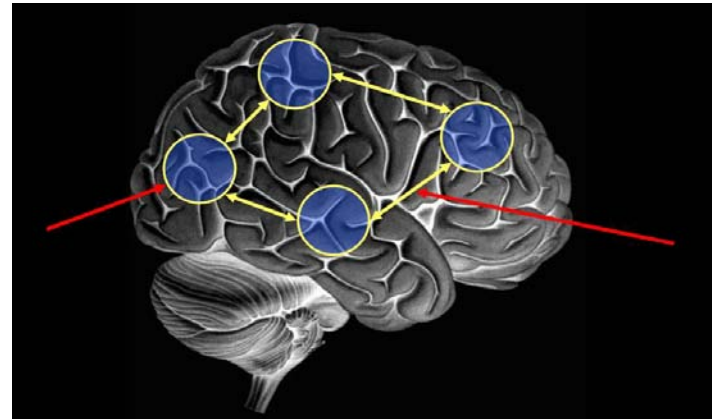


# Models of Effective Connectivity & Dynamic Causal Modelling

*Hanneke den Ouden*

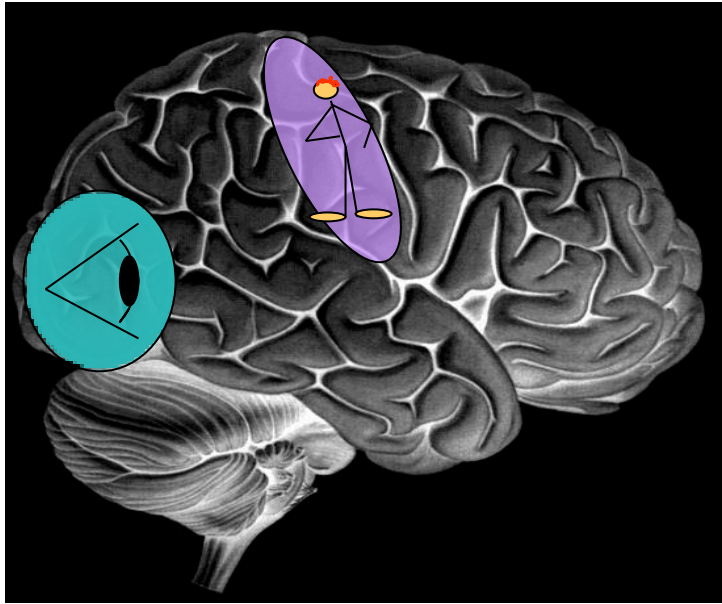
Center for Neural Science  
New York University  
New York, USA

Advanced SPM course  
UKE, Hamburg  
September 21-11, 2011

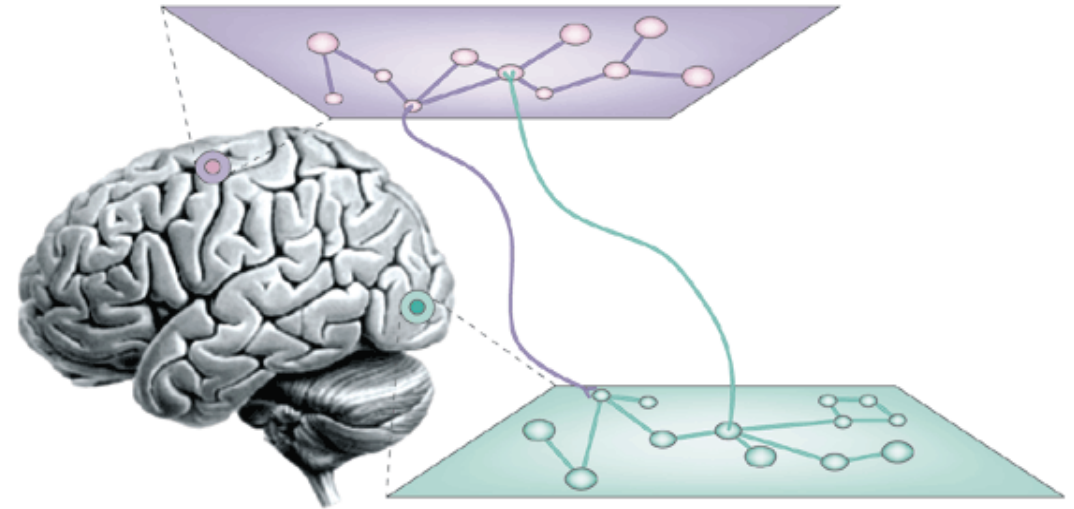


# Principles of Organisation

Functional specialization



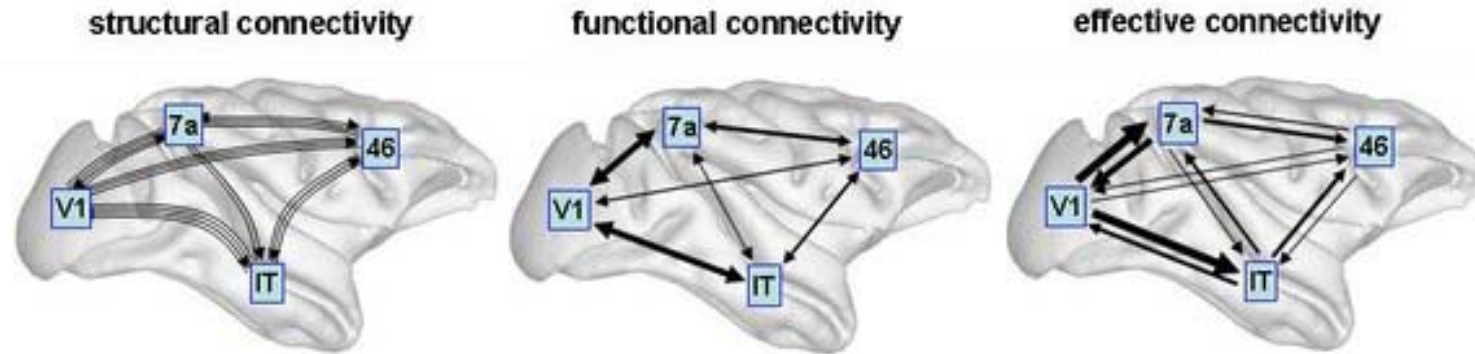
Functional integration



# Overview

- Brain connectivity: Types & definitions
  - Anatomical connectivity
  - Functional connectivity
  - Effective Connectivity
- Dynamic causal models (DCMs)
- Practical examples

# Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

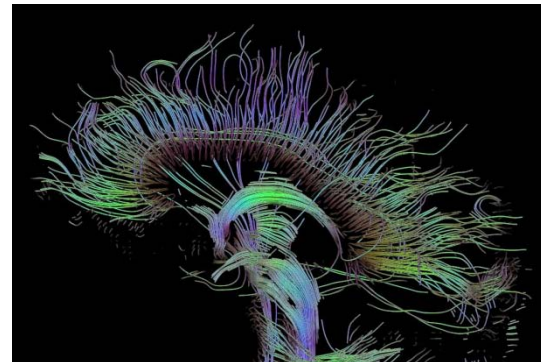
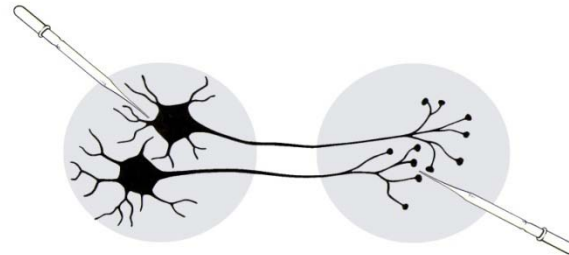
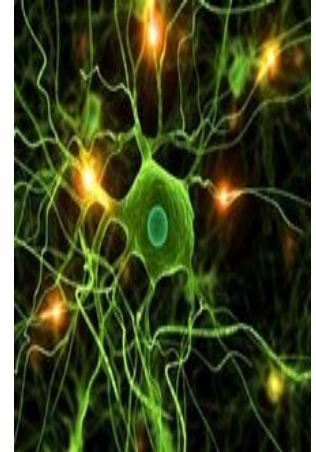
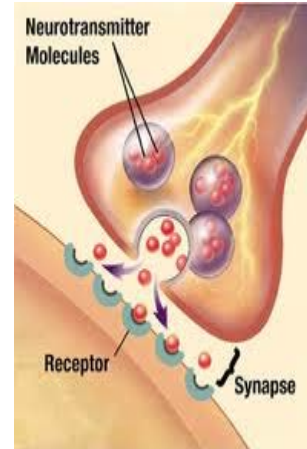
- **anatomical/structural connectivity**  
= presence of axonal connections
- **functional connectivity**  
= statistical dependencies between regional time series
- **effective connectivity**  
= causal (directed) influences between neurons or neuronal populations

# Anatomical connectivity

*Definition:*

*presence of axonal connections*

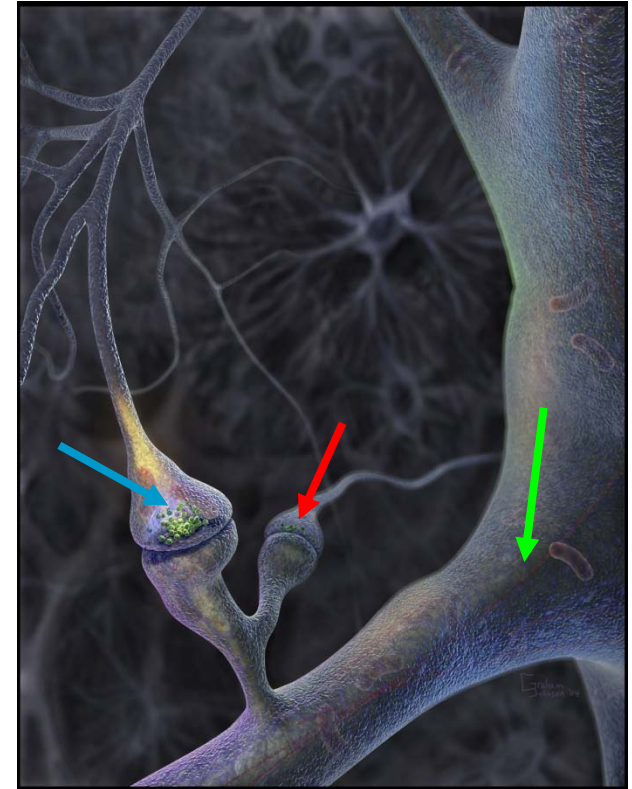
- neuronal communication via synaptic contacts
- Measured with
  - tracing techniques
  - diffusion tensor imaging (DTI)



# Knowing anatomical connectivity is not enough...

- Context-dependent recruiting of connections :
  - Local functions depend on network activity
- Connections show synaptic plasticity
  - change in the structure and transmission properties of a synapse
  - even at short timescales

→ Look at functional and effective connectivity



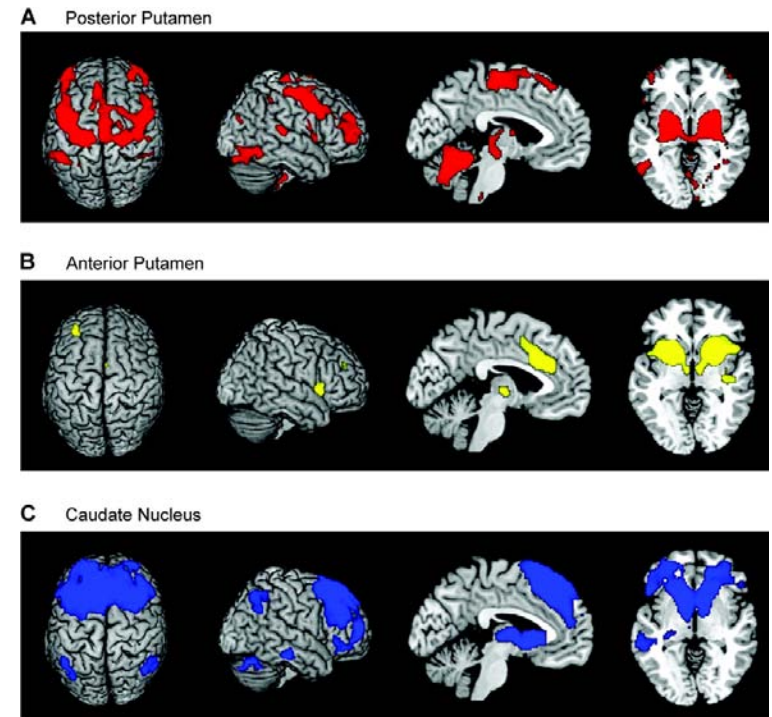
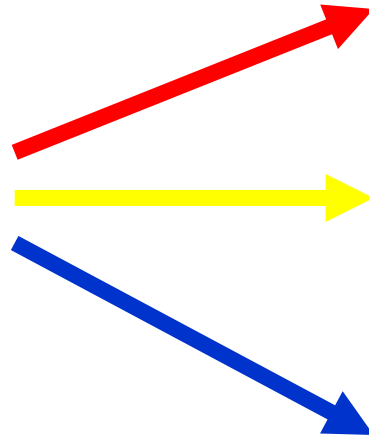
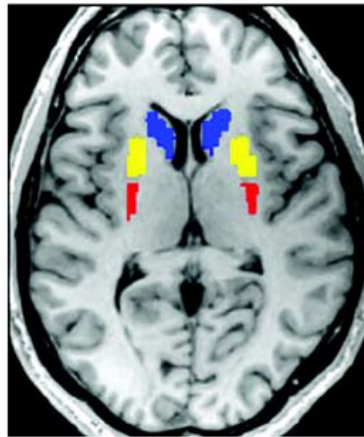
# Functional connectivity

*Definition: statistical dependencies between regional time series*

- Seed voxel correlation analysis
- Coherence analysis
- Eigen-decomposition (PCA, SVD)
- Independent component analysis (ICA)
- any technique describing statistical dependencies amongst regional time series

# Seed-voxel correlation analyses

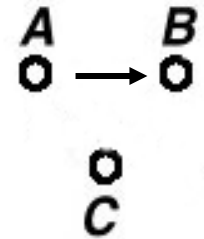
- hypothesis-driven choice of a seed voxel
- extract reference time series
- voxel-wise correlation with time series from all other voxels



# Pros & Cons of functional connectivity analysis

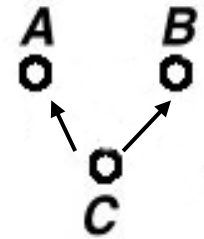
- Pros:

- useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, etc.)

