Towards model-based diagnostics of human brain pathophysiology

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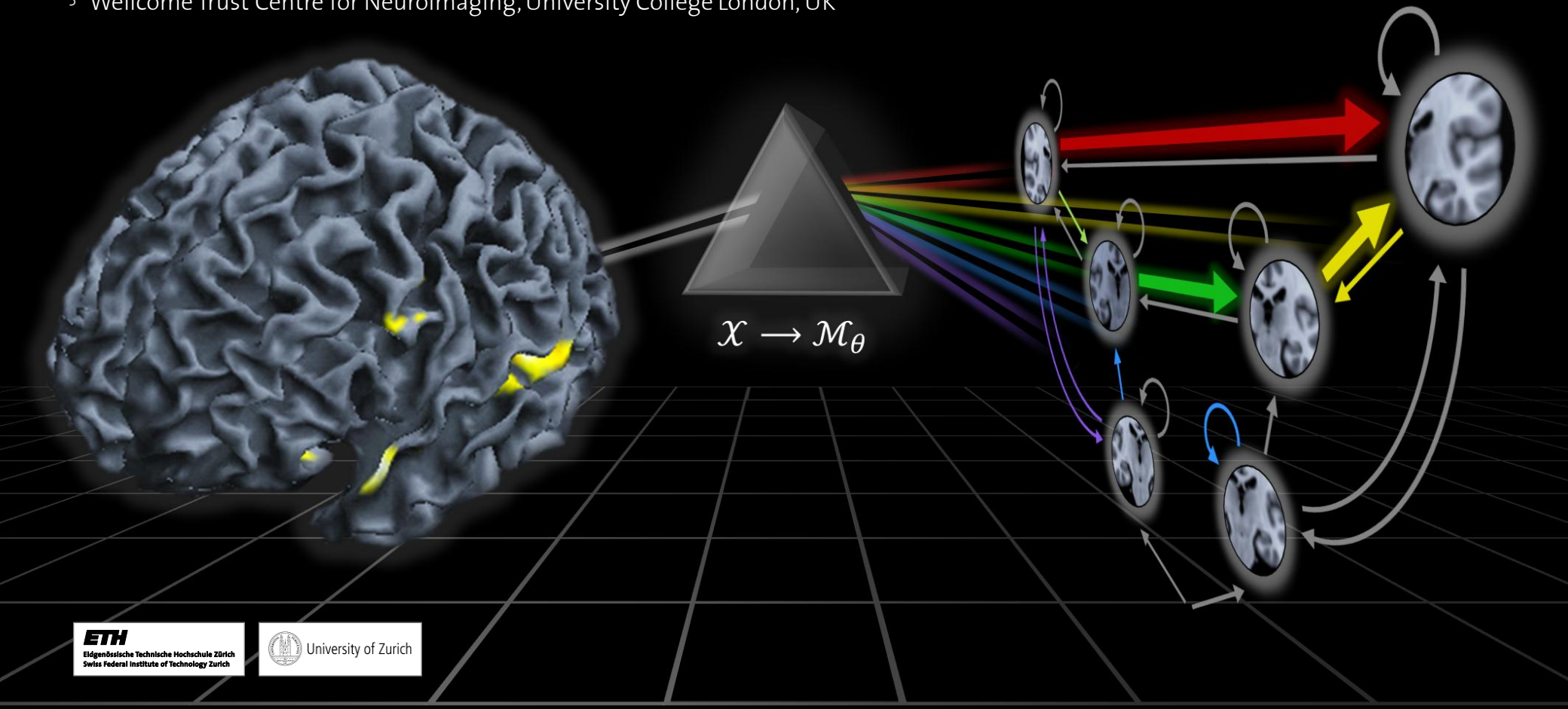


ETH Eidgenössische Technische Hochschule Zürich Swiss Federal Institute of Technology Zurich

University of Zurich

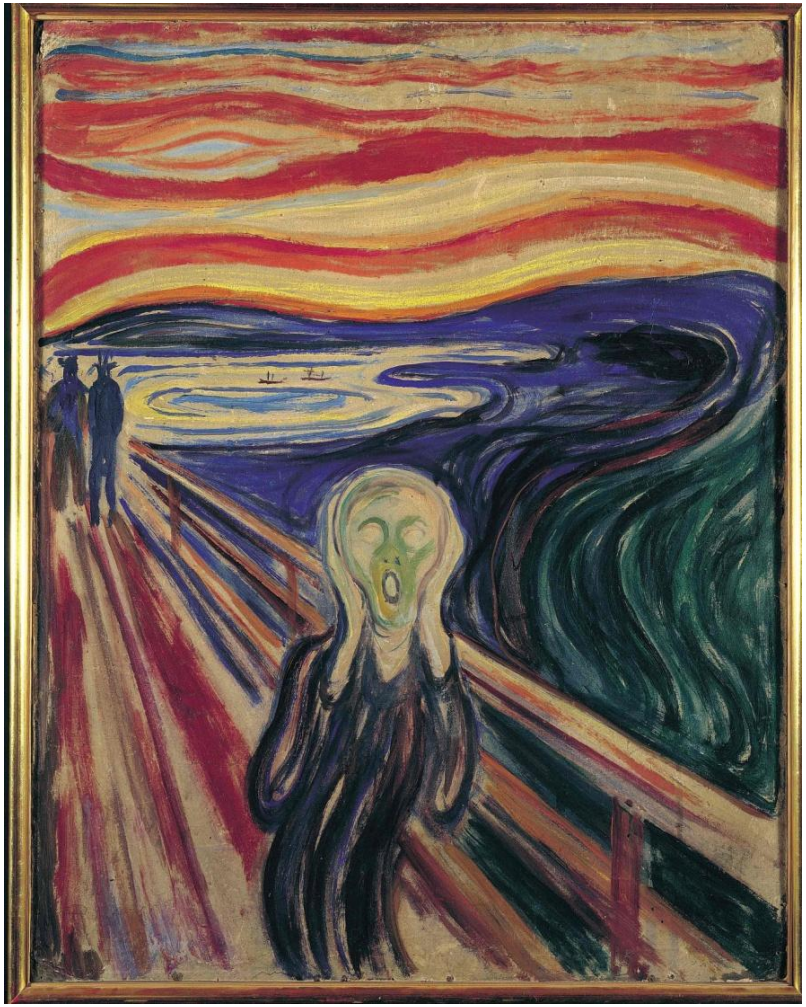
Psychiatric spectrum diseases

Schizophrenia, depression, mania, etc.

