Translational Neuromodeling Unit

University of Zurich[UZH]

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Swiss Federal Institute of Technology Zurich

Dynamic Causal Modeling (DCM):

Advanced Topics

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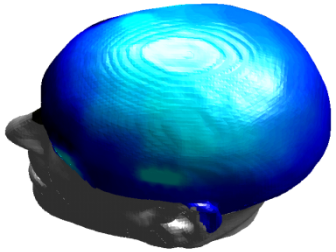
With many thanks for slides & images to: Klaas Enno Stephan, Jakob Heinzle, TNU & FIL

Overview

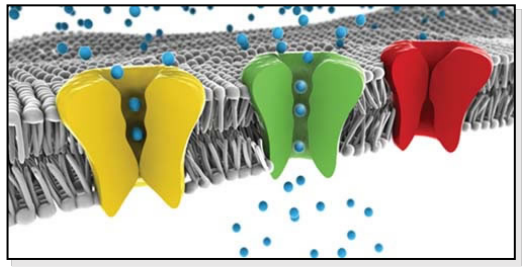
- DCM – basic concepts
- Evolution of DCM for fMRI
- Bayesian model selection (BMS)
- Embedding computational models in DCMs
- Integrating tractography and DCM
- Translational Neuromodeling

GENERATIVE MODEL



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

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



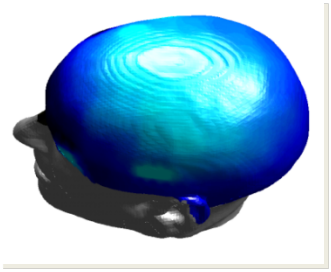
1. enforces mechanistic thinking: how could the data have been caused?
2. generate synthetic data (observations) by sampling from the prior – can model explain certain phenomena at all?
3. inference about model structure: formal approach to disambiguating mechanisms → p(y|m)
4. inference about parameters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

DYNAMIC CAUSAL MODELING

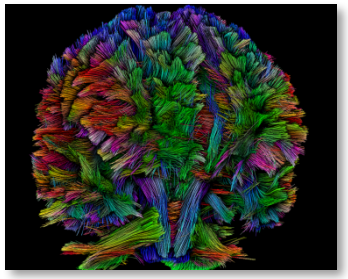
EEG, MEG

dwMRI

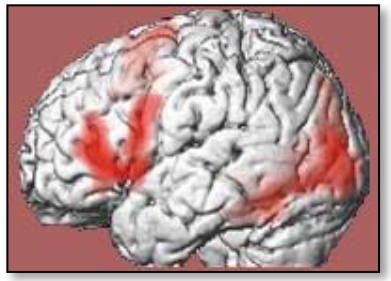
fMRI

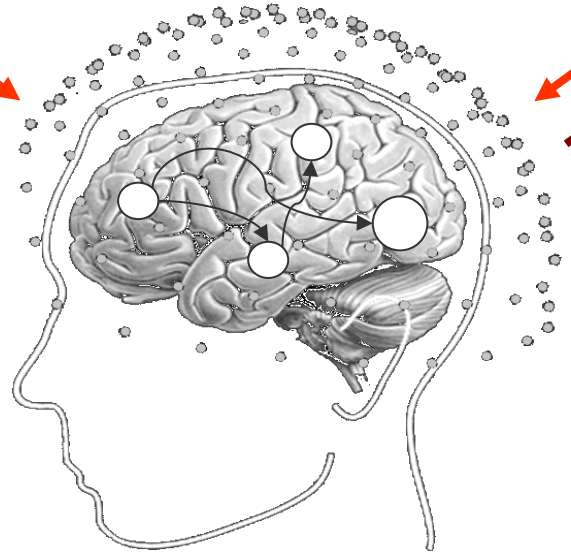


structural priors



structural priors





Forward model:
Predicting measured activity

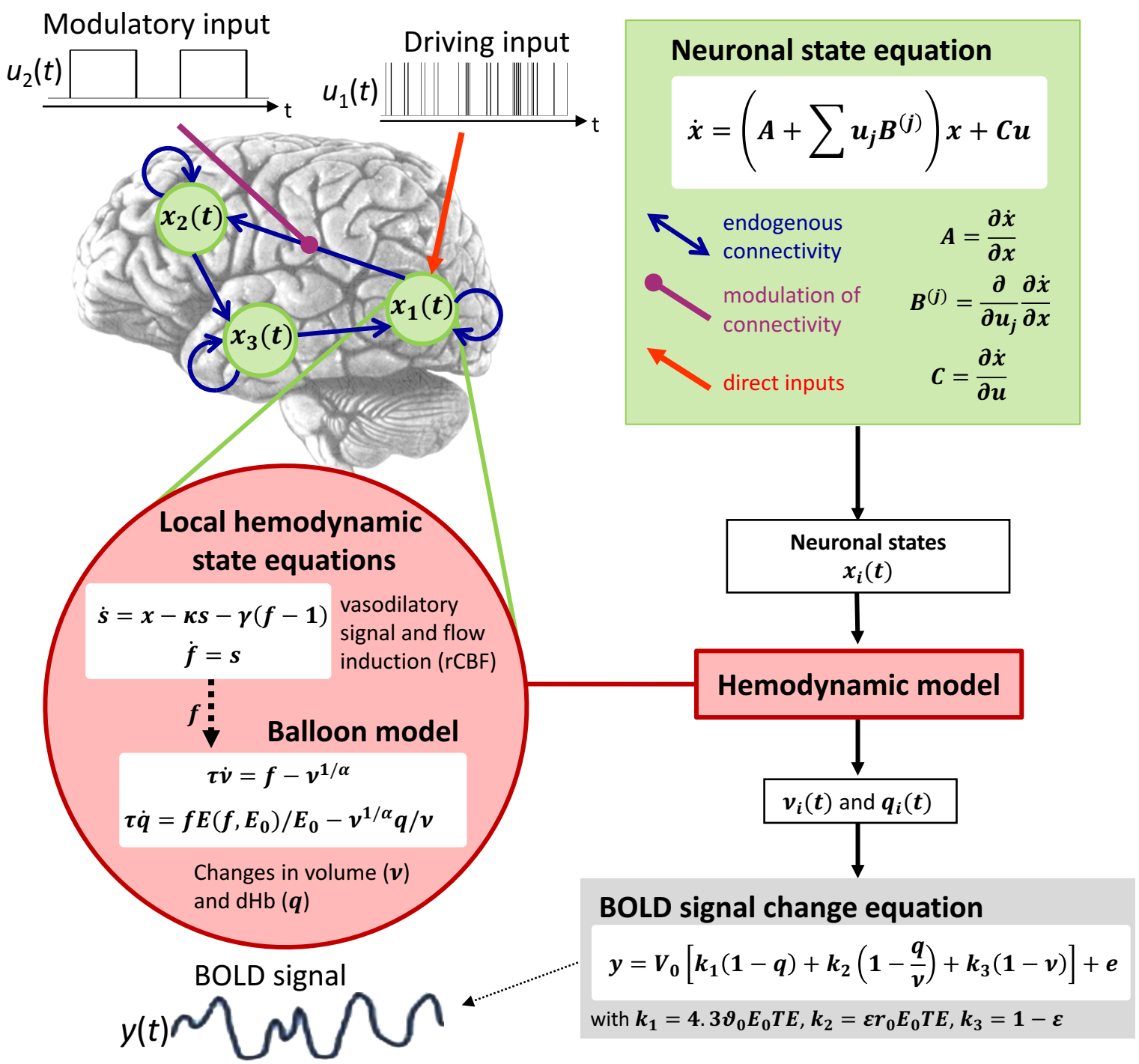
$$y = g(x,\theta) + \varepsilon$$

Model inversion:
Estimating neuronal mechanisms

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

Friston et al. 2003, *NeuroImage*
Stephan et al. 2009b, *NeuroImage*

DCM FOR FMRI



Stephan et al. 2015, *Neuron*

Bayesian system identification

$u(t)$

Neural dynamics

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

Observer function

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

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

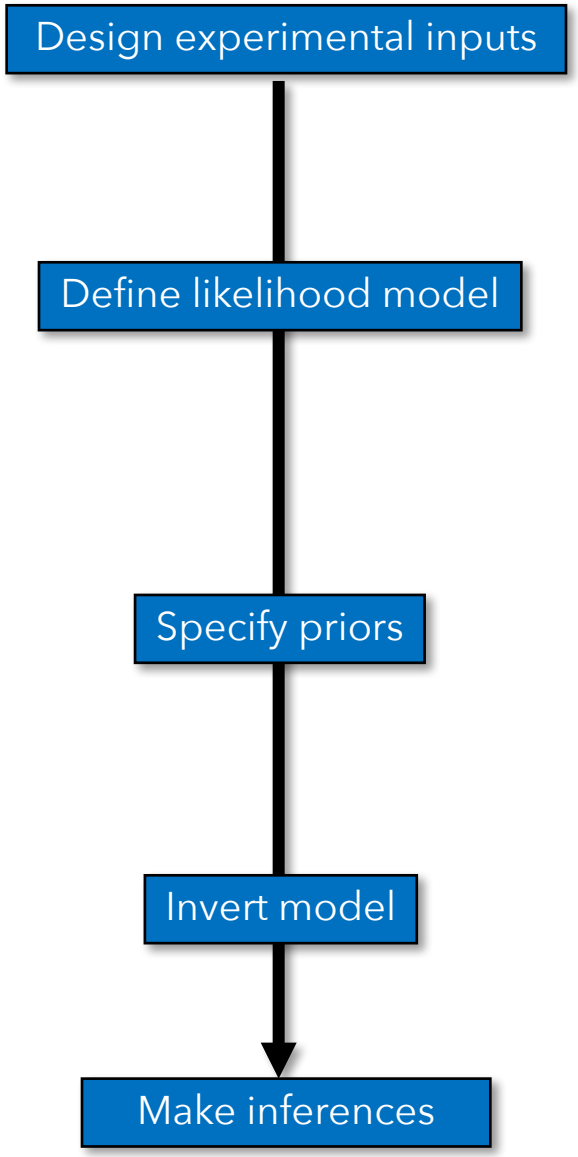
$$p(\theta, m) = N(\mu_\theta, \Sigma_\theta)$$

Inference on model structure

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

Inference on parameters

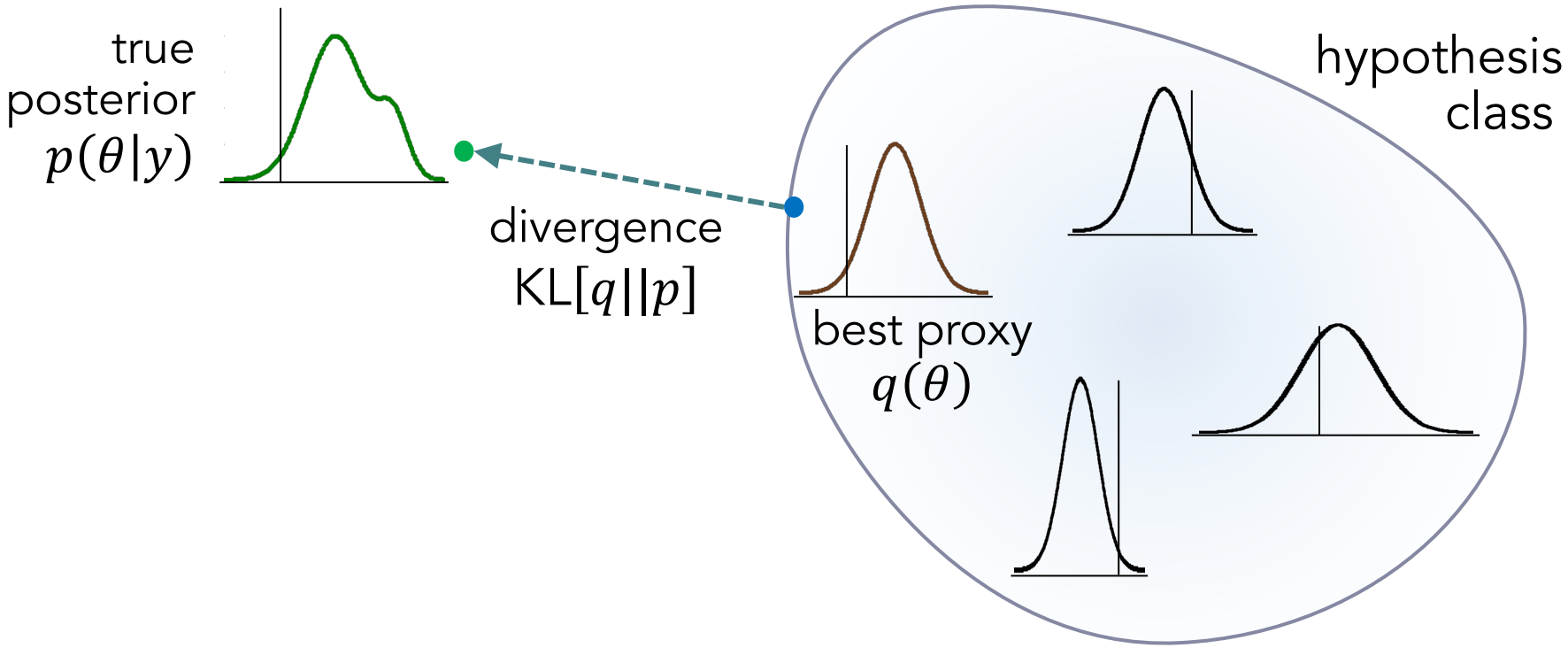
$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta, m)}{p(y \mid m)}$$



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 (VB)

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

divergence ≥ 0 (unknown)

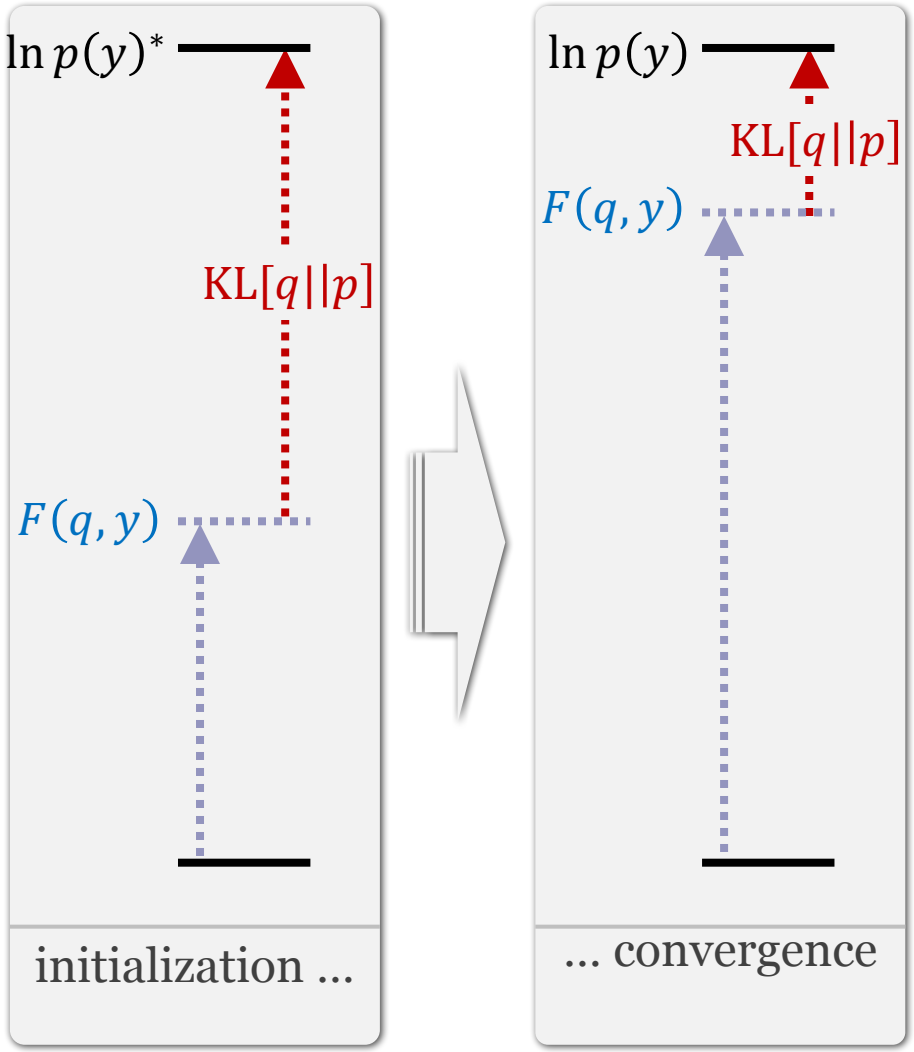
neg. free energy (easy to evaluate for a given q)

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

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

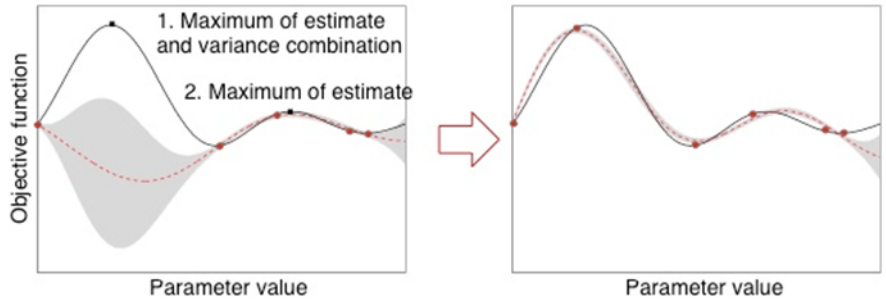
- minimizing $\mathrm{KL}[q||p]$
- tightening $F(q,y)$ as a lower bound to the log model evidence

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



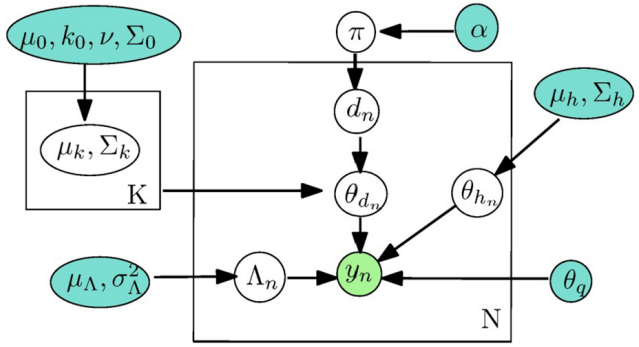
DCM: METHODOLOGICAL DEVELOPMENTS

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

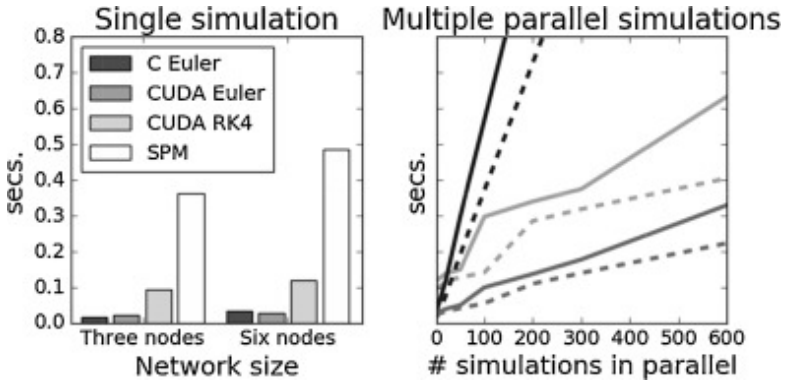


- **Sampling-based estimates of model evidence**
  - Aponte et al. 2015, J. Neurosci. Meth.
  - Raman et al., in preparation

- **Choice of priors → empirical Bayes**
  - Friston et al. 2016, NeuroImage
  - Raman et al. 2016, J. Neurosci. Meth.



