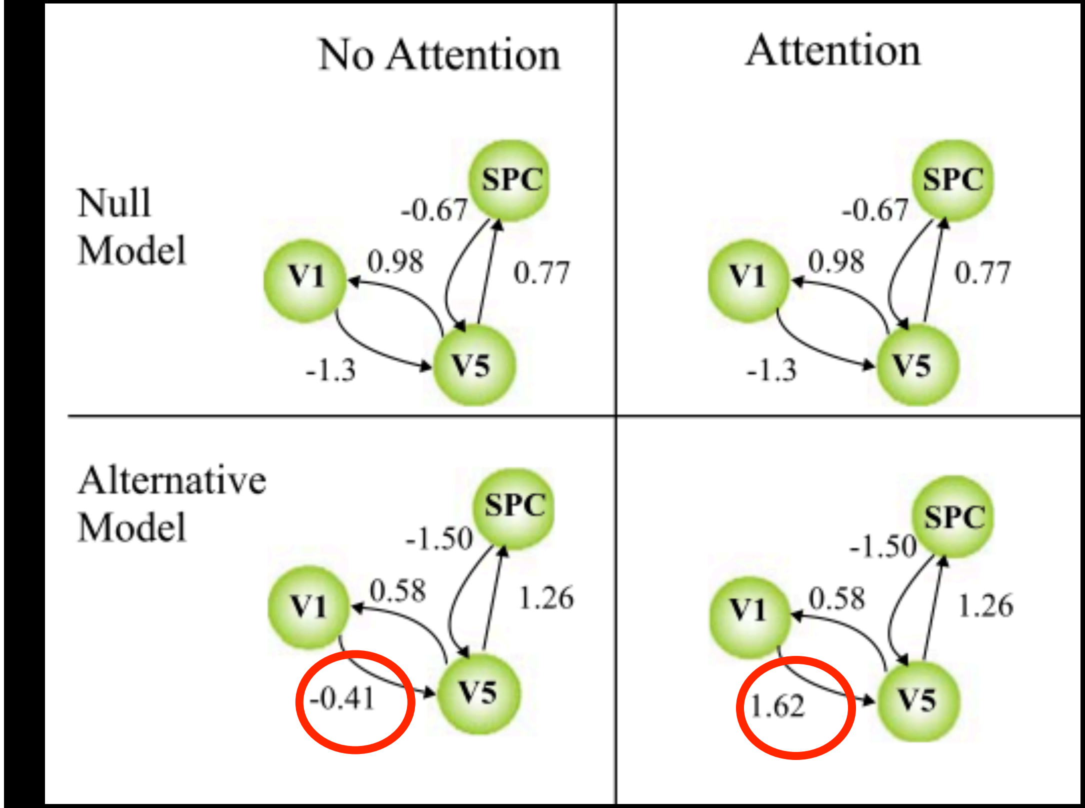
Structural Equation Modeling (SEM)

