DCM for fMRI – Advanced topics

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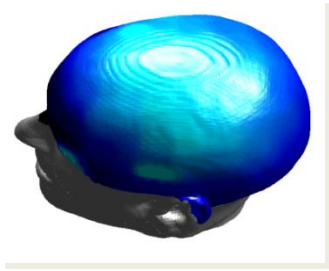
Overview

- DCM: basic concepts
- Evolution of DCM for fMRI
- Bayesian model selection (BMS)
- Translational Neuromodeling

Dynamic causal modeling (DCM)

EEG, MEG

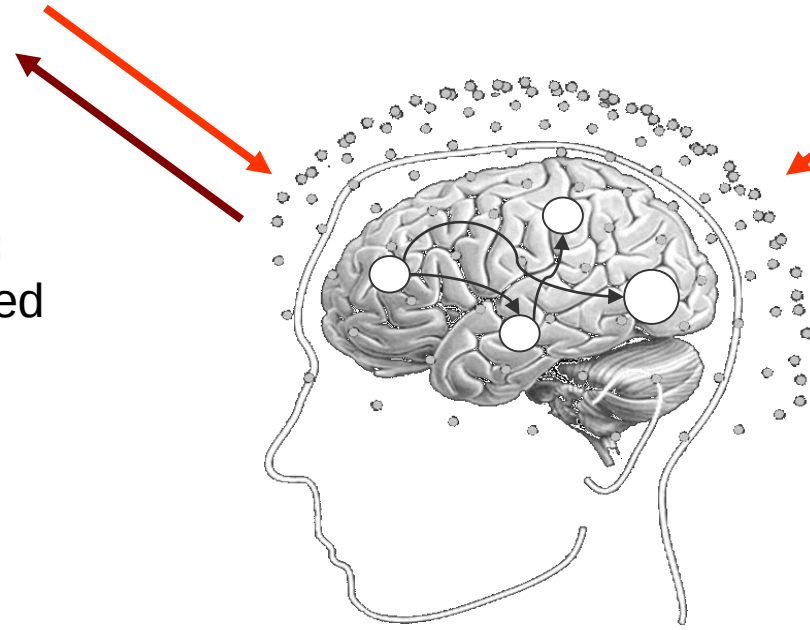


dwMRI

fMRI

structural priors

structural priors



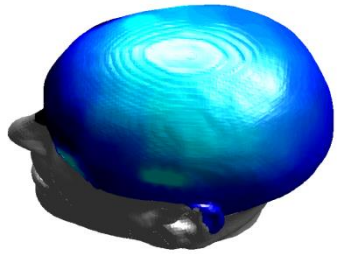
Forward model:
Predicting measured activity

$$y = g(x,\theta) + \varepsilon$$

Model inversion:
Estimating neuronal mechanisms

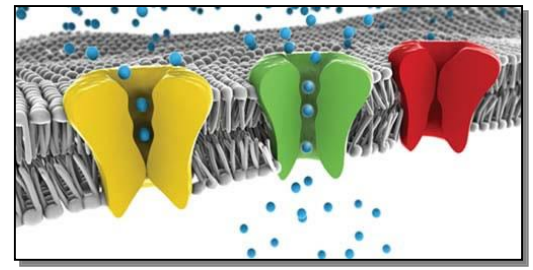
$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$

Generative model

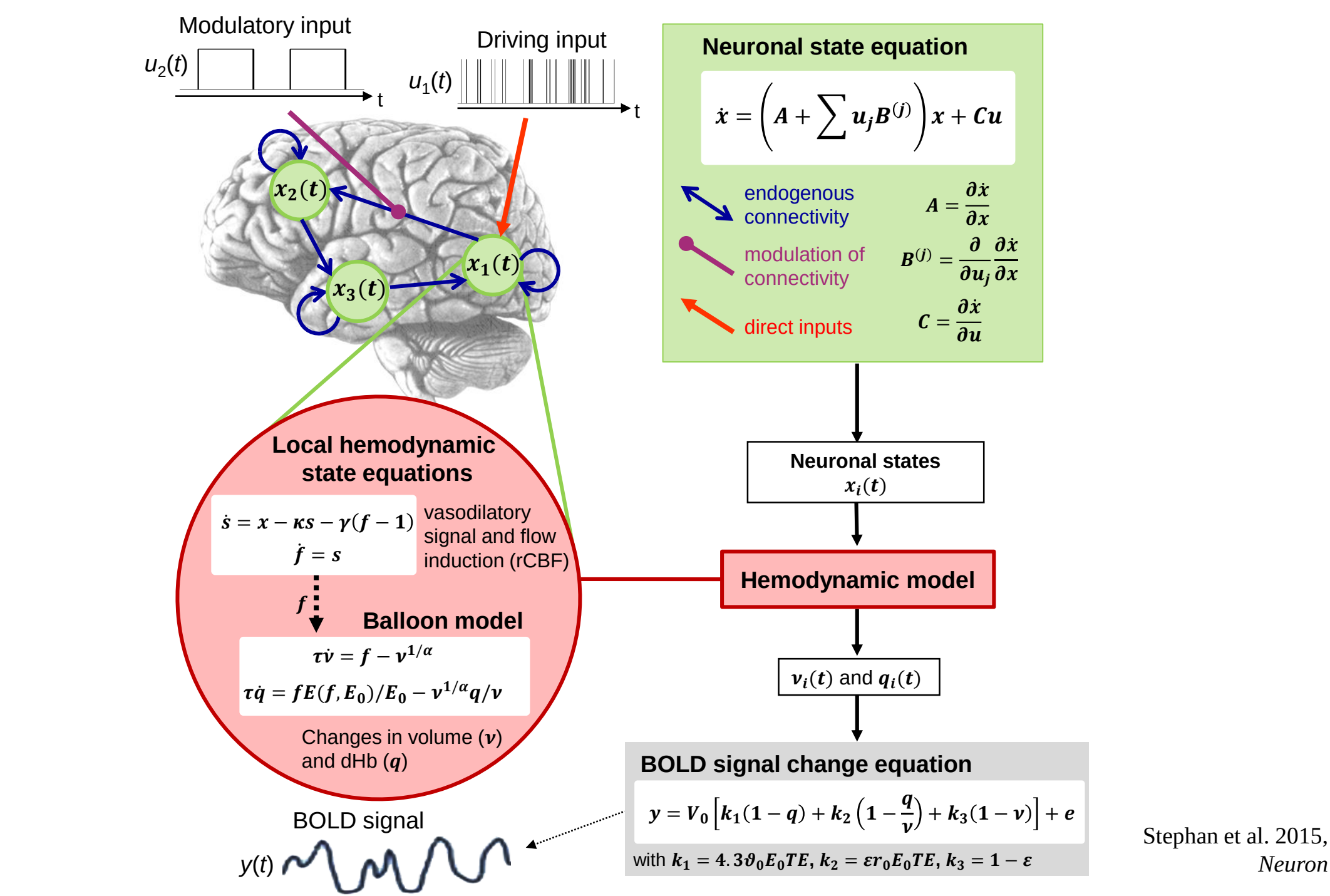


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

$$p(\theta \mid y, m)$$



1. enforces mechanistic thinking: how could the data have been caused?
2. generate synthetic data (observations) by sampling from the prior – can model explain certain phenomena at all?
3. inference about model structure: formal approach to disambiguating mechanisms → p(m|y) or p(y|m)
4. inference about parameters → p(θ|y)



Stephan et al. 2015, *Neuron*

Bayesian system identification

$u(t)$

Neural dynamics

$$dx/dt = f(x,u,\theta)$$

Observer function

$$y = g(x,\theta) + \varepsilon$$

$$p(y \mid \theta, m) = N(g(\theta), \Sigma(\theta))$$

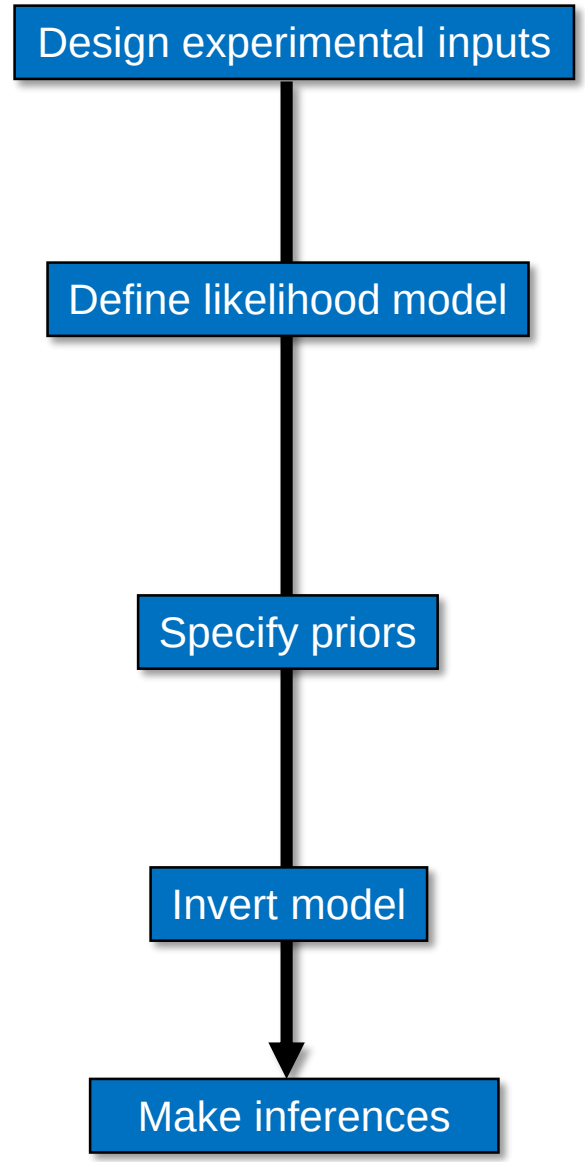
$$p(\theta, m) = N(\mu_\theta, \Sigma_\theta)$$

Inference on model structure

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

Inference on parameters

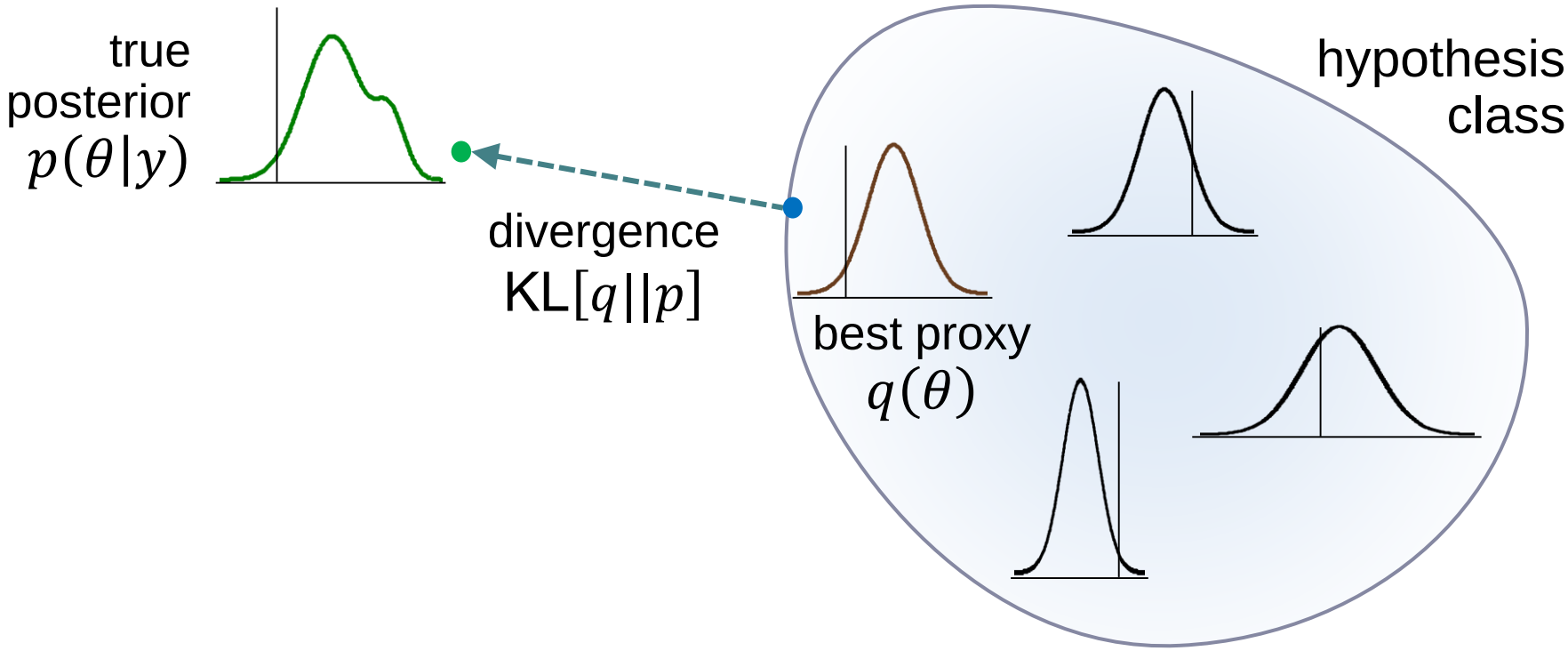
$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta, m)}{p(y \mid m)}$$



Variational Bayes (VB)

Idea: find an approximate density $q(\theta)$ that is maximally similar to the true posterior $p(\theta|y)$.

This is often done by assuming a particular form for q (fixed form VB) and then optimizing its sufficient statistics.



Variational Bayes

$$\ln p(y) = \underbrace{\mathrm{KL}[q||p]}_{\text{divergence}} + \underbrace{F(q,y)}_{\text{neg. free energy}}$$

divergence ≥ 0 (unknown)

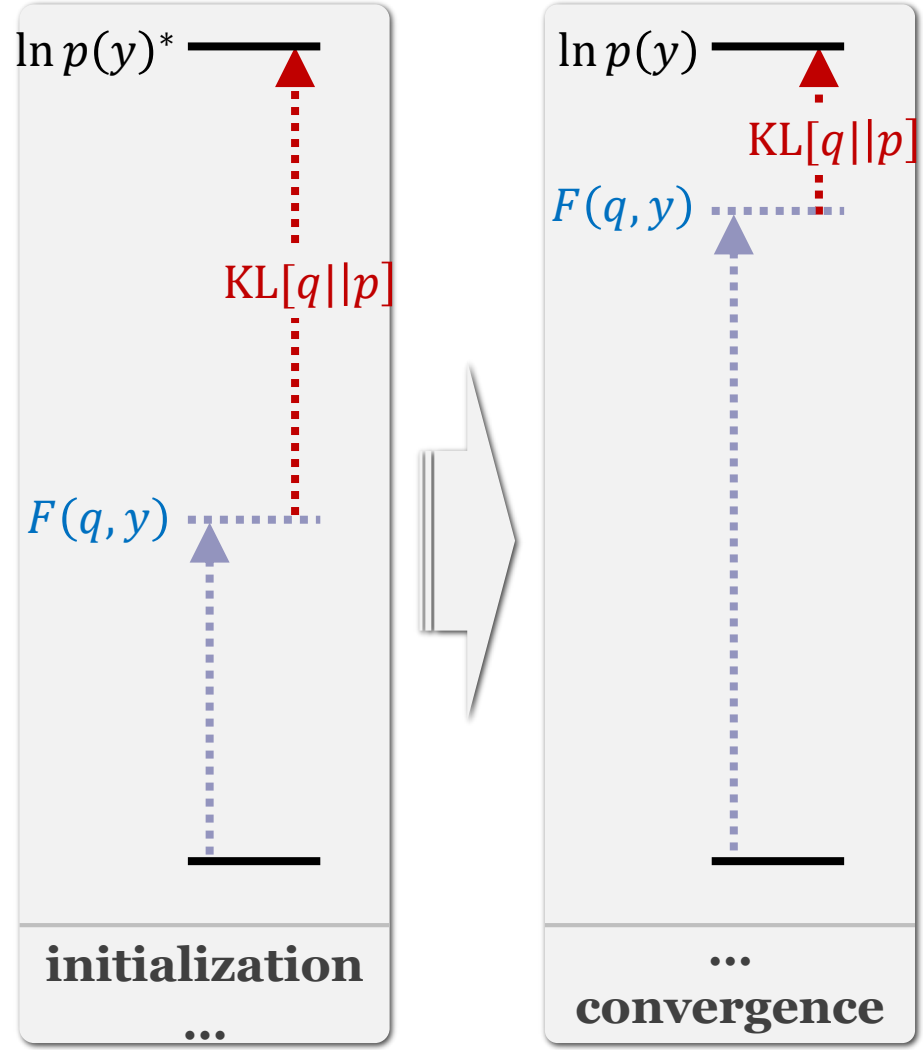
neg. free energy (easy to evaluate for a given q)

$F(q,y)$ is a functional wrt. the approximate posterior $q(\theta)$.

Maximizing $F(q,y)$ is equivalent to:

- minimizing $\mathrm{KL}[q||p]$
- tightening $F(q,y)$ as a lower bound to the log model evidence

When $F(q,y)$ is maximized, $q(\theta)$ is our best estimate of the posterior.



Mean field assumption

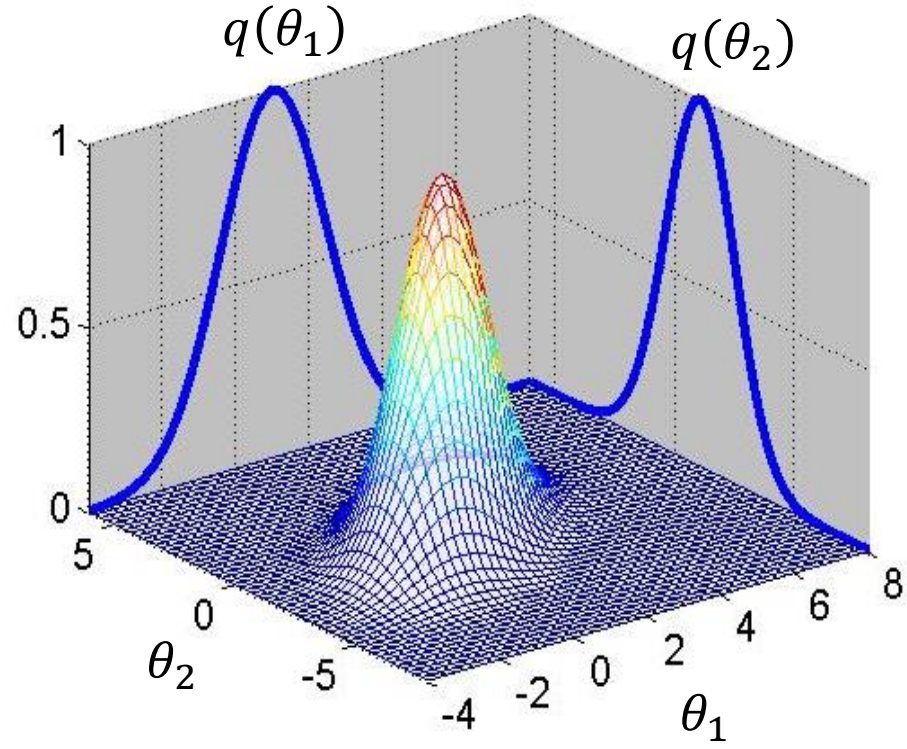
Factorize the approximate posterior $q(\theta)$ into independent partitions:

$$q(\theta) = \prod_i q_i(\theta_i)$$

where $q_i(\theta_i)$ is the approximate posterior for the i^{th} subset of parameters.

For example, split parameters and hyperparameters:

$$p(\theta, \lambda \mid y) \approx q(\theta, \lambda) = q(\theta) q(\lambda)$$



Jean Daunizeau, www.fil.ion.ucl.ac.uk/~jdaunize/presentations/Bayes2.pdf

VB in a nutshell (mean-field approximation)

❶ Neg. free-energy approx. to model evidence.

$$\ln p(y \mid m) = F + KL\left[q(\theta,\lambda), p(\theta,\lambda \mid y)\right]$$

$$F = \left\langle \ln p(y,\theta,\lambda) \right\rangle_q - KL\left[q(\theta,\lambda), p(\theta,\lambda \mid m)\right]$$

❷ Mean field approx.

$$p(\theta,\lambda \mid y) \approx q(\theta,\lambda) = q(\theta)q(\lambda)$$

❸ Maximise neg. free energy wrt. q = minimise divergence, by maximising variational energies

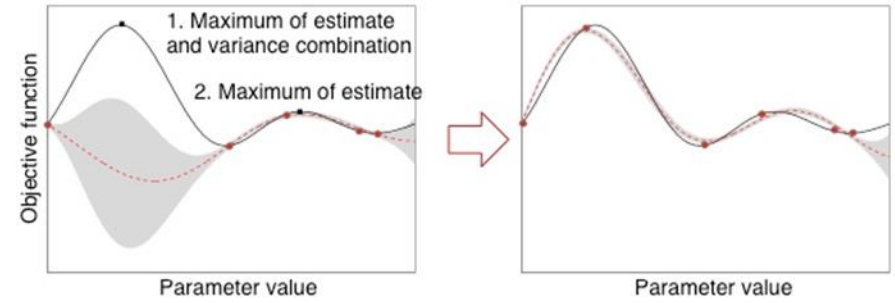
$$q(\theta) \propto \exp(I_\theta) = \exp\left[\left\langle \ln p(y,\theta,\lambda) \right\rangle_{q(\lambda)}\right]$$

$$q(\lambda) \propto \exp(I_\lambda) = \exp\left[\left\langle \ln p(y,\theta,\lambda) \right\rangle_{q(\theta)}\right]$$

❹ Iterative updating of sufficient statistics of approx. posteriors by gradient ascent.

