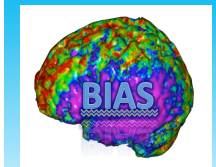

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Statistical Methods for Neuroimaging Data Analysis

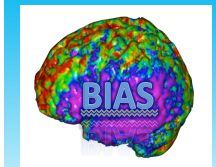
ICSA Canada Chapter 2015 Lecture 2

Brain Connectivity Analysis

Linglong Kong
University of Alberta

ICSA Canada Chapter August 4, 2015 @ Calgary, AB

Special Thanks to Professor Hongtu Zhu at UNC



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Reading materials:

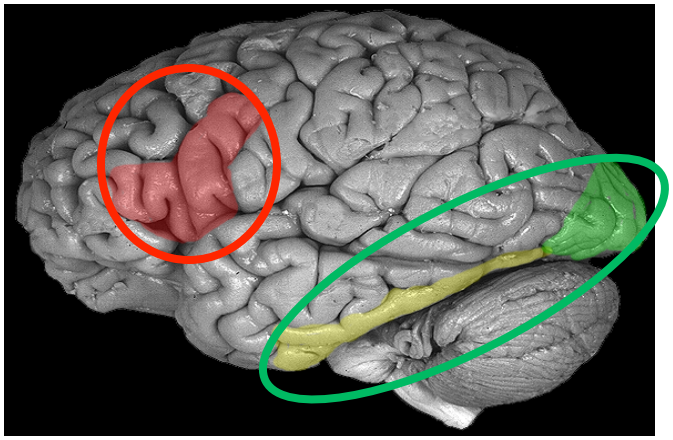
1. Friston, K. J. (2009). Modalities, modes, and models in functional neuroimaging. Science 326, 399-403.
2. Rubinov, M. and Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. NeuroImage 52, 1059–1069.
3. Buckner, R. L., Andrews-Hanna, J. R. and Schacter, D. L. (2008). The brain's default network anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124: 1–38.
4. Honey, C.J., Thivierge, J.P., and Sporns, O. (2010). Can structure predict function in the human brain? NeuroImage 52,766–776.
5. Buckner, R. L., Andrews-Hanna, J. R. and Schacter, D. L. (2008). The brain's default network anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124: 1–38.
6. Van Dijk, K. R. A., …, Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103, 297-321.

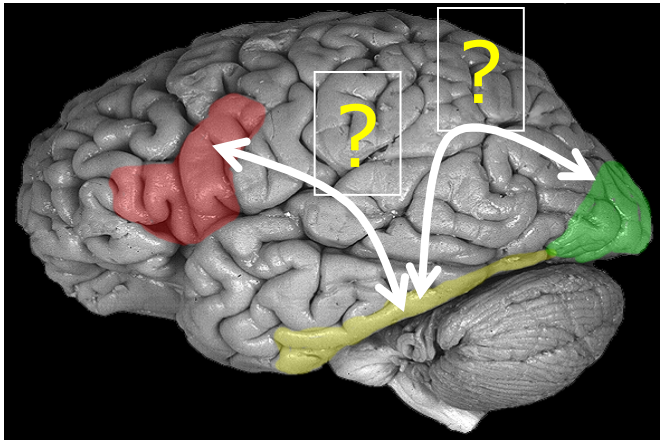
Acknowledgement: Multiple slides were copied from Drs. Lindquist, Rowe, and Huettel, FSL, and SPM training materials.

Brain Connectivity

- Functional Segregation: Human brain mapping has been primarily used to provide maps that show which regions of the brain are activated by specific tasks.

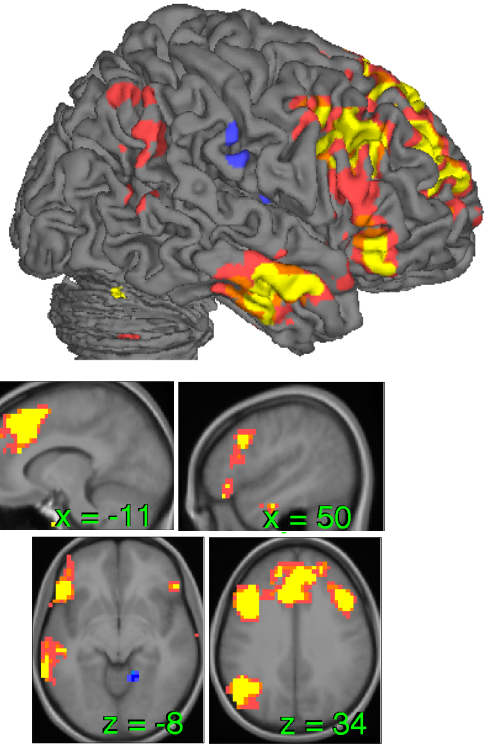
- Recently, there has been an interest in augmenting this type of analysis with brain connectivity studies which describe how various regions interact and how interactions depend on experimental conditions.





Brain Networks

- The current fashion is to call any set of regions activated in a task a network.
- But what does it mean to be a network?
- Set of interconnected regions; information transfer among regions.



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System analyses in functional neuroimaging

Functional segregation

Analyses of regionally specific effects: which areas constitute a neuronal system?

Functional integration

Analyses of inter-regional effects: what are the interactions between the elements of a given neuronal system?

Functional connectivity

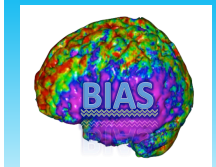
= the temporal correlation between spatially remote neurophysiological events

MECHANISM-FREE

Effective connectivity

= the influence that the elements of a neuronal system exert over another

MECHANISTIC MODEL



Functional Connectivity

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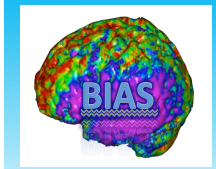
- Functional connectivity is a statement about observed associations among regions and/or performance and physiological variables.
- It does not comment on how these associations are mediated.
- Functional connectivity analysis is usually performed using data-driven transformation methods which make no assumptions about the underlying biology.



Functional Connectivity

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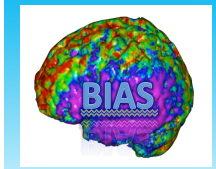
- Methods:
  - Seed analyses
  - Psychophysiological interaction analyses
  - Principle Components Analysis
  - Partial Least Squares
  - Independent Components Analysis



Effective Connectivity

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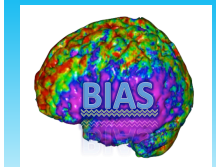
- Effective connectivity analysis is performed using statistical models which make anatomically motivated assumptions and restricts inference to networks comprising of a number of pre-selected regions of interest.

- These methods are hypothesis driven rather than data-driven and most applicable when it is possible to specify the relevant functional areas.



Effective Connectivity

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- Methods:
  - ✧ Structural Equation Modeling
  - ✧ Granger Causality
  - ✧ Dynamic Causal Modeling
  - • Note that Granger causality does not rely on an a priori specified structural model.

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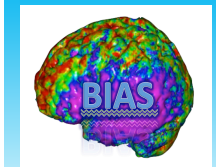
Functional Connectivity



Levels of Analysis

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- Functional connectivity can be applied at different levels of analysis, with different interpretations at each.
- Connectivity across time can reveal networks that are dynamically activated across time.
- Connectivity across trials can identify coherent networks of task related activations.
- Connectivity across subjects can reveal patterns of coherent individual differences.
- Connectivity across studies can reveal tendencies for studies to co-activate within sets of regions.

Bivariate Connectivity

- Simple functional connectivity
  - Region A is correlated with Region B.
  - Provides information about relationships among regions.
  - Can be performed on time series data within a subject, or individual differences (contrast maps, one per subject).

Time Series Connectivity

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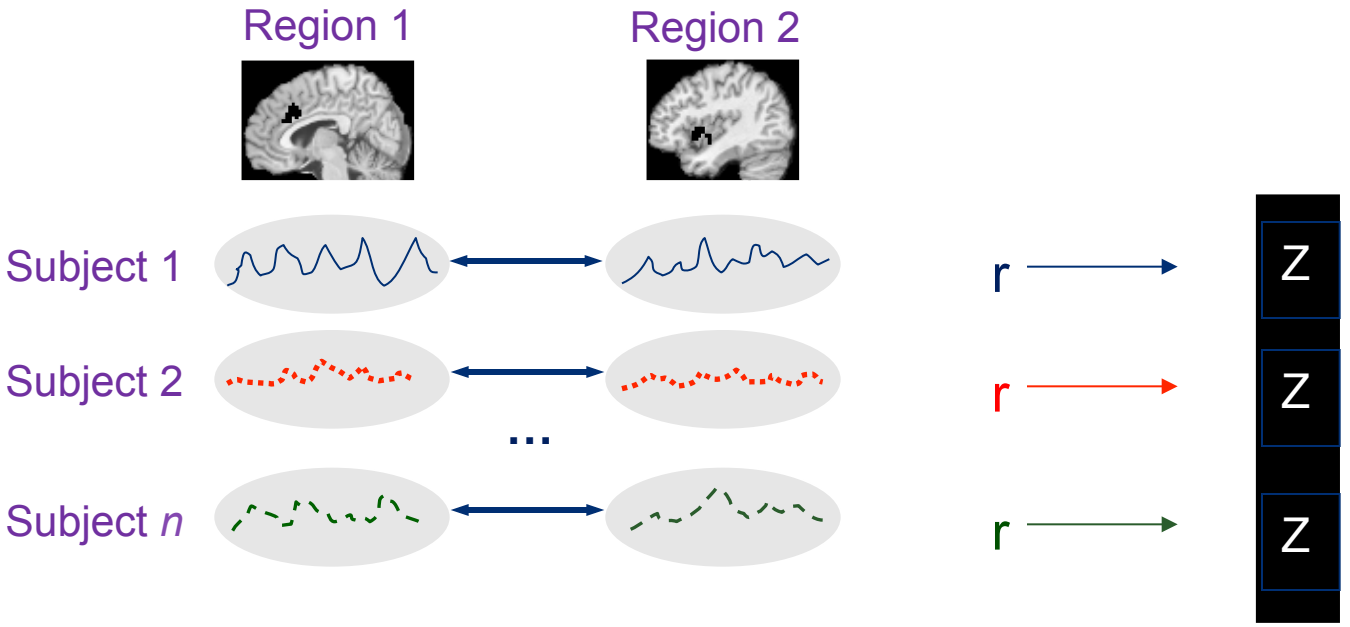
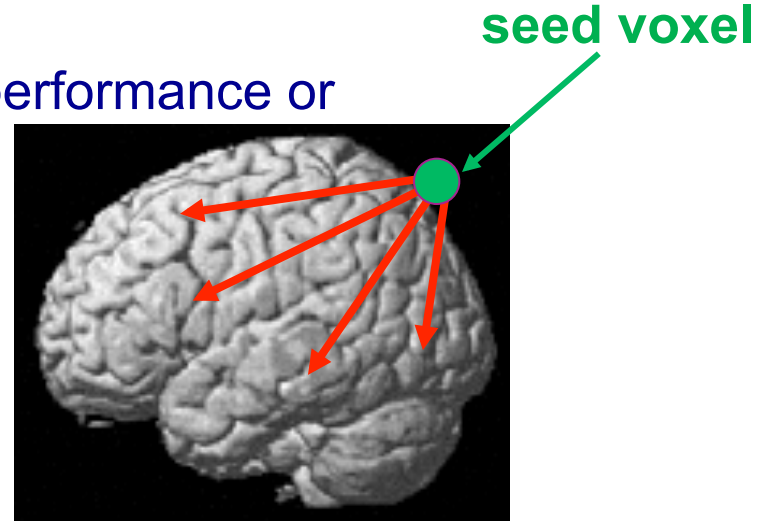
- Calculate the cross-correlation between time series from two separate brain regions.



Seed Analysis

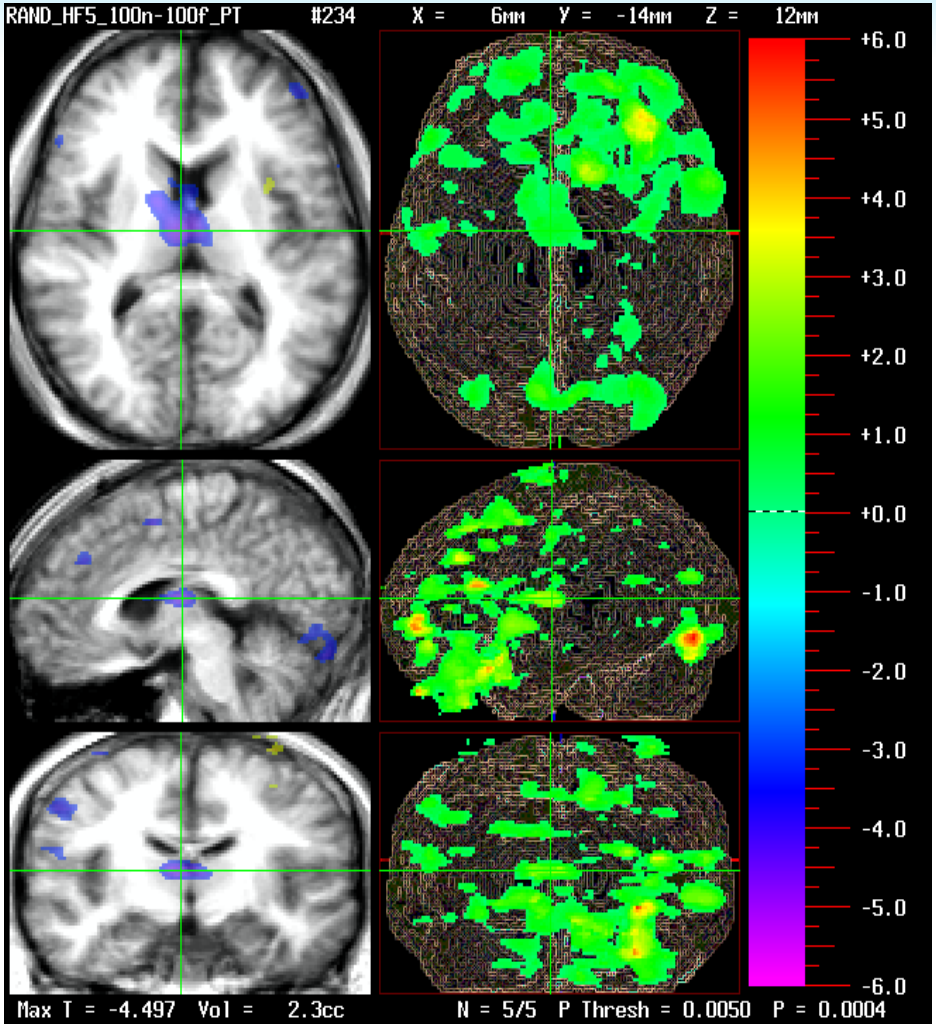
- In seed analysis the cross-correlation is computed between the time course from a predetermined region (seed region) and all other voxels.
- This allows researchers to find regions correlated with the activity in the seed region.
- The seed time course can also be a performance or physiological variable.