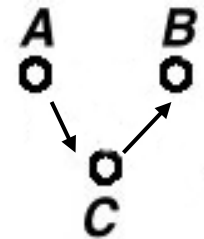


- Cons:

- usually suboptimal for situations where we have a priori knowledge / experimental control
- interpretation of resulting patterns is difficult / arbitrary  
→ no mechanistic insight



Effective connectivity

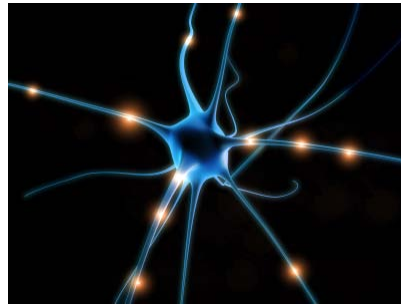


# Effective connectivity

*Definition: causal (directed) influences between neurons or neuronal populations*

- *In vivo* and *in vitro* stimulation and recording

- 
- 
- 
- 
- 



- Models of **causal interactions** among neuronal populations
  - explain *regional effects* in terms of *interregional connectivity*

# Some models for computing effective connectivity from fMRI data

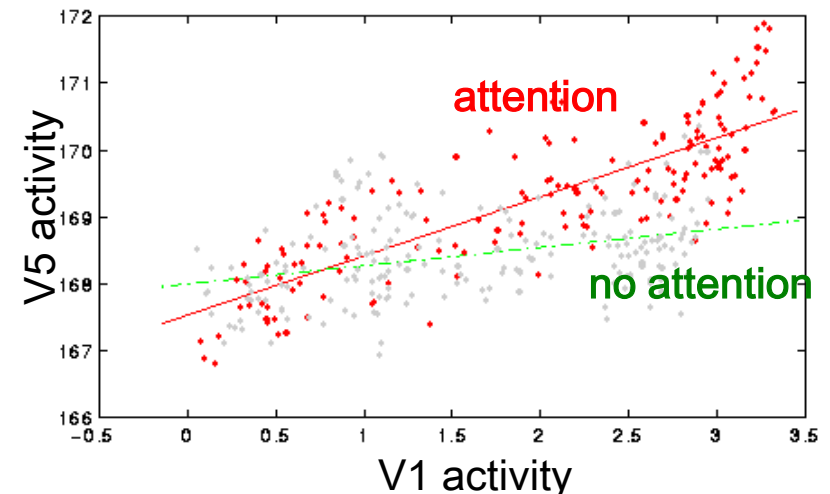
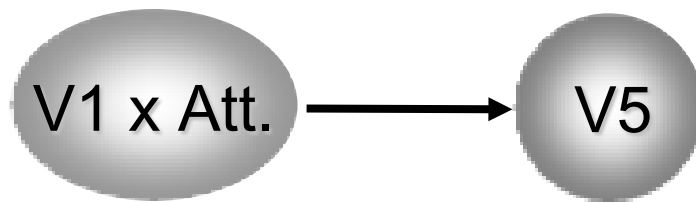
- Structural Equation Modelling (SEM)  
McIntosh et al. 1991, 1994; Büchel & Friston 1997; Bullmore et al. 2000
- regression models  
(e.g. psycho-physiological interactions, PPIs)  
Friston et al. 1997
- Volterra kernels  
Friston & Büchel 2000
- Time series models (e.g. MAR, Granger causality)  
Harrison et al. 2003, Goebel et al. 2003
- Dynamic Causal Modelling (DCM)  
*bilinear*: Friston et al. 2003; *nonlinear*: Stephan et al. 2008

# Psychophysiological interaction (PPI)

- bilinear model of how the psychological context **A** changes the influence of area **B** on area **C** :

$$B \times A \rightarrow C$$

- A PPI corresponds to differences in regression slopes for different contexts.
- Compute the interaction of the timeseries of a seed voxel with the psychological variable



# Pros & Cons of PPIs

- Pros:
  - given a single source region, we can test for its context-dependent connectivity across the entire brain
  - easy to implement
- Cons:
  - only allows to model contributions from a single area
  - ignores time-series properties of the data\*
  - operates at the level of BOLD time series\*

*DCM* needed for more robust statements of effective connectivity.

# Overview

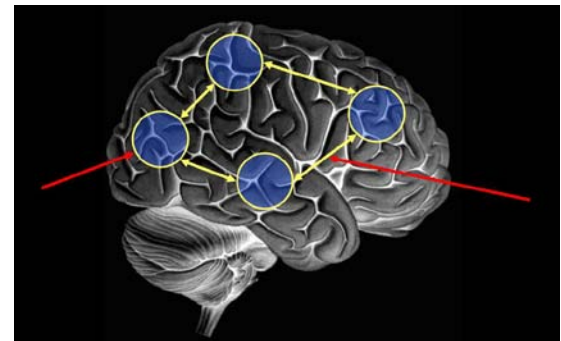
- Brain connectivity: types & definitions
- Dynamic causal models (DCMs)
  - Basic idea
  - Neural level
  - Hemodynamic level
  - Parameter inference
- Practical examples

# Basics of Dynamic Causal Modelling

**DCM allows us to look at how areas within a network interact:**

Investigate functional integration & modulation of specific cortical pathways

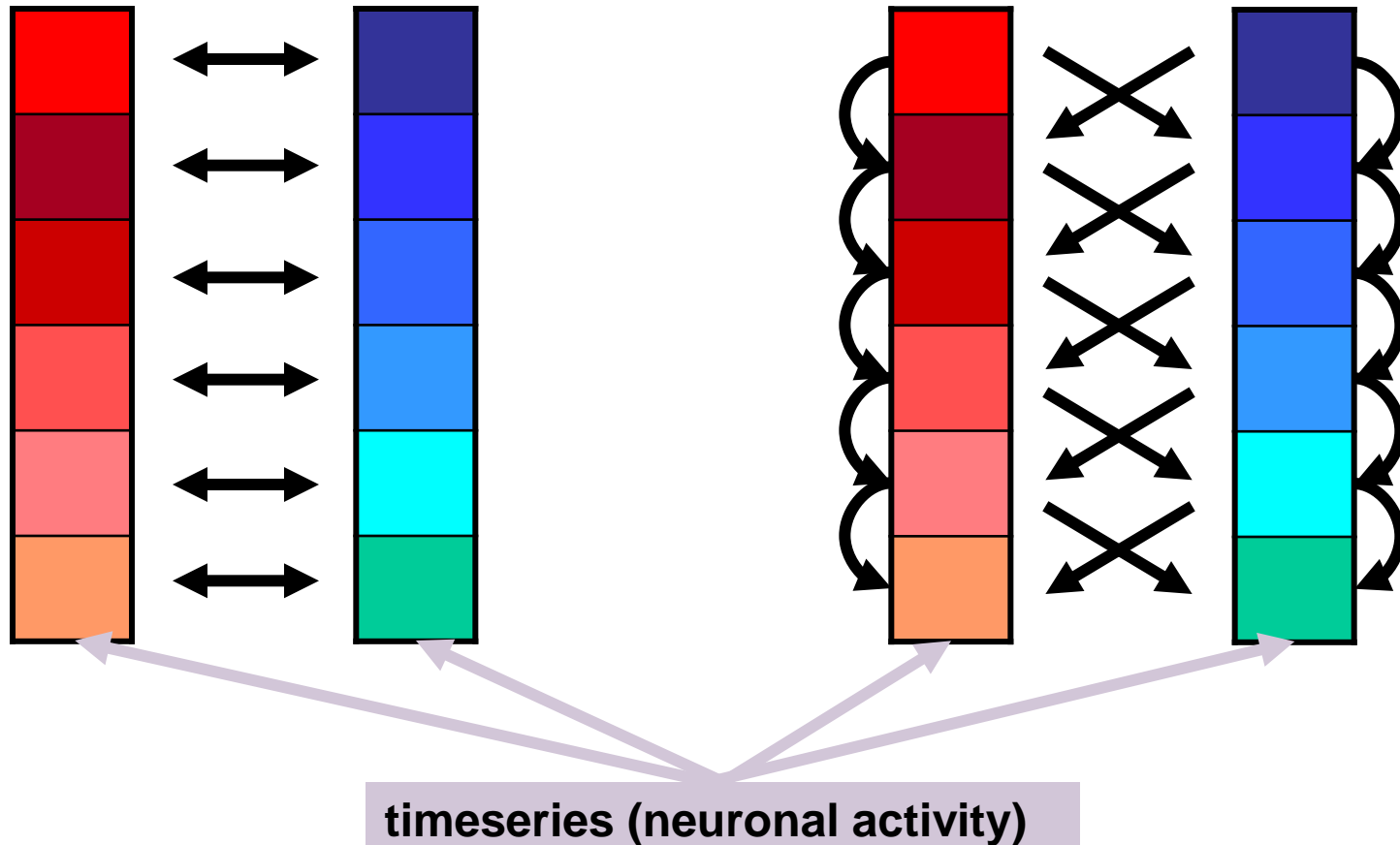
- Temporal dependency of activity within and between areas (causality)



# Temporal dependence and causal relations

Seed voxel approach, PPI etc.

Dynamic *Causal* Models

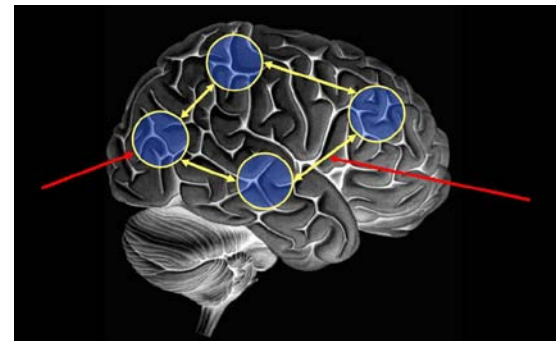


# Basics of Dynamic Causal Modelling

**DCM allows us to look at how areas within a network interact:**

Investigate functional integration & modulation of specific cortical pathways

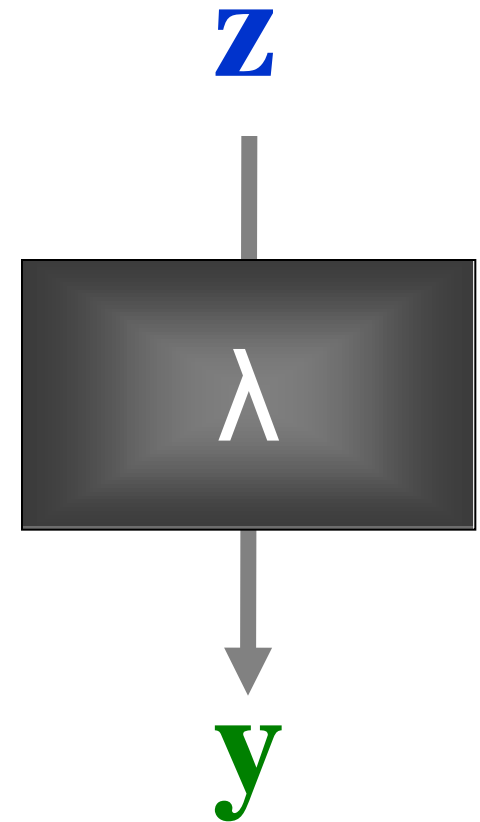
- Temporal dependency of activity within and between areas (causality)
- Separate neuronal activity from observed BOLD responses



# Basics of DCM: Neuronal and BOLD level

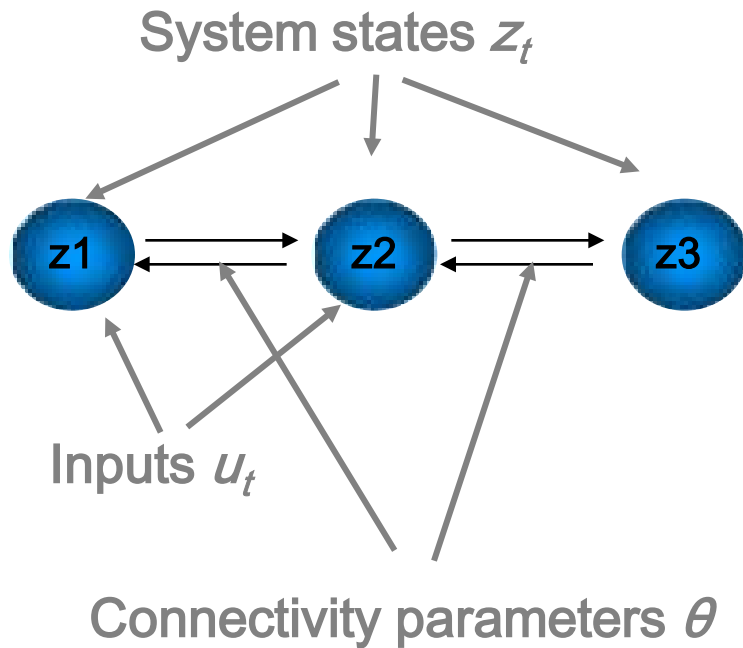
- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).
- The modelled neuronal dynamics ( $\mathbf{z}$ ) are transformed into area-specific BOLD signals ( $\mathbf{y}$ ) by a hemodynamic model ( $\lambda$ ).

The aim of DCM is to estimate parameters at the neuronal level such that the modelled and measured BOLD signals are maximally\* similar.