- 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

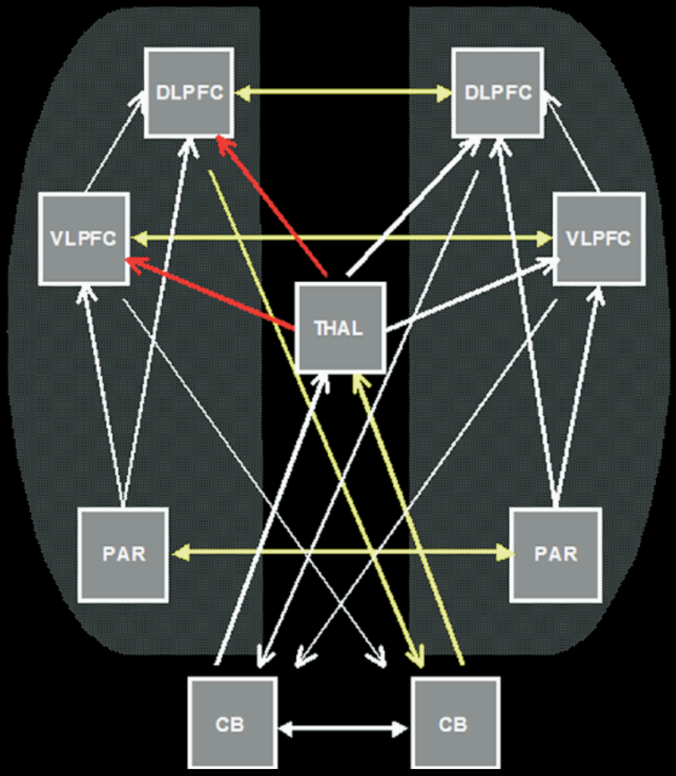
Assessing effects of task context



Penny et al. (2004), *NeuroImage*

- 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

Comparing path coefficients across populations



Patients > controls 🟥

Patients < controls 🟨

Schlösser et al. (2003), *NeuroImage*

Pros and cons of SEM

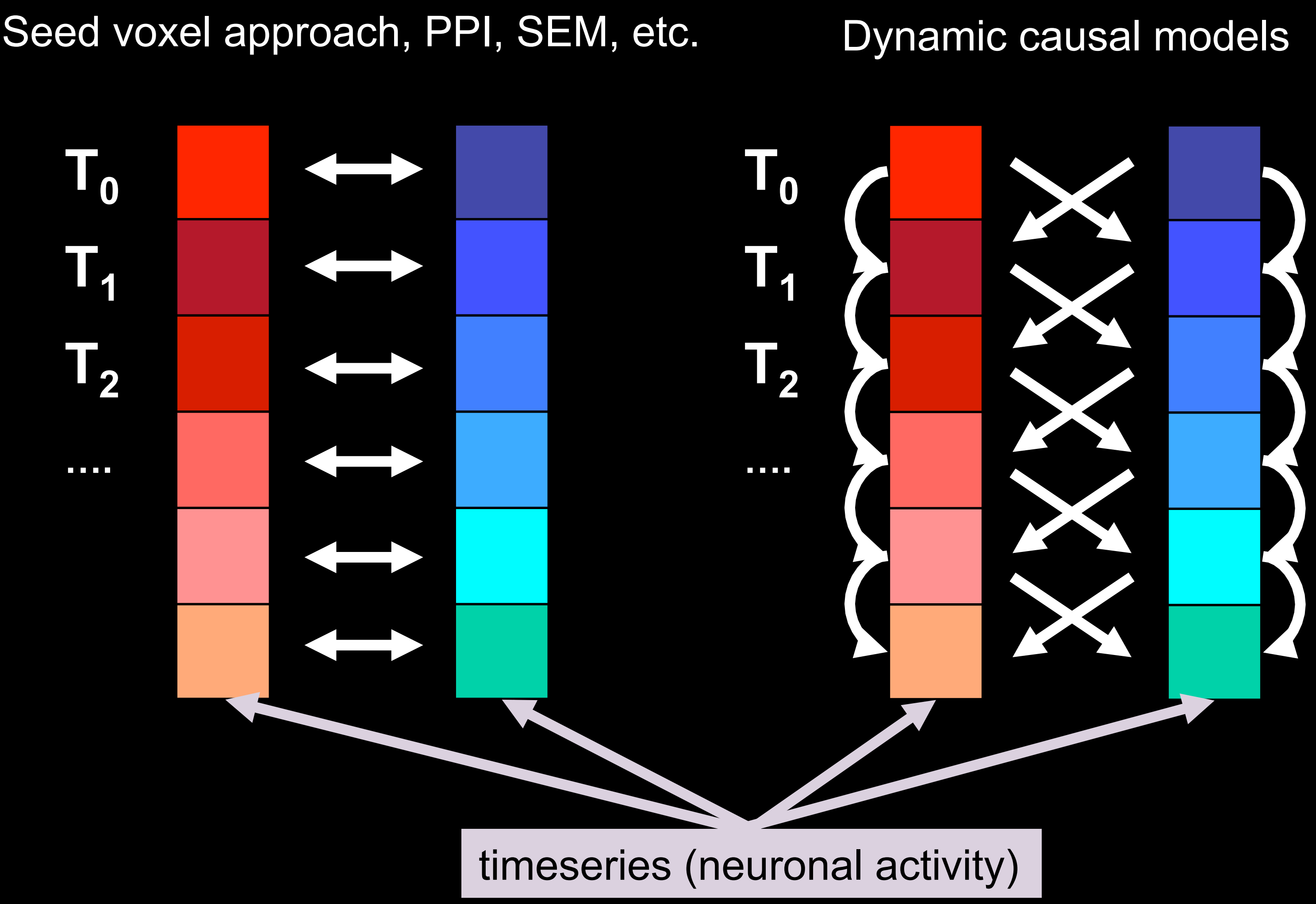
Pros:

- 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?

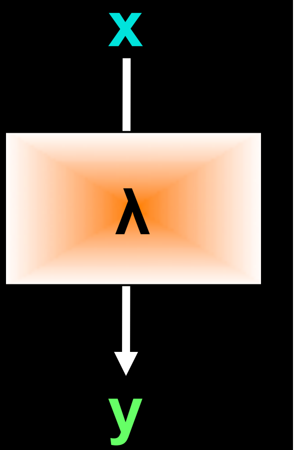
From static to dynamic models...



[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).

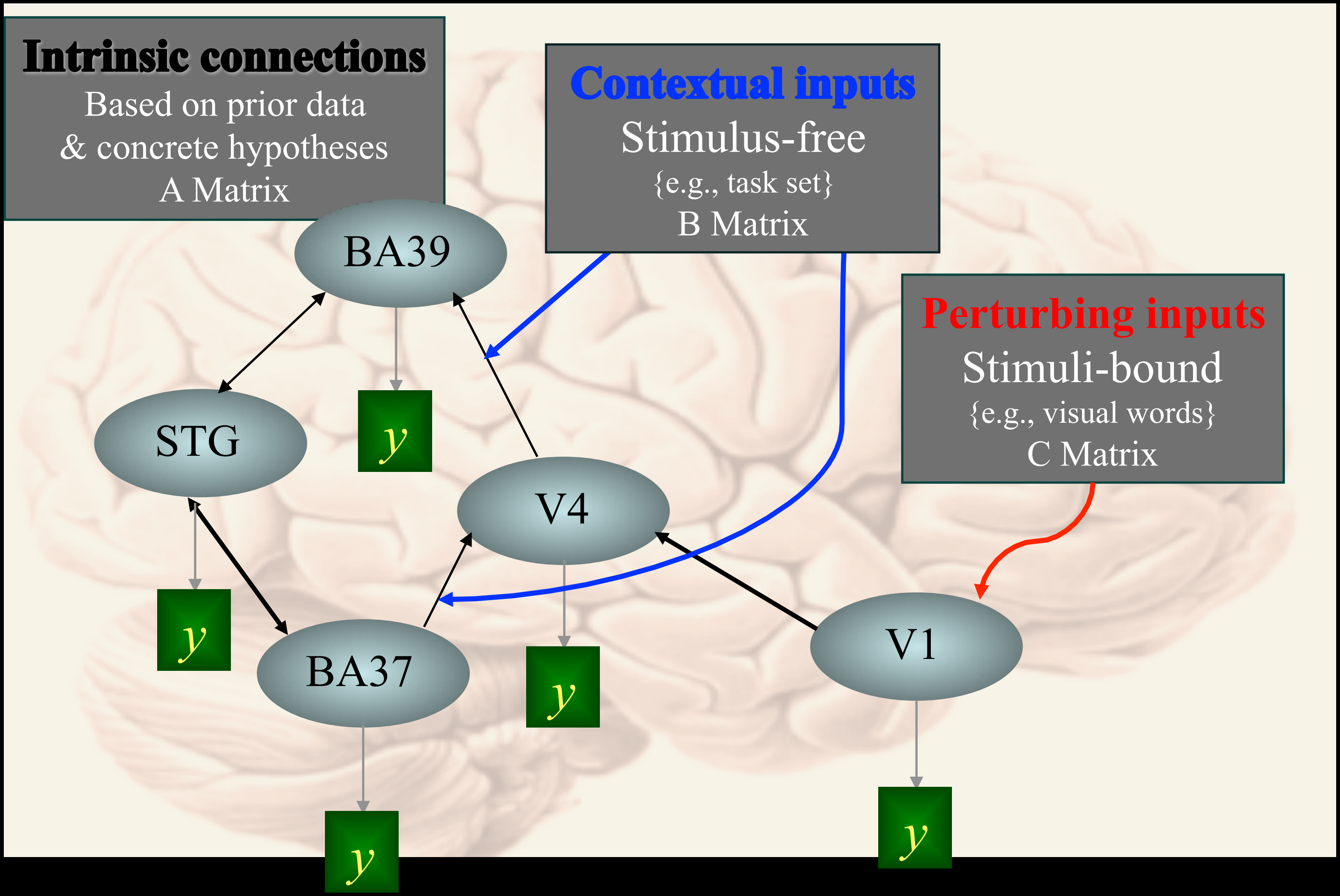


- The modeled neuronal dynamics (x) are transformed into area-specific ‘simulated’ BOLD signals (y) by a hemodynamic model (λ).