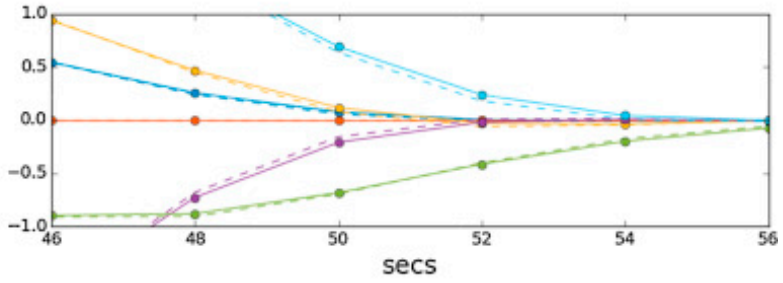
MPDCM: MASSIVELY PARALLEL DCM



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

mpdcm_integrate(dcms)

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



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

www.translationalneuromodeling.org/tapas

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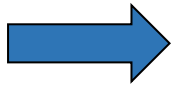
The evolution of DCM in SPM

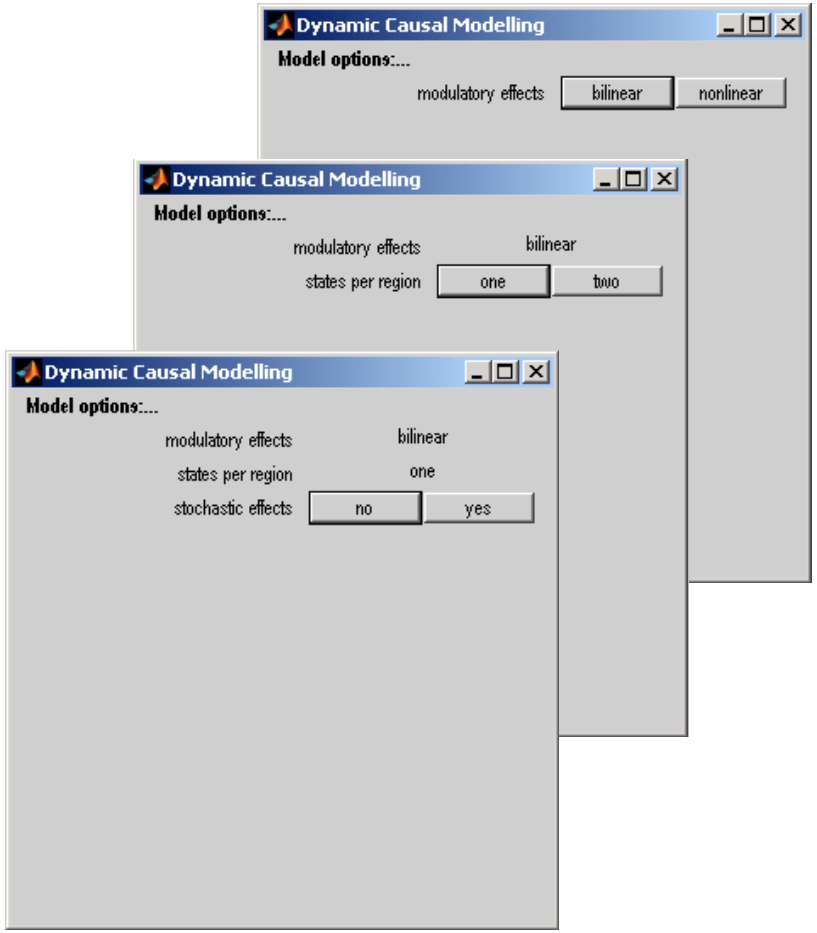
- DCM is not one specific model, but a framework for Bayesian inversion of dynamic system models
- The implementation in SPM has been evolving over time, e.g.
  - improvements of numerical routines (e.g., optimization scheme)
  - change in priors to cover new variants (e.g., stochastic DCMs)
  - changes of hemodynamic model



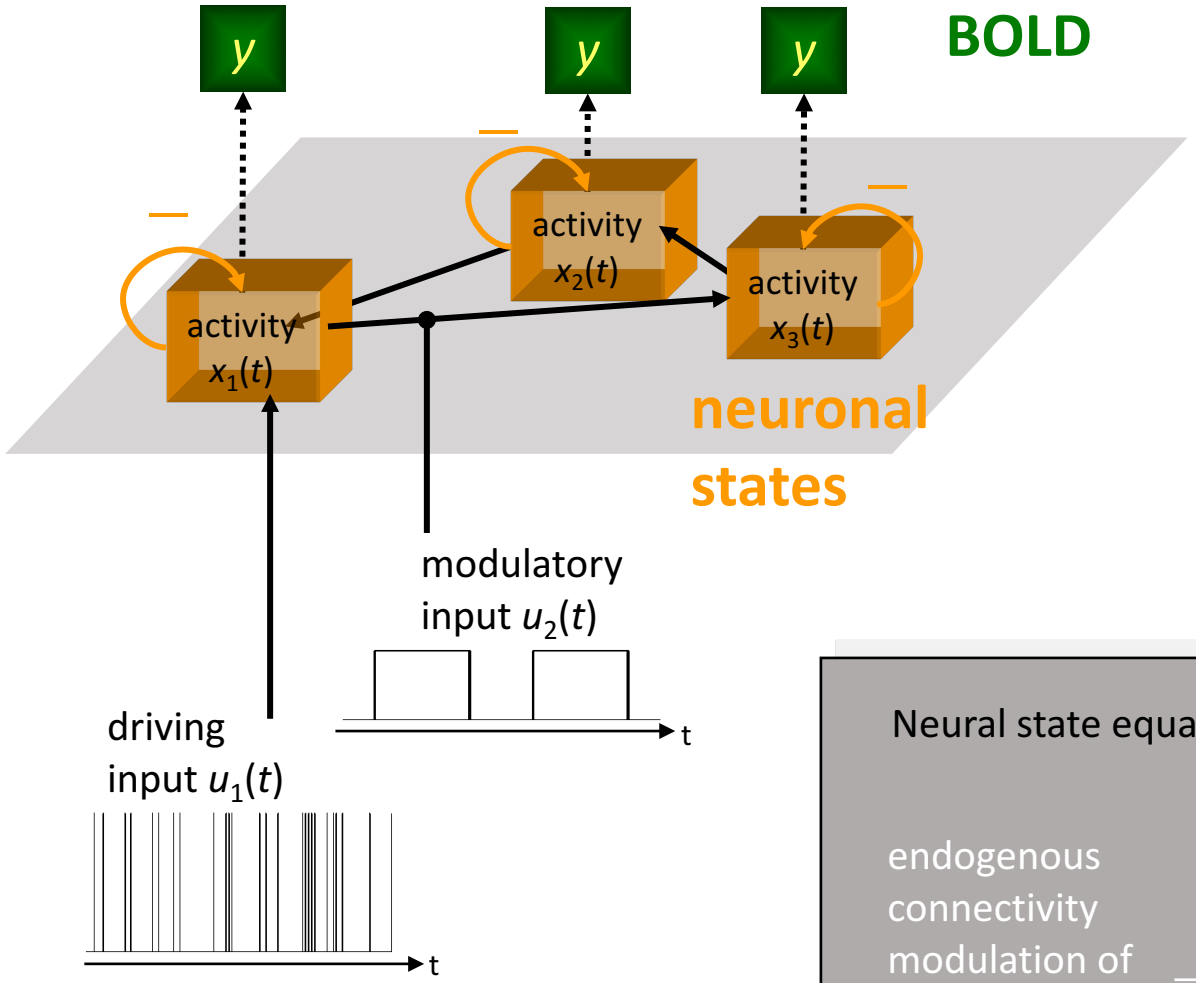
To enable replication of your results, you should ideally state which SPM version (release number) you are using when publishing papers.

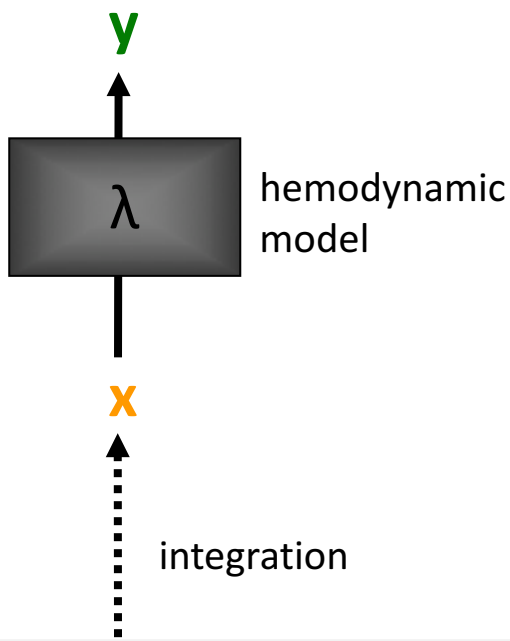
FACTORIAL STRUCTURE OF MODEL SPECIFICATION

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



CLASSICAL DCM





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

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

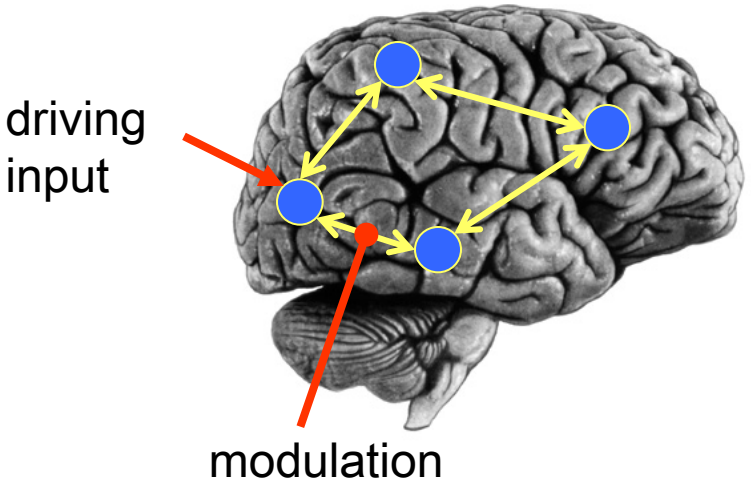
endogenous connectivity → $A = \frac{\partial \dot{x}}{\partial x}$

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

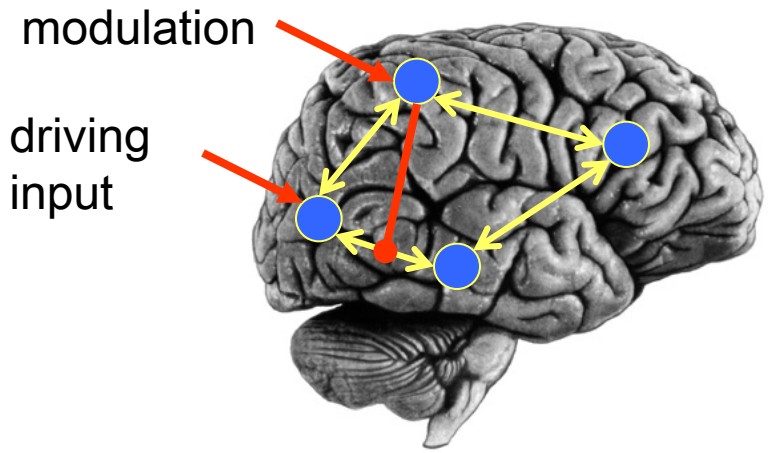
direct inputs → $C = \frac{\partial \dot{x}}{\partial u}$

NON-LINEAR DCM

bilinear DCM



non-linear DCM



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

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

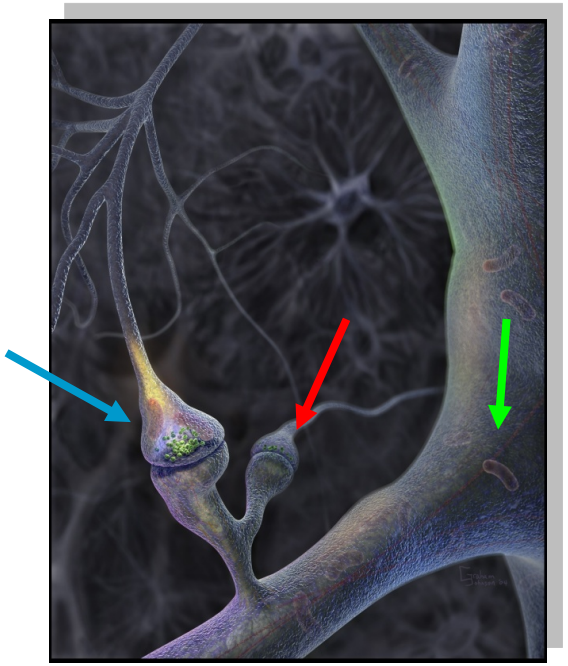
Bilinear state equation:

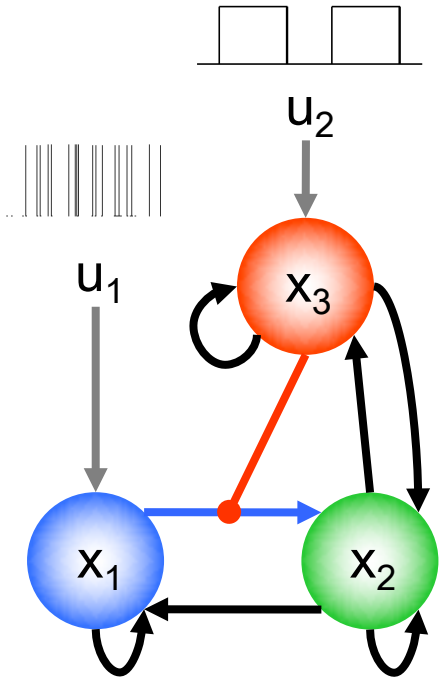
$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)}\right)x + Cu$$

Nonlinear state equation:

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

Non-linear DCM



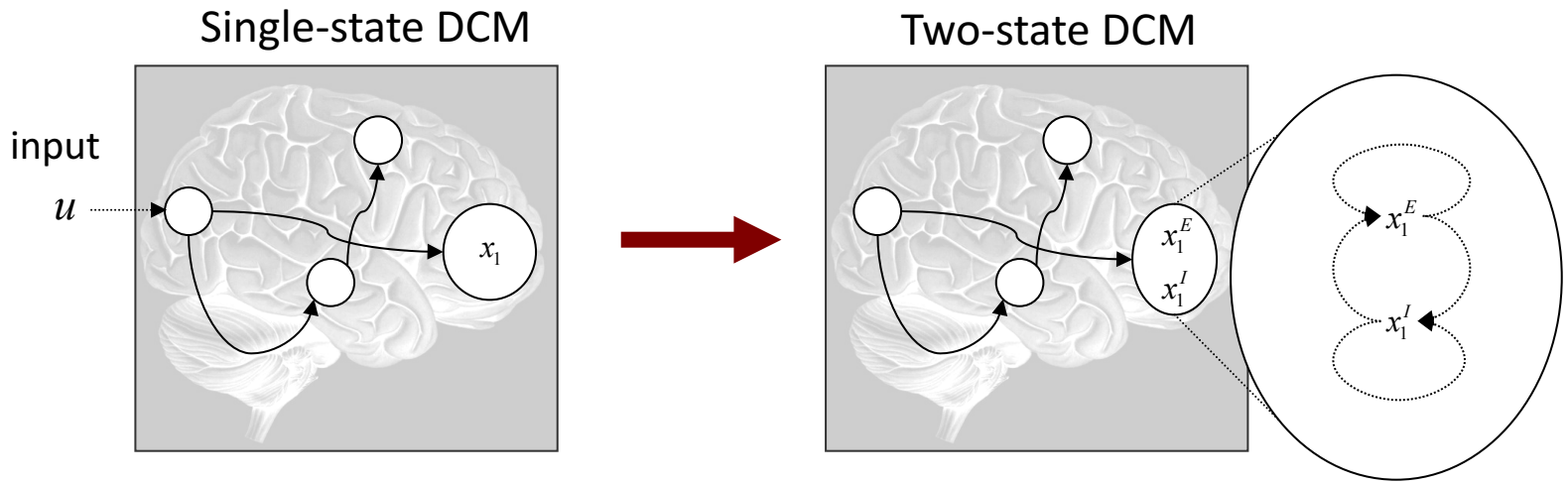


Nonlinear Dynamic Causal Model for fMRI

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

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

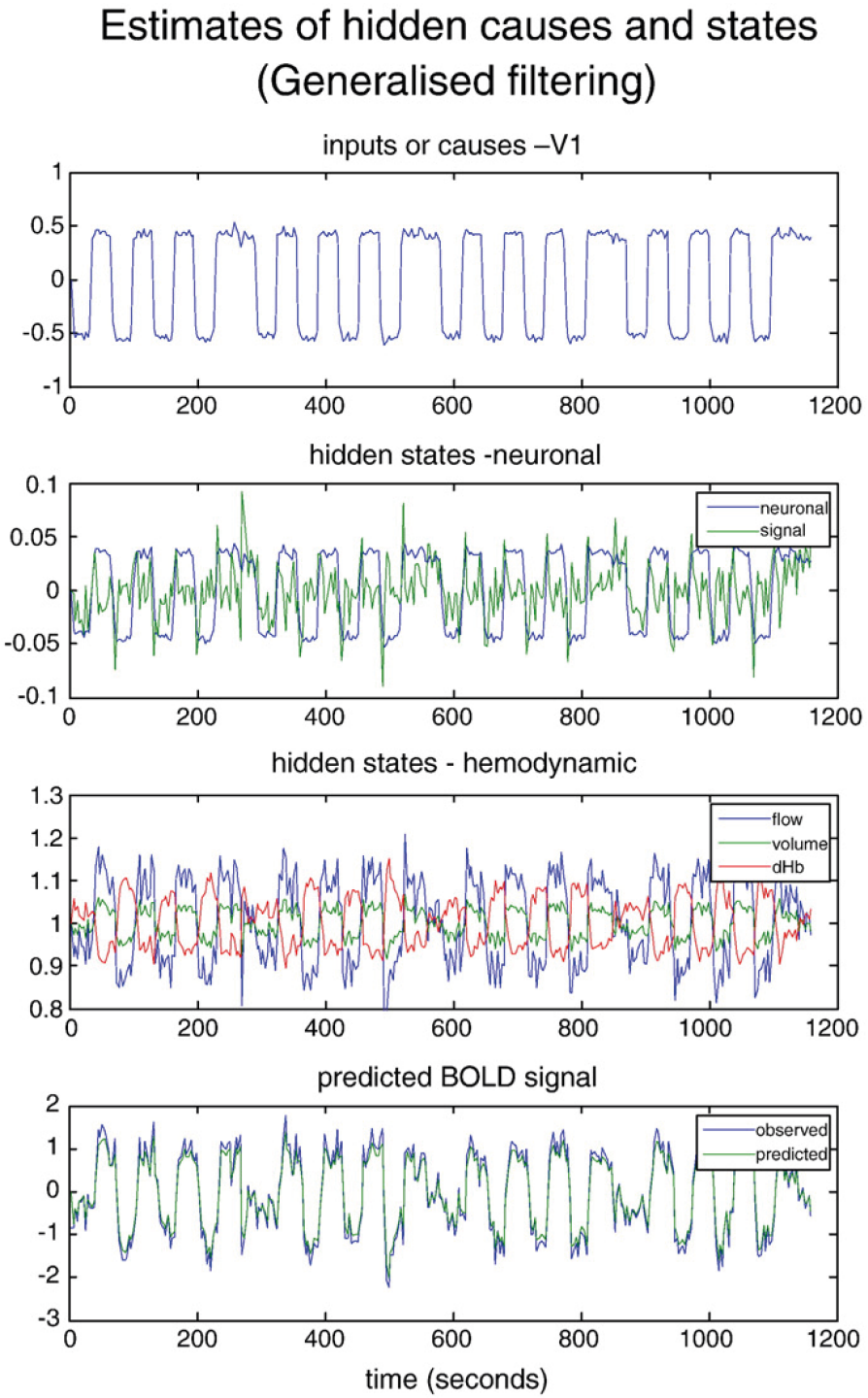
Marreiros et al. 2008, *NeuroImage*

STOCHASTIC DCM

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

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

Li et al. 2011, *NeuroImage*



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 optimization problem with respect to stochastic differential equations with a deterministic approach from linear systems theory → computationally very efficient