# The neuronal system

A System is a set of elements  $z_n(t)$  which interact in a spatially and temporally specific fashion



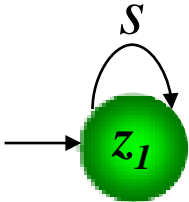
State changes of the system states are dependent on:

- the current state  $z$
- external inputs  $u$
- its connectivity  $\theta$

➔  $\frac{dz}{dt} = F(z, u, \theta)$

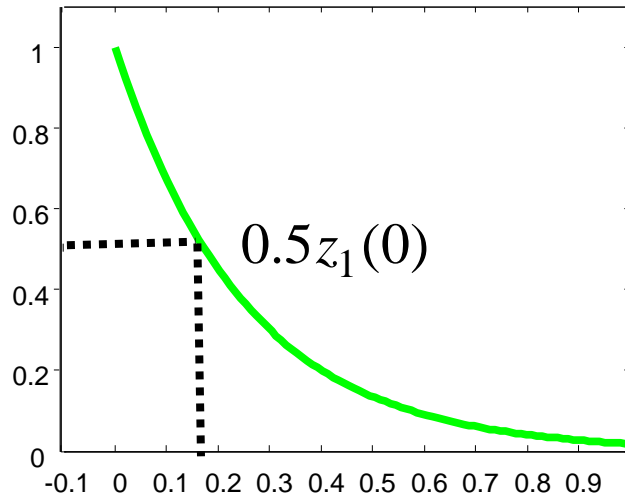
# DCM parameters = rate constants

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



$= \frac{dz_1}{dt} = -sz_1 \quad \longrightarrow \quad z_1(t) = z_1(0) \exp(-st)$

*Decay function*



$$\tau = \ln 2 / s$$

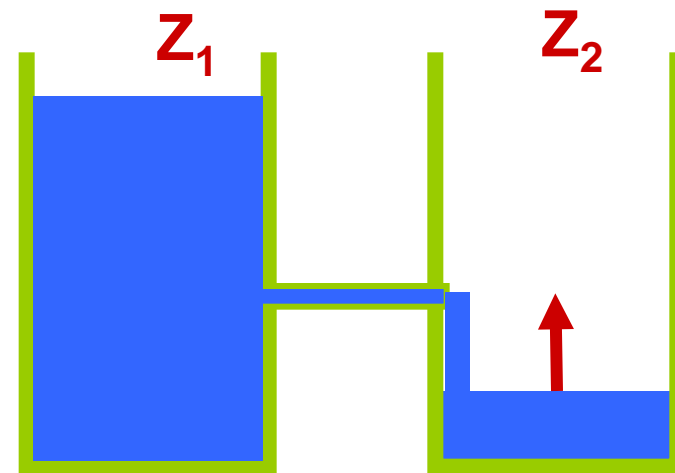
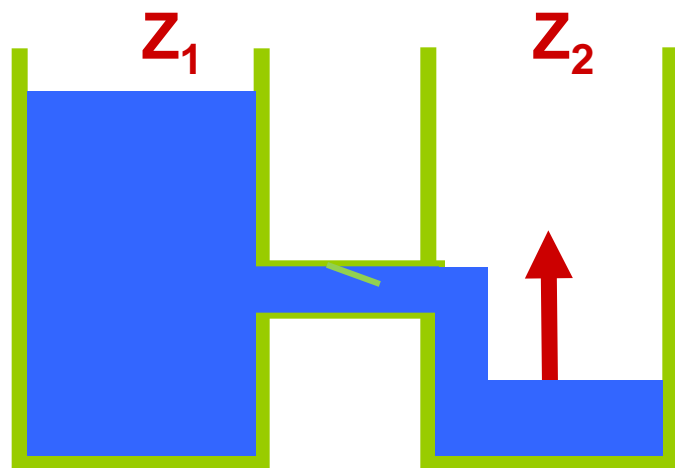
If  $z_1 \rightarrow z_1$  is  $-0.10 \text{ s}^{-1}$  this means that, per unit time, the decrease in activity in  $z_1$  corresponds to 10% of the current activity in  $z_1$

# Connectivity $Z_1 \rightarrow Z_2$

## Strong

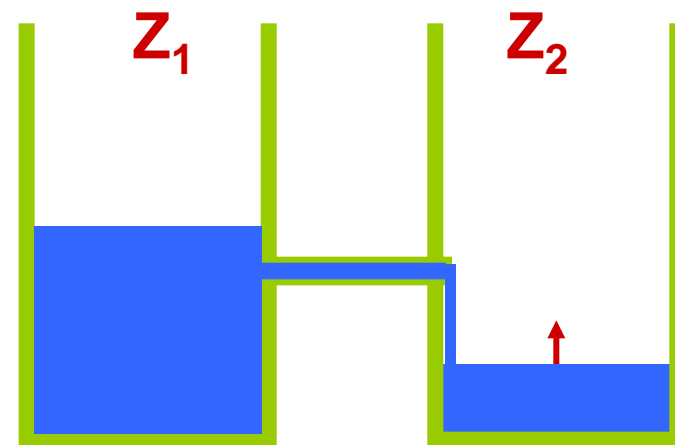
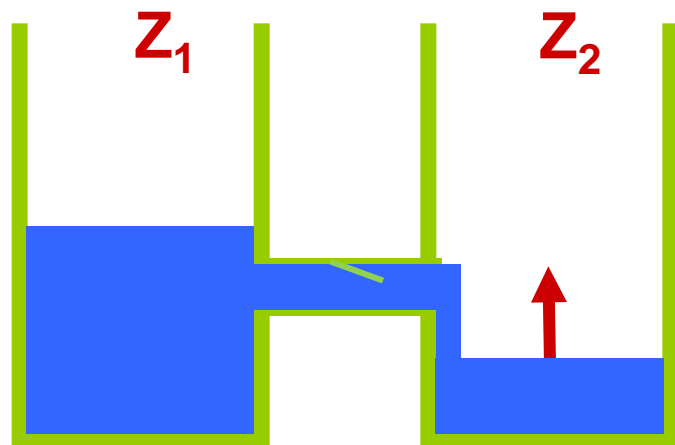
## Weak

### High

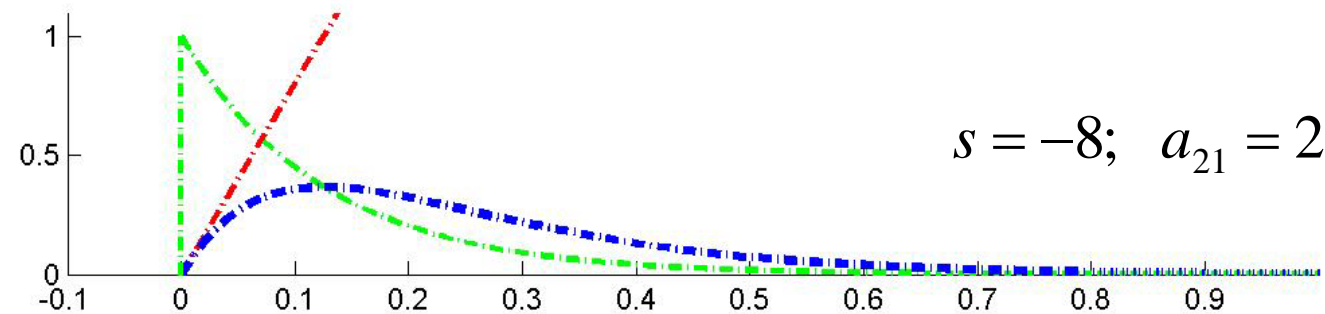
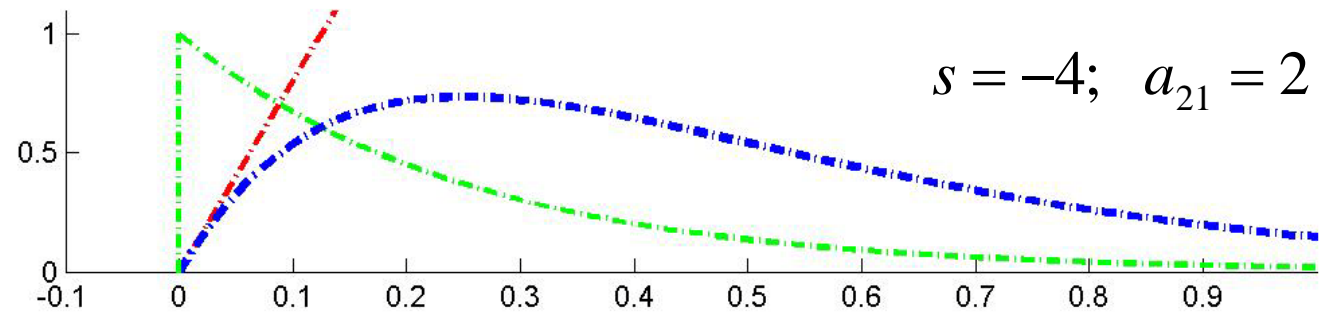
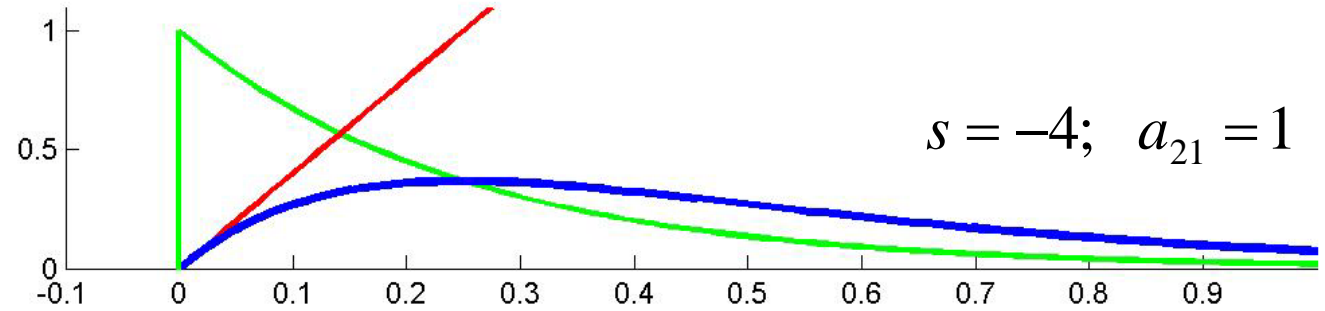
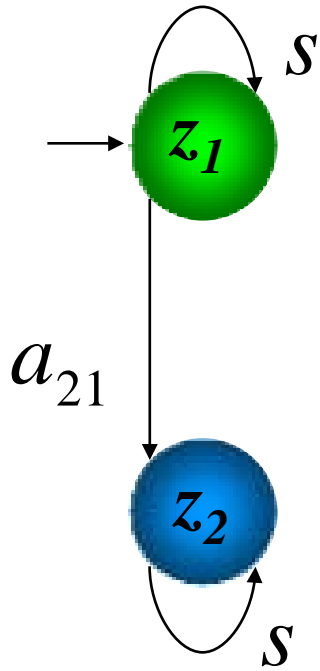


### Activity in $Z_1$

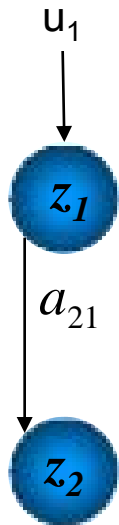
### Low



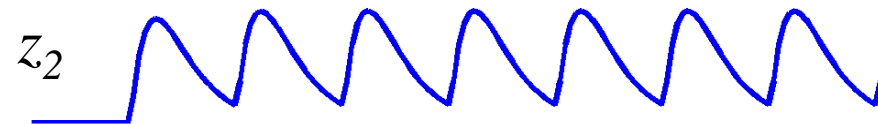
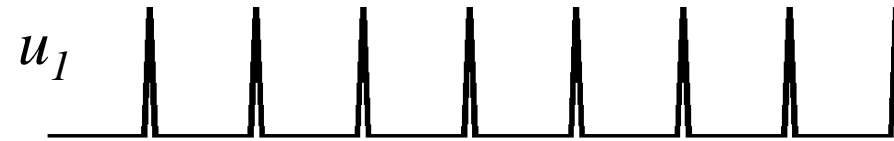
# Linear dynamics: 2 nodes



# Neurodynamics: 2 nodes with input



activity in  $z_2$  is coupled to  $z_1$  via coefficient  $a_{21}$

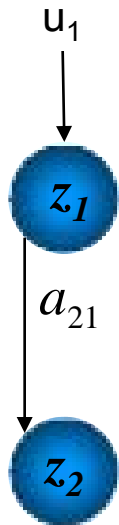


$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$

$$\dot{z}_2 = a_{21}z_1 + a_{22}z_2$$

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

# Neurodynamics: 2 nodes with input



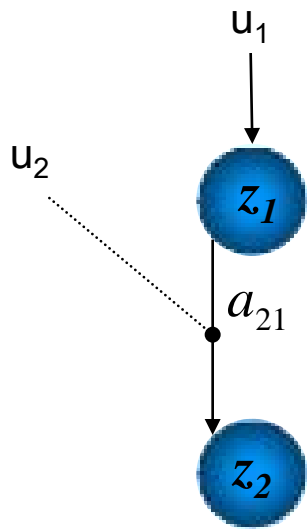
activity in  $z_2$  is coupled to  $z_1$  via coefficient  $a_{21}$

$$\dot{z} = Az + Cu$$
$$\theta = \{A, C\}$$

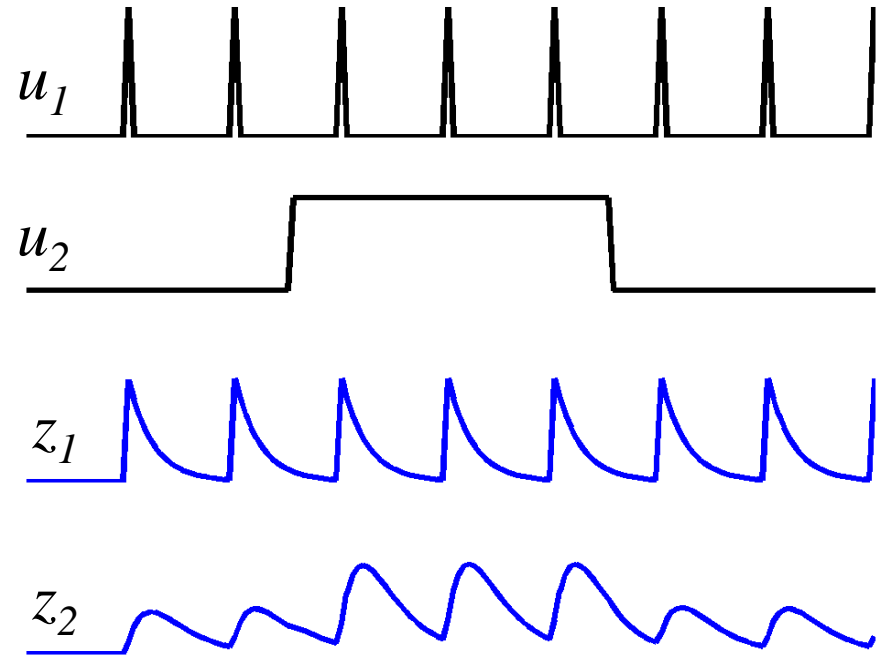
$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$
$$\dot{z}_2 = a_{21}z_1 + a_{22}z_2$$