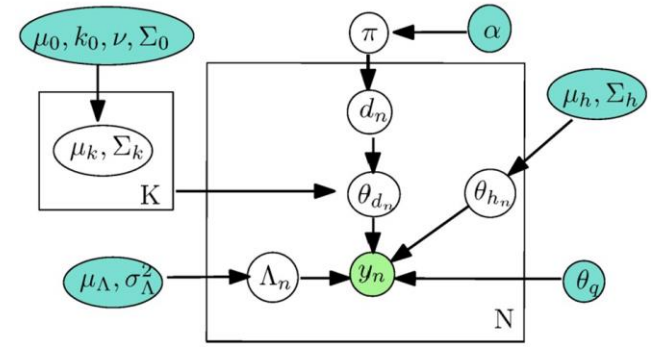
DCM: methodological developments

- **Local extrema → global optimisation schemes for model inversion**
  - **MCMC**
    (Gupta et al. 2015, NeuroImage)
  - **Gaussian processes**
    (Lomakina et al. 2015, NeuroImage)

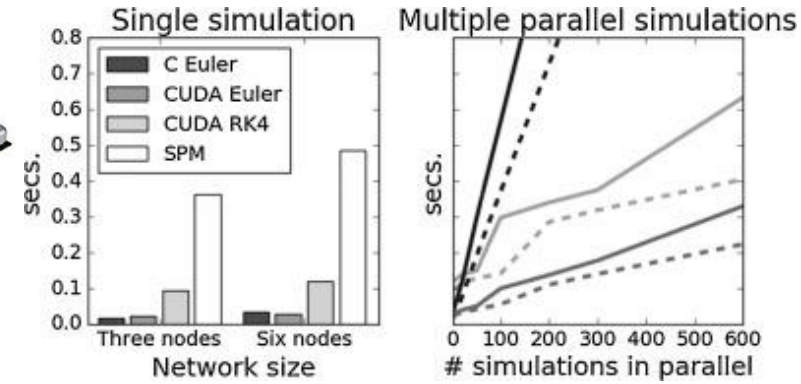


- **Sampling-based estimates of model evidence**
  - Aponte et al. 2015, J. Neurosci. Meth.
  - Raman et al., in preparation

- **Choice of priors → empirical Bayes**
  - Friston et al., submitted
  - Raman et al., submitted



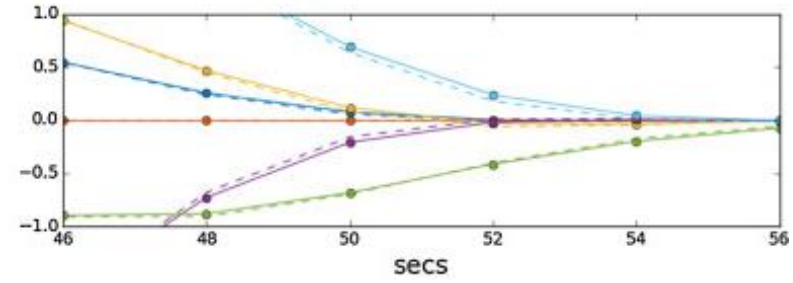
mpdcm: massively parallel DCM



$$\left.\begin{aligned}\dot{x} &= f(x, u_1, \theta_1)\\ \dot{x} &= f(x, u_2, \theta_2)\\ &\vdots\\ \dot{x} &= f(x, u_1, \theta_1)\end{aligned}\right\}$$

mpdcm_integrate(dcms)

$$\left\{\begin{aligned} y_1\\ y_2\\ \vdots\\ y_3\end{aligned}\right.$$



www.translationalneuromodeling.org/tapas

Aponte et al. 2015., *J. Neurosci Meth.*

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The evolution of DCM in SPM

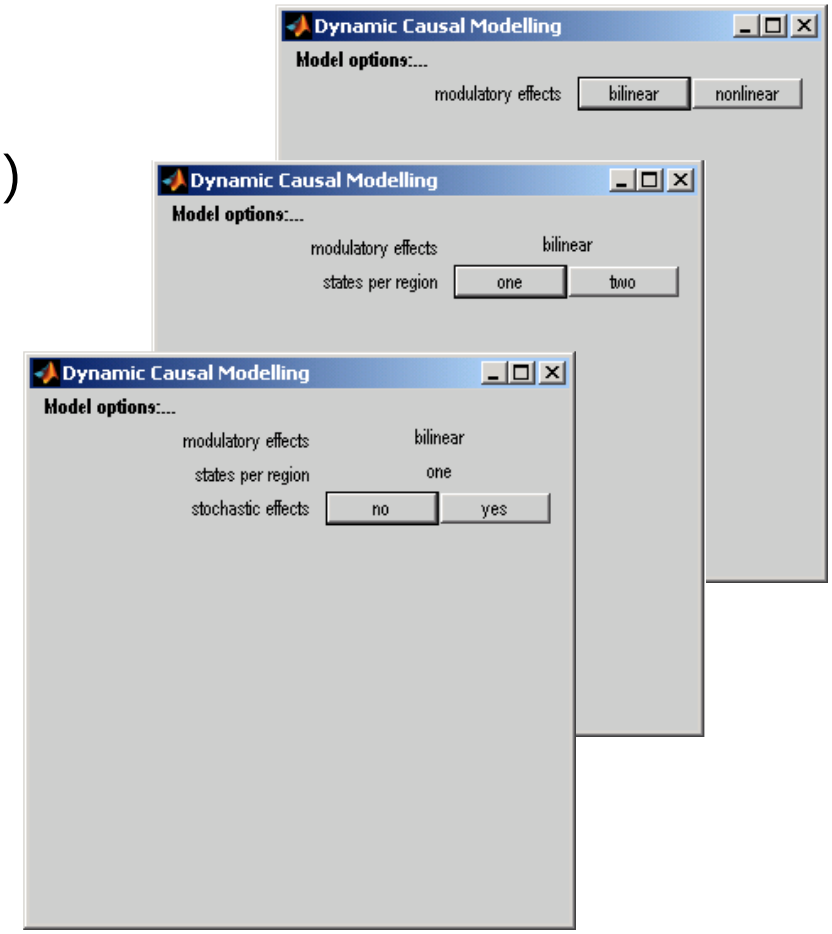
- DCM is not one specific model, but a framework for Bayesian inversion of dynamic system models

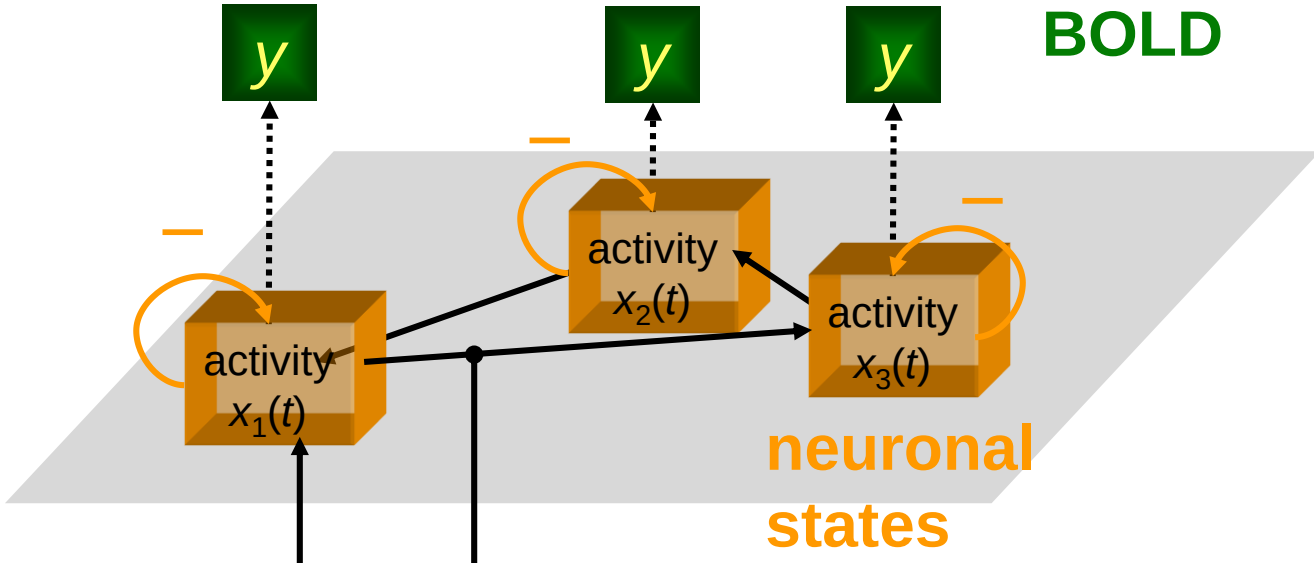
- The implementation in SPM has been evolving over time, e.g.
  - improvements of numerical routines (e.g., optimisation scheme)
  - change in priors to cover new variants (e.g., stochastic DCMs)
  - changes of hemodynamic model

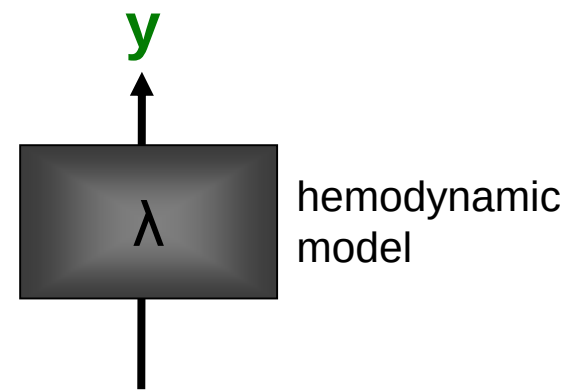
To enable replication of your results, you should ideally state which SPM version (release number) you are using when publishing papers.

Factorial structure of model specification

- Three dimensions of model specification:
  - bilinear vs. nonlinear
  - single-state vs. two-state (per region)
  - deterministic vs. stochastic

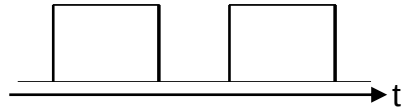




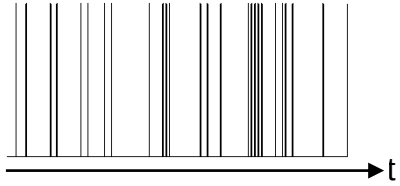


integration

modulatory
input $u_2(t)$



driving
input $u_1(t)$



The classical DCM:
a deterministic, one-state, bilinear model

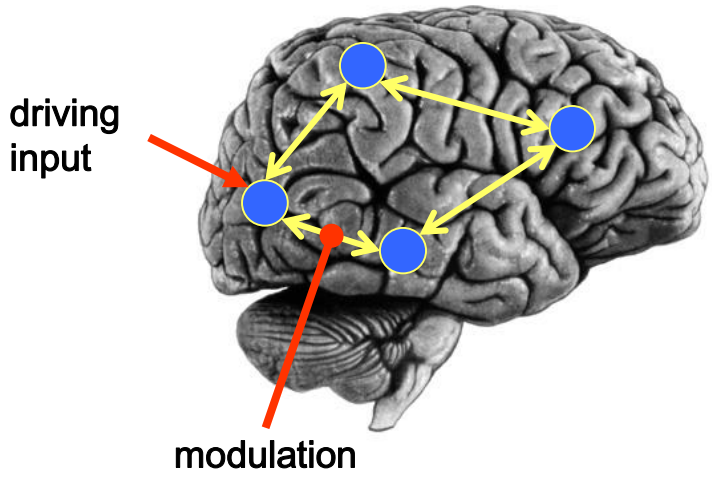
Neural state equation $\dot{x} = (A + \sum u_j B^{(j)})x + Cu$

endogenous connectivity → $A = \frac{\partial \dot{x}}{\partial x}$

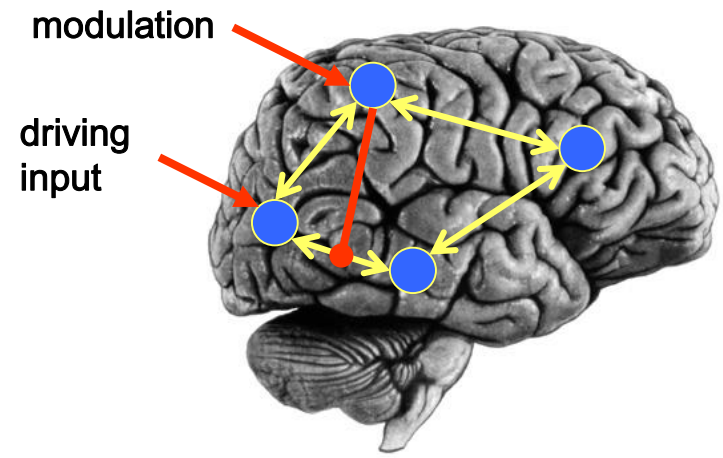
modulation of connectivity → $B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{x}}{\partial x}$

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

bilinear DCM



non-linear DCM



Two-dimensional Taylor series (around $x_0=0$, $u_0=0$):

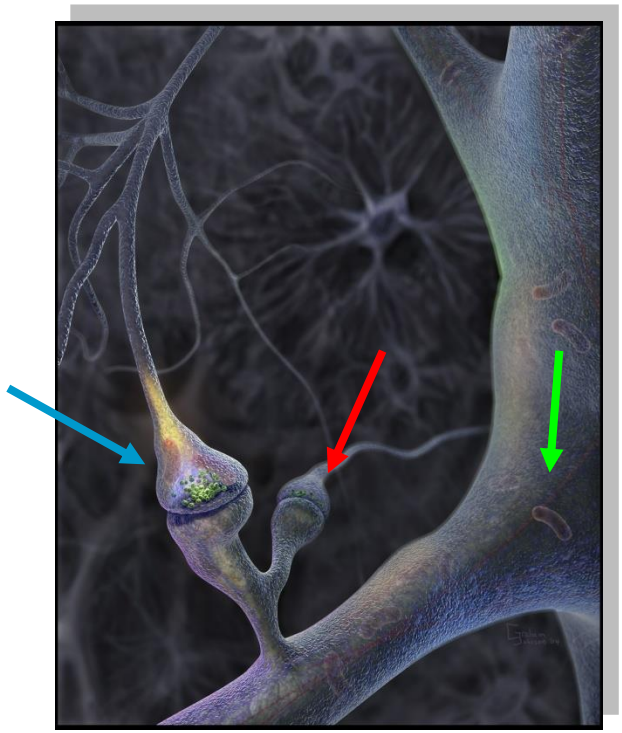
$$\frac{dx}{dt} = f(x,u) \approx f(x_0,0) + \frac{\partial f}{\partial x}x + \frac{\partial f}{\partial u}u + \frac{\partial^2 f}{\partial x \partial u}ux + \frac{\partial^2 f}{\partial x^2}\frac{x^2}{2} + \ldots$$

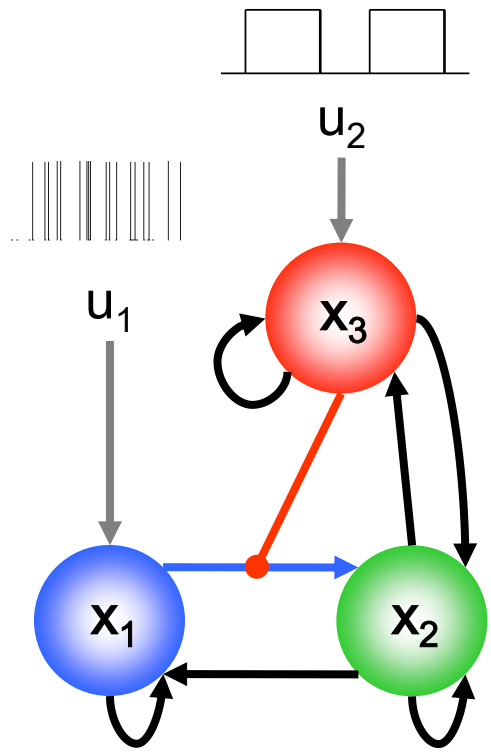
Bilinear state equation:

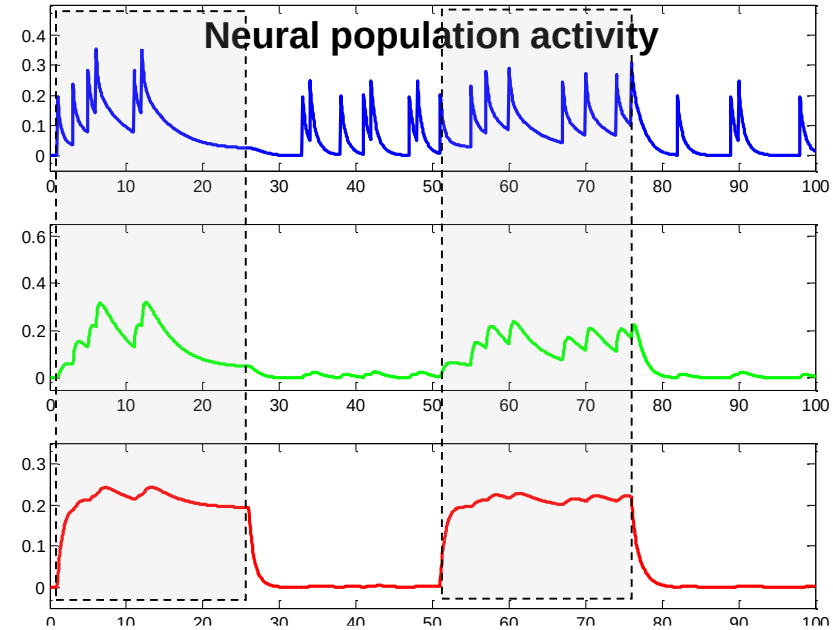
$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)}\right)x + Cu$$

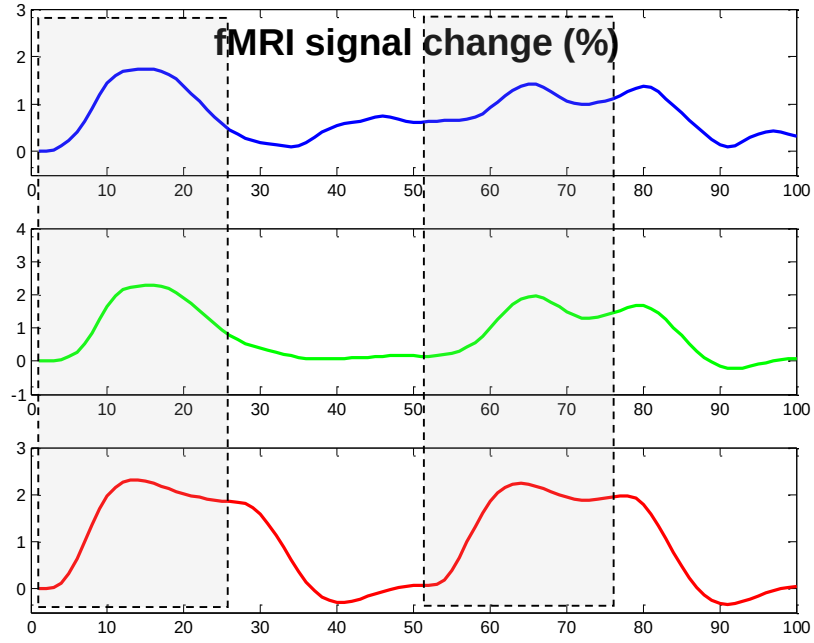
Nonlinear state equation:

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







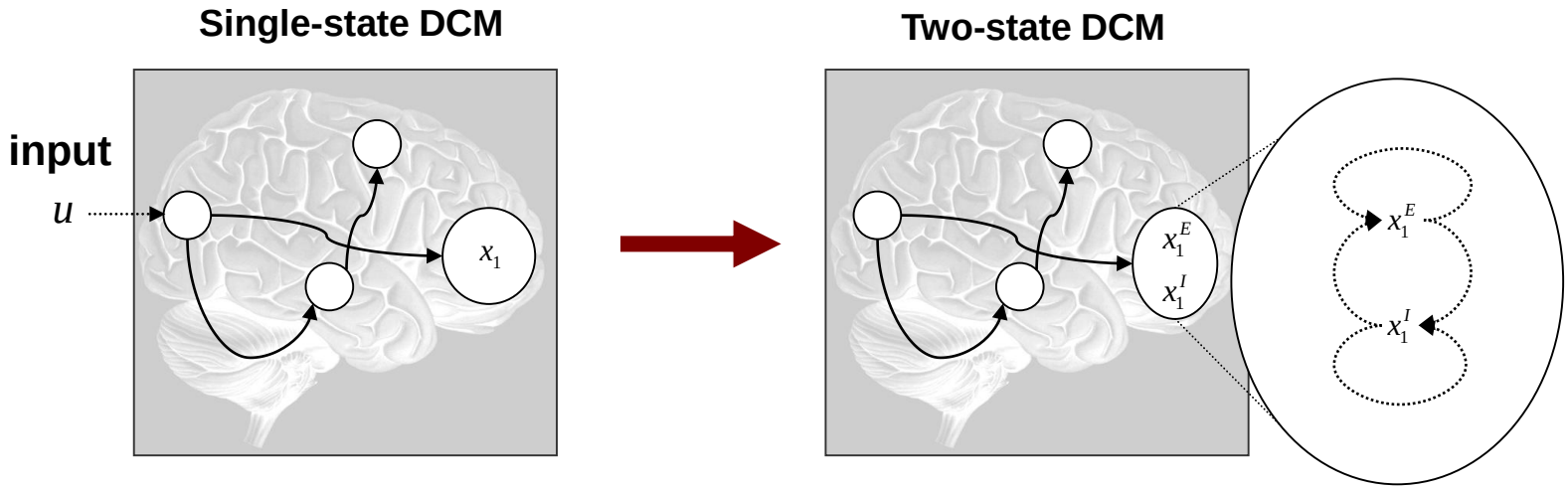


Nonlinear Dynamic Causal Model for fMRI

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

Stephan et al. 2008, *NeuroImage*

Two-state DCM



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

$$\Im_{ij} = A_{ij} + uB_{ij}$$

$$\Im = \begin{bmatrix} \Im_{11} & \cdots & \Im_{1N} \\ \vdots & \ddots & \vdots \\ \Im_{N1} & \cdots & \Im_{NN} \end{bmatrix} \quad x = \begin{bmatrix} x_1 \\ \vdots \\ x_N \end{bmatrix}$$