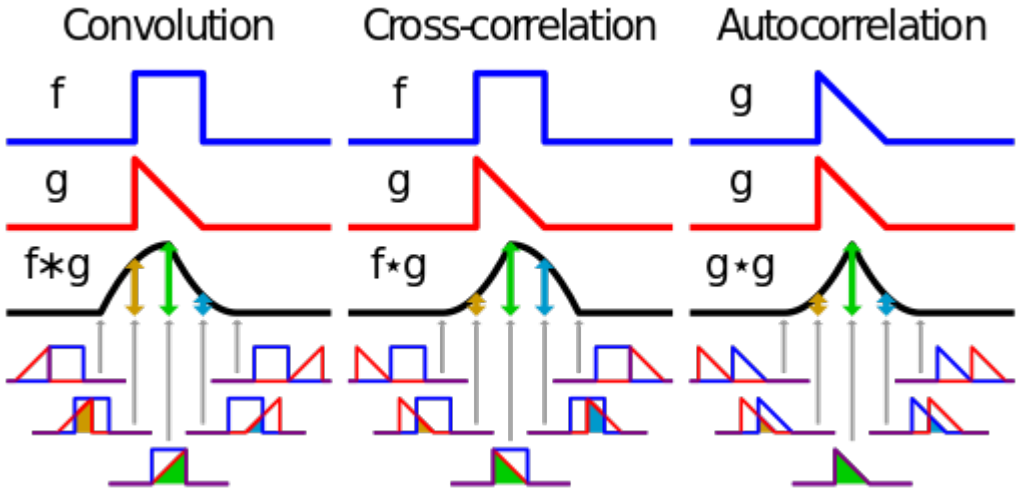
- disadvantages:
  - assumes stationarity

Friston et al. 2014, *NeuroImage*

CROSS-CORRELATION & CONVOLUTION

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

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

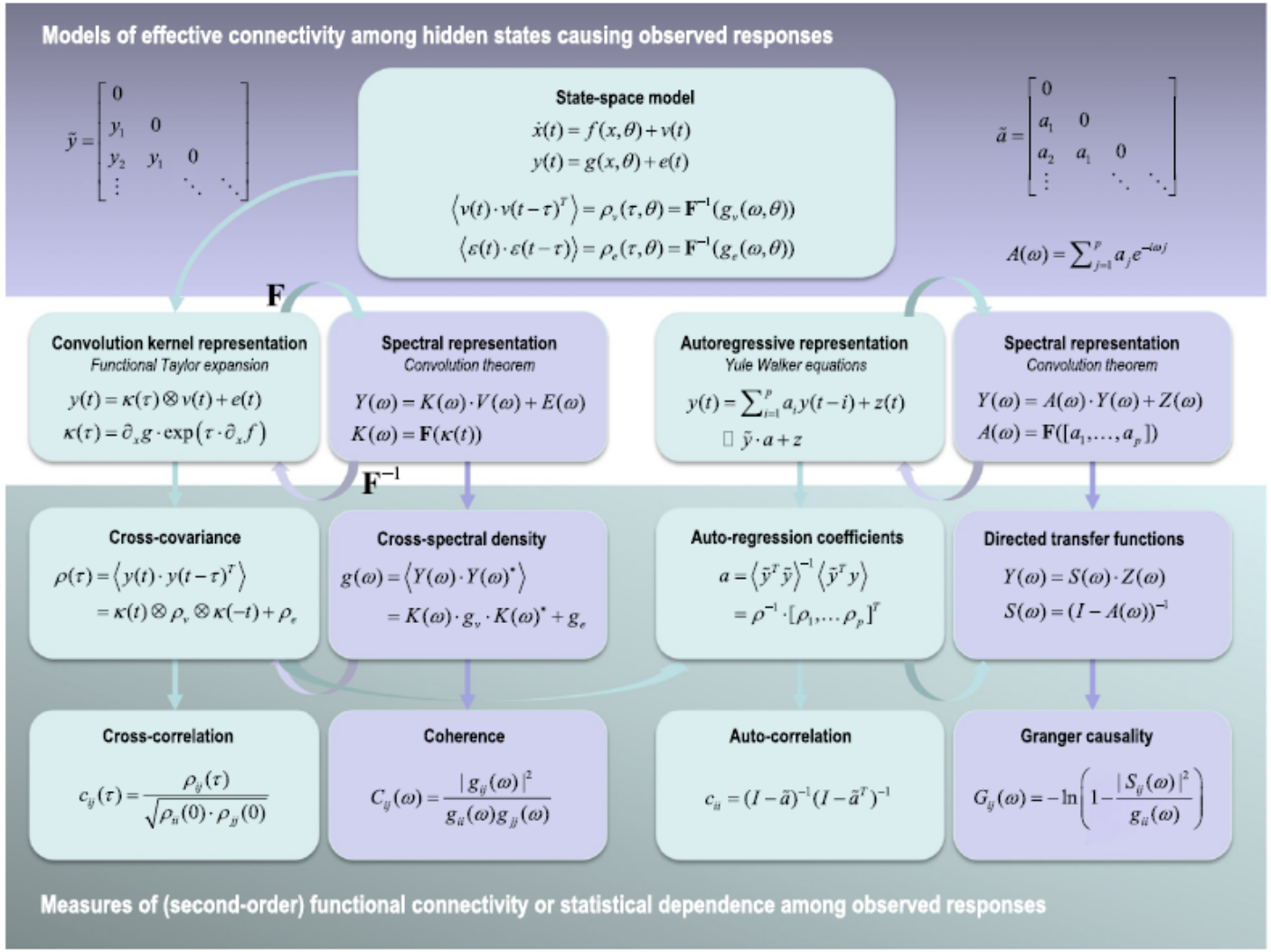


Friston et al. 2014, *NeuroImage*

CROSS-SPECTRA AND CROSS-CORRELATION

cross-spectra
= Fourier transform of cross-correlation function

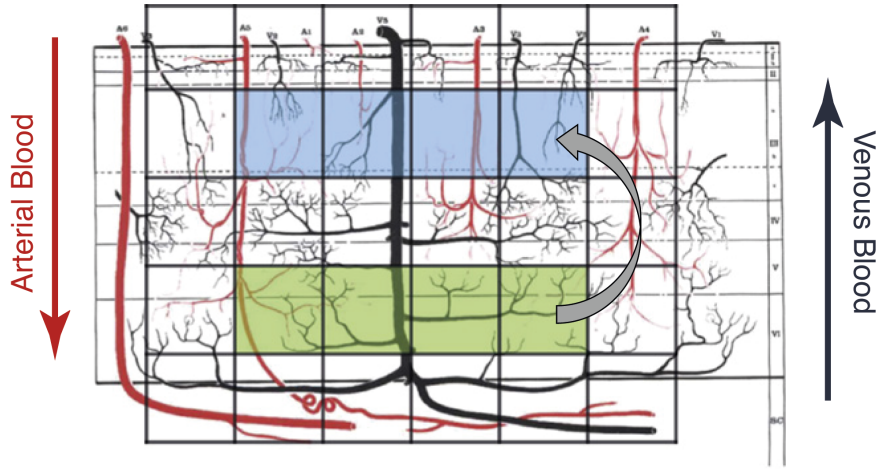
cross-correlation
= generalized form of correlation (at zero lag, this is the conventional measure of functional connectivity)



Friston et al. 2014, *NeuroImage*

LAYERED DCM

- Recent advances in MR imaging made high-resolution fMRI at the sub-millimeter scale feasible
- spatial layout of cortical blood supply becomes an important confound at such high spatial resolution
- extension to hemodynamic model that accounts for these effects by coupling local hemodynamics across layers
- advantage:
  - allows to estimate layer-specific connections in cortex
- disadvantage :
  - computationally expensive



$$\tau_u \frac{dv_u}{dt} = f_u - v_u^{\frac{1}{\alpha}} + \lambda_d v_l^*$$

$$\tau_u \frac{dq_u}{dt} = f_u \frac{1-(1-E_0)^{1/f_u}}{E_0} - v_u^{1/\alpha} \frac{q_u}{v_u} + \lambda_d q_l^*$$

$$\tau_l \frac{dv_l}{dt} = f_l - v_l^{\frac{1}{\alpha}}$$

$$\tau_l \frac{dq_l}{dt} = f_l \frac{1-(1-E_0)^{1/f_l}}{E_0} - v_l^{1/\alpha} \frac{q_l}{v_l}$$

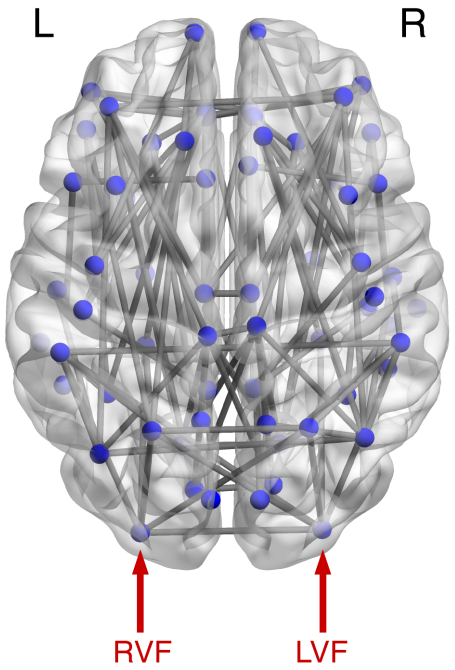
$$\tau_d \frac{dv_l^*}{dt} = -v_l^* + (v_l - 1)$$

$$\tau_d \frac{dq_l^*}{dt} = -q_l^* + (q_l - 1)$$

Heinzle et al. 2016, *NeuroImage*

Regression DCM

- translates a linear DCM in the time domain into a general linear model (GLM) in the frequency domain using Fourier transformation
- this essentially reformulates model inversion as a special case of Bayesian linear regression with unknown variance
- advantage:
  - computationally very efficient, enables effective connectivity analyses in large (whole-brain) networks
- disadvantages:
  - assumes stationarity, fixed HRF, partial independence among parameters

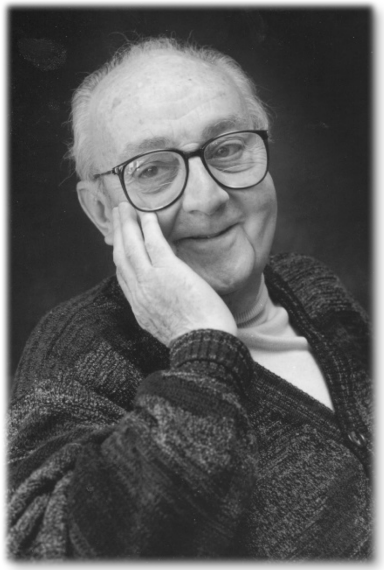


Frässle et al., *under review*

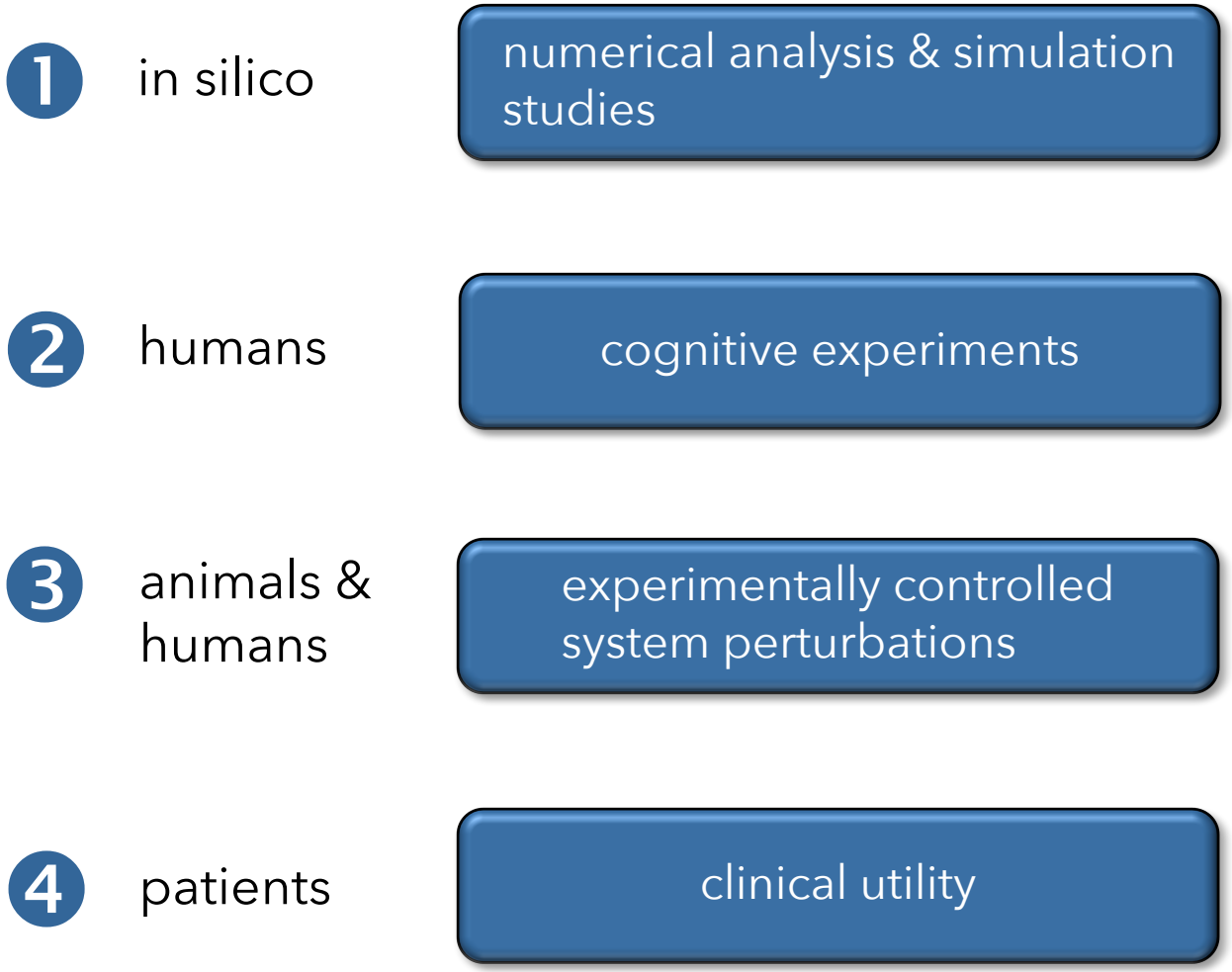
All Models are Wrong

But some are useful

George Edward Pelham Box
(1919-2013)



HIERARCHICAL STRATEGY FOR MODEL VALIDATION

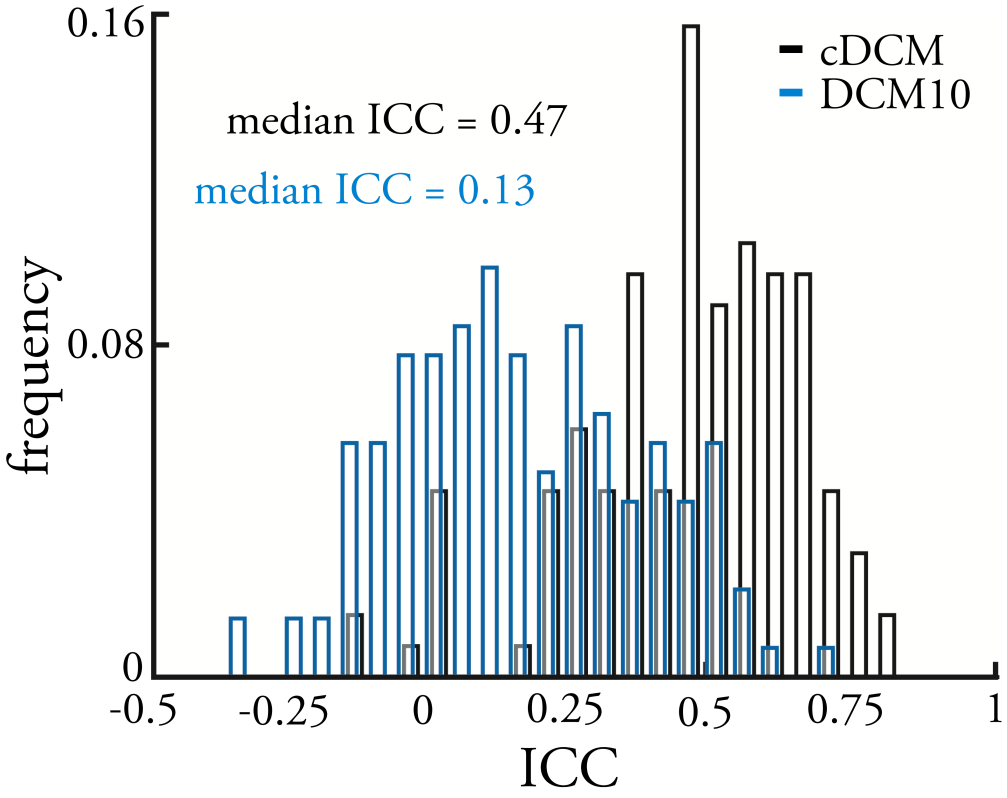


For DCM: >15 published validation studies (incl. 6 animal studies):