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

# Neurodynamics: positive modulation



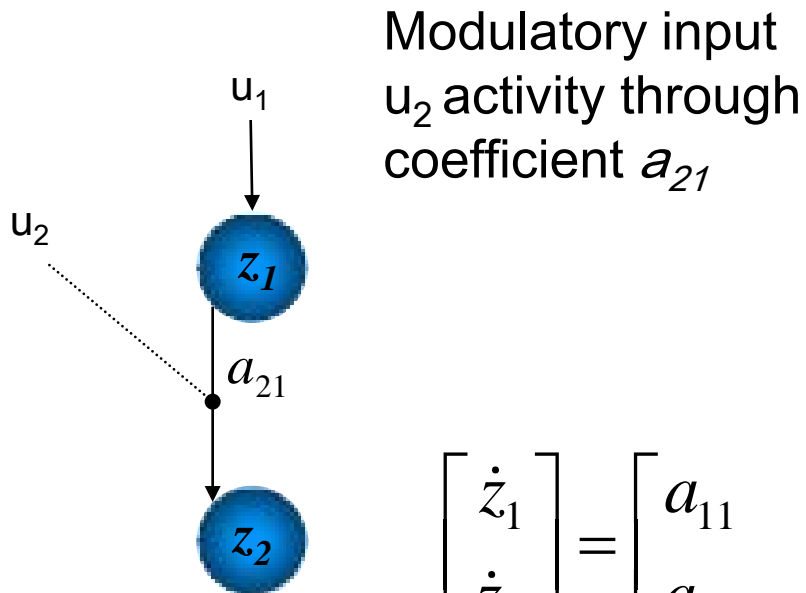
Modulatory input  
 $u_2$  activity through  
coefficient  $a_{21}$



$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$

$$\dot{z}_2 = (a_{21} + b_{21}^2 u_2)z_1 + a_{22}z_2$$

# Neurodynamics: positive modulation



$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$

$$\dot{z}_2 = (a_{21} + b_{21}^2 u_2)z_1 + a_{22}z_2$$

# Bilinear neural state equation in DCM for fMRI

$$\dot{\mathbf{z}} = \left( \mathbf{A} + \sum_{j=1}^m u_j \mathbf{B}^{(j)} \right) \mathbf{z} + \mathbf{C} \mathbf{u}$$

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

state  
changes

connectivity

modulation of  
connectivity

state  
vector

direct  
inputs

external  
inputs

$$\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} + \sum_{j=1}^m u_j \begin{bmatrix} b_{11}^j & \cdots & b_{1n}^j \\ \vdots & \ddots & \vdots \\ b_{n1}^j & \cdots & b_{nn}^j \end{bmatrix} \right\} \begin{bmatrix} z_1 \\ \vdots \\ z_n \end{bmatrix} + \begin{bmatrix} c_{11} & \cdots & c_{1m} \\ \vdots & \ddots & \vdots \\ c_{n1} & \cdots & c_{nm} \end{bmatrix} \begin{bmatrix} u_1 \\ \vdots \\ u_m \end{bmatrix}$$

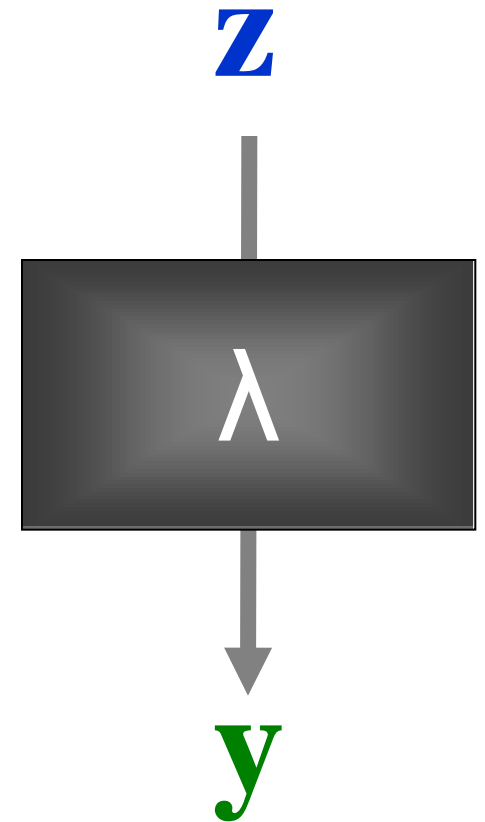
$n$  regions

$m$  mod inputs

$m$  direct inputs

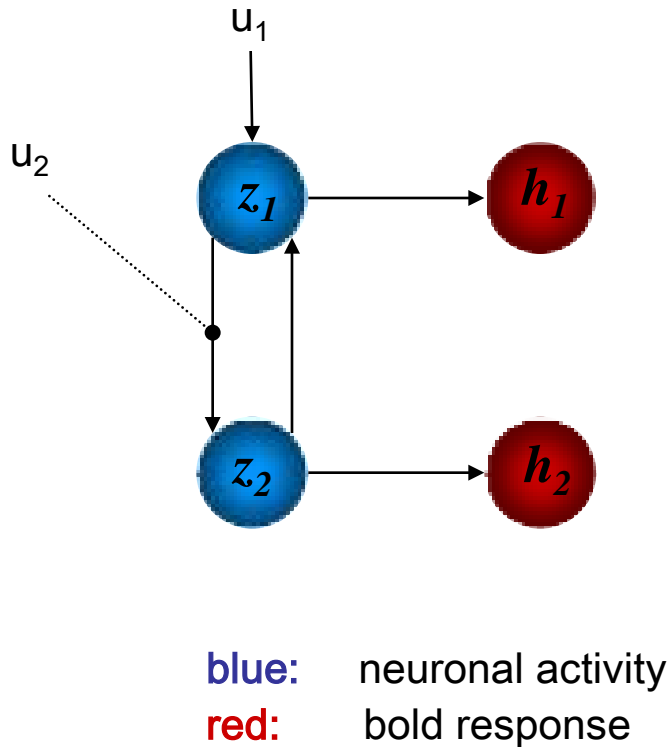
# Basics of DCM: Neuronal and BOLD level

- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).
- The modelled neuronal dynamics ( $\mathbf{z}$ ) are transformed into area-specific BOLD signals ( $\mathbf{y}$ ) by a hemodynamic model ( $\lambda$ ).



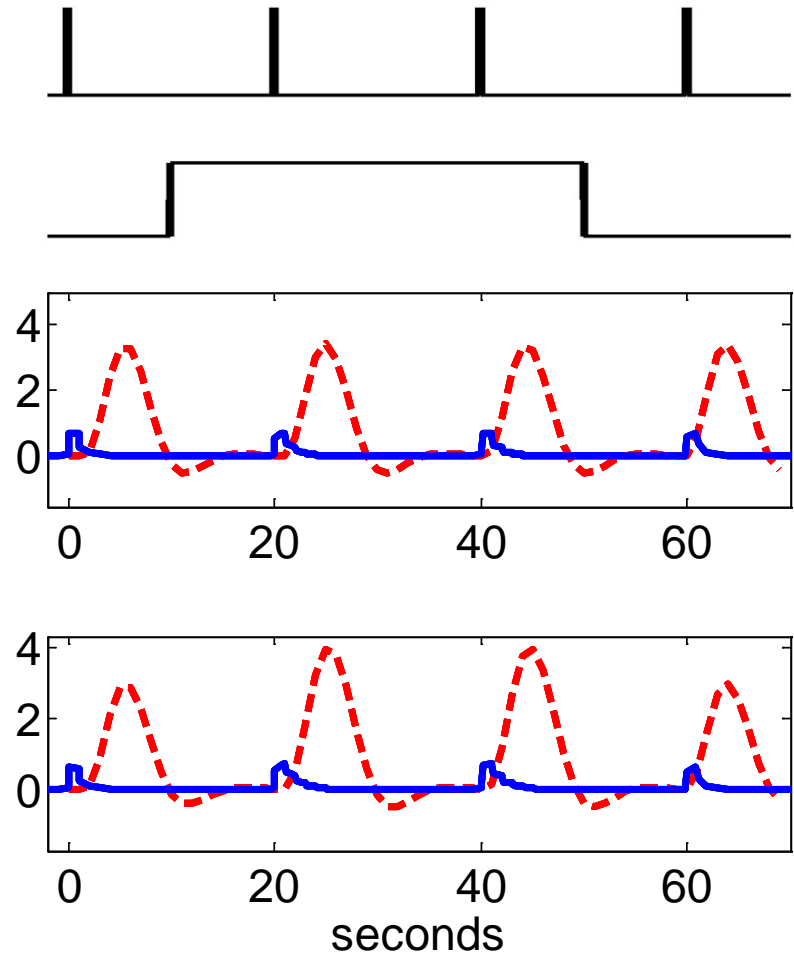
# Haemodynamics: reciprocal connections

$h(u, \theta)$  represents the modelled BOLD response (balloon model) to inputs in this network



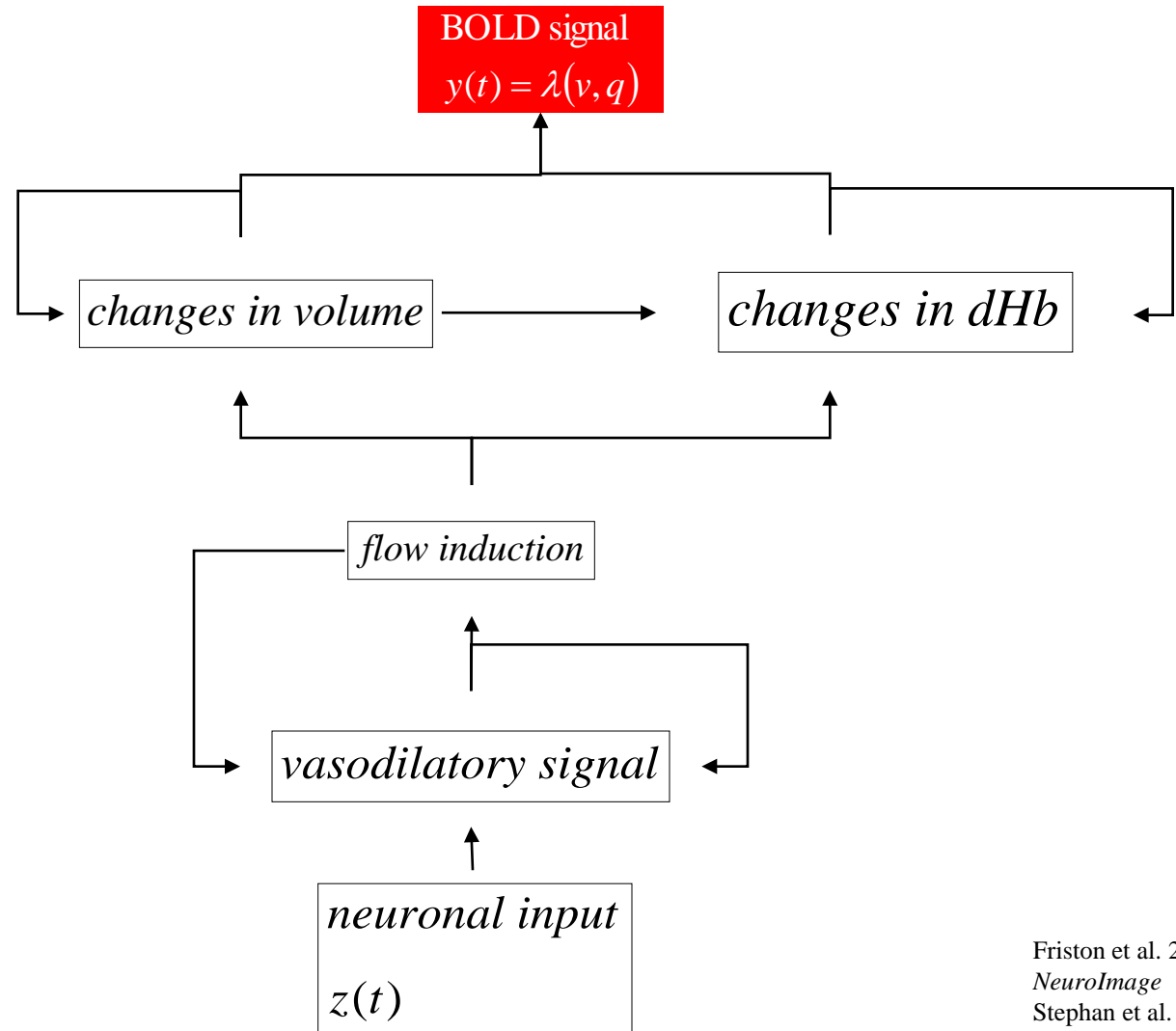
BOLD  
(without noise)

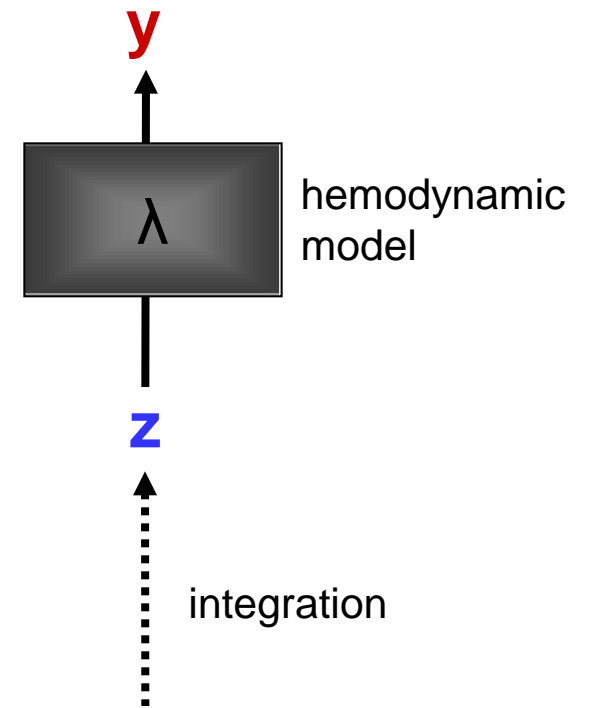
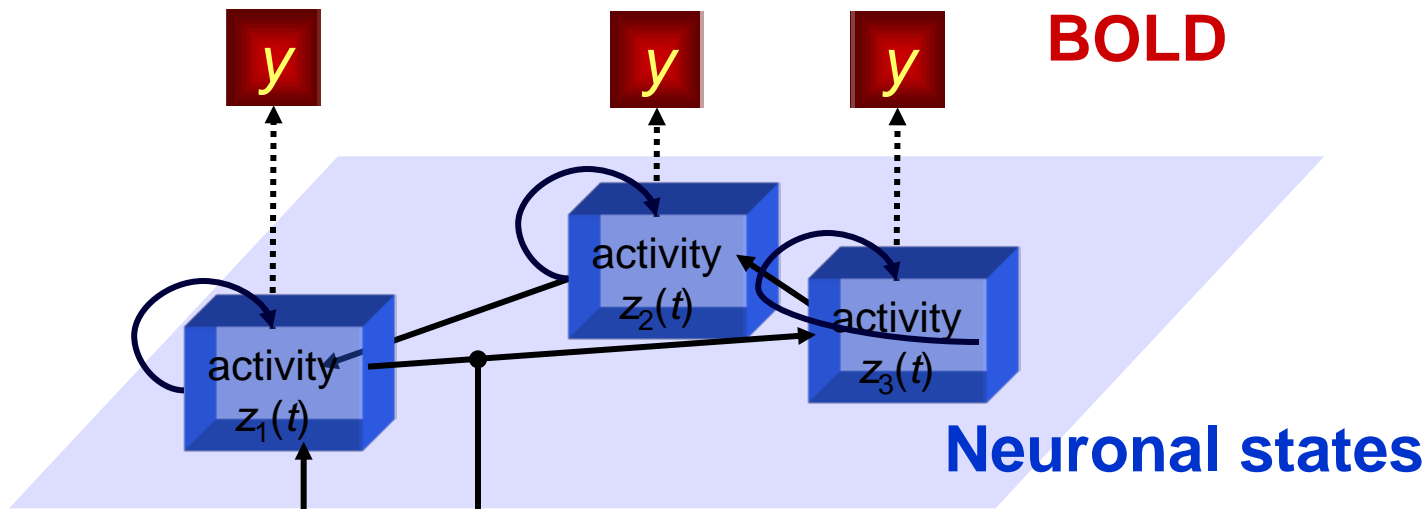
BOLD  
(without noise)



# The hemodynamic “Balloon” model

- 3 hemodynamic parameters
- Important for model fitting, but of no interest
- Computed separately for each area → region-specific HRFs!