- The aim of DCM is to estimate parameters at the neuronal level such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.
  - Model parameters estimated using a Bayesian framework

[slide adapted from K.E. Stephan]

Dynamic causal modeling (DCM)

Schematic overview



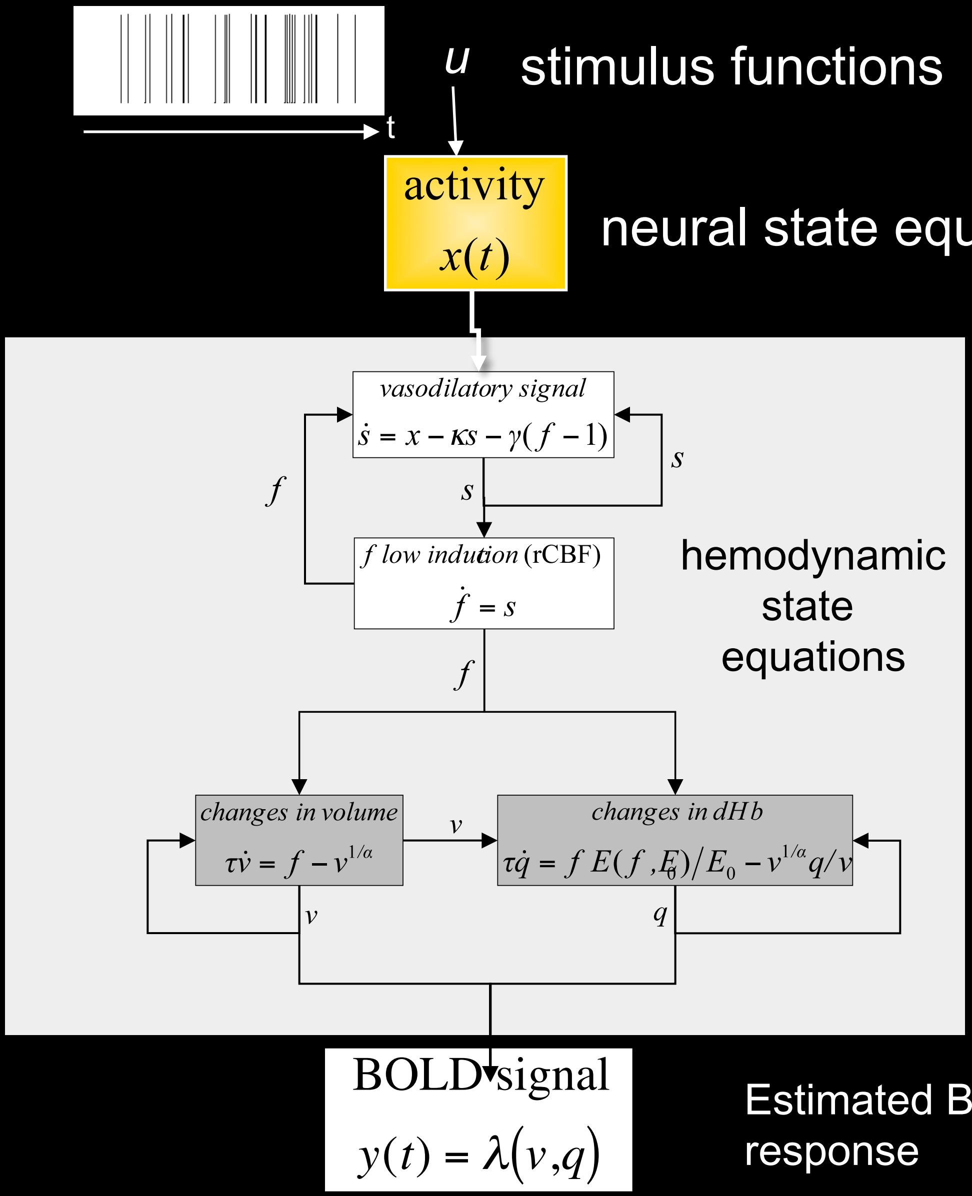
Intrinsic connections
Based on prior data
& concrete hypotheses
A Matrix