SVCA example

Finger-tapping task:

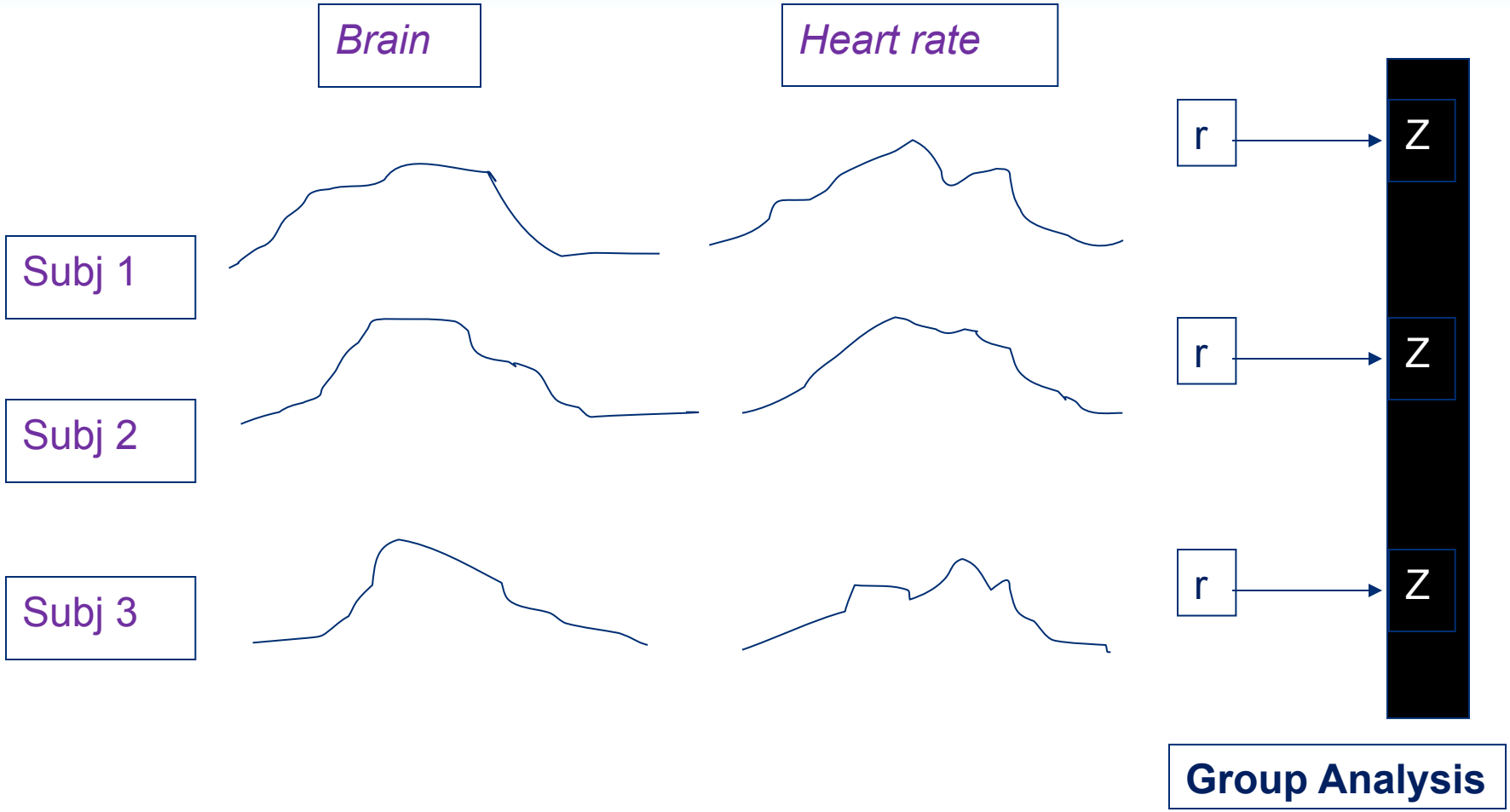
all voxels (p<0.005, uncorrected) that showed changed functional connectivity with the left ant. cerebellum in schizophrenic patients after medication with olanzapine.



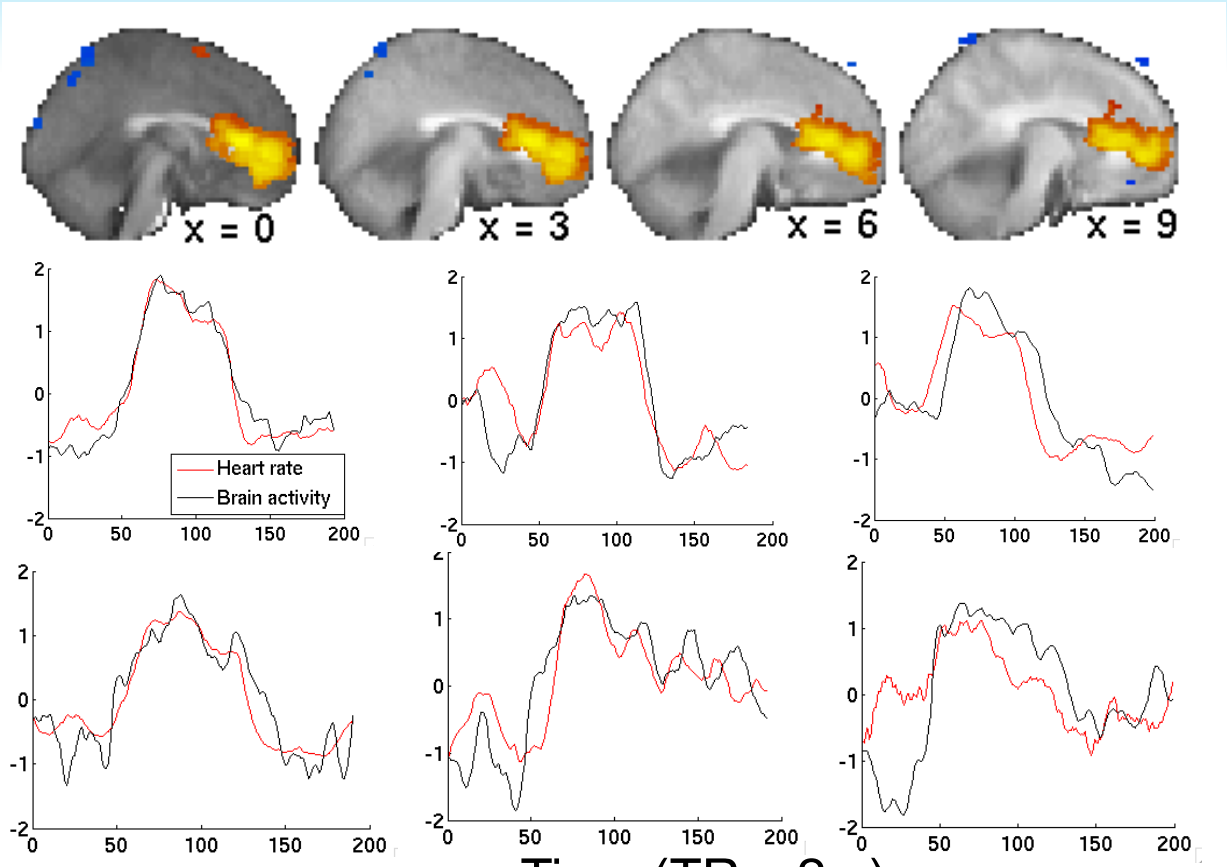
p<0.005, uncorrected

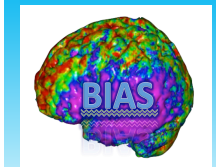
Stephan et al., Psychol. Med. (2001)

Time Series Connectivity



Correlations between brain activity and heart-rate increases





Issues

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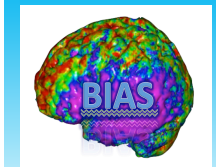
- One of the main problems with time series connectivity is the fact that there may be different hemodynamic lags in different regions:
  - Time series from different regions may not match up, even if neural activity patterns match up.
  - If lags are estimated from data, temporal order may be caused by vascular (uninteresting) or neural (interesting) response.



Beta Series

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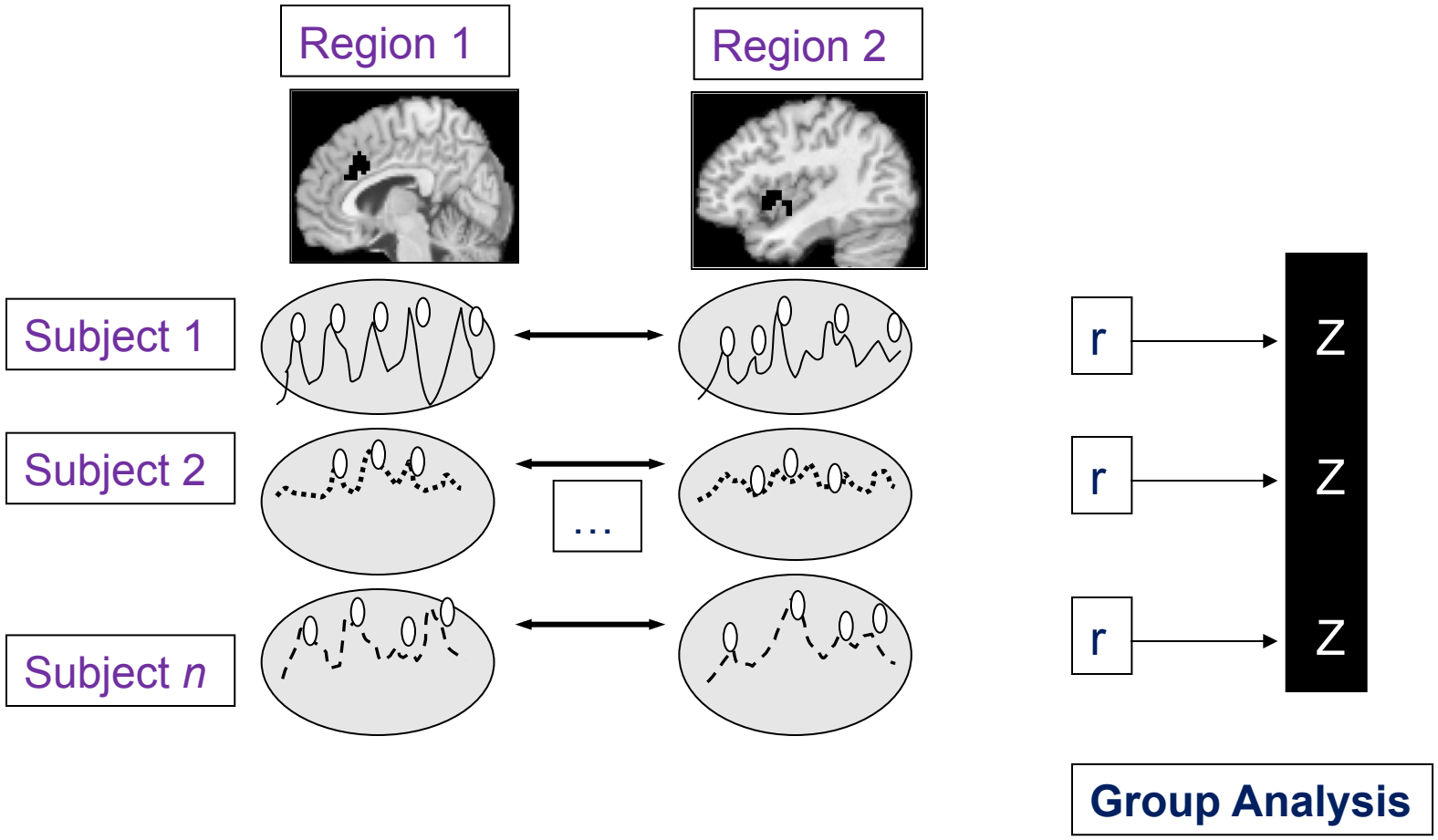
- The beta series approach can be used to minimize issues of inter-region neurovascular coupling.

- Procedure:

  - Fit a GLM to obtain separate parameter estimates for each individual trial.

  - Compute the correlation between these estimates across voxels.


Region 1
Region 2
Subject 1
Subject 2
Subject n
...
r
r
r
Z
Z
Z
Group Analysis

Individual Differences

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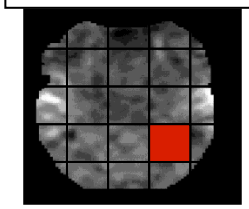
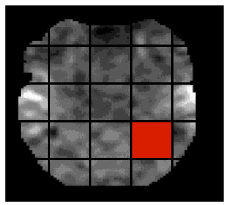
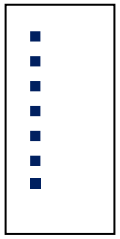
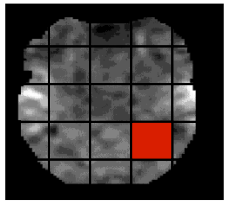
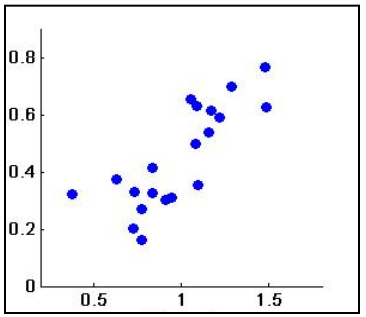
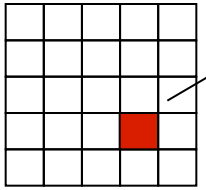
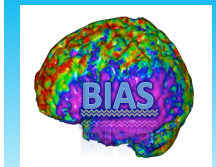
Subject	Contrast Image	Seed Value	Group Results
1		x_1	
2		x_2	
			
N		x_N	







Co-activation across Studies

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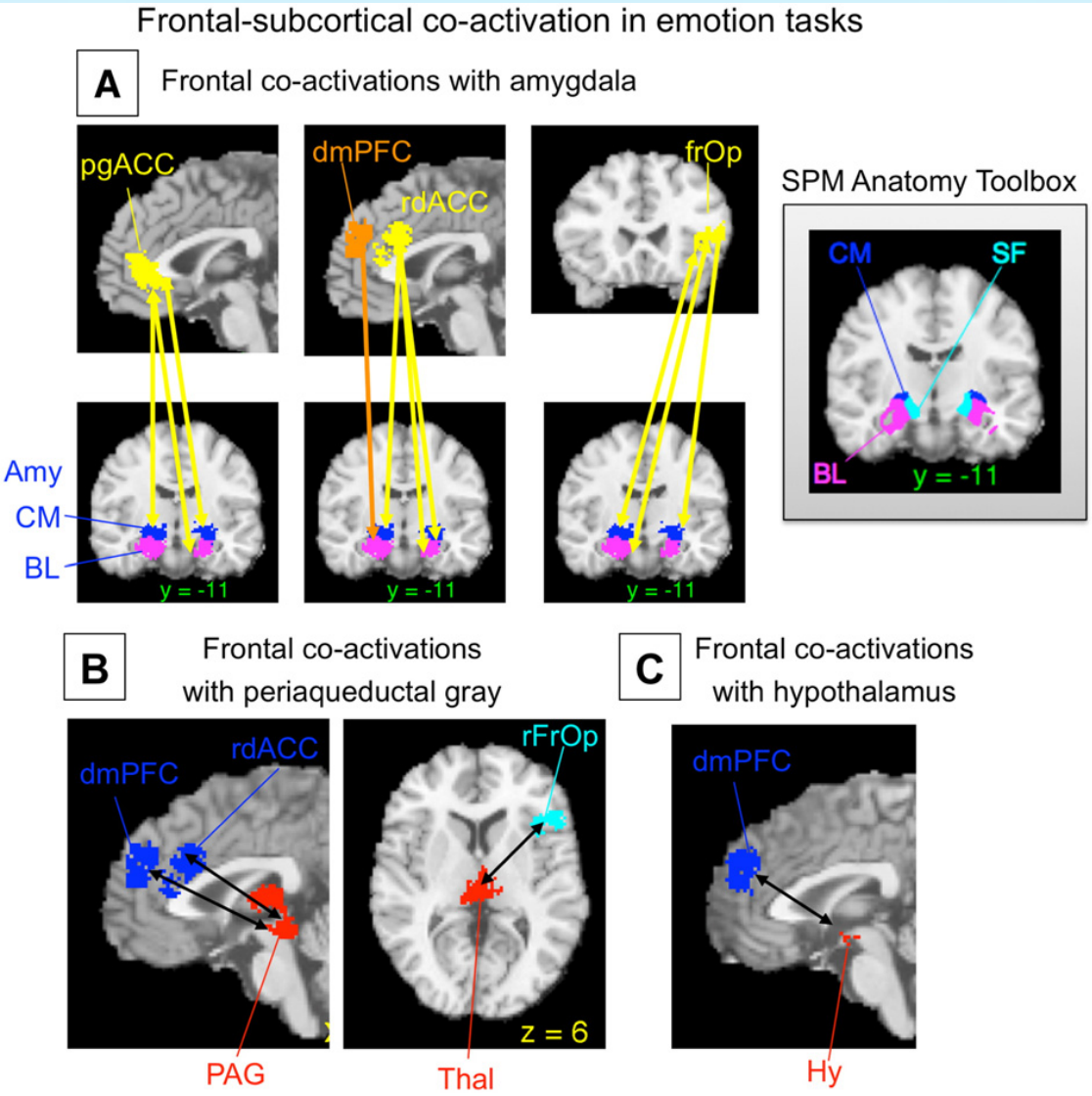
- Meta-analysis can be used to reveal patterns of co-activated regions.
- If two regions are co-activated, studies that activate one region are more likely to activate the other region as well.
- Co-activation is thus a meta-analytic analogue to functional connectivity analyses in individual neuroimaging studies.



