Estimating Connectivity: DCM for FMRI - Theory

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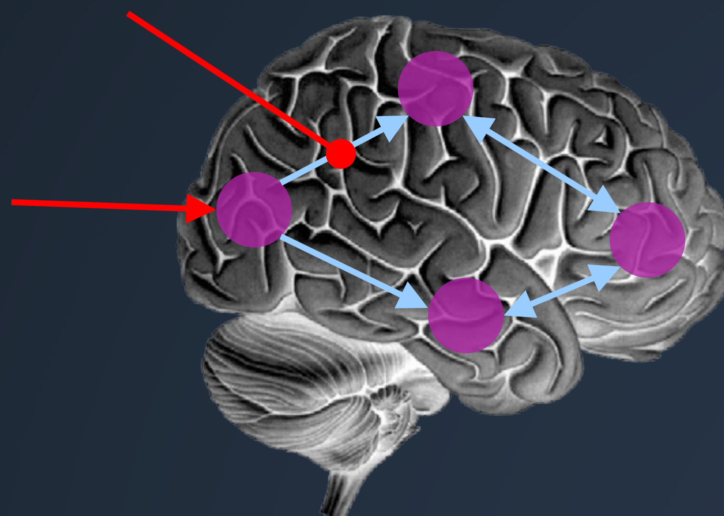

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Translational Neuromodeling Unit

Outline

1. Basics (Jakob)
2. Applications and Examples (Hanneke)
3. Demo (Hanneke & Jakob)

Please feel free to ask questions throughout!

Outline

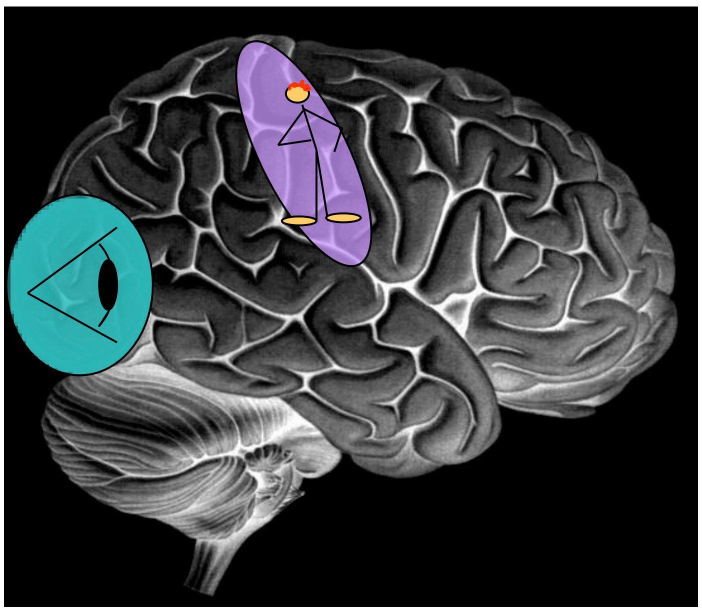
1. Basics (Jakob)
    - what is connectivity?
    - introducing DCM
    - under the hood

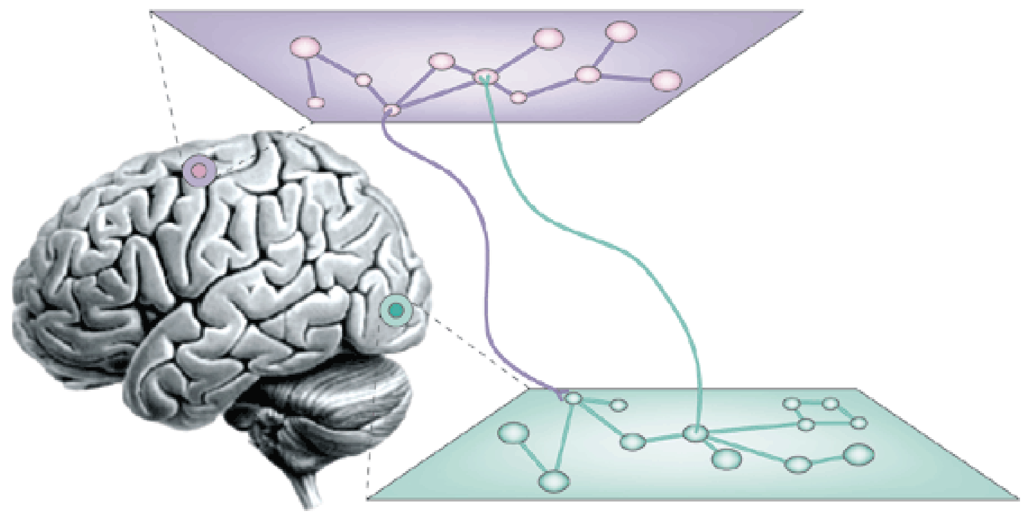
2. Applications and Examples (Hanneke)
3. Demo (Hanneke & Jakob)

Introduction

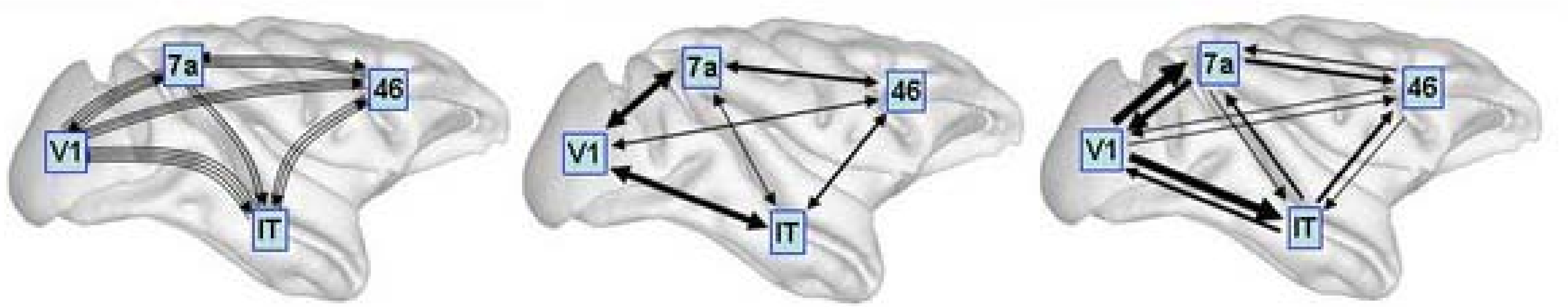
Functional Specialisation

Functional Integration





Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

anatomical/structural connectivity
- presence of physical connections
- DWI, tractography, tracer studies (monkeys)

Context-independent

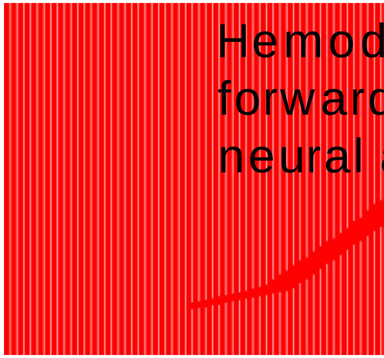
functional connectivity
- statistical dependency between regional time series
- correlations, ICA

Mechanism - free

effective connectivity
- causal (directed) influences between neuronal populations
- DCM

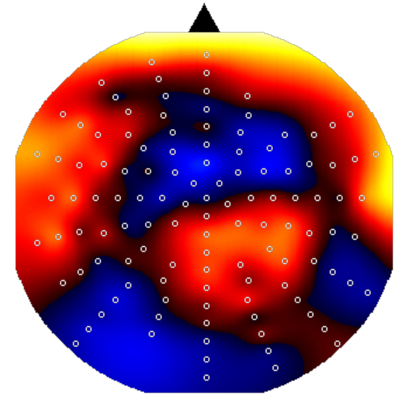
Mechanistic

Dynamic Causal Modelling (DCM)



Hemodynamic
forward model:
neural activity→BOLD

Electromagnetic
forward model:
neural activity→EEG
MEG
LFP



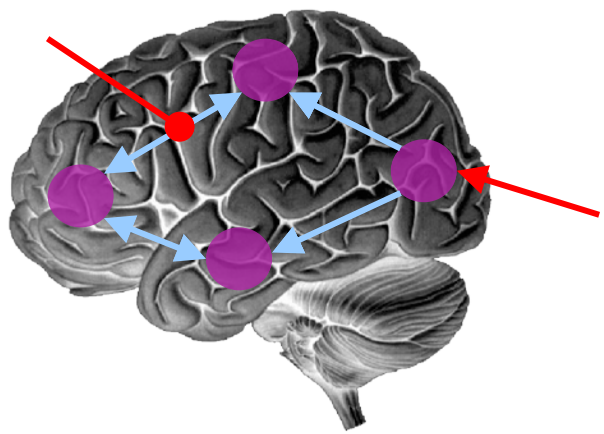
Neural model:

regional interactions →

neural activity:

fMRI

This talk

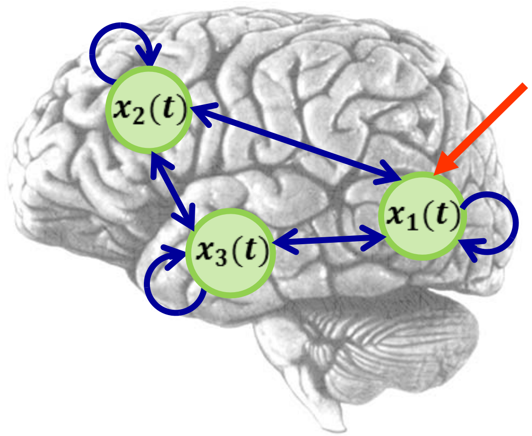


EEG/MEG

Dario Schöbi
→ next talk

DCM approach to effective connectivity

A simple model of a neural network …



$x_i(t)$ Neural node

Input

Connections

… described as a dynamical system …

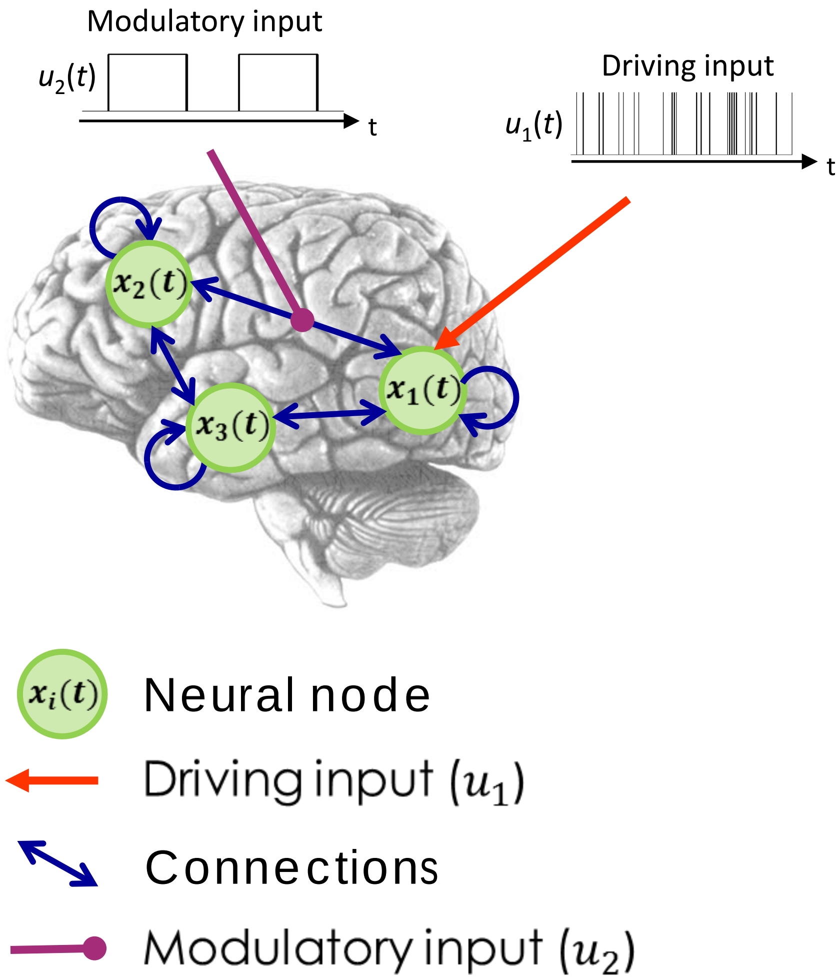
$$\dot{x} = f(x, u, \theta_x)$$

… causes the data (BOLD signal).

$$y = g\left(x, \theta_y\right) + \varepsilon$$

Let the system run with input (u) and parameters (θ_x, θ_y), and you will get a BOLD signal time course y that you can compare to the measured data.

The neural model for DCM for fMRI



Parameter sets…

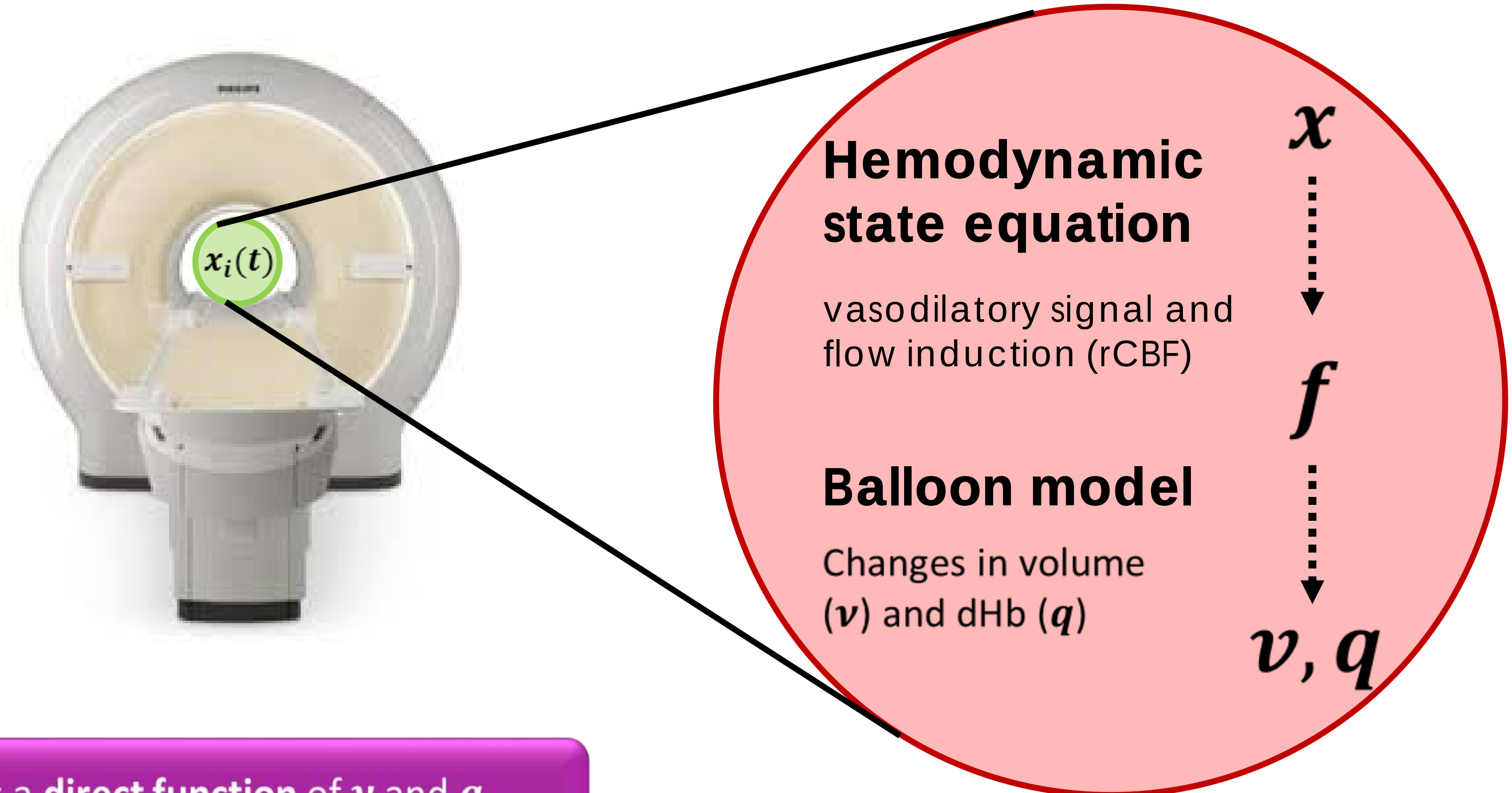
A - fixed connectivity

B - modulation of connectivity

C - weight of driving inputs

… determine dynamics!

