Why is fMRI important for medicine?

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Overview

- Measuring brain activity - an ultrashort summary
- fMRI in a nutshell
- Neurology: clinical examples
- Psychiatry: can fMRI help?

The "human circulation balance"

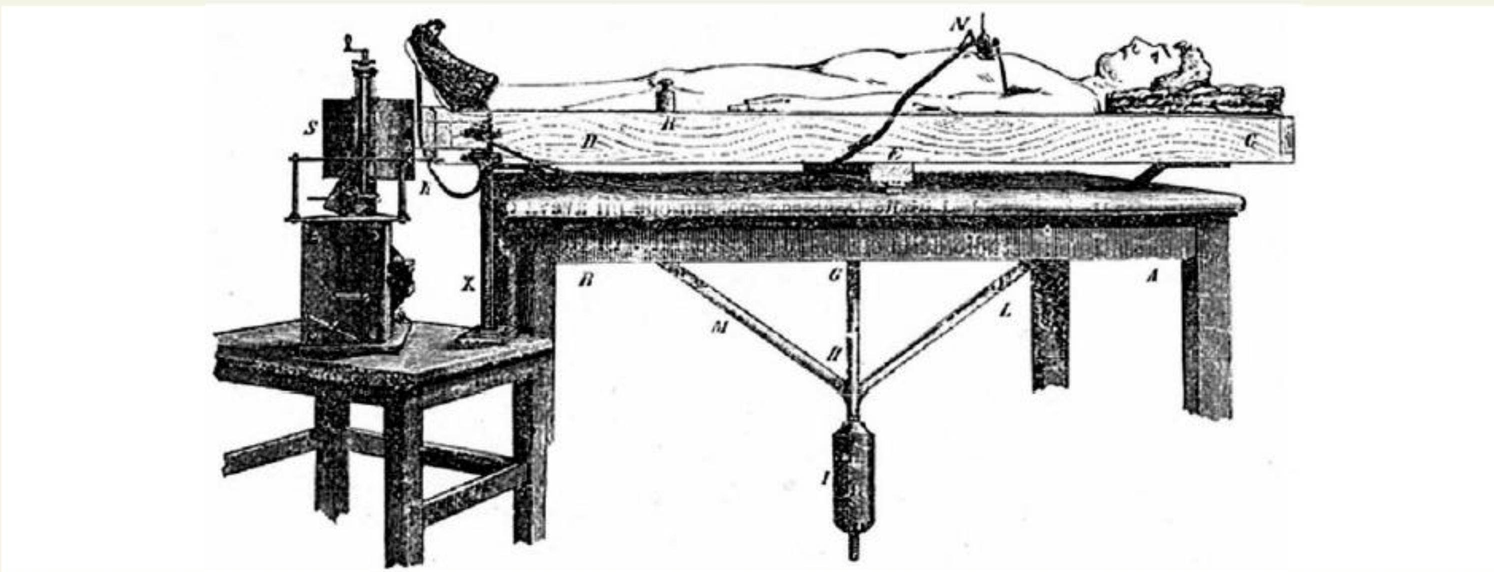
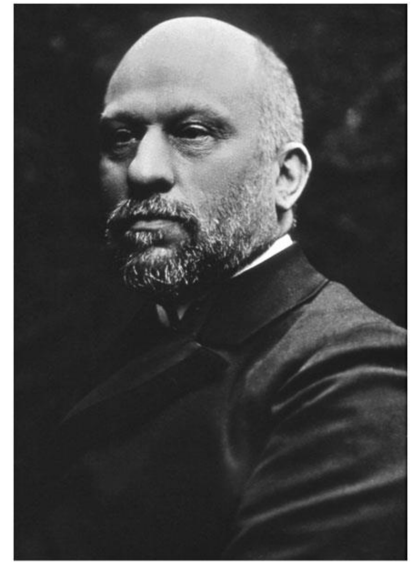


Figure 3 Mosso's 'human circulation balance', used to measure cerebral activity during resting and cognitive states. A and B = wooden table with three apertures on its top; C and D = tilting bed; E = pivot with steel knife fulcrum; G and H = 1 m long iron rod bearing the counterweight; I = cast iron counterweight with screw regulation; M and L = two iron stiffening bars; N = pneumatic pneumograph; R = equilibrating weight; S = kymograph; X = vertical stand for graphic transducers (Angelo Mosso's original drawing, modified and adapted from Mosso, 1884, Atti della Reale Accademia dei Lincei).