- diverse genetic basis, strong gene-environment interactions
  ⇨ genetically based diagnoses impossible
- multiple pathophysiological mechanisms
  ⇨ even when symptoms are similar, causes can differ across patients
- variability in treatment response and outcome

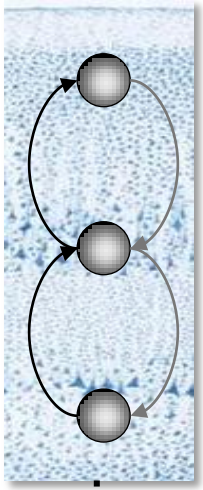
Consequences?

- need to infer on pathophysiological mechanisms in individual patients!

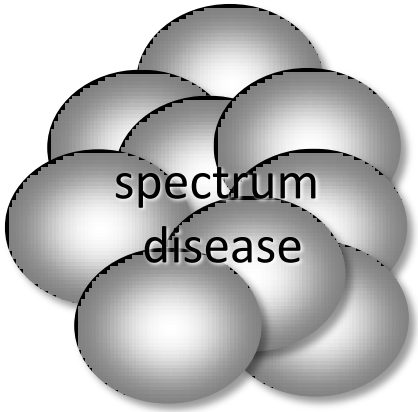


Model-based inference on *individual* pathophysiology

❶ model of neuronal (patho)physiology



❷ application to brain activity data from individual patients



model-based

diagnostic tests

❸ diagnostic classification

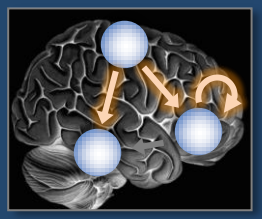
type 1 → treatment X

type 2 → treatment Y

type 3 → treatment Z

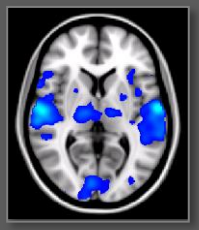
Towards model-based diagnostic tests

Model-based analyses



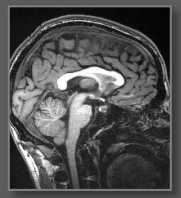
How do patterns of hidden quantities (e.g., connectivity among brain regions) differ between groups?

Activation-based analyses



Which functional differences allow us to separate groups?

Structure-based analyses



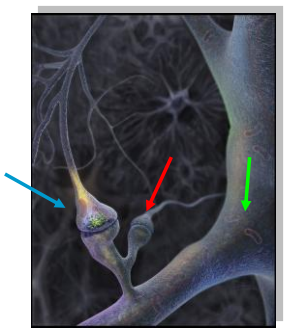
Which anatomical structures allow us to separate patients and healthy controls?

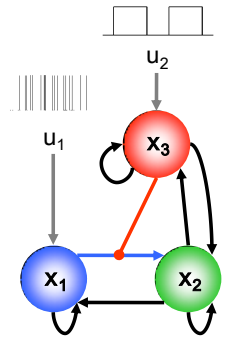
From models of pathophysiology to clinical applications

1. **Developing models of (patho)physiological processes**
   - neuronal: synaptic plasticity, neuromodulation
   - computational: learning, decision making

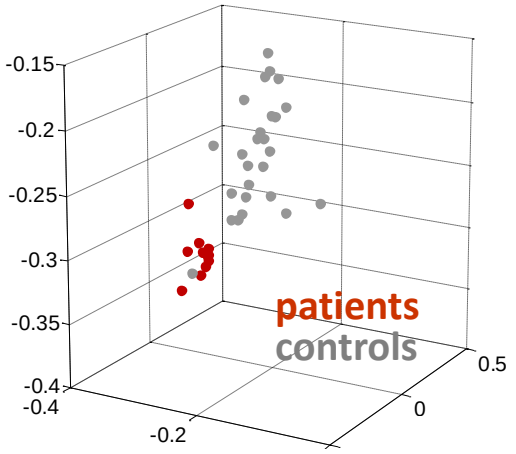
2. **Validation studies in animals & humans**
   - can models detect experimentally induced changes, e.g., specific changes in synaptic plasticity?

3. **Clinical validation studies & translation**
   - clinical validation of classifications
   - predicting diagnosis, therapeutic response, outcome





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



From models of pathophysiology to clinical applications

1

Developing models of (patho)physiological processes

- neuronal: synaptic plasticity, neuromodulation
- computational: learning, decision making

2

Validation studies in animals & humans

- can models detect experimentally induced changes, e.g., specific changes in synaptic plasticity?

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Clinical validation studies & translation

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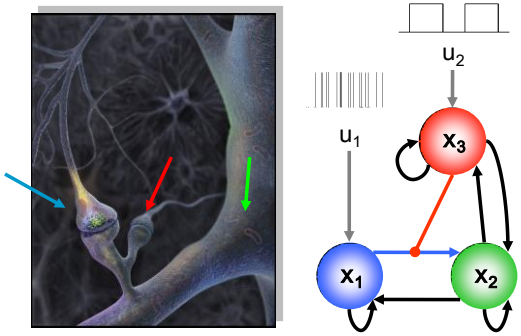

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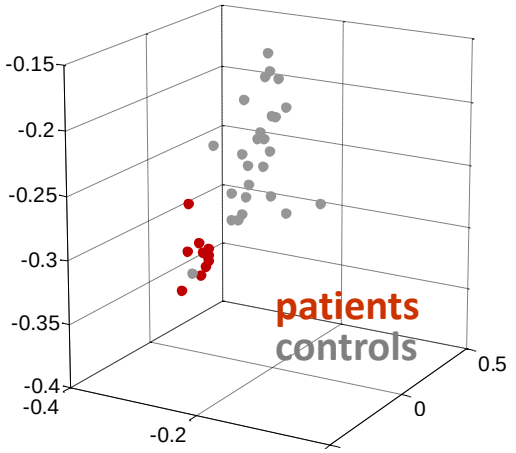
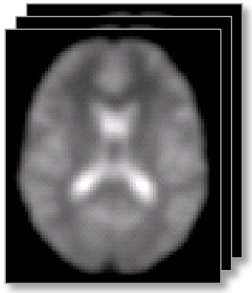
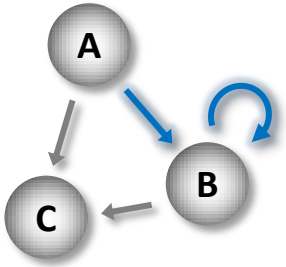