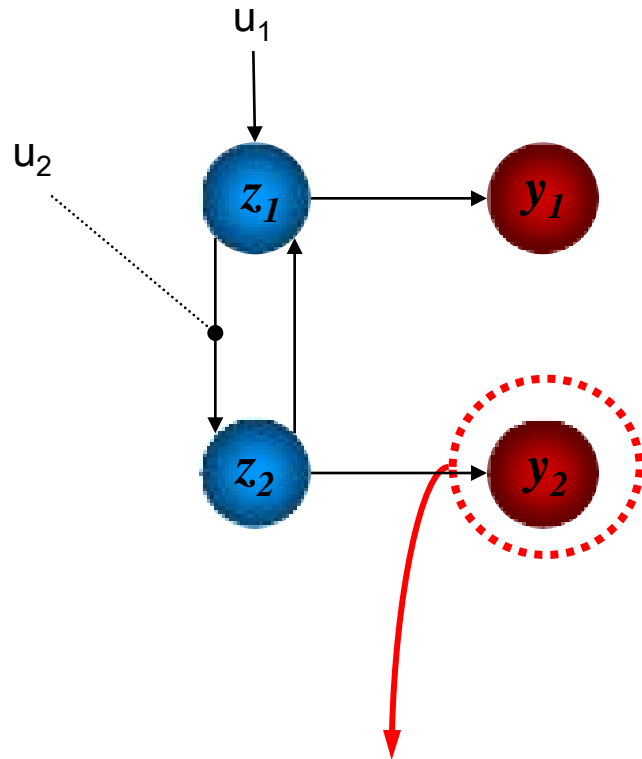
**Neural state equation**  $\dot{z} = (A + \sum u_j B^{(j)})z + Cu$

**endogenous connectivity**  $\longrightarrow A = \frac{\partial \dot{z}}{\partial z}$

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

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

# Measured vs Modelled BOLD signal



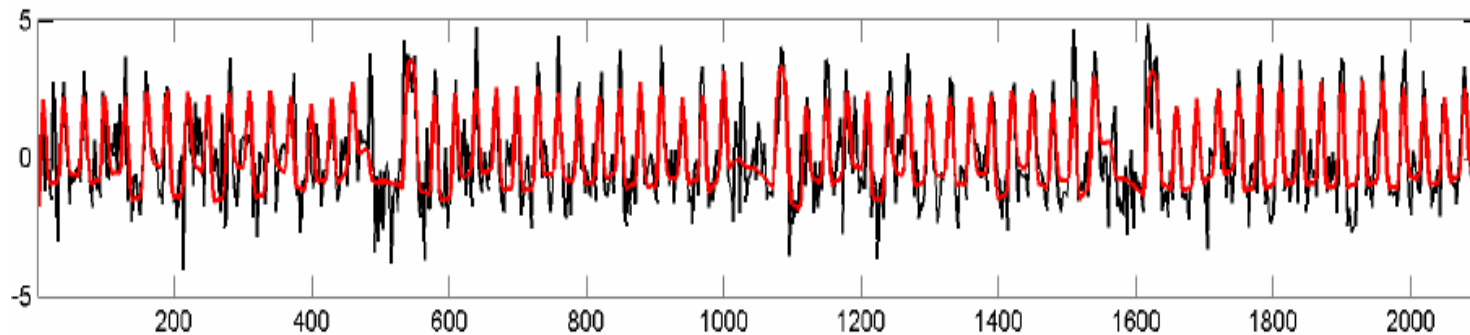
## Recap

The aim of DCM is to estimate

- neural parameters  $\{A, B, C\}$

- hemodynamic parameters

such that the **modelled** and **measured** BOLD signals are maximally similar.



# Bayesian statistics

Express our **prior knowledge** or “belief” about parameters of the model

new data

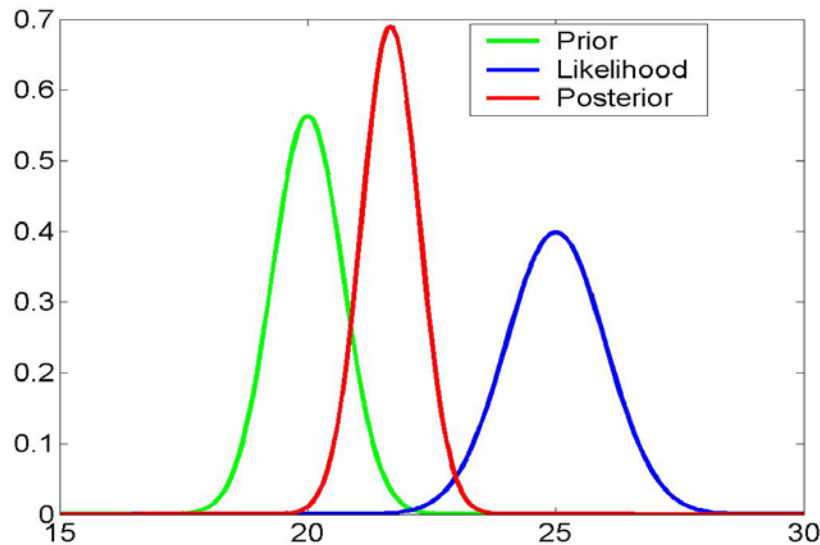
prior knowledge

$$p(y | \theta)$$

$$p(\theta)$$

$$p(\theta | y) \propto p(y | \theta) p(\theta)$$

posterior  $\propto$  likelihood • prior



## Parameters governing

- Hemodynamics in a single region
- Neuronal interactions

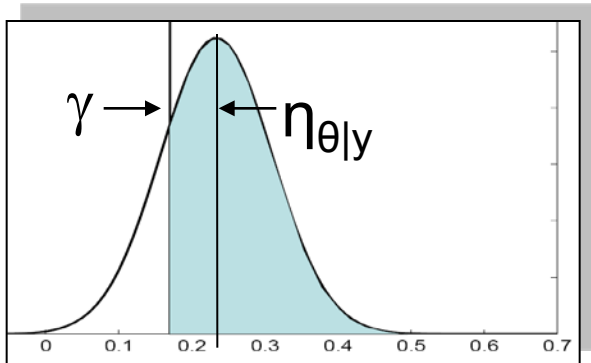
## Constraints (priors) on

- Hemodynamic parameters
  - empirical
- Self connections
  - principled
- Other connections
  - shrinkage

# Inference about DCM parameters:

## Bayesian single subject analysis

- The model parameters are distributions that have a mean  $\eta_{\theta|y}$  and covariance  $C_{\theta|y}$ 
  - Use of the cumulative normal distribution to test the probability that a certain parameter is above a chosen threshold  $\gamma$ :



## Classical frequentist test across Ss

- Test summary statistic: mean  $\eta_{\theta|y}$ 
  - One-sample t-test: Parameter  $> 0$ ?
  - Paired t-test: parameter 1  $>$  parameter 2?

## Bayesian model averaging

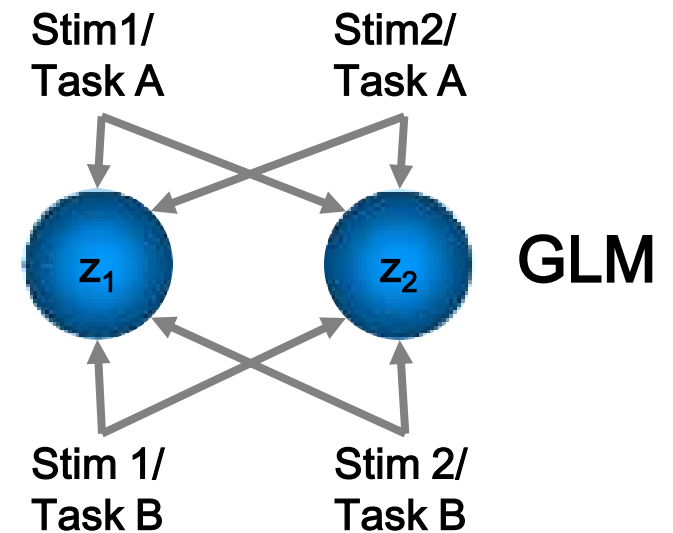
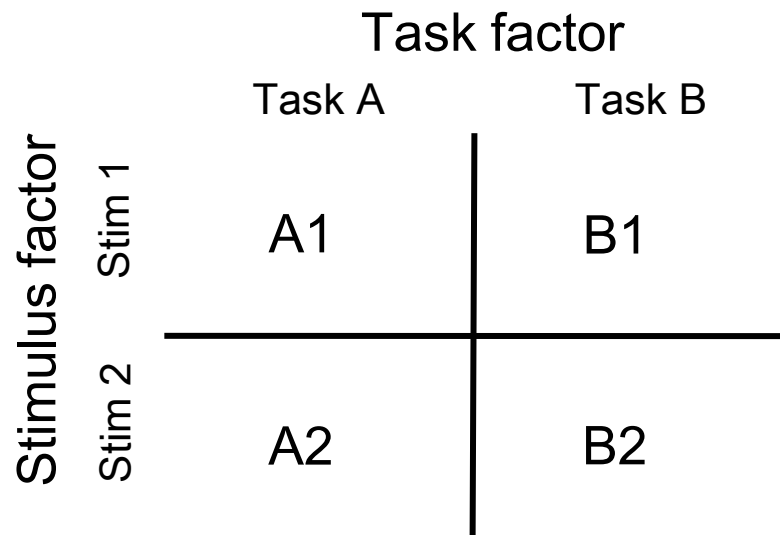
# Overview

- Brain connectivity: types & definitions
- Dynamic causal models (DCMs)
- Practical examples
  - Design of experiments and models
  - Simulated data
  - Connectivity in synesthesia

# Planning a DCM-compatible study

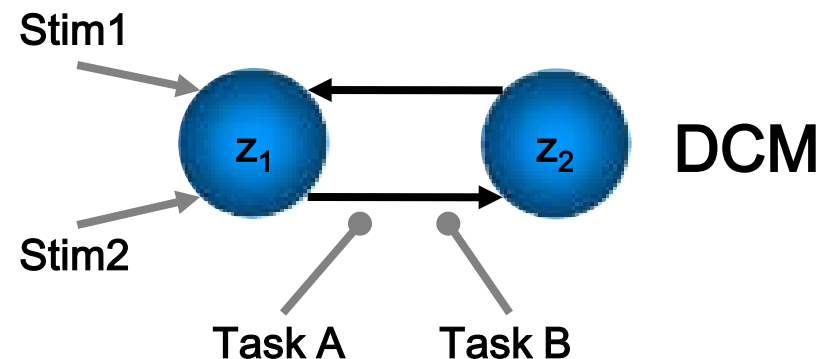
- Suitable experimental design:
  - any design that is suitable for a GLM
  - preferably multi-factorial (e.g. 2 x 2)
    - e.g. one factor that varies the driving (sensory) input
    - and one factor that varies the contextual input
- Hypothesis and model:
  - Define specific *a priori* hypothesis
  - Which parameters are relevant to test this hypothesis?
  - If you want to verify that intended model is suitable to test this hypothesis, then use simulations
  - Define criteria for inference
  - What are the alternative models to test?