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



stimulus functions

activity

$x(t)$

neural state equation

vasodilatory signal

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

flow induction (rCBF)

$\dot{f} = s$

hemodynamic state equations

changes in volume

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

changes in dHb

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

Hemodynamic parameters computed separately for each brain area

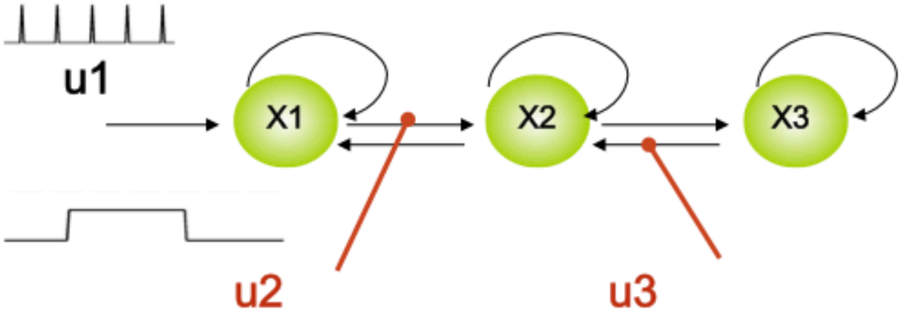
BOLD signal

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

Estimated BOLD response

Dynamic causal modeling (DCM)

Mathematical overview



Neural State Equation

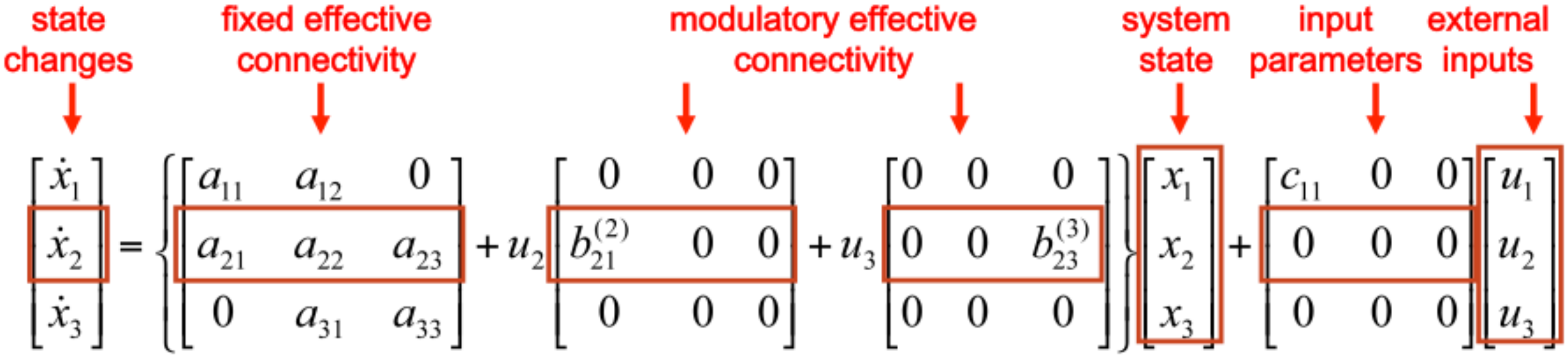
$$\dot{x} = \left(A + \sum_{j=1}^{m} u_j B^{(j)} \right) x + Cu$$