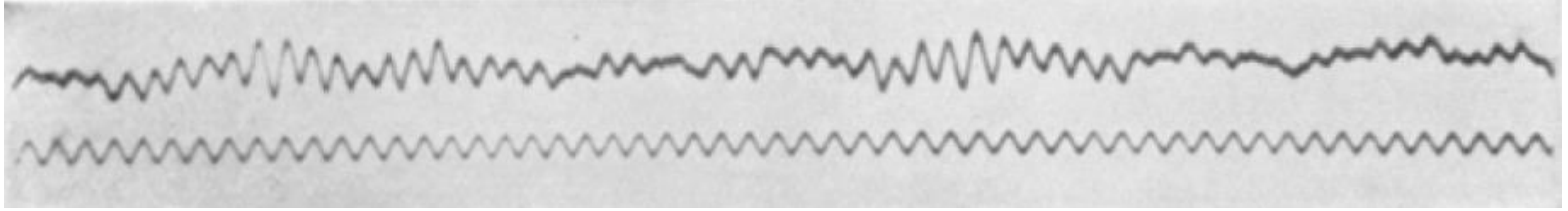


Angelo Mosso
(1846-1910)

Sandrone et al. (2014) *Brain*

Electroencephalography (EEG)

Hans Berger (1873–1941)



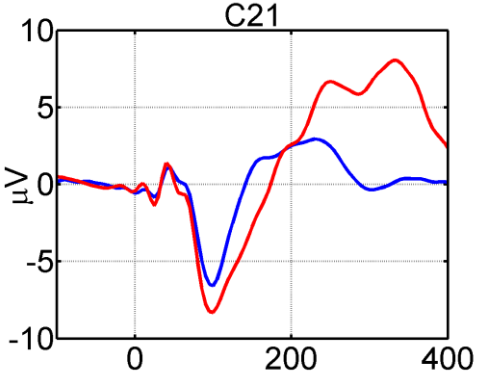
Berger H. Über das Elektrenkephalogramm des Menchen. Archive für Psychiatrie. 1929; 87:527-70., Public Domain, https://commons.wikimedia.org/w/index.php?curid=2900591

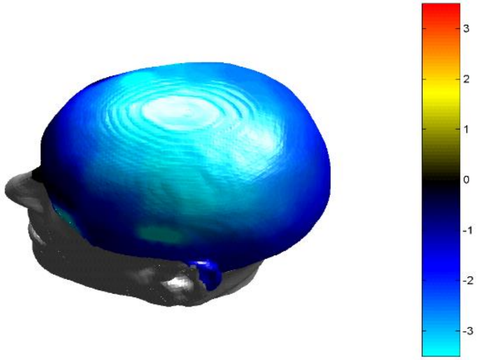
EEG & MEG

- alignment of dendritic trees of pyramidal cell allow measurements of
  - electric potentials (EEG)
  - magnetic fields (MEG)

- excellent temporal resolution (< 1 millisecond)

- limited spatial resolution (≈ 1 cm)

