LIÈGE université
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CRC In vivo Imaging

Functional & effective connectivity in fMRI

SPM Course
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fnrs
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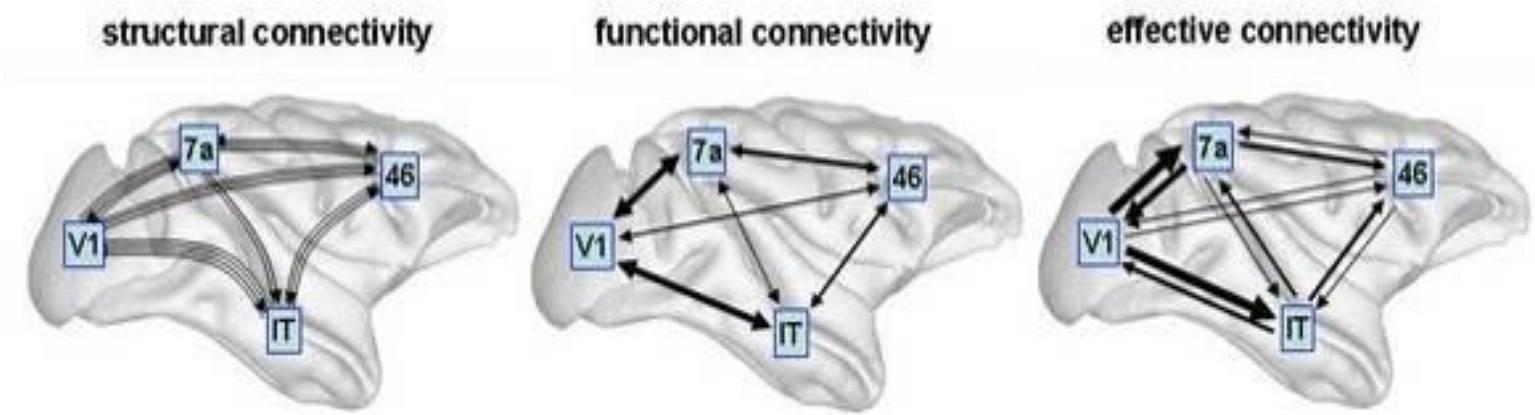
Program

- Functional connectivity
  - Seed-based approaches,
    - Simple correlation
    - Psycho-Physiological Interaction (PPI)
  - Component analysis (ICA)
- Effective connectivity
  - Dynamic Causal Modelling
    - Model definition
    - Group analysis



- 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

Sporns 2007, *Scholarpedia*

Functional connectivity

Definition:

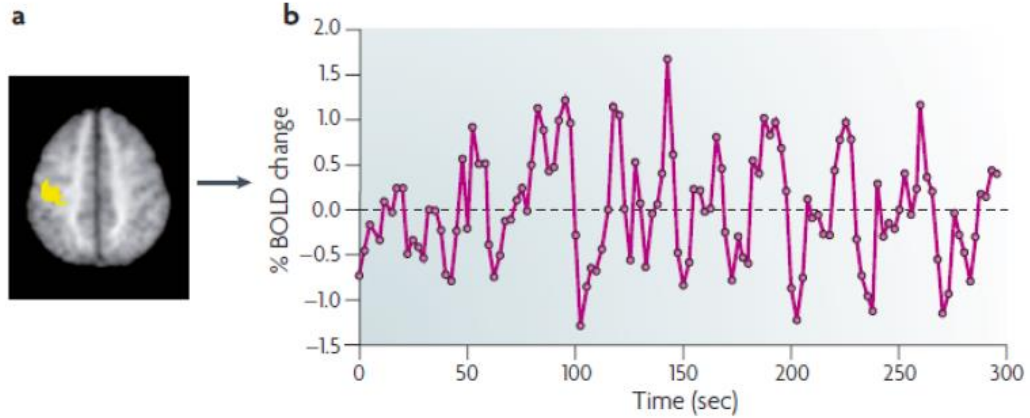
statistical *dependencies between regional time series*

- Seed voxel (fMRI) correlation analysis
- Coherence analysis
- Eigen-decomposition (PCA, SVD)
- Independent component analysis (ICA)

Seed-based for (resting-)fMRI

Pick one (few) region(s) of interest:

- Extract BOLD signal time-series in ROI



Fox & Raichle, 2007, *Nature Reviews, Neuroscience*

- Enter time series as regressor in a GLM & find correlation map

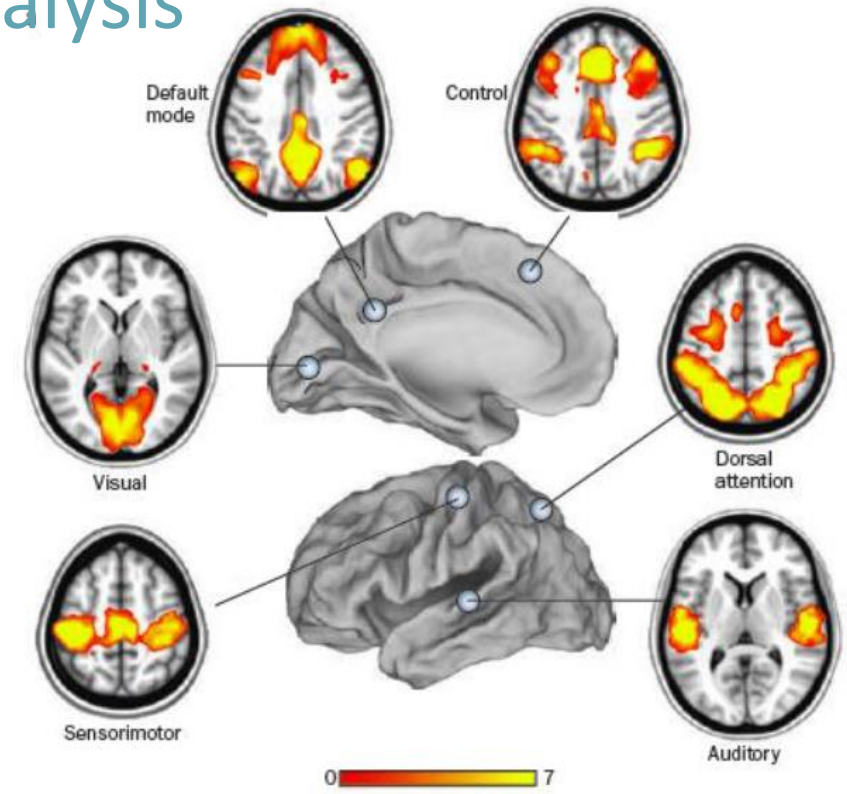
Seed-based resting-fMRI analysis

Multiple/different region of interest

➔ multiple/different correlation maps

Hypothesis driven!