- 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 anesthesia levels (Moran et al. 2011)
- predicts sensory stimulation (Brodersen et al. 2010)

RELIABILITY OF MODEL ESTIMATES

- test-retest reliability refers to the within-subject stability of parameter estimates obtained when applying a method to multiple datasets acquired under the same condition in the same subject
- necessary condition for the use of DCM as a tool for translational neuromodeling.
- local extrema in the objective function and the choice of prior distributions become limiting factors for test-retest reliability.
- global optimization schemes (MCMC, Gaussian processes) and empirical Bayes might come to the rescue



Frässle et al. 2015, *NeuroImage*

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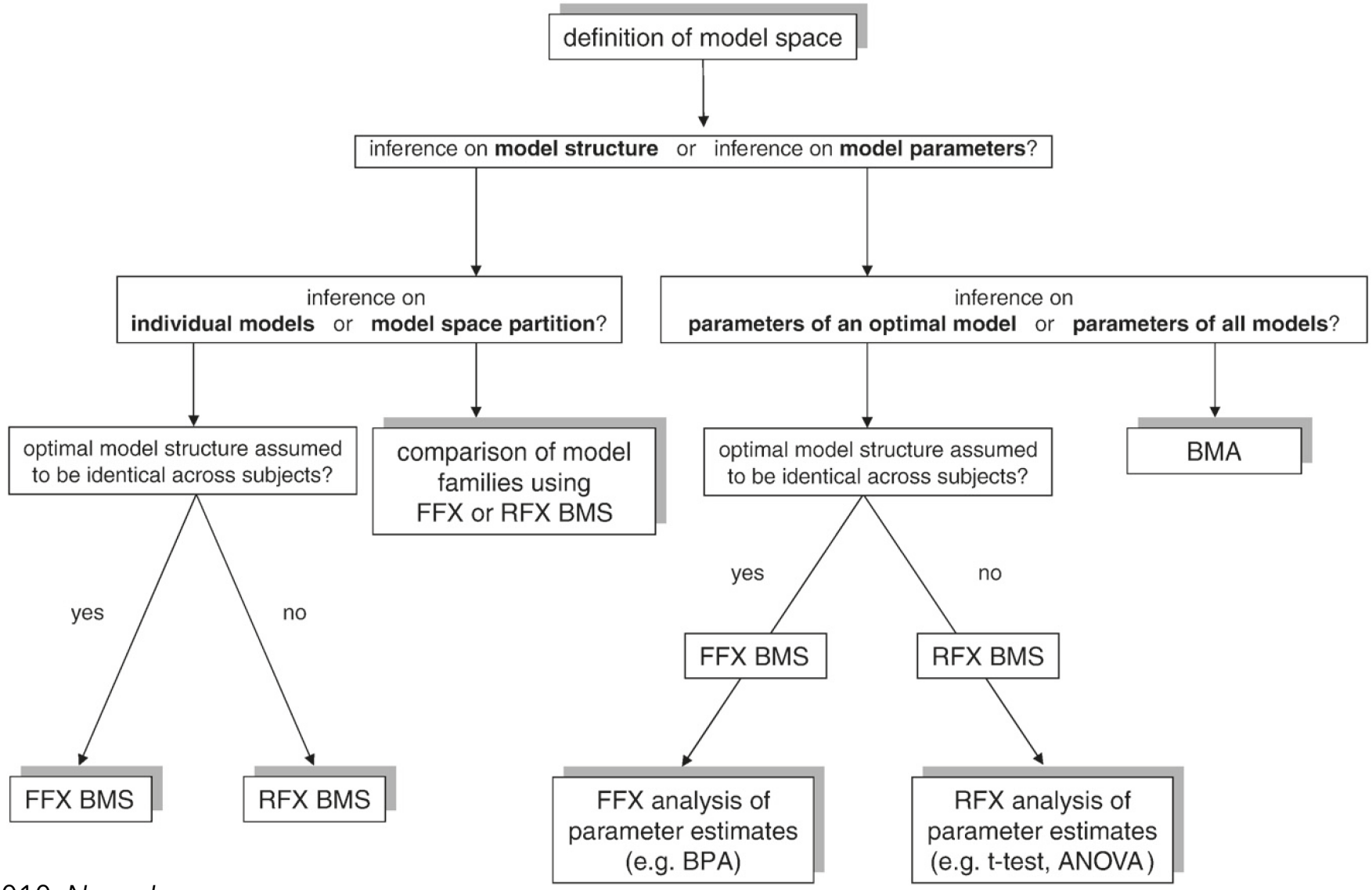
ROADMAP FOR DCM ANALYSES



Stephan et al. 2010, *NeuroImage*

Fixed-effects Bayesian model selection

Bayes factor to compare two models:

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

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

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

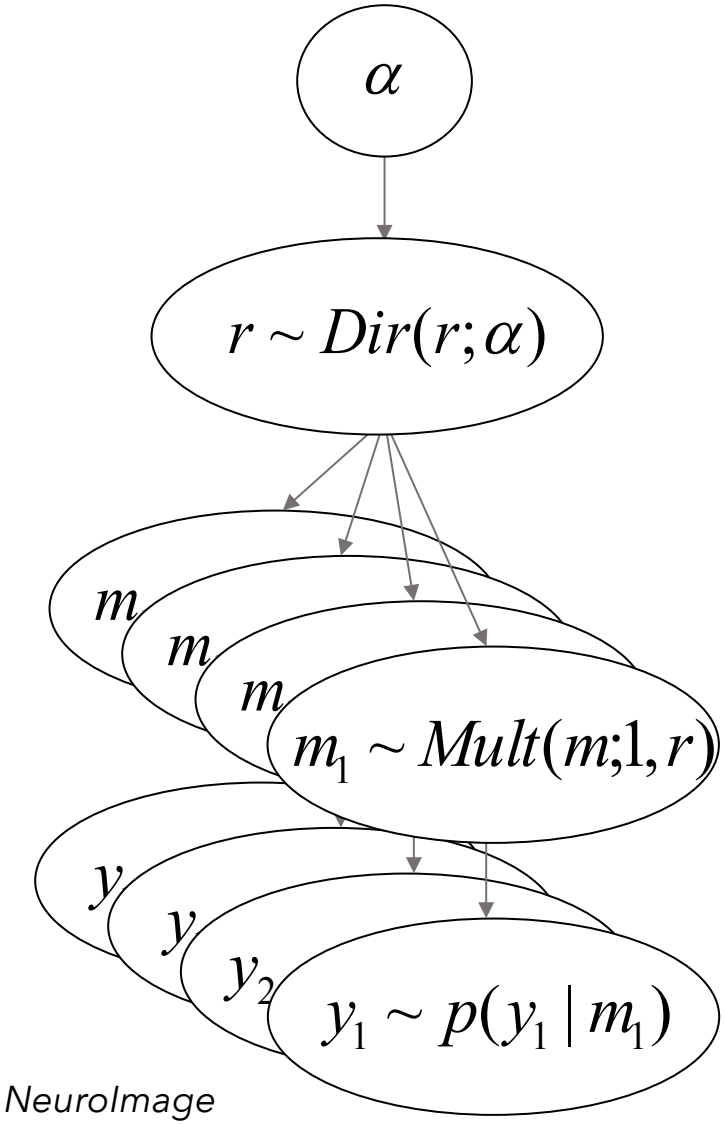
Problems:

- blind with regard to group heterogeneity
- sensitive to outliers

B_{12}	$p(m_1 \mid y)$	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.*

RANDOM-EFFECTS BAYESIAN MODEL SELECTION



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.*

FAMILY-LEVEL BAYESIAN MODEL SELECTION

- partitioning model space into K subsets or families and pooling information over all models in these subsets allows one to compute the probability of a model family, given the data.

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

- family-level inference is possible for both fixed effects and random effects BMS.

- for family level FFX-BMS, the probability of each family is obtained by summing the posterior probabilities of the models it includes.

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

- when families are of equal size, for family level RFX-BMS the posterior model probabilities within families are also simply summed up, exploiting the agglomerative property of the Dirichlet distribution:

$$r_1^* = \sum_{k \in N_1} r_k \, , \ldots , r_j^* = \sum_{k \in N_j} r_k$$

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

BAYESIAN MODEL AVERAGING

- 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

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

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

Overview

- DCM – basic concepts
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- Embedding computational models in DCMs
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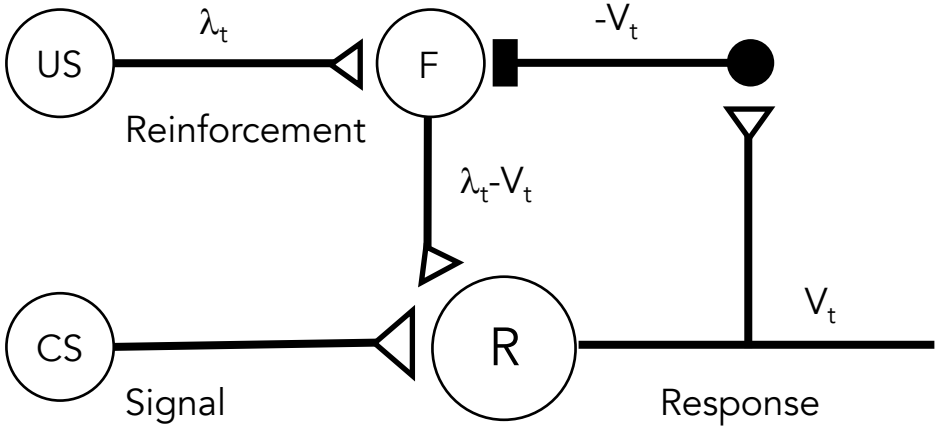
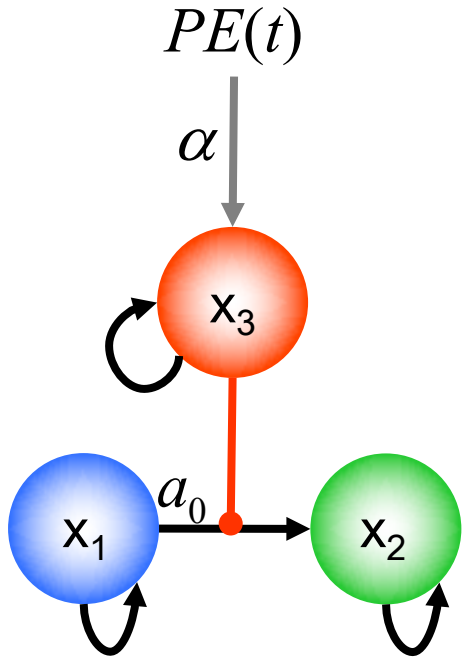
- Translational Neuromodeling

PREDICTION ERRORS DRIVE SYNAPTIC PLASTICITY



McLaren 1989

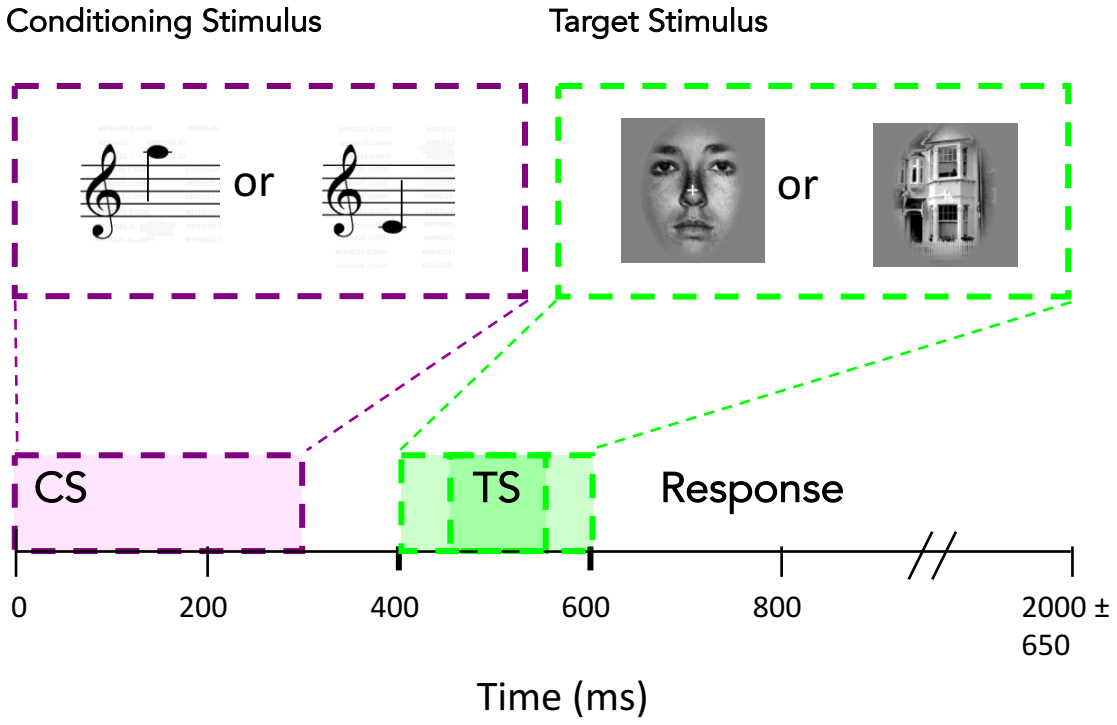


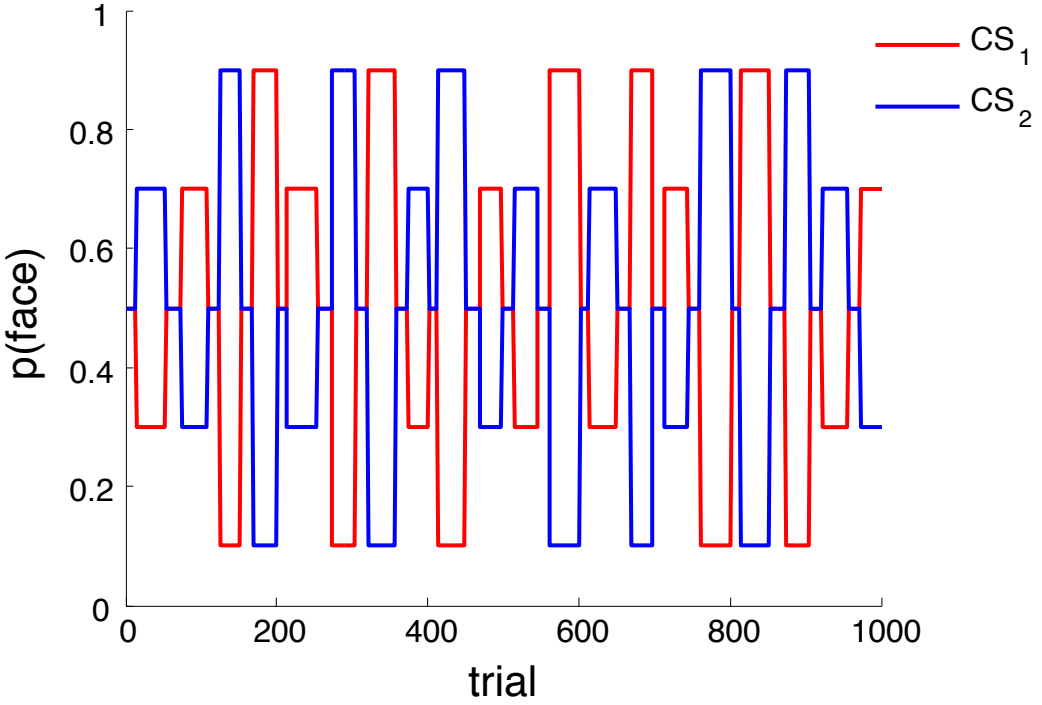
$$w_t = w_0 + \alpha \sum_{k=1}^{t} PE_k$$

$$w_t \approx a_0 + \alpha \int_0^t PE(\tau) d\tau$$

synaptic plasticity during learning = f (prediction error)

LEARNING OF DYNAMIC AUDIO-VISUAL ASSOCIATIONS





den Ouden et al. 2010, *J. Neurosci.*

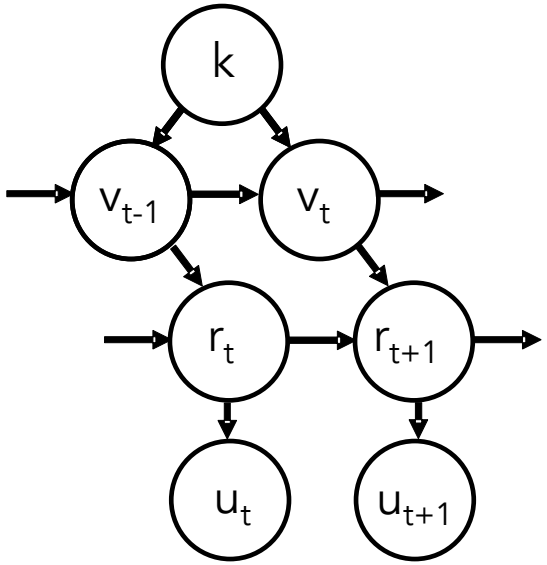
Hierarchical Bayesian learning model

prior on volatility

volatility

probabilistic association

observed events



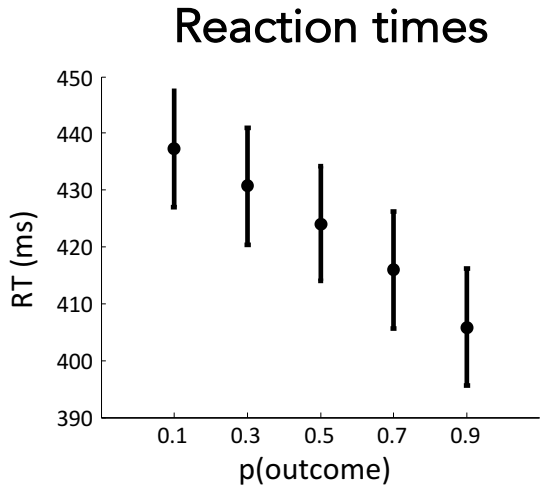
$$p(k) \propto 1$$

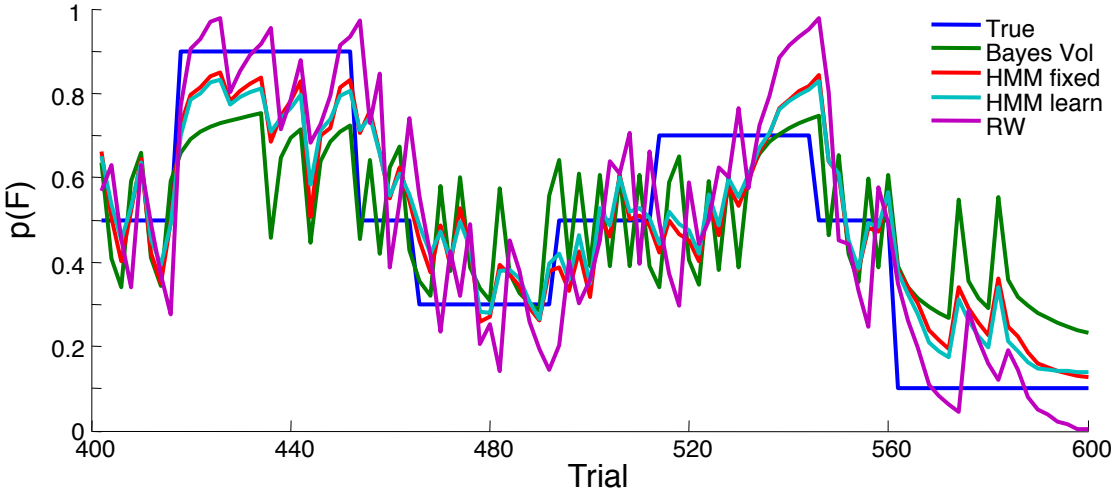
$$p(v_{t+1} \mid v_t, k) \sim N(v_t, \exp(k))$$