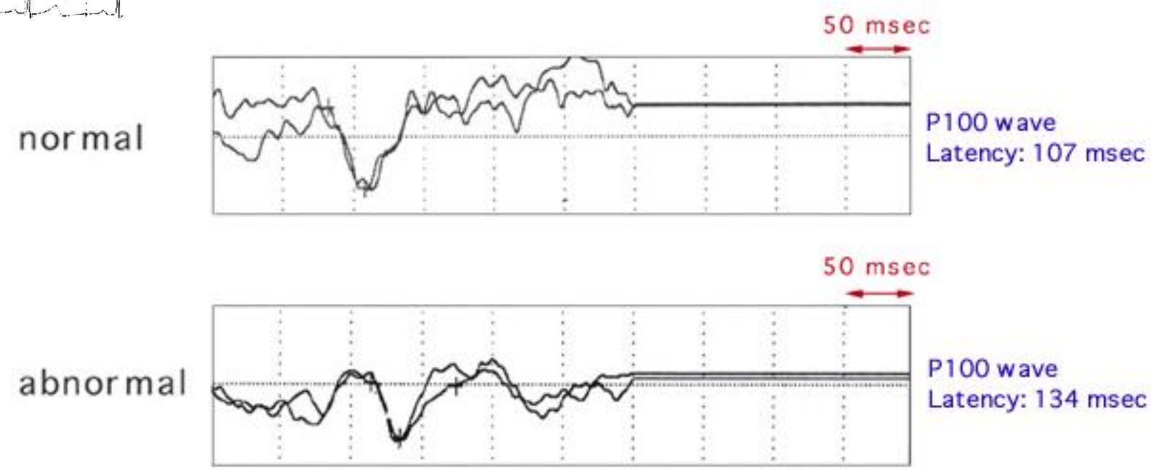




Clinical use of EEG & MEG

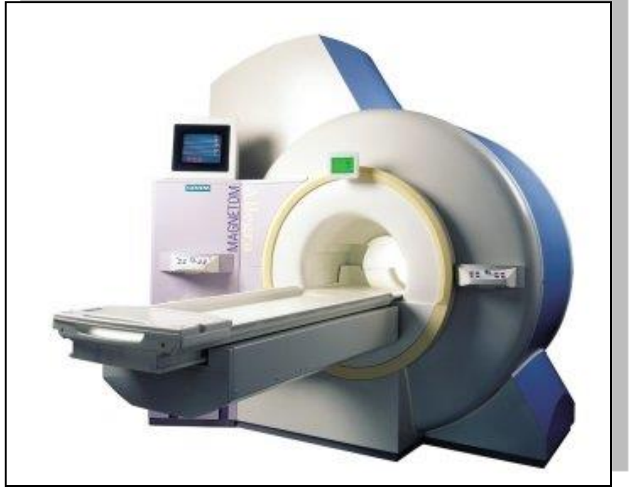
Childhood absence epilepsy

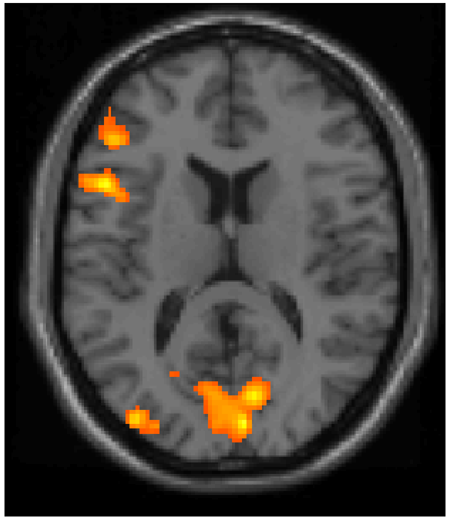
Reduced latency of a visual evoked potential due to demyelination in MS

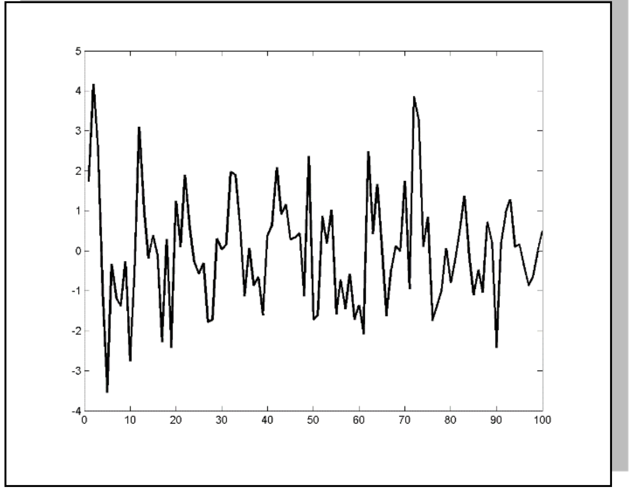


Functional magnetic resonance imaging (fMRI)

- non-invasive, radioactivity-free technique
- hemodynamic signal (blood oxygen level dependent: BOLD signal) as an indirect index of neuronal activity
- temporal resolution in the sub-second range,
  spatial resolution in the micrometer/millimeter range





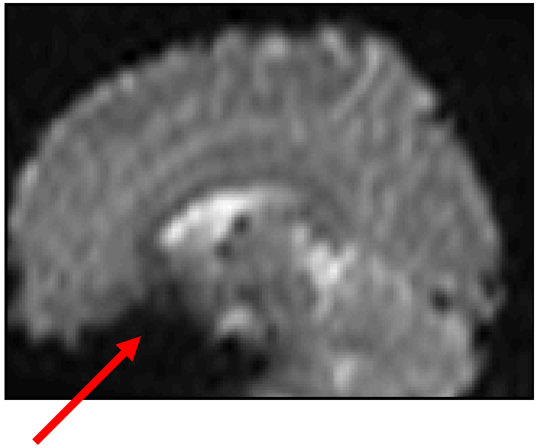


Functional MRI (fMRI)

- Uses *echo planar imaging* (EPI) for fast acquisition of T2*-weighted images.
- Spatial resolution:
  - 2 mm (standard 3T scanner)
  - << 1mm (high-field systems)
- Sampling speed:
  - 1 slice: approx. 50 ms
- Problems:
  - distortion and signal dropouts in certain regions
  - sensitive to head motion of subjects during scanning
- Requires spatial pre-processing and statistical analysis.

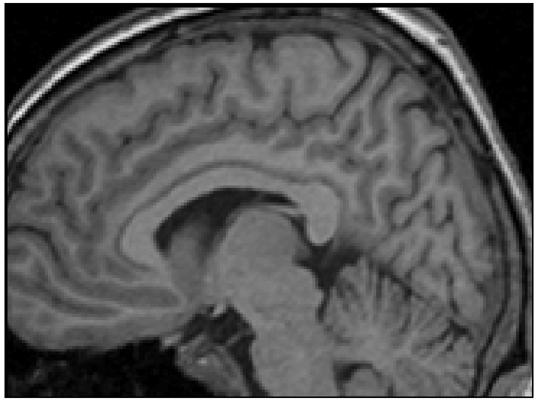
What is it that makes T2* weighted images "functional"?

EPI
(T2*)



dropout

T1



Where in neurology do you think is functional MRI used?