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

$$\Im_{ij}^{\bullet\bullet} = \mu_{ij}^{\bullet\bullet} \exp(A_{ij}^{\bullet\bullet} + uB_{ij}^{\bullet\bullet})$$

$$\Im = \begin{bmatrix} \Im_{11}^{EE} & \Im_{11}^{EI} & \cdots & \Im_{1N}^{EE} & 0 \\ \Im_{11}^{IE} & \Im_{11}^{II} & & 0 & 0 \\ \vdots & & \ddots & & \vdots \\ \Im_{N1}^{EE} & 0 & & \Im_{NN}^{EE} & \Im_{NN}^{EE} \\ 0 & 0 & \cdots & \Im_{NN}^{IE} & \Im_{NN}^{II} \end{bmatrix} \quad x = \begin{bmatrix} x_1^E \\ x_1^I \\ \vdots \\ x_N^E \\ x_N^I \end{bmatrix}$$

Extrinsic (between-region) coupling

Intrinsic (within-region) coupling

Marreiros et al. 2008, *NeuroImage*

Stochastic DCM

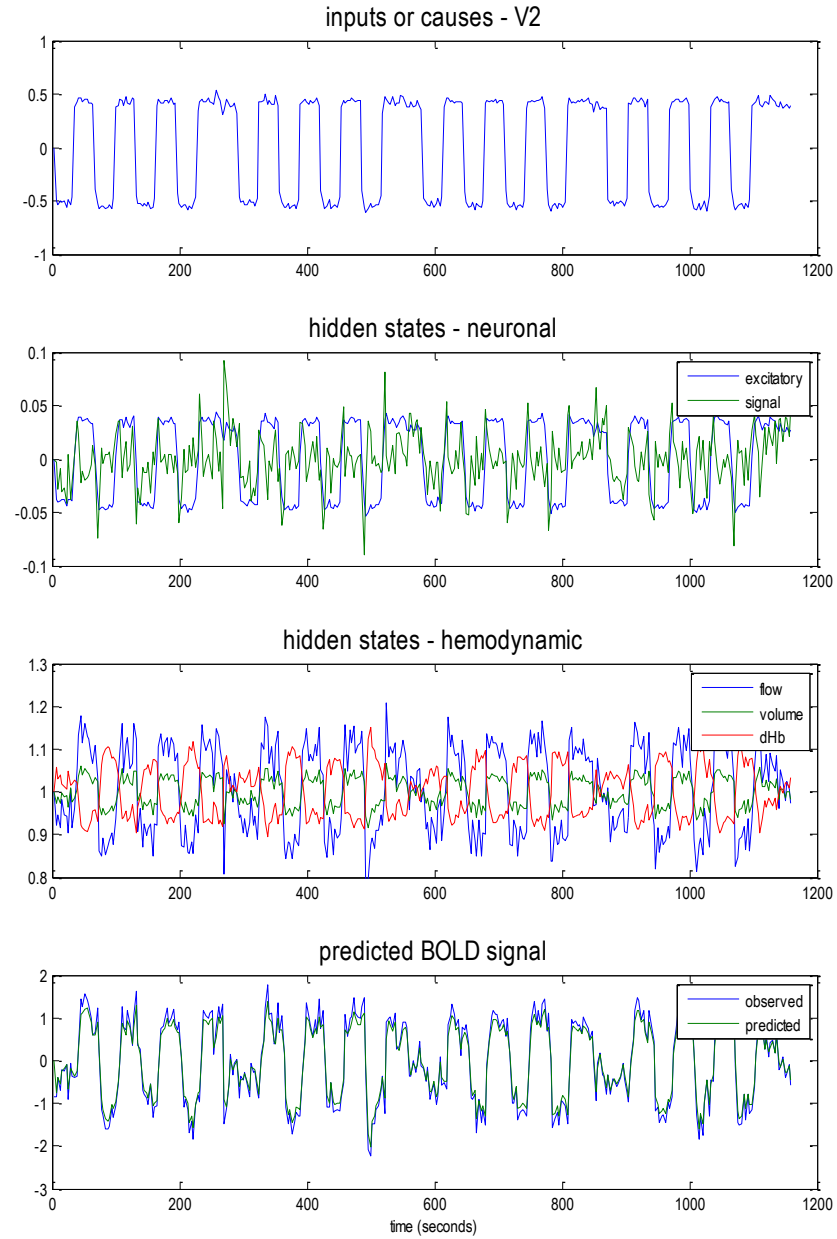
$$\frac{dx}{dt} = (A + \sum_j u_j B^{(j)})x + Cv + \omega^{(x)}$$

$$v = u + \omega^{(v)}$$

- all states are represented in generalised coordinates of motion
- random state fluctuations $w^{(x)}$ account for endogenous fluctuations,
  have unknown precision and smoothness
  $\rightarrow$ two hyperparameters
- fluctuations $w^{(v)}$ induce uncertainty about how inputs influence neuronal activity
- can be fitted to resting state data

Li et al. 2011, *NeuroImage*

Estimates of hidden causes and states (Generalised filtering)



Spectral DCM

- deterministic model that generates predicted cross-spectra in a distributed neuronal network or graph

- finds the effective connectivity among hidden neuronal states that best explains the observed functional connectivity among hemodynamic responses

- advantage:
  - replaces an optimisation problem wrt. stochastic differential equations with a deterministic approach from linear systems theory
    → computationally very efficient

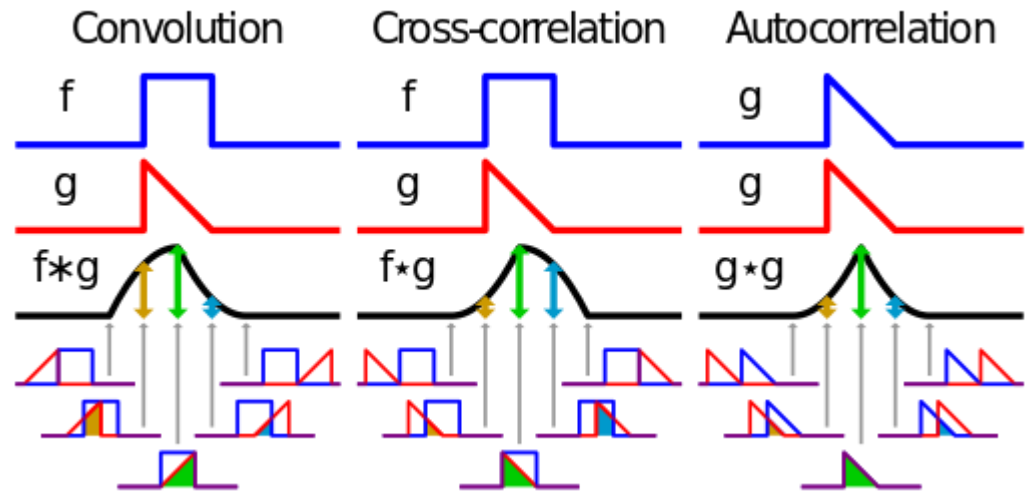
- disadvantages:
  - assumes stationarity

Friston et al. 2014, *NeuroImage*

Cross-correlation & convolution

- cross-correlation = measure of similarity of two waveforms as a function of the time-lag of one relative to the other
  - slide two functions over each other and measure overlaps at all lags
- related to the pdf of the difference beteween two random variables
  → a general measure of similarity between two time series

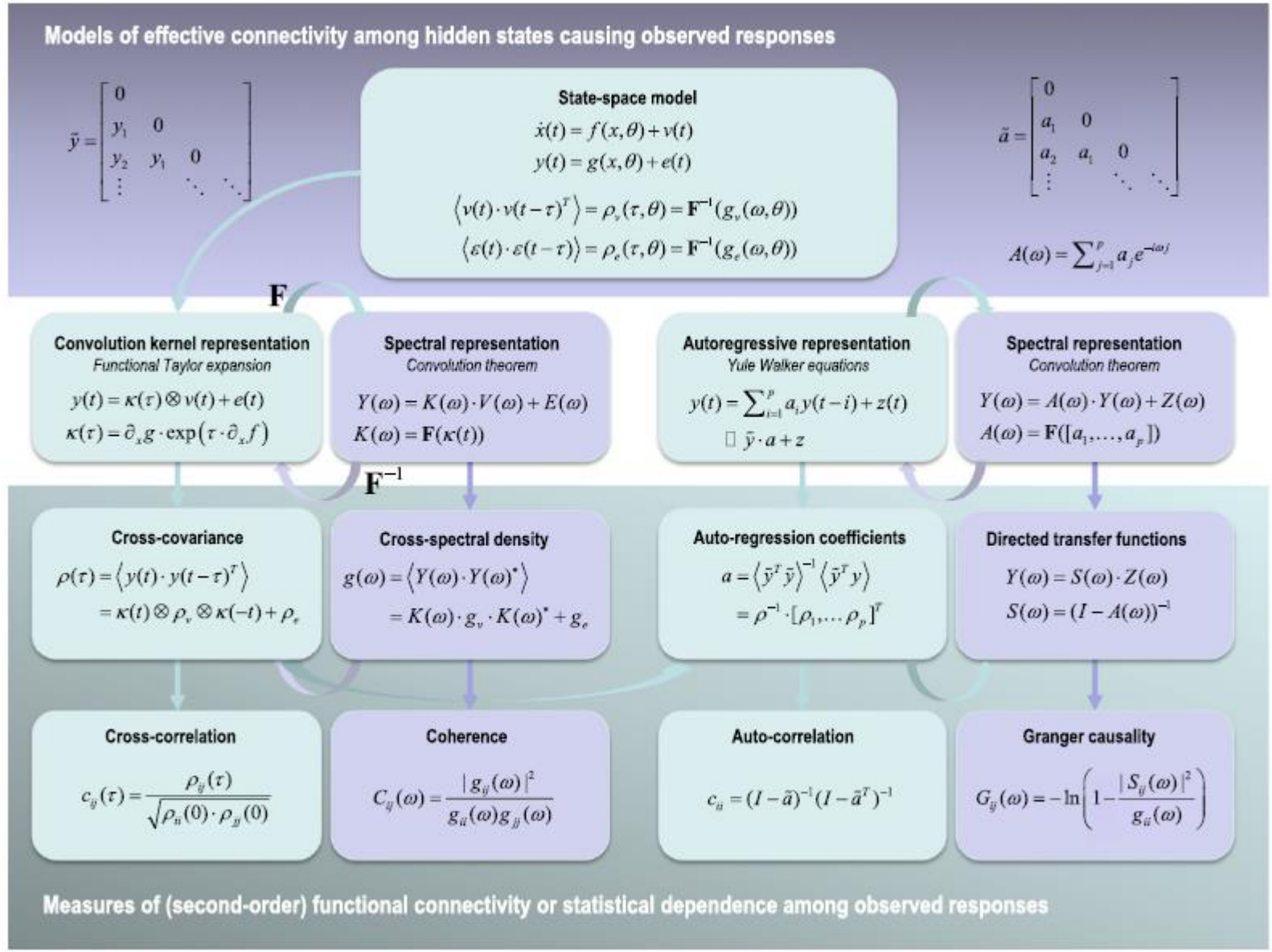
$$(f \star g)(\tau) \stackrel{\text{def}}{=} \int_{-\infty}^{\infty} f^*(t)\ g(t+\tau)\,dt$$



Source: *Wikipedia*

cross-spectra
= Fourier transform of cross-correlation

cross-correlation
= generalized form of correlation (at zero lag, this is the conventional measure of functional connectivity)

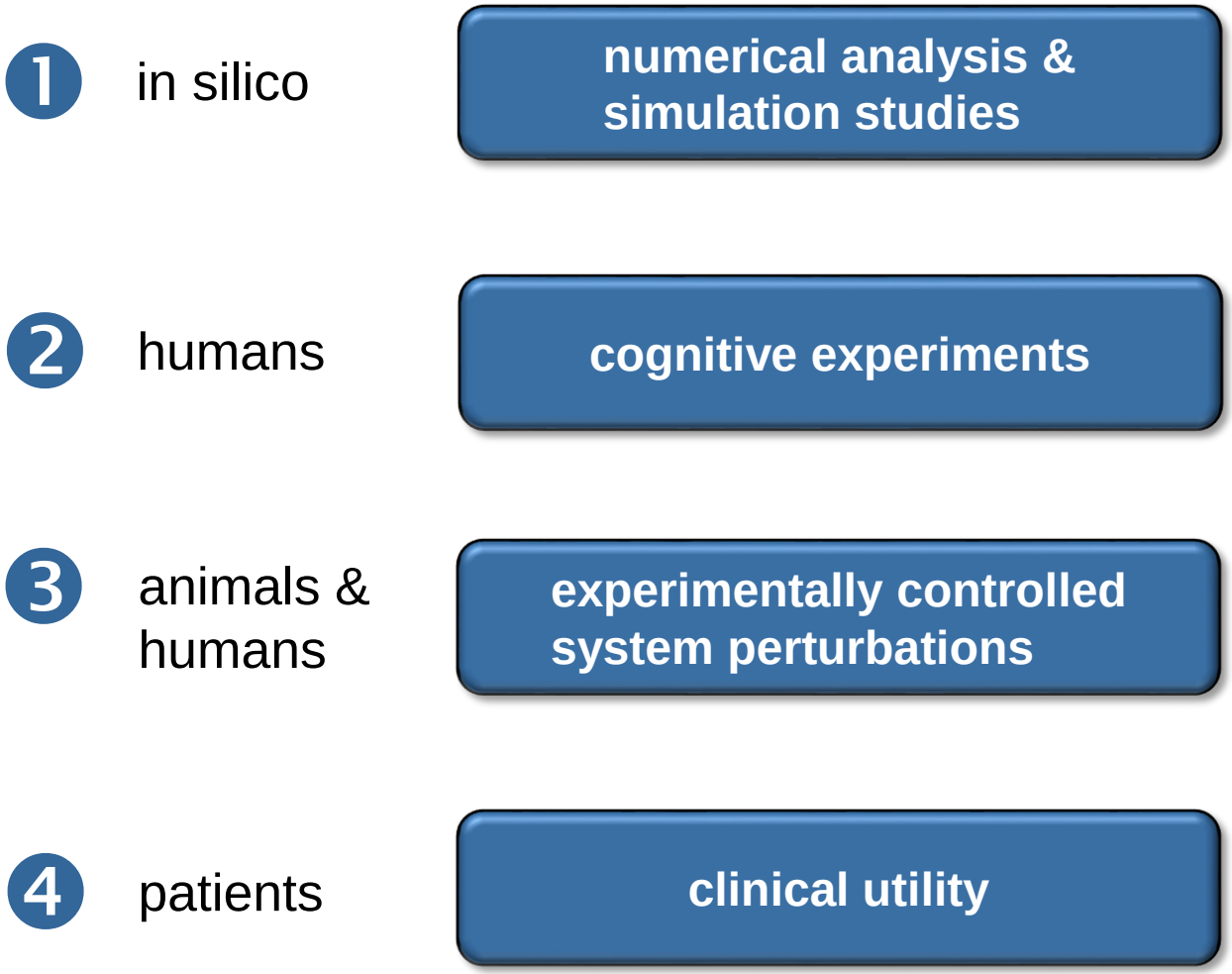


Friston et al. 2014, *NeuroImage*

**“All models are wrong,
but some are useful.”**

George E.P. Box (1919-2013)

Hierarchical strategy for model validation



For DCM: >15 published validation studies (incl. 6 animal studies):

- infers site of seizure origin (David et al. 2008)
- infers primary recipient of vagal nerve stimulation (Reyt et al. 2010)
- infers synaptic changes as predicted by microdialysis (Moran et al. 2008)
- infers fear conditioning induced plasticity in amygdala (Moran et al. 2009)
- tracks anaesthesia levels (Moran et al. 2011)
- predicts sensory stimulation (Brodersen et al. 2010)

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Generative models & model selection

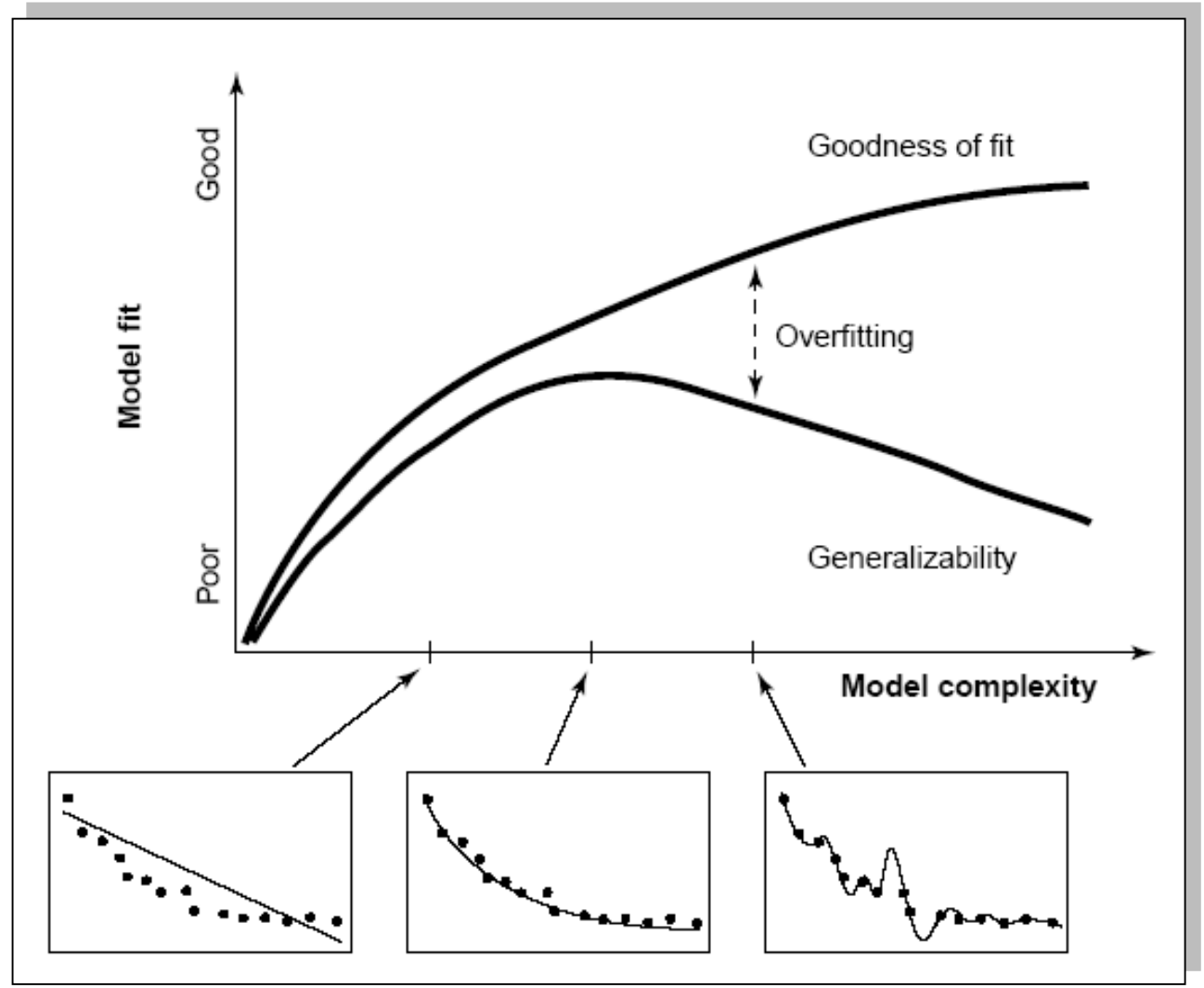
- any DCM = a particular generative model of how the data (may) have been caused
- generative modelling: comparing competing hypotheses about the mechanisms underlying observed data
  - $\rightarrow$ a priori definition of hypothesis set (model space) is crucial
  - $\rightarrow$ determine the most plausible hypothesis (model), given the data
- model selection $\neq$ model validation!
  - $\rightarrow$ model validation requires external criteria (external to the measured data)

Model comparison and selection

Given competing hypotheses on structure & functional mechanisms of a system, which model is the best?

Which model represents the best balance between model fit and model complexity?

For which model m does $p(y|m)$ become maximal?

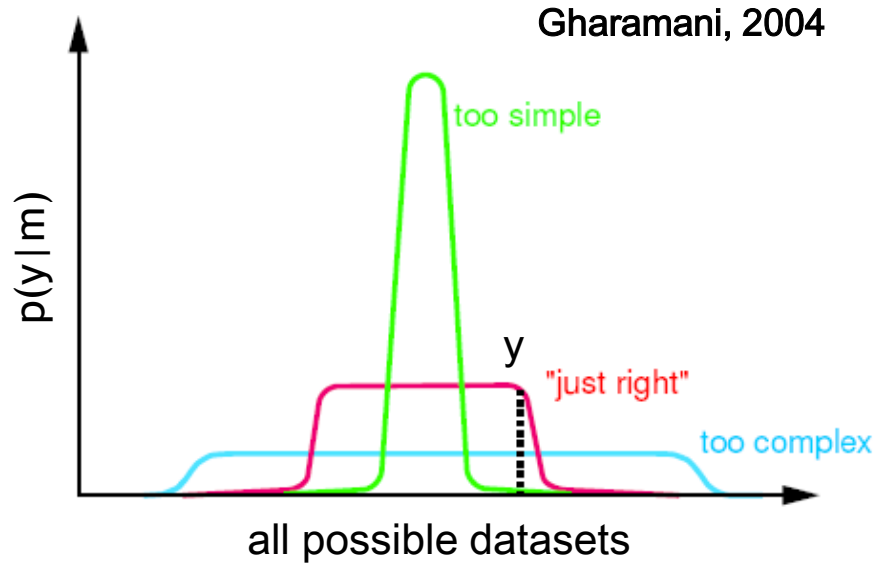


Pitt & Miyung (2002) *TICS*

Bayesian model selection (BMS)

Model evidence (marginal likelihood):

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



→ accounts for both accuracy and complexity of the model

→ "If I randomly sampled from my prior and plugged the resulting value into the likelihood function, how close would the predicted data be – on average – to my observed data?"