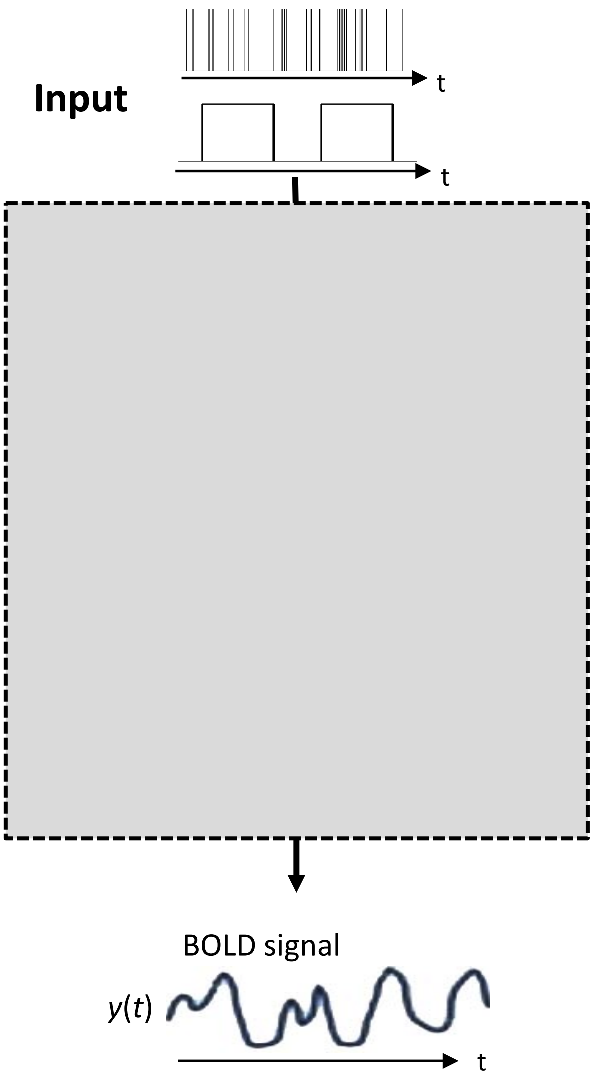
From neural activity to the BOLD signal



BOLD signal is a **direct function** of v and q

$$y = \frac{\Delta S}{S_0} = g(v, q) + \varepsilon$$

Summary – the full model



Summary – the full model

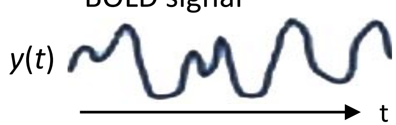
Inputs

Neuronal states
$x_i(t)$

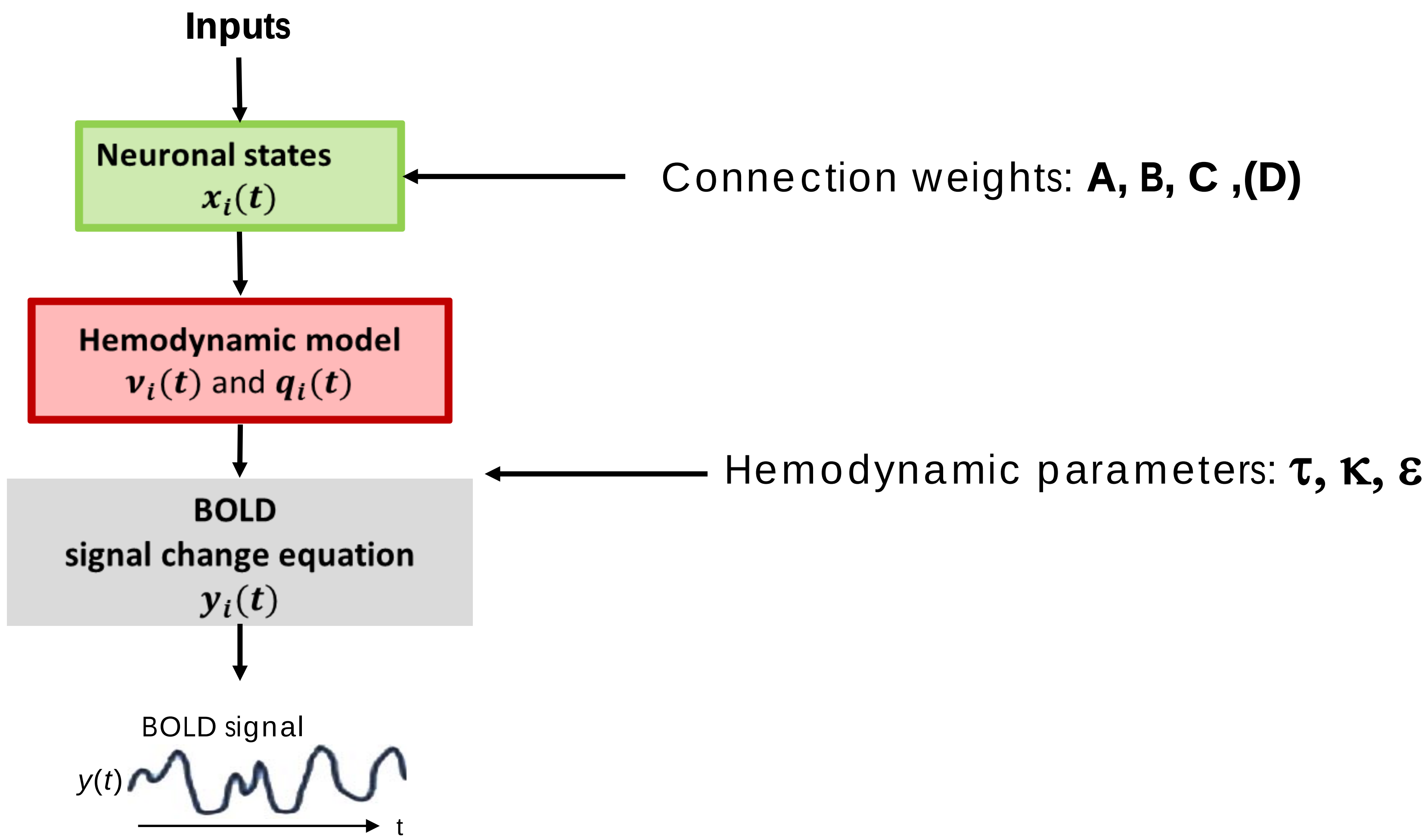
Hemodynamic model
$v_i(t)$ and $q_i(t)$

BOLD
signal change equation
$y_i(t)$

BOLD signal



Summary – parameters of interest

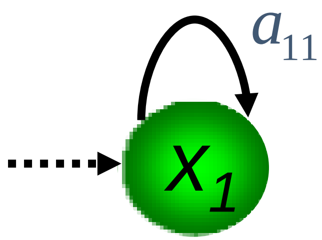


Under the hood 1:

The neural state equation

So what are these ‘neural parameters’?

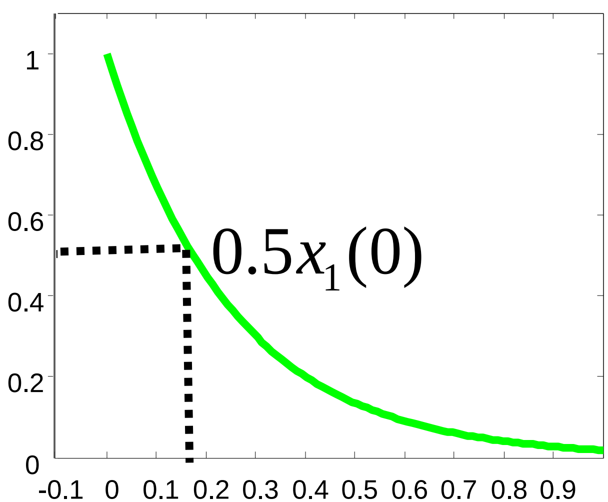
- **Neural parameters are ‘rate constants’:**

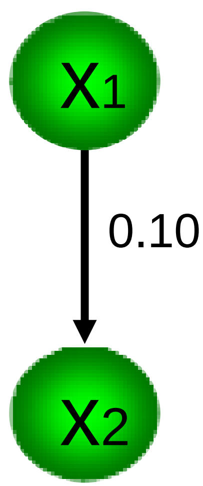


$$= \quad \frac{dx_1}{dt} = a_{11}x_1 \longrightarrow x_1(t) = x_1(0)\cdot\exp(a_{11}t)$$

if $a_{11} < 0$, then $\exp(a_{11}t) < 1$,
so x will decay over time

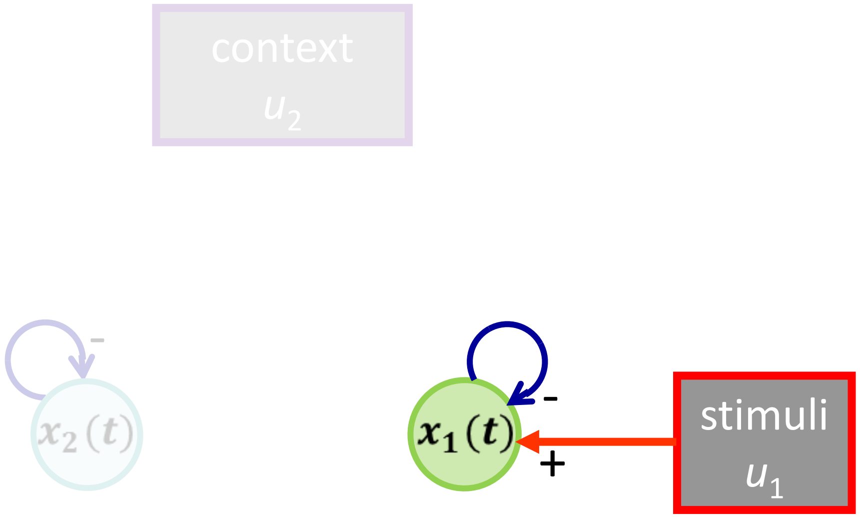
Decay function



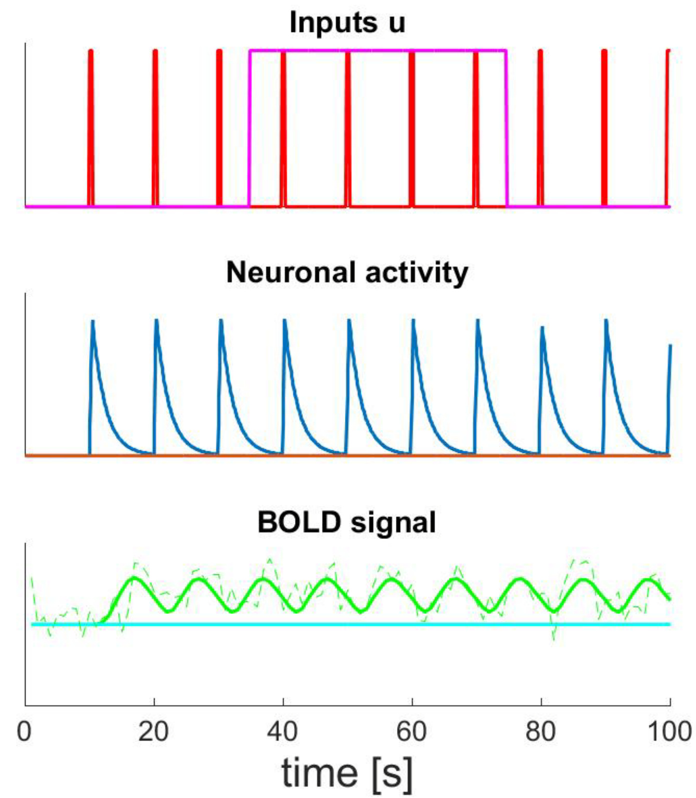


If x1→x2 is 0.10 s^{-1} this means that, per unit time, the increase in activity in x2 corresponds to 10% of the current activity in x1

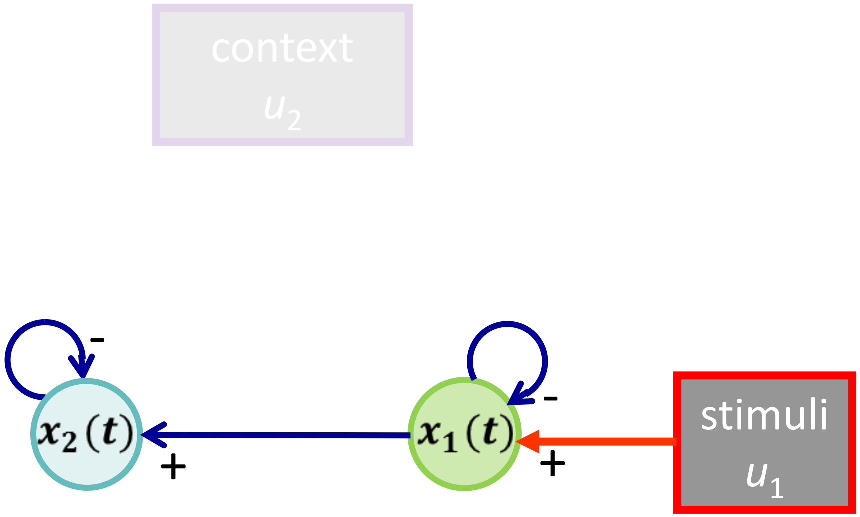
Example dynamics 1: Single node

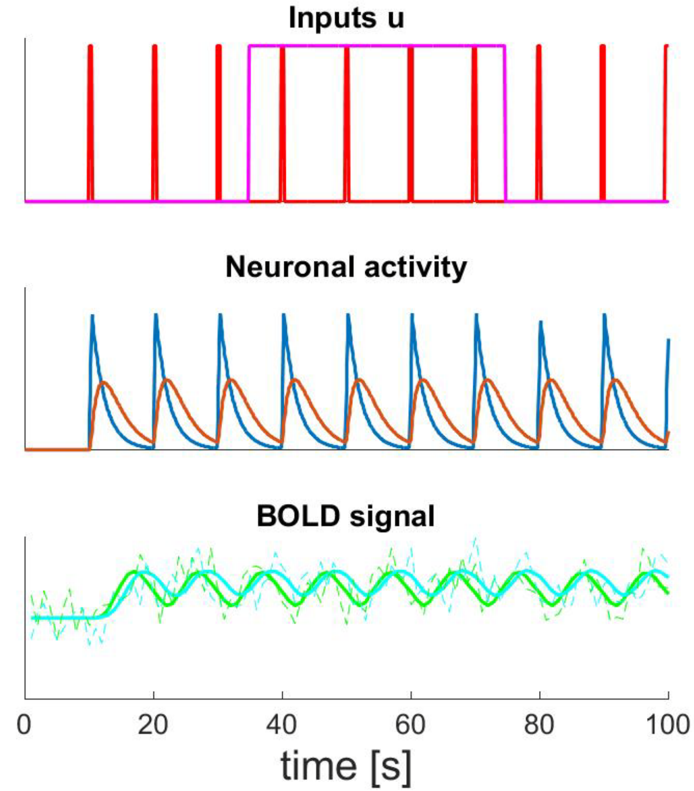


$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$



Example dynamics 2: Connected nodes

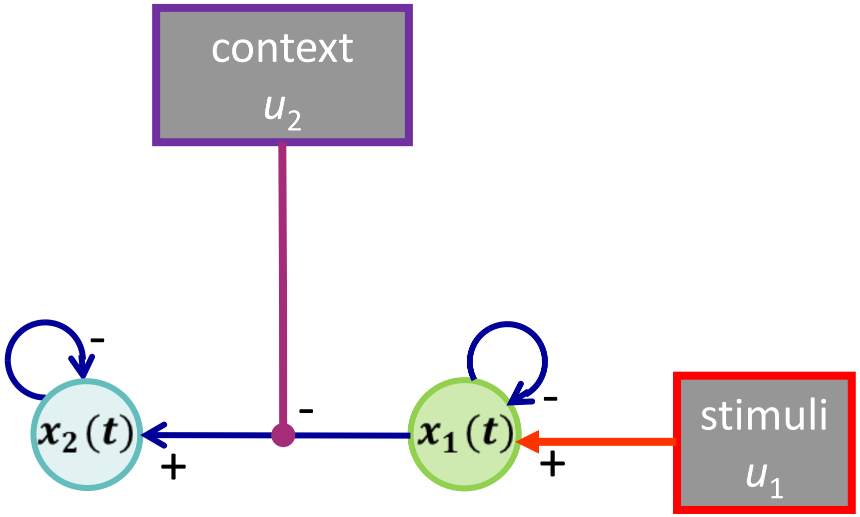


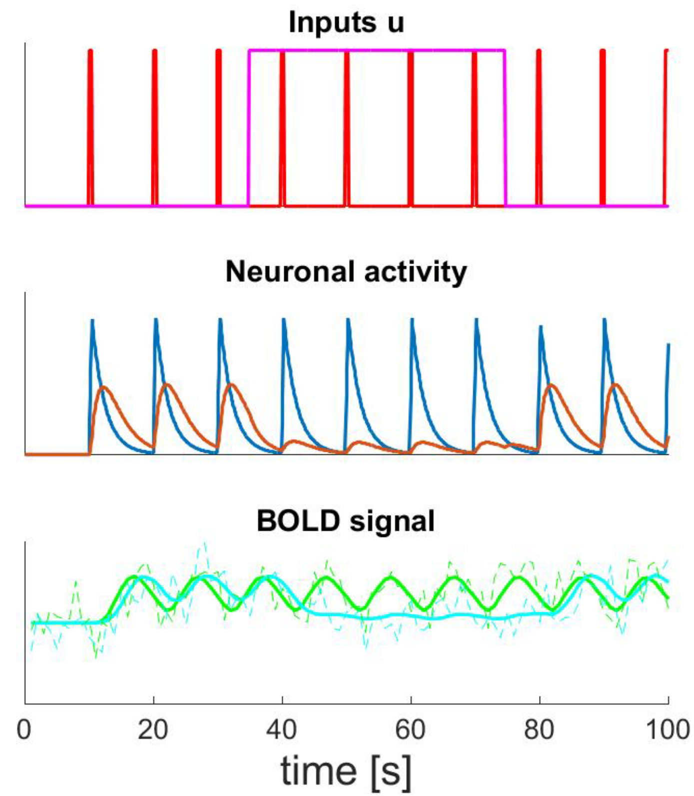


$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$
$$\dot{x}_2 = a_{22}x_2 + a_{21}x_1$$

$$\boldsymbol{x} = \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & \sigma \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Example dynamics 3: Modulation of connection