Clinical case: Preoperative language mapping in epilepsy

- 8-minute auditory semantic decision task
- 5 patients who had focal epilepsy and electrocortical stimulation (ECS)
- good fMRI/ECS agreement

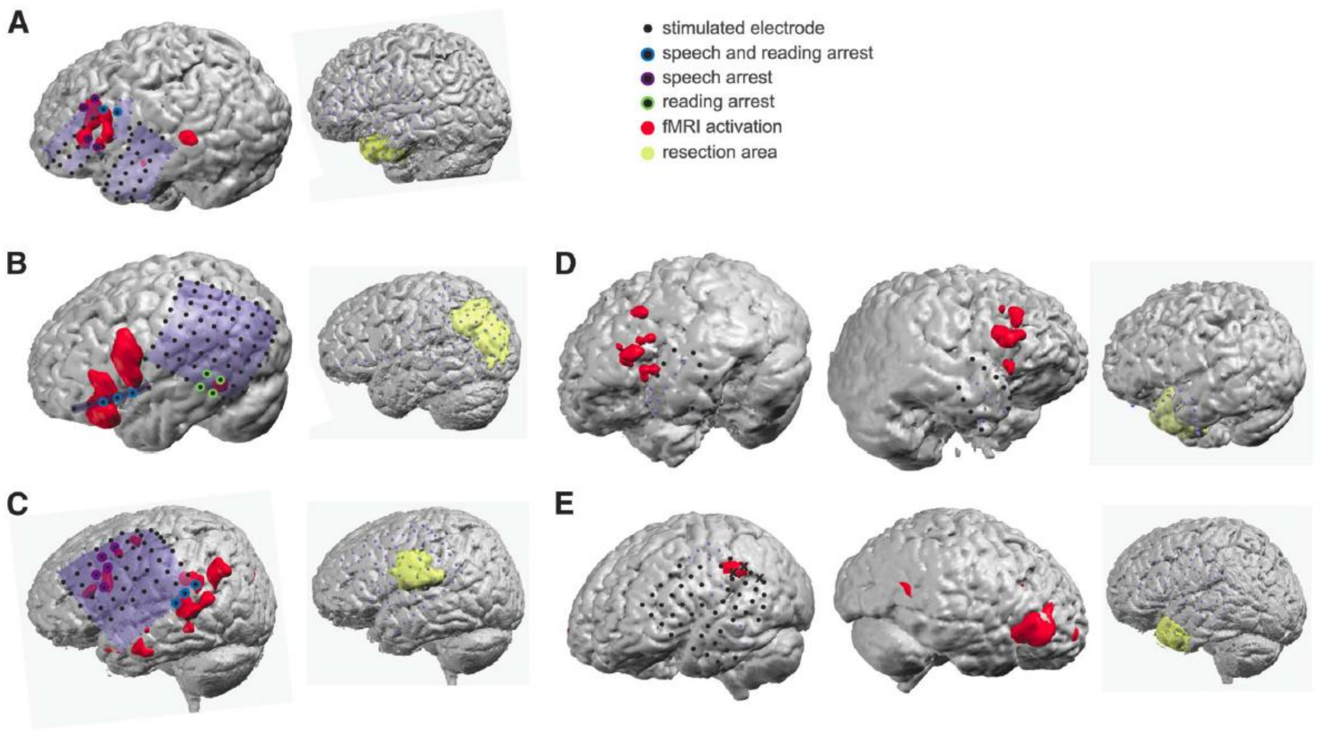
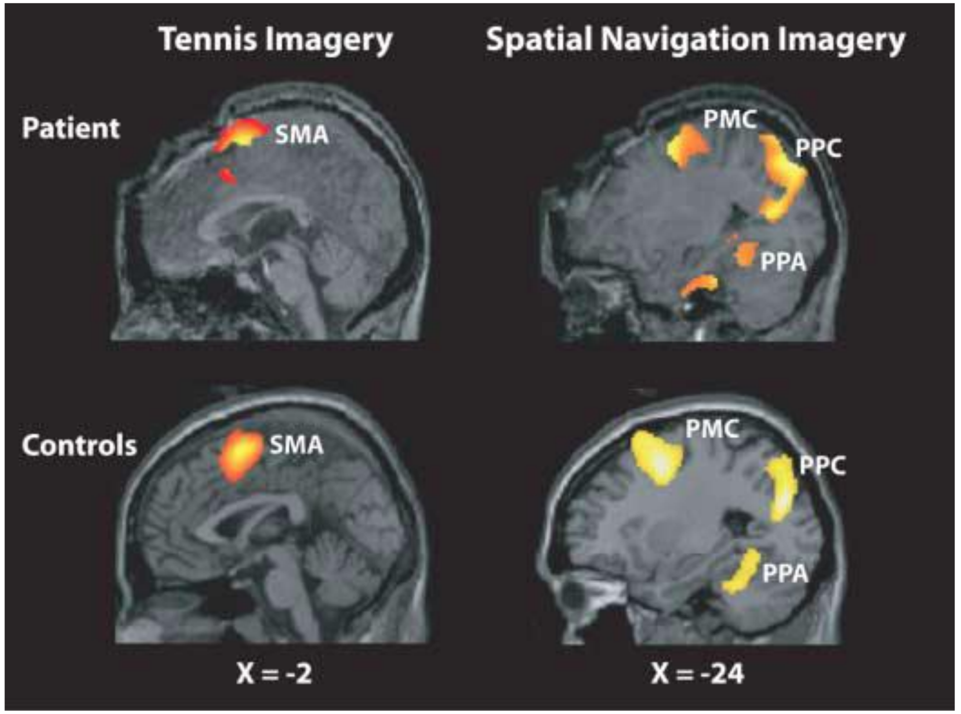