Model-based classification by generative embedding



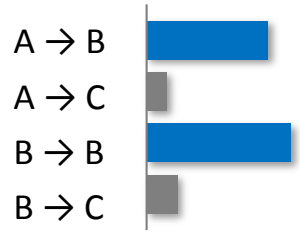
measurements from
an individual subject

**step 1 —
model inversion**



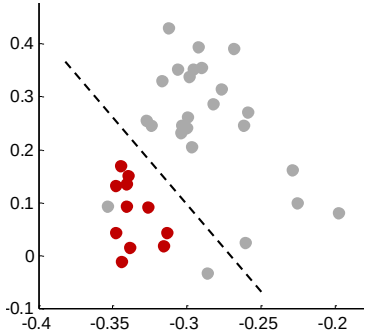
subject-specific
inverted generative model

**step 2 —
kernel construction**



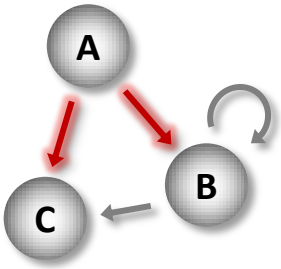
subject representation in the
generative score space

**step 3 —
analysis**



separating hyperplane to
discriminate between groups

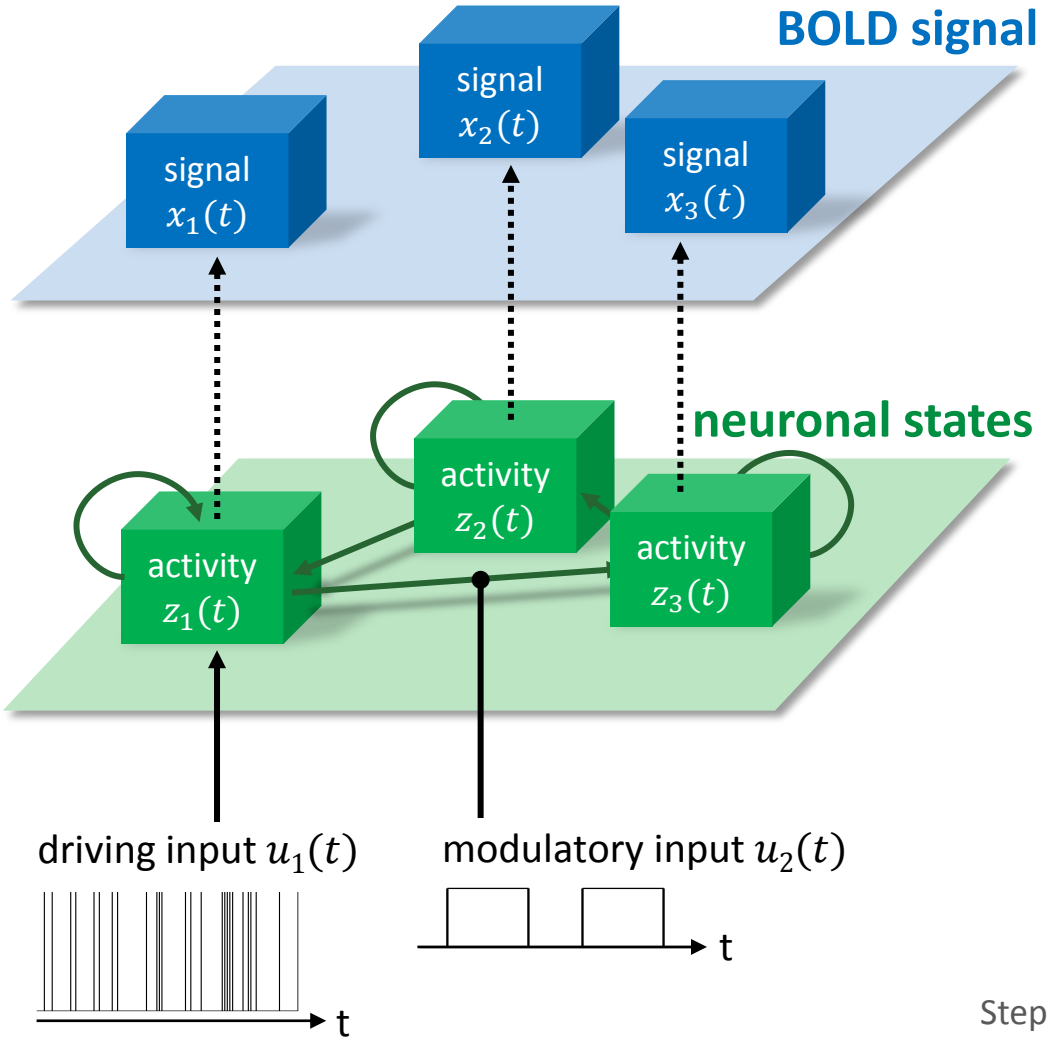
**step 4 —
interpretation**



jointly discriminative
connection strengths

Brodersen et al. (2011) *NeuroImage;* Brodersen et al. (2011) *PLoS Comput Biol*

Choosing a generative model: DCM for fMRI



haemodynamic forward model

$$x = g(z, \theta_h)$$

neural state equation

$$\dot{z} = \left(A + \sum u_j B^{(j)}\right) z + Cu$$

intrinsic connectivity

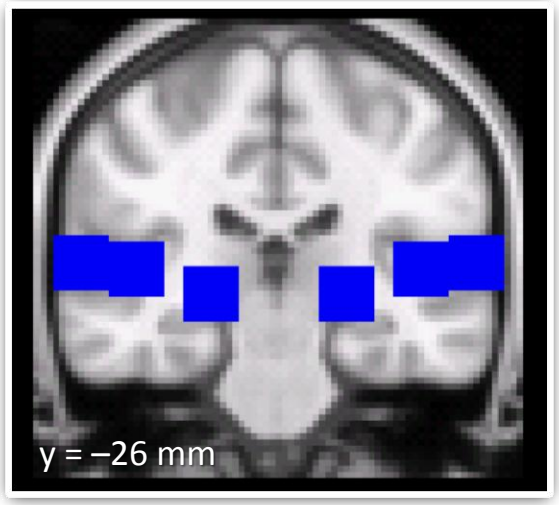
modulation of connectivity

direct inputs

Friston, Harrison & Penny (2003) *NeuroImage*
Stephan & Friston (2007) *Handbook of Brain Connectivity*