$$p(r_{t+1} \mid r_t, v_t) \sim Dir(r_t, \exp(v_t))$$

Behrens et al. 2007, *Nat. Neurosci.*

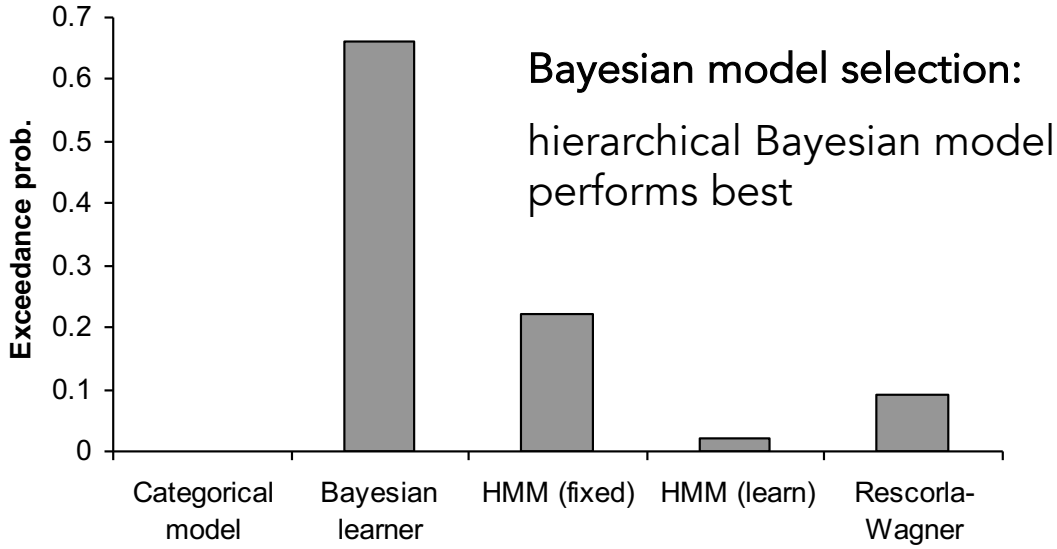
EXPLAINING RTS BY DIFFERENT LEARNING MODELS





5 alternative learning models:

- categorical probabilities
- hierarchical Bayesian learner
- Rescorla-Wagner
- Hidden Markov models (2 variants)

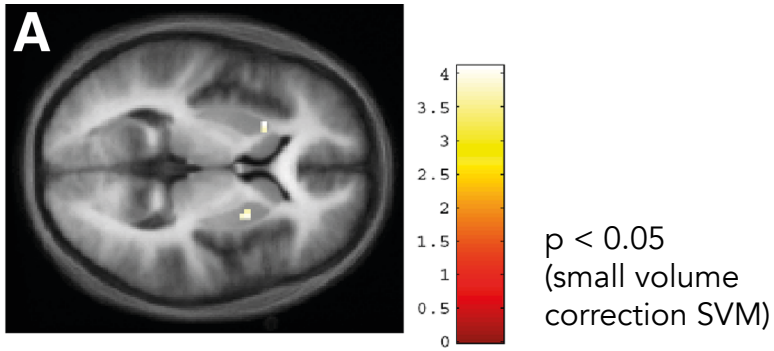


Bayesian model selection:

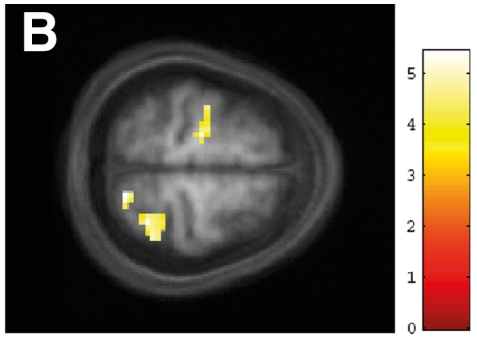
hierarchical Bayesian model performs best

den Ouden et al. 2010, *J. Neurosci.*

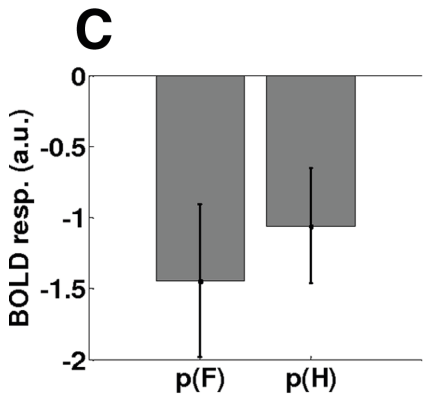
STIMULUS-INDEPENDENT PREDICTION ERROR

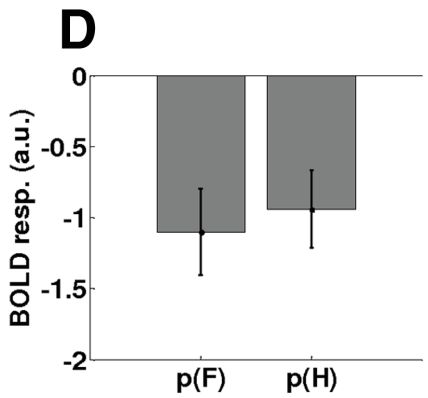


p < 0.05
(small volume
correction SVM)



p < 0.05
(cluster-level whole-
brain corrected)

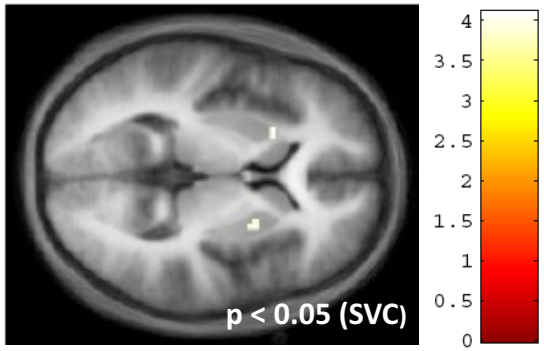




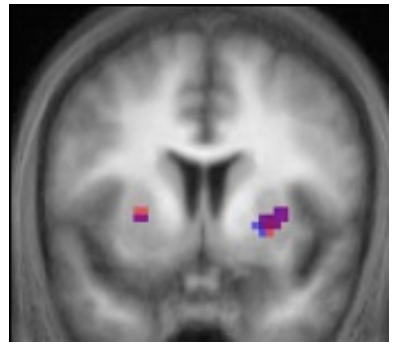
den Ouden et al. 2010, *J. Neurosci.*

Prediction error (PE) activity in the putamen

PE during active sensory learning

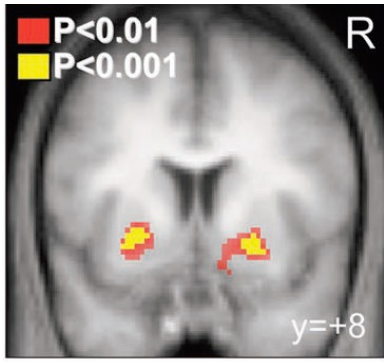


PE during incidental sensory learning



den Ouden et al. 2009, *Cerebral Cortex*

PE during reinforcement learning



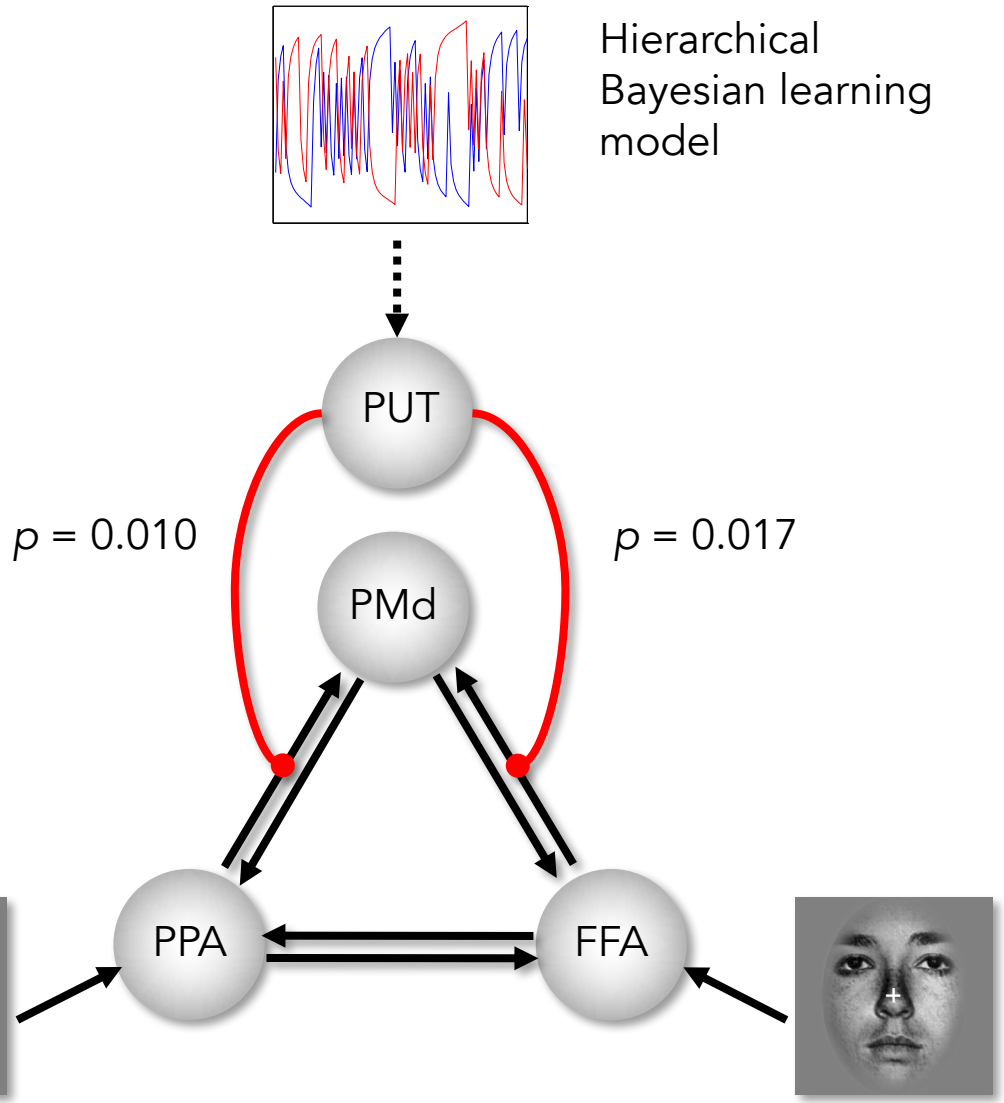
O'Doherty et al. 2004, *Science*

PE = "teaching signal" for synaptic plasticity during learning

Could the putamen be regulating trial-by-trial changes of task-relevant connections?

Prediction errors control plasticity during AVL

- Prediction error activity in the putamen exerts non-linear modulatory influences on the connections from visual areas to premotor cortex.
- Influence of visual areas on premotor cortex is:
  - stronger for surprising stimuli
  - weaker for expected stimuli



den Ouden et al. 2010, *J. Neurosci.*

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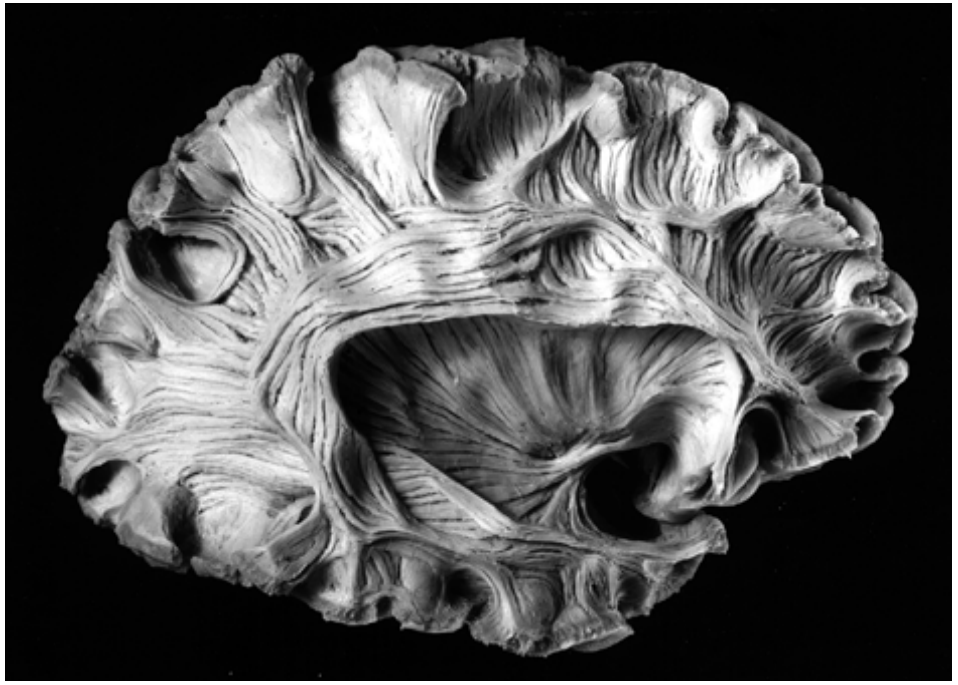
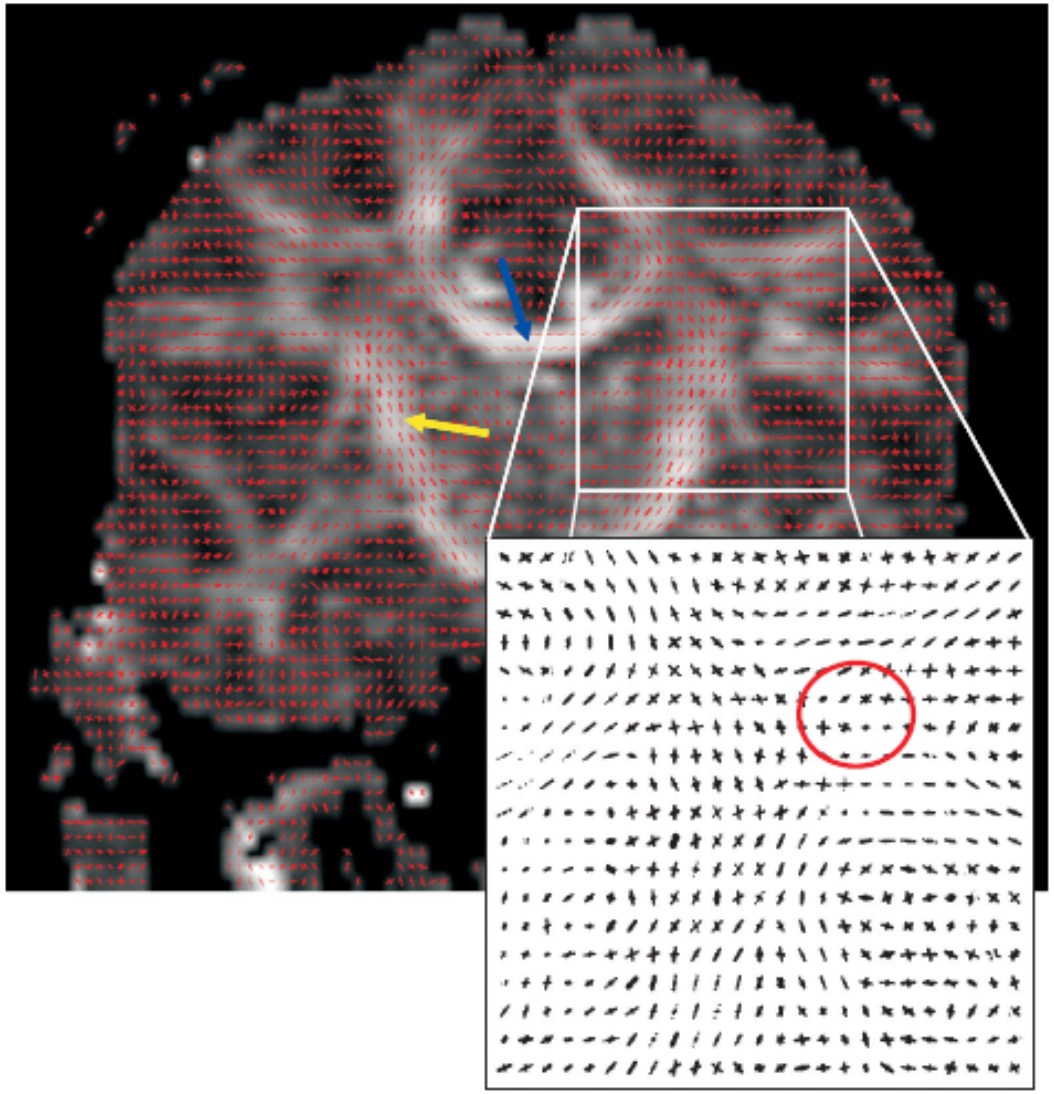
Diffusion-weighted imaging