Co-activated regions show a tendency to be activated in the same studies, as assessed with Kendall's tau. Arrows show significant co-activation.

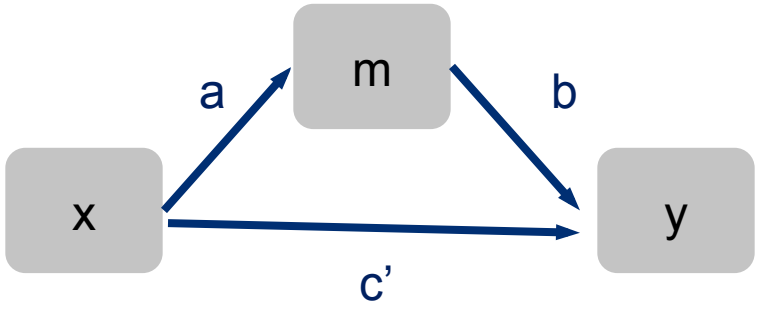
Wager et al.

Mediation

- Mediation (Baron & Kenny, 1986)
  - The relationship between regions A and B is mediated by M
  - Can identify functional pathways spanning > 2 regions
  - Can be performed on time series data within a subject, or individual differences (contrast maps, one per subject)
  - Also: Test of whether task-related activations in B are mediated, or explained, by M.

Demonstrating Mediation

Full model, with mediator



$m = i_m + ax + e_m$

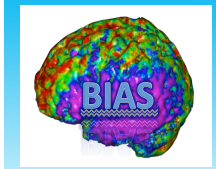
$y = i_y + bm + c'x + e'_y$

Reduced model, without mediator

$y = i_{y'} + cx + e_y$

Baron and Kenny (1986) – conjunction of 3 effects:

1) ***c* effect: There is a relationship to be mediated**
2) ***a* effect: initial variable related to mediator**
3) ***b* effect: mediator relates to outcome**



Decomposition of Effects

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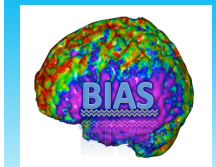
- The mediation framework allows us to decompose the total effect of x on y as follows:

Total effect = Direct effect + Mediated effect

- Does *m* explain some of the x-y relationship?
  - Test c – c', which is equivalent to significance of a*b product.



Test of Mediation

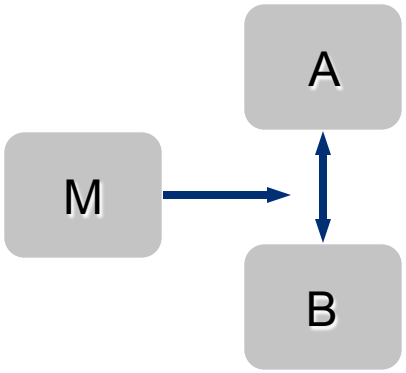
- Sobel test:

$$Z = \frac{ab}{(b^2 se(a)^2 + a^2 se(b)^2)^{1/2}}$$

  - Z ~ N(0, 1), standard normal distribution
  - Assumes a, b are normally distributed
  - Usually conservative (p-values higher than needed)

- Bootstrap test

Moderation



- Moderation (Baron & Kenny, 1986)
  - The relationship between regions A and B is moderated by M
  - Connectivity between A and B depends on state (level) of M
  - Can be performed on time series data within a subject, or individual differences (contrast maps, one per subject)
  - M can be task state or other variable

- In SPM, on time series data: “Psychophysiological interaction” (PPI)

A Simple Path Model

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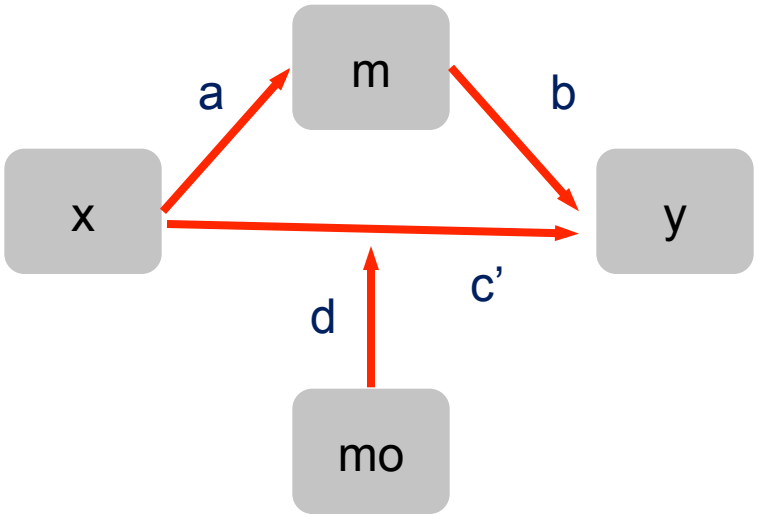
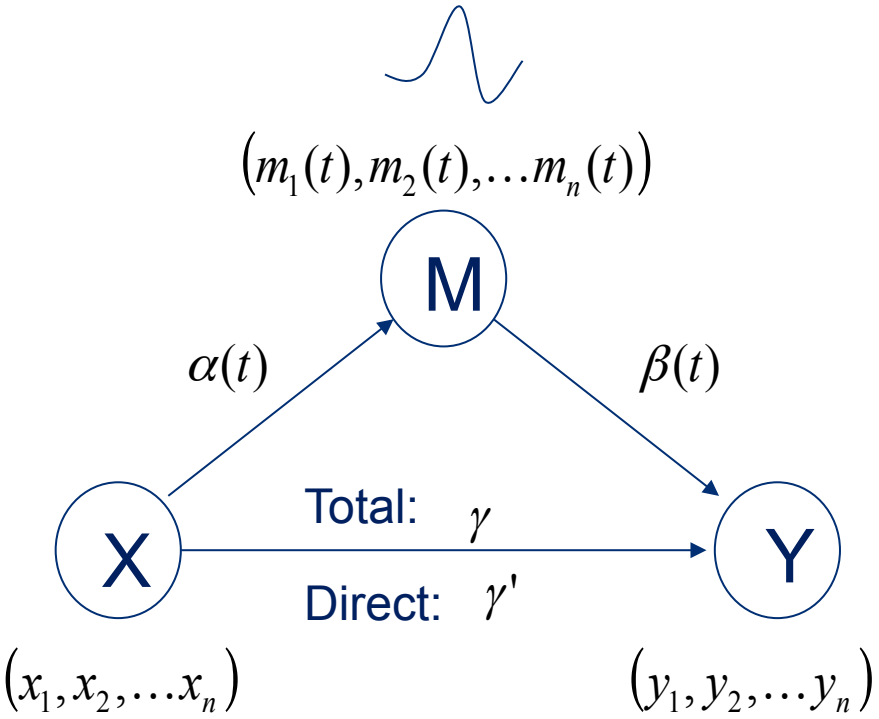
Full model, with mediator and moderator



$m = i_m + ax + e_m$

$y = i_y + bm + c'x + d(mo*x) + e'_y$

Functional Mediation

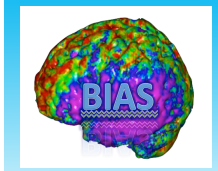


$$y_i = \gamma x_i + \varepsilon_{i,x}(t)$$

$$m_i(t) = \alpha(t) x_i + \varepsilon_{i,m}(t)$$

$$y_i = \int_0^T \beta(s) m_i(s) ds + \gamma' x_i + \varepsilon_{i,y}(t)$$

$$\gamma = \gamma' + \int_0^T \alpha(s)\beta(s) ds$$



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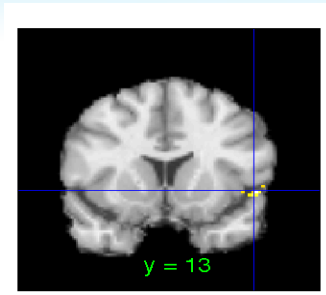
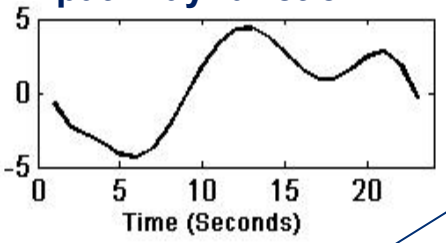
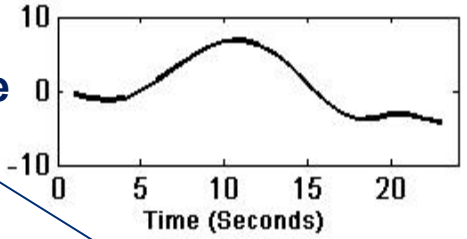


pathway function

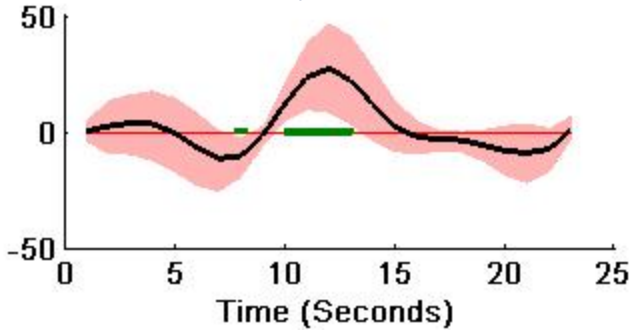


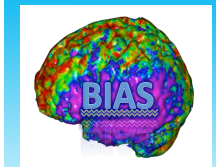
Brain Response



Temperature → **Pain Rating**

pathway function





Multivariate Methods

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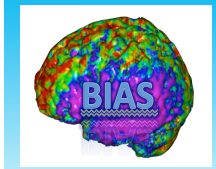
- We often use multivariate methods to study functional connectivity.
- When using multivariate methods observations at each voxel are considered jointly.
- This has the potential to allow for better understanding of how different brain regions interact with one another.



Principal Components Analysis

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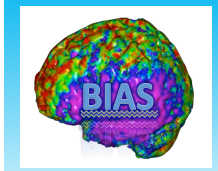
- Principal components analysis involves finding spatial modes, or eigenimages, in the data.
- Spatial modes are the patterns that account for most of the variance-covariance structure in the data.
- The eigenimages are obtained using singular value decomposition (SVD), which decomposes the data into two sets of orthogonal vectors that correspond to patterns in space and time.



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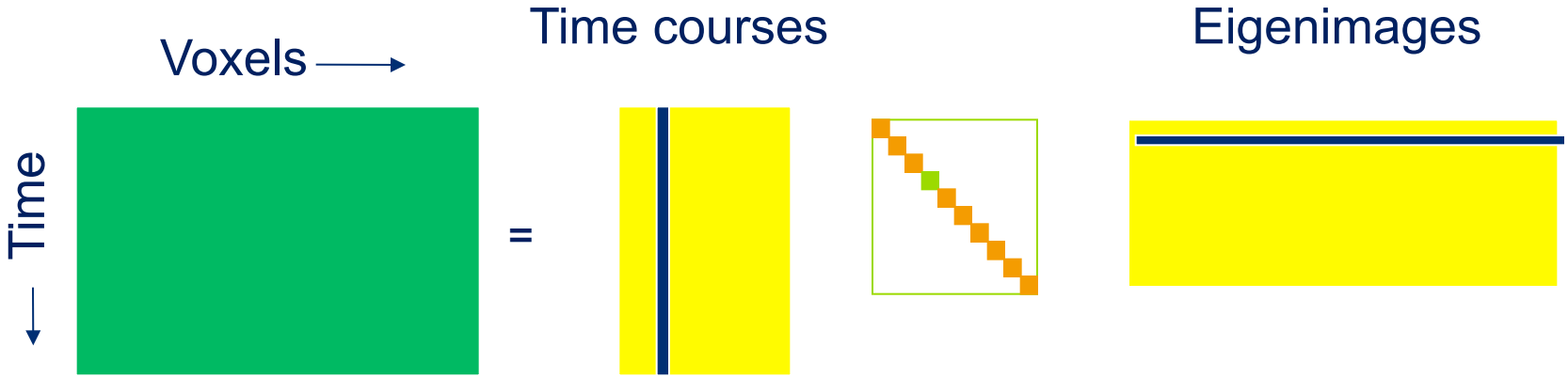
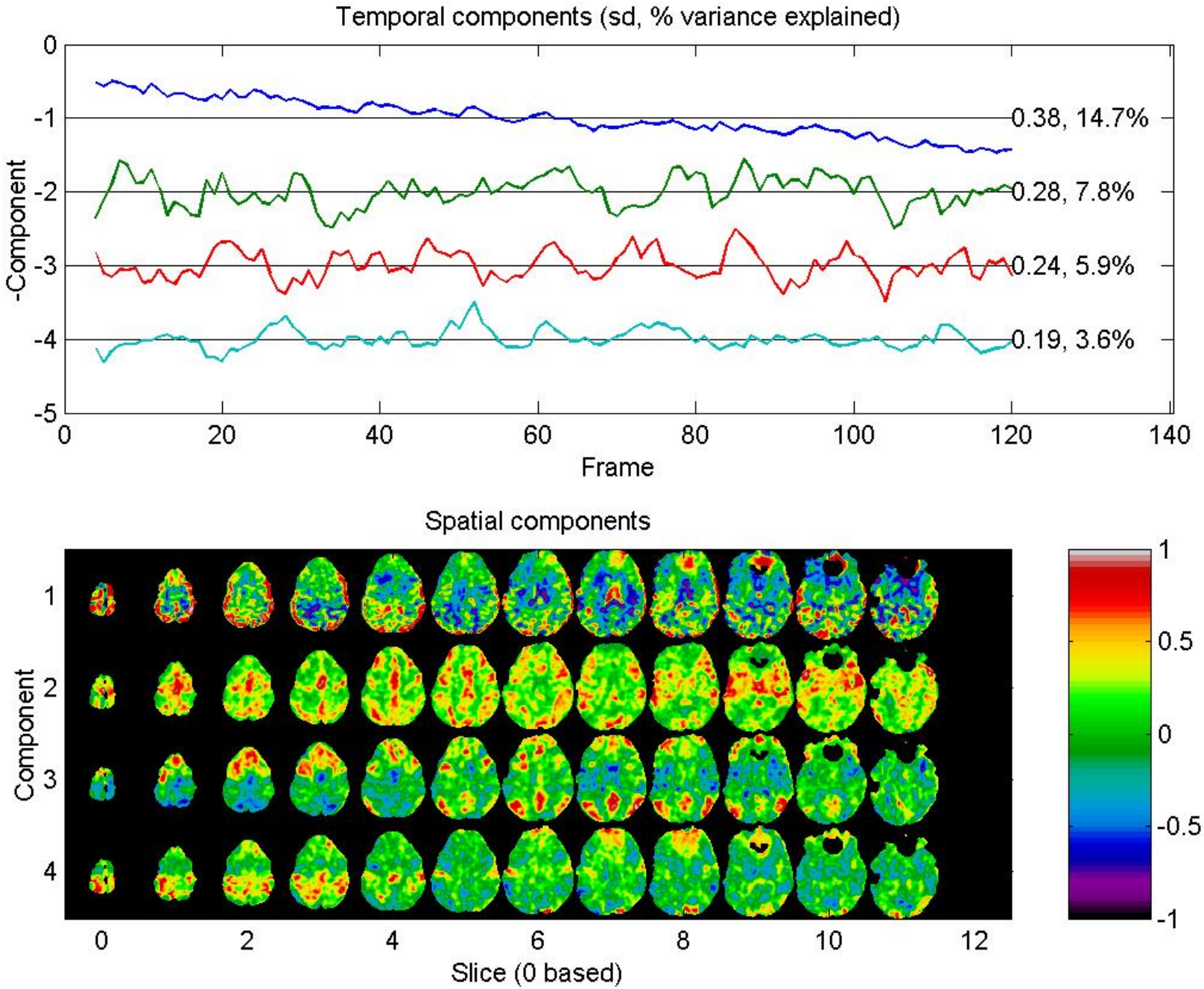
$$\mathbf{X} = \mathbf{U}\mathbf{S}\mathbf{V}^T$$



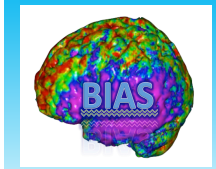
$$\mathbf{X} = s_1\mathbf{u}_1\mathbf{v}_1^T + s_2\mathbf{u}_2\mathbf{v}_2^T + \ldots + s_N\mathbf{u}_N\mathbf{v}_N^T$$

Each column of U correspond to the time-dependent profiles associated with each eigenimage.