Need to account for confounding signal: drift, blood pulsation, breathing, global signal,…



Zhang & Raichle, 2010, *Nature Reviews, Neurology*

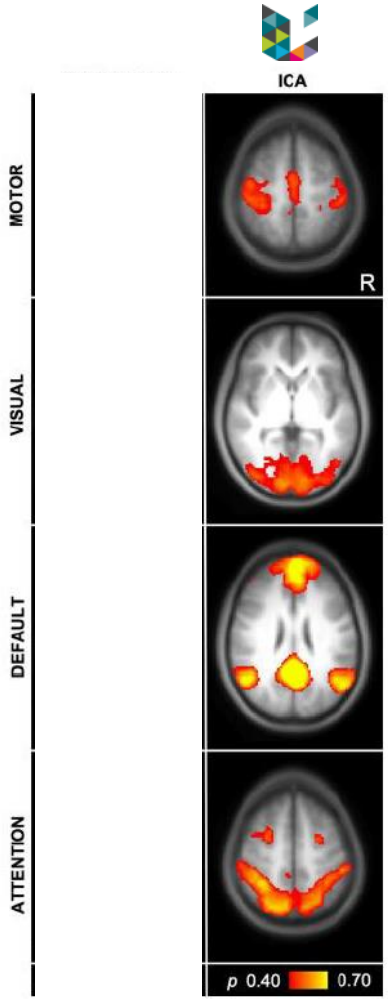
Model-free resting-fMRI analysis

Decompose original fMRI time series into linear combination of

- orthogonal basis vectors, PCA
- independent components, ICA

i.e. data driven approach.

➔ A few basis/component maps per subject



Van Dijk, 2010, J. Neurophysiol

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Psycho-Physiological Interaction

- Bilinear model of the change in coupling between regions A and B, depending on the psychological context C:

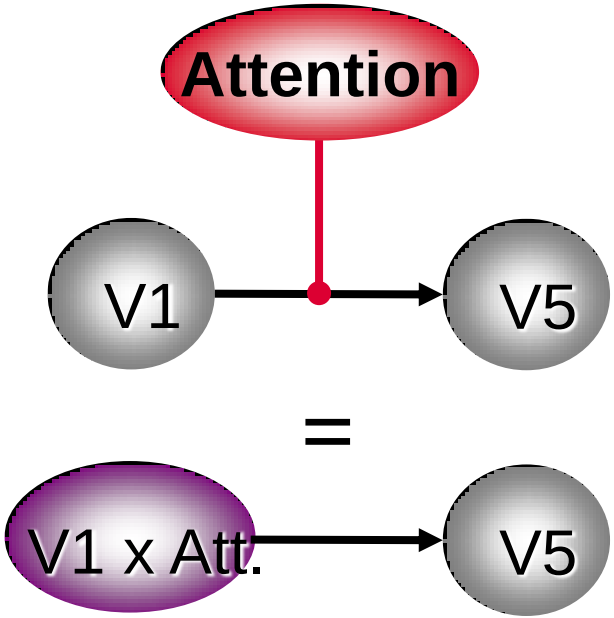
  A x C → B

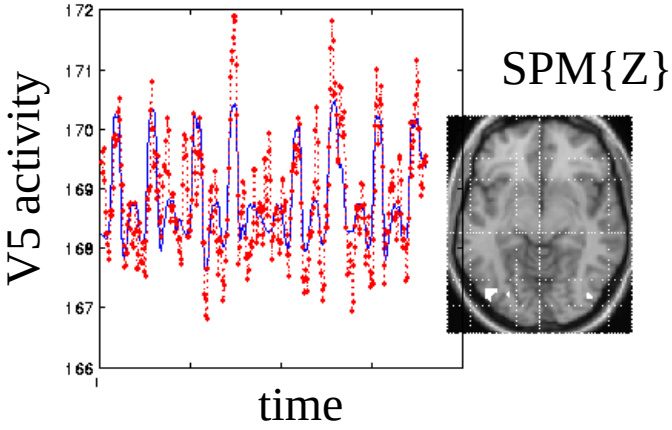
- C can be a
  - contrast of two conditions (C_1=1, C_2= -1, 0 else) or
  - a parametric variable.

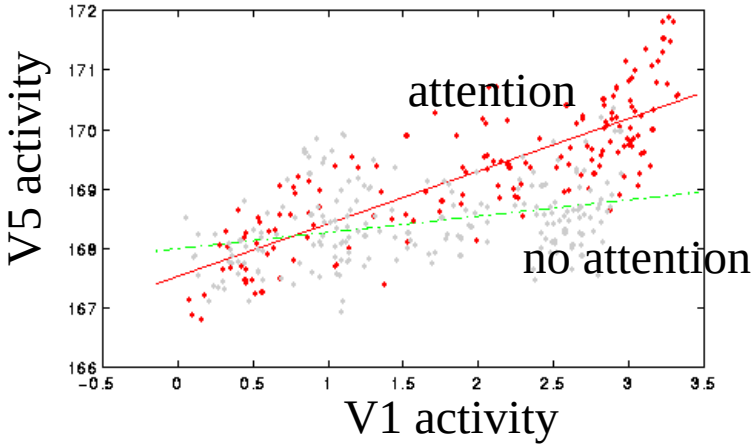
- A PPI corresponds to a context-dependent difference in the slope of the regression between two regional time series.