$$\theta = \{A, B, C\}$$

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + c_1u_1$$

$$\dot{x}_2 = \left(a_{21} + u_2 b_{21}^{(2)}\right)x_1 + a_{22}x_2 + \left(a_{23} + u_3 b_{23}^{(3)}\right)x_3$$

$$\dot{x}_3 = a_{32}x_2 + a_{33}x_3$$



state changes

fixed effective connectivity

modulatory effective connectivity

system state

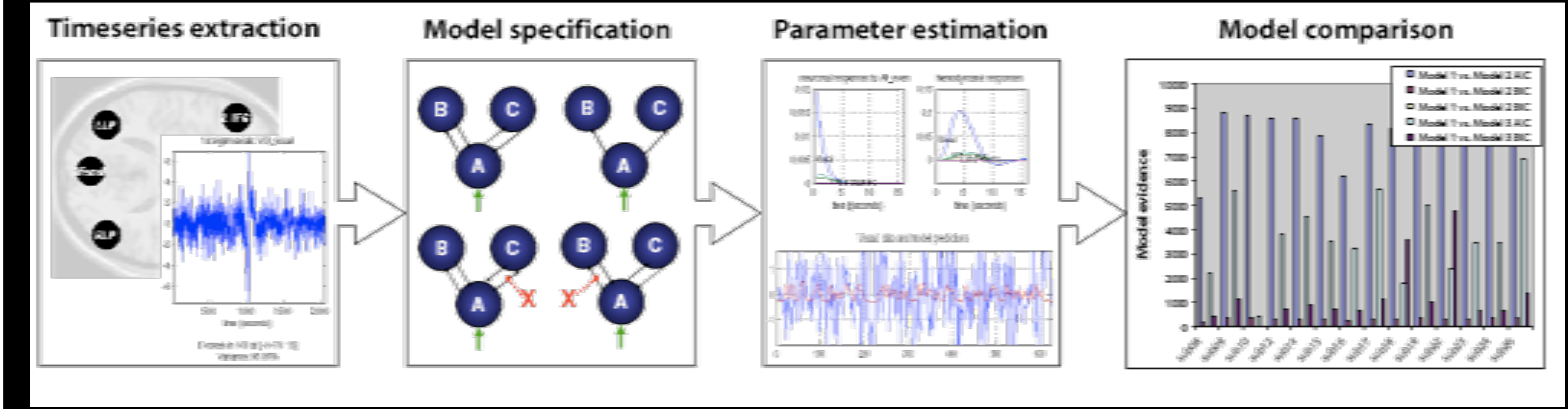
input parameters

external inputs

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

[slide adapted from Hanneke den Ouden; SPM Course]