# Multifactorial design: explaining interactions with DCM

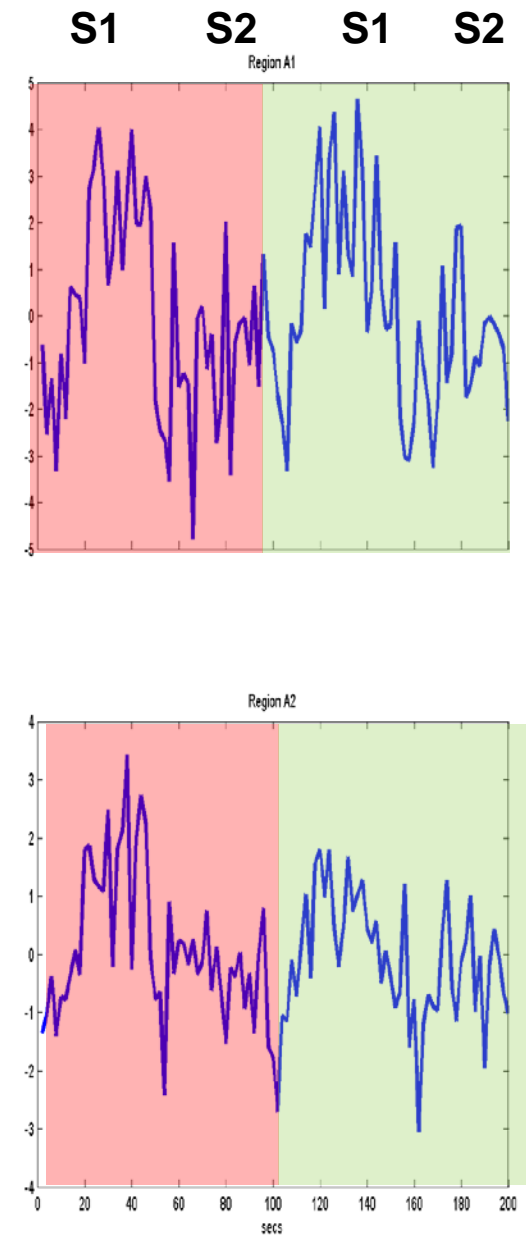
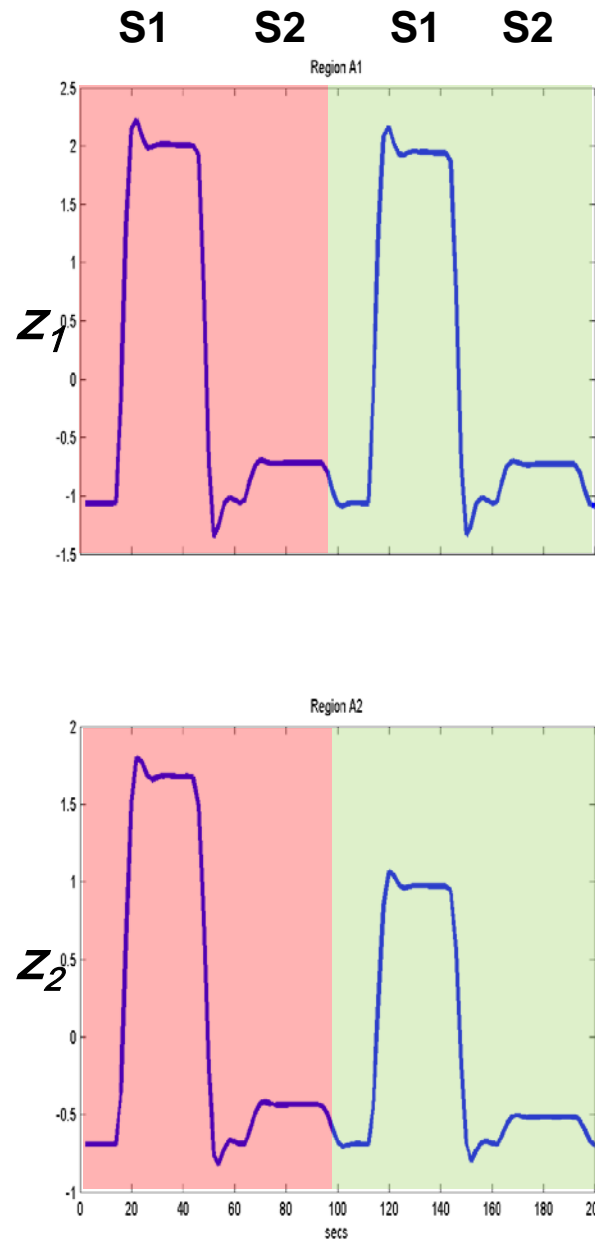
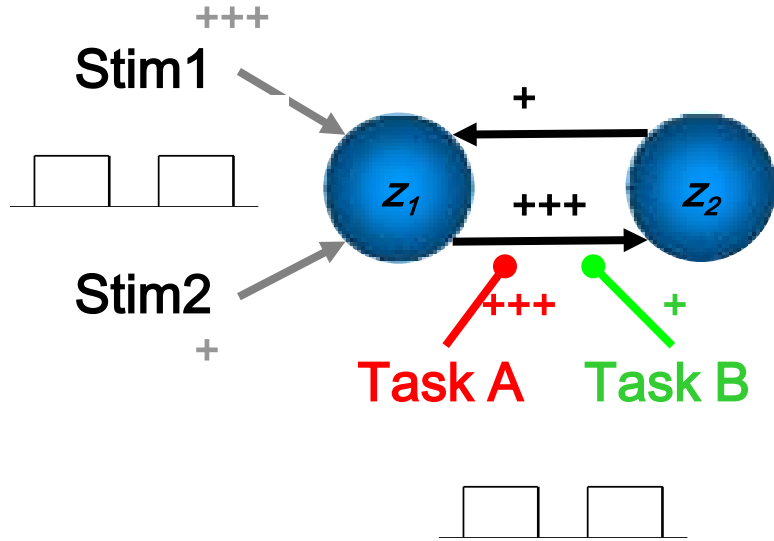


Let's assume that an SPM analysis shows a main effect of stimulus in  $z_1$  and a stimulus  $\times$  task interaction in  $z_2$ .

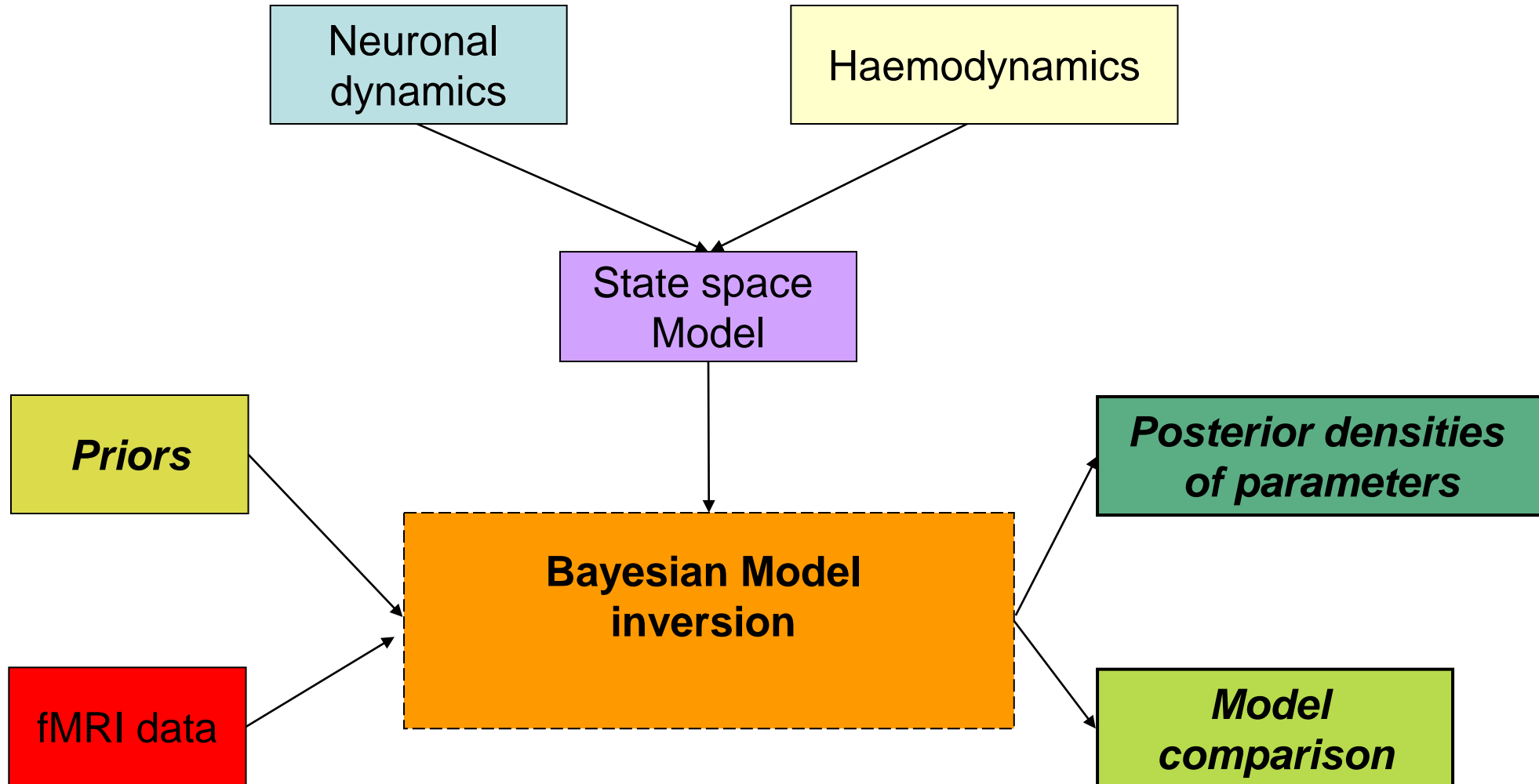
How do we model this using DCM?



# Simulated data



# DCM roadmap



# In short, DCM....

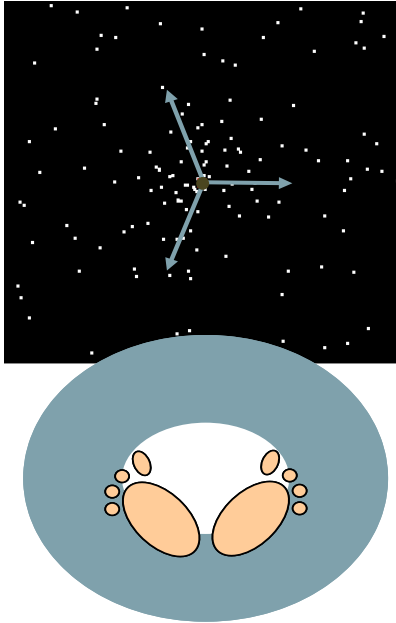
- enables us to **infer effective neuronal connectivity** from fMRI data
- models the same phenomena as a GLM
  - **explaining experimentally induced variance** in local responses based on (modulation of) connectivity
  - So if you have no ‘blobs’, it’s not meaningful\*
- allows you to **test mechanistic hypotheses about observed effects**
- is a generic approach to modeling experimentally perturbed dynamic systems.
  - can also be used for M/EEG or LFP recordings
  - just with a different forward model (=‘translation’ of neuronal activity to measured signal)

**So much for theory,  
time for the real thing!**



# DCM practical

## Paradigm



**Stimuli** 250 radially moving dots at 4.7 degrees/s

**Pre-Scanning: speed changes**

5 x 30s trials with 5 speed changes (reducing to 1%)

Task - detect change in radial velocity

**Scanning: no speed changes**

4 conditions

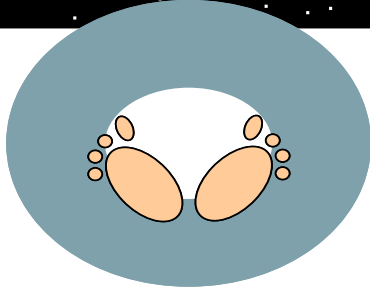
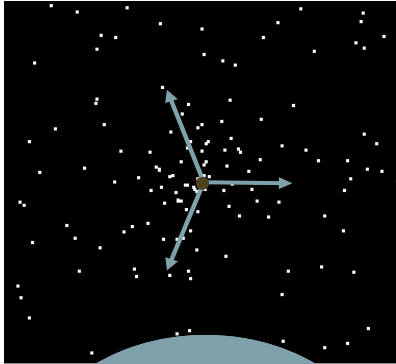
- |                       |             |
|-----------------------|-------------|
| - fixation only       | baseline    |
| - observe static dots | + photic    |
| - observe moving dots | + motion    |
| - task on moving dots | + attention |

## Parameters

- blocks of 10 scans
- 360 scans total
- TR = 3.22 seconds

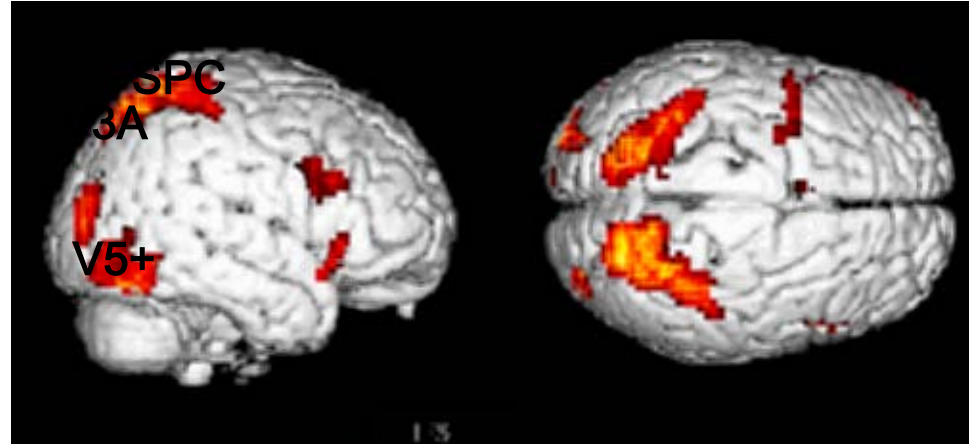
# DCM practical

## Paradigm



- fixation only
- observe static dots + photic
- observe moving dots + motion
- task on moving dots + attention

## Results



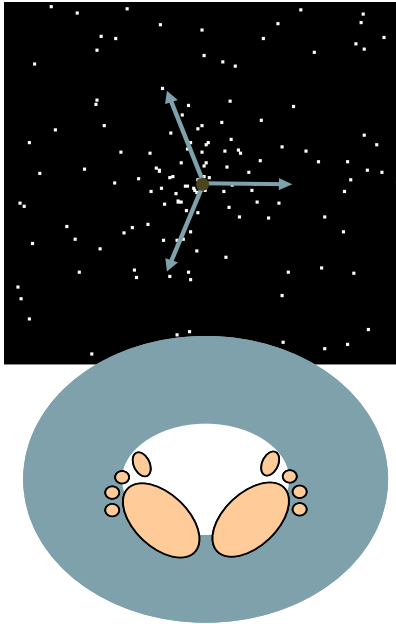
### Attention – No attention

Büchel & Friston 1997, Cereb. Cortex  
Büchel et al. 1998, Brain

- V1
- V5
- V5 + parietal cortex

# DCM practical

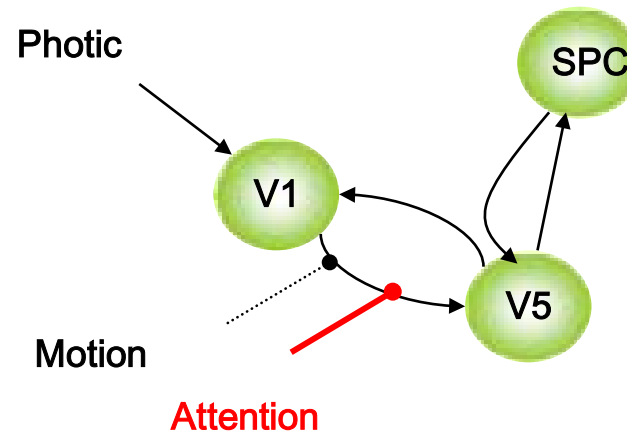
## Paradigm



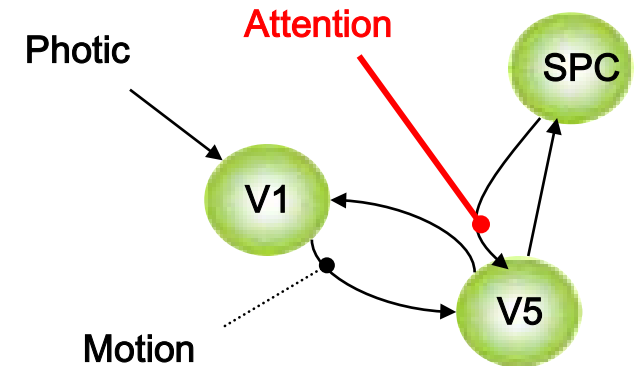
- fixation only
- observe static dots
- observe moving dots
- task on moving dots