FIGURE 4. *Coregistration of fMRI activations and ECS in patient 1 (fMRI activations: P < .05, FWE-corrected) (**A**), patient 4 (P < .001, uncorrected) (**B**), patient 10 (P < .001, uncorrected) (**C**), patient 3 (P < .001, uncorrected) (**D**), and patient 8 (P < .001, uncorrected) (**E**). × indicates the dysfunctional contacts in patient 8. fMRI, functional magnetic resonance imaging; ECS, electrocortical stimulation; FWE, family-wise error.*

Genetti et al. 2013, *Neurosurgery*

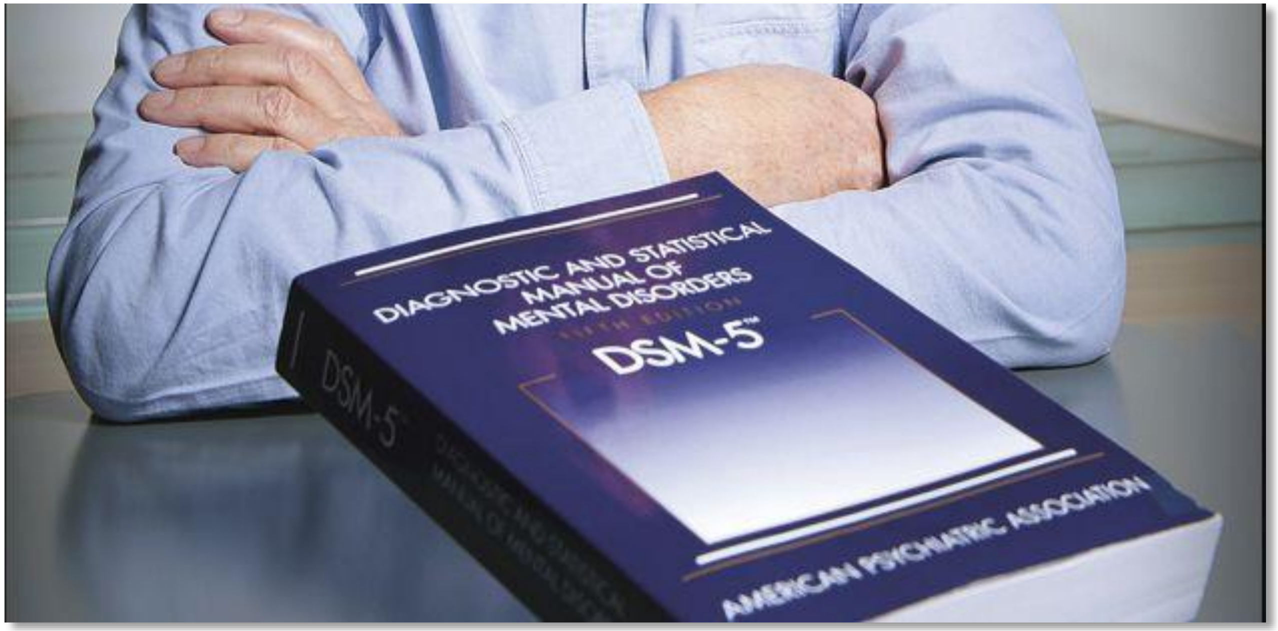
Clinical case: Detecting awareness in disorders of consciousness

- coma, vegetative state, minimally conscious state
- vegetative state: patients who emerge from coma appear to be awake but show no signs of awareness
- single patient, severe traumatic brain injury, five months unresponsive, preserved sleep-wake cycles
- imagery fMRI paradigm:
  - "imagine playing tennis"
  - "imagine visiting all of the rooms of your house, starting from the front door"