$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$
$$\dot{x}_2 = a_{22}x_2 + a_{21}x_1 + u_2 b_{21}^{(2)} x_1$$

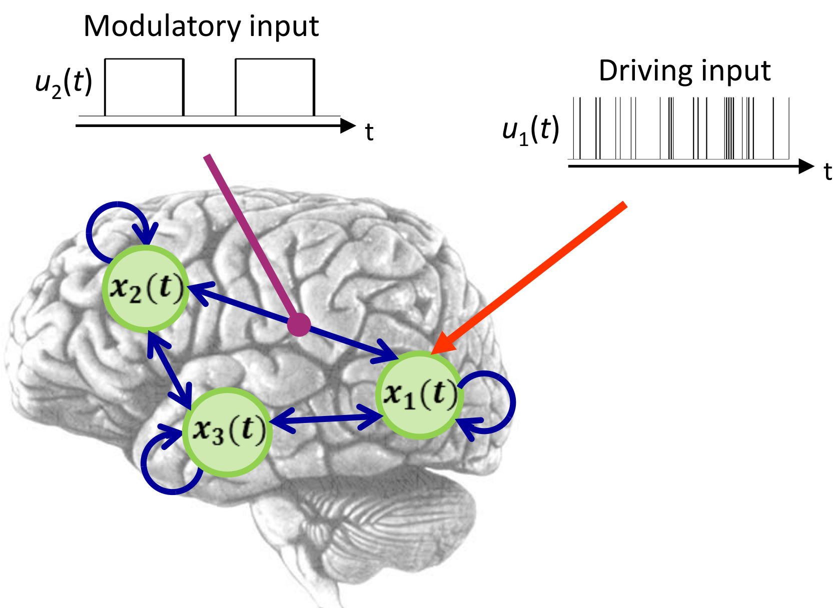
$$\boldsymbol{x} = \begin{bmatrix}\dot{x}_1\\ \dot{x}_2\end{bmatrix} = \left(\begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix} + u_2\begin{bmatrix}0 & 0\\ b_{21}^{(2)} & 0\end{bmatrix}\right)\cdot\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \begin{bmatrix}c_{11} & 0\\ 0 & 0\end{bmatrix}\cdot\begin{bmatrix}u_1\\ u_2\end{bmatrix}$$

Example dynamics 3: Modulation of connection

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

$$\boldsymbol{x} = \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \left(\boxed{\begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix}} + u_2 \boxed{\begin{bmatrix} 0 & 0 \\ b_{21}^{(2)} & 0 \end{bmatrix}} \right) \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \boxed{\begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix}} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Neural State equation



State changes

External modulatory inputs

Current state

External driving inputs

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

$$\boldsymbol{\theta} = \{\boldsymbol{A}, \boldsymbol{B}^1, \ldots, \boldsymbol{B}^m, \boldsymbol{C}\}$$

Fixed connectivity weights

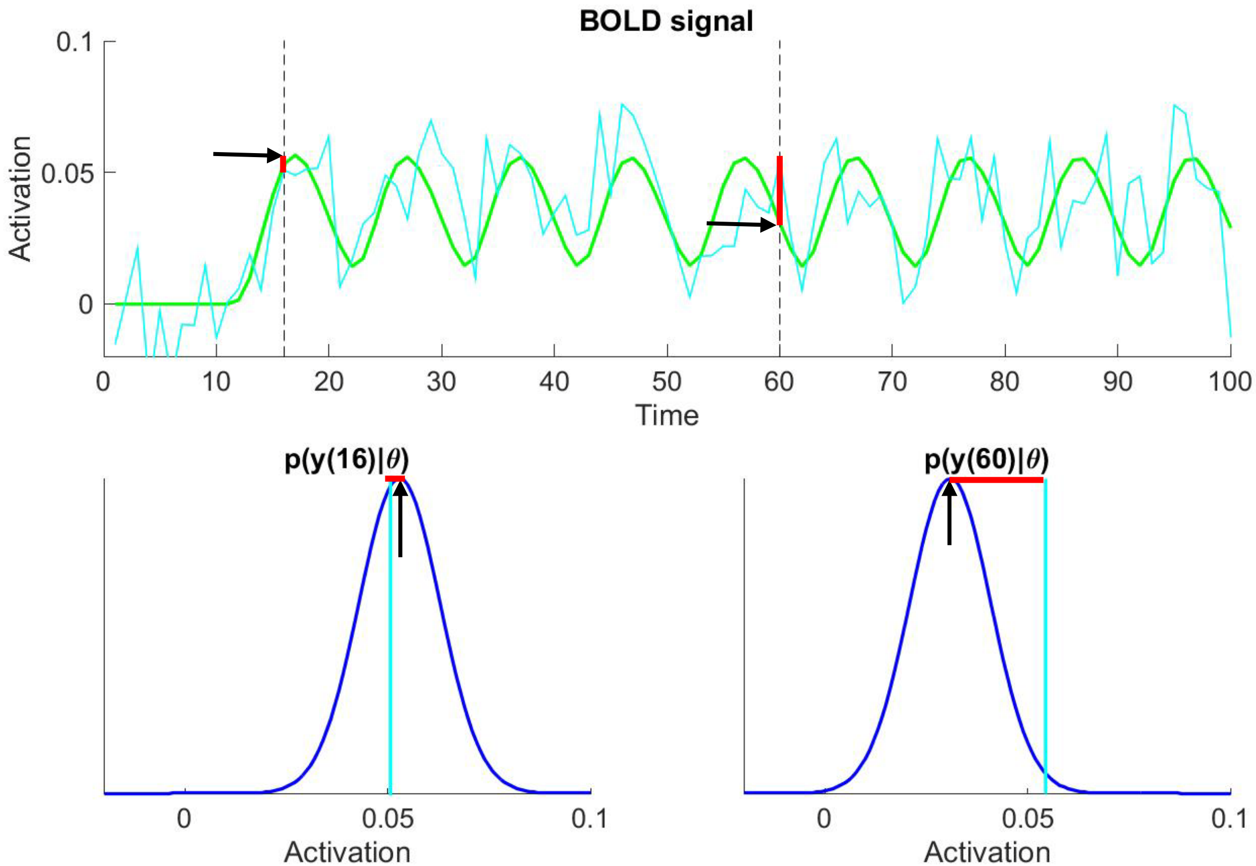
Weights (strength) of connectivity modulation

Weights for direct inputs

Under the hood 2:

from modelled BOLD to estimated parameters

Likelihood Function: What is a good fit?



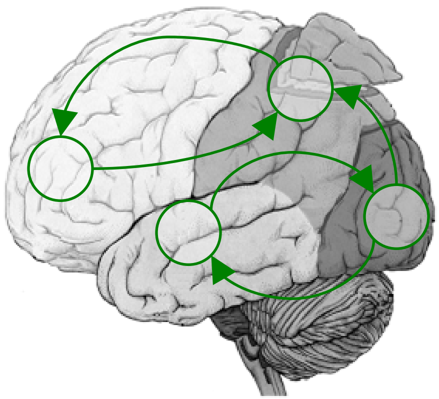
$$p(y|\theta,m) = \prod_t p(y(t)|\theta,m)$$

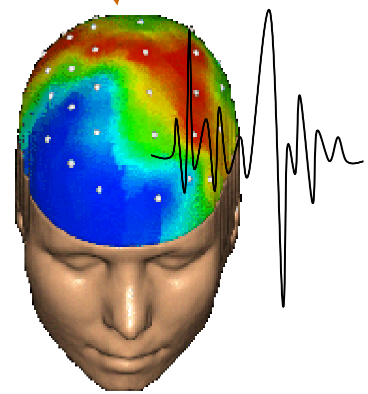
Bayesian inference – forward and inverse problem

forward problem

$$p\left(y \middle| \vartheta, m\right)$$

likelihood





posterior distribution

$$p\left(\vartheta \middle| y, m\right)$$

inverse problem

Model estimation: combining priors and data

Likelihood = Probability of data

- Derived from dynamical system
  - Gaussian noise

Priors (constraints):

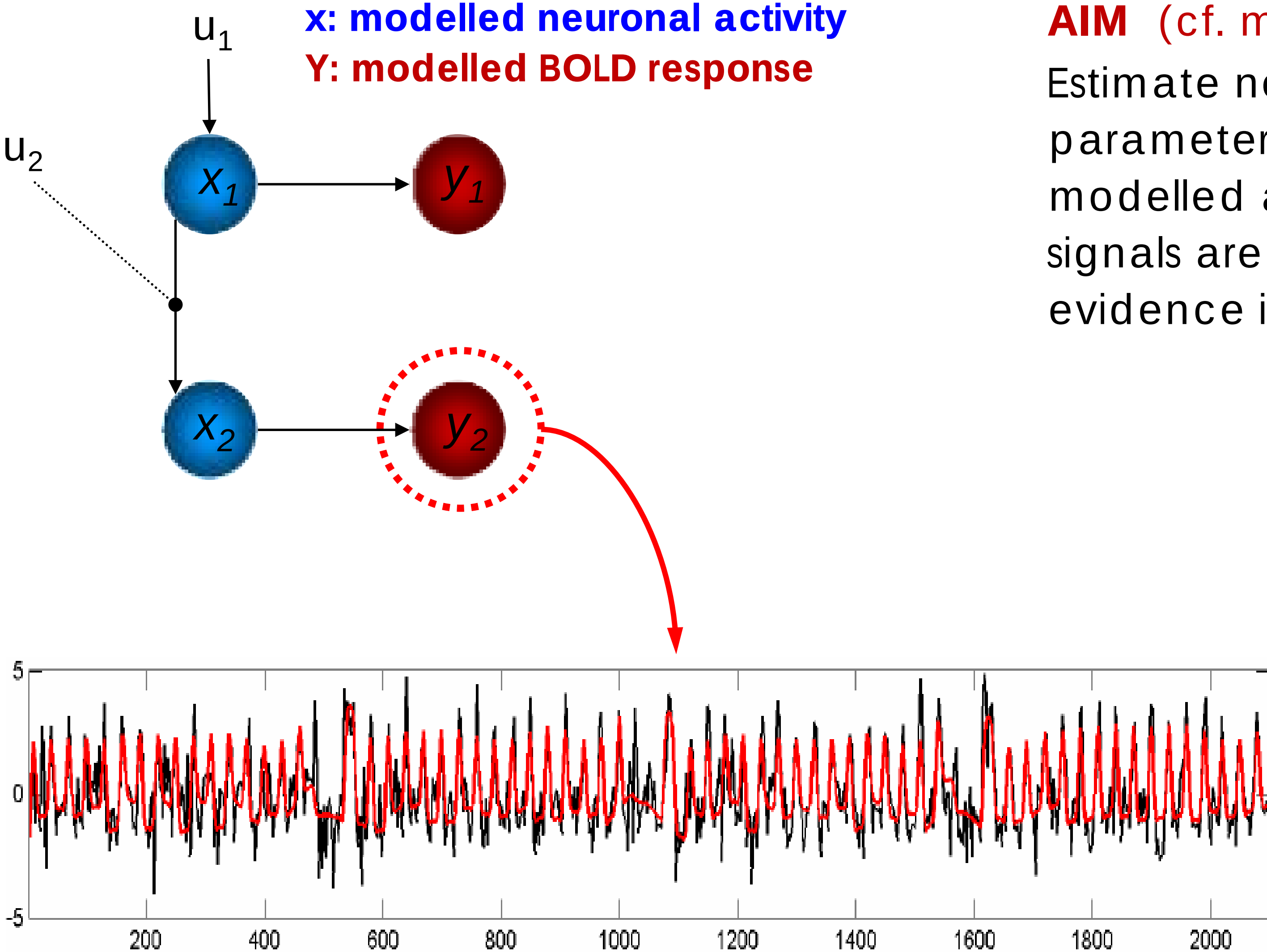
- Hemodynamic parameters
  - empirical
- Neural parameters
  - self connections: principled
  - other parameters (inputs, connections): shrinkage

$$p(\theta|y,m) = \frac{\boxed{p(y|\theta,m)} \cdot \boxed{p(\theta|m)}}{p(y|m)}$$

Parameter estimation: Bayesian inversion

x: modelled neuronal activity

Y: modelled BOLD response

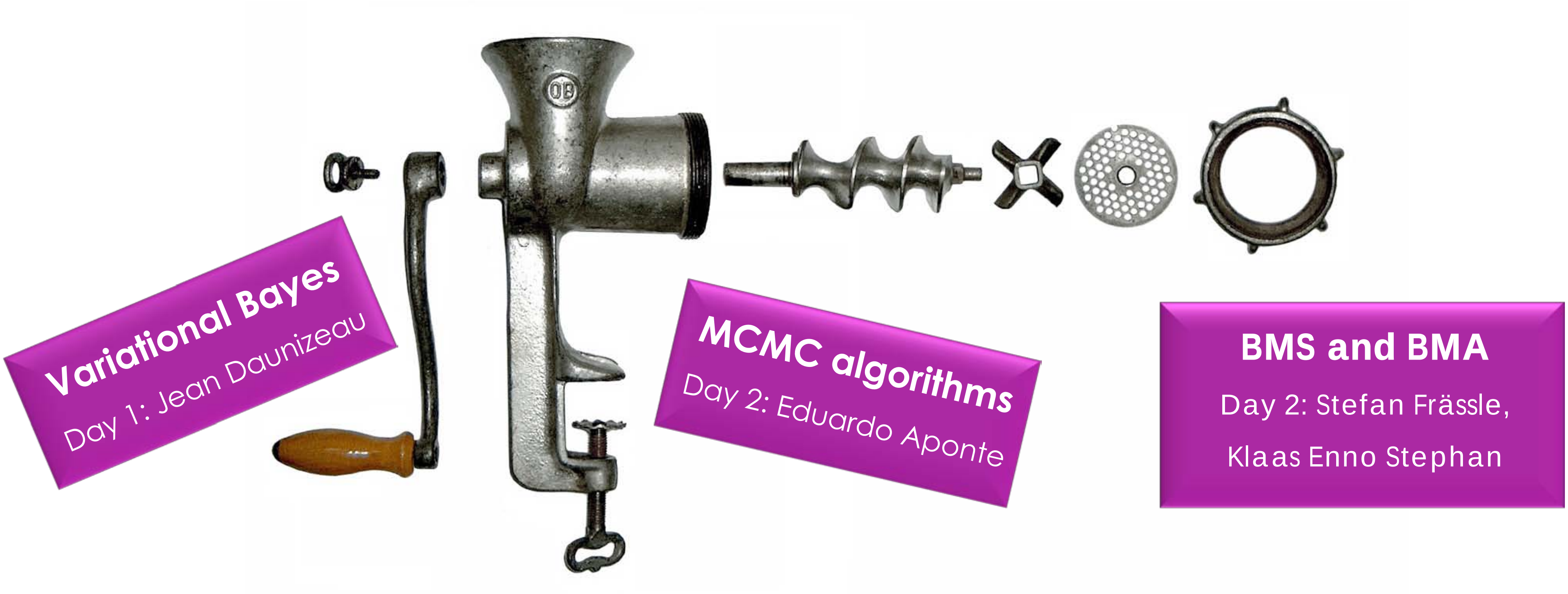


AIM (cf. manual)

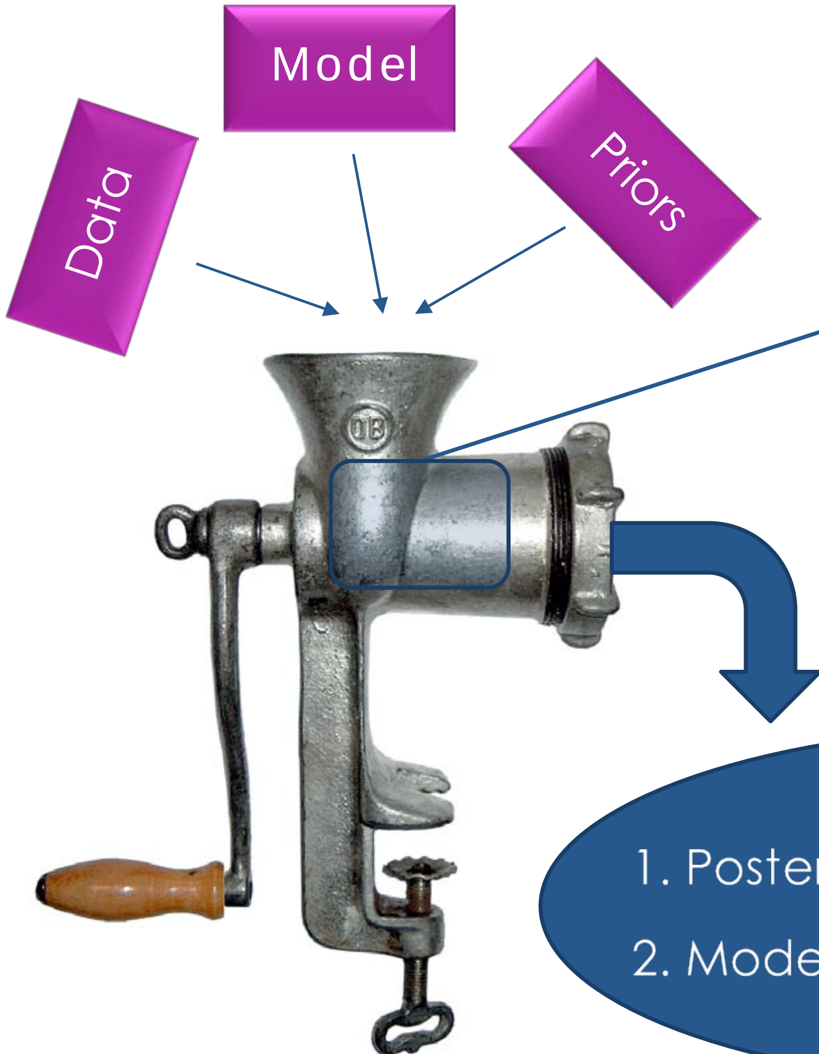
Estimate neural & hemodynamic parameters such that the modelled and measured BOLD signals are similar (i.e. model evidence is optimised).