Example: diagnosing stroke patients

L

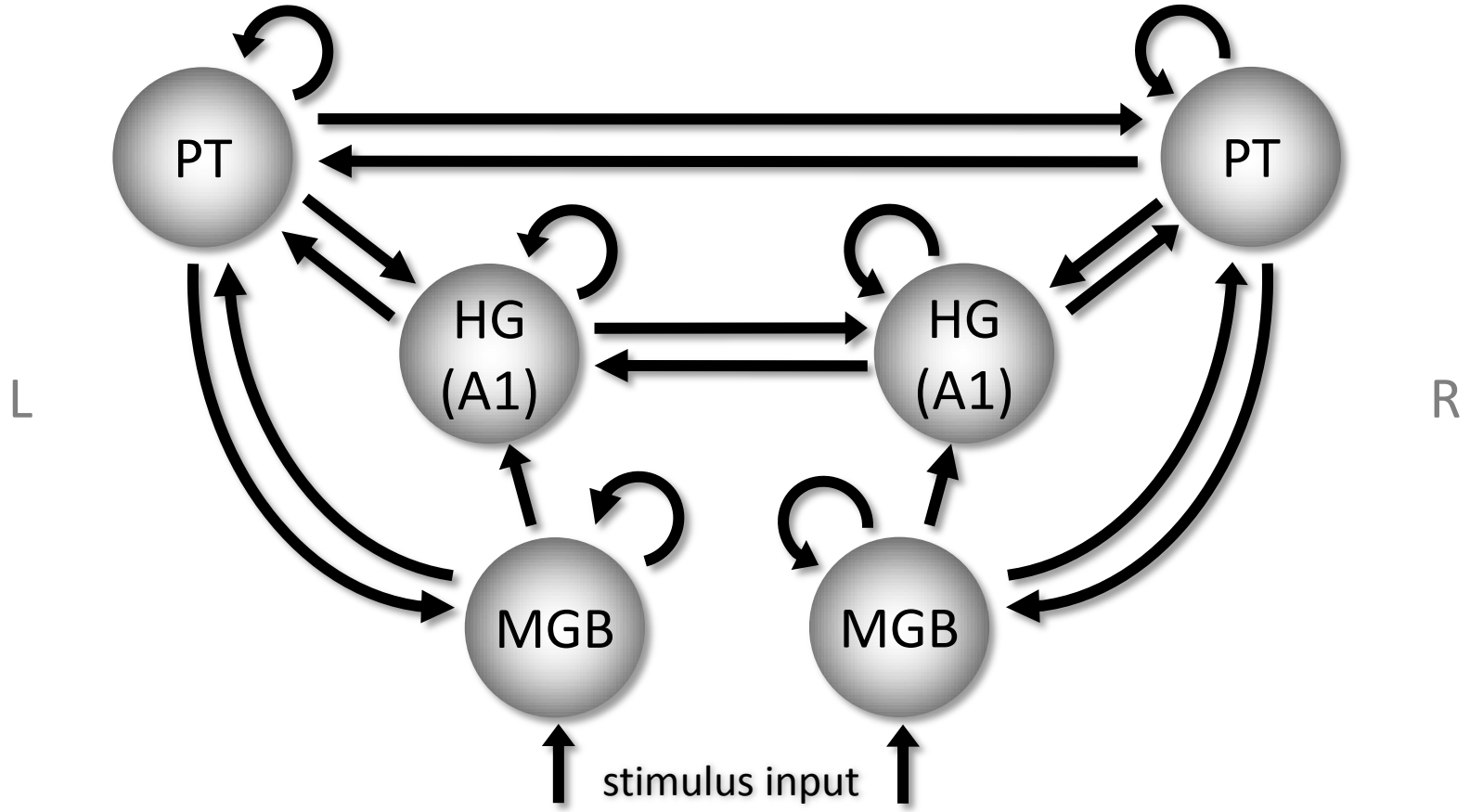


anatomical
regions of interest

R

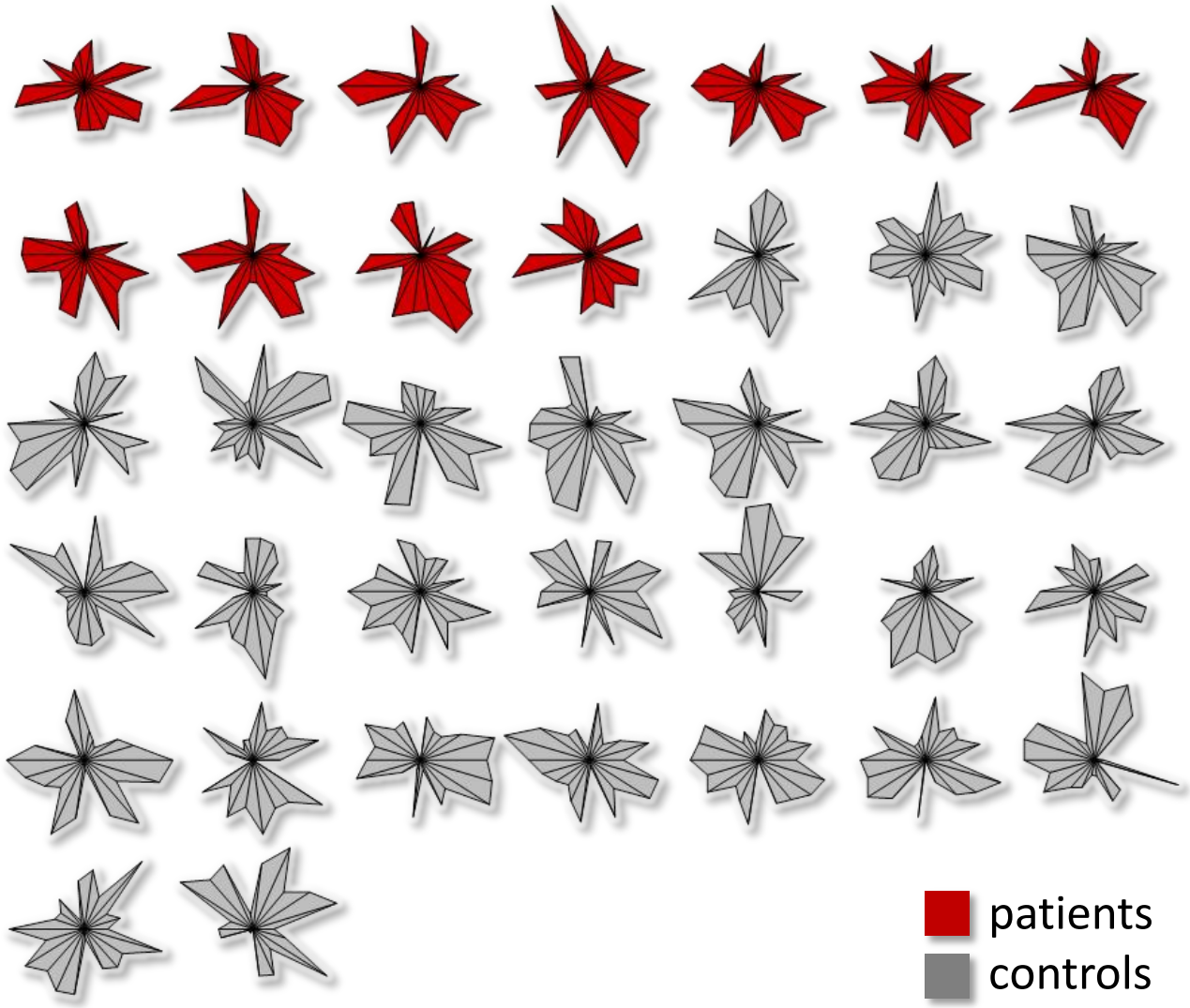
Brodersen et al. (2011) *NeuroImage;* Brodersen et al. (2011) *PLoS Comput Biol*