Various approximations, e.g.:

- negative free energy, AIC, BIC

McKay 1992, *Neural Comput.*
Penny et al. 2004a, *NeuroImage*

Model space (hypothesis set) M

Model space M is defined by prior on models.

Usual choice: flat prior over a small set of models.

$$p(m) = \begin{cases} 1/|M| \text{ if } m \in M \\ 0 \text{ if } m \notin M \end{cases}$$

In this case, the posterior probability of model i is:

$$p(m_i \mid y) = \frac{p(y \mid m_i)\,p(m_i)}{\sum_{j=1}^{|M|} p(y \mid m_j)\,p(m_j)} = \frac{p(y \mid m_i)}{\sum_{j=1}^{|M|} p(y \mid m_j)}$$

Approximations to the model evidence in DCM

Logarithm is a monotonic function

Maximizing log model evidence
= Maximizing model evidence

Log model evidence = balance between fit and complexity

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

Akaike Information Criterion: $AIC = \log p(y \mid \theta, m) - p$

Bayesian Information Criterion: $BIC = \log p(y \mid \theta, m) - \frac{p}{2} \log N$

No. of parameters

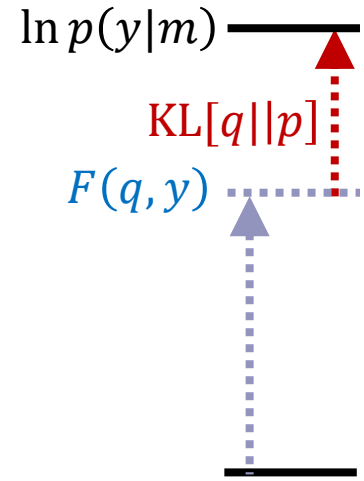
No. of data points

Penny et al. 2004a, *NeuroImage*

The (negative) free energy approximation F

F is a lower bound on the log model evidence, where the bound is determined by the KL divergence between an approximate posterior q and the true posterior::

$$\log p(y \mid m) = F + KL\left[q(\theta), p(\theta \mid y, m)\right]$$



Like AIC/BIC, F is an accuracy/complexity tradeoff:

$$F = \underbrace{\left\langle \log p(y \mid \theta, m) \right\rangle}_{accuracy} - \underbrace{KL\left[q(\theta), p(\theta \mid m)\right]}_{complexity}$$

The complexity term in *F*

- In contrast to AIC & BIC, the complexity term of the negative free energy *F* accounts for parameter interdependencies.

$$KL\left[q(\theta), p(\theta \mid m)\right]$$

$$= \frac{1}{2}\ln\left|C_\theta\right| - \frac{1}{2}\ln\left|C_{\theta|y}\right| + \frac{1}{2}\left(\mu_{\theta|y} - \mu_\theta\right)^T C_\theta^{-1}\left(\mu_{\theta|y} - \mu_\theta\right)$$

- determinant = measure of “volume” (space spanned by the eigenvectors of the matrix)

- The complexity term of *F* is higher
  - the more independent the prior parameters (↑ effective DFs)
  - the more dependent the posterior parameters
  - the more the posterior mean deviates from the prior mean

Bayes factors

To compare two models, we could just compare their log evidences.

But: the log evidence is just some number – not very intuitive!

A more intuitive interpretation of model comparisons is made possible by Bayes factors:

positive value, [0; ∞[

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

Kass & Raftery classification:

B_{12}	$p(m_1\|y)$	Evidence
1 to 3	50-75%	weak
3 to 20	75-95%	positive
20 to 150	95-99%	strong
≥ 150	≥ 99%	Very strong

Kass & Raftery 1995, *J. Am. Stat. Assoc.*

Fixed effects BMS at group level

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

$$GBF_{ij} = \prod_k BF_{ij}^{(k)}$$

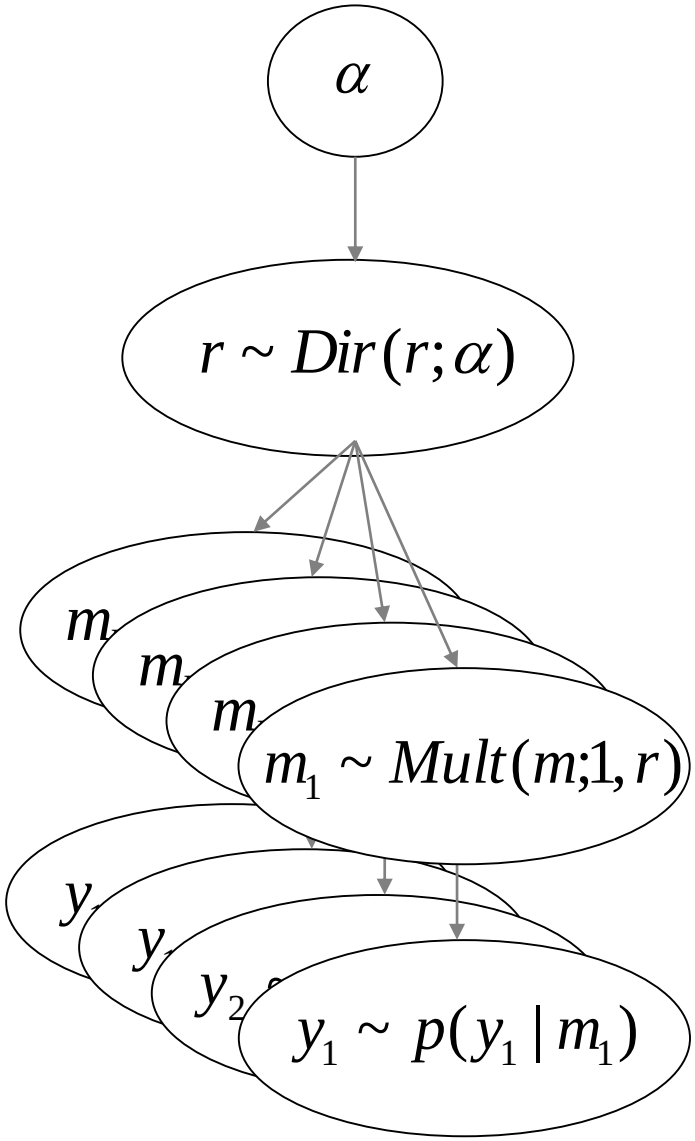
Average Bayes factor (ABF):

$$ABF_{ij} = \sqrt[K]{\prod_k BF_{ij}^{(k)}}$$

Problems:

- blind with regard to group heterogeneity
- sensitive to outliers

Random effects BMS for heterogeneous groups



Dirichlet parameters α
= "occurrences" of models in the population

Dirichlet distribution of model probabilities r

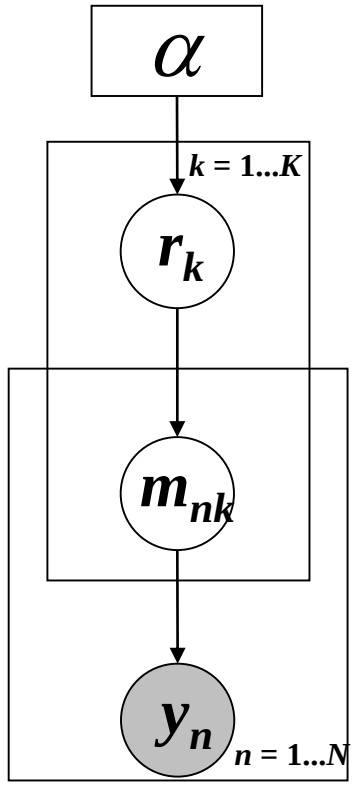
Multinomial distribution of model labels m

Measured data y

Model inversion by Variational Bayes (VB) or MCMC

Stephan et al. 2009a, *NeuroImage*
Penny et al. 2010, *PLoS Comp. Biol.*

Random effects BMS for heterogeneous groups



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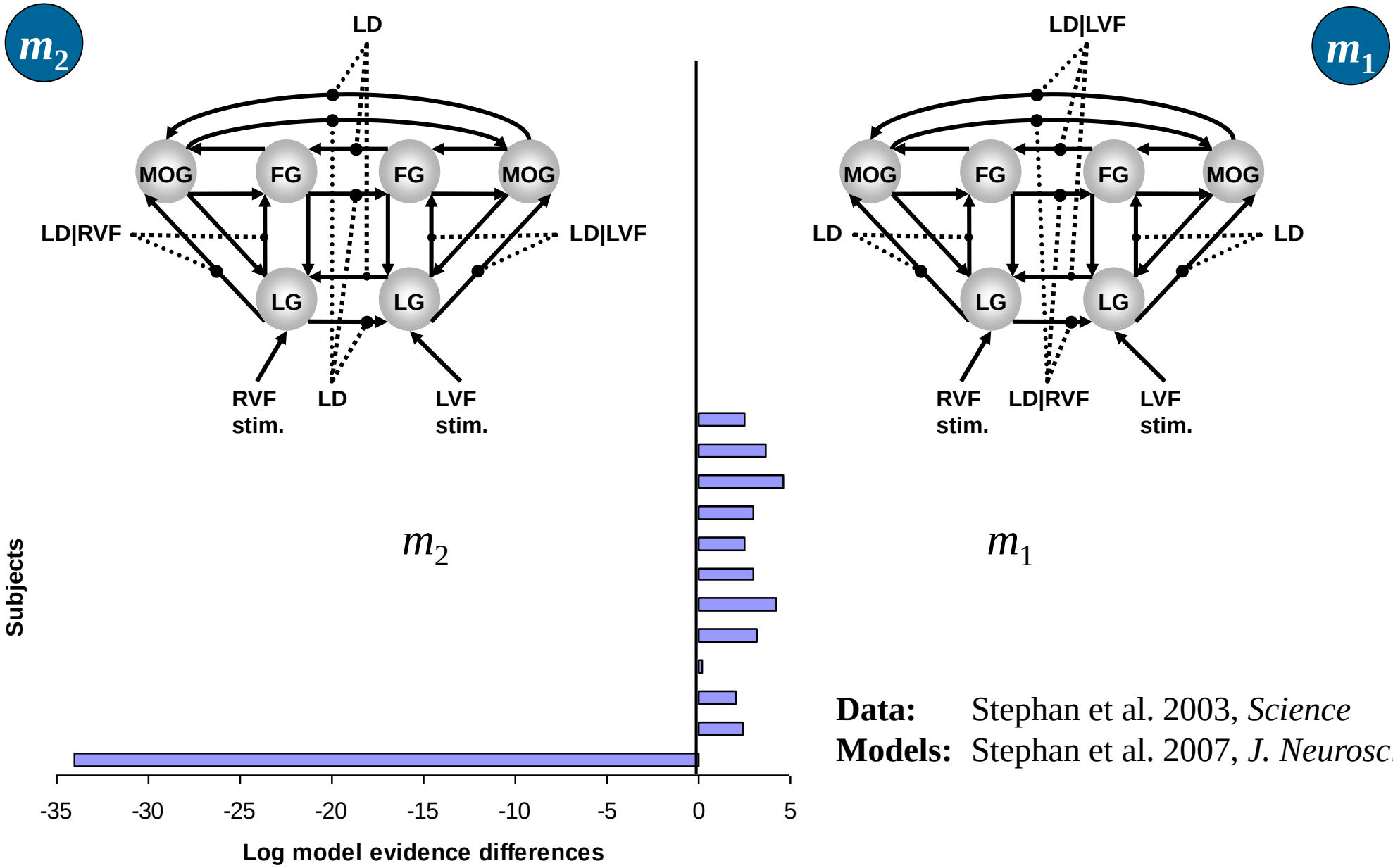
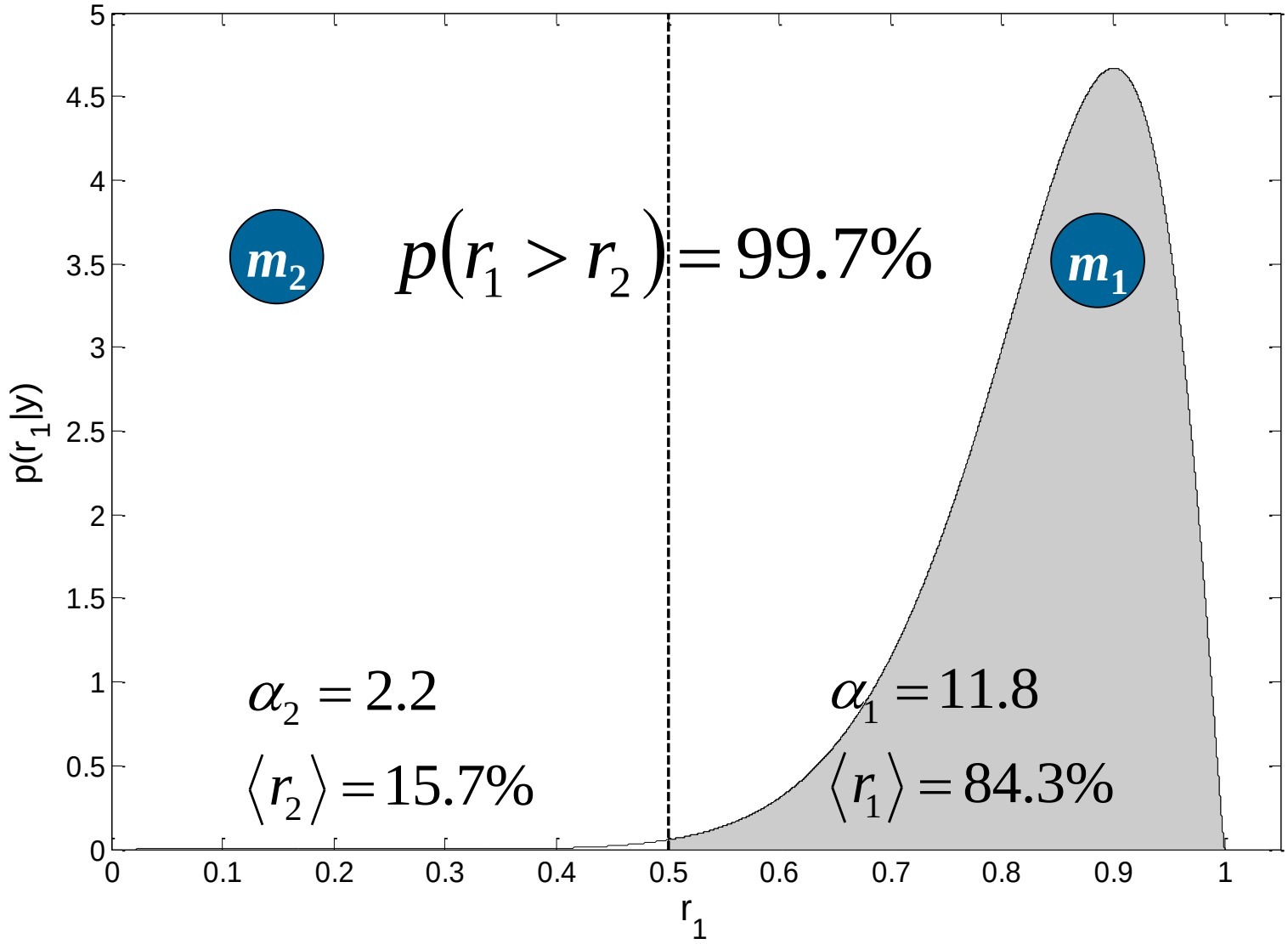


Data: Stephan et al. 2003, *Science*

Models: Stephan et al. 2007, *J. Neurosci.*



Stephan et al. 2009a, *NeuroImage*

How can we report the results of random effects BMS?

1. **Dirichlet parameter estimates**

$$\alpha$$

2. **expected posterior probability** of obtaining the k-th model for any randomly selected subject

$$\left\langle r_k \right\rangle_q = \alpha_k / (\alpha_1 + \ldots + \alpha_K)$$

3. **exceedance probability** that a particular model *k* is more likely than any other model (of the *K* models tested), given the group data

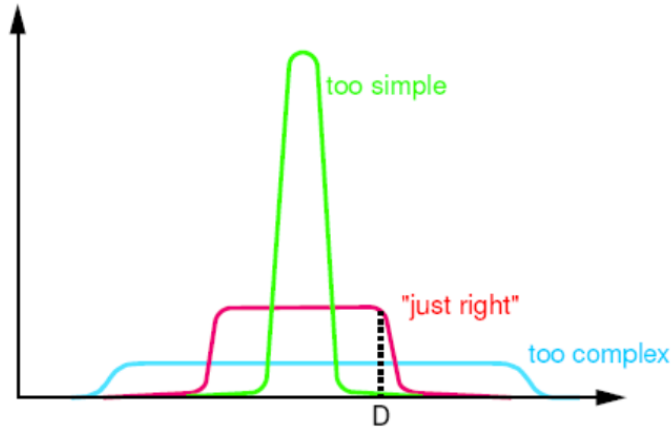
$$\exists k \in \{1...K\}, \forall j \in \{1...K \mid j \neq k\}:$$

$$\varphi_k = p(r_k > r_j \mid y; \alpha)$$

4. **protected exceedance probability**: see below

Overfitting at the level of models

- ↑ #models ⇒ ↑ risk of overfitting
- solutions:
  - regularisation: definition of model space = choosing priors p(m)
  - family-level BMS
  - Bayesian model averaging (BMA)



posterior model probability:

$$p(m \mid y)$$

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

BMA:

$$p(\theta \mid y)$$

$$= \sum_m p(\theta \mid y, m) p(m \mid y)$$

Model space partitioning or: Comparing model families

- partitioning model space into K subsets or families:

$$M = \{ f_1, \ldots, f_K \}$$

- pooling information over all models in these subsets allows one to compute the probability of a model family, given the data

$$p(f_k)$$

- effectively removes uncertainty about any aspect of model structure, other than the attribute of interest (which defines the partition)

Stephan et al. 2009, *NeuroImage*
Penny et al. 2010, *PLoS Comput. Biol.*

Family-level inference: fixed effects

- We wish to have a uniform prior at the family level:

$$p(f_k) = \frac{1}{K}$$

- This is related to the model level via the sum of the priors on models:

$$p(f_k) = \sum_{m \in f_k} p(m)$$

- Hence the uniform prior at the family level is:

$$\forall m \in f_k : p(m) = \frac{1}{K|f_k|}$$

- The probability of each family is then obtained by summing the posterior probabilities of the models it includes:

$$p(f_k \mid y_{1..N}) = \sum_{m \in f_k} p(m \mid y_{1..N})$$

Penny et al. 2010, *PLoS Comput. Biol.*

Family-level inference: random effects

- The frequency of a family in the population is given by:

$$s_k = \sum_{m \in f_k} r_m$$

- In RFX-BMS, this follows a Dirichlet distribution, with a uniform prior on the parameters α (see above).

$$p(s) = Dir(\alpha)$$

- A uniform prior over family probabilities can be obtained by setting:

$$\forall m \in f_k : \alpha_{prior}(m) = \frac{1}{|f_k|}$$

Stephan et al. 2009, *NeuroImage*
Penny et al. 2010, *PLoS Comput. Biol.*

Family-level inference: random effects – a special case

- When the families are of equal size, one can simply sum the posterior model probabilities within families by exploiting the agglomerative property of the Dirichlet distribution:

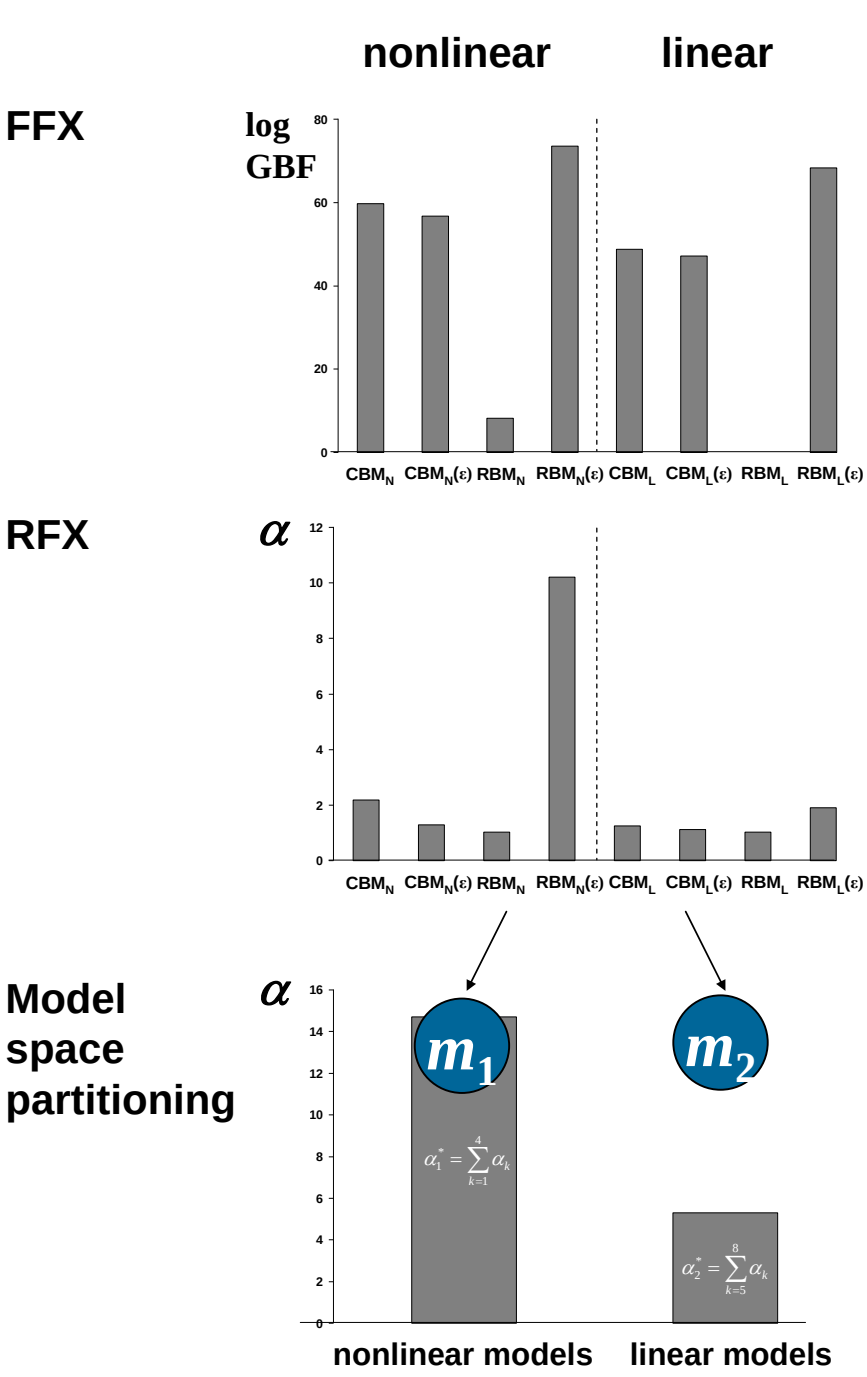
$$\left(r_1, r_2, ..., r_K\right) \sim Dir\left(\alpha_1, \alpha_2, ..., \alpha_K\right)$$