## Dynamic Causal Models

Model 1 (forward):  
attentional modulation  
of V1→V5: forward



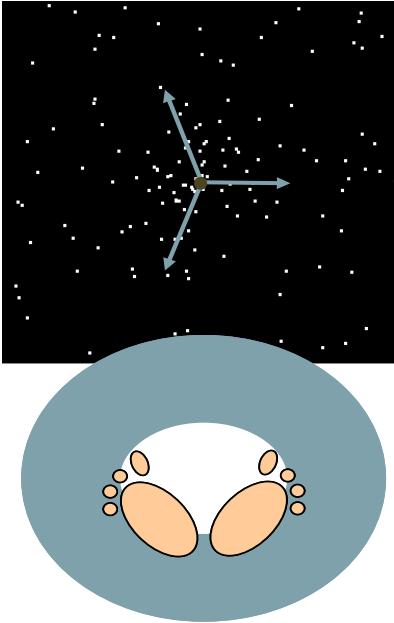
Model 2 (backward):  
attentional modulation  
of SPC→V5: backward



Bayesian model selection: Which model is optimal?

# DCM practical

## Paradigm



- fixation only
- observe static dots
- observe moving dots
- task on moving dots

## Ingredients for a DCM

Specific hypothesis/question

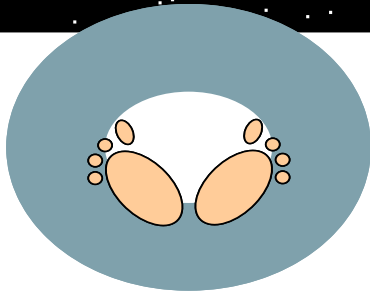
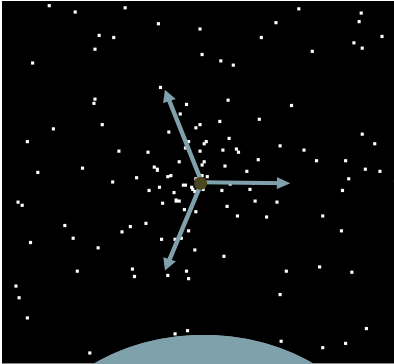
Model: based on hypothesis

Timeseries: from the SPM

Inputs: from design matrix

# DCM practical

## Paradigm



- fixation only
- observe static dots
- observe moving dots
- task on moving dots

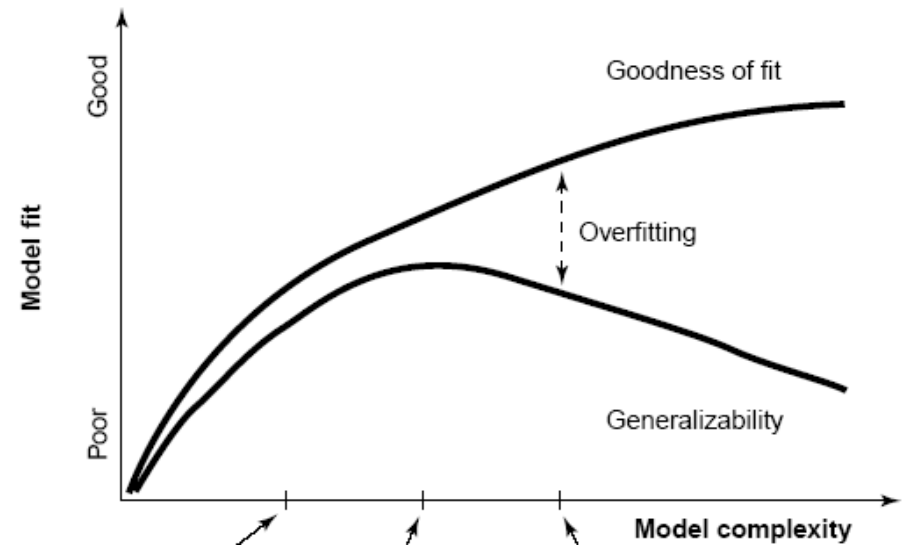
## DCM – GUI basic steps

- 1** Extract the time series (from all regions of interest)
- 2** Specify the model
- 3** Estimate the model
- 4** Review the estimated model
- 5** Repeat steps 2 and 3 for all models in model space
- 6** Compare models

# Model comparison

# Model comparison

Model evidence: The optimal balance of fit and complexity

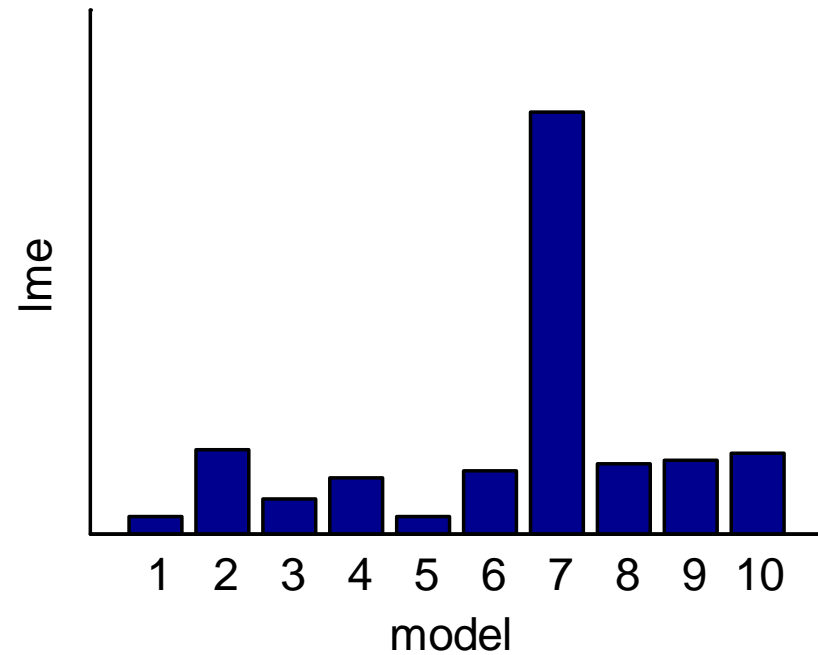
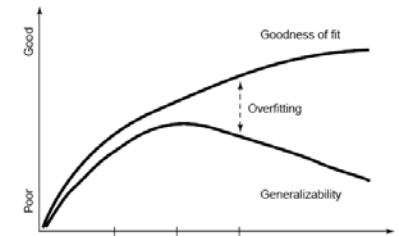


# Model comparison

Model evidence: The optimal balance of fit and complexity

Comparing models

- Which is the best model?



# Model comparison

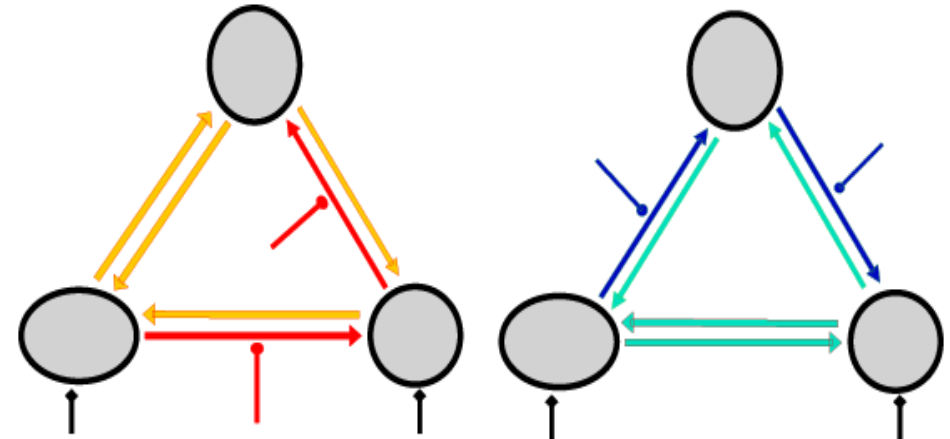
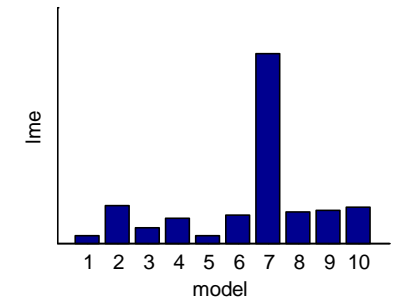
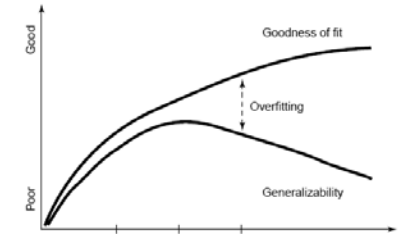
Model evidence: The optimal balance of fit and complexity

Comparing models

- Which is the best model?

Comparing families of models

- What type of model is best?
  - Feedforward vs feedback
  - Parallel vs sequential processing
  - With or without modulation



# Model comparison

Model evidence: The optimal balance of fit and complexity

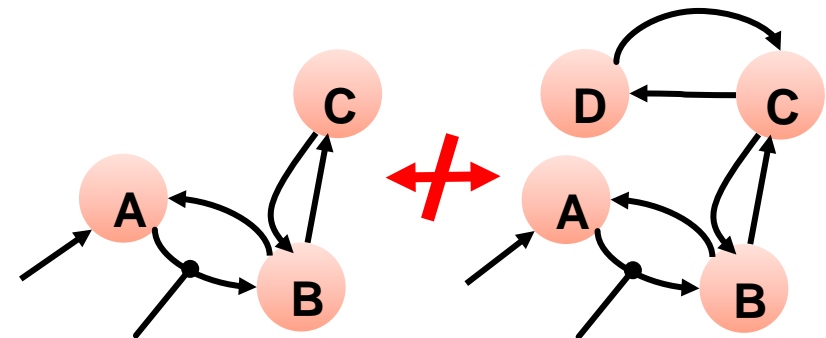
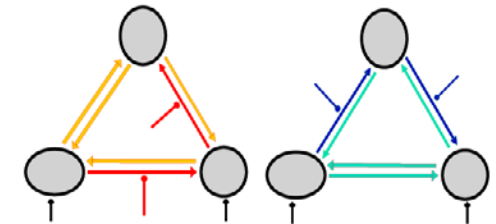
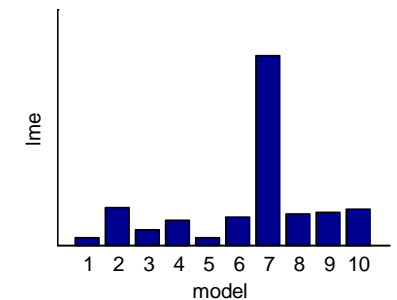
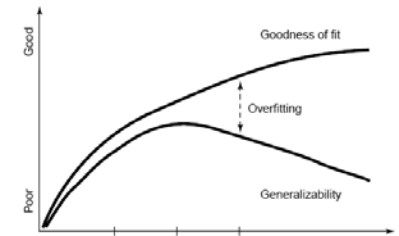
## Comparing models

- Which is the best model?

## Comparing families of models

- What type of model is best?
  - Feedforward vs feedback
  - Parallel vs sequential processing
  - With or without modulation

Only compare models with the same data



**Bottom-up or top-down:  
Connectivity reflects individual differences in  
grapheme-color synesthesia**

**Tessa M. van Leeuwen**

**Hanneke E. M. den Ouden, Peter Hagoort**

**Journal of Neuroscience, 2011**

# Synesthesia

- Specific sensory stimuli lead to unusual, additional experiences.
- Grapheme-color synesthesia: written letters → color
- Involuntary, automatic; stable over time, prevalence ~4%

Sensory experiences of synesthetes differ across individuals:

## Projectors

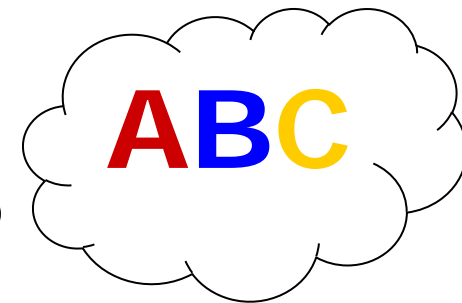
- External colocalised with letters

ABC

## Associators

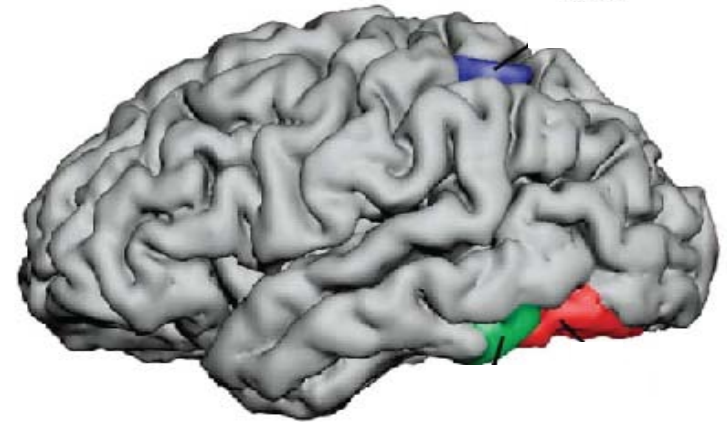
- internal association

ABC



# Brain areas involved

- ventral-occipital color area V4
- superior parietal lobule (SPL)  
(same in projectors & associators)



Hubbard, 2007

- Potential cause: aberrant **cross-activation** between brain areas

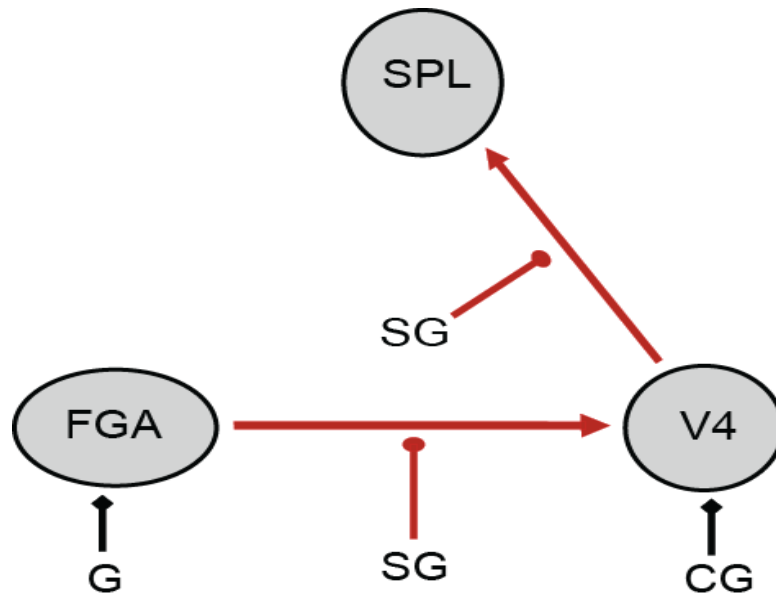
→ Can changes in *coupling* (effective connectivity) during synesthesia explain activity in V4?