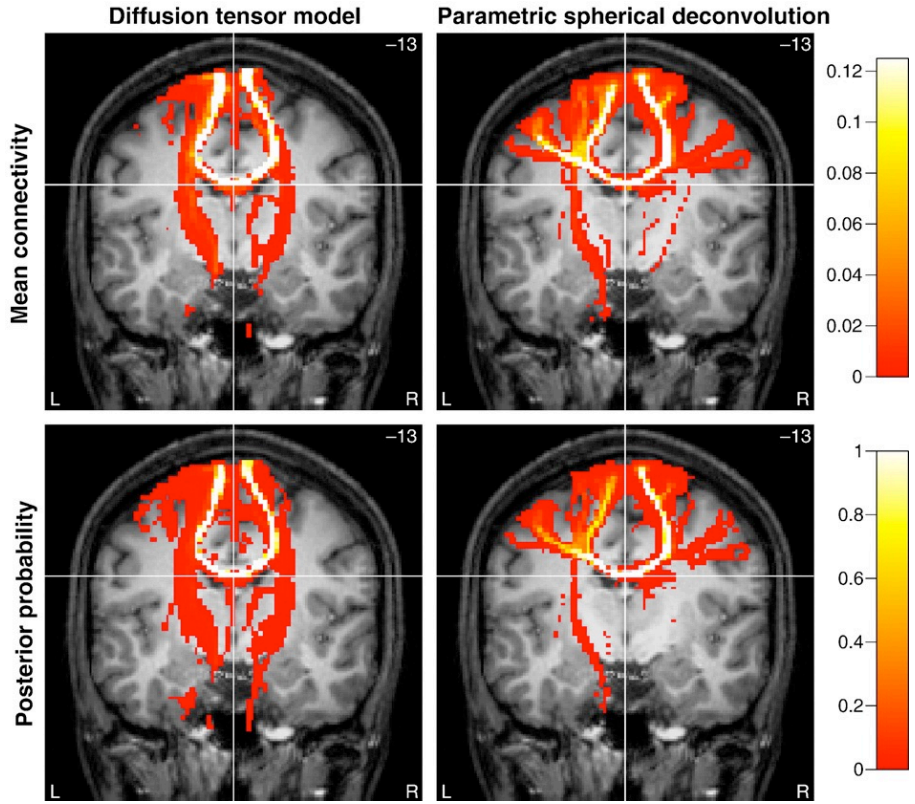




Parker & Alexander 2005, *Phil. Trans. B*

PROBABILISTIC TRACTOGRAPHY

- computes local fibre orientation density by spherical deconvolution of the diffusion-weighted signal
- estimates the spatial probability distribution of connectivity from given seed regions
- anatomical connectivity = proportion of fibre pathways originating in a specific source region that intersect a target region
- If the area or volume of the source region approaches a point, this measure reduces to method by Behrens et al. (2003)



Kaden et al. 2007, *Neuroimage*

Integration of tractography and DCM

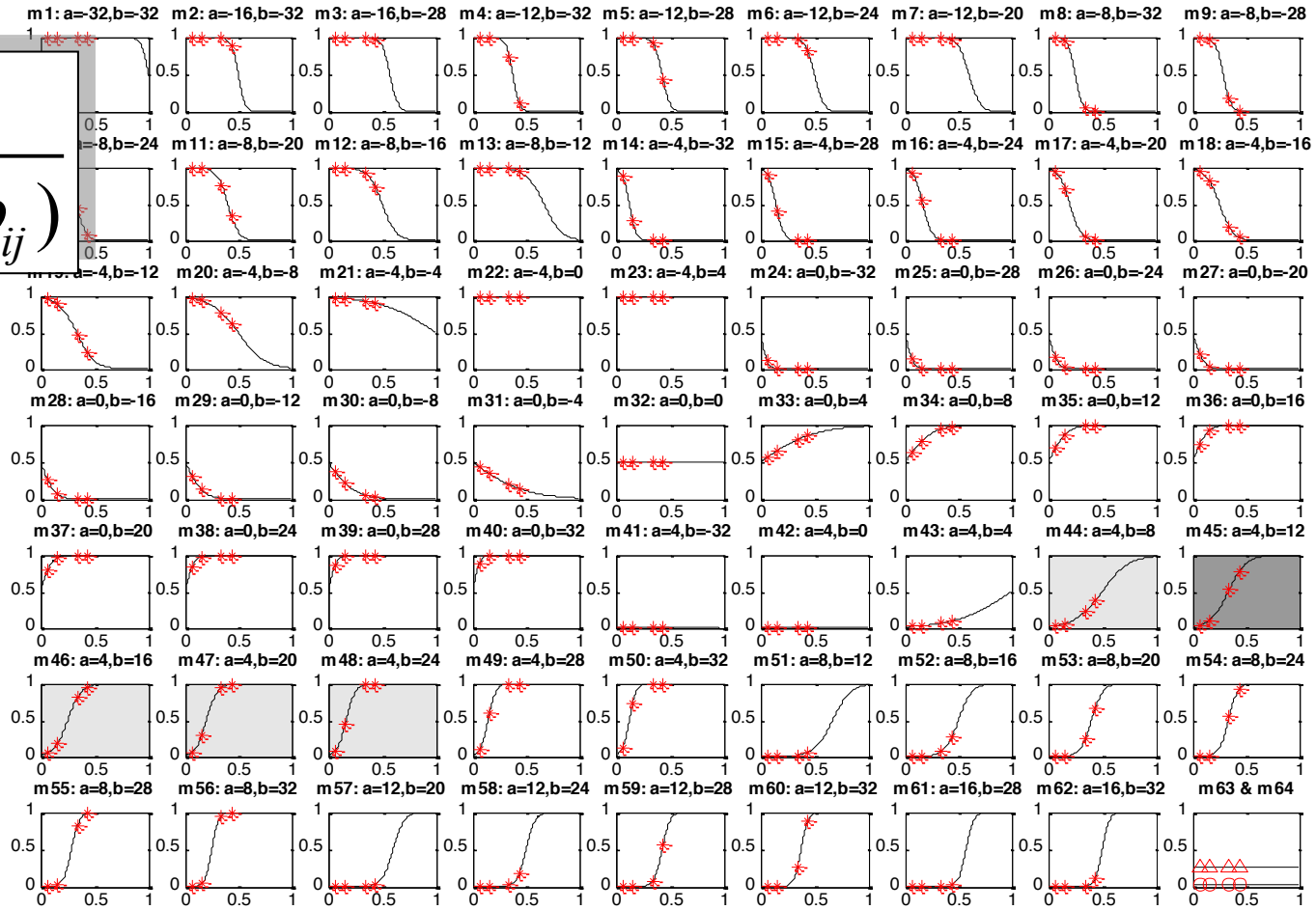
How to integrate information from probabilistic tractography in DCM?

Stephan et al. 2009b, *Neuroimage*

MODELS WITH ANATOMICALLY INFORMED PRIORS (OF AN INTUITIVE FORM) WERE SUPERIOR TO ANATOMICALLY UNINFORMED ONES

$$\Sigma_{ij} = \frac{\Sigma_0}{1 + \Sigma_0 \exp(\alpha - \beta\varphi_{ij})}$$

- 64 different mappings by systematic search across hyperparameters α and β
- yields anatomically informed (intuitive and counterintuitive) and uninformed priors



Stephan et al. 2009b, *Neuroimage*

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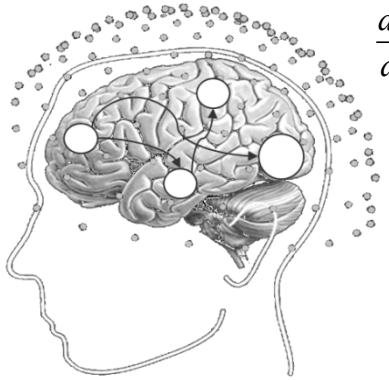
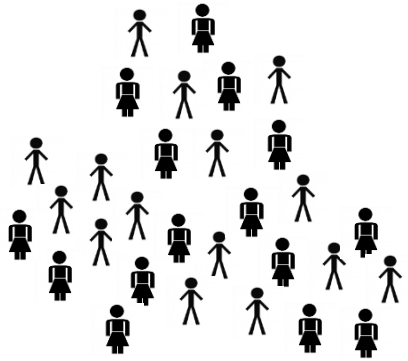
Translational Neuromodeling

❶ Computational assays:
Models of disease mechanisms



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

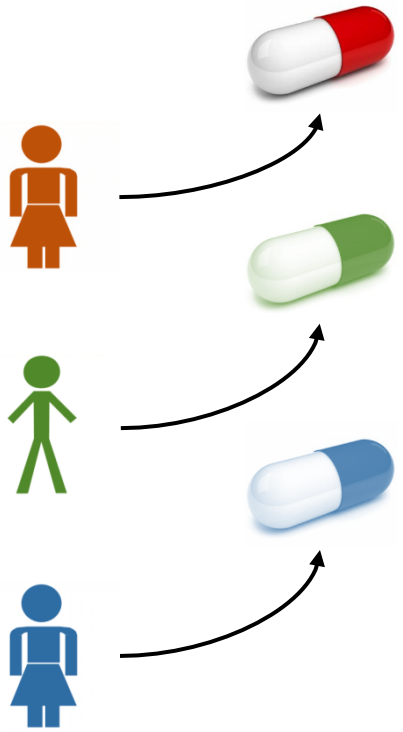


❷ Application to brain activity and behaviour of individual patients

❸ Detecting mechanistic subgroups
(based on inferred mechanisms)

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

❹ Individual treatment prediction



COMPUTATIONAL ASSAYS

Symptoms

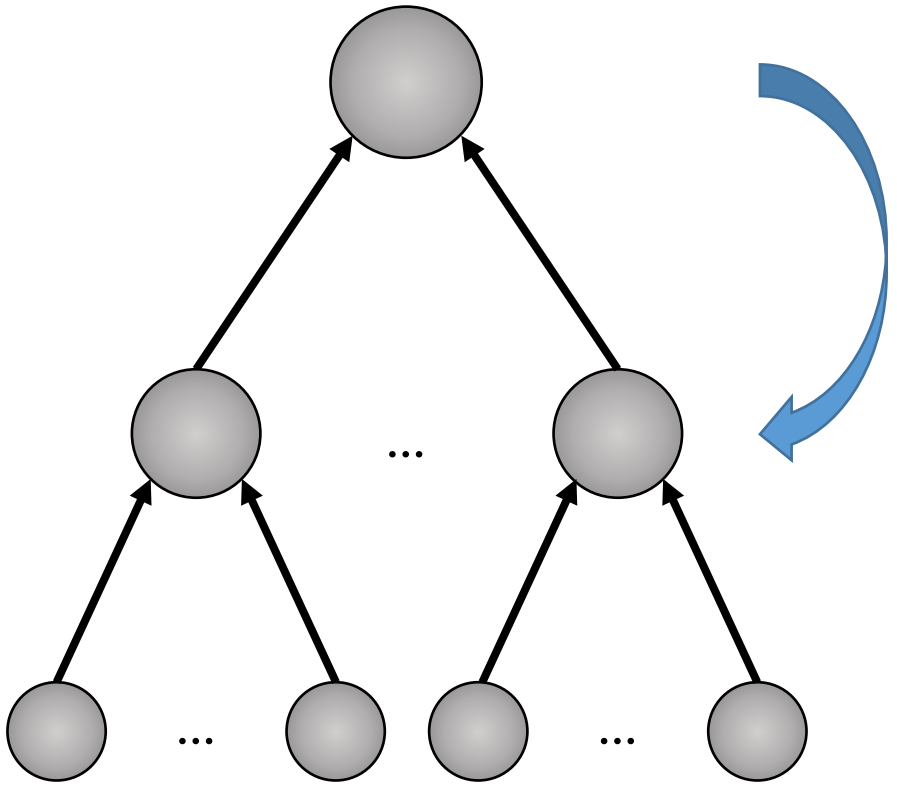
(behaviour or physiological data)

Mechanisms

(computational, physiological)

Causes

(aetiology)



differential diagnosis of alternative disease mechanisms

spectrum dissection into mechanistically distinct subgroups

prediction of clinical trajectories and treatment response

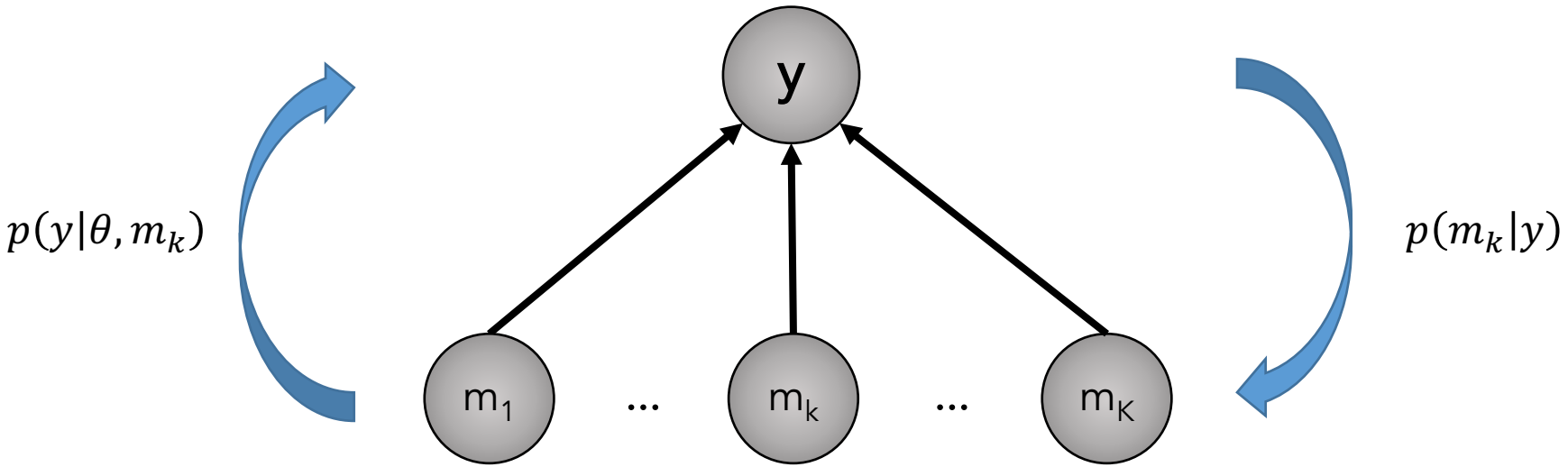
DIFFERENTIAL DIAGNOSIS BY MODEL SELECTION

Symptoms

(behaviour or physiological data)

Hypothetical mechanisms

(computational, physiological)



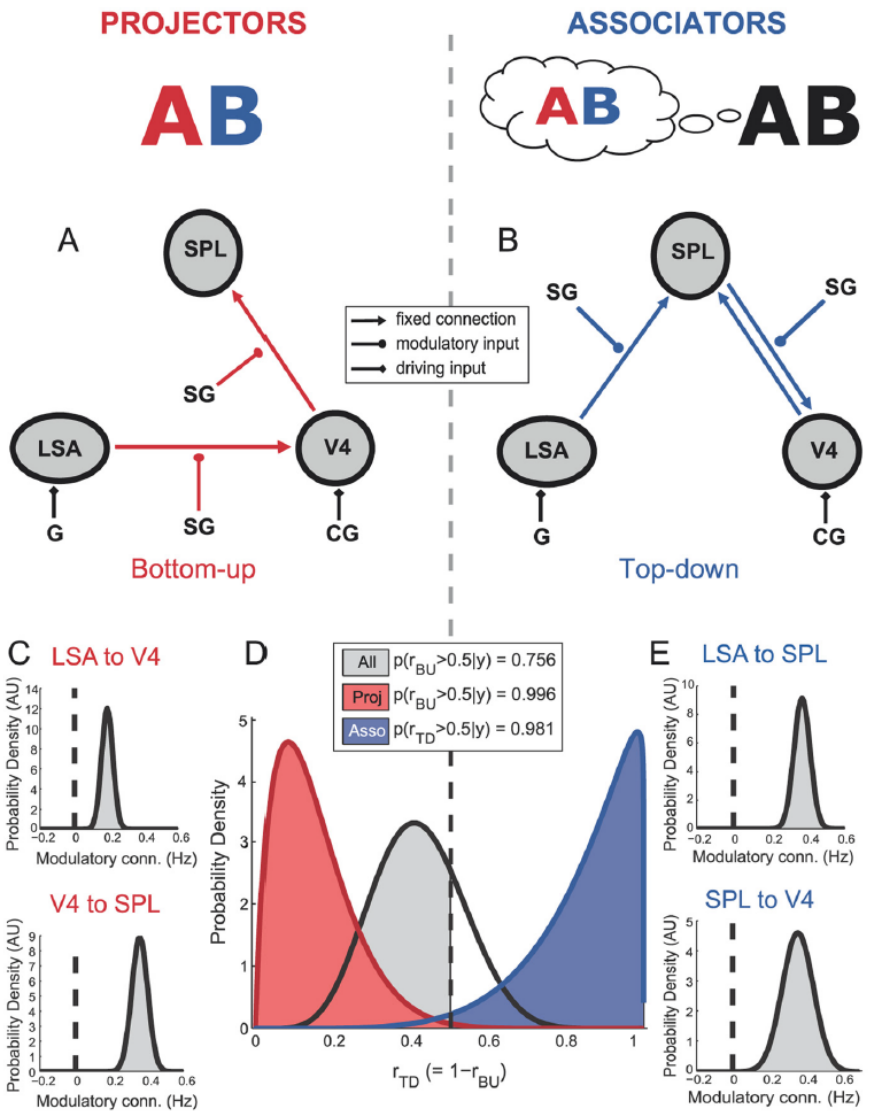
Posterior model probability

$$p(m_k|y) = \frac{p(y|m_k)p(m_k)}{\sum_k p(y|m_k)p(m_k)}$$

Stephan et al. 2016, *NeuroImage*

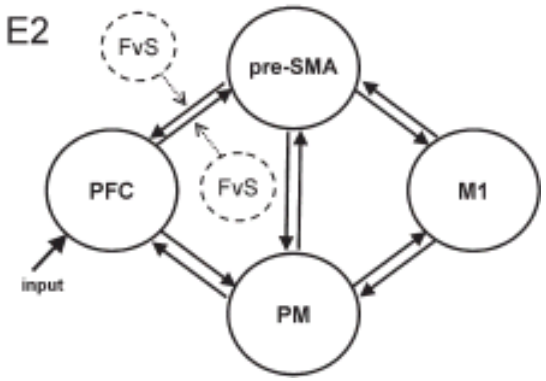
BAYESIAN MODEL SELECTION: SYNAESTHESIA

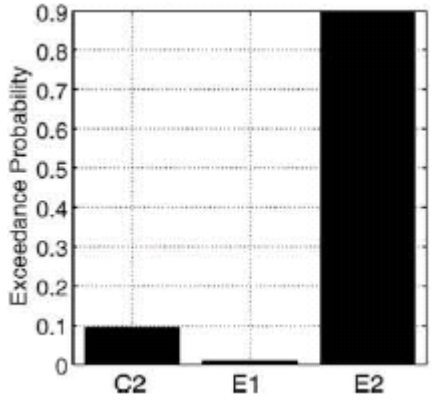
- "projectors" experience colour externally co-localized with a presented grapheme
- "associators" report an internally evoked association
- across all subjects: no evidence for either model
- but BMS results map precisely onto projectors (bottom-up) and associators (top-down)