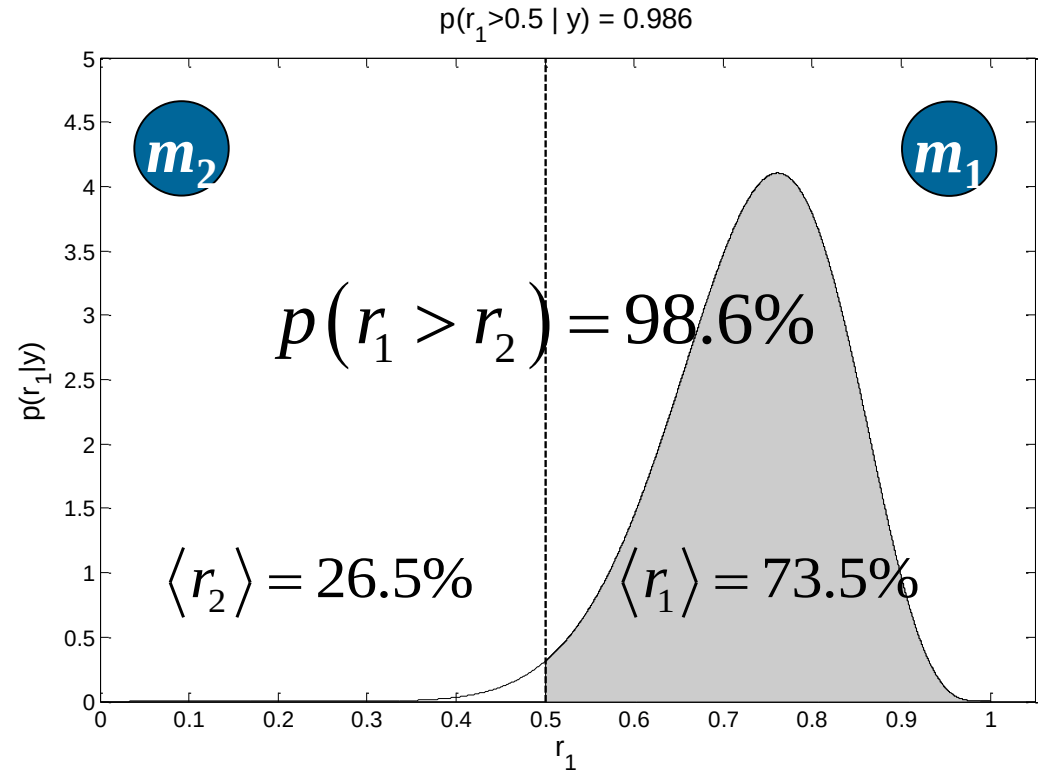
$$\Rightarrow r_1^* = \sum_{k \in N_1} r_k, r_2^* = \sum_{k \in N_2} r_k, ..., r_J^* = \sum_{k \in N_J} r_k$$

$$\sim Dir\left(\alpha_1^* = \sum_{k \in N_1} \alpha_k, \alpha_2^* = \sum_{k \in N_2} \alpha_k, ..., \alpha_J^* = \sum_{k \in N_J} \alpha_k\right)$$

Stephan et al. 2009, *NeuroImage*

Model space partitioning: comparing model families





Stephan et al. 2009, *NeuroImage*

Bayesian Model Averaging (BMA)

- abandons dependence of parameter inference on a single model and takes into account model uncertainty
- represents a particularly useful alternative
  - when none of the models (or model subspaces) considered clearly outperforms all others
  - when comparing groups for which the optimal model differs

single-subject BMA:

$$p(\theta \mid y)$$

$$= \sum_m p(\theta \mid y, m) p(m \mid y)$$

group-level BMA:

$$p(\theta_n \mid y_{1..N})$$

$$= \sum_m p(\theta_n \mid y_n, m) p(m \mid y_{1..N})$$

NB: $p(m|y_{1..N})$ can be obtained by either FFX or RFX BMS

Penny et al. 2010, *PLoS Comput. Biol.*

Protected exceedance probability: Using BMA to protect against chance findings

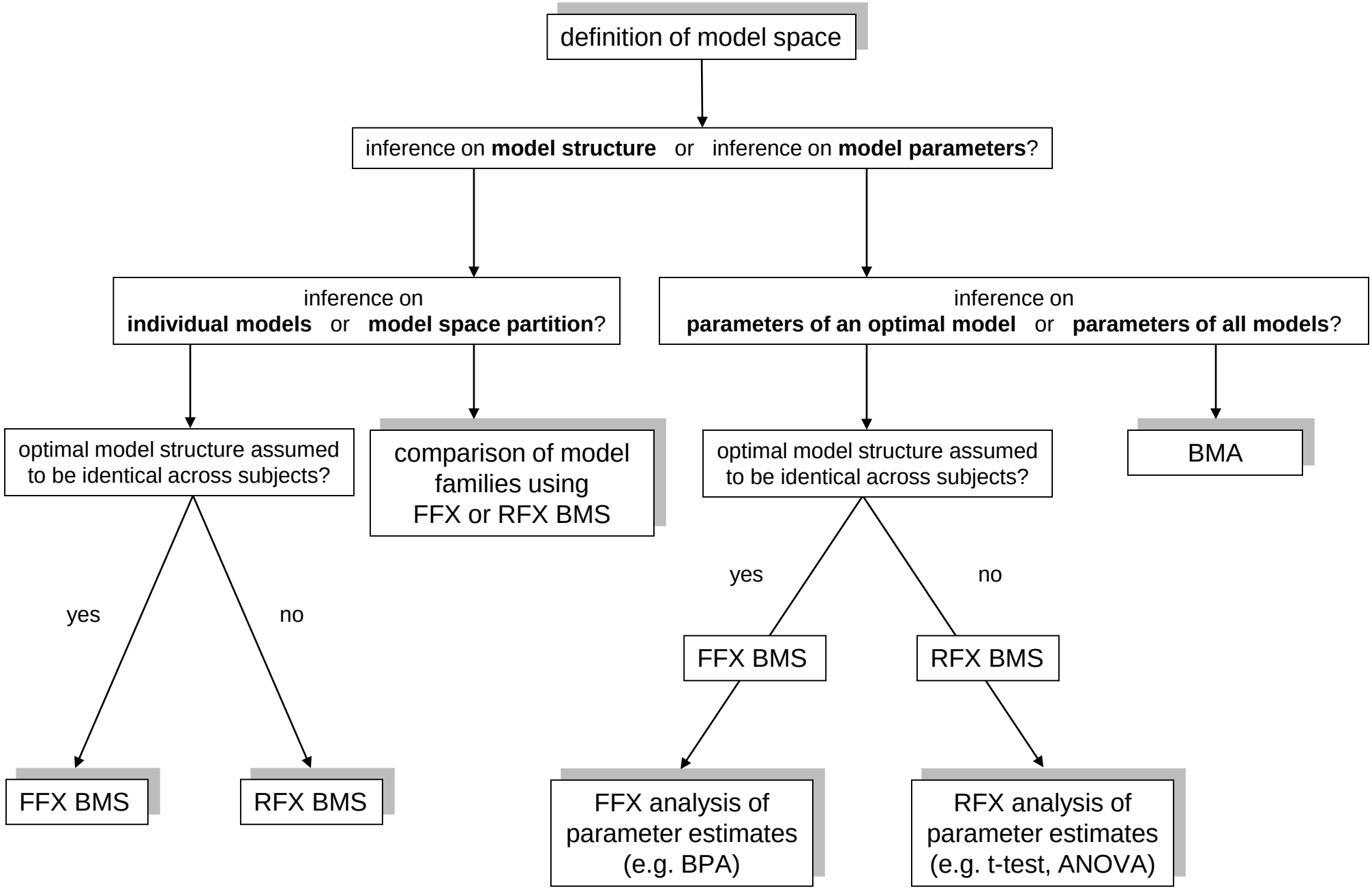
- EPs express our confidence that the posterior probabilities of models are different – under the hypothesis H_1 that models differ in probability: $r_k \neq 1/K$
- does not account for possibility "null hypothesis" H_0: $r_k = 1/K$
- **Bayesian omnibus risk (BOR)** of wrongly accepting H_1 over H_0:

$$P_o = \frac{1}{1 + \frac{p(m|H_1)}{p(m|H_0).}}$$

- **protected EP**: Bayesian model averaging over H_0 and H_1:

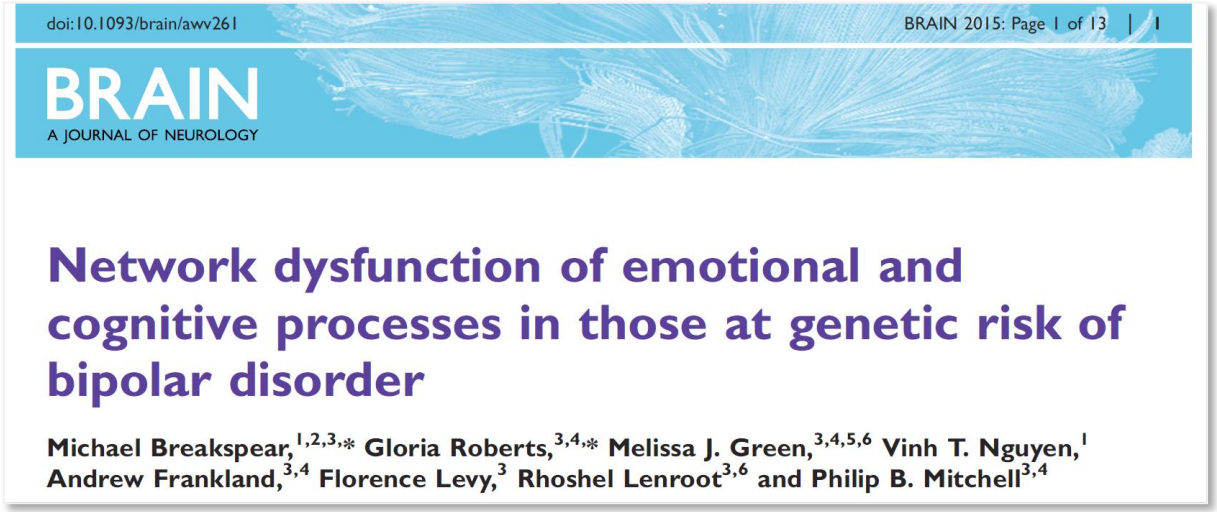
$$\begin{aligned}\tilde{\varphi}_k &= P(r_k \geq r_{k' \neq k}|y) \\ &= P(r_k \geq r_{k' \neq k}|y, H_1)P(H_1|y) + P(r_k \geq r_{k' \neq k}|y, H_0)P(H_0|y) \\ &= \varphi_k(1 - P_0) + \frac{1}{K}P_0\end{aligned}$$

Rigoux et al. 2014, *NeuroImage*



Stephan et al. 2010, *NeuroImage*

Two empirical example applications

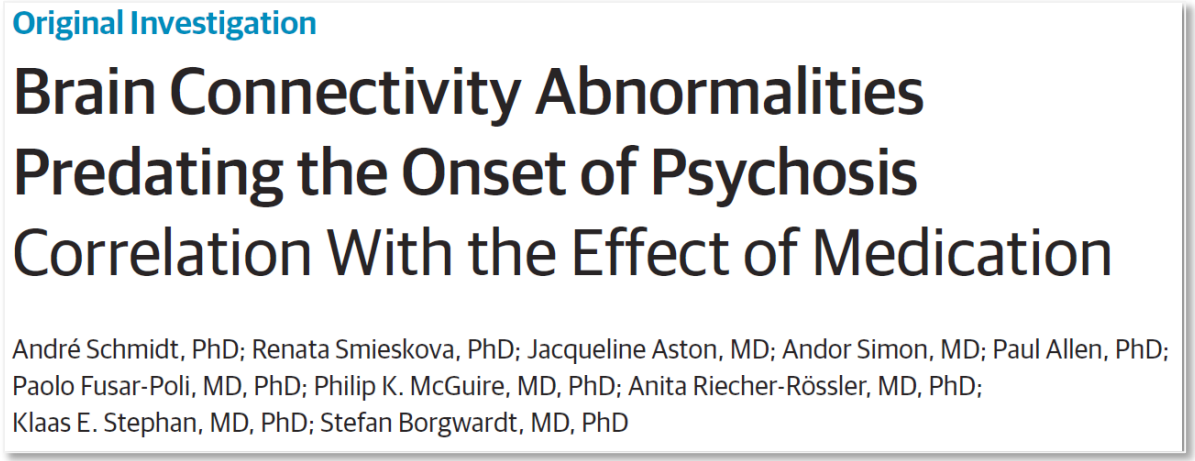

doi:10.1093/brain/awv261 BRAIN 2015: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Network dysfunction of emotional and cognitive processes in those at genetic risk of bipolar disorder

Michael Breakspear,[1,2,3,*] Gloria Roberts,[3,4,*] Melissa J. Green,[3,4,5,6] Vinh T. Nguyen,[1] Andrew Frankland,[3,4] Florence Levy,[3] Rhoshel Lenroot[3,6] and Philip B. Mitchell[3,4]

Breakspear et al. 2015, *Brain*


Original Investigation

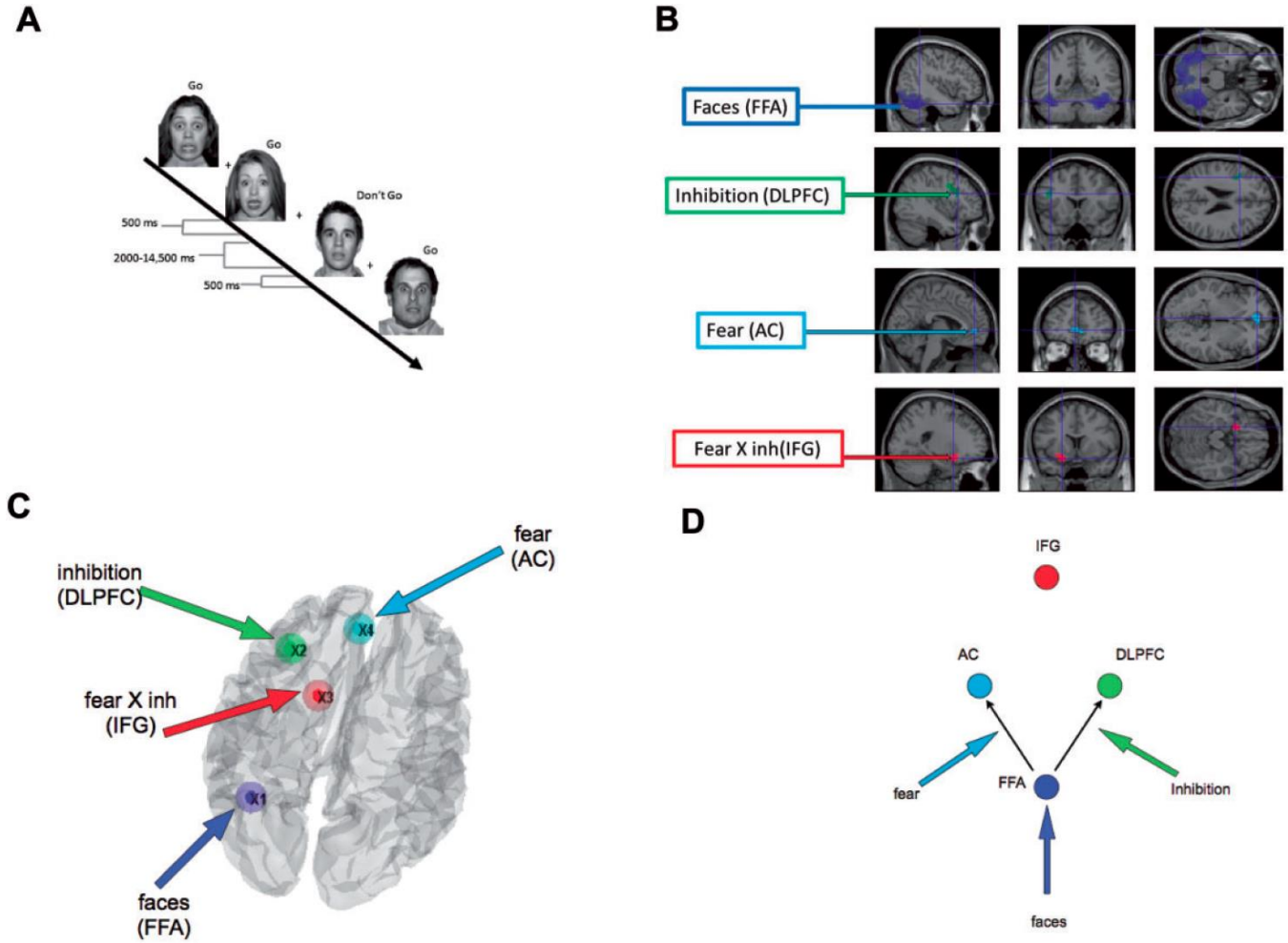
Brain Connectivity Abnormalities Predating the Onset of Psychosis
Correlation With the Effect of Medication

André Schmidt, PhD; Renata Smieskova, PhD; Jacqueline Aston, MD; Andor Simon, MD; Paul Allen, PhD; Paolo Fusar-Poli, MD, PhD; Philip K. McGuire, MD, PhD; Anita Riecher-Rössler, MD, PhD; Klaas E. Stephan, MD, PhD; Stefan Borgwardt, MD, PhD

Schmidt et al. 2013, *JAMA Psychiatry*

Go/No-Go task to emotional faces (bipolar patients, at-risk individuals, controls)

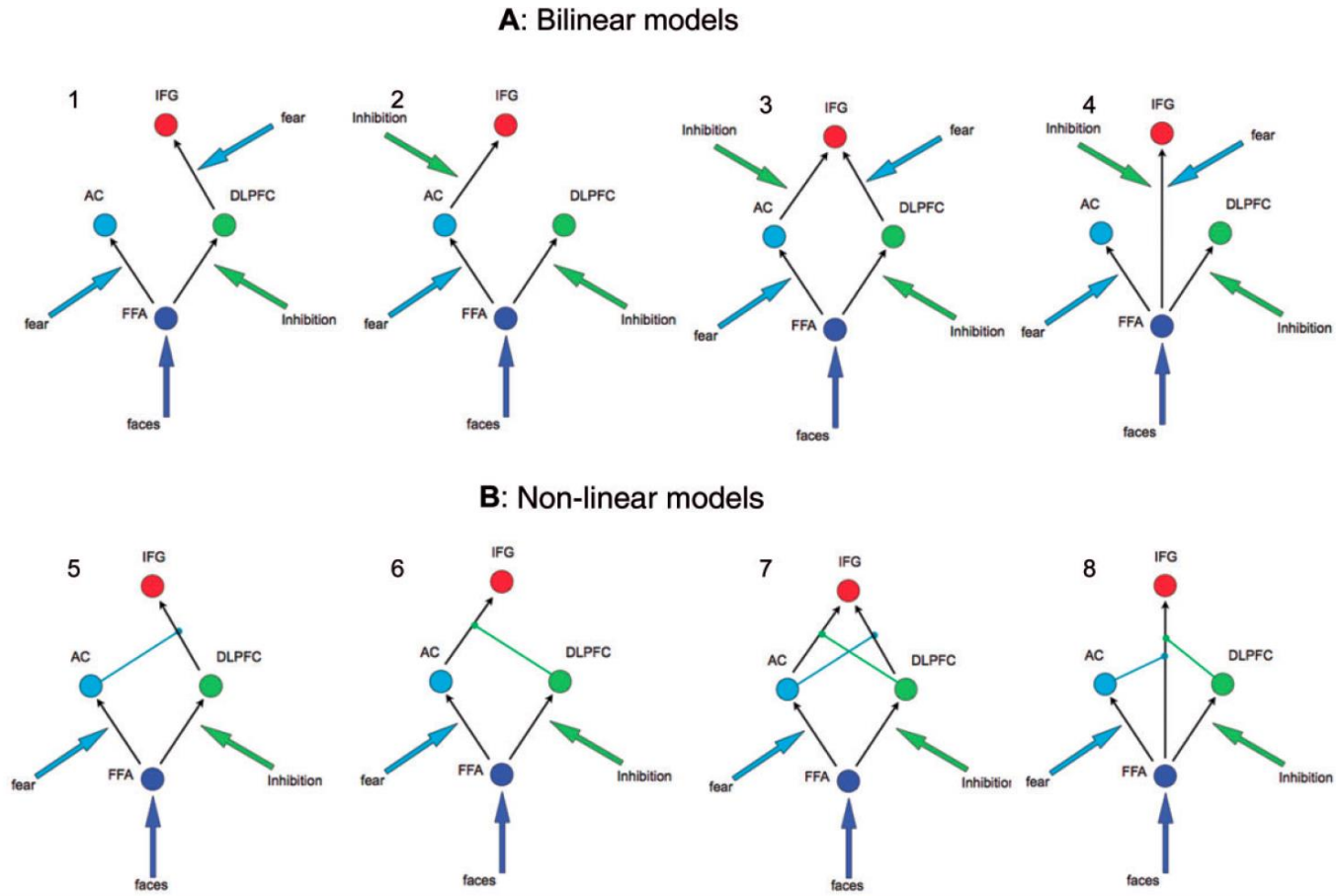
- Hypoactivation of left IFG in the at-risk group during fearful distractor trials
- DCM used to explain interaction of motor inhibition and fear perception
- That is: what is the most likely circuit mechanism explaining the fear x inhibition interaction in IFG?