PPI example

Attentional modulation of V1→V5

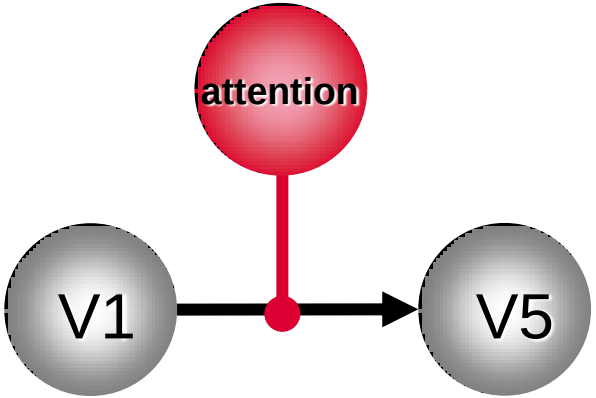






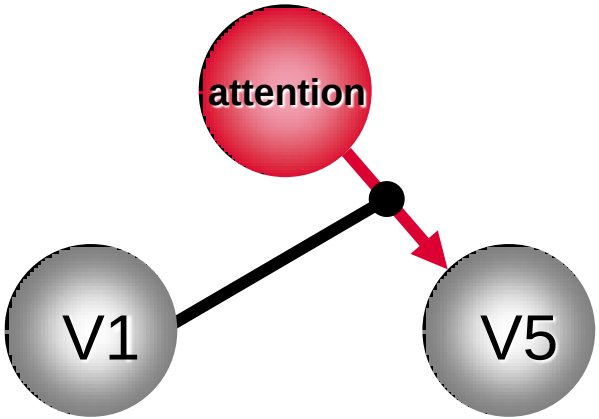
PPI statistical model & interpretation

$$y = [V_1 \times C] \cdot \beta_1 + V_1 \cdot \beta_2 + C \cdot \beta_3 + G \cdot \beta_G + \varepsilon$$



Modulation of V1→V5 by attention

Two possible interpretations!



Modulation of the impact of attention on V5 by V1.

PPI interpretation & practicalities

PPI analysis = mean of identifying regions whose responses can be explained in terms of an interaction $(C * x_n)$ between :

- Activity in a specified area (x_n, physiological factor)
- Some experimental effect (C, psychological factor)

Practicality:

- Measured signal x = neuronal activity x_n convolved with hrf, $conv(x_n,hrf) = x$
- No mixing of BOLD signal and psychological factor C

$$Conv\ (C,hrf) * x \neq conv\ ((C * x_n),hrf)$$

- `spm_peb_ppi.m` deals with this deconvolution & convolution…

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Effective connectivity

Definition:

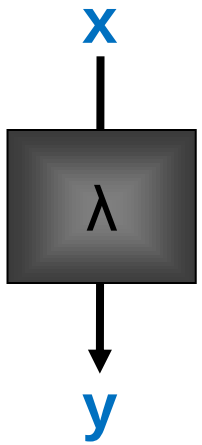
***causal** (directed) influences between neurons or neuronal populations*

- Structural Equation Modelling (SEM)
  McIntosh et al. 1991, 1994; Büchel & Friston 1997; Bullmore et al. 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

Typically relying on some *model* of the activity!

DCM principles

- DCM allows to model a cognitive system at the neuronal level (which is not directly accessible for fMRI).
- The modelled neuronal dynamics (x) 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 such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.

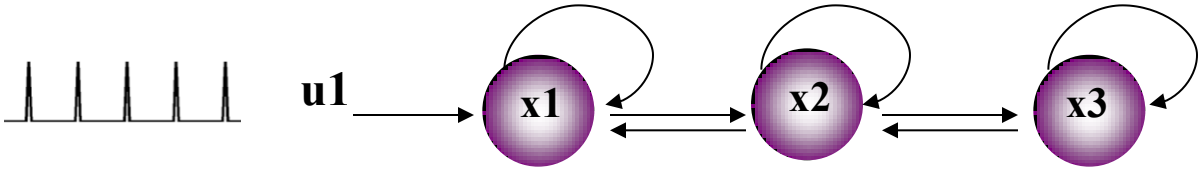


DCM model, neuronal level

- Brain ≈ non-linear, deterministic system
- State changes in time entirely depend on:
  - the current state ($\boldsymbol{x}$)
  - external inputs into the system ($\boldsymbol{u}$), i.e. perturbation
  - intrinsic system structure & properties ($\boldsymbol{\theta_n}$)

$$\dot{x} = F(z, u, q^n) \Rightarrow \begin{bmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \begin{bmatrix} f_1(x_1 \ldots x_n, u, q_n) \\ \vdots \\ f_n(x_1 \ldots x_n, u, q_n) \end{bmatrix}$$

Linear DCM



Neuronal State Equation

$$\dot{x} = Ax + Cu$$

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

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

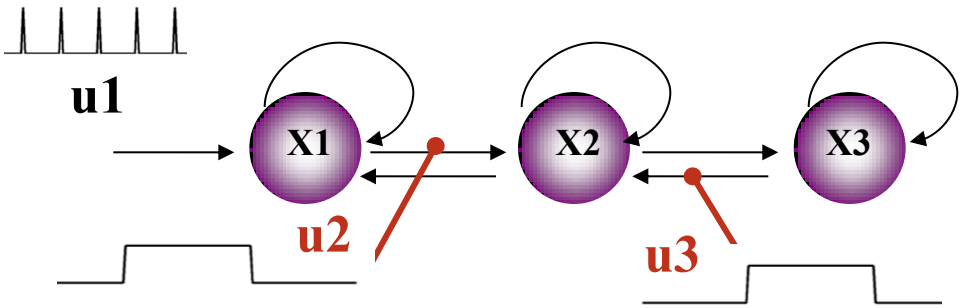
$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{23}x_3$$

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

state changes | effective connectivity | system state | input parameters | external inputs