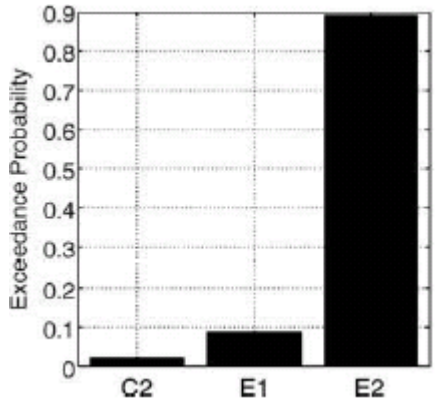
Van Leeuwen et al. 2011, *J. Neurosci.*

BAYESIAN MODEL SELECTION: PARKINSON'S DISEASE



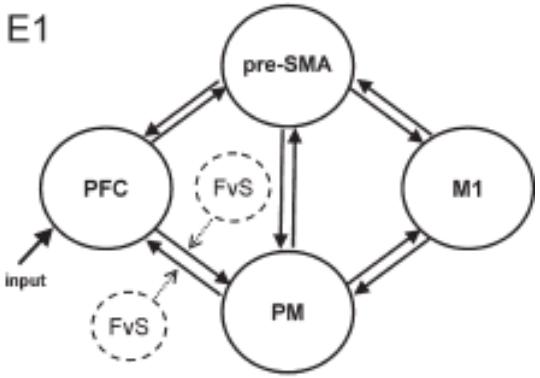


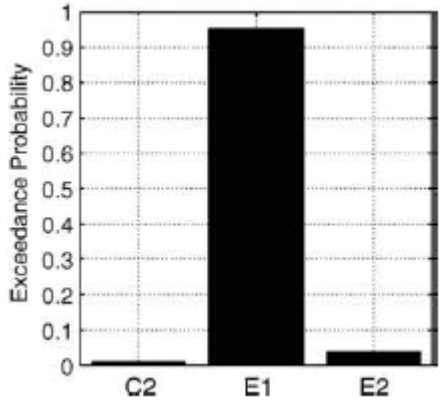
Age-matched controls



PD patients on medication

Selection of action modulates connections between PFC and SMA



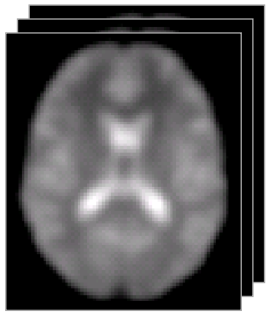


PD patients off medication

DA-dependent functional disconnection of the SMA

Rowe et al. 2010, *NeuroImage*

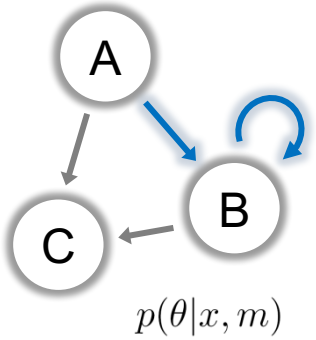
GENERATIVE EMBEDDING (SUPERVISED): CLASSIFICATION



measurements from
an individual subject

step 1 —
model inversion

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



$p(\theta|x,m)$

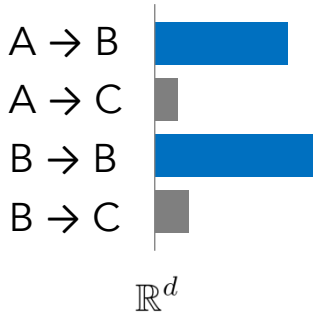
subject-specific
inverted generative model

step 2 —
kernel construction

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

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

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

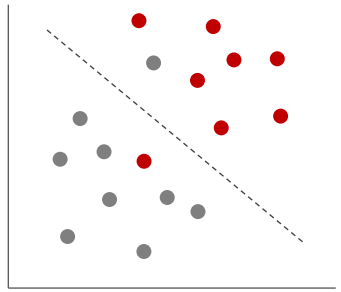


$\mathbb{R}^d$

subject representation in the
generative score space

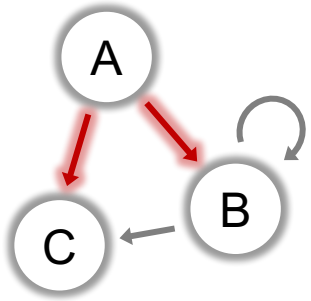
step 3 —
support vector classification

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



separating hyperplane fitted to
discriminate between groups

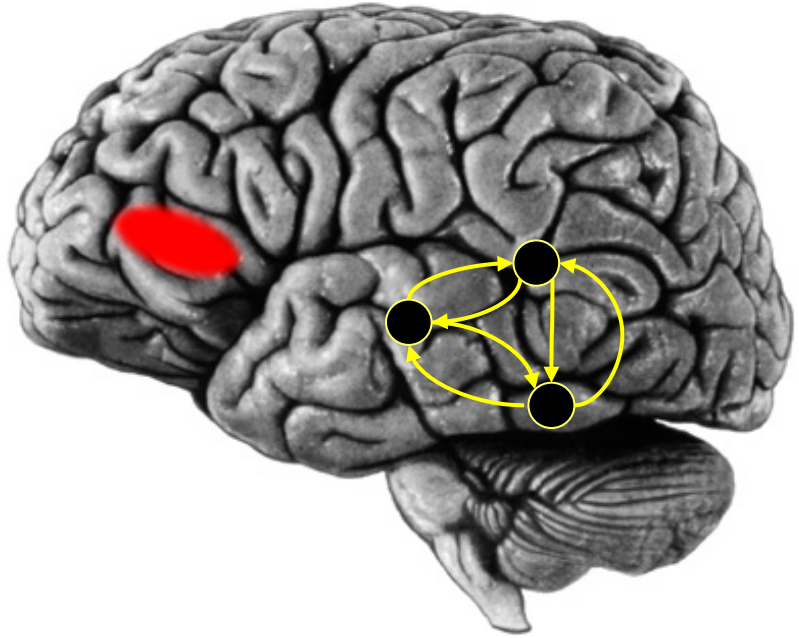
step 4 —
interpretation



jointly discriminative
model parameters

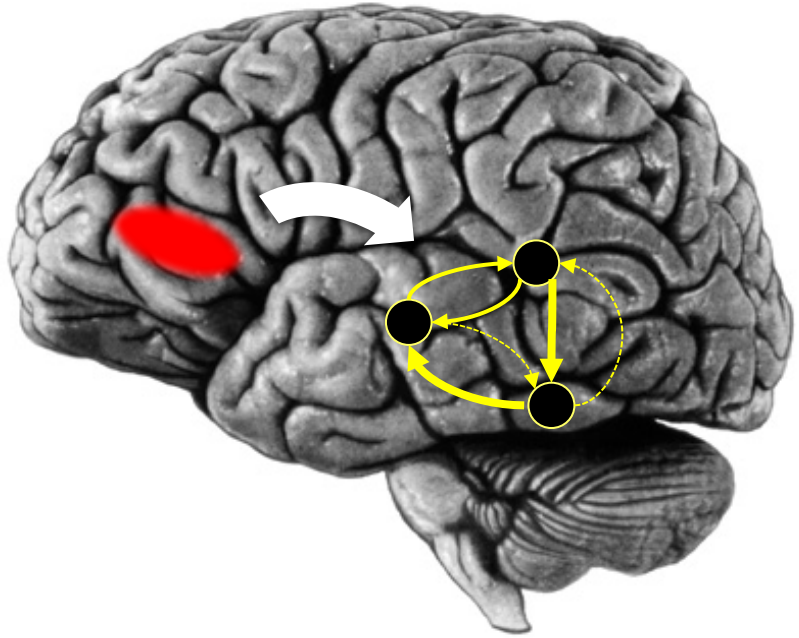
Brodersen et al. 2011, *PLoS Comput. Biol.*

Discovering remote or "hidden" brain lesions



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

Discovering remote or "hidden" brain lesions

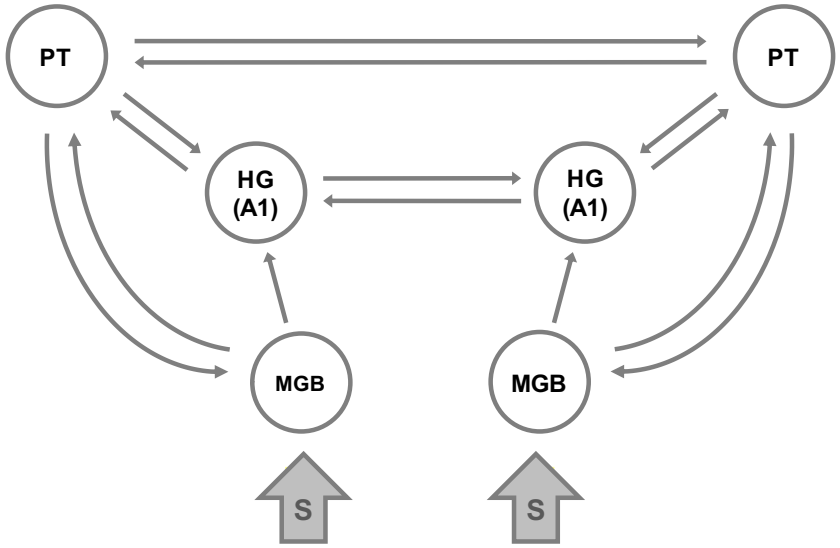


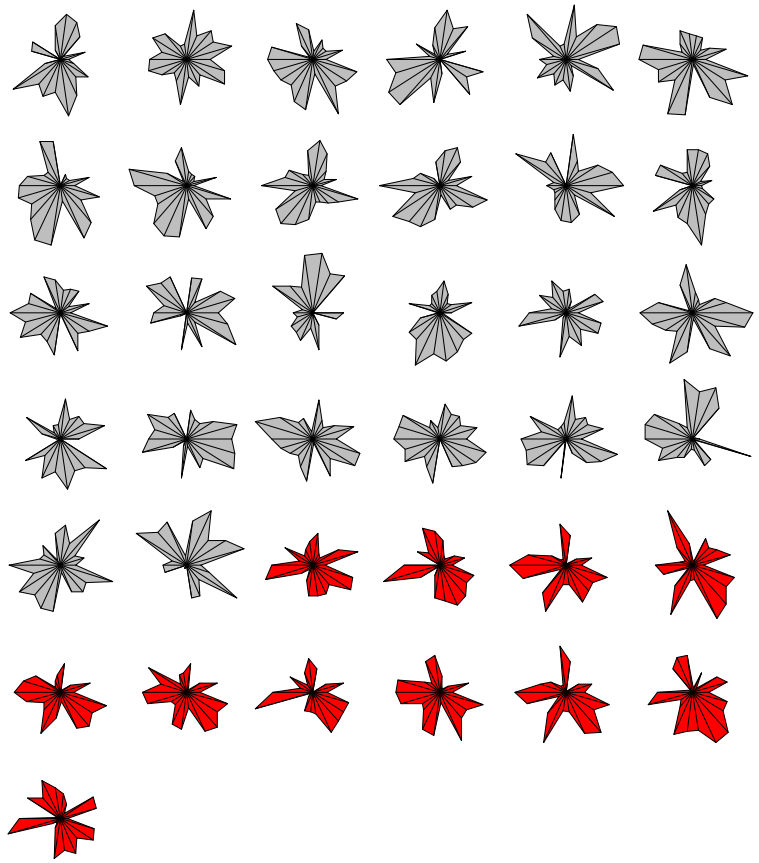
Brodersen et al. 2011, *PLoS Comput. Biol.*

CONNECTIONAL FINGERPRINTS:

APHASIC PATIENTS (N=11) VS. CONTROLS (N=26)

6-region DCM of auditory areas during passive speech listening

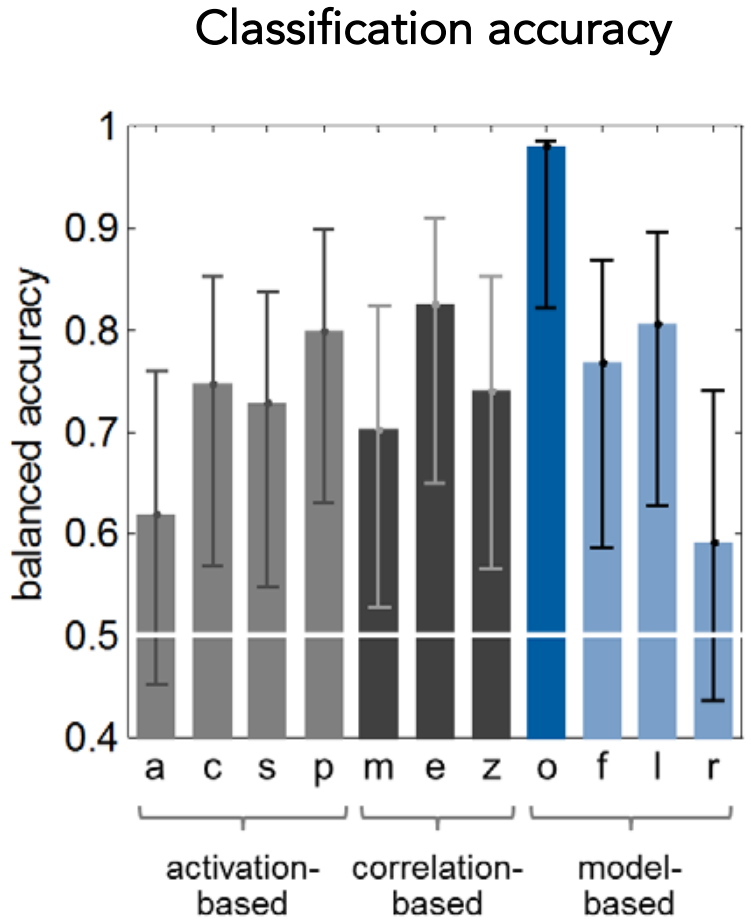




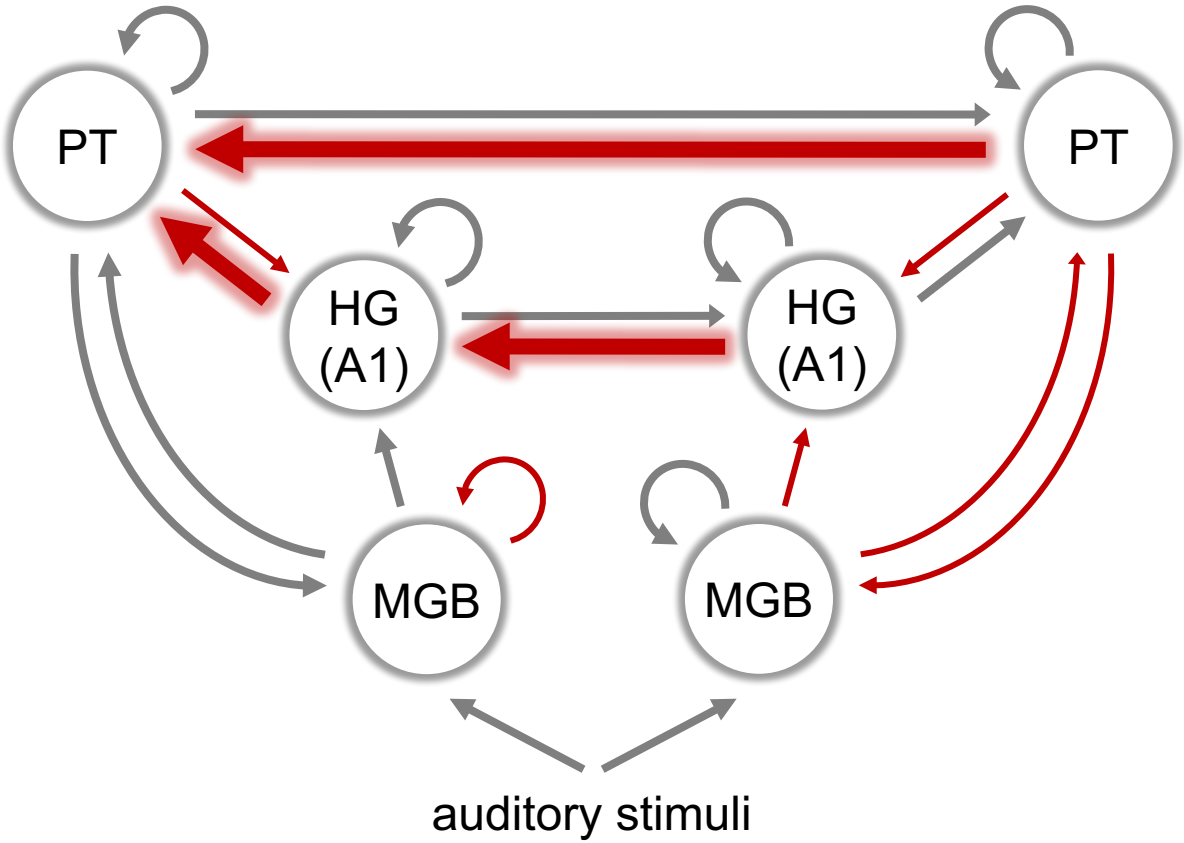
Brodersen et al. 2011, *PLoS Comput. Biol.*

Schofield et al. 2012, *J. Neurosci.* (fMRI data from speech recognition task)

PREDICTING PRESENCE/ABSENCE OF "HIDDEN" LESION



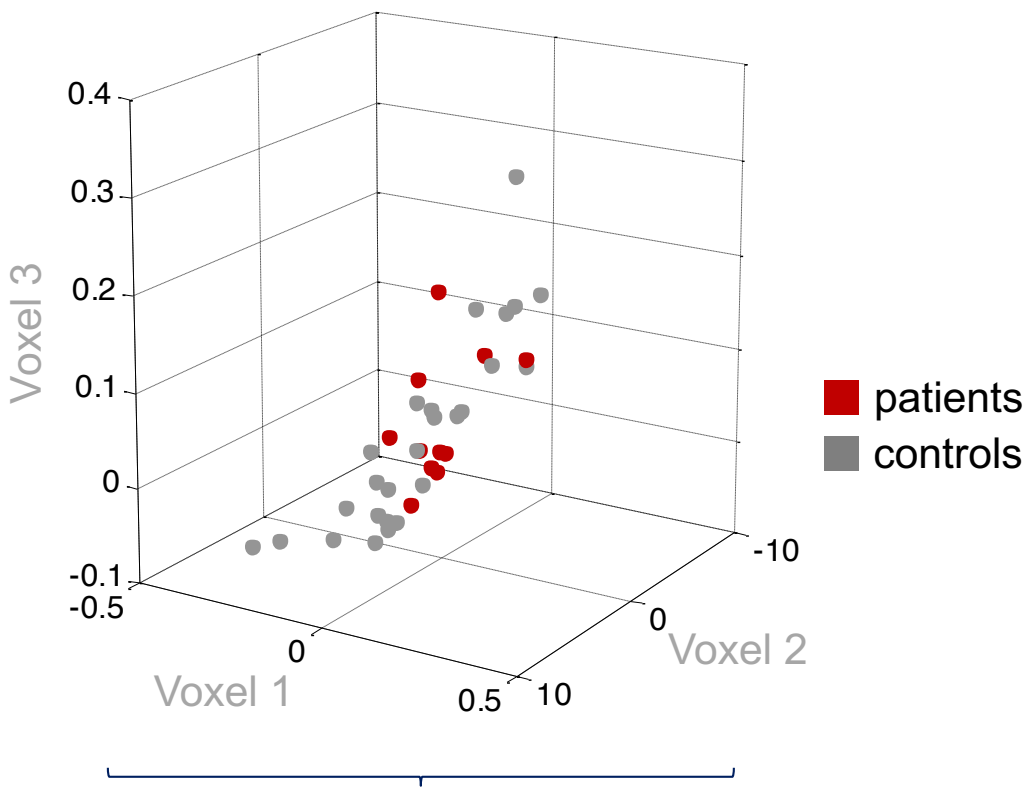
Brodersen et al. 2011, *PLoS Comput. Biol.*