Each column of V defines a distributed brain region that can be displayed as an image (eigenimages).


Temporal components (sd, % variance explained)
-Component
0
-1
-2
-3
-4
-5
0.38, 14.7%
0.28, 7.8%
0.24, 5.9%
0.19, 3.6%
0
20
40
60
80
100
120
140
Frame
Spatial components
Component
1
2
3
4
0
2
4
6
8
10
12
Slice (0 based)
1
0.5
0
-0.5
-1

Worsley



Independent Components Analysis

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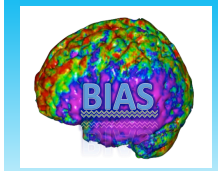
- Independent Components Analysis (ICA) is a family of techniques used to extract independent signals from some source signal.

- ICA provides a method to blindly separate the data into spatially independent components.

- The key assumption is that the data set consists of *p* spatially independent components, which are linearly mixed and spatially fixed.



Cocktail Party Problem

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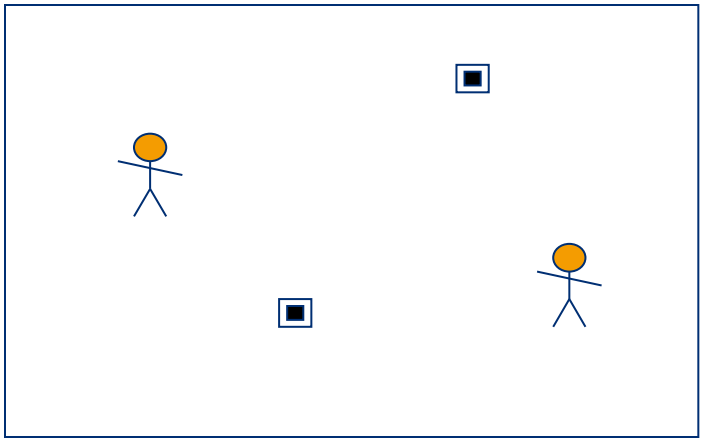
Two people are talking simultaneously in a room with two microphones



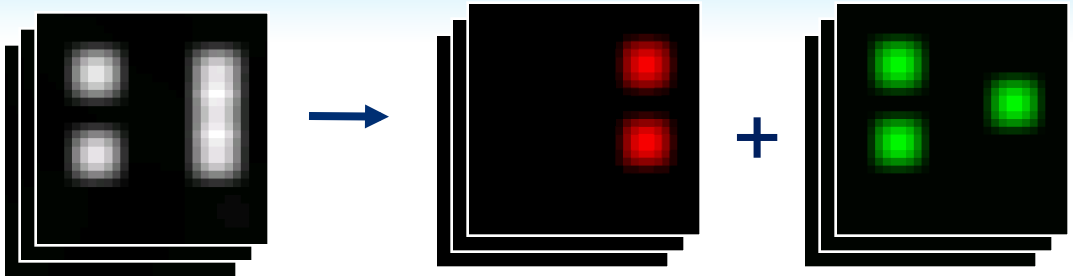
Speakers: $s_1(t)$ and $s_2(t)$.

Microphones: $x_1(t)$ and $x_2(t)$

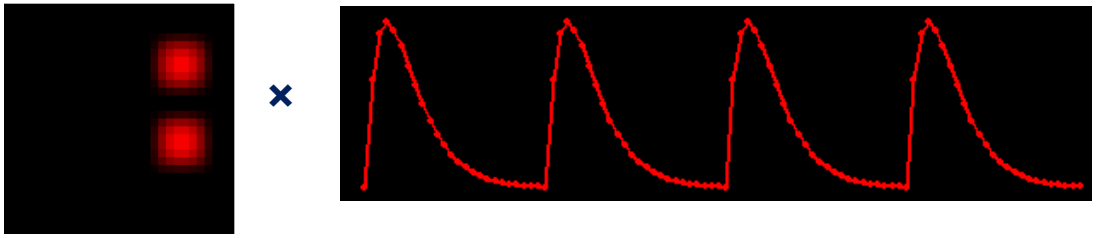
$$x_1(t) = a_{11}s_1(t) + a_{12}s_2(t)$$
$$x_2(t) = a_{21}s_1(t) + a_{22}s_2(t)$$

$$\mathbf{X = AS}$$

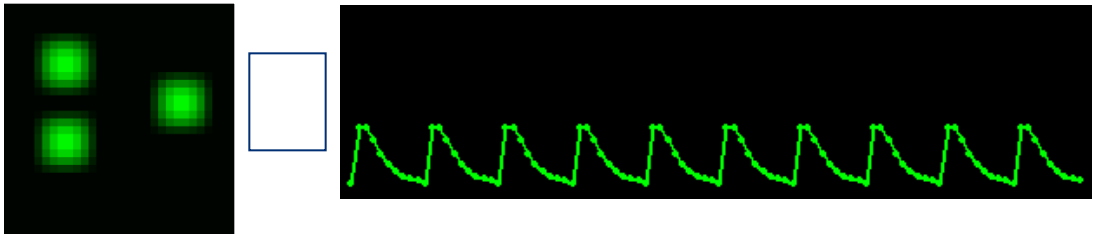
ICA of fMRI



fMRI data



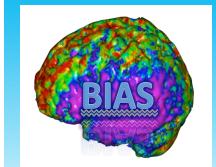
Source 1 Time course 1



Source 2 Time course 2

fMRI data is assumed to be a linear mixture of statistically independent sources, **s**.

Vince Calhoun



Problem Formulation

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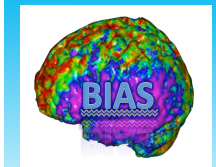
- We want to solve:

$$\mathbf{X} = \mathbf{AS}$$

where **A** is the mixing matrix, **S** is the source matrix and **X** is the data matrix. Both **A** and **S** are unknown.

- Assume that Cov(**X**)=**I** and **A** is orthogonal.

- Find **A** such that $\mathbf{S}=\mathbf{A}^{T}\mathbf{X}$.



Assumptions

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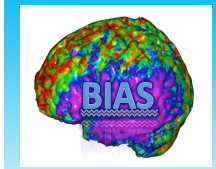
- ICA is able the solve this problem by exploiting some key assumptions.
- Assumptions:
  - Linear mixing of sources.
  - The components s_i are statistically independent.
  - The components s_i are non-Gaussian.



Mutual Information

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- One approach is to minimize the mutual information between different components.
- This is equivalent to minimizing the Kullback-Leibler divergence between the joint density and the product of the marginal densities.
- The Kullback-Leibler divergence is a measure of similarity between two density functions.

ICA for fMRI

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- It is assumed that the fMRI data can be modeled by identifying sets of voxels whose activity both vary together over time and are maximally different from the activity in other sets.

- Decompose the data set into a set of spatially independent component maps with a set of corresponding time-courses.

Overview

Data

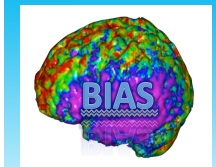
Mixing Matrix

Components

$$\mathbf{X} = \mathbf{AS}$$

where the matrix S contains statistically independent maps in its rows each with an internally consistent time-course contained in the associated column of the mixing matrix A.

Use an ICA algorithm to find **A** and **S**.



Comments

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- Unlike PCA which assumes an orthonormality constraint, ICA assumes statistical independence among a collection of spatial patterns.
- Independence is a stronger requirement than orthonormality.
- However, in ICA the spatially independent components are not ranked in order of importance as they are when performing PCA.

Types of ICA

- An ICA that decomposes the original data into spatially statistically independent components is called spatial ICA (sICA).
- It is possible to switch the order and make the temporal dynamics independent. This is called temporal ICA (tICA)
- Spatial ICA is more common in fMRI data analysis.

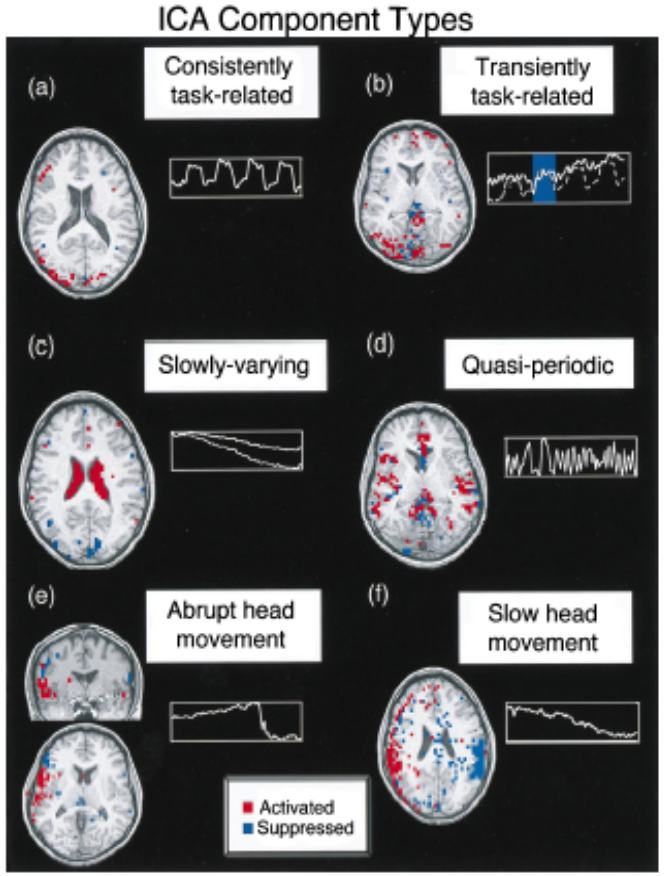
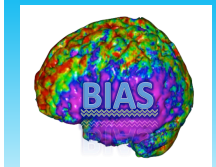


FIG. 1. Different classes of components detected by ICA decomposition of Stroop task fMRI data. (red, $\tau = 2.8$; blue, $\tau = 2.0$). Negative τ values mean those voxels are activated opposite to the plotted time course. (a) Consistently task-related (CTR) component. (b) Transiently task-related (TTR) component. The dotted line shows the time course of the consistently task-related component for comparison. (c) Slowly varying, non-task-related component. The active region for this component was mostly localized to the ventricular system. The lower line shows the mean time course of the active voxels for this component. (d) Quasi-periodic component. This component was largely active in a single slice and had a dominant period of about 12 sec. The spatial distributions of such components were highly reproducible between trials. (e) Suspected abrupt head movement. Note abrupt change in time course, suggesting an abrupt head movement. (f) Component with a "ring-like" spatial structure suggestive of a head movement.



Multi-subject Analysis

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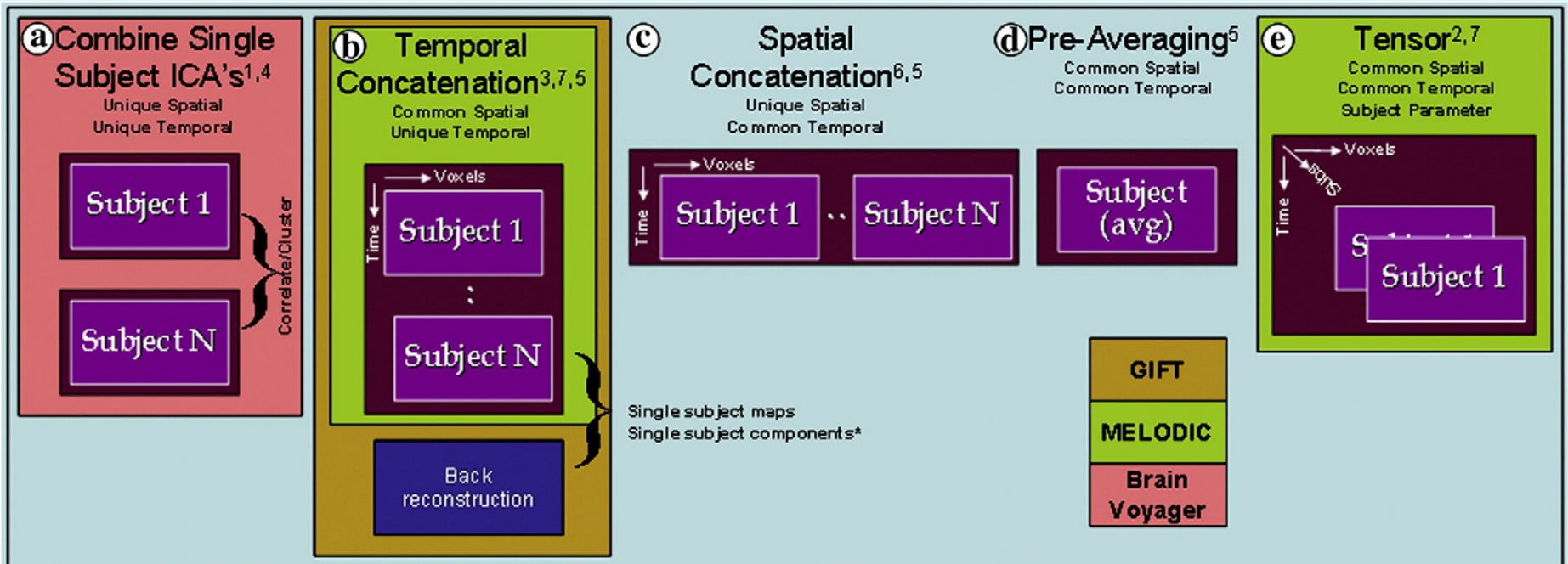
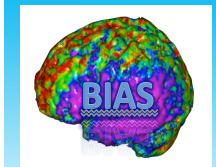
- Using ICA to analyze fMRI data from multiple subjects raises several questions.
  - How should components be combined across subjects?
  - How should the final results be thresholded and/or presented?
- There are several approaches:
  - Stack time courses (forces time courses to be the same)
  - Stack images and back-reconstruct (allows time courses to vary, allows some flexibility in images)
  - Stack into a cube (forces images and time courses to be the same)

Overview



1) Calhoun VD, Adali T, McGinty V, Pekar JJ, Watson T, Pearlson GD. (2001): fMRI Activation In A Visual-Perception Task: Network Of Areas Detected Using The General Linear Model And Independent Component Analysis. NeuroImage 14(5):1080-1088.
2) Beckmann CF, Smith SM. (2005): Tensorial extensions of independent component analysis for multisubject FMRI analysis. NeuroImage 25(1):294-311.
3) Calhoun VD, Adali T, Pearlson GD, Pekar JJ. (2001): A Method for Making Group Inferences from Functional MRI Data Using Independent Component Analysis. Hum.Brain Map. 14(3):140-151.
4) Esposito F, Scarabino T, Hyvarinen A, Himberg J, Formisano E, Comani S, Tedeschi G, Goebel R, Seifritz E, Di SF. (2005): Independent component analysis of fMRI group studies by self-organizing clustering. Neuroimage. 25(1):193-205.
5) Schmithorst VJ, Holland SK. (2004): Comparison of three methods for generating group statistical inferences from independent component analysis of functional magnetic resonance imaging data. J.Magn Reson.Imaging 19(3):365-368.
6) Svensen M, Kruggel F, Benali H. (2002): ICA of fMRI Group Study Data. NeuroImage 16:551-563.
7) Guo Y, Giuseppe P. (In Press): A unified framework for group independent component analysis for multi-subject fMRI data. NeuroImage.