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

Bilinear DCM



Neuronal State Equation

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

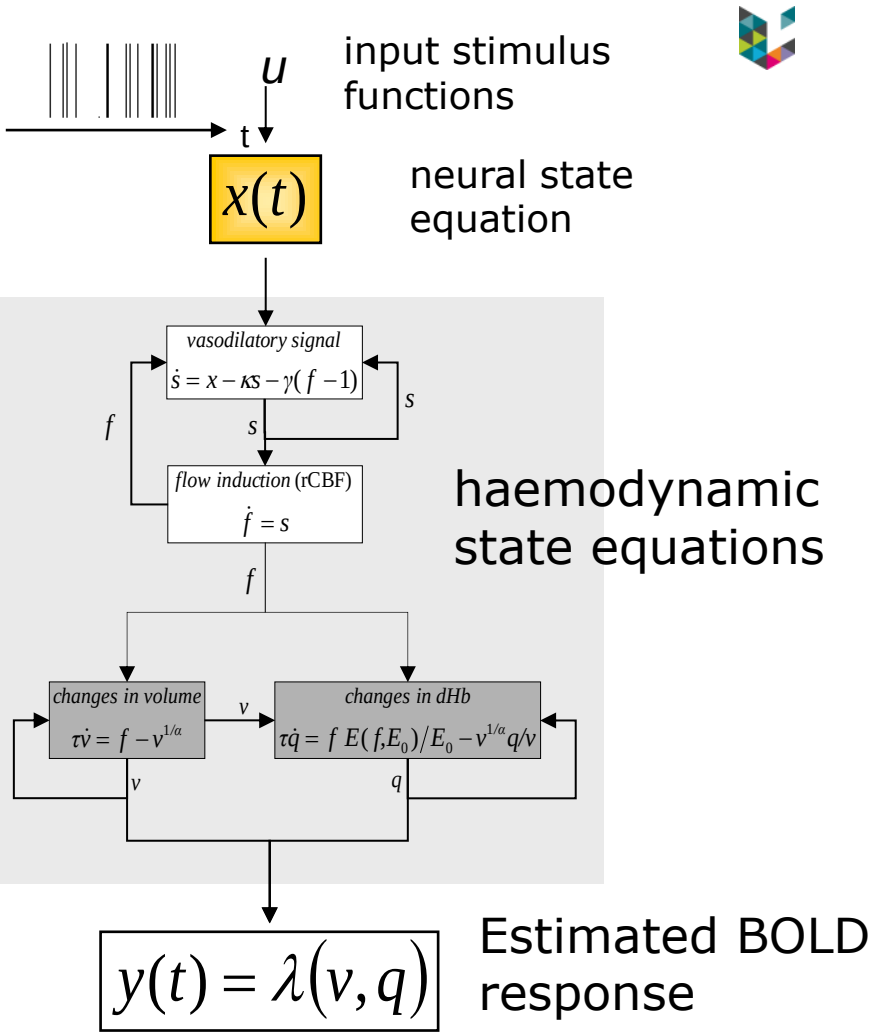
$$q = \{A, B, C\}$$

state changes | fixed effective connectivity | modulatory effective connectivity | system state | input parameters | external inputs

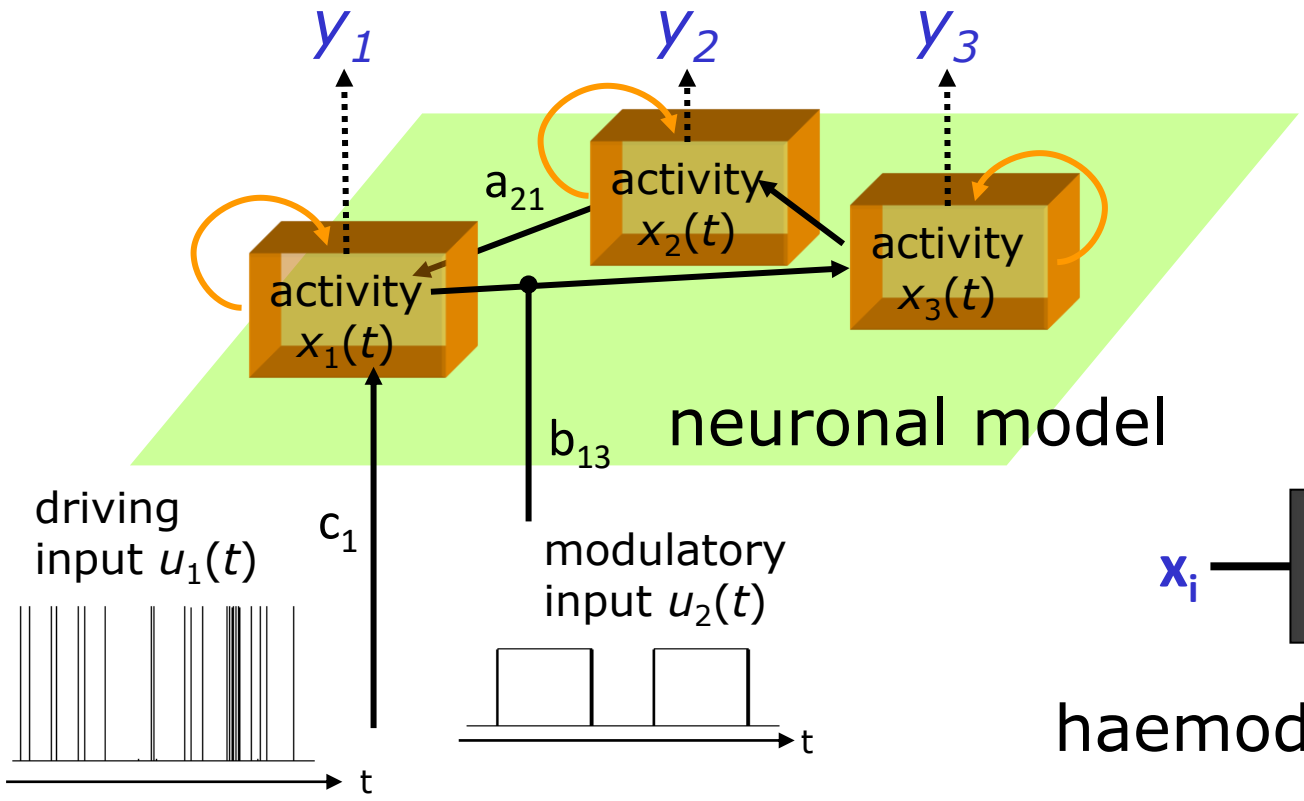
$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 & 0 \\ b_{21}^{(2)} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + u_3 \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & b_{23}^{(3)} \\ 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

Haemodynamic output function

- Haemodynamic parameters:
  - empirically determined *a priori* distributions
  - important for model fitting, but of no interest for statistical inference
- Computed separately for each area
  → ROI specific hrf



DCM neuronal & haemodynamic models



haemodynamic model

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Generative models & model selection

- any DCM = a particular generative model of how the data (may) have been caused
- generative modelling: comparing competing hypotheses about the mechanisms underlying observed data

  → a priori definition of hypothesis set (model space) is crucial

  → determine the most plausible hypothesis (model), given the data
- model selection ≠ model validation!