Schofield et al. 2012, *J. Neurosci.* (fMRI data from speech recognition task)

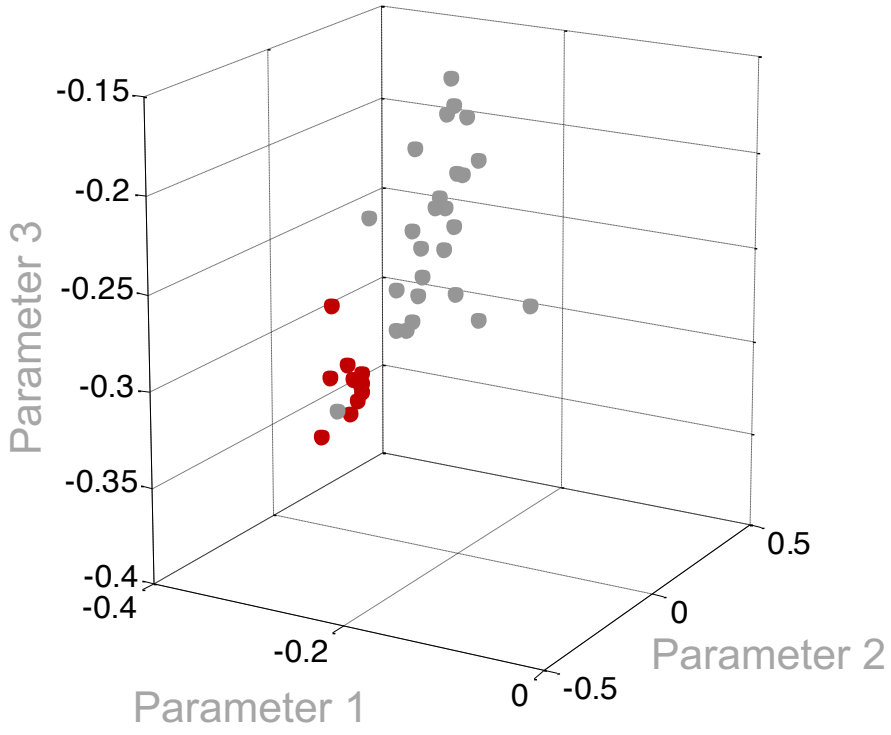
PREDICTING PRESENCE/ABSENCE OF "HIDDEN" LESION

Voxel-based activity space



classification accuracy
75%

Model-based parameter space

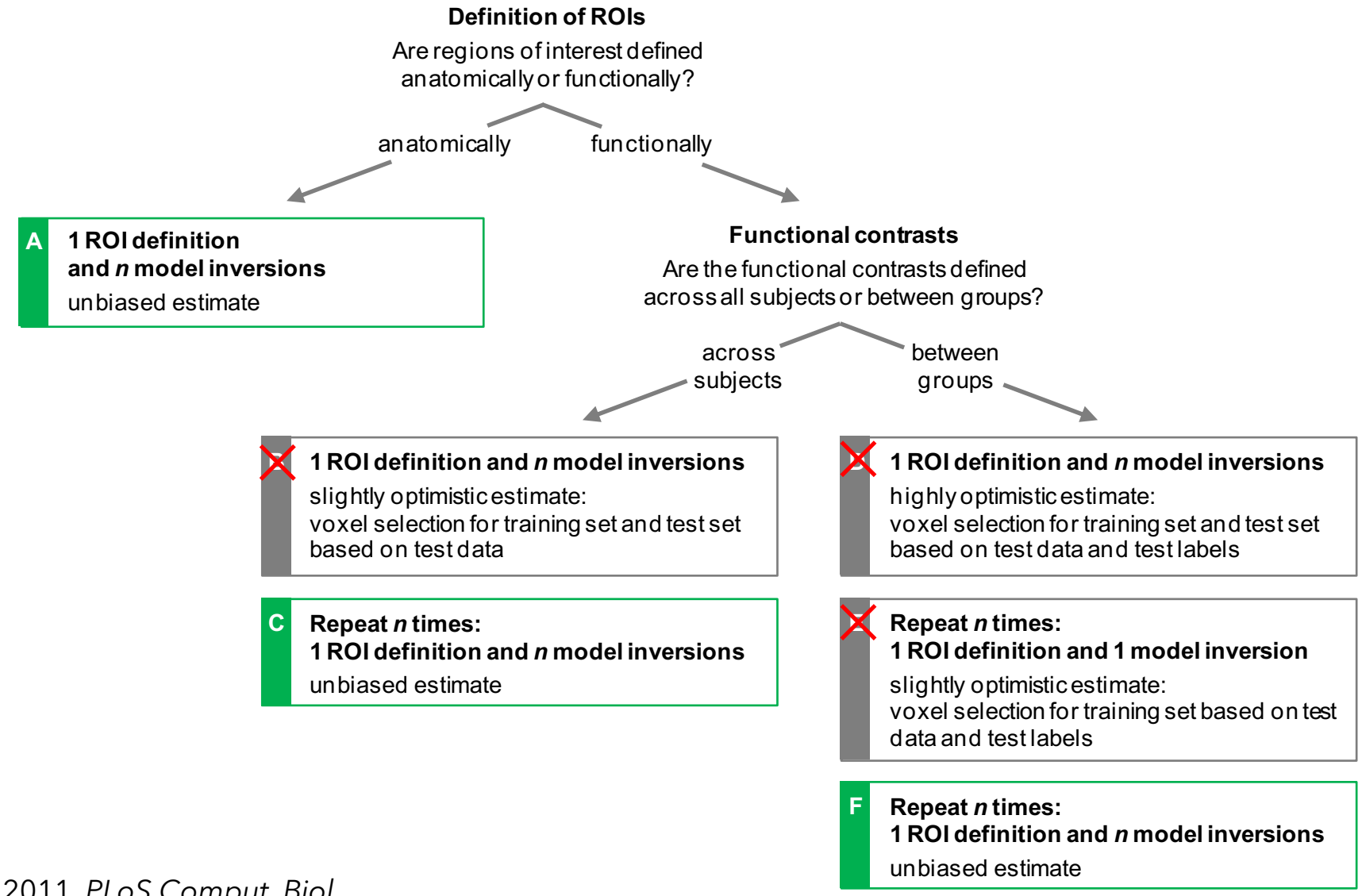


classification accuracy
98%

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

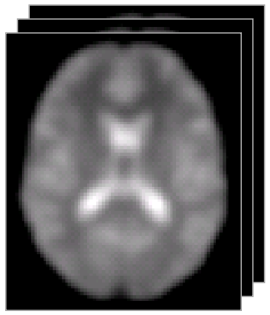
Schofield et al. 2012, *J. Neurosci.* (fMRI data from speech recognition task)

BEST-PRACTICE GUIDELINES FOR GENERATIVE EMBEDDING



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

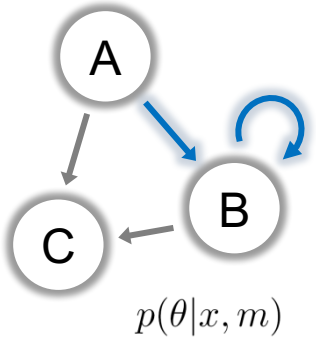
GENERATIVE EMBEDDING (UNSUPERVISED): CLUSTERING



measurements from
an individual subject

step 1 —
model inversion

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



$p(\theta|x, m)$

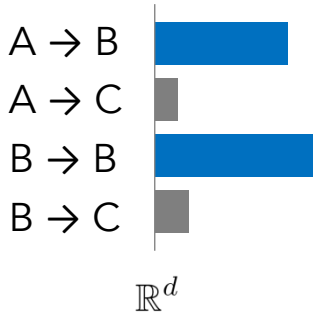
subject-specific
inverted generative model

step 2 —
kernel construction

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

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

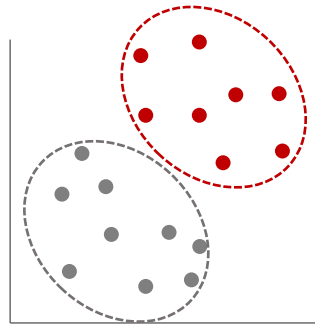
$k_\mathcal{M} : \mathcal{M}_\Theta \times \mathcal{M}_\Theta \to \mathbb{R}$



$\mathbb{R}^d$

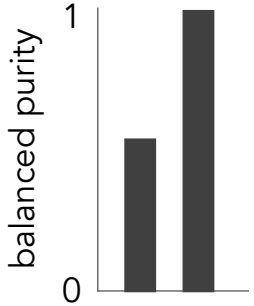
subject representation in the
generative score space

step 3 —
clustering



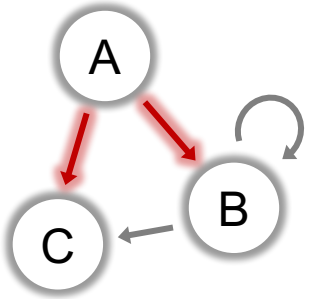
emerging groups of similar
subjects?

step 4 —
validation



agreement with
aetiology or clinical facts?

step 5 —
interpretation



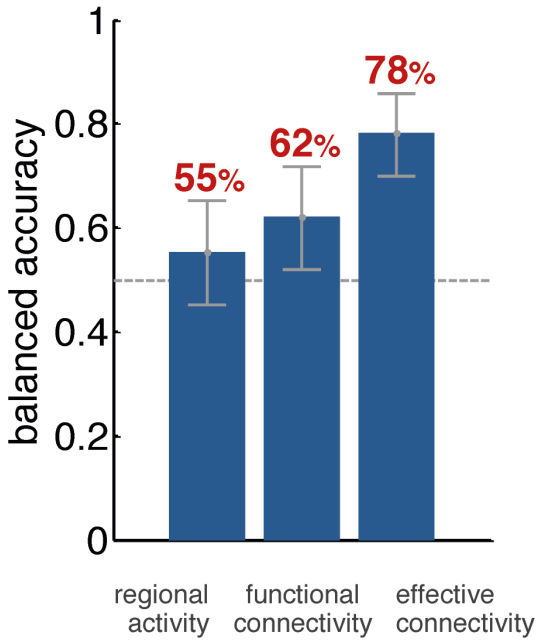
jointly discriminative
model parameters

Brodersen et al. 2014, *Neuroimage: Clinical*

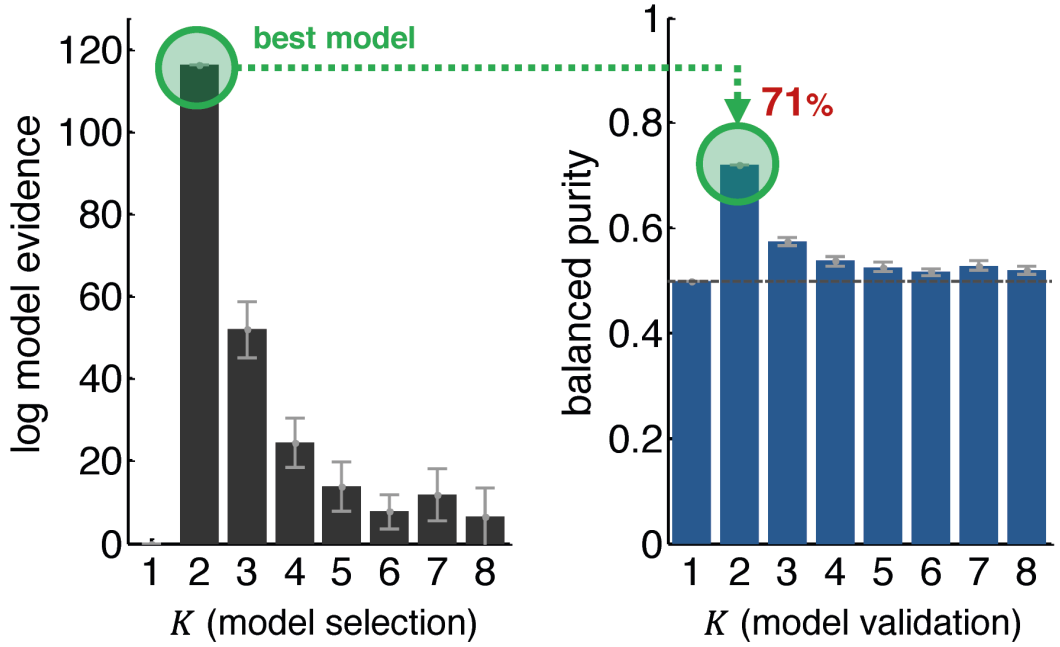
Generative embedding of variational Gaussian mixture models

Schizophrenic patients (N=41) vs. controls (N=42)

Supervised:
SVM classification



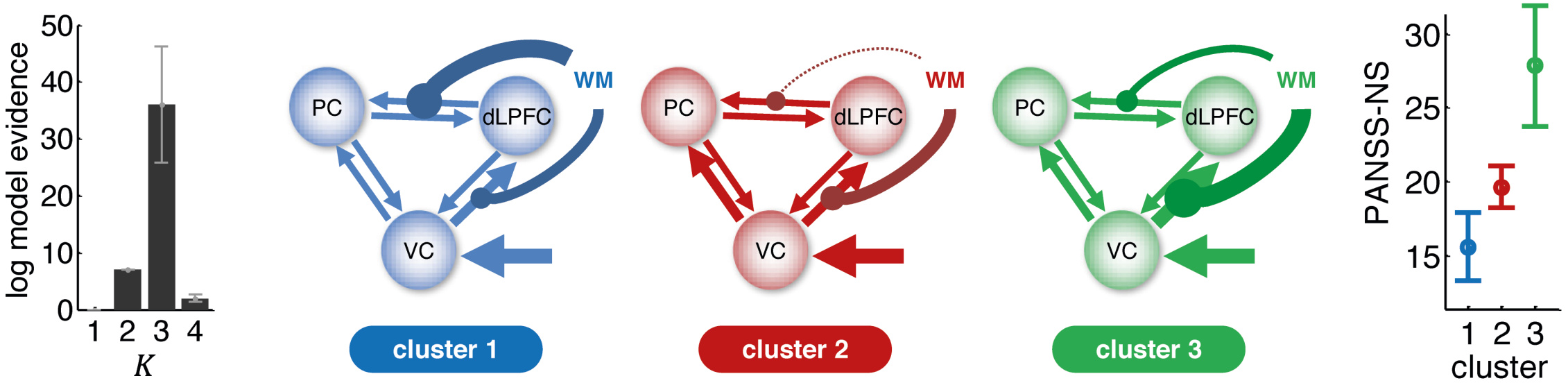
Unsupervised:
GMM clustering



Brodersen et al. 2014, *NeuroImage: Clinical*

Deserno et al. 2012, *J. Neurosci.* (fMRI data from working memory task)

DETECTING SUBGROUPS OF PATIENTS IN SCHIZOPHRENIA

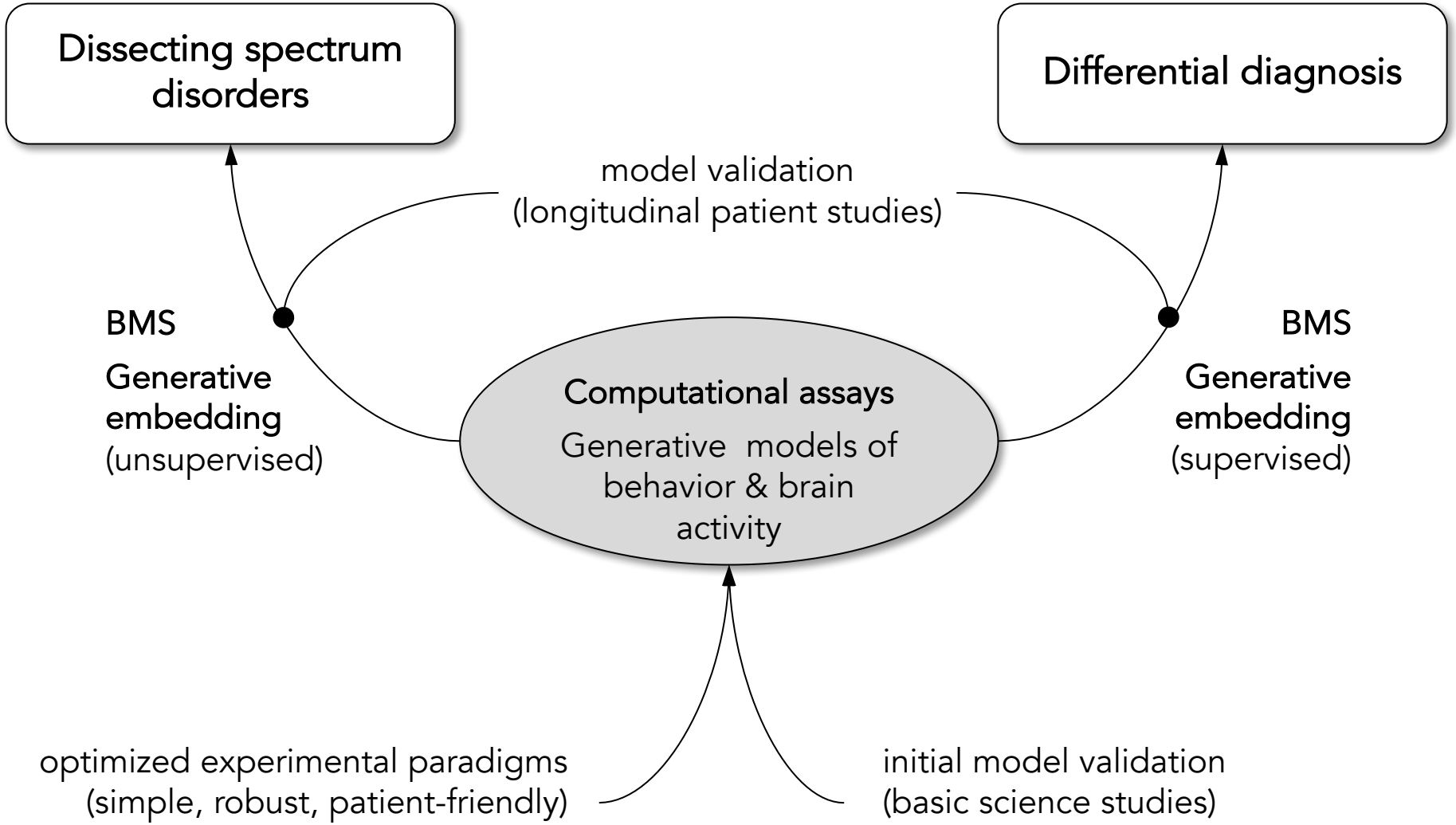


- three distinct subgroups (total N = 41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the positive and negative symptom scale (PANSS)

Brodersen et al. 2014, *Neuroimage: Clinical*

Deserno et al. 2012, *J. Neurosci.* (fMRI data from working memory task)

ROADMAP FOR TRANSLATIONAL NEUROMODELING



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

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