Breakspear et al. 2015, *Brain*

Model space

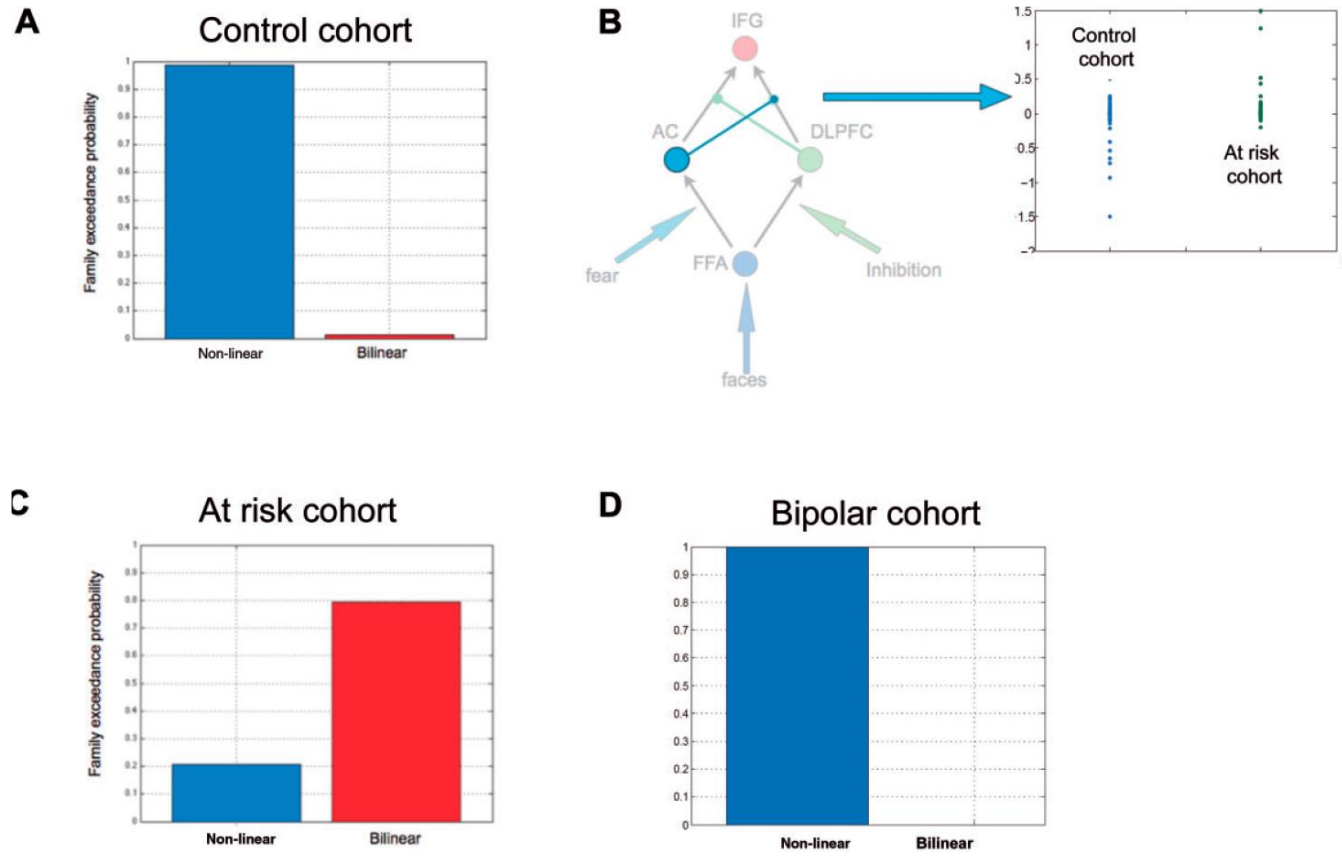
- models of serial (1-3), parallel (4) and hierarchical (5-8) processes



Breakspear et al. 2015, *Brain*

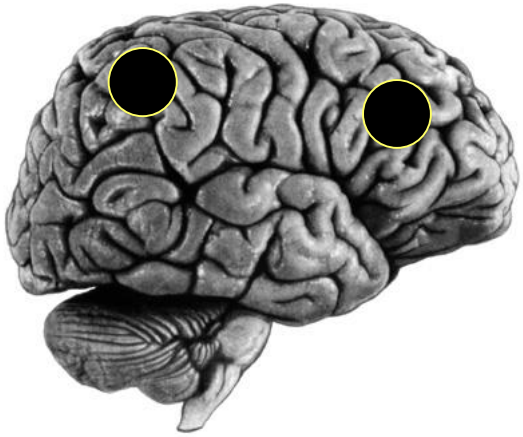
Family-level BMS

- family-level comparison: nonlinear models more likely than bilinear ones in both healthy controls and bipolar patients
- at-risk group: bilinear models more likely
- significant group difference in ACC modulation of DLPFC→IFG interaction

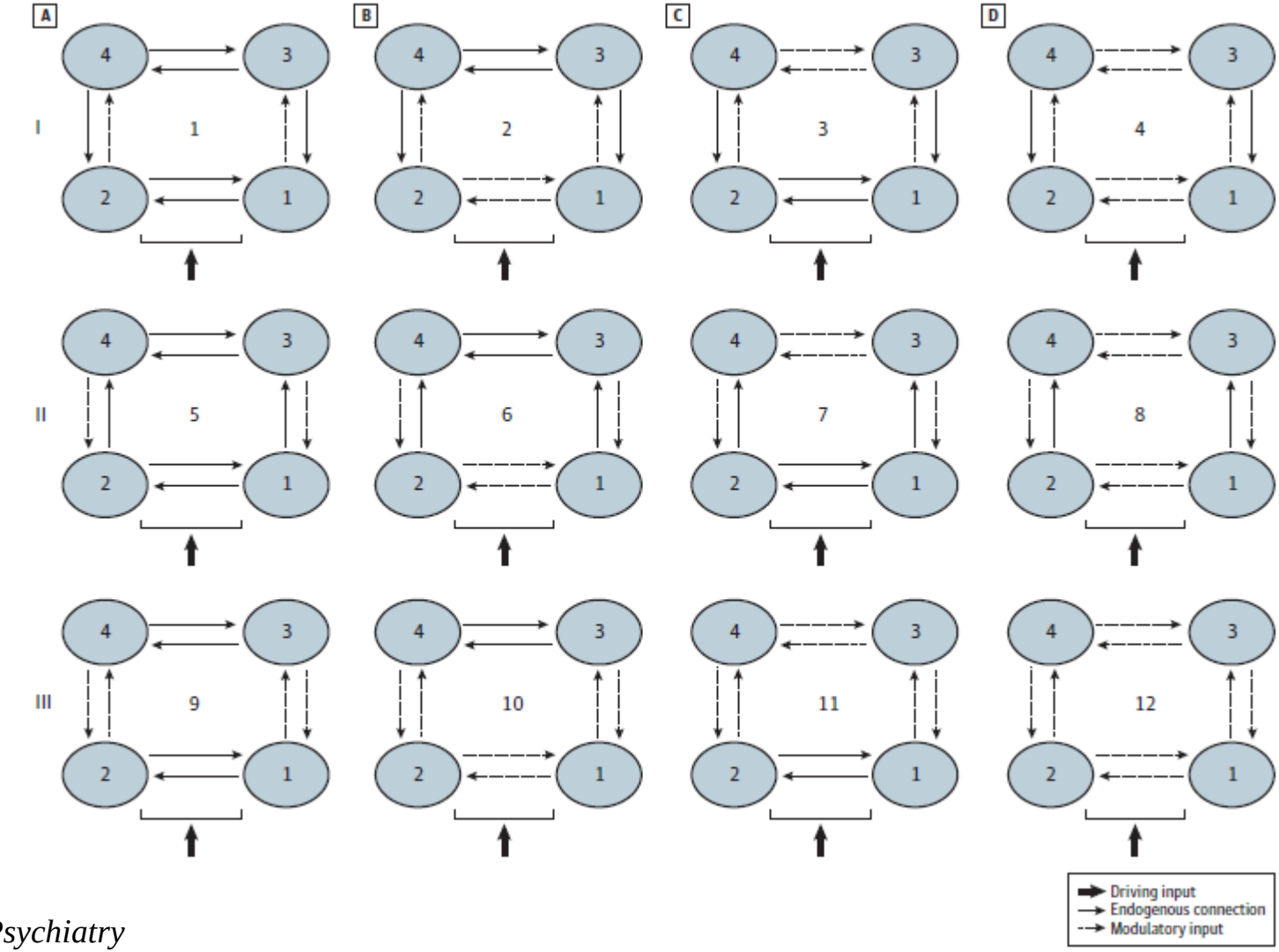


Breakspear et al. 2015, *Brain*

Prefrontal-parietal connectivity during working memory in schizophrenia

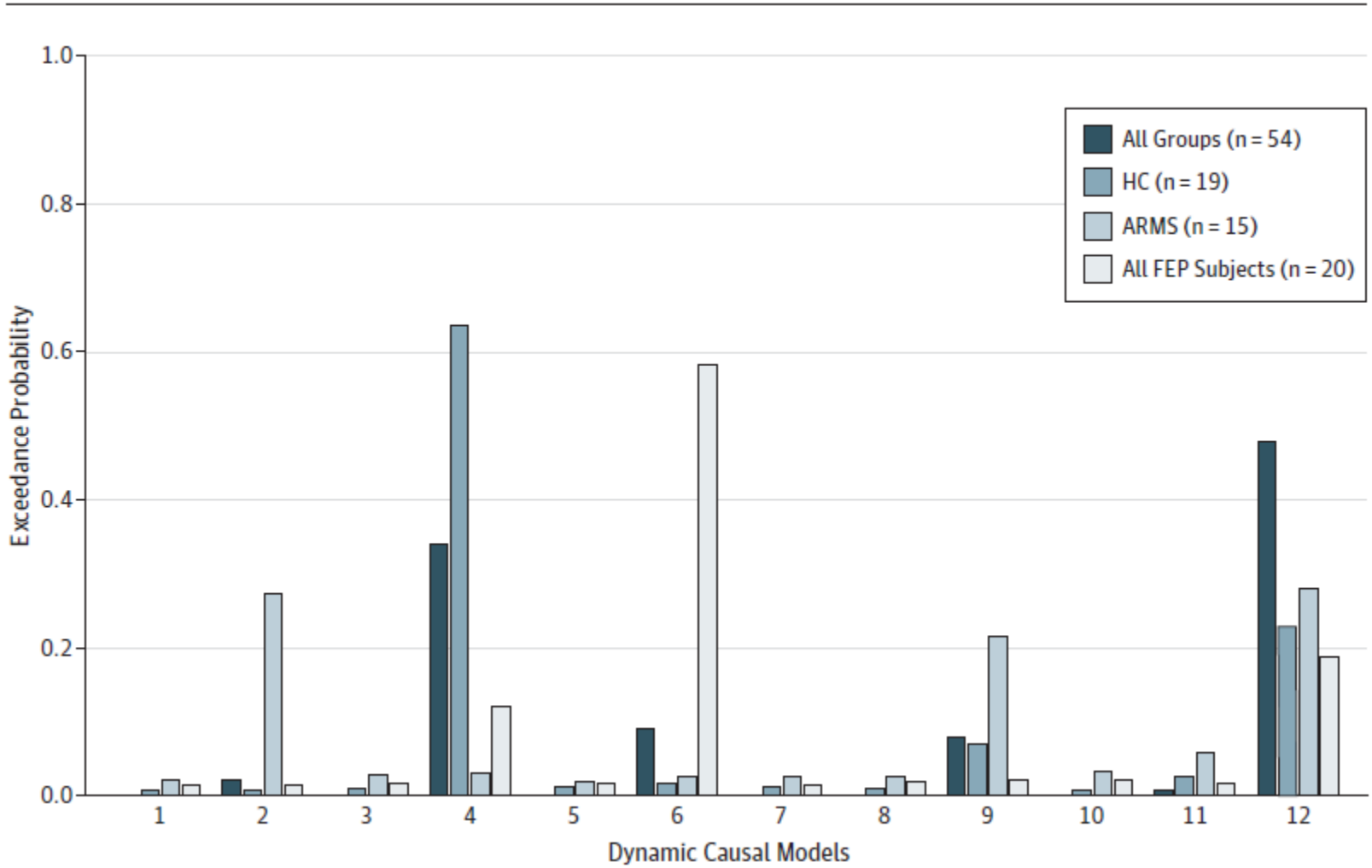


- 17 at-risk mental state (ARMS) individuals
- 21 first-episode patients (13 non-treated)
- 20 controls



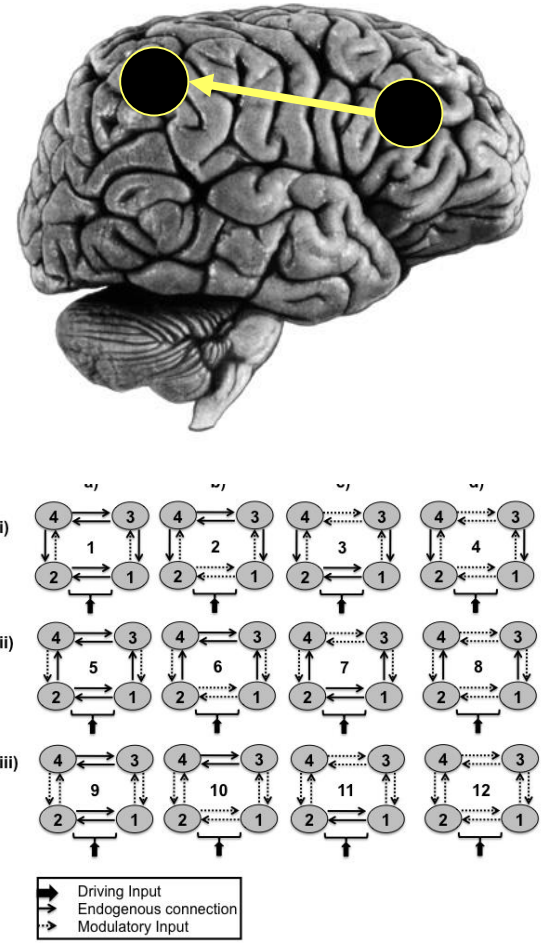
Schmidt et al. 2013, *JAMA Psychiatry*

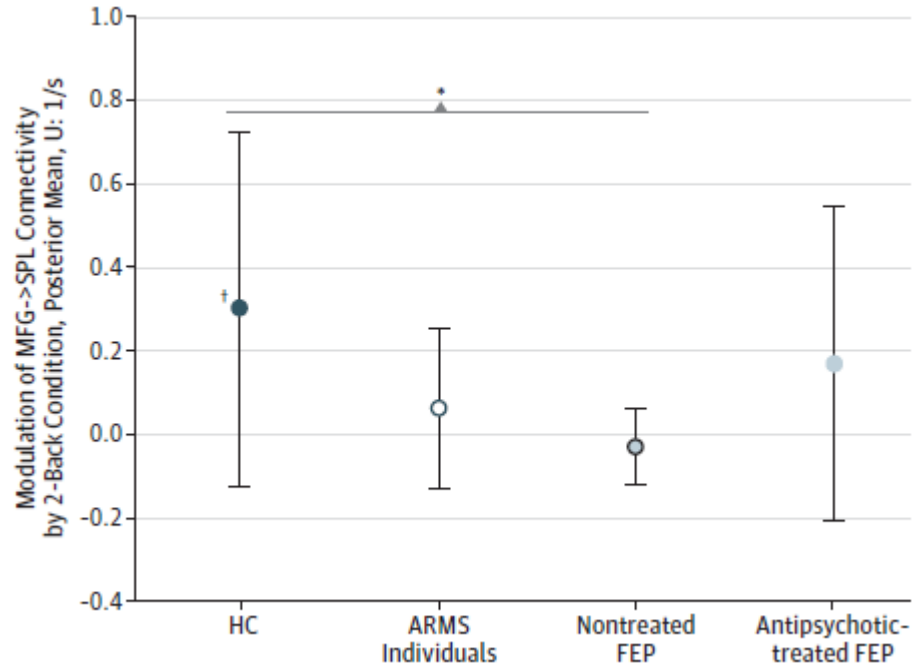
BMS results for all groups



Schmidt et al. 2013, *JAMA Psychiatry*

BMA results: PFC → PPC connectivity





17 ARMS, 21 first-episode (13 non-treated), 20 controls

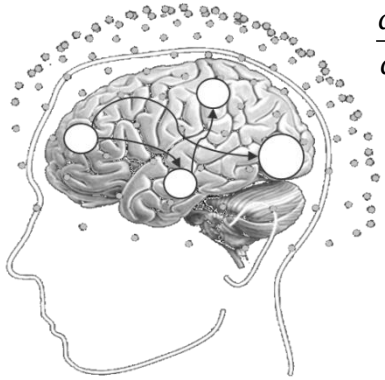
Schmidt et al. 2013, *JAMA Psychiatry*

Overview

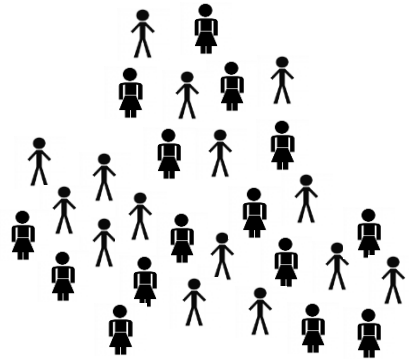
- DCM: basic concepts
- Evolution of DCM for fMRI
- Bayesian model selection (BMS)
- Translational Neuromodeling

Translational Neuromodeling

❶ Computational assays: Models of disease mechanisms

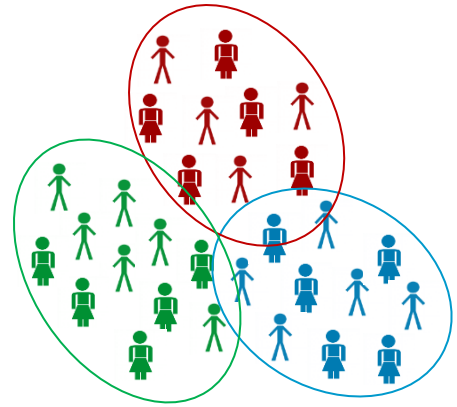


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



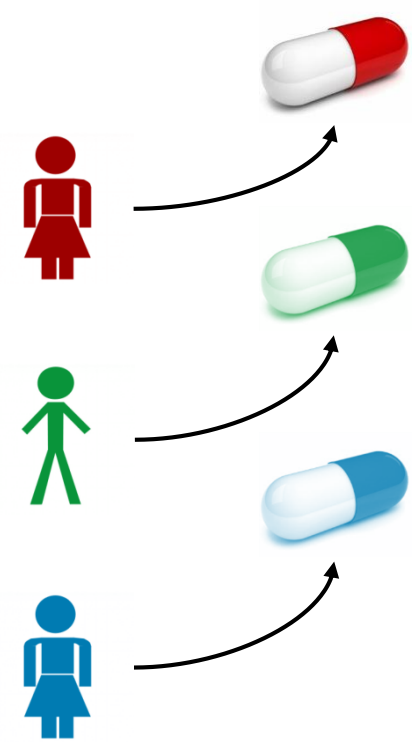
❷ Application to brain activity and behaviour of individual patients

❸ Detecting physiological subgroups (based on inferred mechanisms)