Model estimation: running the machinery

- Goal: Find posterior of parameters $p(\theta|y,m)$ that maximises model evidence $p(y|m)$ given data and priors.



Model estimation: running the machinery



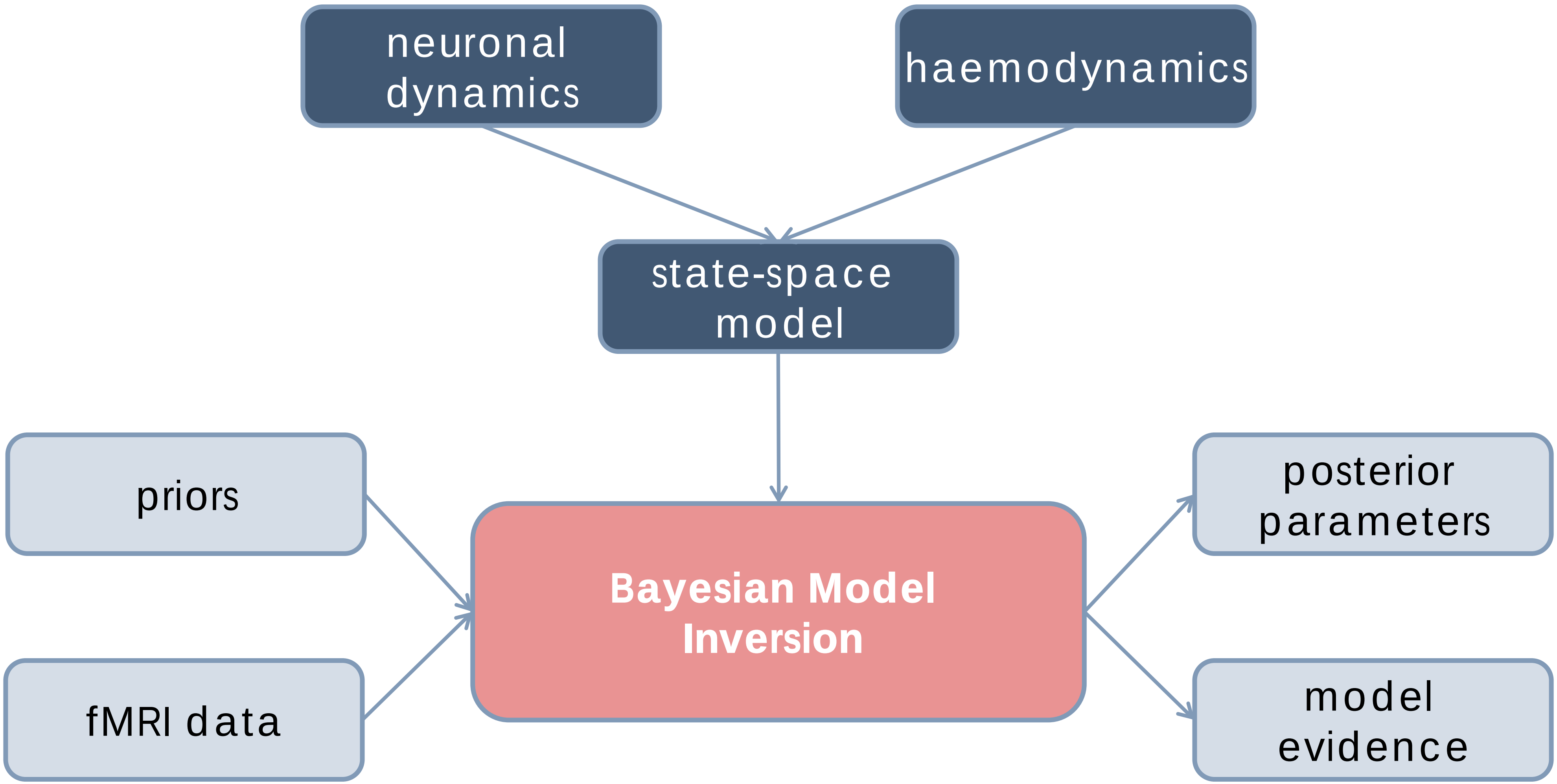
Expectation-Maximization algorithm

<u>Iterative procedure:</u>

1. Compute model response using current set of parameters
2. Compare model response with data
3. Improve parameters, if possible

1. Posterior parameters - $p(\boldsymbol{\theta}|\boldsymbol{y},\boldsymbol{m})$
2. Model evidence - $p(\boldsymbol{y}|\boldsymbol{m})$

DCM Roadmap


neuronal dynamics
haemodynamics
state-space model
priors
Bayesian Model Inversion
posterior parameters
fMRI data
model evidence

Outline

1. Basics (Jakob)

2. Applications and Examples (Hanneke)
   - understanding perception in synesthesia
   - psychopharmacology
   - psychiatry

3. Demo (Hanneke & Jakob)

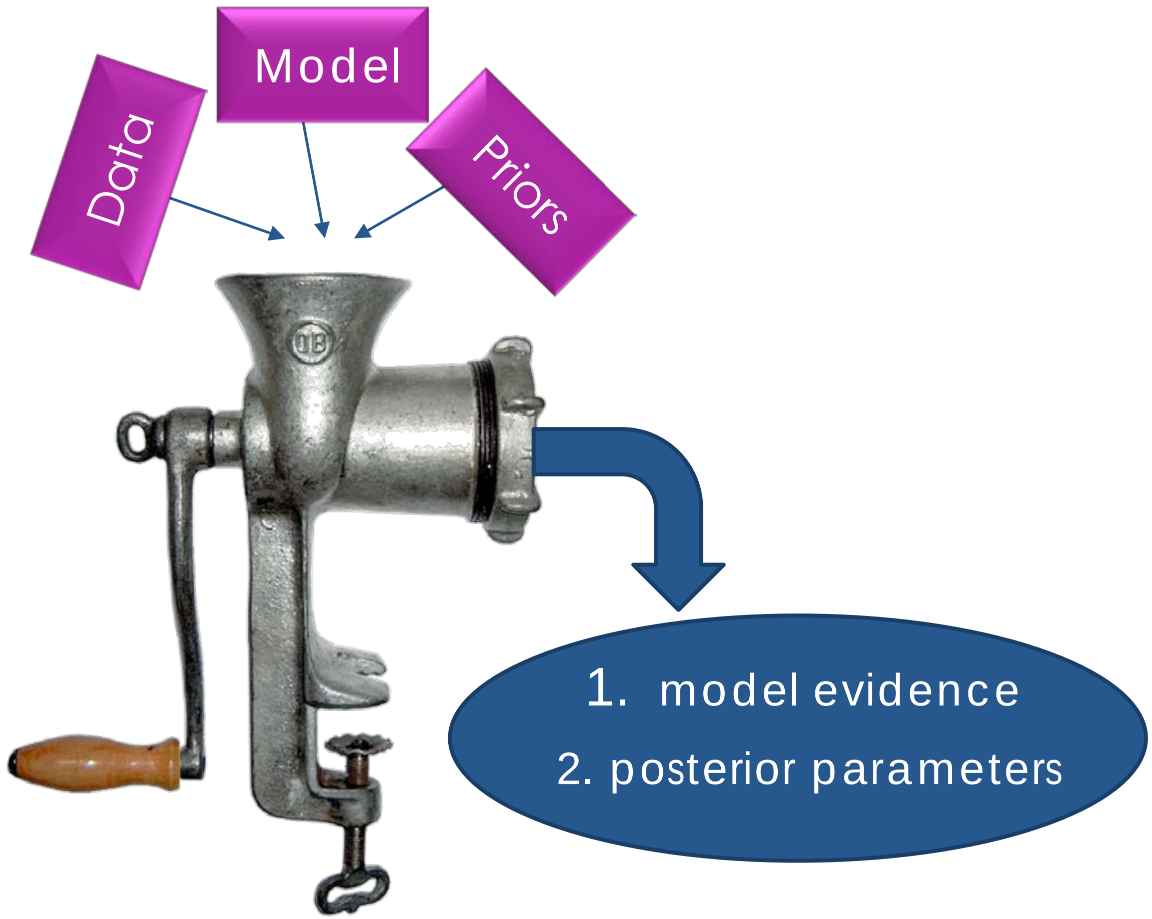
What questions can we answer using DCM?

Model comparison

- using model evidence

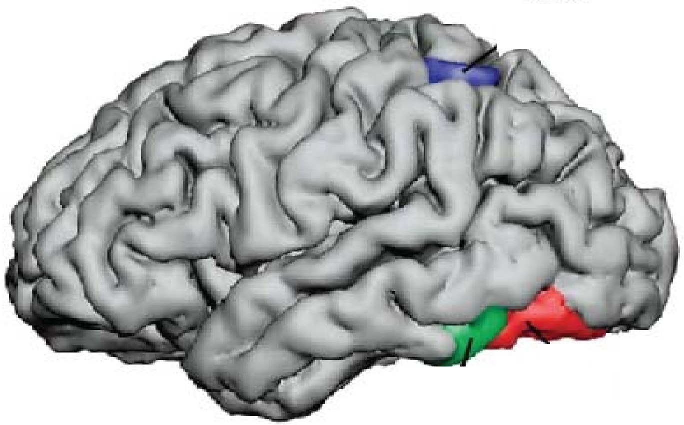
Parameter inference

- using posterior parameter estimates



Example 1: Brain Connectivity in Synesthesia

- Specific sensory stimuli lead to unusual, additional experiences
- Grapheme-color synesthesia: **color**
- Involuntary, automatic; stable over time, prevalence ~4%
- Potential cause: aberrant **cross-activation/coupling** between brain areas
  - grapheme encoding area
  - color area V4
  - superior parietal lobule (SPL)

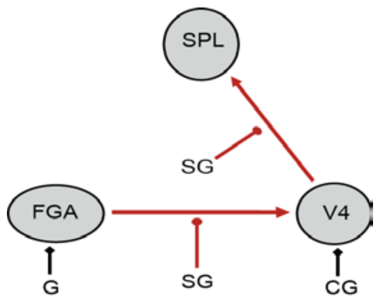


Hubbard, 2007

Bottom-up or Top-down "cross-activation"?

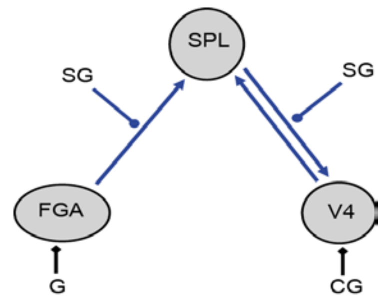
Bottom-up

(*Ramachandran & Hubbard, 2001*)



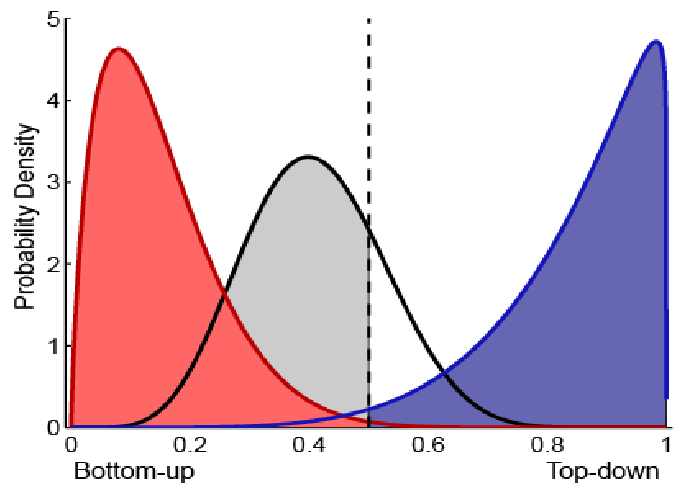
Top-down

(*Grossenbacher & Lovelace, 2001*)

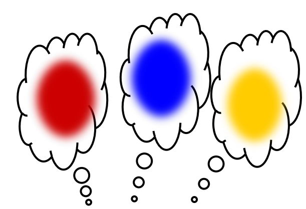


Projectors

ABC



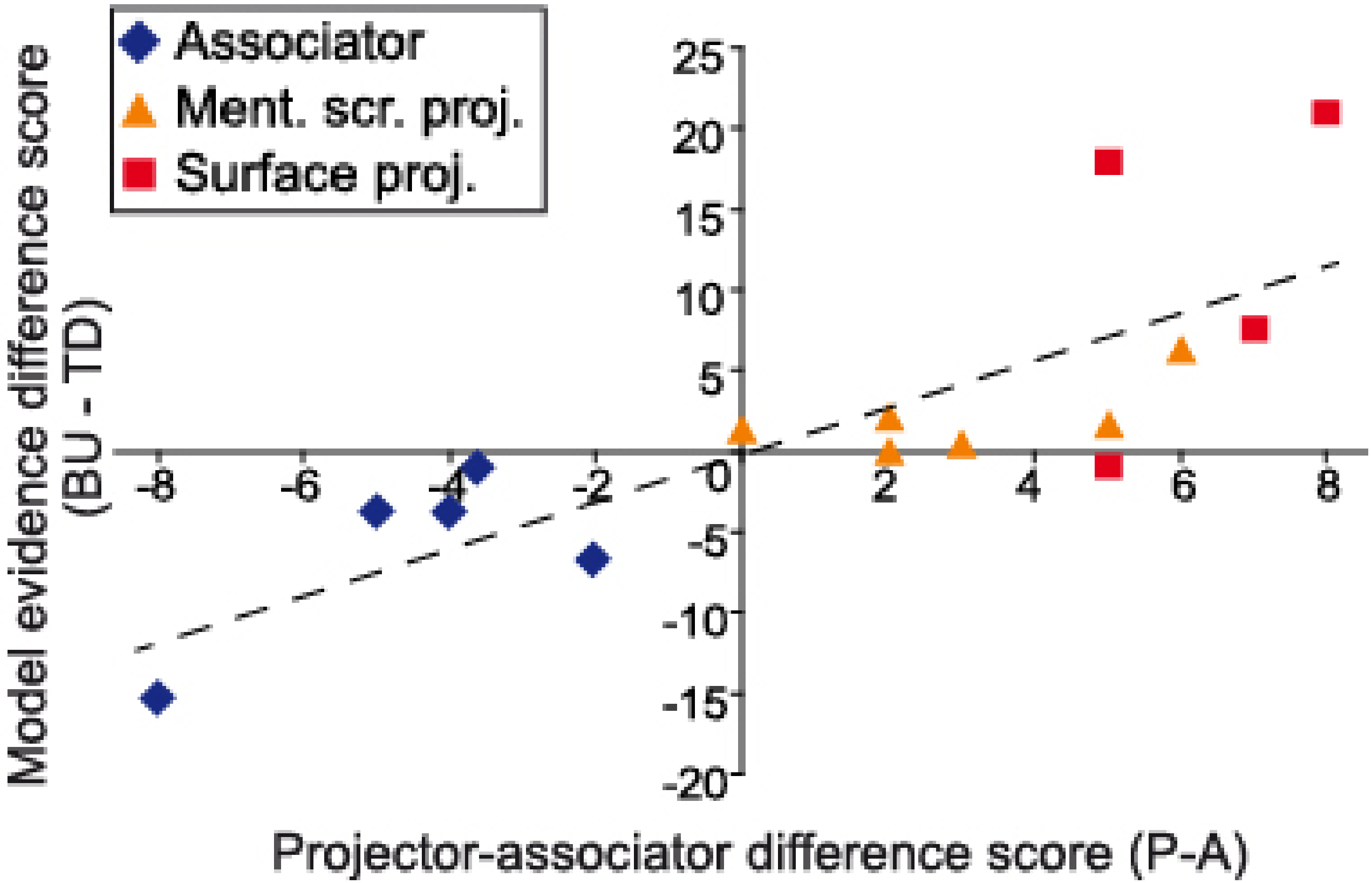
Associators



ABC

Van Leeuwen, den Ouden, Hagoort (2011) *JNeurosci*

Model evidence predicts sensory experience



Van Leeuwen, den Ouden, Hagoort (2011) *JNeurosci*

What questions can we answer using DCM?

Model comparison

What is the functional architecture of a network of brain regions?