  → model validation requires external criteria (external to the measured data)

(Log) model evidence

- Model evidence

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

- Log model evidence = balance between fit and complexity

$$\log p(y \mid m) = accuracy(m) - complexity(m)$$
$$= \log p(y \mid \theta, m) - complexity(m)$$

- F = “negative free energy approximation”
  = lower bound on log model evidence

https://en.wikipedia.org/wiki/Marginal_likelihood

Bayesian model selection (BMS)

- comparing two models

  = comparing their (log) evidences (or rather F)

- intuitive interpretation of model comparisons with ***Bayes factors***:

$$B_{12} = \frac{p(y \mid m_1)}{p(y \mid m_2)} \quad \Rightarrow \quad \log B_{12} = \log p(y \mid m_1) - \log p(y \mid m_2)$$

- Interpretation

B_{12}	$Log\ B_{12}$	$p(m_1 \mid y)$	Evidence
1 to 3	0 to 1	50-75%	weak
3 to 20	1 to 3	75-95%	positive
20 to 150	3 to 5	95-99%	strong
≥ 150	≥ 5	≥ 99%	very strong

Fixed-effect BMS

- Assumptions: All subjects use the **same** model!

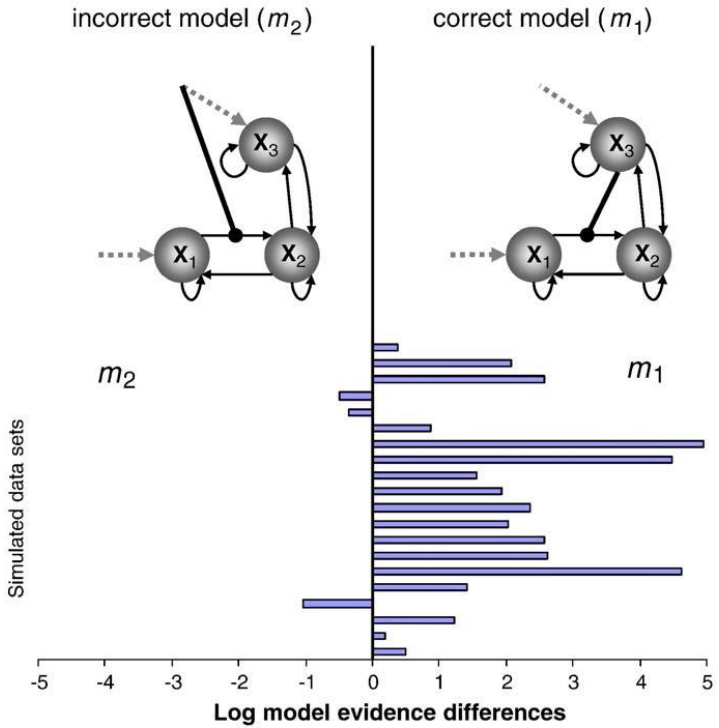
  $\rightarrow$ Model variability due to noise in data

- Group Bayes factor (GBF) for 1...*K* subjects:

$$GBF_{ij} = \prod_k BF_{ij}^{(k)} \quad \Rightarrow \quad \log GBF_{ij} = \sum_k \log BF_{ij}^{(k)}$$

$$\text{with} \quad BF_{ij} = \frac{p(y \mid m_i)}{p(y \mid m_j)} \quad \Rightarrow \quad \log BF_{ij} = \log p(y \mid m_i) - \log p(y \mid m_j)$$

Fixed-effect BMS



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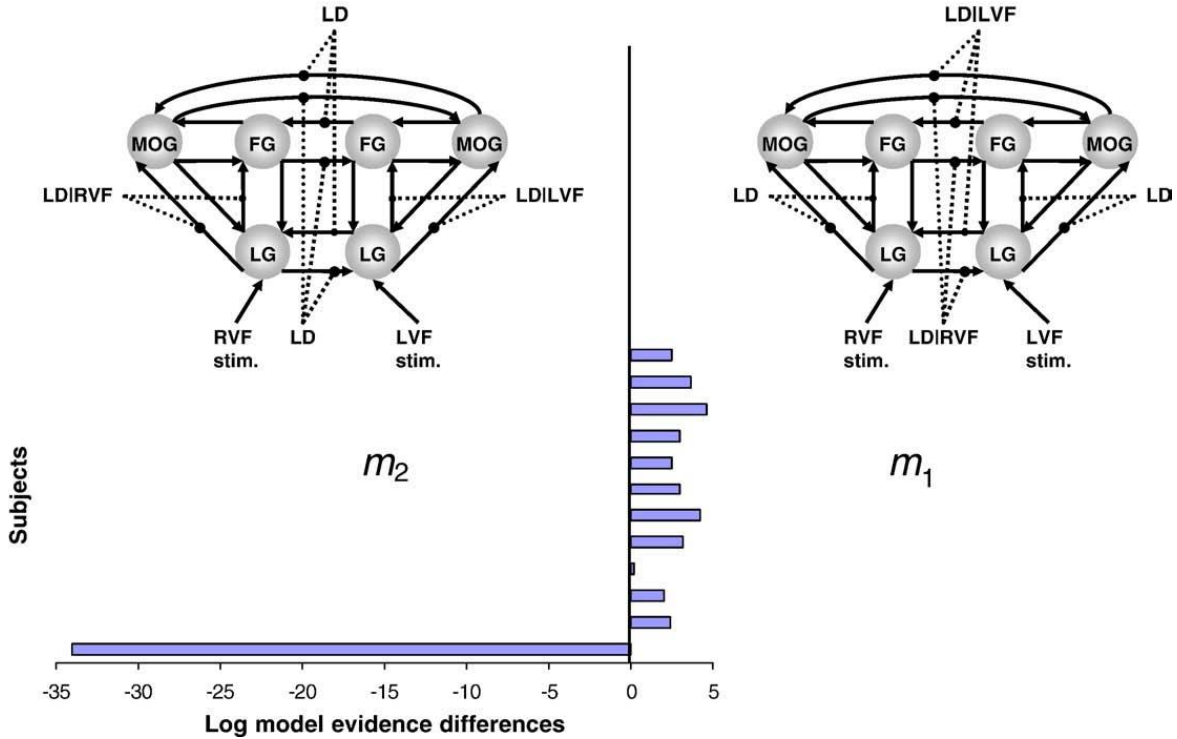
<u>Problems:</u>