- disease mechanism A
- disease mechanism B
- disease mechanism C

❹ Individual treatment prediction

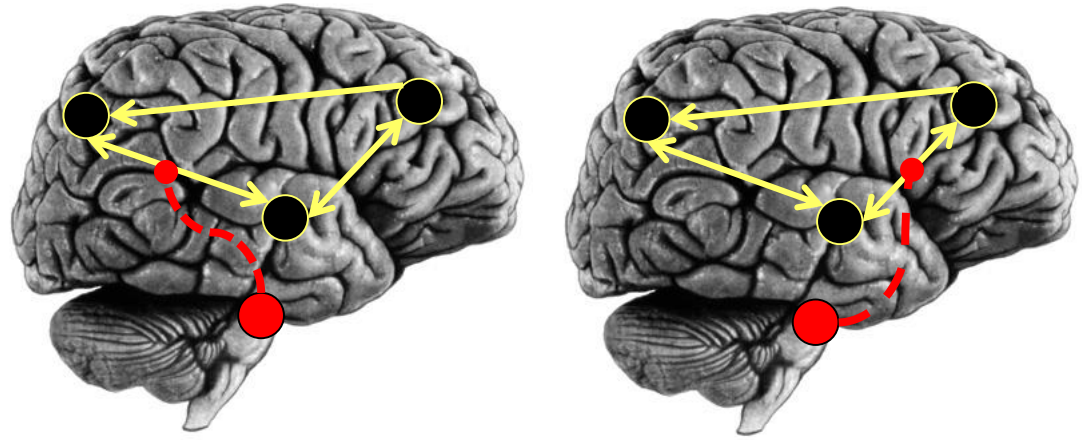


Stephan et al. 2015, *Neuron*

Model-based predictions for single patients

model structure

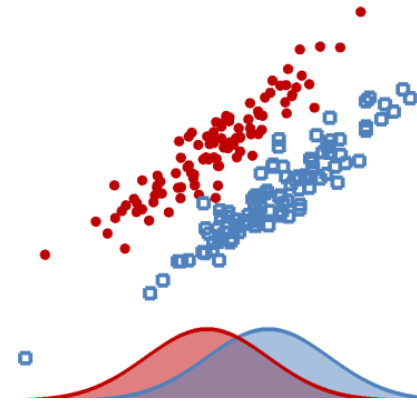
→ ***BMS***



DA

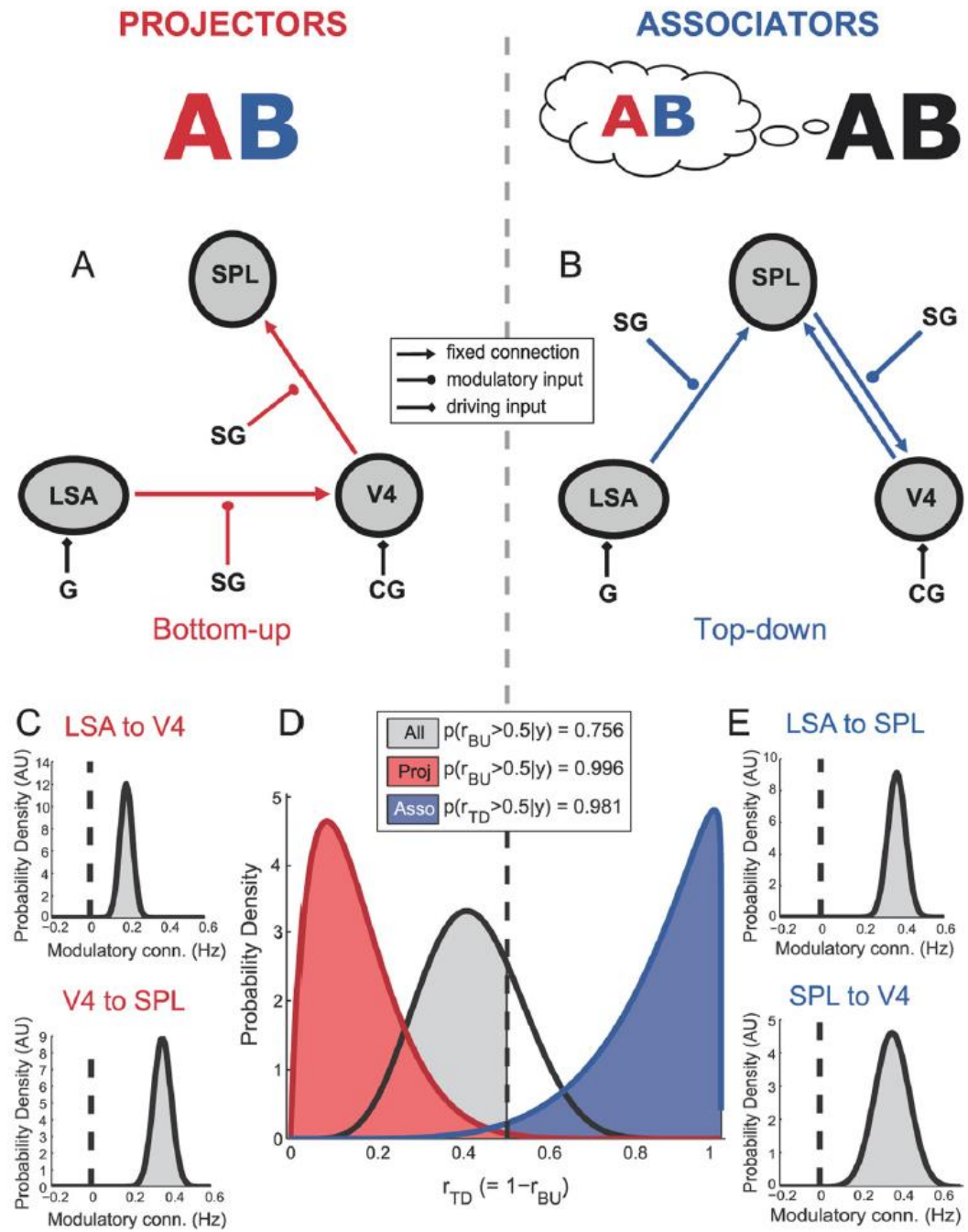
parameter estimates

→ ***model-based decoding (generative embedding)***



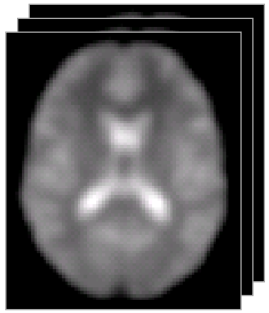
Synaesthesia

- “projectors” experience color externally colocalized with a presented grapheme
- “associators” report an internally evoked association
- across all subjects: no evidence for either model
- but BMS results map precisely onto projectors (bottom-up mechanisms) and associators (top-down)



van Leeuwen et al. 2011, *J. Neurosci.*

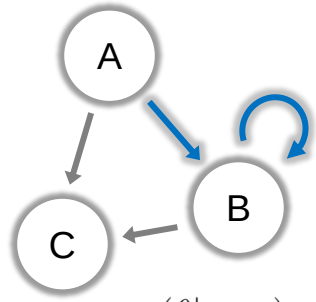
Generative embedding (supervised): classification



measurements from
an individual subject

**step 1 —
model inversion**

$\mathcal{X} \to \mathcal{M}_\Theta$



$p(\theta|x, m)$

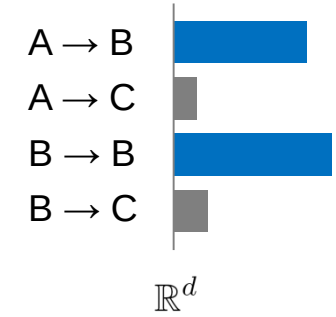
subject-specific
inverted generative model

**step 2 —
kernel construction**

$\mathcal{M}_\Theta \to \mathbb{R}^d$

$k : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$

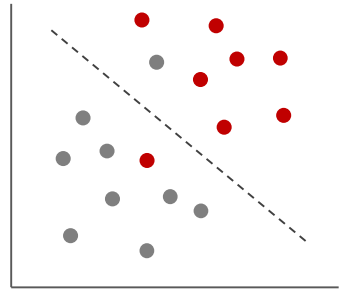
$k_\mathcal{M} : \mathcal{M}_\Theta \times \mathcal{M}_\Theta \to \mathbb{R}$



subject representation in the
generative score space

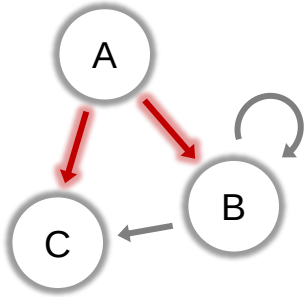
**step 3 —
support vector classification**

$$\hat{c} = \text{sgn}\left(\sum_i^n \alpha_i^* k(x_i, x) + b^*\right)$$



separating hyperplane fitted to
discriminate between groups

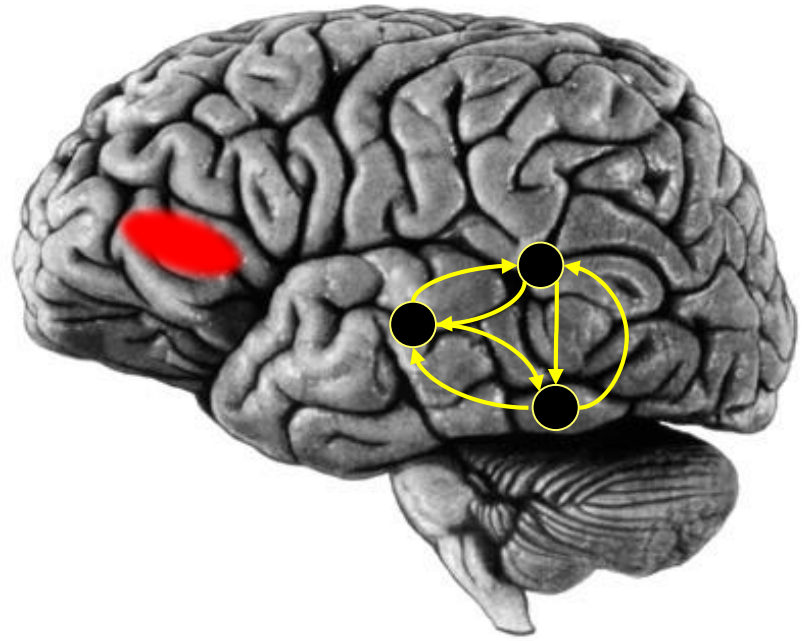
**step 4 —
interpretation**



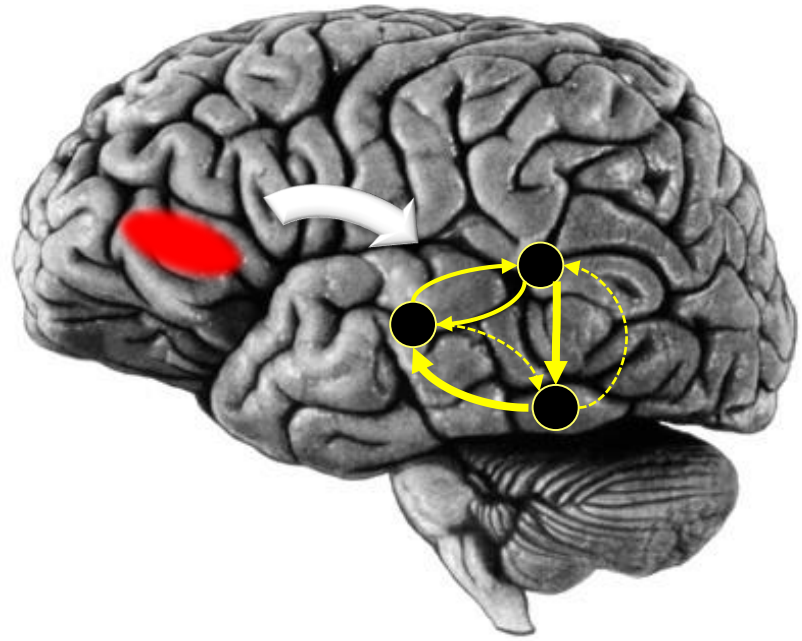
jointly discriminative
model parameters

Brodersen et al. 2011, *PLoS Comput. Biol.*

Discovering remote or “hidden” brain lesions

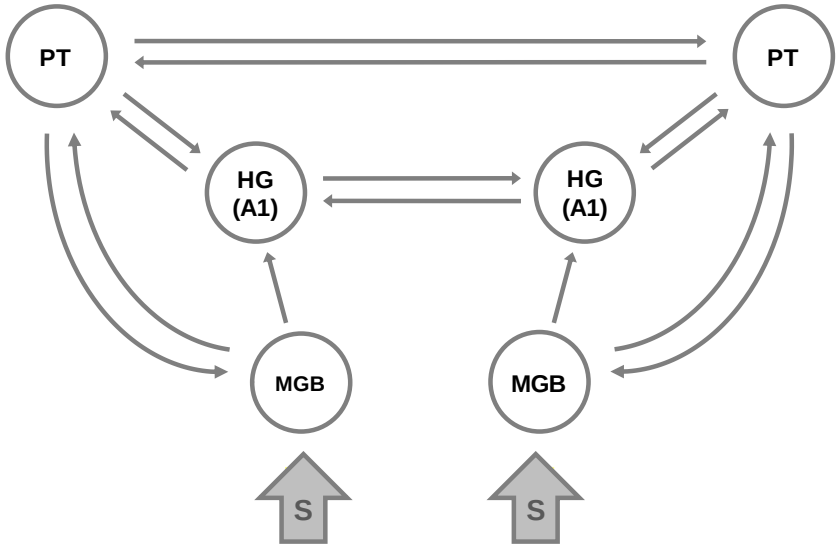


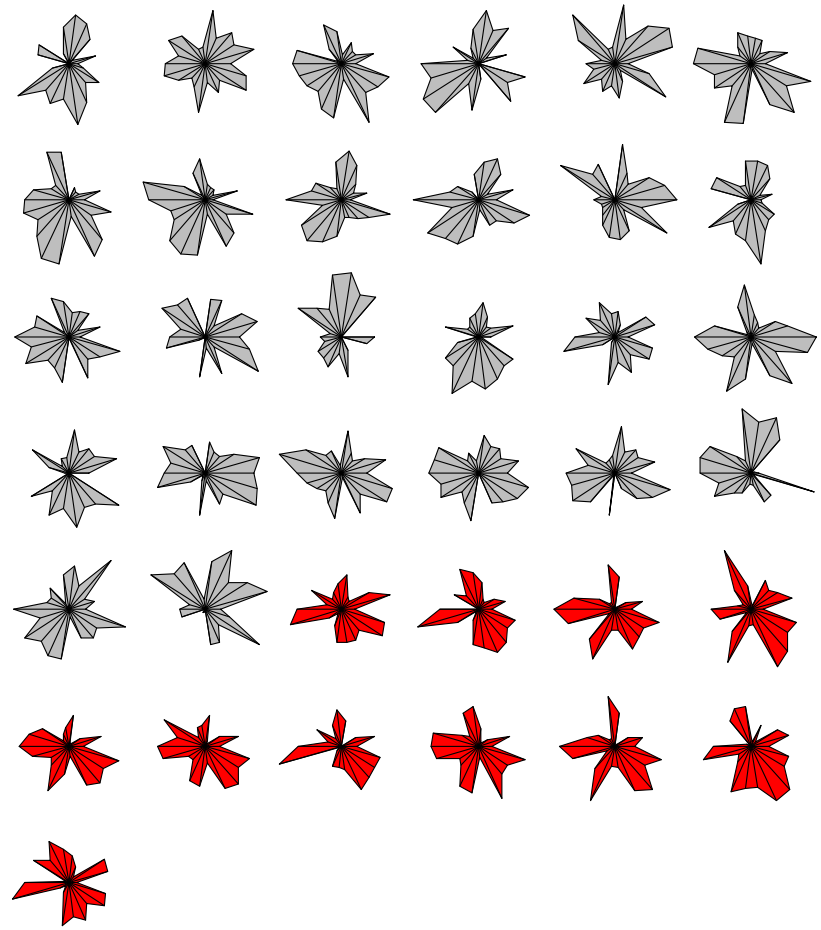
Discovering remote or “hidden” brain lesions



Connectional fingerprints : aphasic patients (N=11) vs. controls (N=26)

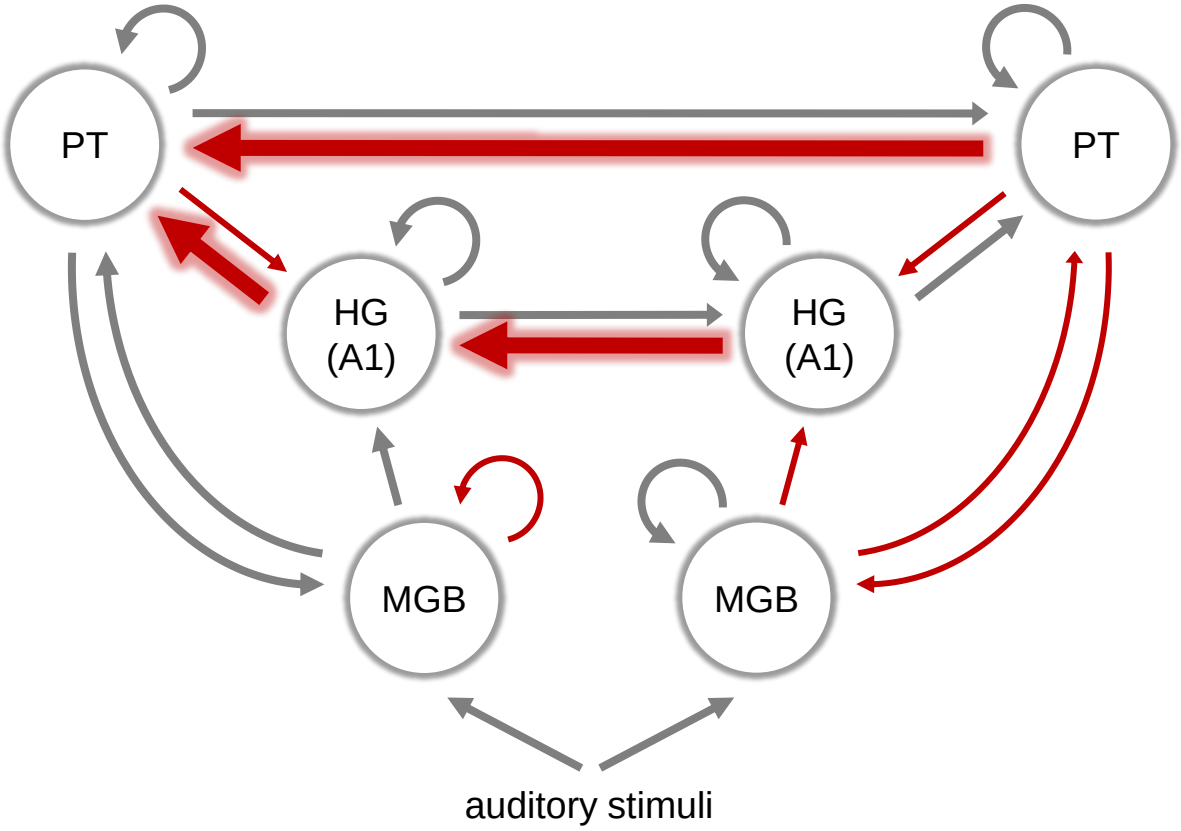
6-region DCM of auditory areas during passive speech listening

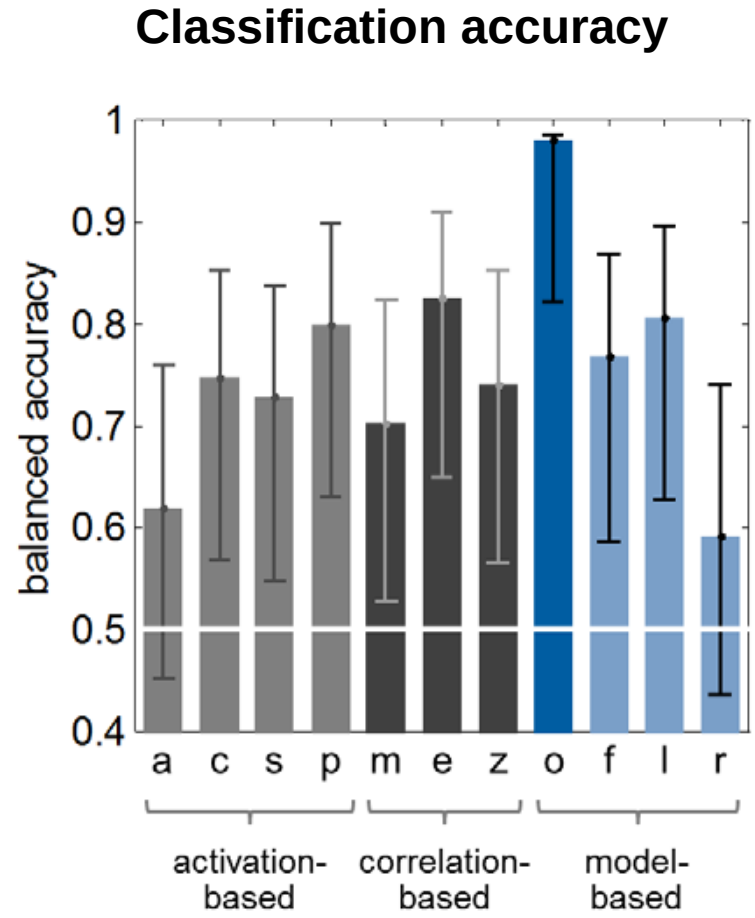




Brodersen et al. 2011, *PLoS Comput. Biol.*

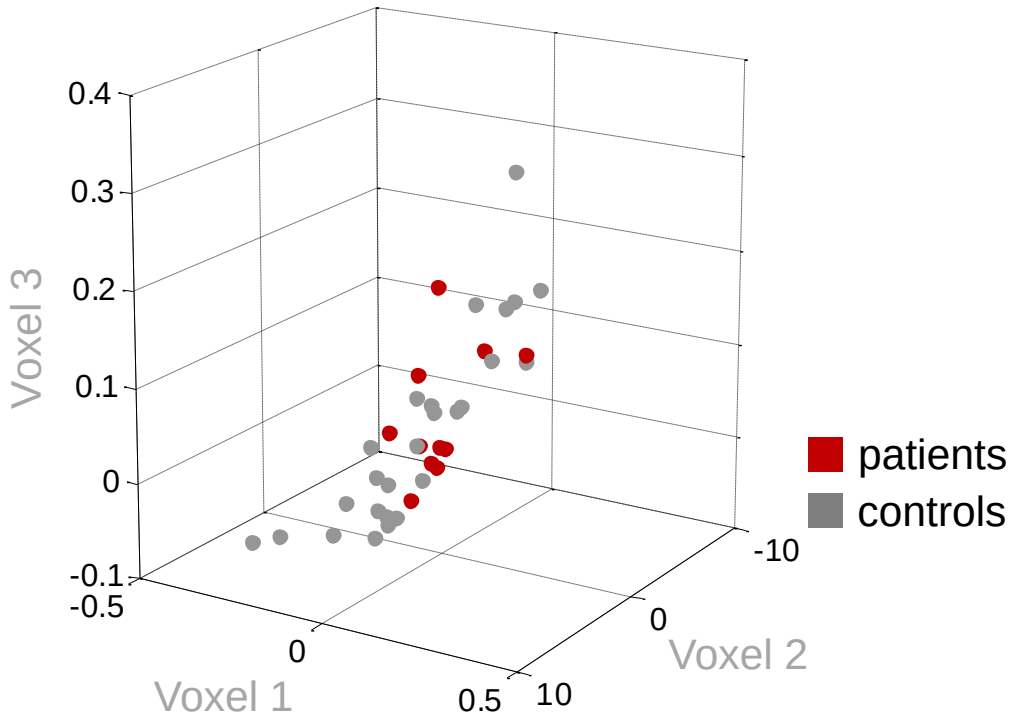
Can we predict presence/absence of the "hidden" lesion?