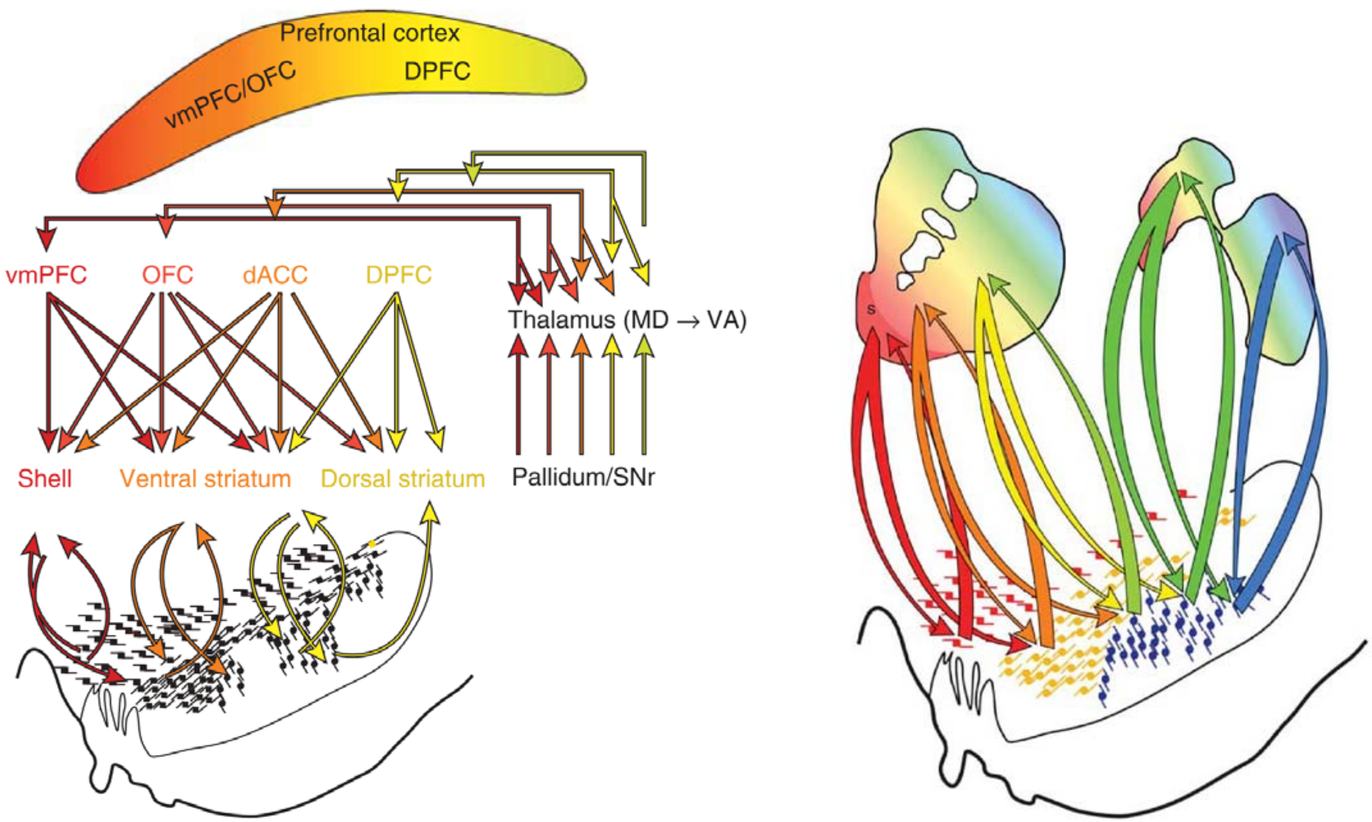
bottom-up vs. top-down drive of V4 in color-grapheme synesthesia

Are optimal models different between groups?

optimal model predicts sensory experience in color-grapheme synesthesia

Parameter inference

how does dopamine modulate striatal architecture?

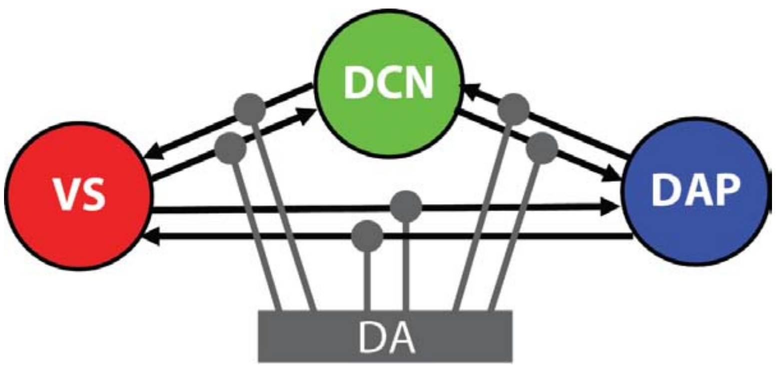


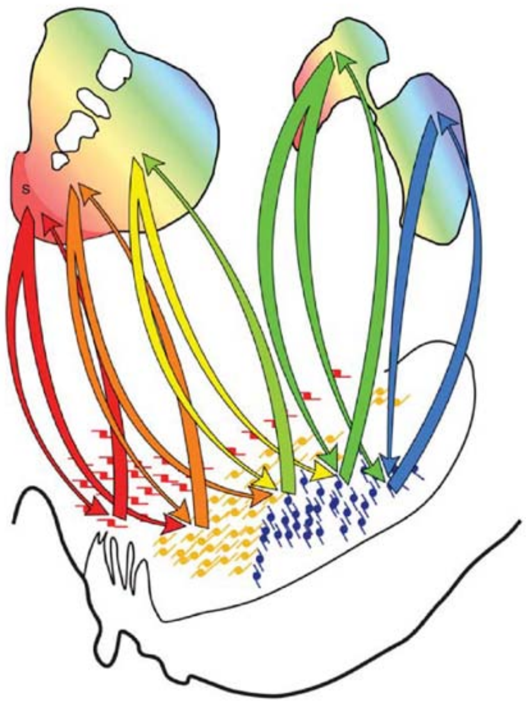
How does dopamine modulate striatal architecture?

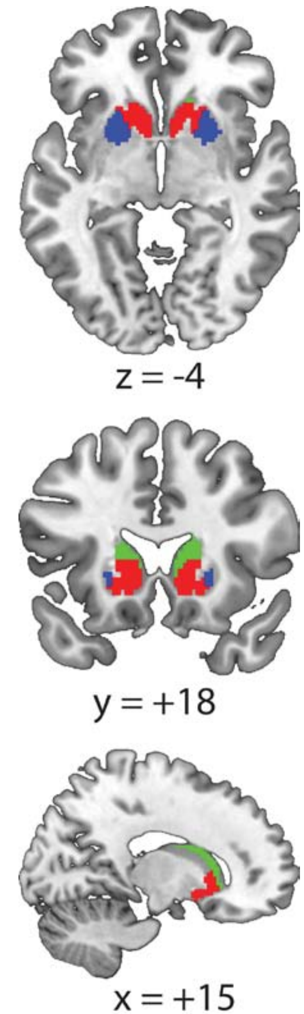
roi definition → model comparison → parameter evaluation

DA manipulation: agonist (bromocriptine) & antagonist (sulpiride)

resting state fMRI + dynamic causal modelling



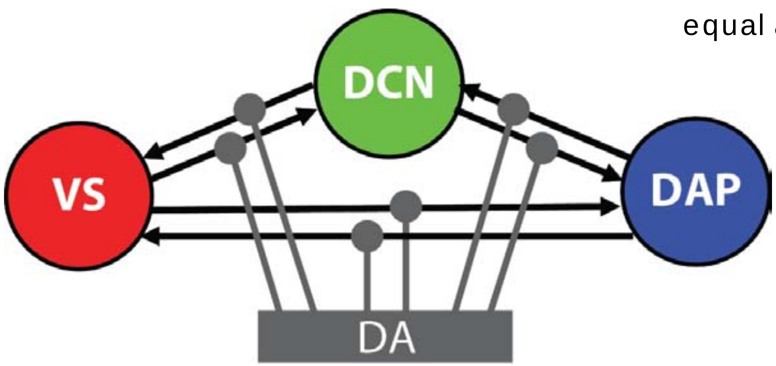


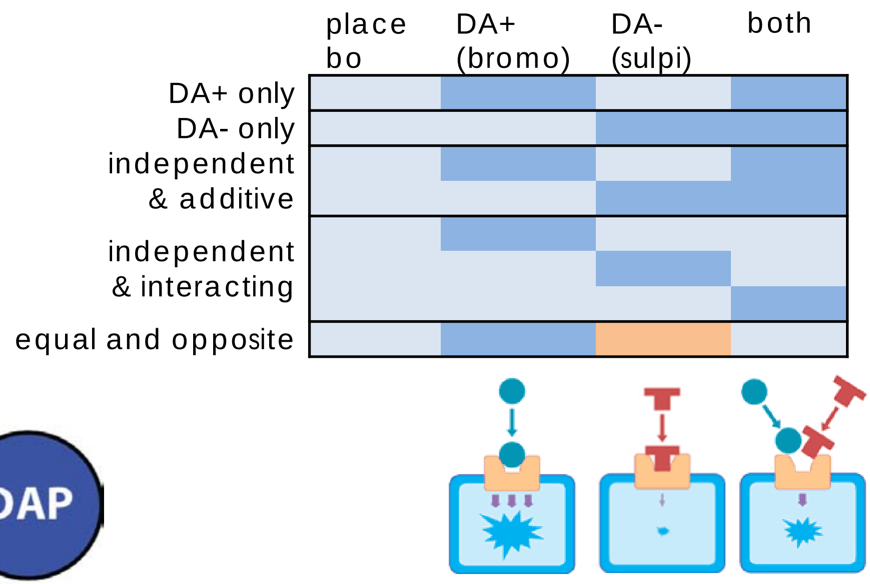


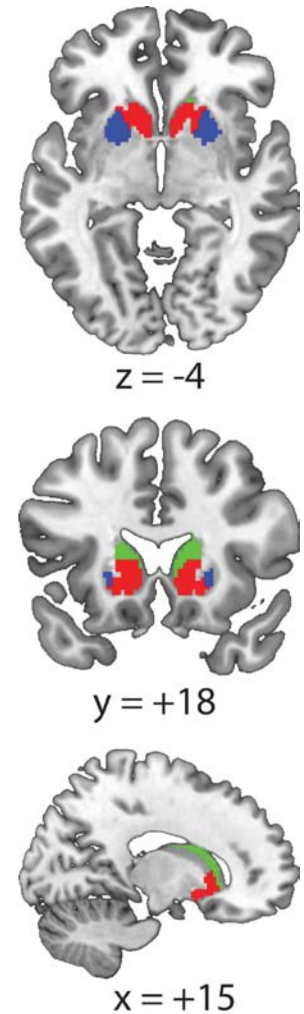
How does dopamine modulate striatal architecture?

roi definition → **model comparison** → parameter evaluation

- inputs



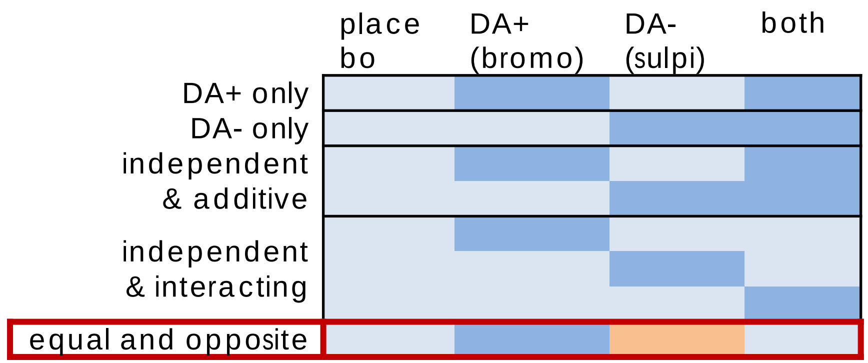


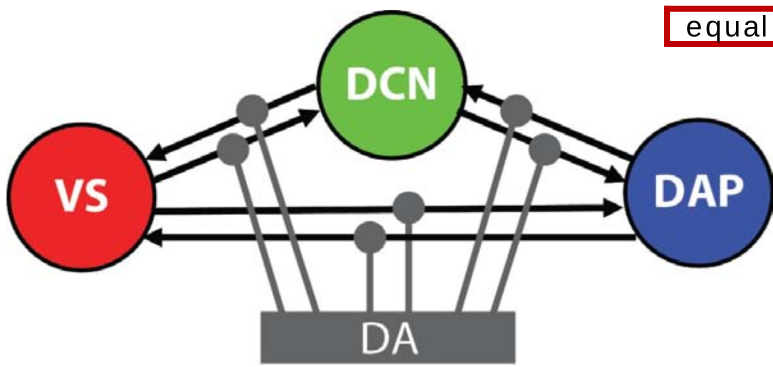


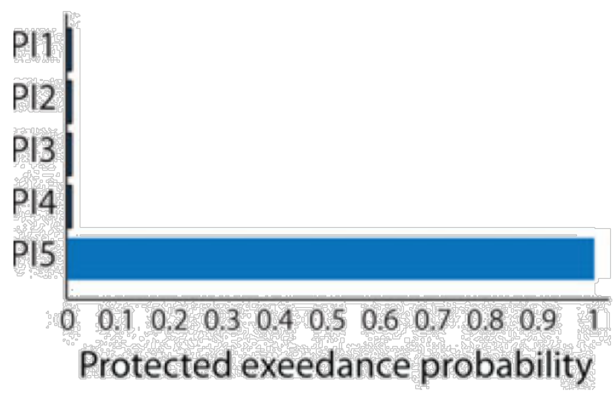
How does dopamine modulate striatal architecture?

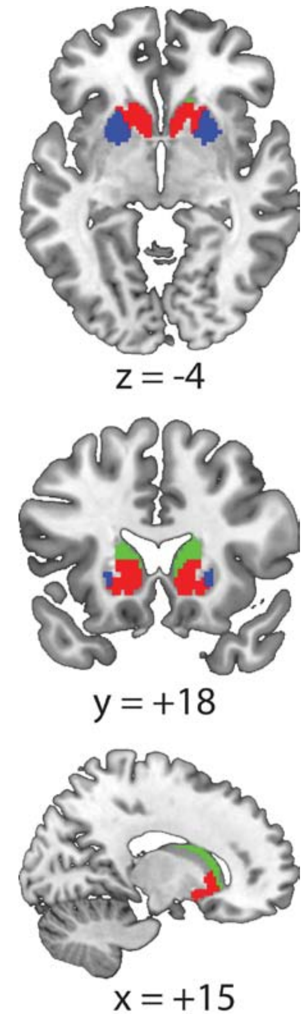
roi definition → **model comparison** → parameter evaluation

- inputs :(ant)agonists have opposite effects





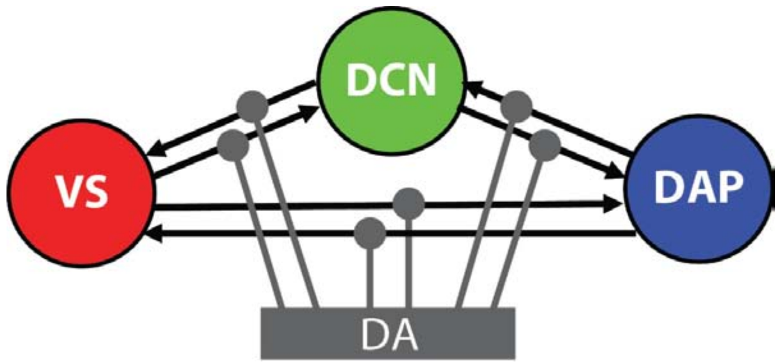


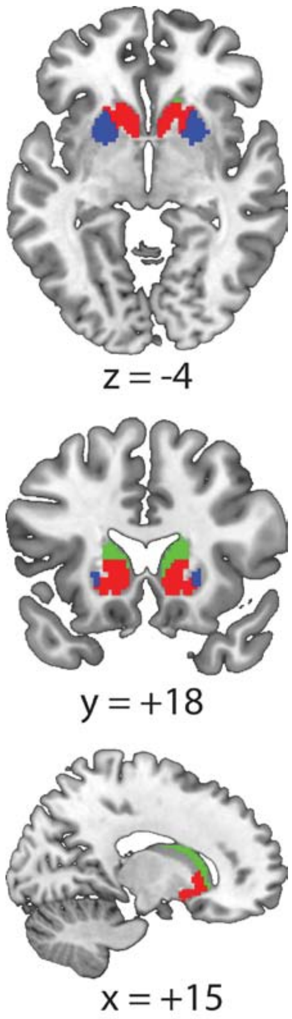


How does dopamine modulate striatal architecture?