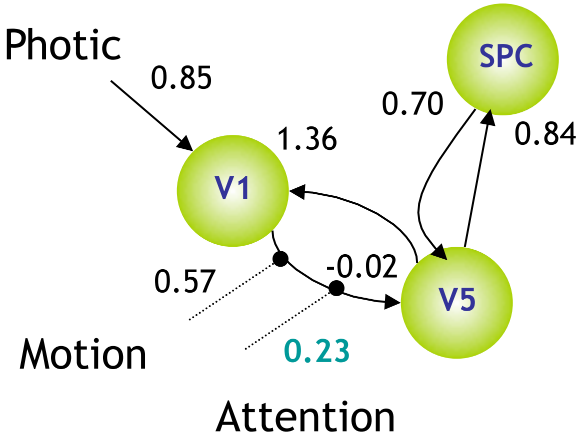
The DCM processing stream



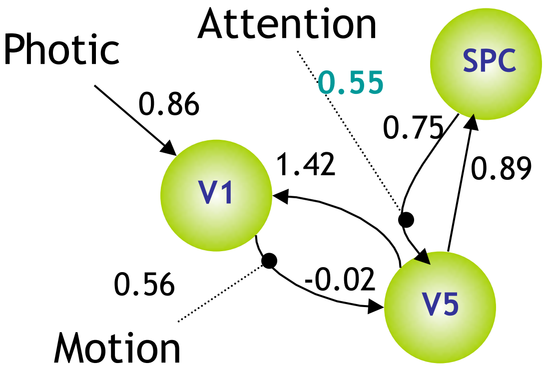
[slide from Melina Uncapher]

Model comparison

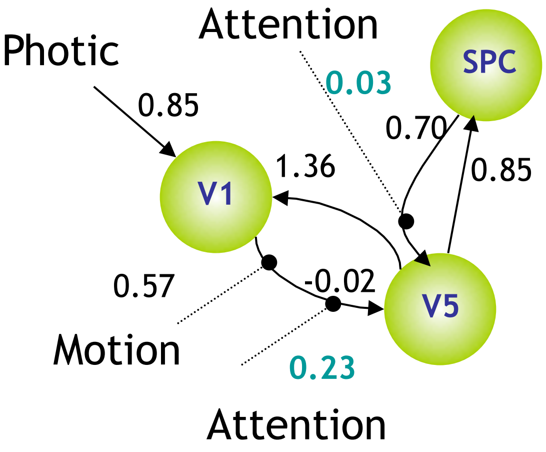
Model 1:
attentional modulation of V1→V5