Group ICA

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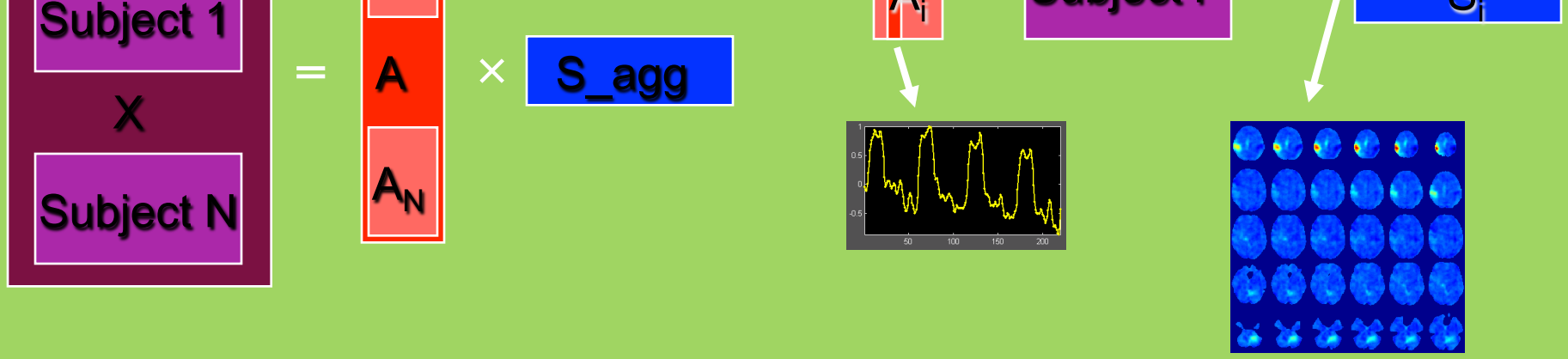
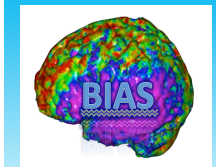
- Group ICA is based on temporal concatenation.
- It decomposes the group matrix, and estimates through back-reconstruction the spatial weights for each subject for a component of interest.
- For each subject the spatial weights at each voxel are treated as random variables, and a one-sample t-test is used to test whether that voxel loaded significantly on that component in the group.

Group ICA


Data
ICA
Back-reconstruction
Subject 1
X
Subject N
=
A1
A
AN
×
S_agg
−1
Ai
×
Subject i
=
Si



Tensor ICA

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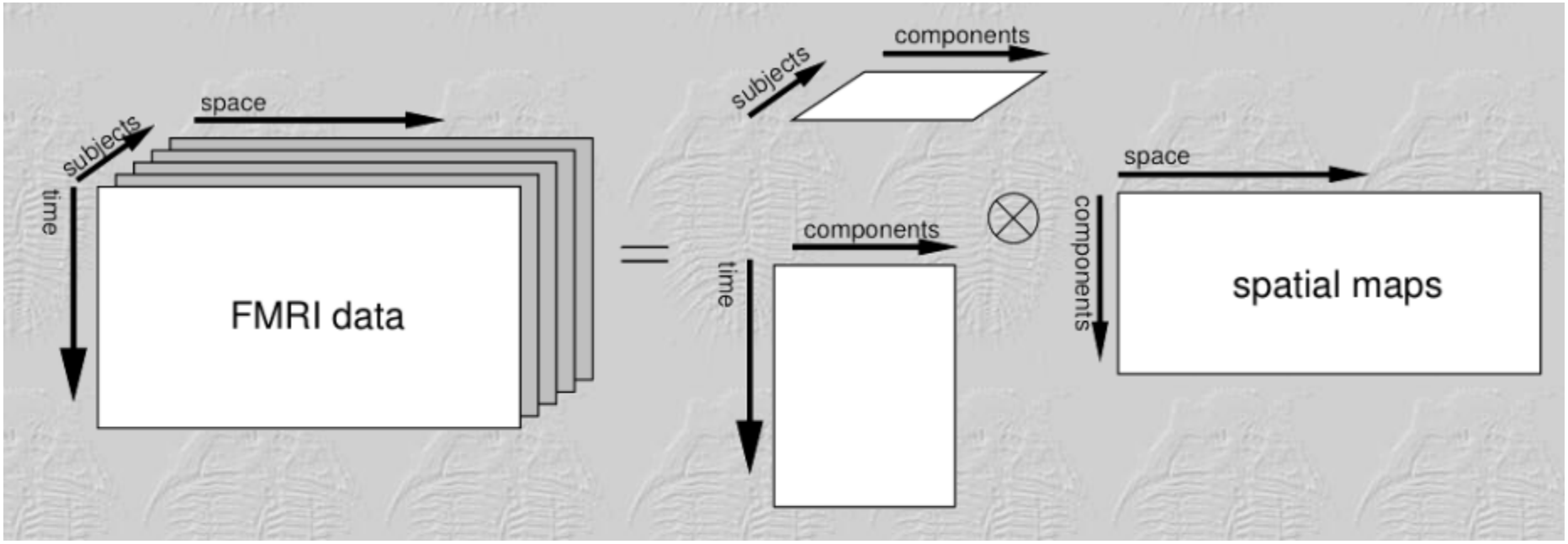
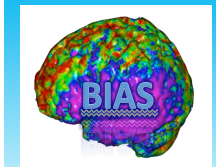
- Tensor ICA decomposes a three-way data set into a set of independent spatial maps together with associated time courses and subject modes.

- This allows us to characterize the signal variation across the temporal, spatial and subject/session domain for each component.

Tensor ICA


space
subjects
time
FMRI data
components
subjects
components
time
space
components
spatial maps



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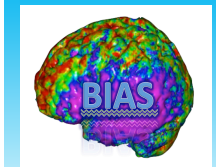
Effective Connectivity



Effective Connectivity

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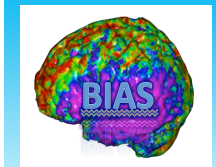
- Effective connectivity is the influence one neuronal system exerts over another.

- Effective connectivity depends on two models:

  - A neuroanatomical model that describes which areas are connected.

  - A mathematical model that describes how areas are connected.



Structural Equation Modelling

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- Structural equation Modeling (SEM) was first applied to imaging data by McIntosh and Gonzalez-Lima (1991).
- SEM allows for the analysis of more complicated models consisting of many different ROIs.
- Instead of considering variables individually the emphasis in SEM lies on the variance-covariance structure of the data.

SEM

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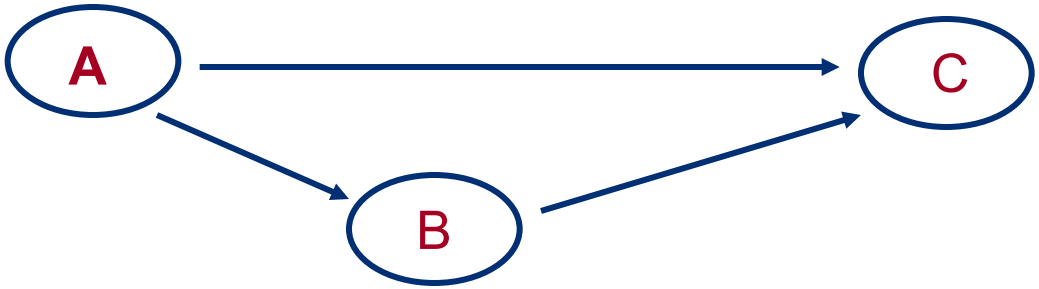
Structural Equation Models comprise a set of regions and a set of directed connections

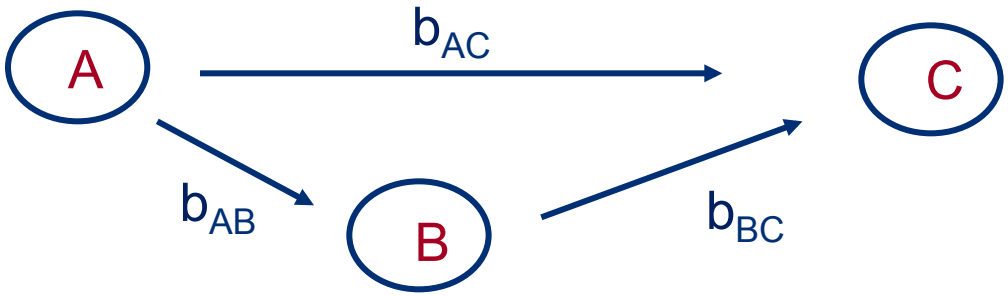


A **causal relationship is attributed to the connections. An arrow from A to B implies A causes B.**

Note: **Causal relationships are assumed** *apriori*.

SEM

Further define path coefficients between the various nodes.



- **The coefficients imply a set of correlations among the regions.**
- **A path coefficient is the expected change in activity of one region given a unit change in the region influencing it.**
- **The path coefficient indicates the average influence across the time interval measured.**

SEM

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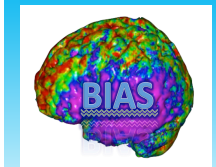
- The covariance of the data represents how the activities in two or more regions are related.
- In SEM we seek to minimize the difference between the observed covariance matrix and the one implied by the structure of the model.
- The parameters of the model are adjusted to minimize the difference between the observed and modeled covariance matrix.



Set-Up

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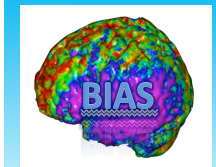
- Consider a network consisting of N different regions, where the activity at time *t* is given by the vector y_t which is of length N.
- Further suppose the data consists of T separate time points.
- We can write the full data as $\mathbf{Y} = (y_1, \ldots y_T)$
- Next, assume that the network activity is independent from sample to sample, i.e. y_i is independent of y_j for all $i \neq j$.
- This is not particularly realistic, but heuristic corrections exist.



Set-Up

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Under this assumption we can write the likelihood of the data as

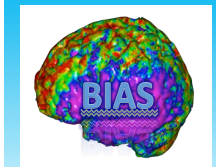
$$p(Y \mid \theta) = \prod_{t=1}^{T} p(y_t \mid \theta)$$

where θ are the parameters of the SEM.

Further suppose that

$$y_t \sim N(0, \Sigma(\theta))$$

The covariance matrix is a function of the connectivity parameters contained in θ.



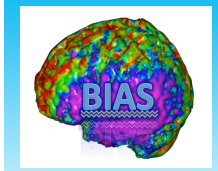
The form of $\Sigma(\theta)$ is specified by how the activity in various regions are related to one another, i.e.

$$y_t = My_t + e_t$$

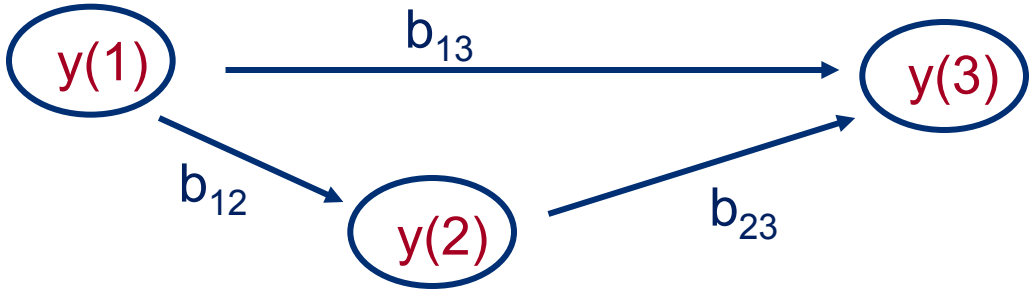
where *M* now describes the set of path coefficients.

The M_{ij} term of the matrix represents a connection between regions *i* and *j*.

The noise term e_t is normally distributed with mean 0 and covariance matrix $R=diag\{\sigma_1^2, ... \sigma_N^2\}$.



Example



$$y_t = My_t + e_t$$

$$\begin{bmatrix} y_t(1) \\ y_t(2) \\ y_t(3) \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ b_{12} & 0 & 0 \\ b_{13} & b_{23} & 0 \end{bmatrix} \begin{bmatrix} y_t(1) \\ y_t(2) \\ y_t(3) \end{bmatrix} + \begin{bmatrix} e_t(1) \\ e_t(2) \\ e_t(3) \end{bmatrix}$$

We can rewrite y_t as

$$y_t = (I - M)^{-1} e_t$$

Hence, we can write the covariance matrix of y_t as

$$\Sigma(\theta) = (I - M)^{-1} R\left((I - M)^{-1}\right)^T$$

The parameters θ are the unknown elements of the matrices M and R.

Find the parameters θ that maximize the likelihood function:

$$y_t \sim N(0, \Sigma(\theta))$$

This gives us the desired path coefficients.

Inference

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- All inference regarding the path coefficients rests on the use of nested or stacked models.
- A more complex model is compared to a simpler model nested within the first model.
- If the complex model fits a particular dataset significantly better, then the additional parameters of this model are needed in the subsequent analyses.
- Given a constrained model, which is defined by the omission of a pathway, hypothesis testing may be construed as evidence for or against the pathway by nesting it in a free model where the pathway is included.
- If the difference in goodness of fit is highly unlikely to have occurred by chance, the connection can be declared active.