Brodersen et al. 2011, *PLoS Comput. Biol.*

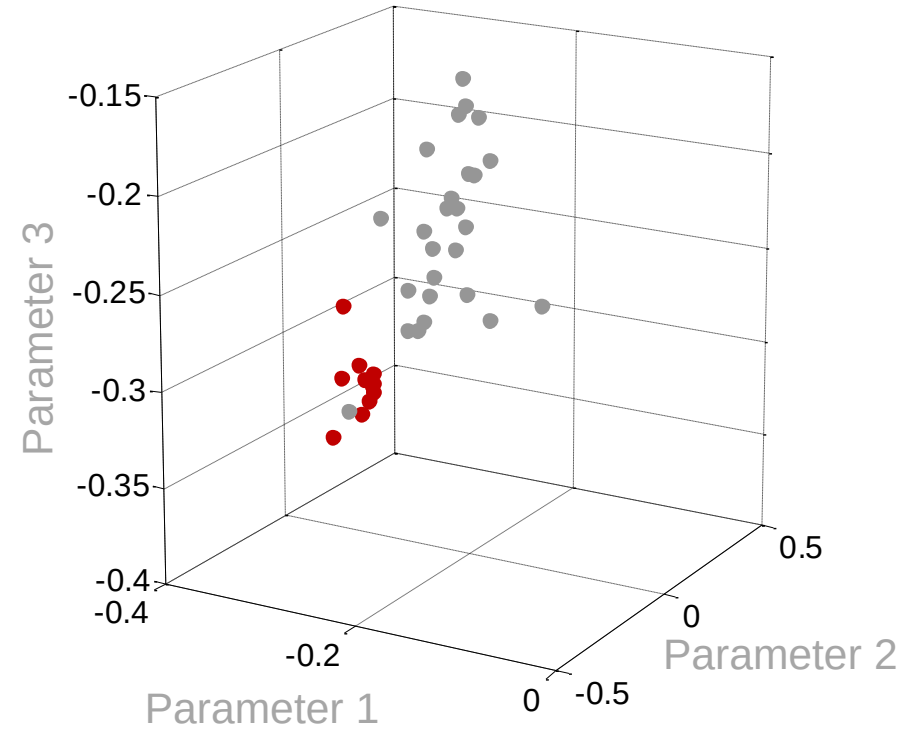
Voxel-based activity space



classification accuracy

75%

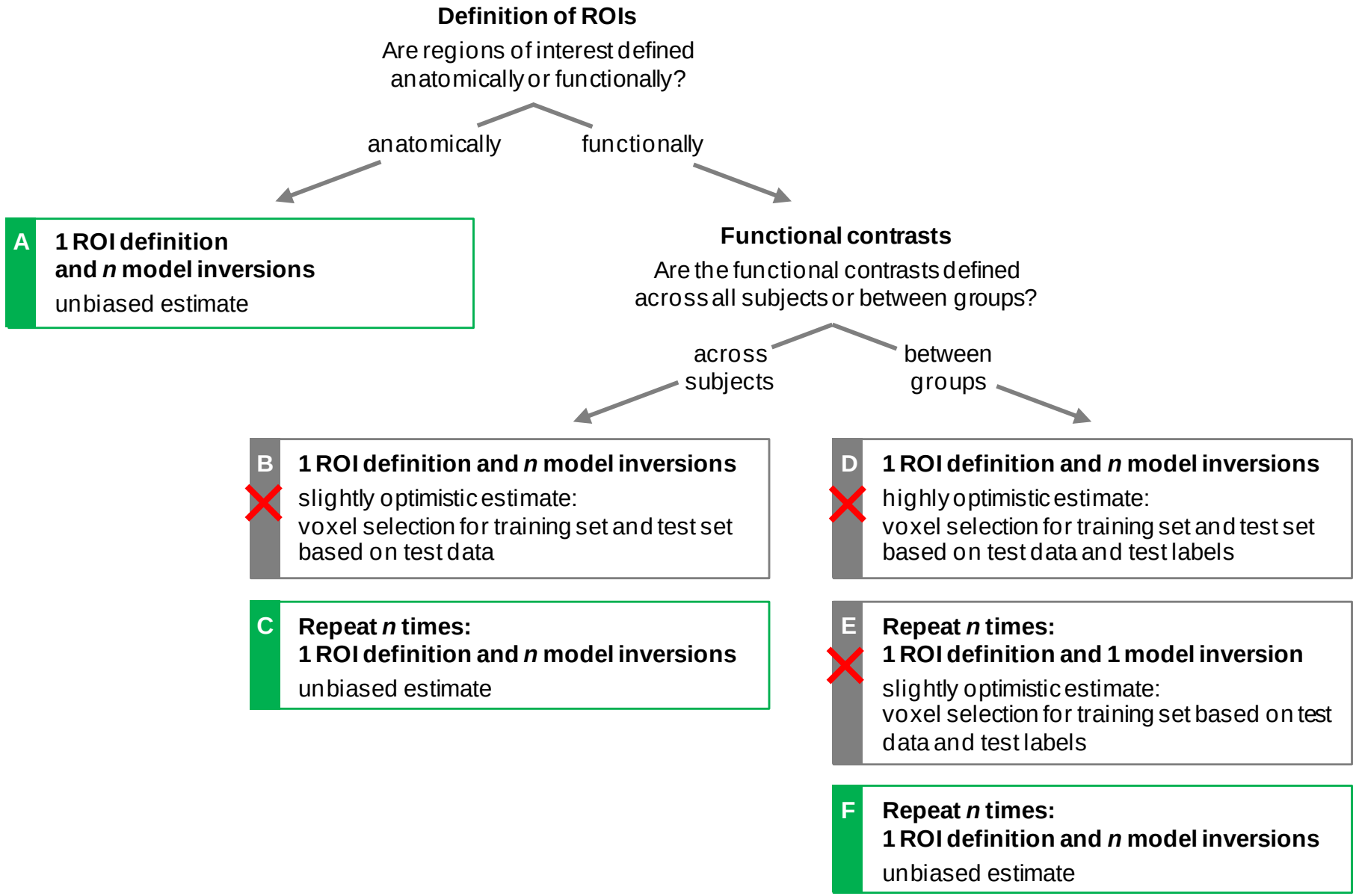
Model-based parameter space



classification accuracy

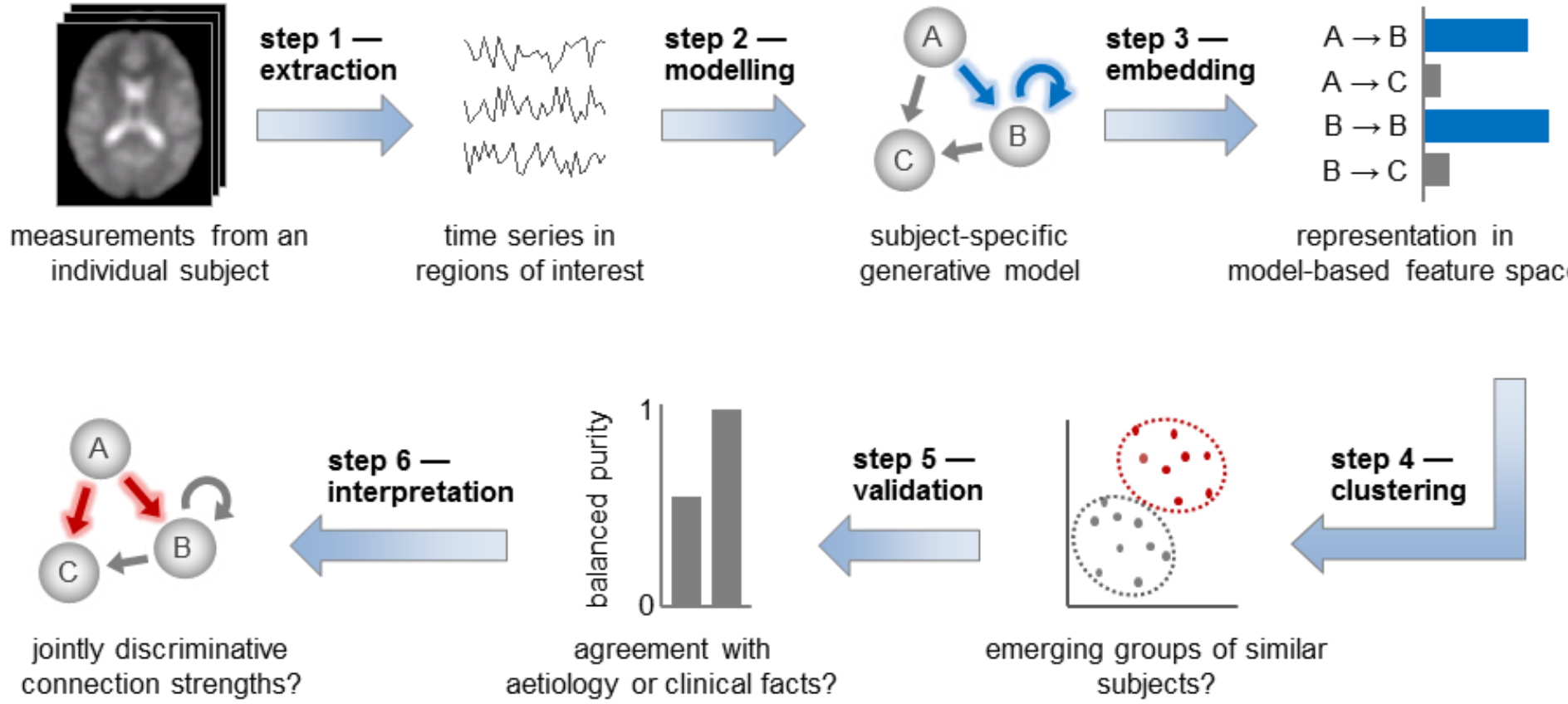
98%

Brodersen et al. 2011, *PLoS Comput. Biol.*



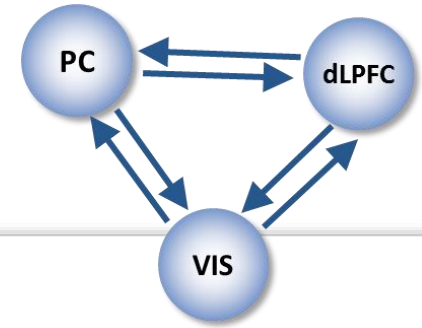
Brodersen et al. 2011, *PLoS Comput. Biol.*

Generative embedding (unsupervised): detecting patient subgroups

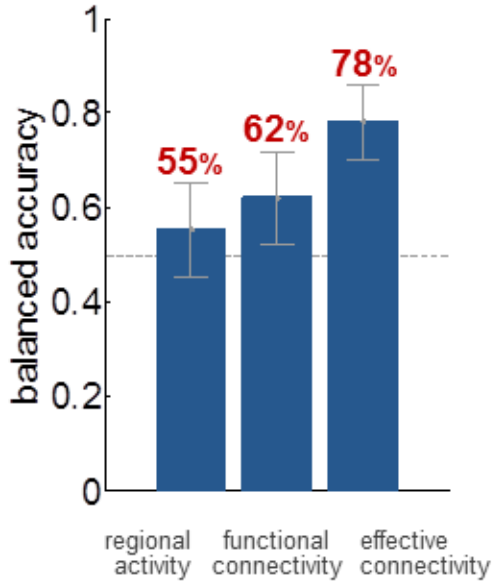


Brodersen et al. 2014, *NeuroImage: Clinical*

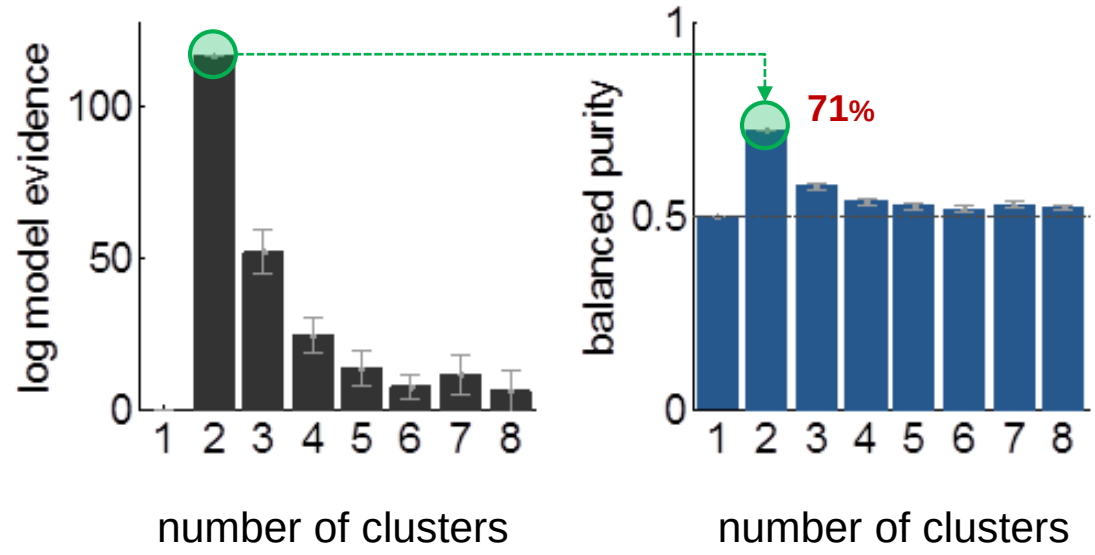
Generative embedding of variational Gaussian Mixture Models



Supervised:
SVM classification



Unsupervised:
GMM clustering

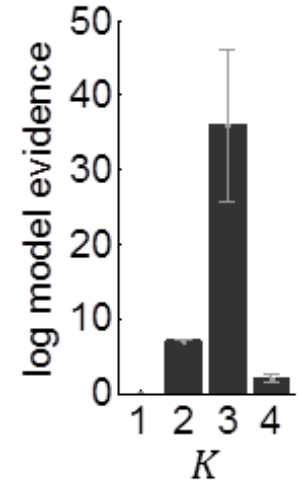


- 42 controls vs. 41 schizophrenic patients
- fMRI data from working memory task (Deserno et al. 2012, J. Neurosci)

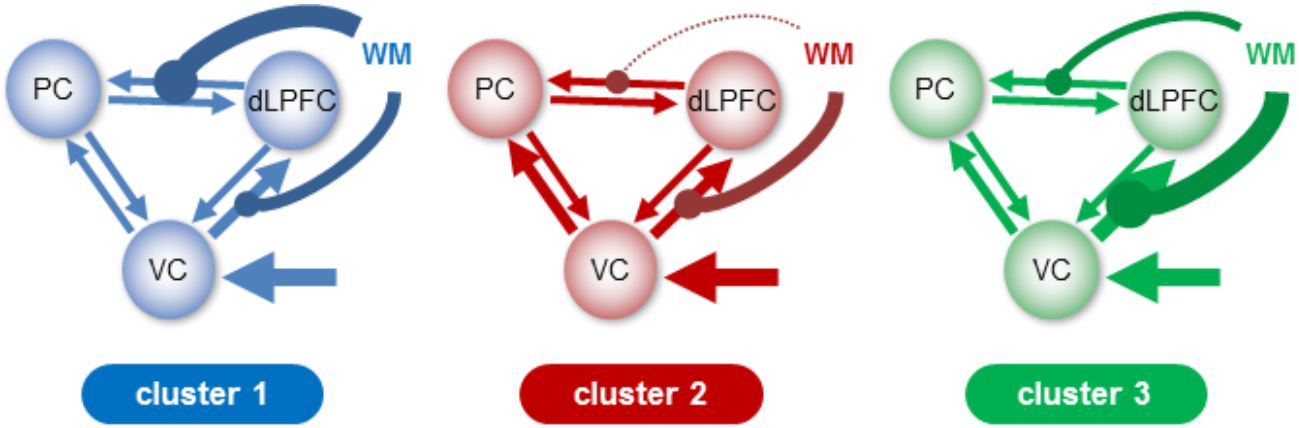
Brodersen et al. (2014) *NeuroImage: Clinical*

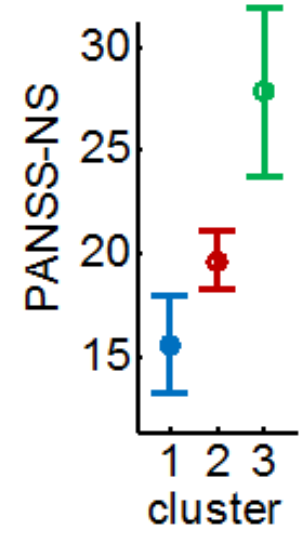
Detecting subgroups of patients in schizophrenia

Optimal cluster solution

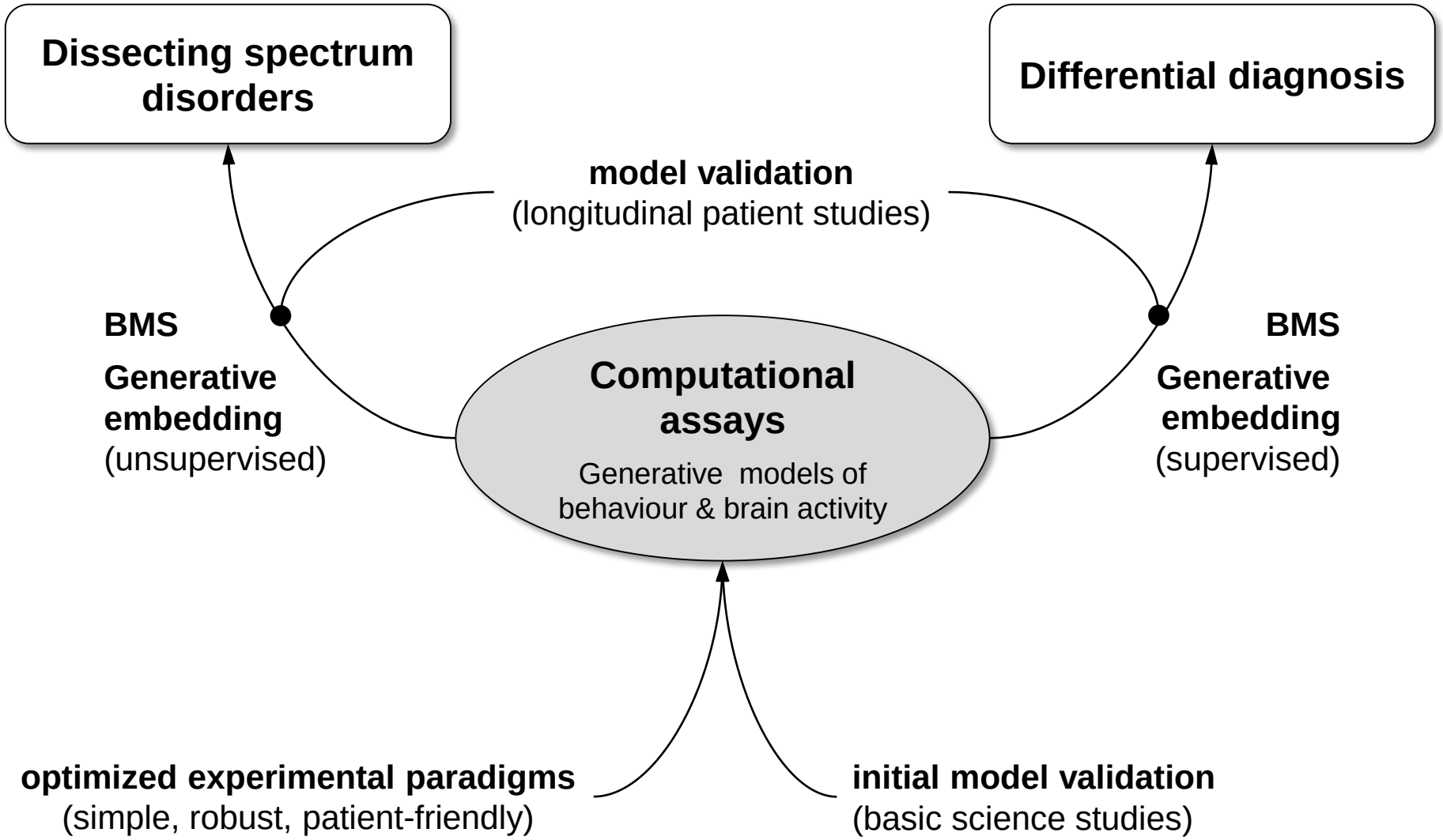


- three distinct subgroups (total N=41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)





Brodersen et al. (2014) *NeuroImage: Clinical*



Stephan & Mathys 2014, *Curr. Opin. Neurobiol.*

Further reading: DCM for fMRI and BMS – part 1

- Aponte EA, Raman S, Sengupta B, Penny WD, Stephan KE, Heinzle J (2015) mpdcm: A Toolbox for Massively Parallel Dynamic Causal Modeling. Journal of Neuroscience Methods, in press
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- Penny WD, Stephan KE, Mechelli A, Friston KJ (2004b) Modelling functional integration: a comparison of structural equation and dynamic causal models. NeuroImage 23 Suppl 1:S264-274.

Further reading: DCM for fMRI and BMS – part 2

- Penny WD, Stephan KE, Daunizeau J, Joao M, Friston K, Schofield T, Leff AP (2010) Comparing Families of Dynamic Causal Models. PLoS Computational Biology 6: e1000709.
- Penny WD (2012) Comparing dynamic causal models using AIC, BIC and free energy. Neuroimage 59: 319-330.
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- Stephan KE, Harrison LM, Penny WD, Friston KJ (2004) Biophysical models of fMRI responses. Curr Opin Neurobiol 14:629-635.
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Thank you