Model 2:
attentional modulation of SPC→V5



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

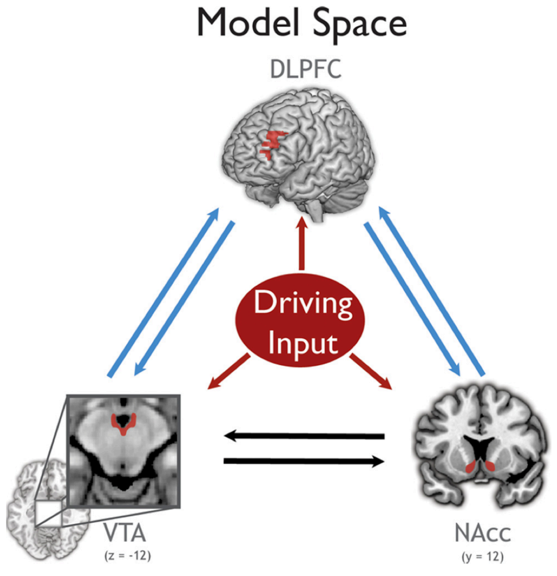


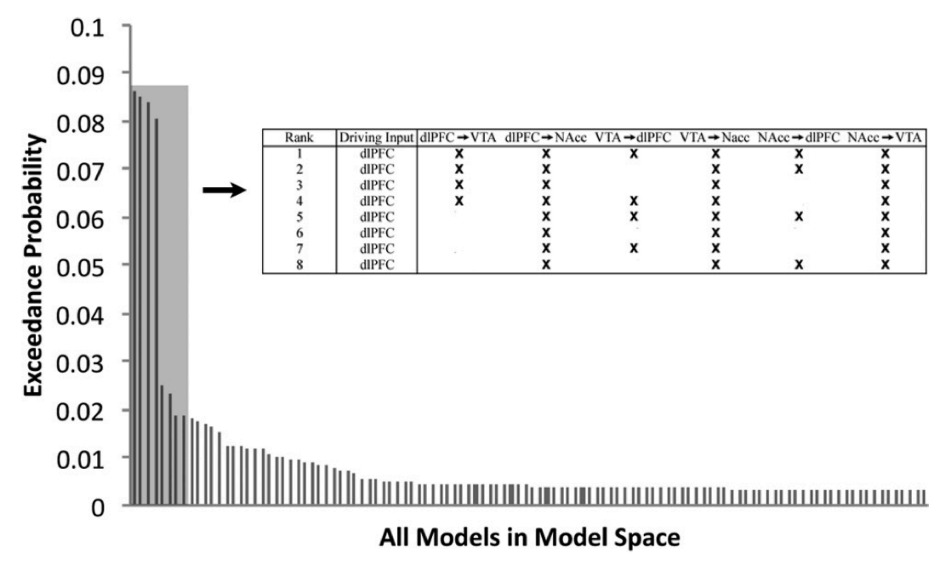
Bayesian model selection: Model 1 better than model 2; model 1 and model 3 equal

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

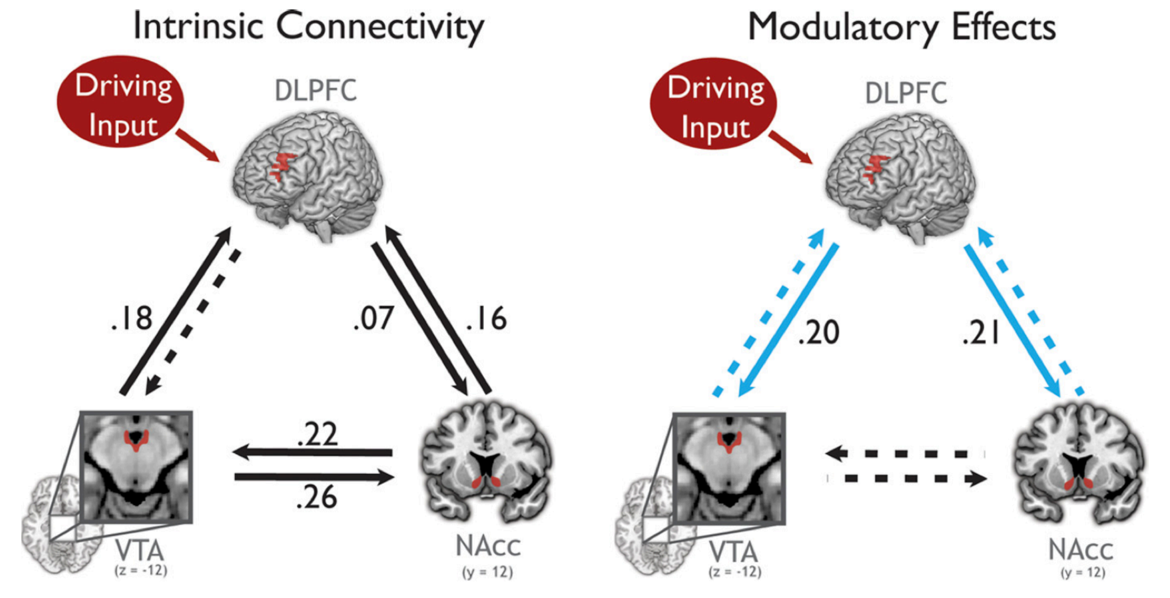
Attention primarily modulates V1→V5 pathway

A recent DCM analysis example





Rank	Driving Input	dlPFC→VTA	dlPFC→NAcc	VTA→dlPFC	VTA→Nacc	NAcc→dlPFC	NAcc→VTA
1	dlPFC	x	x	x	x	x	x
2	dlPFC	x	x		x	x	x
3	dlPFC	x	x		x		x
4	dlPFC	x	x	x	x		x
5	dlPFC		x	x	x	x	x
6	dlPFC		x		x		x
7	dlPFC		x	x	x		x
8	dlPFC		x		x	x	x



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!