roi definition → **model comparison** → parameter evaluation

- inputs: (ant)agonists have opposite effects
- connections

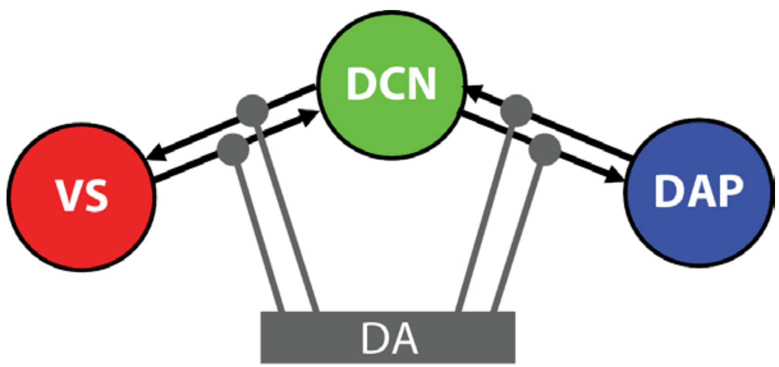


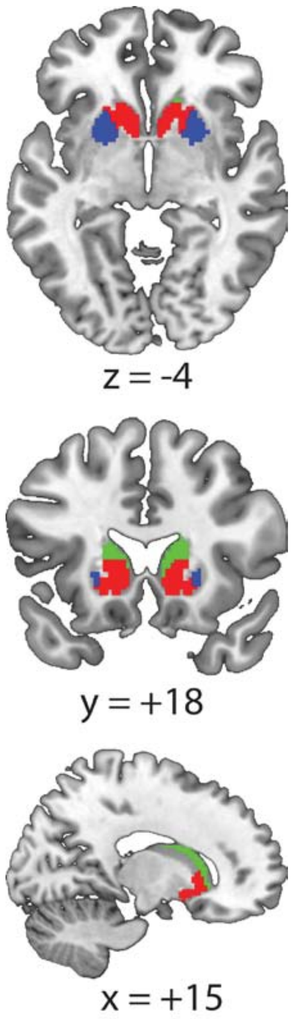


How does dopamine modulate striatal architecture?

roi definition → **model comparison** → parameter evaluation

- inputs: (ant)agonists have opposite effects
- connections: dopamine modulation follows striatal hierarchy

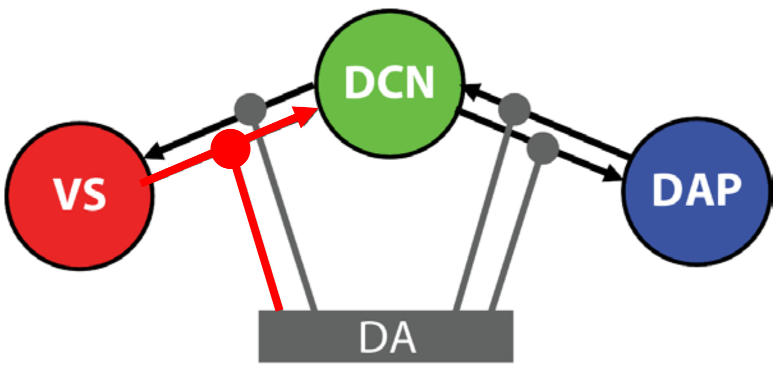


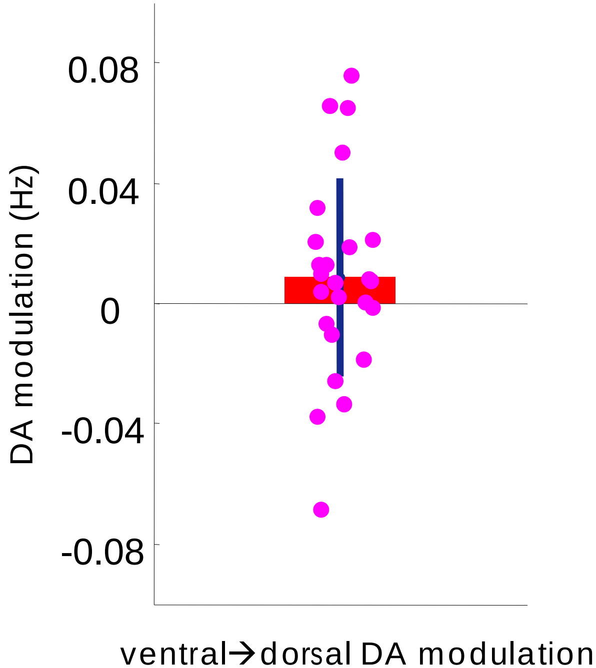


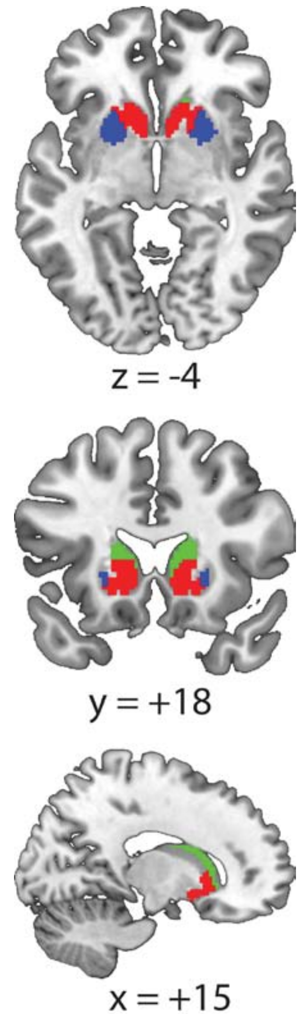
How does dopamine modulate striatal architecture?

roi definition → model comparison → **parameter evaluation**

- dopamine manipulation on average not different from 0?







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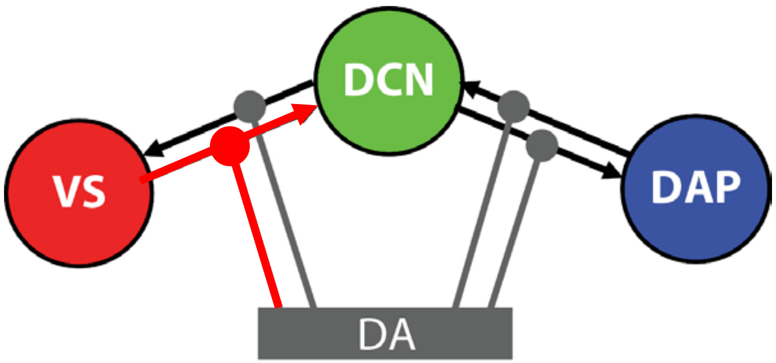
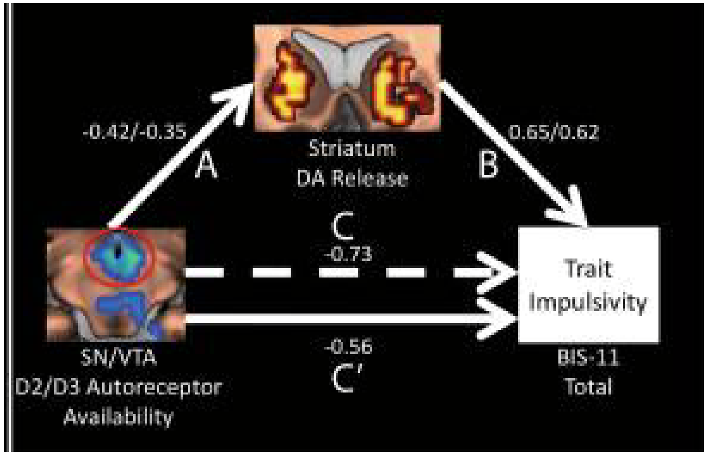
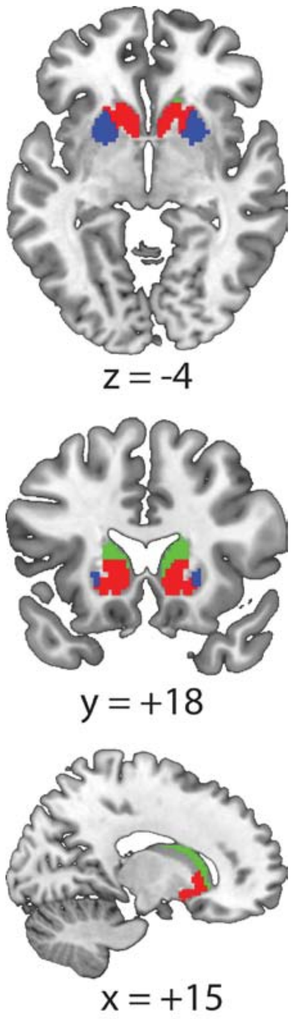




Treadway ea. (2010) Science

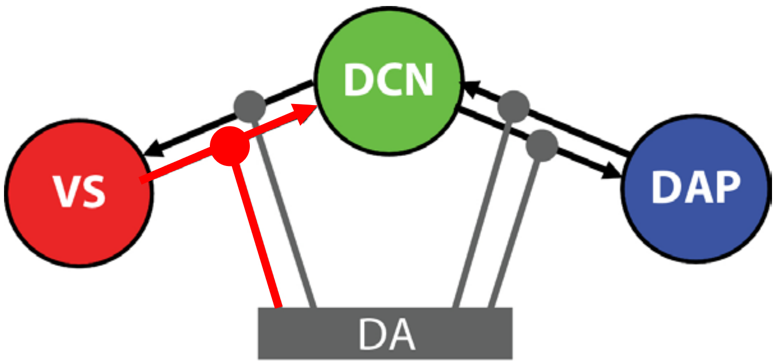


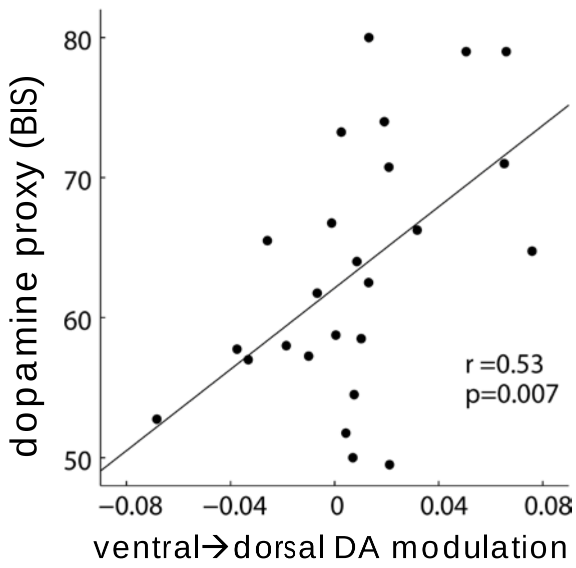
Piray , den Ouden ea. (2016) *Cerebral Cortex*

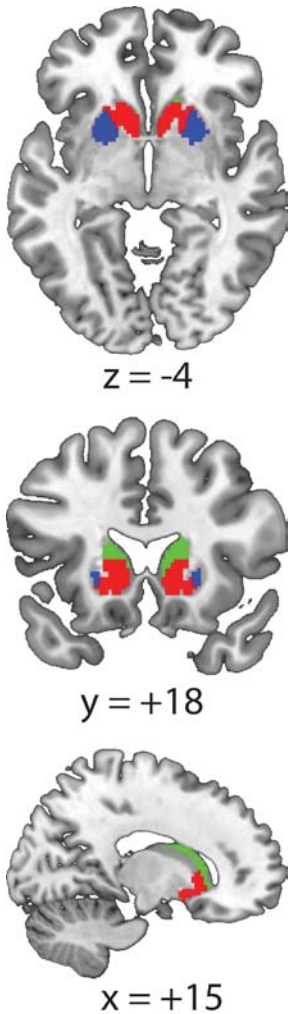
How does dopamine modulate striatal architecture?

roi definition → model comparison → **parameter evaluation**

- dopamine manipulation on average not different from 0?
- trait impulsivity predicts DA modulation of connectivity







What questions can we answer using DCM?

Model comparison

What is the functional architecture of a network of brain regions?

bottom-up vs. top-down drive of V4 in color-grapheme synesthesia

Are optimal models different between groups?

optimal model predicts sensory experience in color-grapheme synesthesia

Which connections are modulated by experimental manipulations?

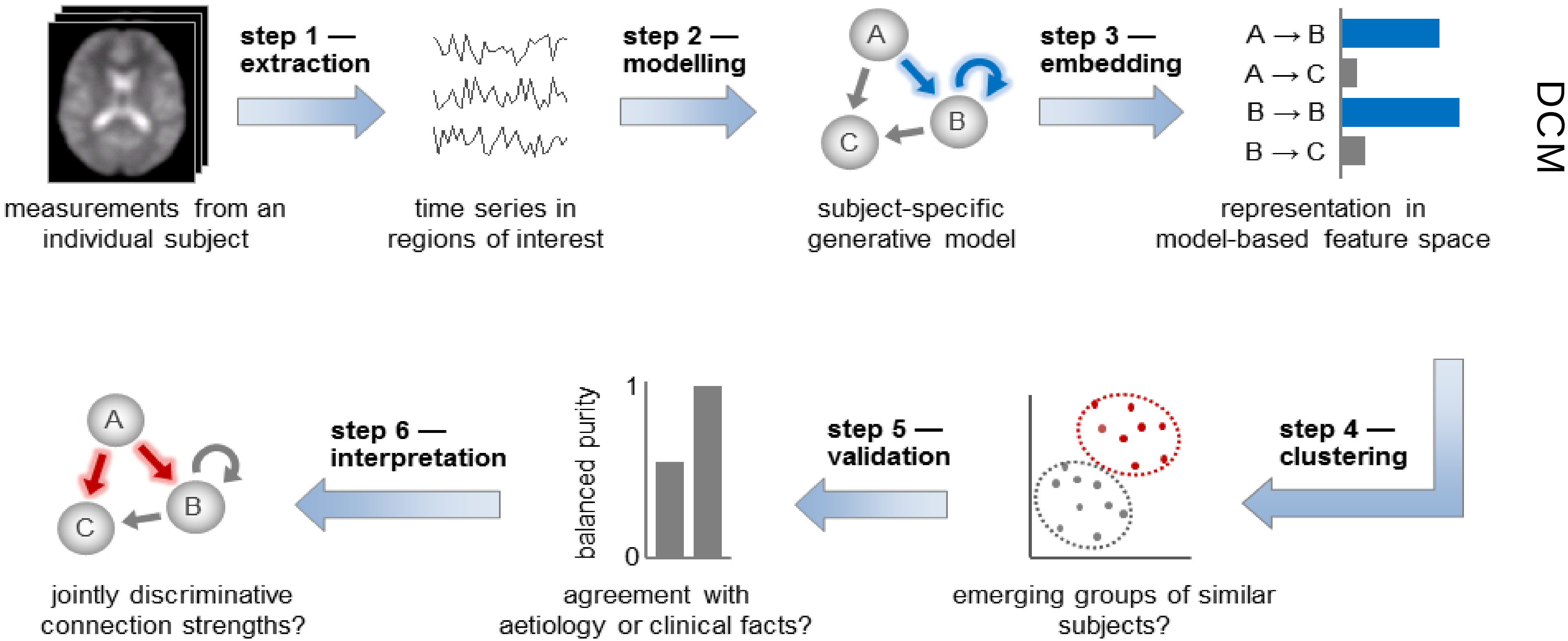
dopaminergic modulation follows striatal hierarchy

Parameter inference

Are parameters different between individuals ?

Trait impulsivity predicts degree of dopaminergic modulation of striatal coupling

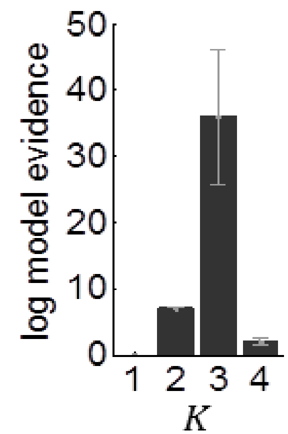
Generative embedding:
DCM as physiologically motivated feature extraction



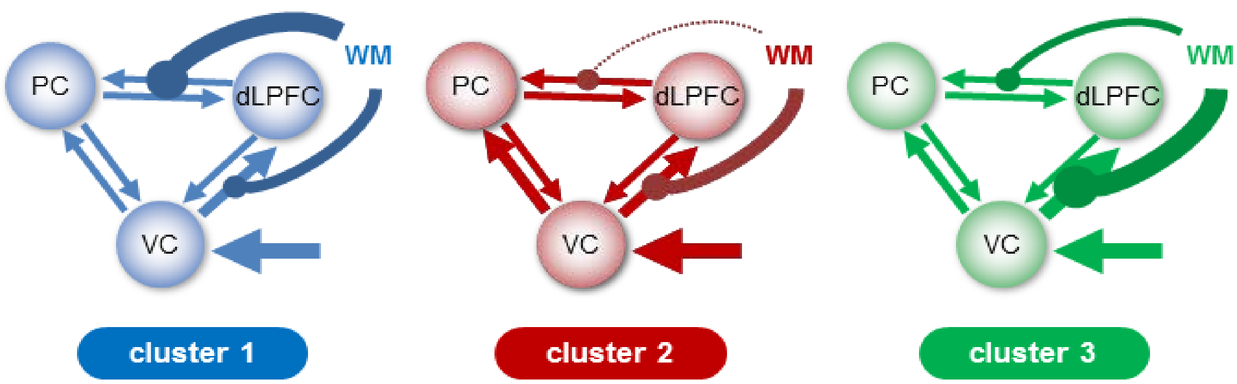
Brodersen et al., NeuroImage: Clinical, 2014

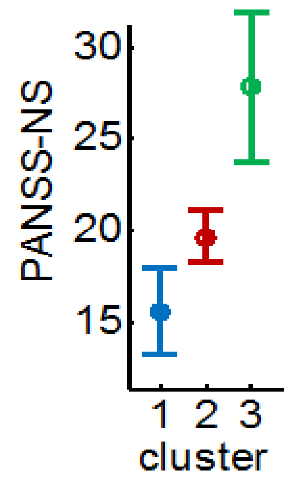
Detecting subgroups of patients in schizophrenia

- DCM of working memory task
- **clustering**
  three distinct subgroups (N=41)
- **validation: clinical score**
  subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)
- **future:** assess **differential** prognosis, treatment prediction etc. of subclusters



Optimal cluster solution





Relation to clinical score

What questions can we answer using DCM?