Owen et al. 2006, *Science*

Diagnostic classification in psychiatry



Psychiatric disorders = spectrum diseases

polygenetic basis

gene-environment interactions

environmental variation

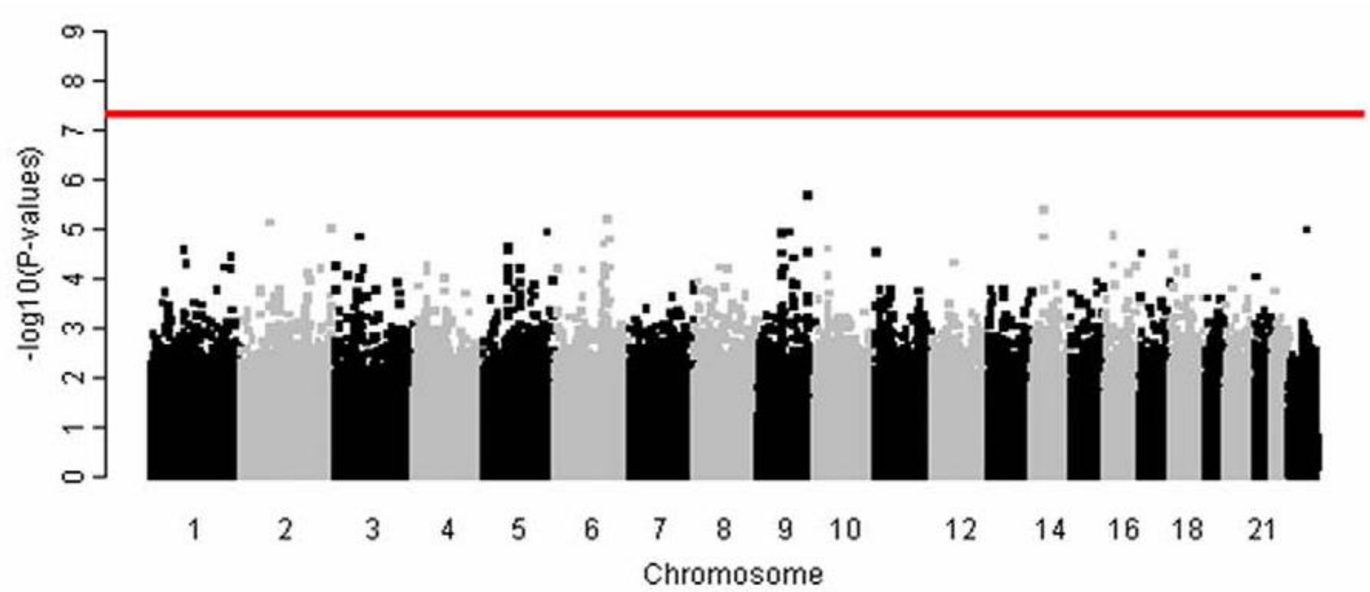
variability in clinical trajectory and treatment response

multiple disease mechanisms

OPEN ACCESS Freely available online

PLOS | MEDICINE

Genetic Predictors of Response to Serotonergic and Noradrenergic Antidepressants in Major Depressive Disorder: A Genome-Wide Analysis of Individual-Level Data and a Meta-Analysis



"After quality control, a dataset of 1,790 individuals with high-quality genome-wide genotyping provided adequate power to test the hypotheses that antidepressant response or a clinically significant differential response to the two classes of antidepressants could be predicted from a single common genetic polymorphism. None of the more than half million genetic markers significantly predicted response to antidepressants overall, serotonin reuptake inhibitors, or noradrenaline reuptake inhibitors, or differential response to the two types of antidepressants..."

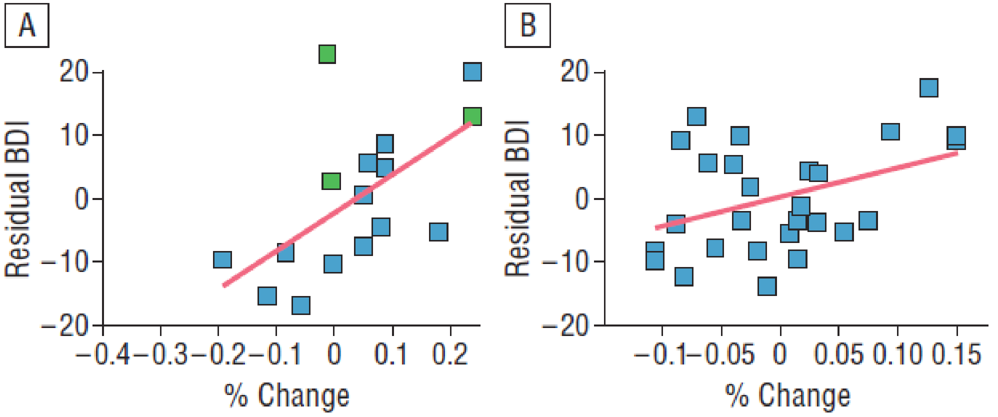
Tansey et al. 2012, *PLoS Med.* 9: e1001326