Example

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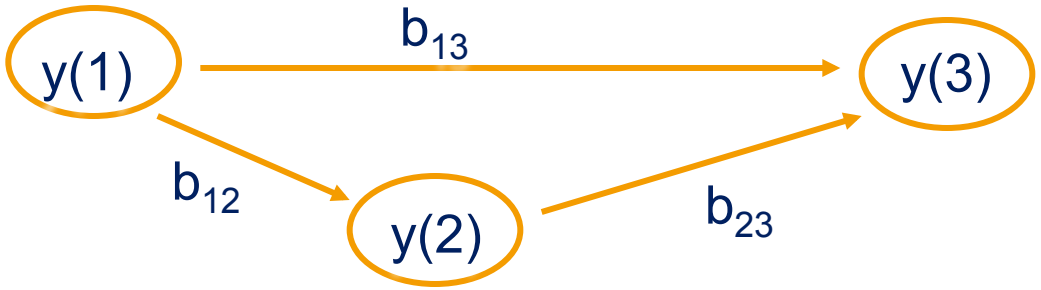
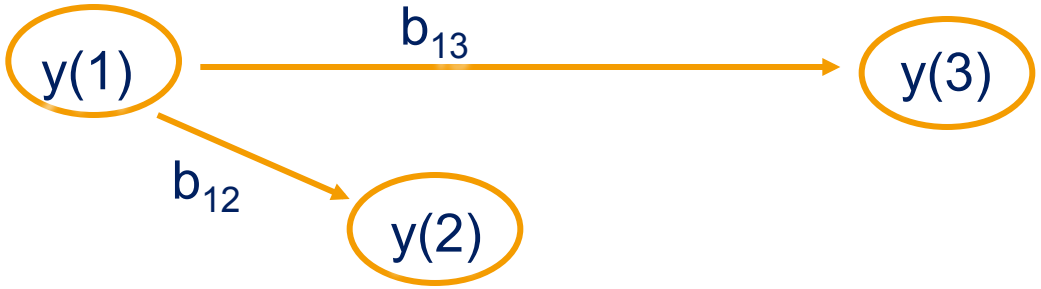
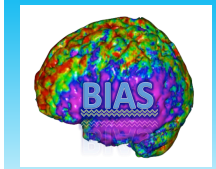
Fixed



Constrained



$$H_0 : b_{23} = 0$$



Likelihood Ratio Test

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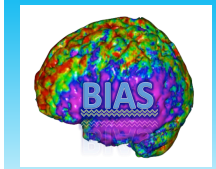
- The likelihood ratio test (LRT) is a statistical test of the goodness-of-fit between two models.
- A relatively more complex model is compared to a simpler model to determine whether it fits the dataset significantly better.
- If so, the additional parameters in the more complex model need to be included.



Comparing Conditions

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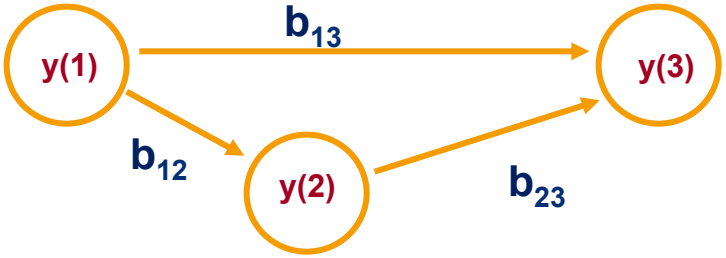
- We can take a similar approach to making inference about changes in effective connectivity between different experiment conditions.
- First partition the data according to the different experimental conditions.
- Next create a null-model where path coefficients are constrained to be equal between conditions and an alternative model where certain coefficients of interest are allowed to vary.

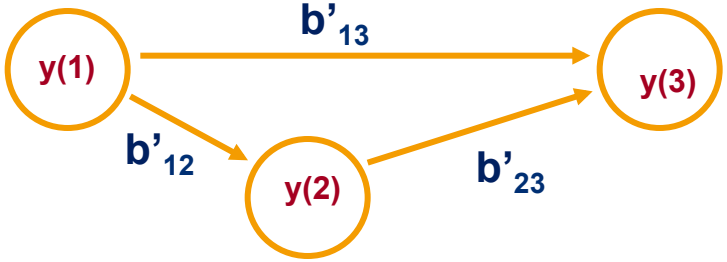
Example

Null-model

Condition 1

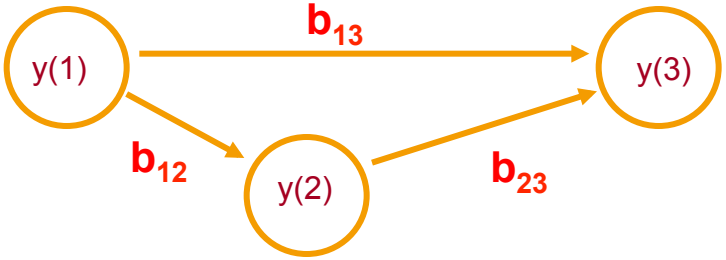


Condition 2

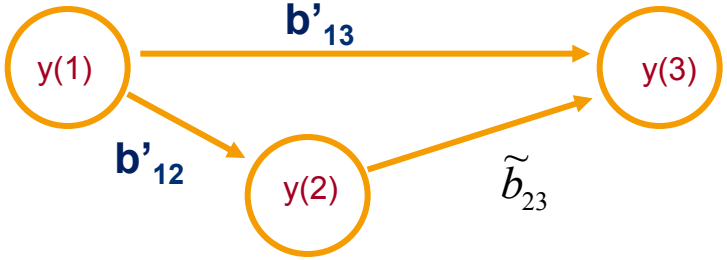


Alternative model

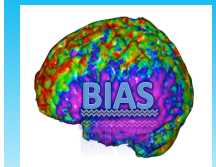
Condition 1



Condition 2



$$H_0 : \tilde{b}_{23} = b_{23}$$



Comparing Conditions

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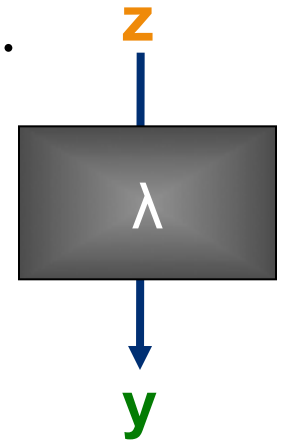
- Use the LRT to test whether there are significant differences between the models.
- If a significant difference exists we reject the hypothesis that the path coefficients are equal in both conditions.
- SEM discounts temporal information. Hence, permuted data sets produce the same path coefficients as the original data.
- We can compensate for temporal autocorrelation by using corrected degrees of freedom.
- However, models that include the temporal order of the data may be more appropriate.

Neuronal Interactions

- It is important to note that the measurements used in each of the connectivity studies we have described so far are hemodynamic in nature and this limits an interpretation of the results at the level of neuronal interactions.

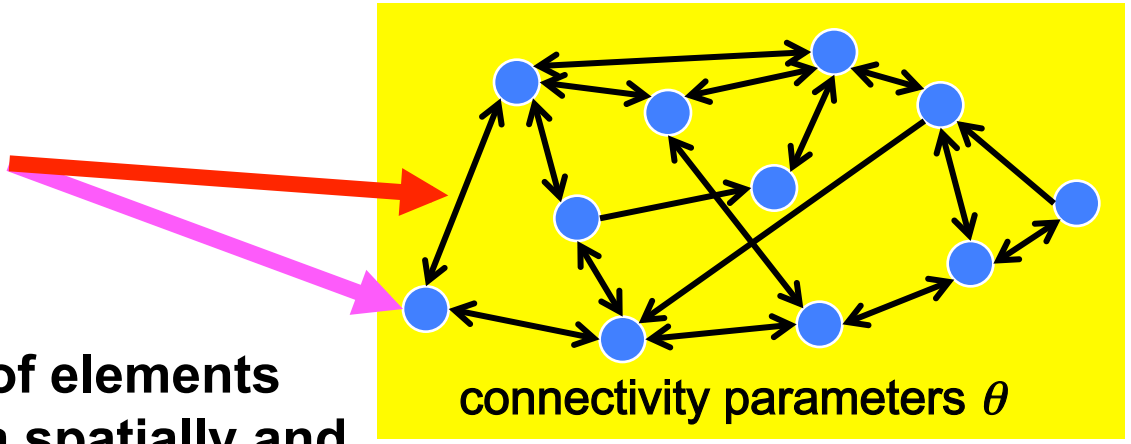
- Dynamic Casual Modeling (Friston *et. al.*) is an attempt to move the connectivity analysis to the neuronal level.
- The modelled neuronal dynamics (z) is transformed into area-specific BOLD signals (y) by a hemodynamic forward model (λ).

- The aim of DCM is to estimate parameters at the neuronal level (computed separately for each area) such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.



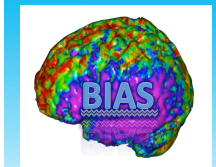
Dynamic Casual Modeling

- Dynamic Causal Modeling (DCM) is an attempt to model neuronal interactions using hemodynamic time series.
- DCM treats the brain as a deterministic nonlinear dynamic system that is subject to inputs and produces outputs.
- It makes inference about the coupling among brain areas and how the coupling is influenced by changes in experimental context.



System = a set of elements which interact in a spatially and temporally specific fashion

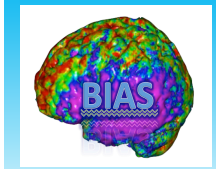
System state *z(t)* $\dot{z} = F(z, u, \theta)$



- DCM is based on a neuronal model of interacting cortical regions, supplemented with a forward model of how neuronal activity is transformed into a measured response.

- Effective connectivity is parameterized in terms of the coupling among unobserved neuronal activity in different regions.

- We can estimate these parameters by perturbing the system and measuring the response.



State-space Model

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- DCM is a state-space model.
- The initial formulation of DCM did not consider noise and was therefore a deterministic state-space model stated in terms of ordinary differential equations.
- More recent versions of DCM have been in terms of stochastic differential equations.

State changes of a system are dependent on:

- **the current state**
- **external inputs**
- **its connectivity**
- **time constants & delays**

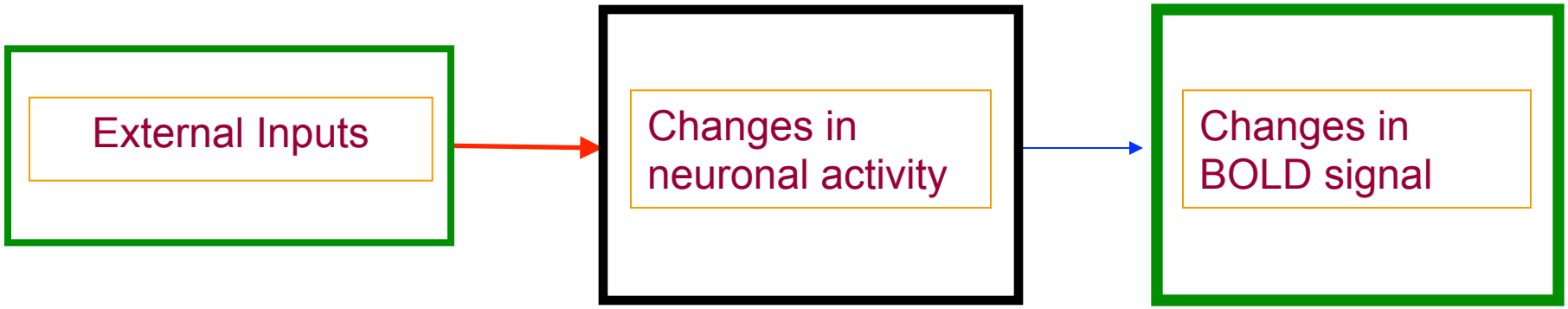
System state *z(t)*

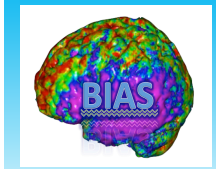
$$\dot{z} = F(z, u, \theta)$$

Dynamic Casual Modeling

In DCM a distinction is made between the neuronal level and the hemodynamic level.

Experimental inputs cause changes in effective connectivity expressed at the neuronal level which in turn cause changes in the observed hemodynamics.





Dynamic Casual Modeling

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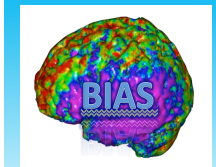
- DCM uses a bilinear model for the neuronal level and an extended Balloon model for the hemodynamic level.
- In a DCM model we have *J* experimental inputs and *N* outputs (one for each region).
- Each region has five state variables, four corresponding to the hemodynamic model and a fifth corresponding to neuronal activity.



Neurodynamics

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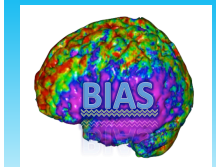
Define the neuronal states as:

$$z = \left(z_1, \ldots z_N\right)^T$$

The effective connectivity model is described by:

$$\dot{z} = F(z, u, \theta)$$

where F is a non-linear function describing the influences that z and u exert upon changes in the neuronal states.



Bilinear form

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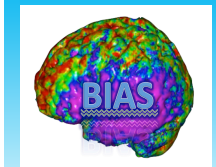
The model consists of a bivariate nonlinear function.

We can approximate such a function using a bilinear approximation:

$$f(x,u) \approx ax + bxu + cu$$

where

$$a = \frac{\partial f}{\partial x} \qquad b = \frac{\partial^2 f}{\partial x \partial u} \qquad c = \frac{\partial f}{\partial u}$$



Neurodynamics

The effective connectivity model

$$\dot{z} = F(z, u, \theta)$$

can be rewritten in bilinear form as:

$$\dot{z}_t = \left(A + \sum_{j=1}^{J} u_t(j) B^j \right) z_t + C u_t$$

where z_t is the neuronal activity at time t (latent) and $u_t(j)$ is the jth of J inputs at time t (known).

- The matrix A represents the first order connectivity among regions in the absence of input. It specifies which regions are connected and whether these connections are uni- or bidirectional.

- The matrix C represents the extrinsic influence of inputs on neuronal activity. It specifies which inputs are connected to which regions.

- The matrices B_j represent the change in coupling induced by the jth input. It specifies which intrinsic connections are changed by which inputs.

Interpretation

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- The units of connection are per unit time and therefore correspond to rates.

- A strong connection means an influence that is expressed quickly or with a small time constant.