Example: diagnosing stroke patients

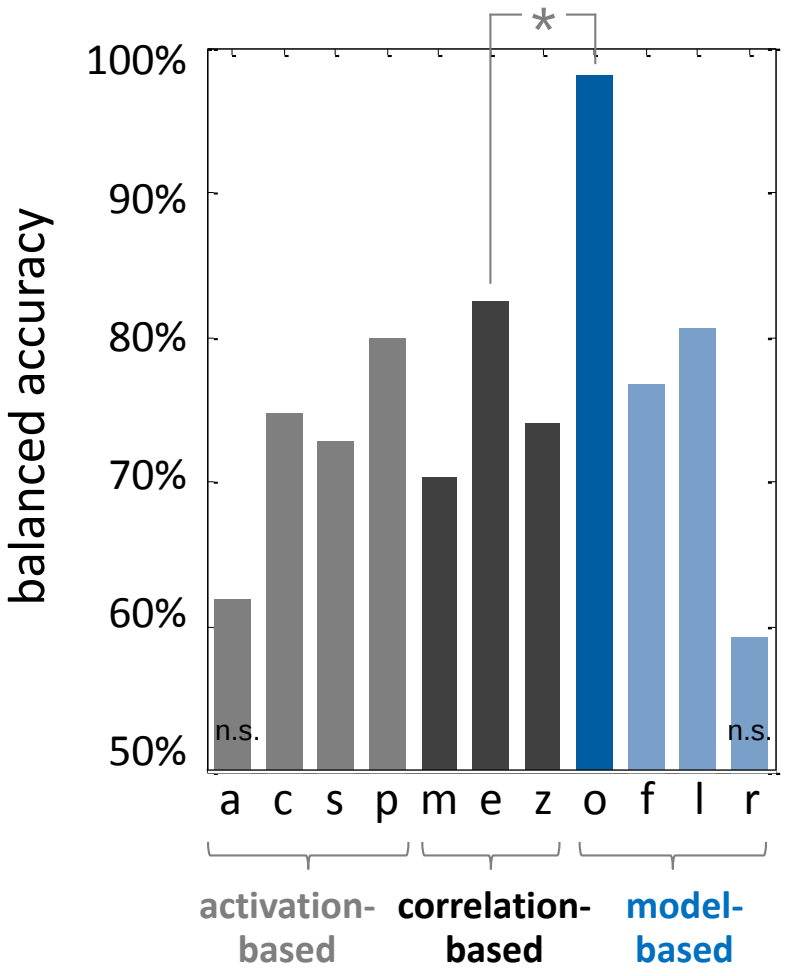


Brodersen et al. (2011) *NeuroImage;* Brodersen et al. (2011) *PLoS Comput Biol*

Multivariate analysis: connectional fingerprints



Classification performance



Activation-based analyses

- **a** anatomical feature selection
- **c** mass-univariate contrast feature selection
- **s** locally univariate searchlight feature selection
- **p** PCA-based dimensionality reduction

Correlation-based analyses

- **m** correlations of regional means
- **e** correlations of regional eigenvariates
- **z** Fisher-transformed eigenvariates correlations

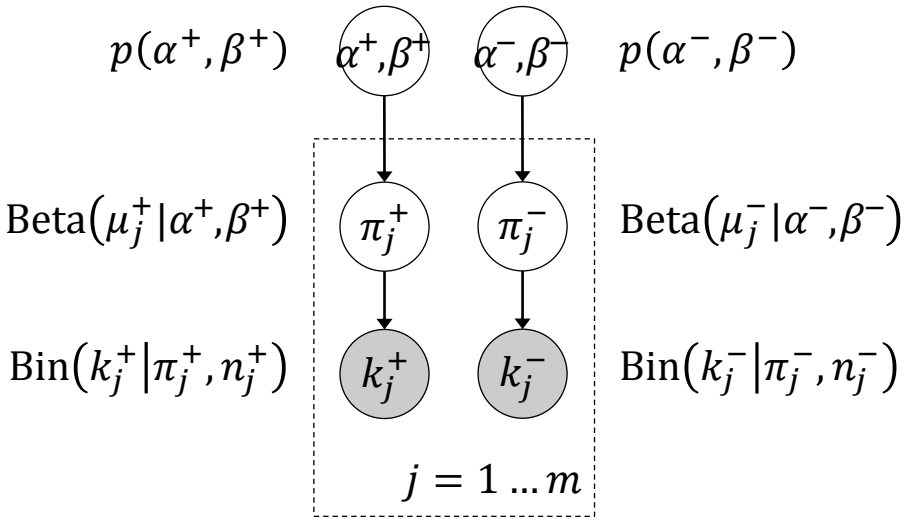
Model-based analyses

- **o** gen.embed., original full model
- **f** gen.embed., less plausible feedforward model
- **l** gen.embed., left hemisphere only
- **r** gen.embed., right hemisphere only

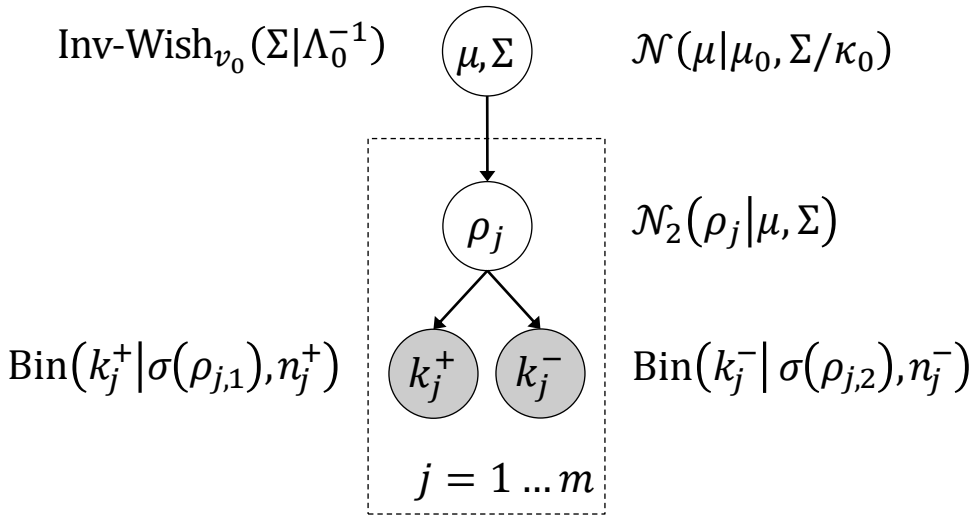
Brodersen et al. (2011) *PLoS Comput Biol*