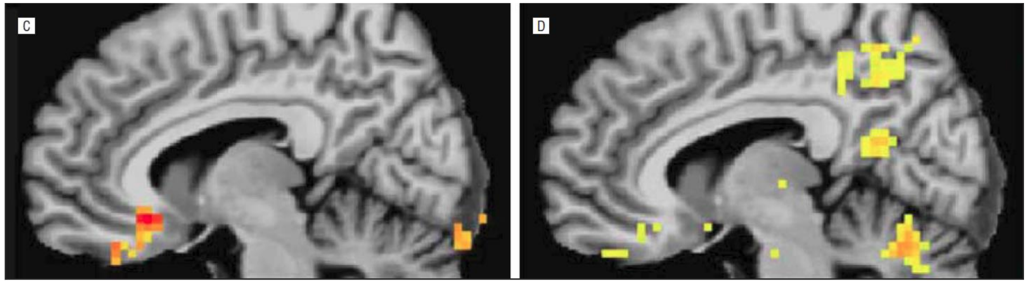
Using neuroimaging to predict treatment response

- local differences in activity?
- differences in patterns of activity?
- differences in functional connectivity?

Local differences in activity?

- 49 patients with depression in two groups
- subgenual ACC activity in response to visually presented negative words
- predicts residual severity after cognitive therapy (CT)
- predicts remission under CT:
  - Sensitivity 38%
  - Specificity 95%

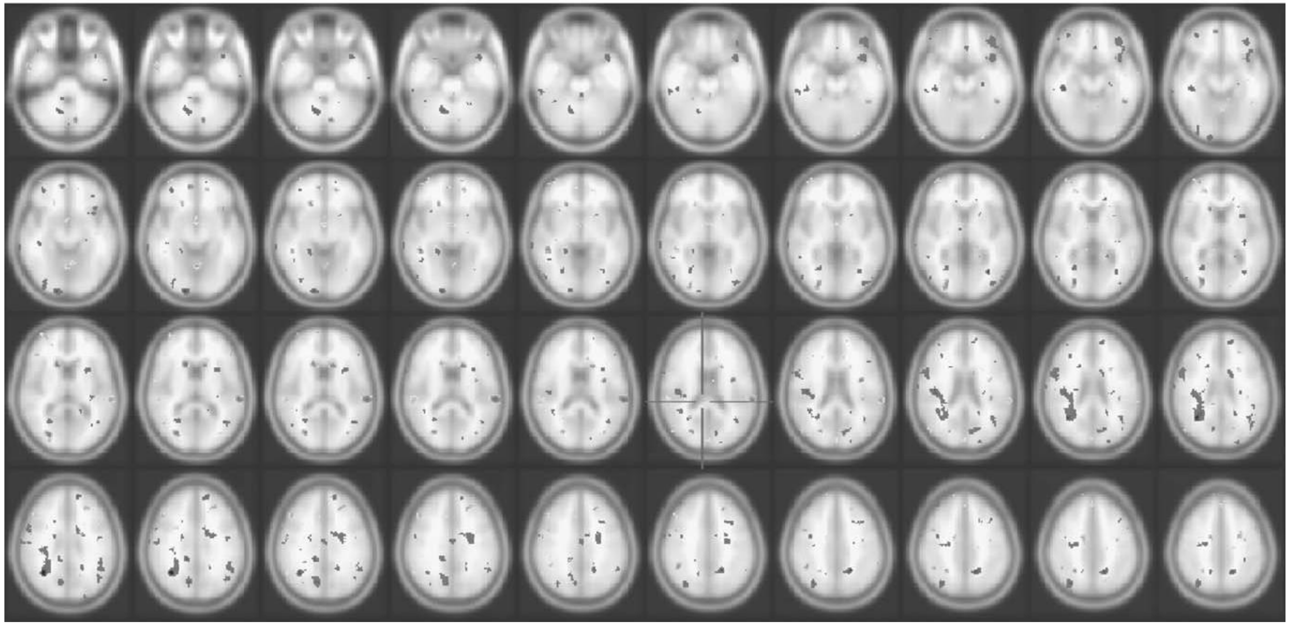




Siegle et al. 2012, *Arch. Gen. Psychiatry*

Differences in patterns of activity?