DCM parameters=rate constants

Integration of a first-order linear differential equation gives an exponential

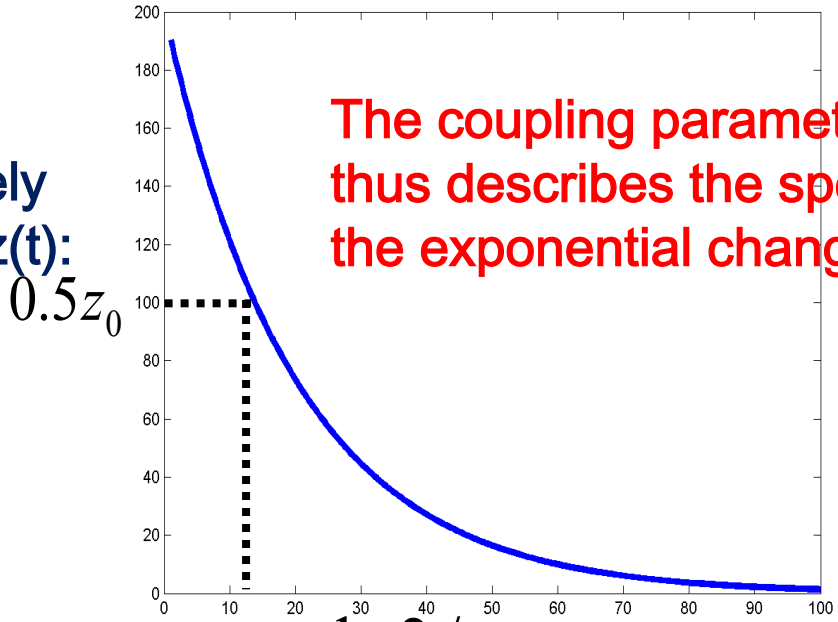
$$\frac{dz}{dt} = az \Rightarrow z(t) = z_0 \exp(at)$$

Coupling parameter a is inversely proportional to the half life τ of z(t):

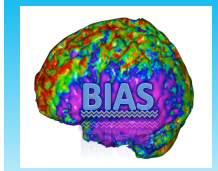
$$z(\tau) = 0.5 z_0$$

$$= z_0 \exp(a\tau)$$

$$\Rightarrow a = \ln 2 / \tau$$



The coupling parameter a thus describes the speed of the exponential change in z(t)



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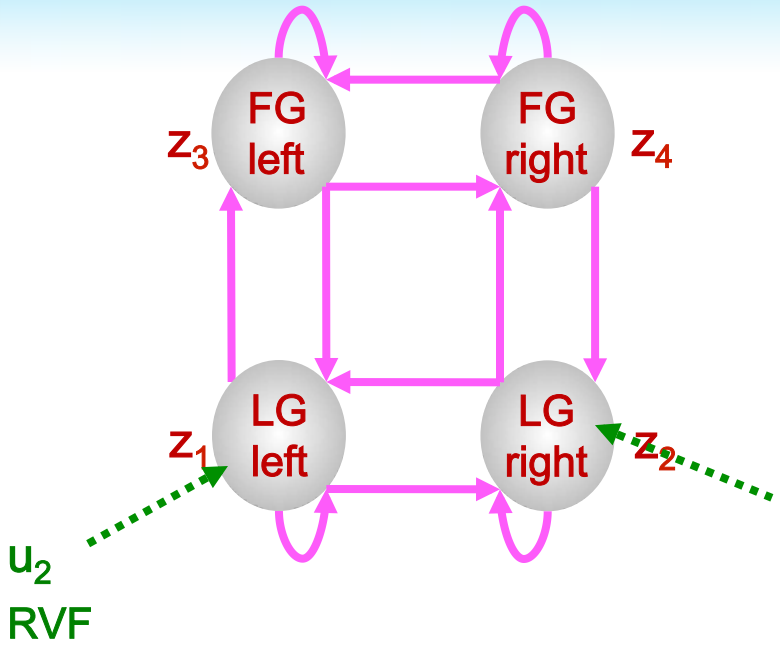
Example: linear dynamic system



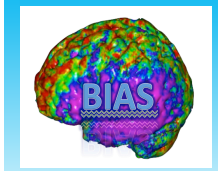
LG = lingual gyrus
FG = fusiform gyrus

Visual input in the
- left (LVF)
- right (RVF)
visual field.

$$\dot{z} = Az + Cu$$

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

$$\dot{z}_1 = a_{11}z_1 + a_{12}z_2 + a_{13}z_3 + c_{12}u_2$$
$$\dot{z}_2 = a_{21}z_1 + a_{22}z_2 + a_{24}z_4 + c_{21}u_1$$
$$\dot{z}_3 = a_{31}z_1 + a_{33}z_3 + a_{34}z_4$$
$$\dot{z}_4 = a_{42}z_2 + a_{43}z_3 + a_{44}z_4$$



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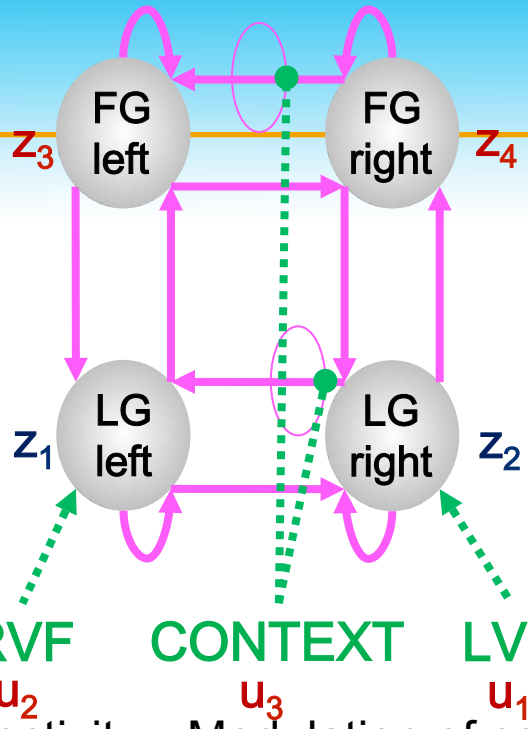
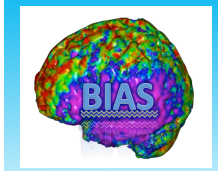
Extension: bilinear dynamic system



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

Intrinsic connectivity | Modulation of connectivity | Direct inputs

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \\ \dot{z}_3 \\ \dot{z}_4 \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & 0 & a_{24} \\ a_{31} & 0 & a_{33} & a_{34} \\ 0 & a_{42} & a_{43} & a_{44} \end{bmatrix} + u_3 \begin{bmatrix} 0 & b_{12}^3 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_{34}^3 \\ 0 & 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} z_1 \\ z_2 \\ z_3 \\ z_4 \end{bmatrix} + \begin{bmatrix} 0 & c_{12} & 0 \\ c_{21} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$



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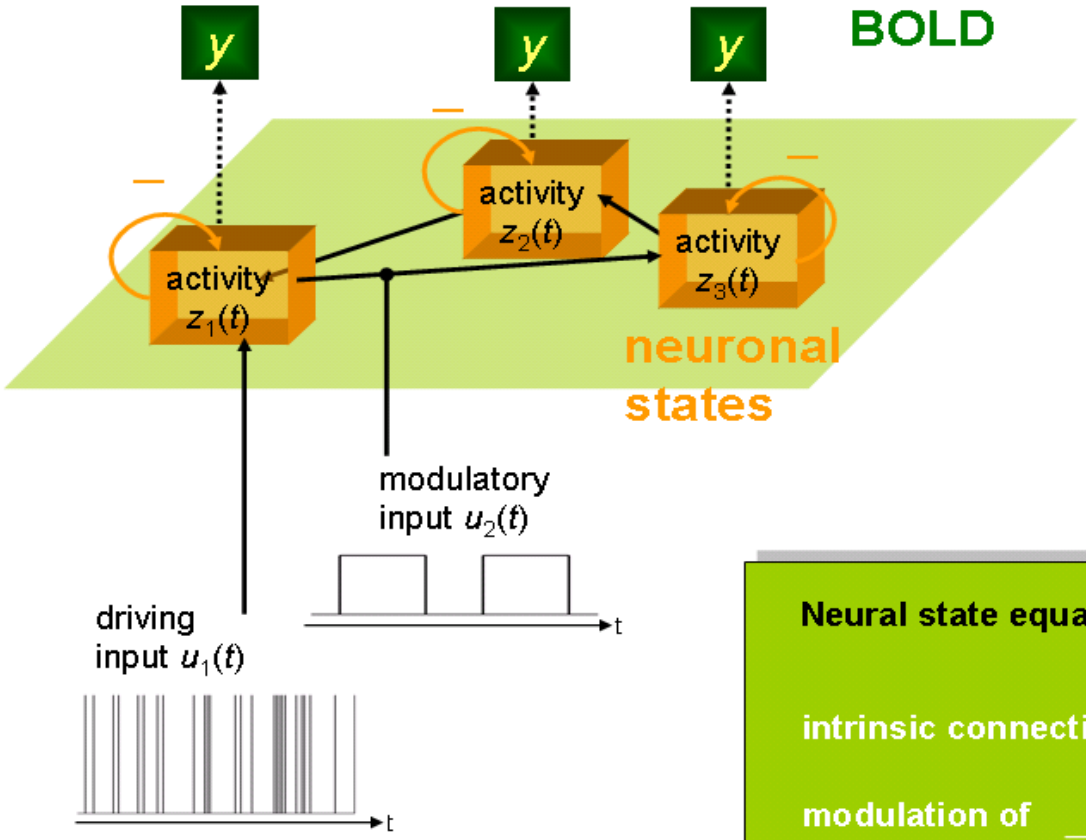
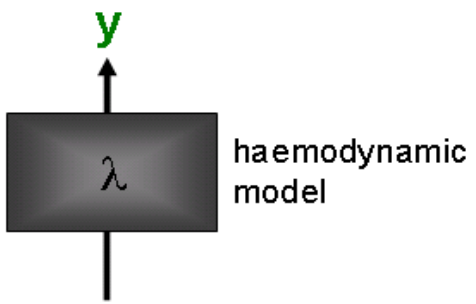




integration

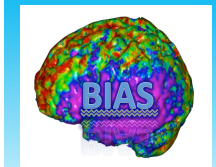
Neural state equation $\dot{z} = (A + \sum u_j B^{(j)})z + Cu$

intrinsic connectivity → $A = \frac{\partial \dot{z}}{\partial z}$

modulation of connectivity → $B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{z}}{\partial z}$

direct inputs → $C = \frac{\partial \dot{z}}{\partial u}$

Stephan & Friston (2006),
Handbook of Connectivity



Hemodynamics

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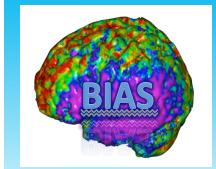
- The neuronal activities in each region cause changes in blood volume and deoxyhmoglobin that, in turn, cause changes in the observed BOLD response.

- The hemodynamics are described using an extended Balloon model, which involves a set of hemodynamic state variables, state equations and hemodynamic parameters θ^h.



Extended Balloon Model

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Activity-dependent signal:

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

Flow induction:

$$\dot{f} = s$$

Changes in volume:

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

Changes in dHb:

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

Hemodynamic response

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

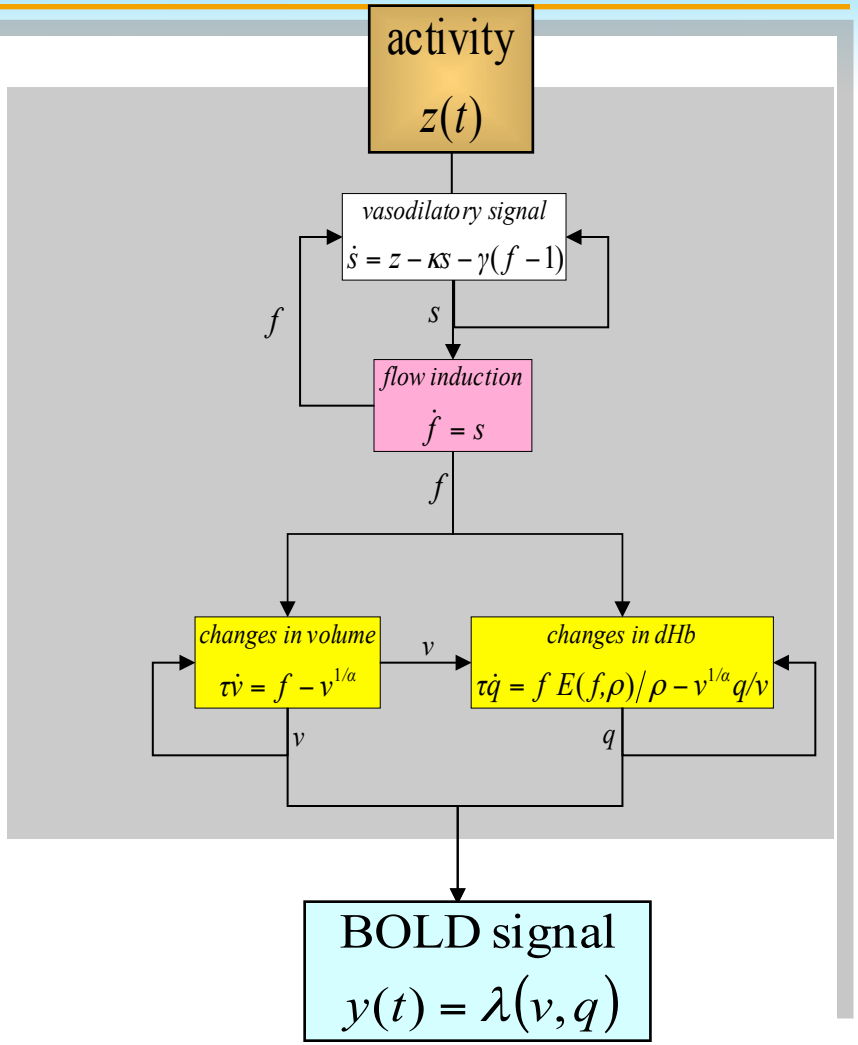
The hemodynamic "Balloon" model

- 5 hemodynamic parameters:

$$\theta^h = \{\kappa, \gamma, \tau, \alpha, \rho\}$$

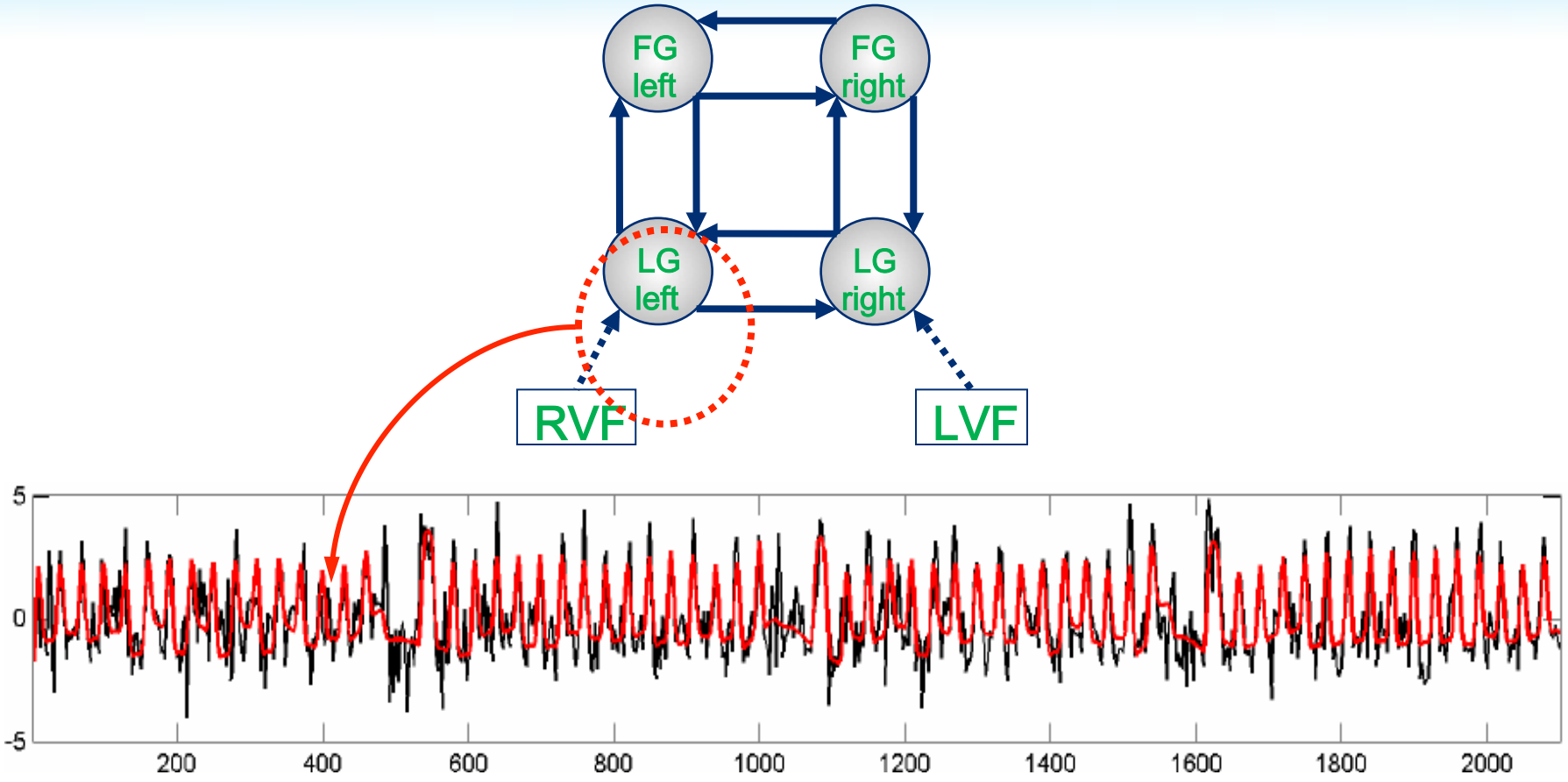
important for model fitting, but of no interest for statistical inference

- Empirically determined *a priori* distributions.
- Computed separately for each area (like the neural parameters)
  → region-specific HRFs!