# DCMs

## Bottom-up

Does cross-activation result from bottom-up, direct influences from grapheme areas on color area V4 within the fusiform gyrus?

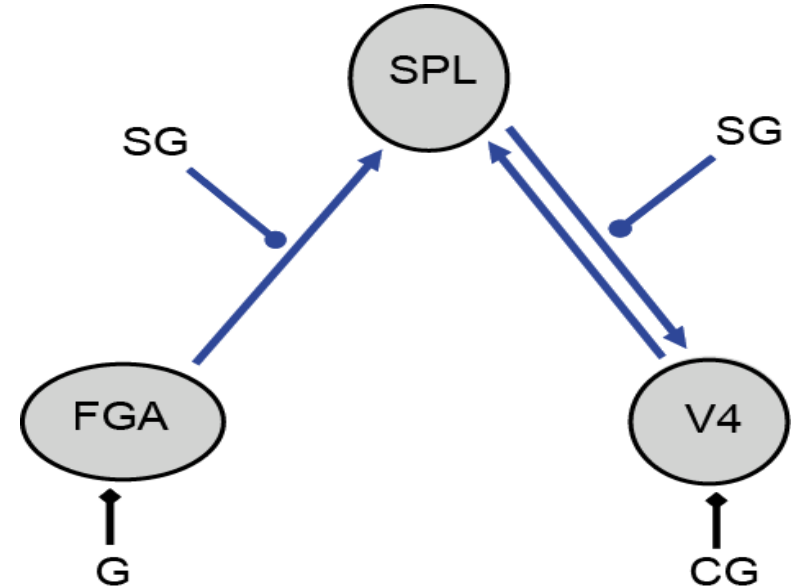
*(Ramachandran & Hubbard, 2001)*



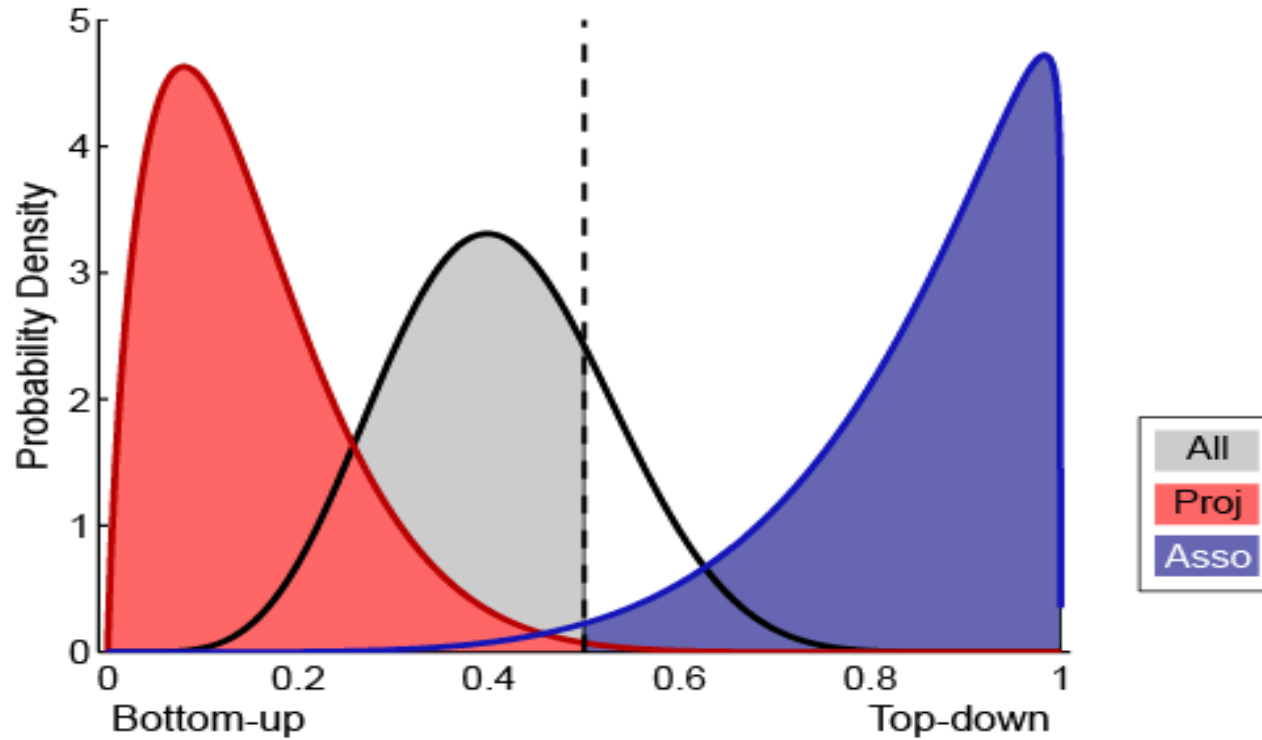
## Top-down

Or is cross-activation mediated top-down through higher-order multi-modal areas like the SPL?

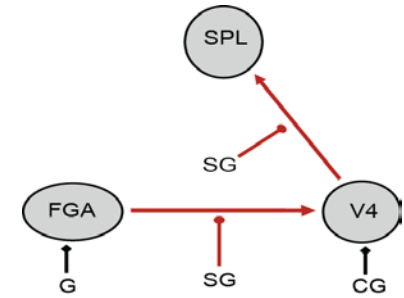
*(Grossenbacher & Lovelace, 2001)*



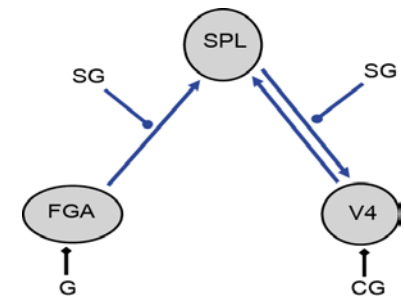
# DCM Results



Bottom-up



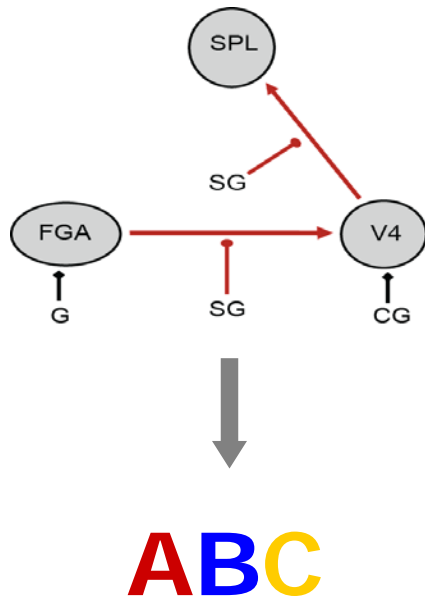
Top-down



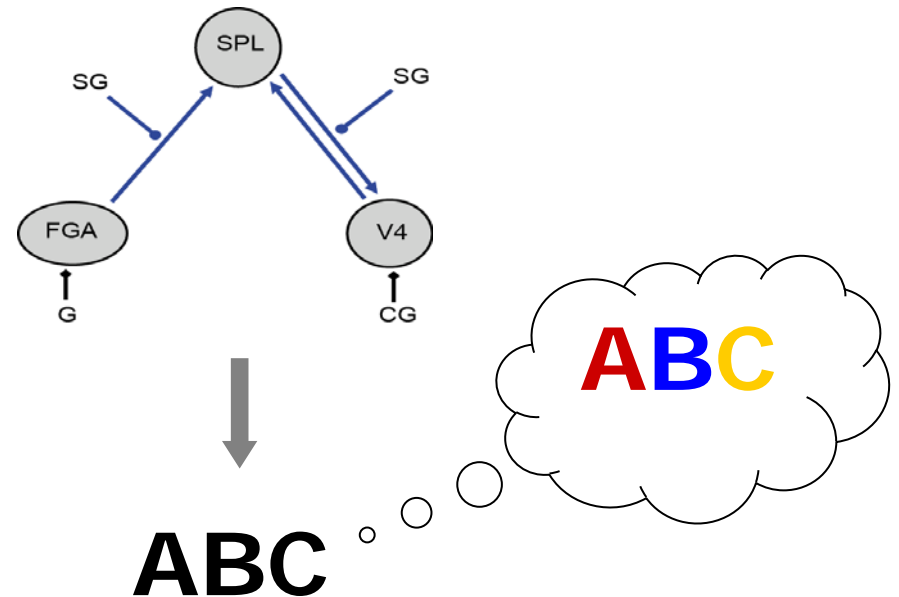
- **Projectors:** bottom-up > top-down (XP=0.996)
- **Associators:** top-down > bottom-up (XP=0.981)

# Conclusions

## Projectors



## Associators



- Direction of coupling determines subjective experiences
  - Bottom-up coupling: 'out there'
  - Top-down coupling: 'in the mind's eye'

→ **Conscious experiences can be determined by functional coupling**

extra slides

# Bayesian model selection (BMS)

Model evidence:

$$p(y | m) = \int p(y | \theta, m) p(\theta | m) d\theta$$

- ➔ accounts for both accuracy and complexity of the model
- ➔ allows for inference about structure (generalisability) of the model
- ➔ integral usually not analytically solvable

Log model evidence = balance between fit and complexity

$$\begin{aligned} \log p(y | m) &= \text{accuracy}(m) - \text{complexity}(m) \\ &= \log p(y | \theta, m) - \text{complexity}(m) \end{aligned}$$

Various approximations to the log model evidence

- AIC
  - BIC
  - *negative free energy F*
- Differ in the complexity term

# Bayes factors

To compare two models, we just need to compare their evidences.

But: the model evidence is just a number (depending on the units, amount of variance) – not very intuitive!

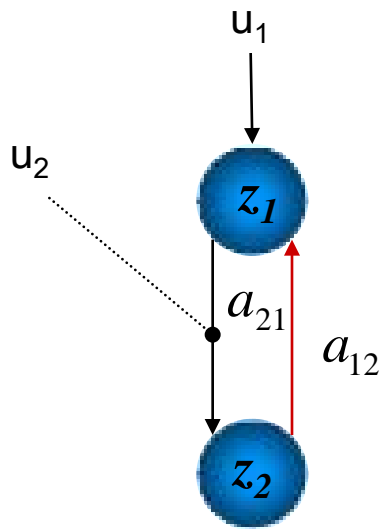
Bayes factor: look at the of the evidences:

$$B_{12} = \frac{p(y | m_1)}{p(y | m_2)}$$

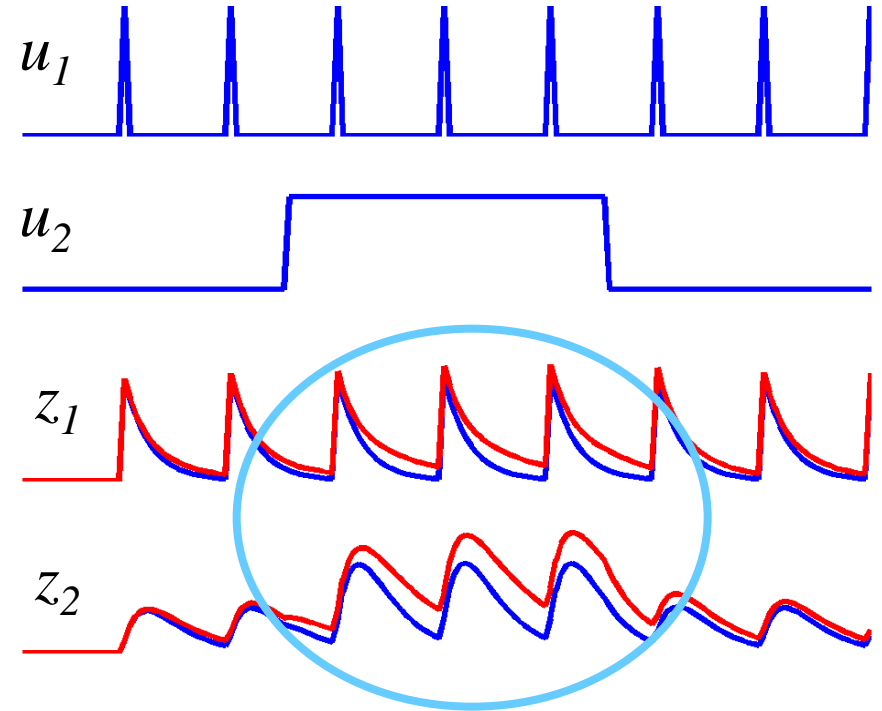
## *Raftery classification*

$B_{12}$	Evidence
1 to 3	weak
3 to 20	positive
20 to 150	strong
$\geq 150$	Very strong

# Neurodynamics: reciprocal connections



reciprocal  
connection  
disclosed by  $u_2$



$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s \begin{bmatrix} -1 & a_{12} \\ a_{21} & -1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 \\ b_{21}^2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1$$