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Clustering of WM DCM differentiates clinical scores in schizophrenia

Parameters as physiologically informed summary statistics

- Simple classical or Bayesian statistics on parameters
- Clustering analysis
- Mediation analysis

... and many more!

Discussion questions

- **Why is this DCM useful?**
  - Allows for mechanistic explanation of fMRI data and to compare this between groups.
- **Where can we use DCM?**
  - For example in the settings discussed.
- **Where can‘t we use DCM?**
  - It is not optimal for data mining / ‘data-driven’ analyses
- **What do you like about DCM?**
  - Forces to make hypotheses explicit and mechanistic and, if successful, provides “close” link to physiology
- **What are the most common mistakes made?**
  - No careful specification of model space (demo)
    - missing models, inclusion of nodes with no activation
  - Trying to build an entire brain!
  - Interpretation of results (often due to not understanding the DCM)
  - Fixed effects model comparison when not warranted
  - Lack of quality checking of models

Estimating Connectivity: DCM for FMRI - Demo

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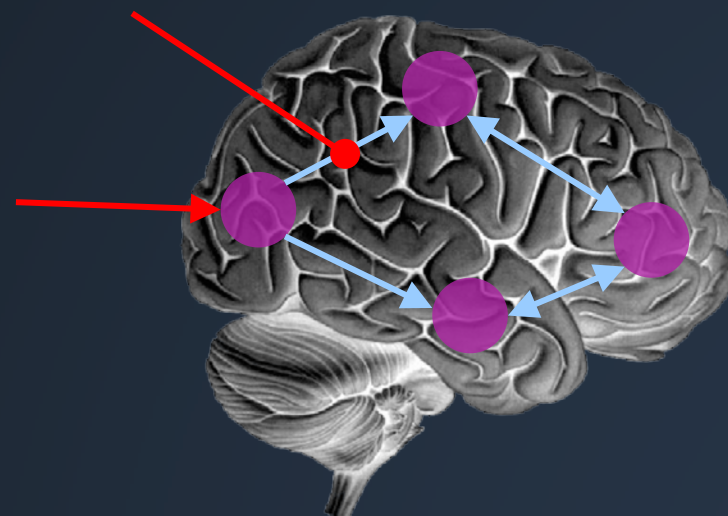


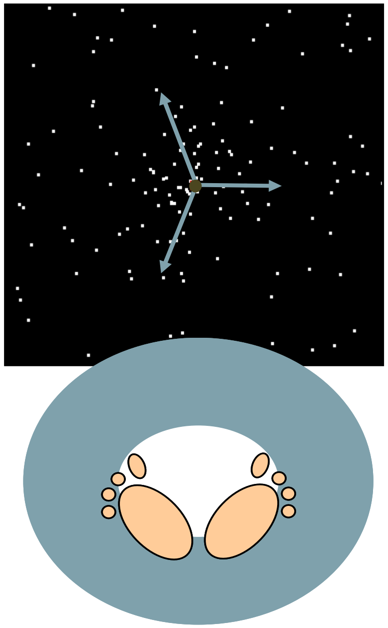
University of Zurich[UZH]

ETH zürich

Translational Neuromodeling Unit

Attention to motion in the visual system

Paradigm



Stimuli radially moving dots

Pre-Scanning

5 x 30s trials with 5 speed changes

Task - detect change in radial velocity

Scanning (no speed changes)

F A F N F A F N S ....

F - fixation

S - observe static dots + photic

N - observe moving dots + motion

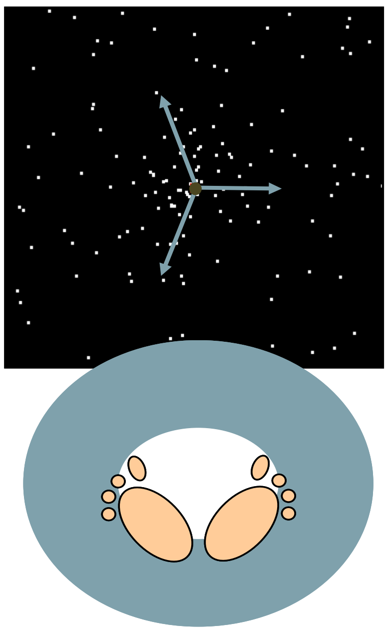
A - attend moving dots + attention

Parameters

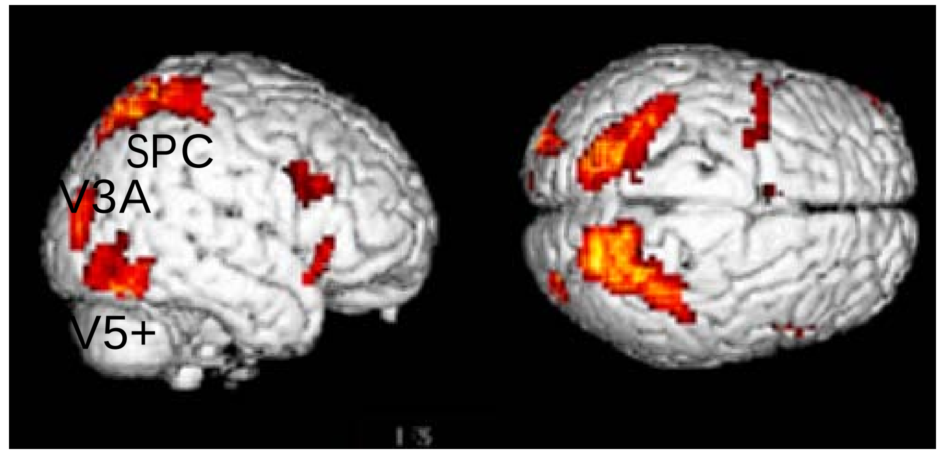
- blocks of 10 scans
- 360 scans total
- TR = 3.22 seconds

Attention to motion in the visual system

Paradigm

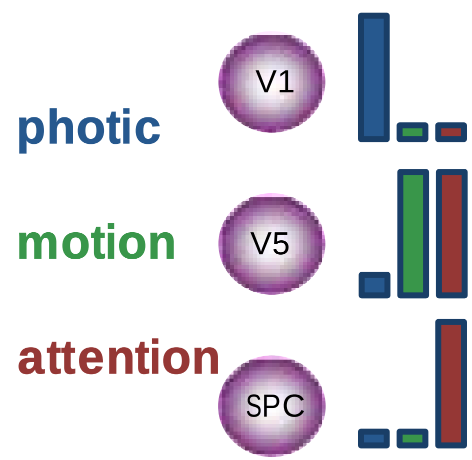


Results



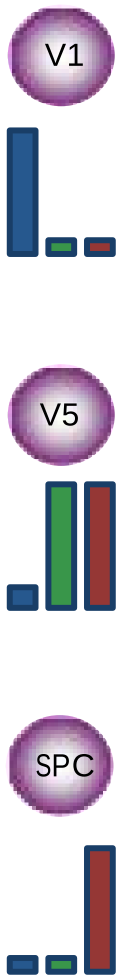
Attention – No attention

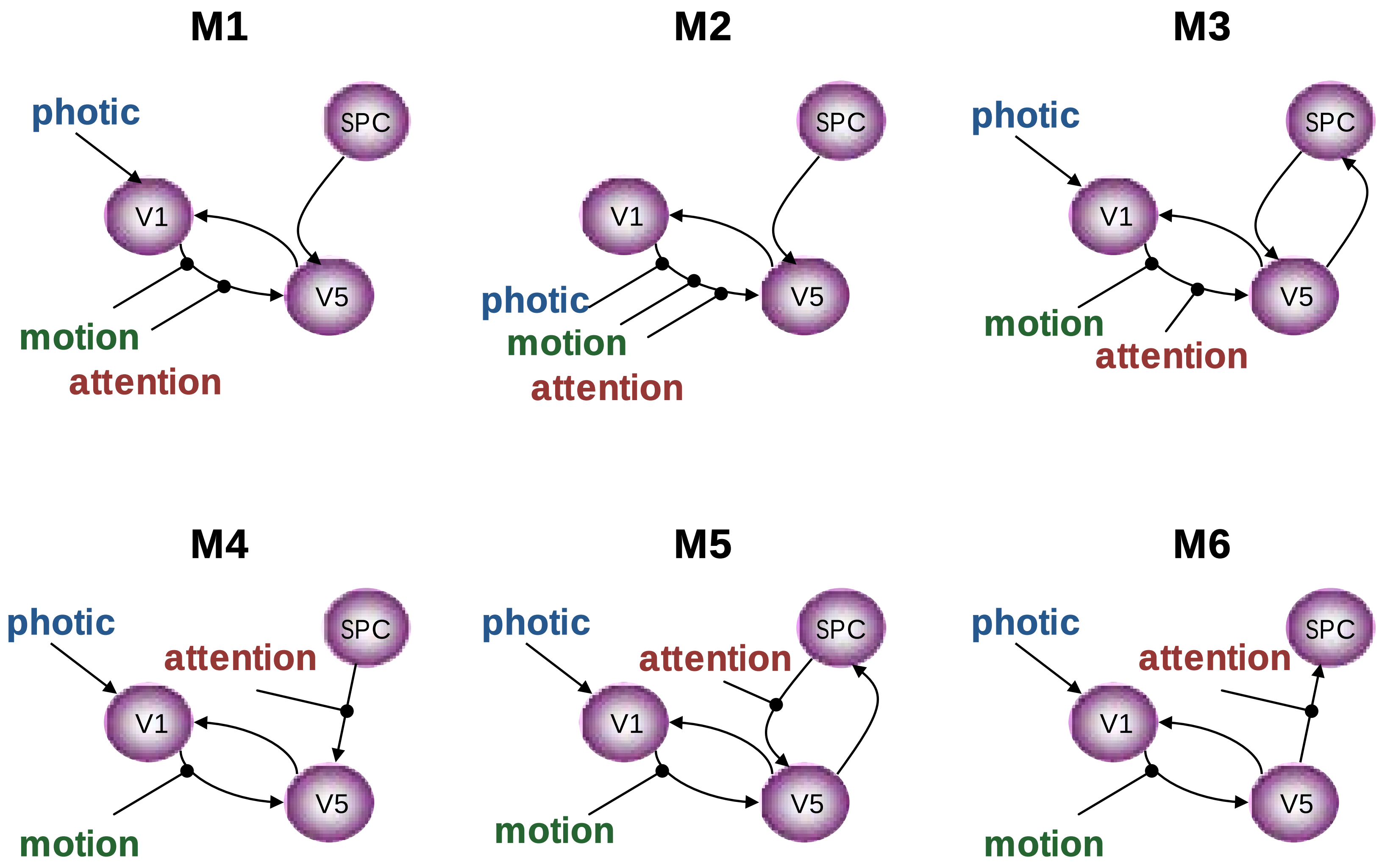
Büchel & Friston 1997, Cereb. Cortex
Büchel et al. 1998, Brain



- fixation only
- observe static dots + photic → V1
- observe moving dots + motion → V5
- task on moving dots + attention → V5 + parietal cortex

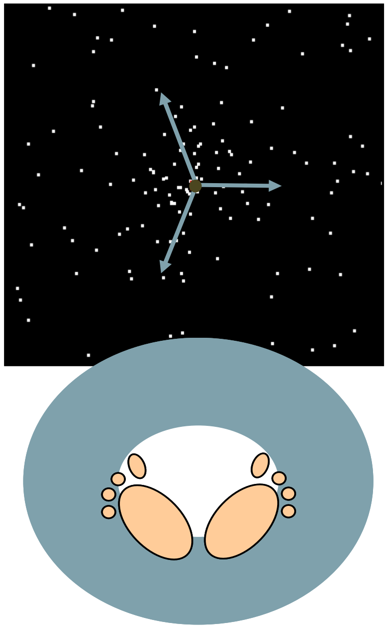
Quiz: can this DCM explain the data?





Attention to motion in the visual system

Paradigm



Ingredients for a DCM

Specific hypothesis/question

Model:	based on hypothesis
Timeseries:	from the SPM
Inputs:	from design matrix

Attention to motion in the visual system

DCM – GUI basic steps

1 – Extract the time series (from all regions of interest)

2 – Specify the model

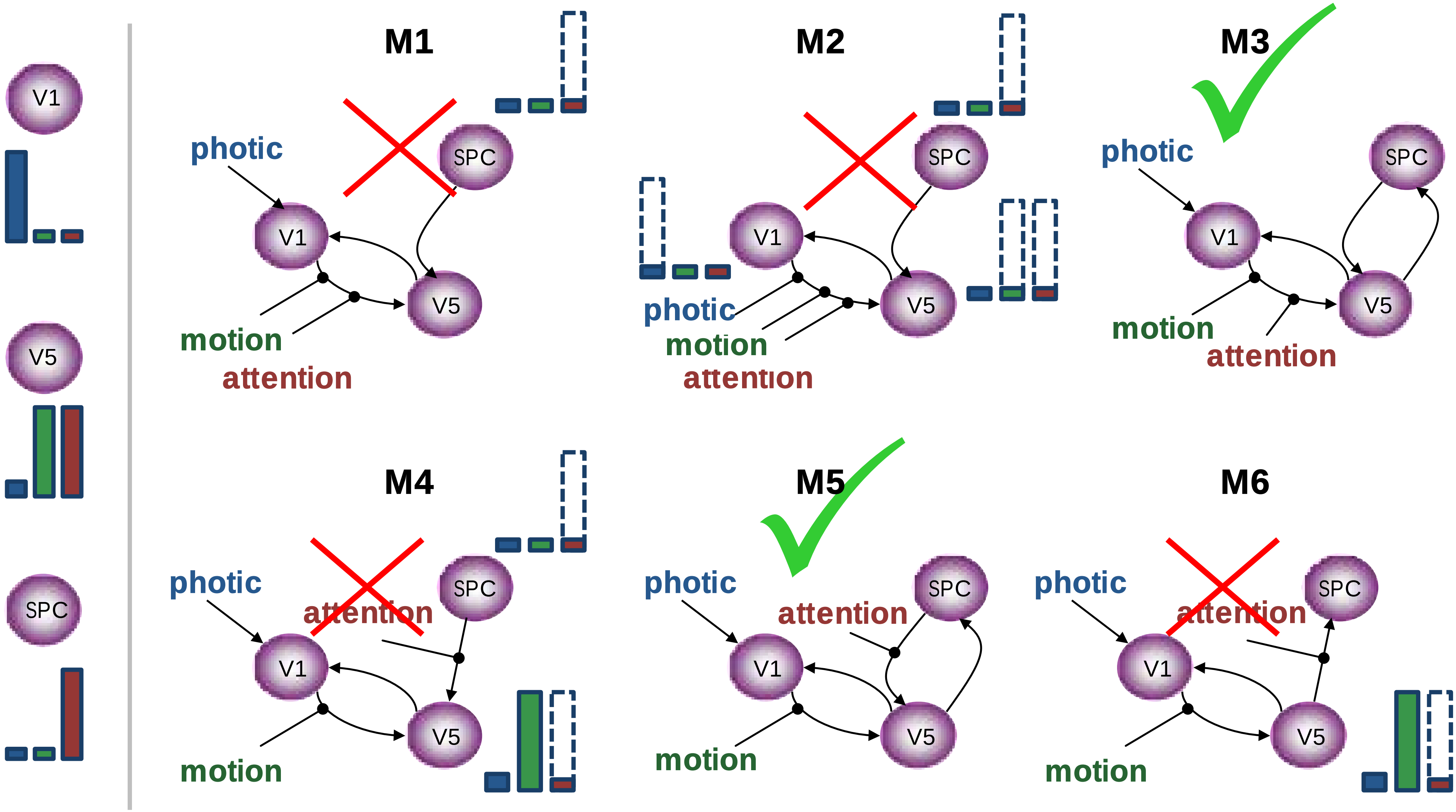
3 – Estimate the model

4 – Repeat steps 2 and 3 for all models in model space

5 – Compare models

6 – OPTIONAL: do parameter inference on optimal model (potentially after model averaging)

Quiz: can this DCM explain the data?



Additional information - references

Literature: To get started...