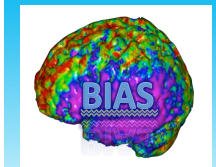
Friston et al. 2000, *NeuroImage*

Example: modelled BOLD signal



black: observed BOLD signal

red: modelled BOLD signal



States Equations

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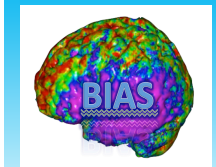
Neuronal state:

Neuronal activity - z_t with parameters θ^c.

Hemodynamic states:

Vasodilatory signal - s_t
Inflow - f_t
Blood volume - v_t
Deoxygenation content - q_t

The observed data: $y_t=\lambda(q_t,v_t)$ with parameters θ^h.



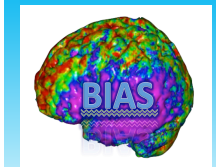
Combining the neuronal and hemodynamic states *x={z,s,f,v,q}* gives us the following model:

$$\dot{x} = f(x, u, \theta)$$

$$y = \lambda(x)$$

All neurodynamic and hemodynamic parameters are contained in $\theta = \left(\theta^c, \theta^h\right)$

To generate data from a DCM, one integrates the neurodynamics together with the hemodynamics.



Normal priors are placed on θ.

The posterior distribution of θ is equal to the likelihood times the prior divided by the evidence:

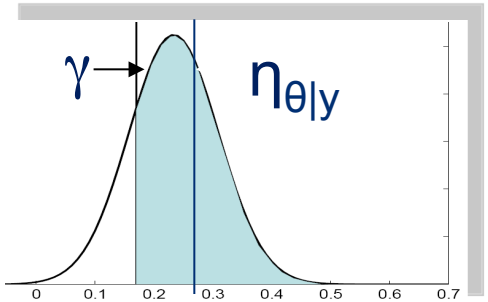
$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta \mid m)}{p(y \mid m)}$$

An optimization scheme is used to estimate parameters that maximize the posterior probability.

The posterior density is used to make inferences about the connections

- Bayesian parameter estimation in DCM: Gaussian assumptions about the posterior distributions of the parameters
- Use of the cumulative normal distribution to test the probability by which a certain parameter (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:

$$p = \phi_N\left(\frac{c^T\eta_{\theta|y} - \gamma}{\sqrt{c^T C_{\theta|y} c}}\right)$$



γ can be chosen as zero ("does the effect exist?") or as a function of the expected half life τ of the neural process: γ = ln 2 / τ

Different models can be compared using the evidence for each model.

Given models $m=i$ and $m=j$, the Bayes factor is

$$B_{ij} = \frac{p(y \mid m = i)}{p(y \mid m = j)}$$

When $B_{ij}>1$, the data favors model i over model j.

When $B_{ij}<1$, the data favors model j over model i.

Comments

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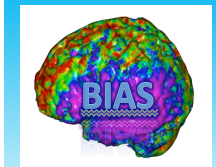
- DCM models interactions at the neuronal rather than the hemodynamic level.
- It is therefore more biologically accurate than the other models described today.
- However, it is quite computationally demanding. It is limited to 8 regions in SPM.



Granger Causality

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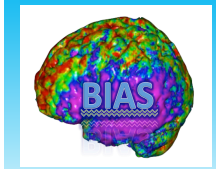
- Granger causality is a technique that was originally developed in economics that has recently been applied to connectivity studies.

- It does not rely on the a priori specification of a structural model, but rather is an approach for quantifying the usefulness of past values from various brain regions in predicting current values in other regions.

- Granger causality provides information about the temporal precedence of relationships among two regions, but it is in some sense a misnomer because it does not actually provide information about causality.



Set Up

- Let x and y be two time courses of length *N* extracted from two brain regions.

- Each time course is modeled using a linear autoregressive model of the M^{th} order

$$x[n] = \sum_{m=1}^{M} a[i]x[n-m] + \varepsilon_x[n]$$

$$y[n] = \sum_{m=1}^{M} b[i]y[n-m] + \varepsilon_y[n]$$

- Here ε_x and ε_y are both white noise, while a and b are model parameters.

- Next, expand each model using the autoregressive terms from the other signal.

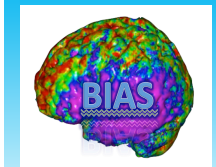
$$x[n] = \sum_{m=1}^{M} a[i]x[n-m] + \sum_{m=1}^{M} b[i]y[n-m] + \varepsilon_x[n]$$

$$y[n] = \sum_{m=1}^{M} b[i]y[n-m] + \sum_{m=1}^{M} a[i]x[n-m]\varepsilon_y[n]$$

- The current value depends both on the past M values its own time course, but also the past M values of the other time course.

- Using these models one can test whether the history of x has any predictive value on the current value of y (and vice versa).

- If the model fit is significantly improved by the inclusion of the cross-autoregressive terms, it provides evidence that the history of one of the time courses can be used to predict the current value of the other and a "Granger-causal" relationship is inferred.



Measuring Influence

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- Geweke has proposed a measure of linear dependence $F_{x,y}$ between x[n] and y[n] which implements Granger causality in terms of vector autoregressive models.

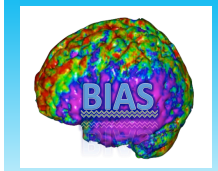
- The term $F_{x,y}$ can be decomposed into the sum of three components:

$$F_{x,y} = F_{x \to y} + F_{y \to x} + F_{x \cdot y}$$

- $F_{x,y}$ is a measure of the total linear dependence between x and y.
  - If nothing about the current value of x (or y) can be explained by a model containing all values of y (or x) then $F_{x,y}$ will be 0.

- $F_{x \to y}$ and $F_{y \to x}$ are measures of linear directed influence from x to y and y to x, respectively.
  - If past values of x improve the prediction of the current value of y, then $F_{x \to y} > 0$.
  - A similar interpretation holds for $F_{y \to x}$.

- $F_{x \cdot y}$ is a measure of the undirected instantaneous influence between the series.
  - The improvement in the prediction of the current value of x (or y) by including the current value of y (or x) in a linear model already containing the past values of x and y.



Computation

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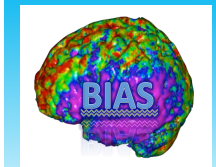
Null model

$$x[n] = \sum_{m=1}^{M} A_x[m]x[n-m] + \varepsilon_x[n] \qquad \text{var}(\varepsilon_x[n]) = \mathbf{\Sigma}_1$$

$$y[n] = \sum_{m=1}^{M} A_y[m]y[n-m] + \varepsilon_y[n] \qquad Var(\varepsilon_y[n]) = \mathbf{T}_1$$

Further, let $\mathbf{q}[n] = \begin{bmatrix} x[n] \\ y[n] \end{bmatrix}$ **where**

$$\mathbf{q}[n] = \sum_{m=1}^{M} \mathbf{A}_q[m]\mathbf{q}[n-m] + \varepsilon_q[n] \qquad Var(\varepsilon_q[n]) = \mathbf{Y} = \begin{bmatrix} \mathbf{\Sigma}_2 & \mathbf{C} \\ \mathbf{C}^T & \mathbf{T}_2 \end{bmatrix}$$



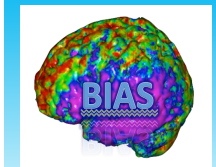
Total linear dependence between x and y:

$$F_{x,y} = F_{x \to y} + F_{y \to x} + F_{x \cdot y}$$

where

$$F_{x,y} = \ln\left(|\,\mathbf{\Sigma}_1\,| \cdot |\,\mathbf{T}_1\,| \,/\, |\,\mathbf{Y}\,|\right) \qquad F_{x \to y} = \ln\left(|\,\mathbf{T}_1\,| \,/\, |\,\mathbf{T}_2\,|\right)$$

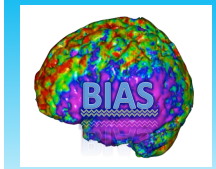
$$F_{x \cdot y} = \ln\left(|\,\mathbf{\Sigma}_2\,| \cdot |\,\mathbf{T}_2\,| \,/\, |\,\mathbf{Y}\,|\right) \qquad F_{y \to x} = \ln\left(|\,\mathbf{\Sigma}_1\,| \,/\, |\,\mathbf{\Sigma}_2\,|\right)$$



- If past values of x improve on the prediction of the current value of y, then $F_{x \to y}$ is large.

- A similar interpretation, but in the opposite direction, holds for $F_{y \to x}$.

- The difference between the two terms can be used to infer which regions history is more influential on the other. This difference is referred to as Granger Causality.



Granger Causality Map

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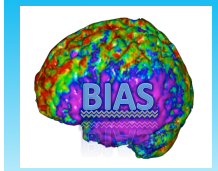
- A Granger Causality Map (GCM) is computed with respect to a single selected reference region (e.g., seed region).

- It maps both sources of influence to the reference region and targets of influence from the reference region over the brain.



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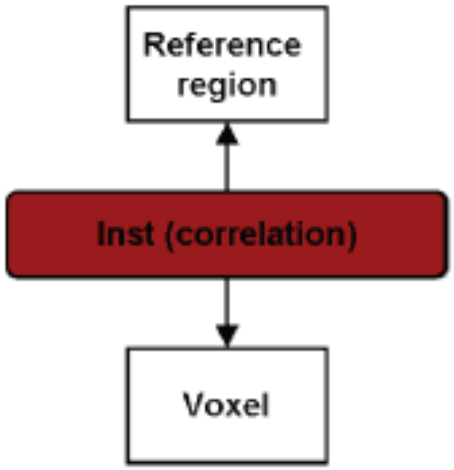
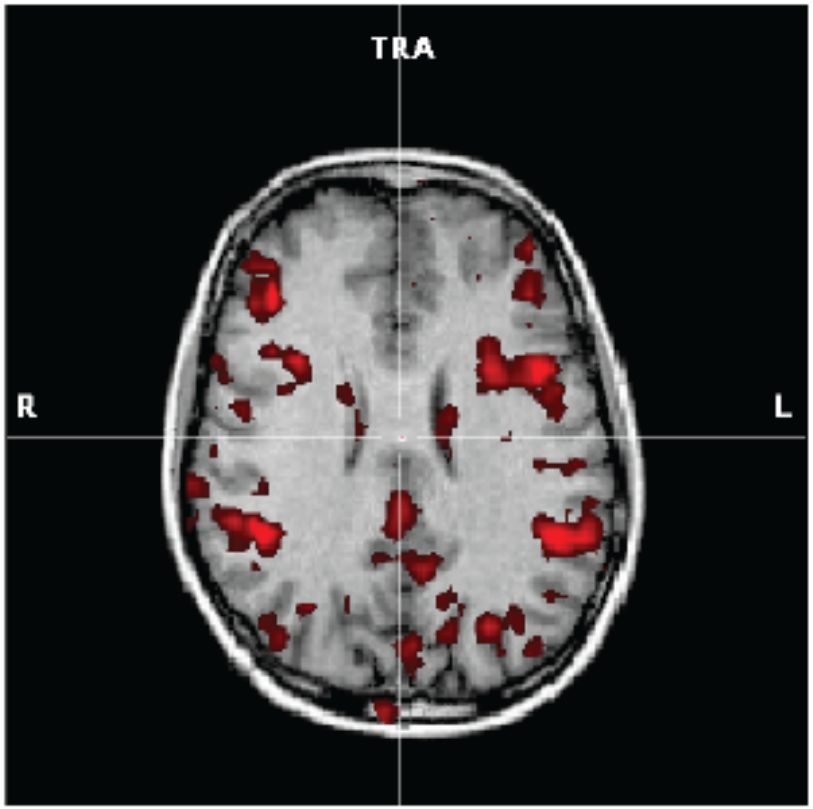
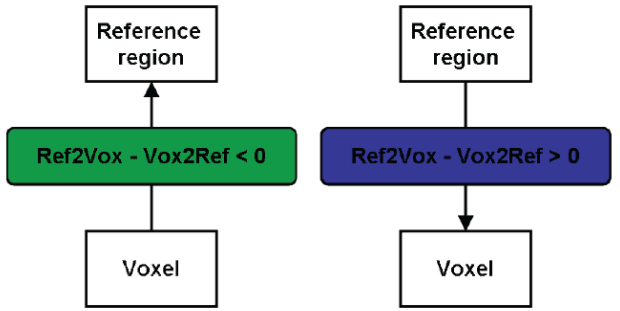
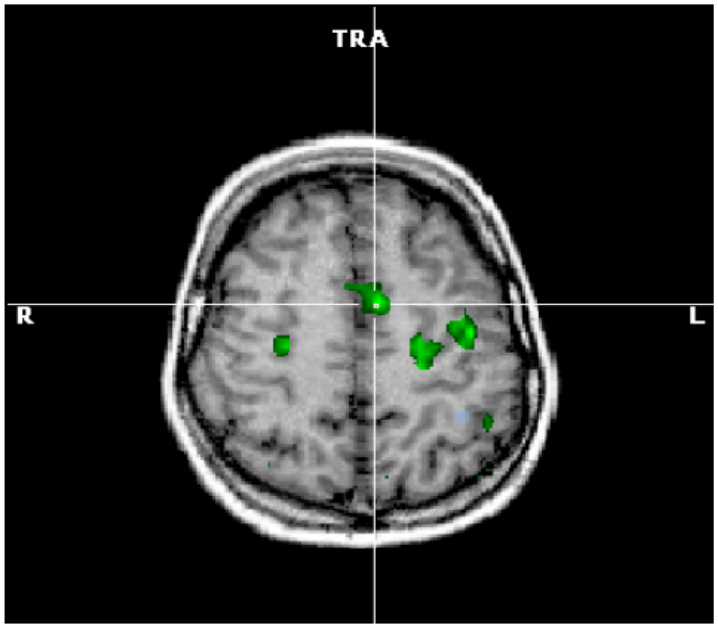
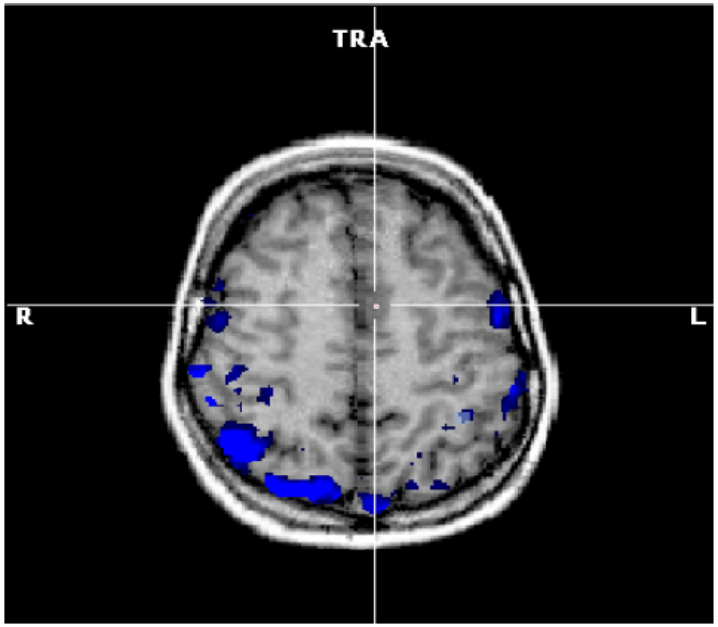
Granger Causality Mapping





Granger Causality Mapping

dGCM = Ref2Vox – Vox2Ref