blind with regard to group heterogeneity & sensitive to outliers

Fixed-effect BMS

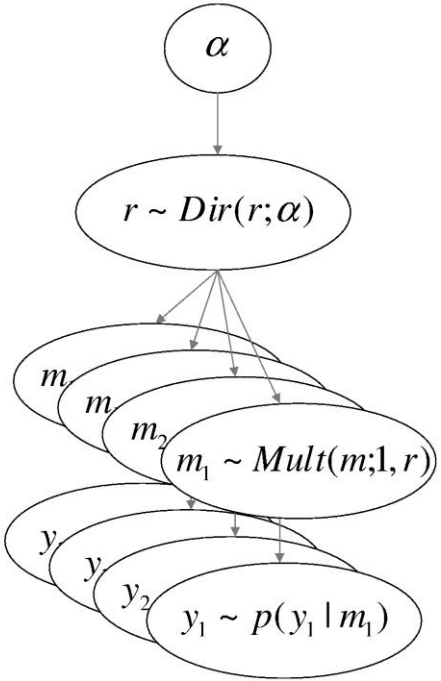


Random-effect BMS

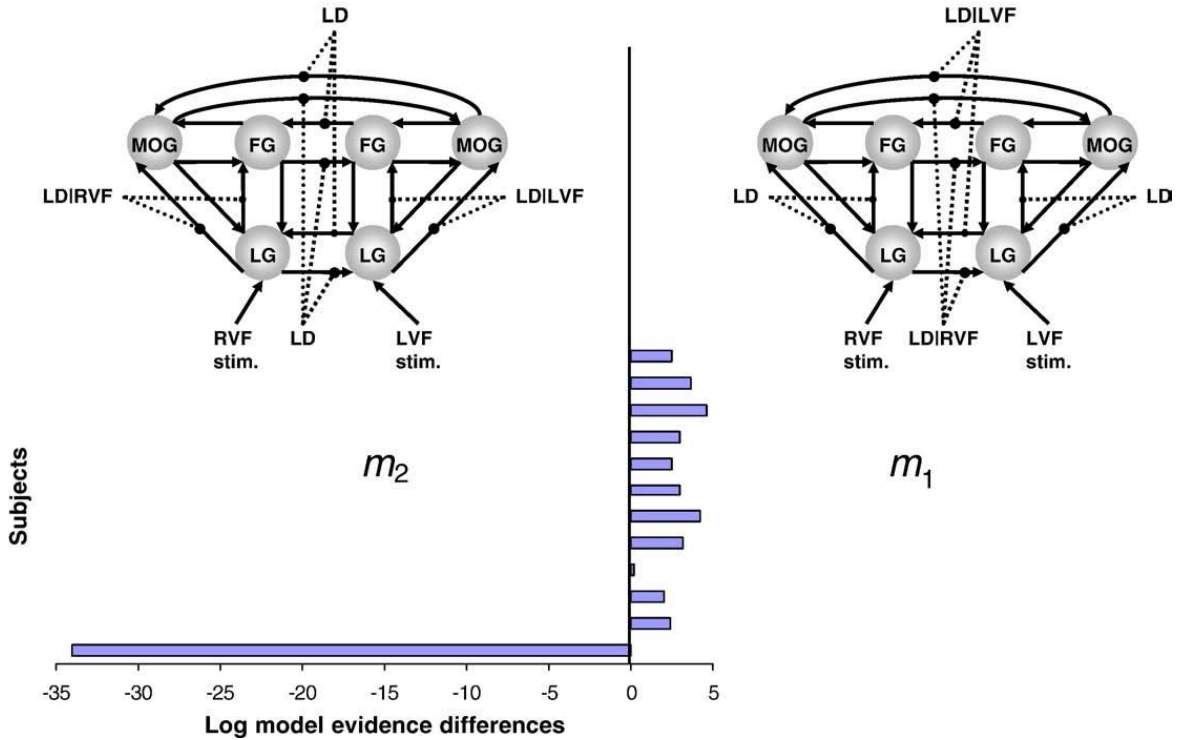
- Assumptions: Each subject may use a **different** model!