Full Bayesian approach to performance evaluation

Full Bayesian
mixed-effects inference
(beta-binomial model)

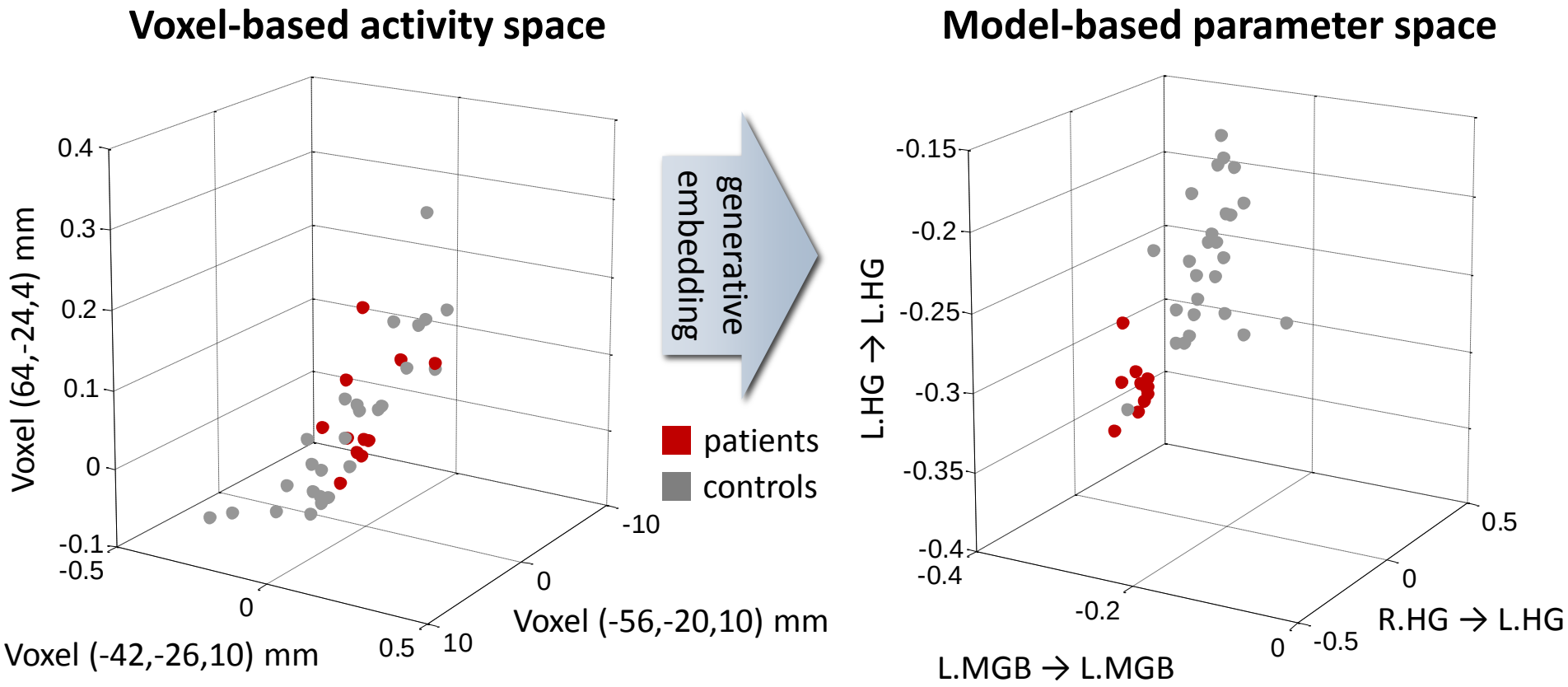


Full Bayesian
mixed-effects inference
(normal-binomial model)



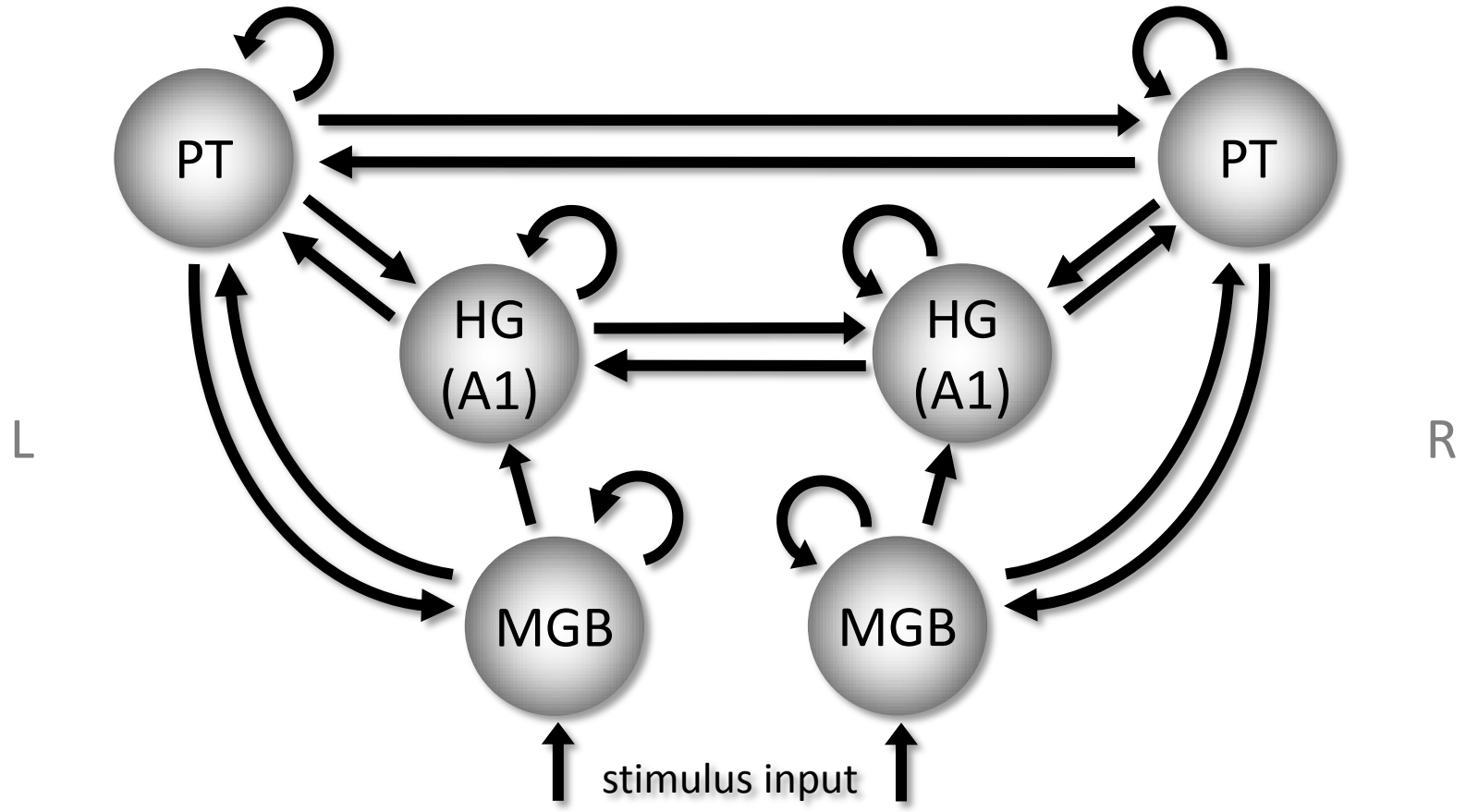
Brodersen, Mathys, Chumbley, Daunizeau, Stephan *(in preparation)*