- 10 Simple Rules for DCM (2010). Stephan et al. *NeuroImage 52*
- Understanding DCM: ten simple rules for the clinician (2012). Kahan & Foltynie. *Neuroimage 83*
- The first DCM paper: Dynamic Causal Modelling (2003). Friston et al. *NeuroImage* 19:1273-1302.
- Physiological validation of DCM for fMRI: Identifying neural drivers with functional MRI: an electrophysiological validation (2008). David et al. *PLoS Biol.* 6 2683–2697
- Hemodynamic model: Comparing hemodynamic models with DCM (2007). Stephan et al. *NeuroImage* 38:387-401
- Nonlinear DCM:Nonlinear Dynamic Causal Models for FMRI (2008). Stephan et al. *NeuroImage* 42:649-662
- Two-state DCM: Dynamic causal modelling for fMRI: A two-state model (2008). Marreiros et al. *NeuroImage* 39:269-278
- Stochastic DCM: Generalised filtering and stochastic DCM for fMRI (2011). Li et al. *NeuroImage* 58:442-457
- Bayesian model comparison: Comparing families of dynamic causal models (2010). Penny et al. *PLoS Comput Biol.* 6(3):e1000709

Literature: Validation studies of DCM

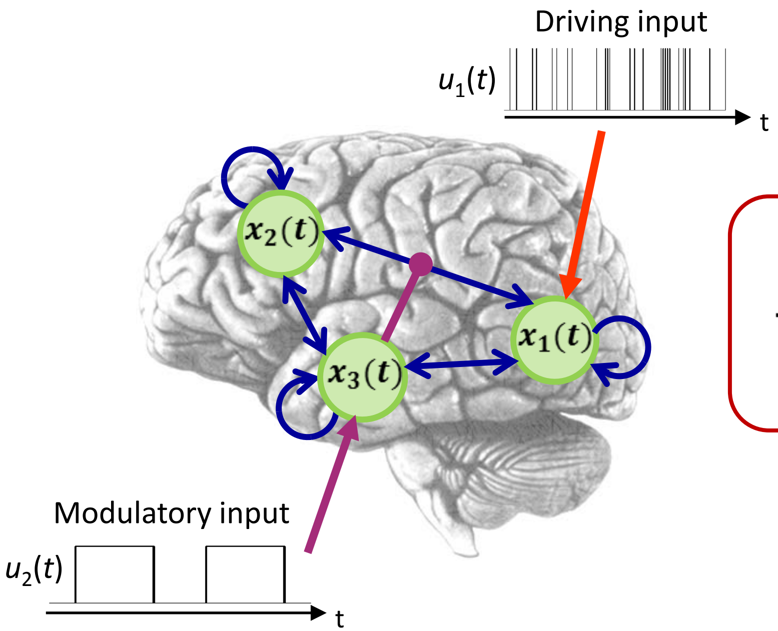
- reliability (reproducibilty)
  - parameter estimates are highly reliable across sessions (Schuyler et al. 2010)
  - model selection results are highly reliable across sessions (Rowe et al. 2010)
- face validity
  - simulations and empirical studies (Stephan et al. 2007, 2008)
- construct validity
  - comparison with SEM (Penny et al. 2004)
  - comparison with large-scale spiking neuron models (Lee et al. 2006)
- predictive validity:
  - infer correct site of seizure origin (David et al. 2008)
  - infer primary recipient of vagal nerve stimulation (Reyt et al. 2010)
  - infer synaptic changes as predicted from microdialysis (Moran et al. 2008)
  - infer conditioning-induced plasticity in amygdala (Moran et al. 2009)
  - track anaesthesia levels (Moran et al. 2011)
  - predict sensory stimulation (Brodersen et al. 2010)
  - infer DA induced changes in AMPA/NMDA ratio from MEG (Moran et al. 2011)
  - predict presence/absence of remote lesion (Brodersen et al. 2011)

Literature: Advanced DCM tools

- Nonlinear DCM for fMRI: *Could connectivity changes be mediated by another region? (Stephan et al. 2008, Neuroimage)*
- Embedding computational models in DCMs: *DCM can be used to make inferences on parametric designs like SPM (den Ouden et al. 2010, J Neurosci.)*
- DCM as a summary statistic: clustering and classification: *Classify patients, or even find new sub-categories (Brodersen et al. 2011, Neuroimage)*
- Integrating tractography and DCM: *Prior variance is a good way to embed other forms of information, test validity (Stephan et al. 2009, NeuroImage)*
- Stochastic / spectral DCM: *Model resting state studies / background fluctuations (Li et al. 2011, Neuroimage; Daunizeau et al. 2009, Physica D; Friston et al. 2014, Neuroimage)*
- DCM for Layered fMRI: *Model high resolution fMRI data of cortical layers (Heinzle et al. 2014, Neuroimage)*
- MPDCM toolbox: *Use Markov chain Monte Carlo methods to invert DCMs (Aponte et al. 2016, J Neurosci Methods)*
- Hierarchical Generative Embedding for DCM: *Use a hierarchical Bayesian model for unsupervised clustering of DCM (Raman et al. 2016, J Neurosci Methods)*
- Empirical Bayes for DCM: *Use empirical Bayes for DCM group studies (Friston et al. 2016, Neuroimage)*

Additional information - equations

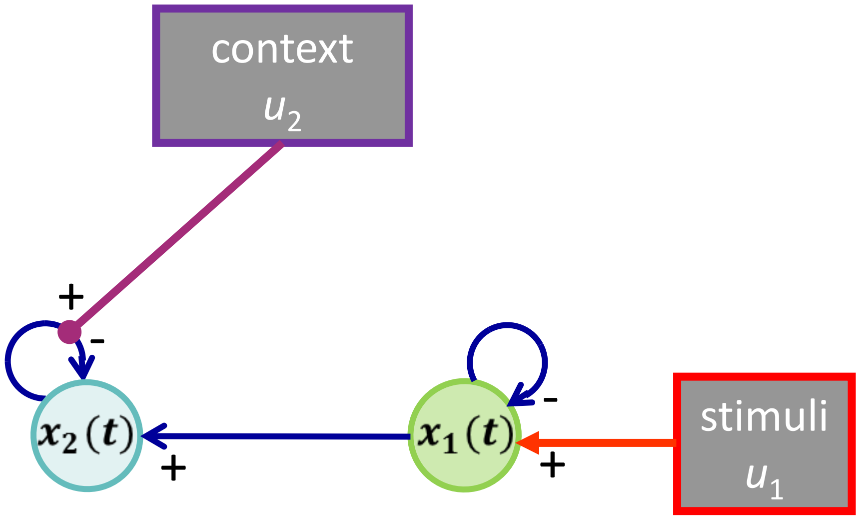
The neural equations – non-linear model

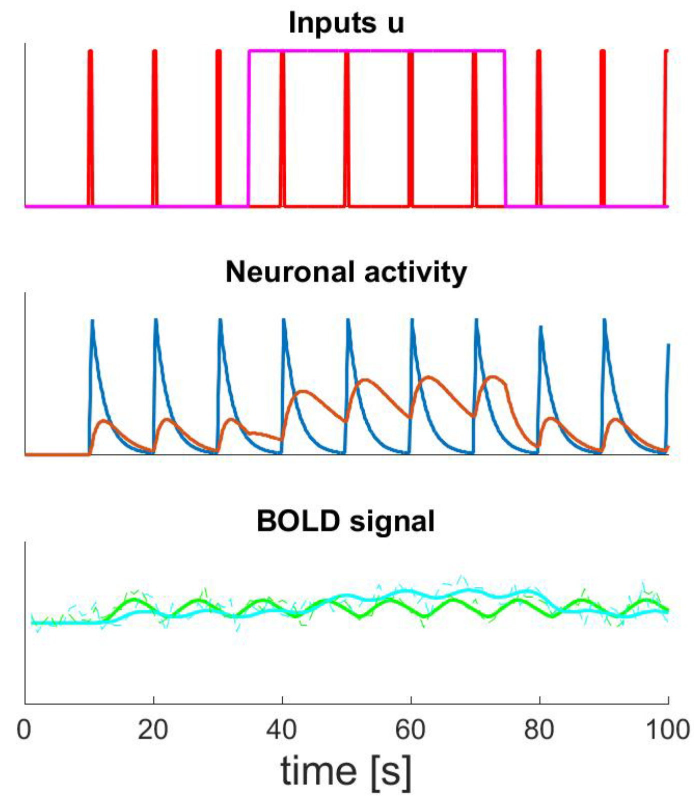


$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} x_j D^{(j)} \right) x + Cu$$

Parameters A, B, C and D define connectivity!

Example traces 4: Modulation of self-connection



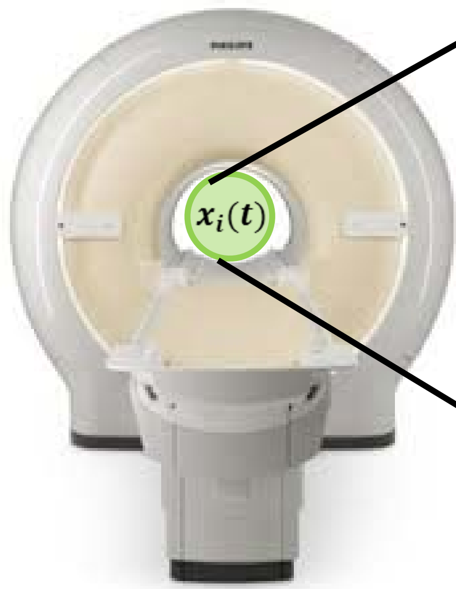


$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$

$$\dot{x}_2 = a_{22}x_2 + a_{21}x_1 + u_2 b_{22}^{(2)} x_2$$

$$\boldsymbol{x} = A\boldsymbol{x} + C\boldsymbol{u} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ 0 & b_{22}^{(2)} \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Hemodynamic model and BOLD signal equation



Local hemodynamic state equation

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

vasodilatory signal and flow Induction (rCBF)

f

Balloon model

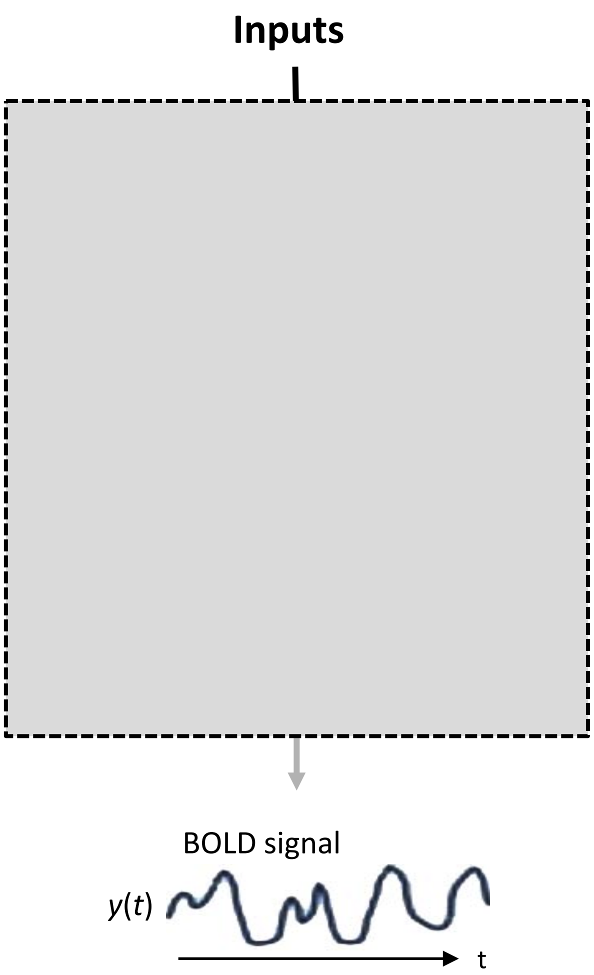
$$\tau \dot{v} = f - v^{1/\alpha}$$
$$\tau \dot{q} = f E(f, E_0)/E_0 - v^{1/\alpha} q/v$$

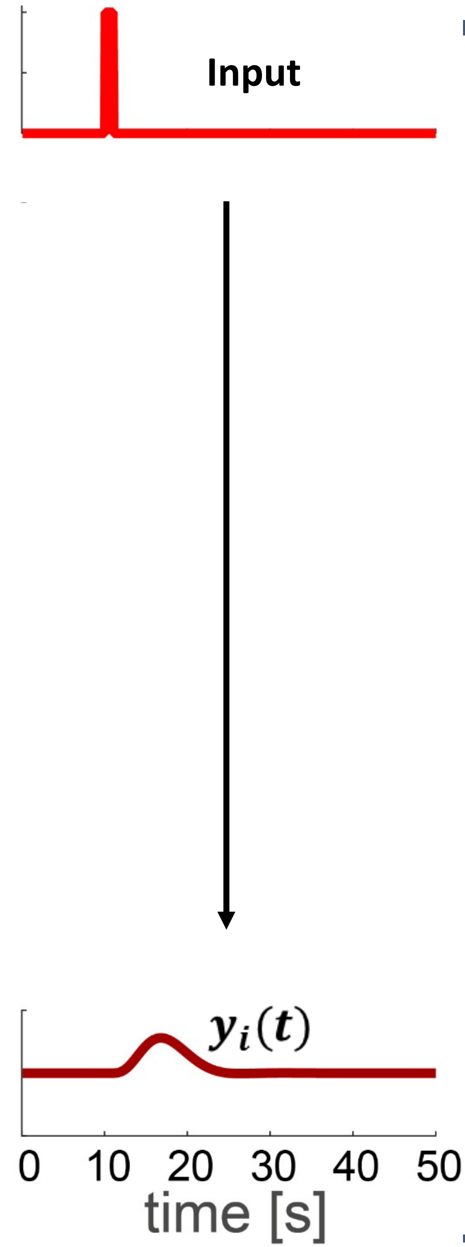
Changes in volume (v) and dHb (q)

BOLD signal change equation

$$y = \frac{\Delta S}{S_0} \approx V_0 \left[k_1(1 - q) + k_2\left(1 - \frac{q}{v}\right) + k_3(1 - v) \right]$$

Summary – the full model





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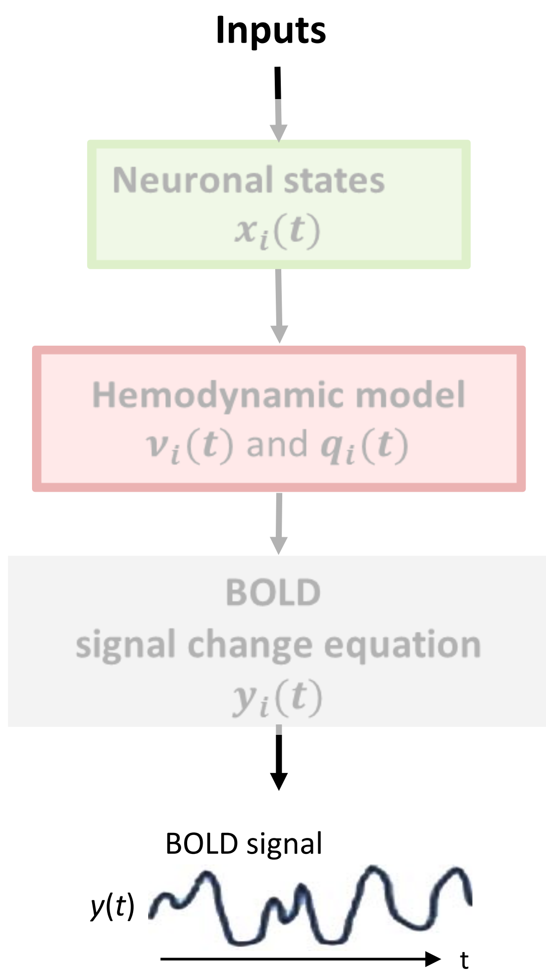

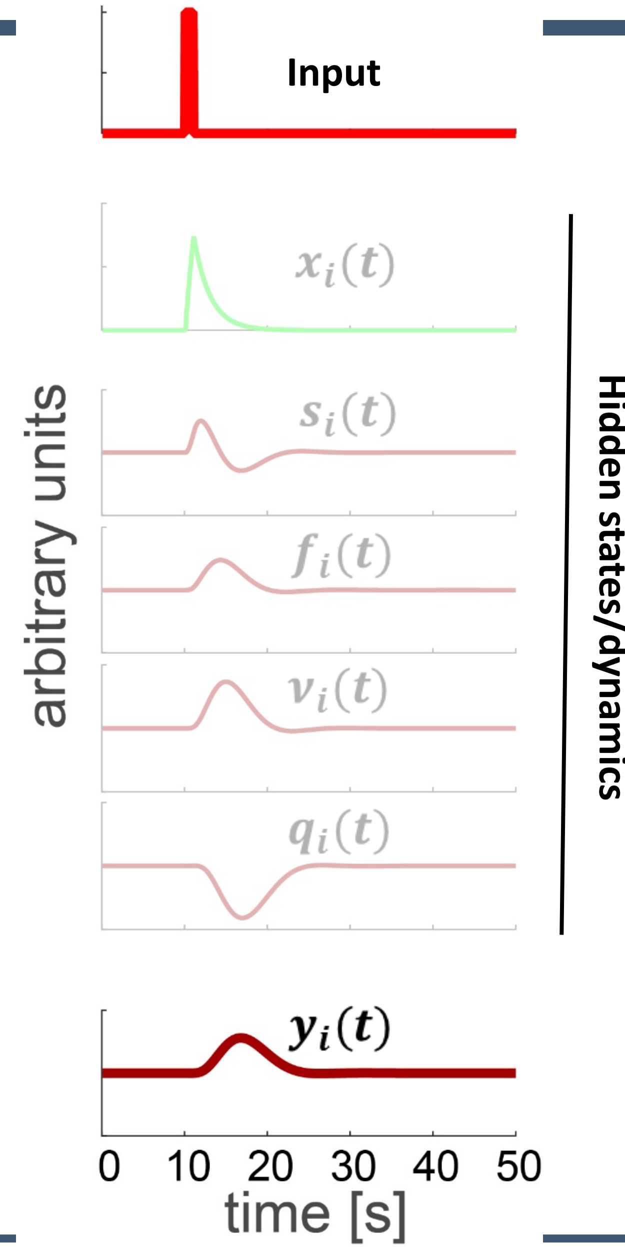

Summary – parameters of interest