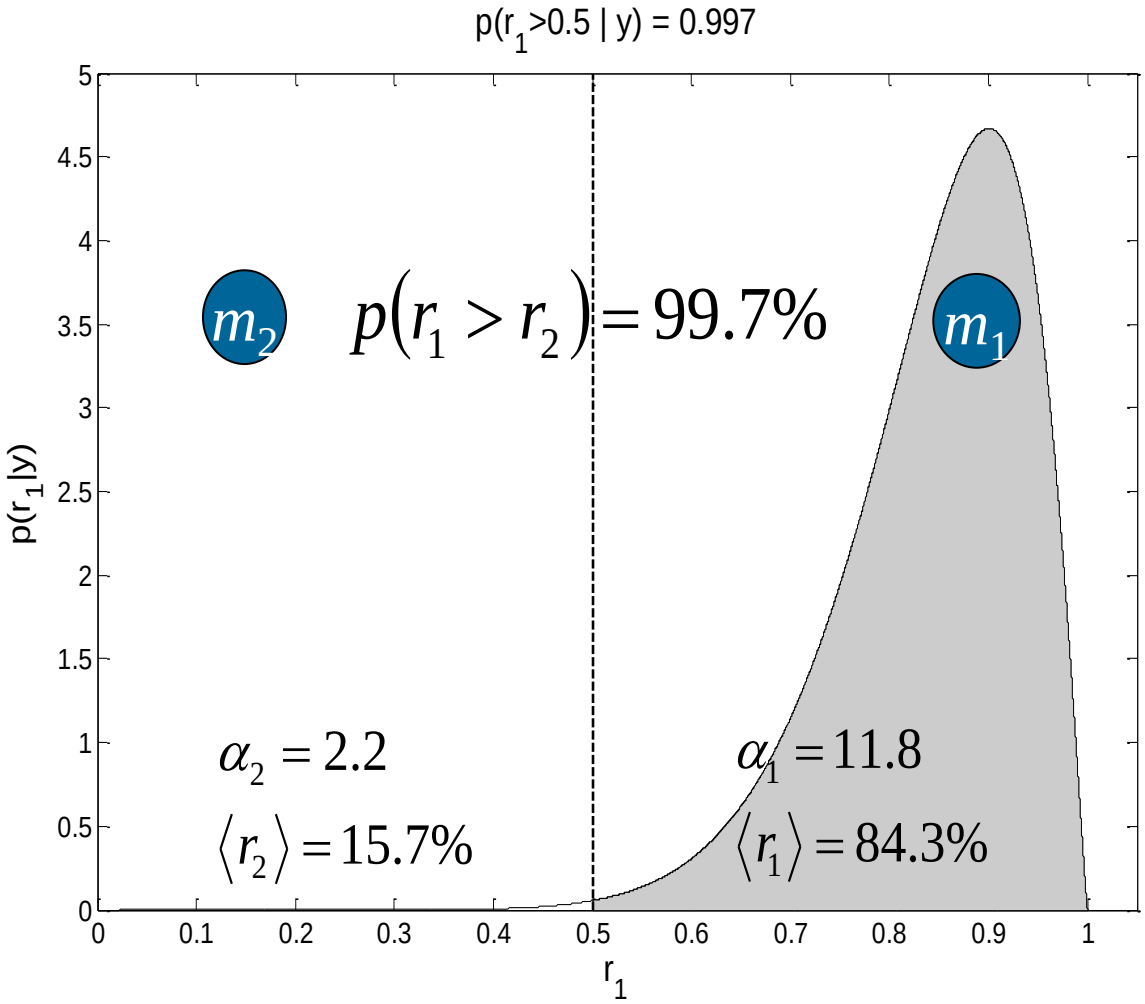
  $\rightarrow$ Distribution of model

- Dirichlet parameters α
  = “occurrences” of models in the population
- Dirichlet distribution of model probabilities r
- Multinomial distribution of model labels m
- Model inversion based on measured data y



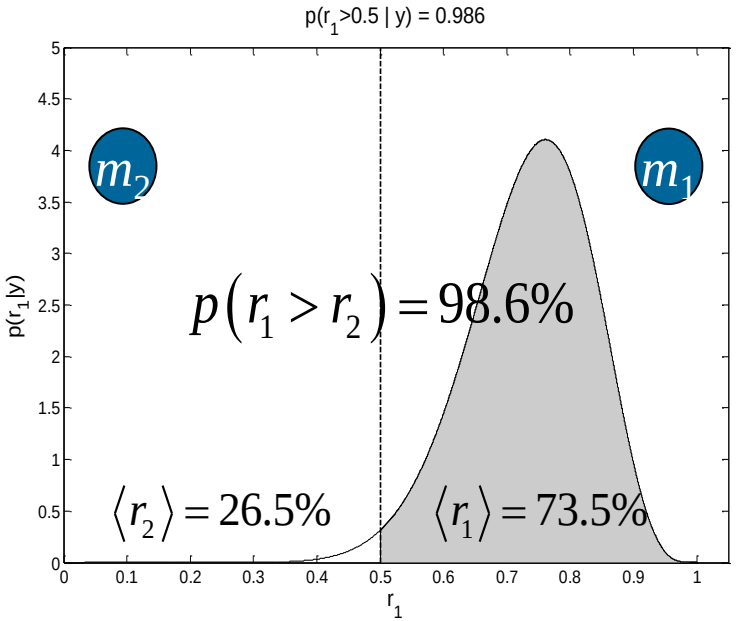
Random-effect BMS

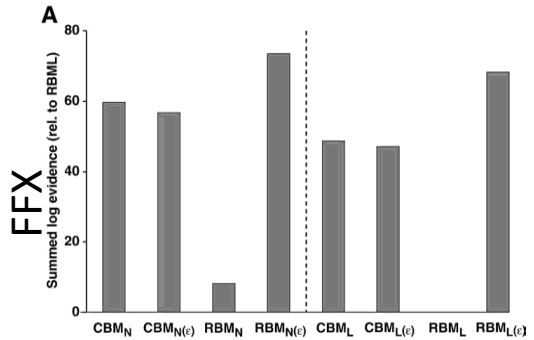


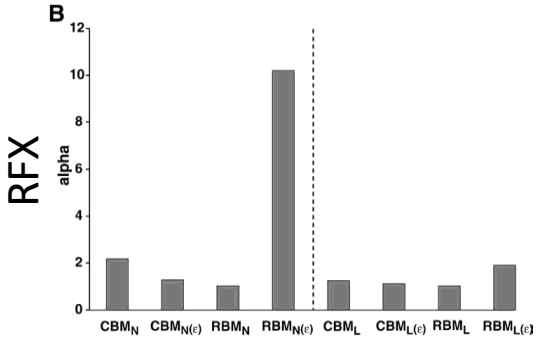

p(r1>0.5 | y) = 0.997
m2
p(r1 > r2) = 99.7%
m1
α2 = 2.2
⟨r2⟩ = 15.7%
α1 = 11.8
⟨r1⟩ = 84.3%
p(r1|y)
r1
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
0.1
0.2
0.3
0.4
0.6
0.7
0.8
0.9