The generative projection

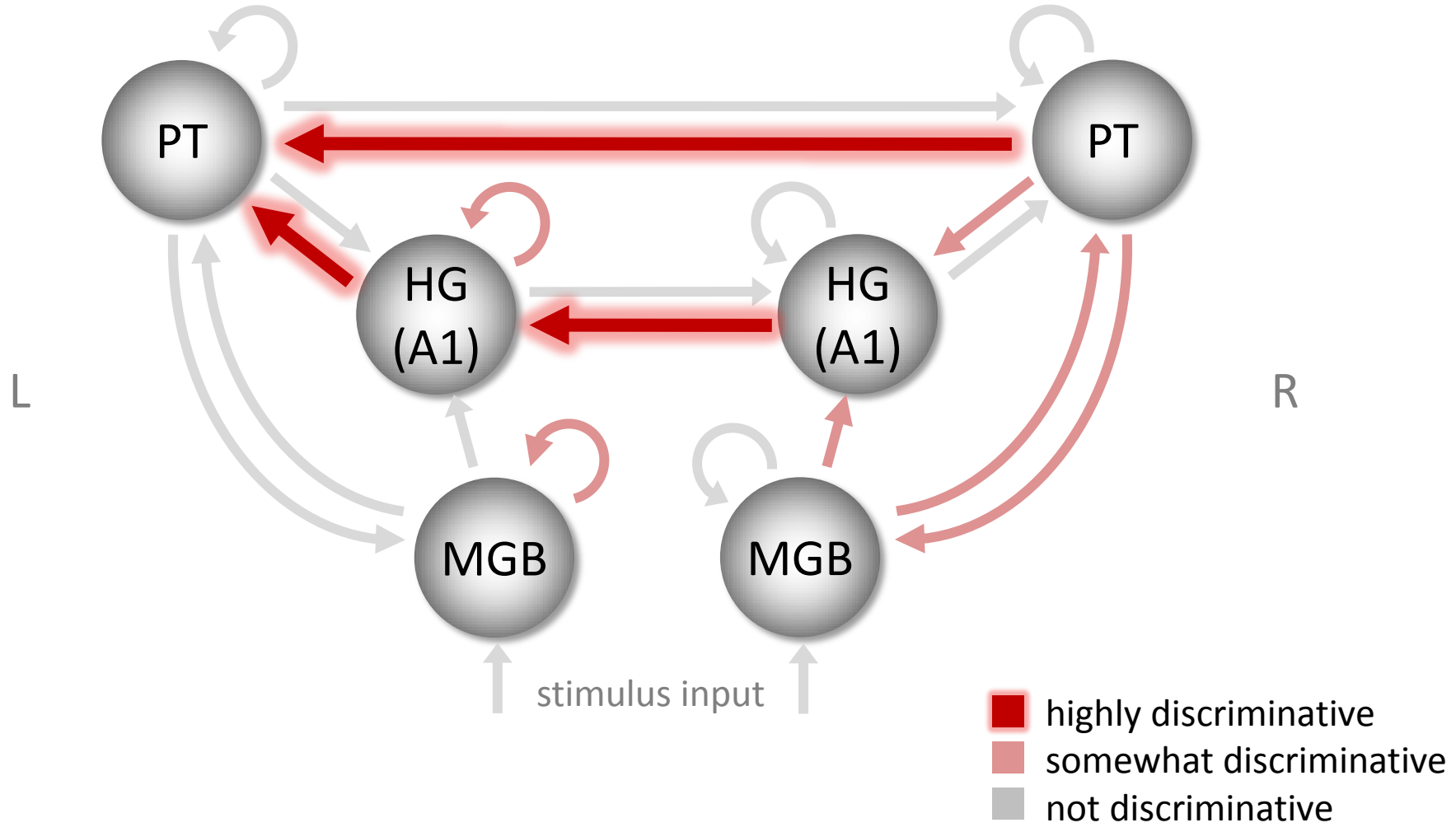


Brodersen et al. (2011) *PLoS Comput Biol*

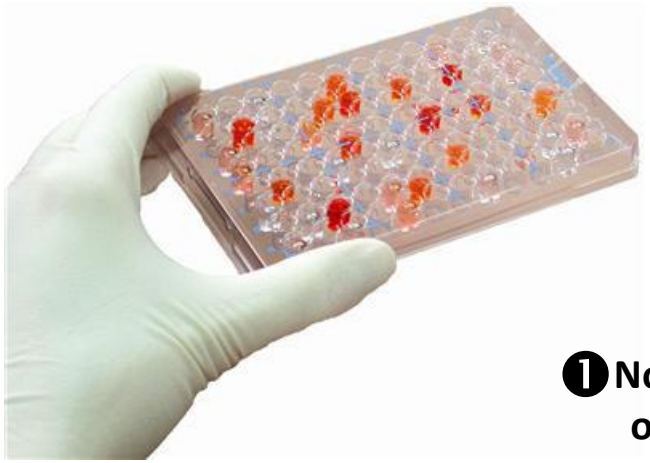
Discriminative features in model space

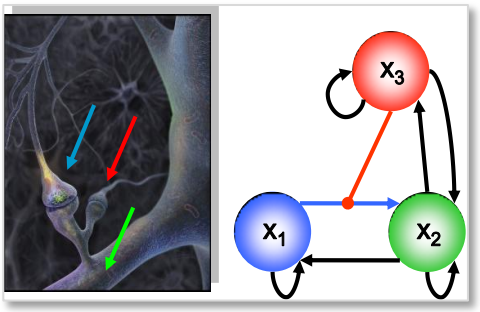


Discriminative features in model space

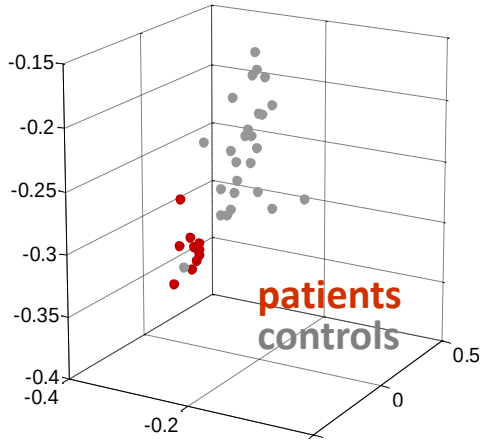


Summary

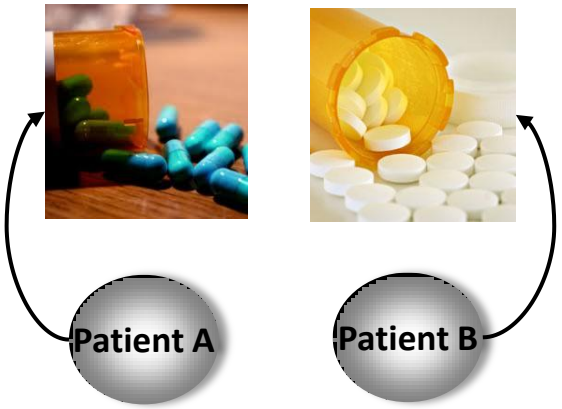




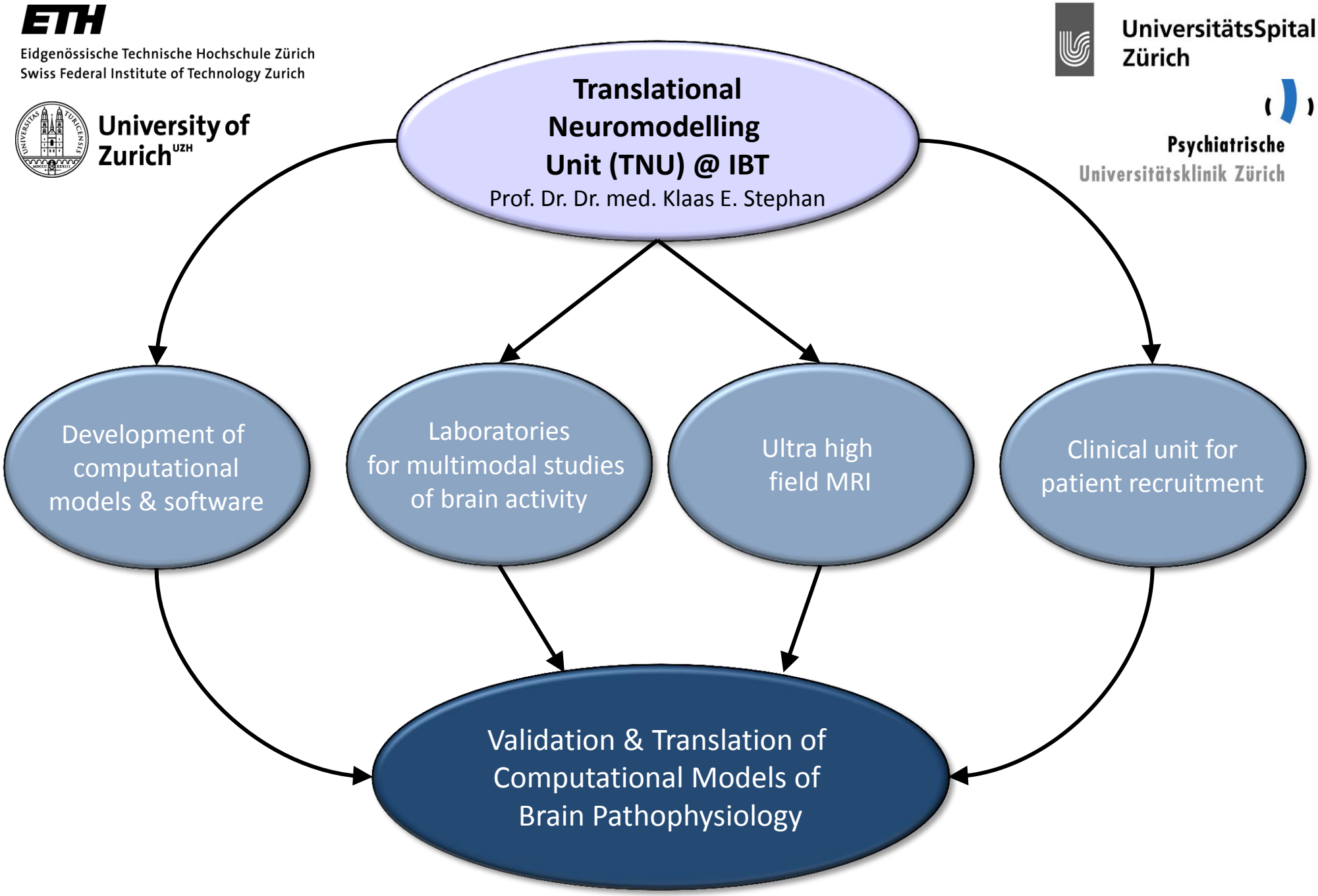
❶ Non-invasive, model-based assays of human brain pathophysiology



❷ Quantitative diagnostics



❸ Individualized treatment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Translational Neuromodelling Unit (TNU) @ IBT
Prof. Dr. Dr. med. Klaas E. Stephan
Development of computational models & software
Laboratories for multimodal studies of brain activity
Ultra high field MRI
Clinical unit for patient recruitment
Validation & Translation of Computational Models of Brain Pathophysiology

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H. den Ouden
L. Harrison

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* listed alphabetically