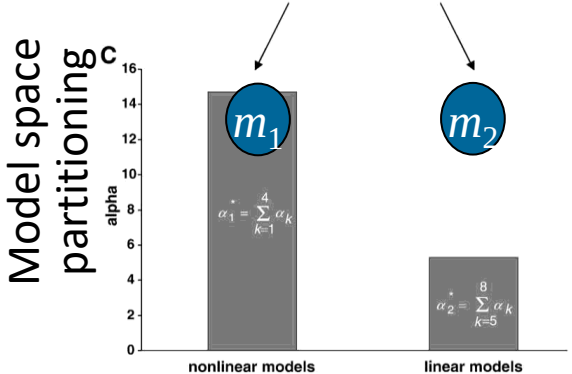
Model space partitioning

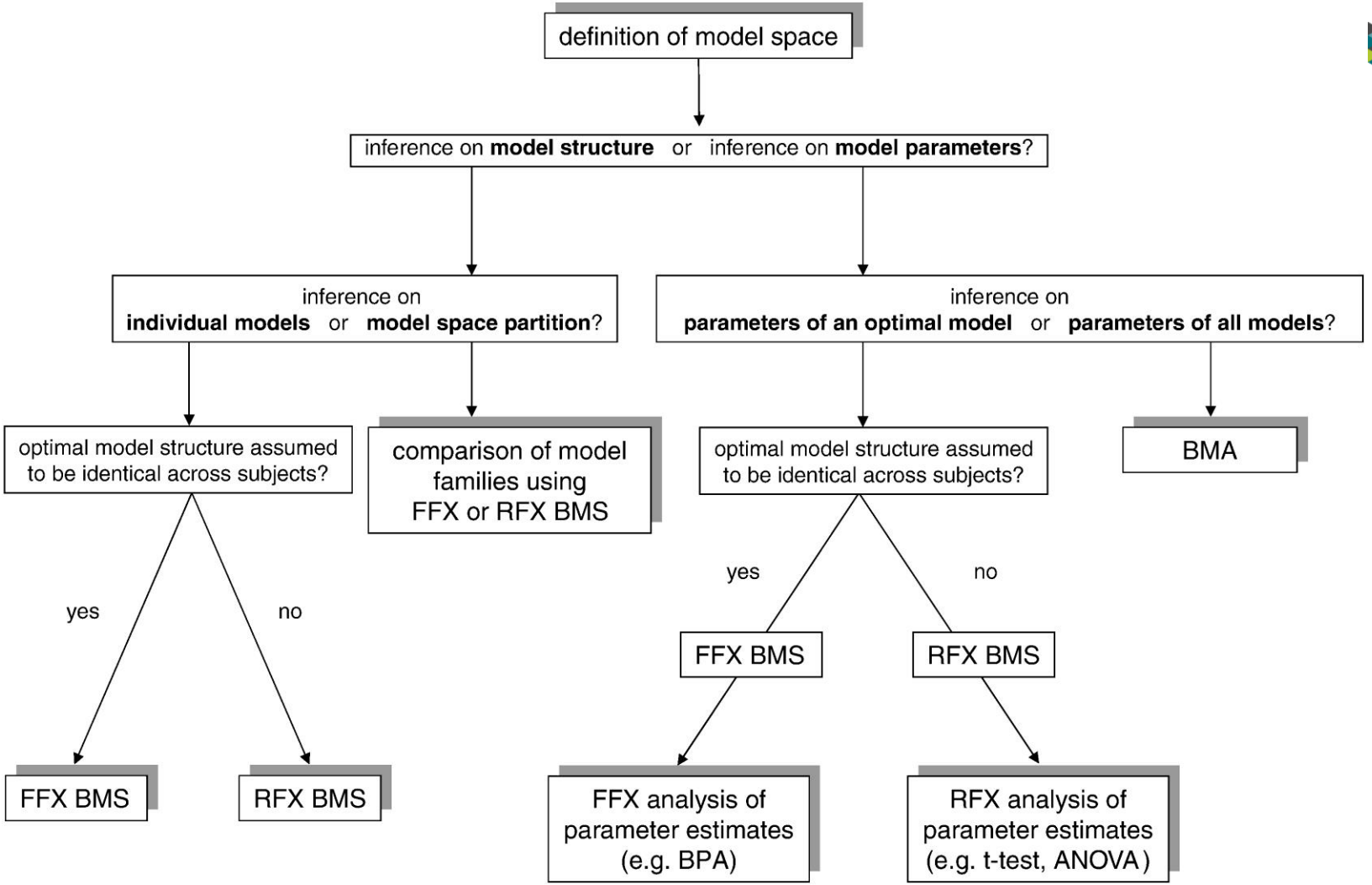
Comparing model **families**










definition of model space
inference on **model structure** or inference on **model parameters**?
inference on **individual models** or **model space partition**?
inference on **parameters of an optimal model** or **parameters of all models**?
optimal model structure assumed to be identical across subjects?
comparison of model families using FFX or RFX BMS
optimal model structure assumed to be identical across subjects?
BMA
yes
no
yes
no
FFX BMS
RFX BMS
FFX BMS
RFX BMS
FFX analysis of parameter estimates (e.g. BPA)
RFX analysis of parameter estimates (e.g. t-test, ANOVA)

Last but not least:

"Essentially, all models are wrong, but some are useful."

Box, George E. P.; Norman R. Draper (1987)

References

- Connectivity papers (44 till 2013!) @FIL
  https://www.fil.ion.ucl.ac.uk/spm/doc/biblio/Keyword/CONNECTIVITY.html
- DCM papers (49 till 2016!) @FIL
  https://www.fil.ion.ucl.ac.uk/spm/doc/biblio/Keyword/DCM.html
- DCM example scripts & tutorial
  https://github.com/pzeidman/dcm-peb-example

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Thank you for your attention!

Slides from Klaas Stephan, Peter Zeidman, et al.