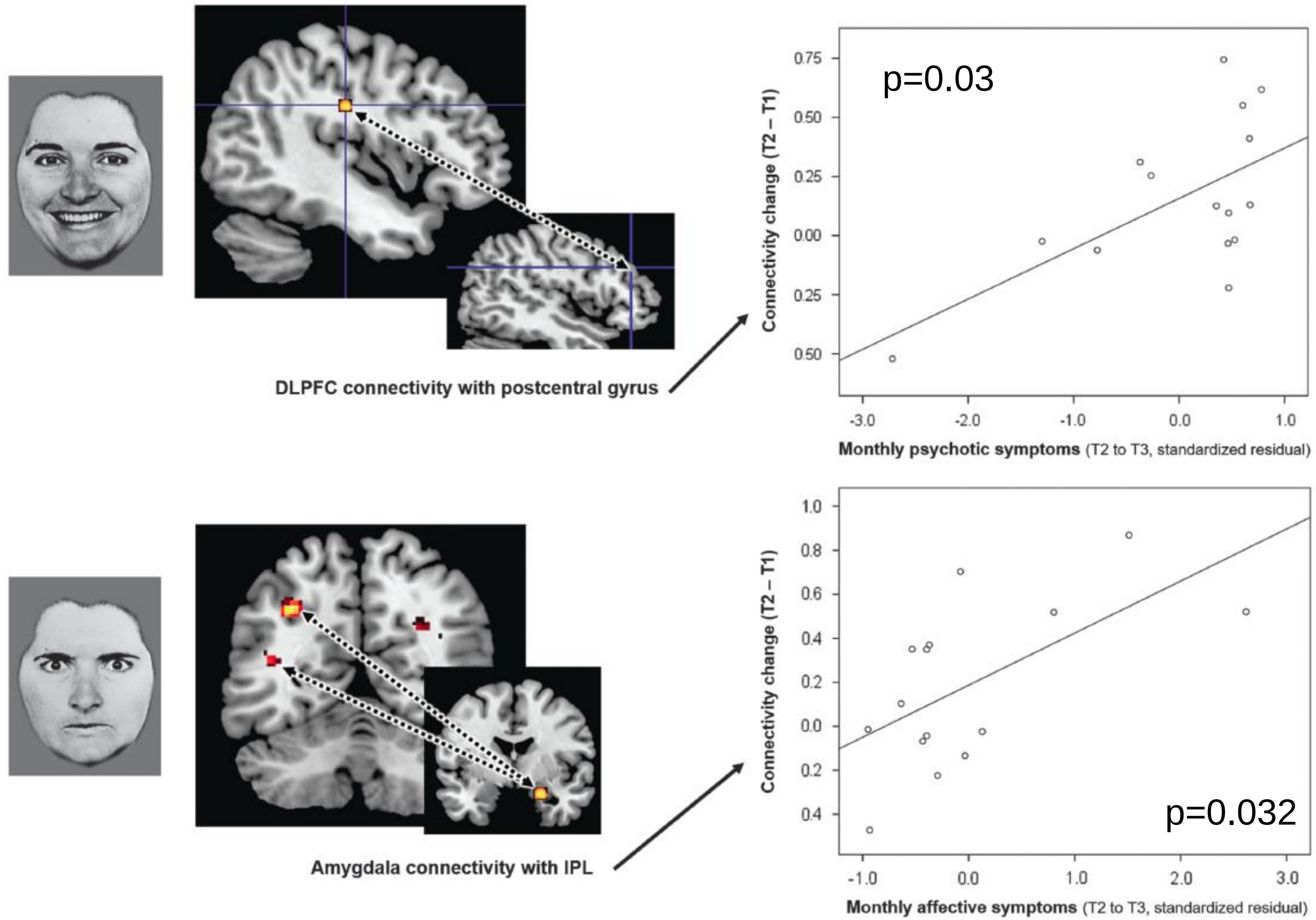
- visual presentation of sad facial expressions
- 16 medication-free patients in an acute episode of major depression, before beginning treatment with CBT
- PCA of whole-brain activity predicts clinical response to CBT (SVM, sensitivity 71%, specificity 86%)



Costafreda et al. 2009, *Neuroreport*

Differences in functional connectivity?

- 22 patients with paranoid schizophrenia
- treatment with CBT
- clinical follow-up over 8 years
- prefrontal and amygdala connections predict long-term positive and affective symptoms, respectively



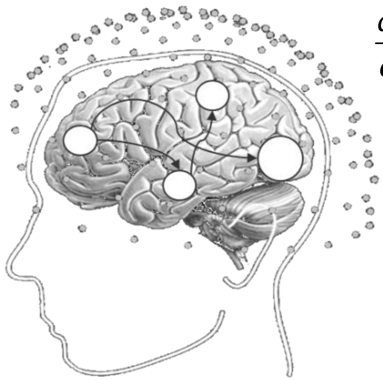
Mason et al. 2017, *Transl. Psychiatry*

But...

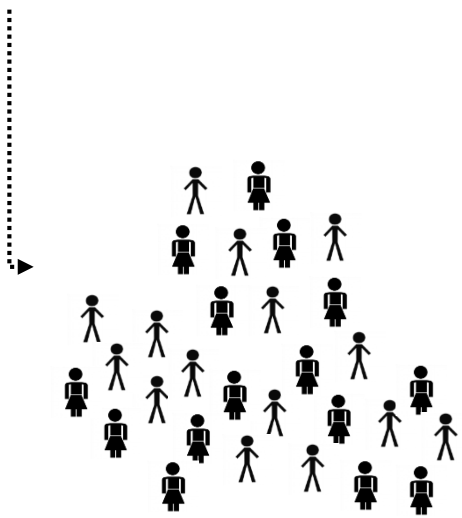
- predictions far from perfect
- no mechanistic interpretability
- no view of an emerging nosology that maps onto (patho)physiology

Translational Neuromodeling

❶ **Computational assays:**
Models of disease mechanisms

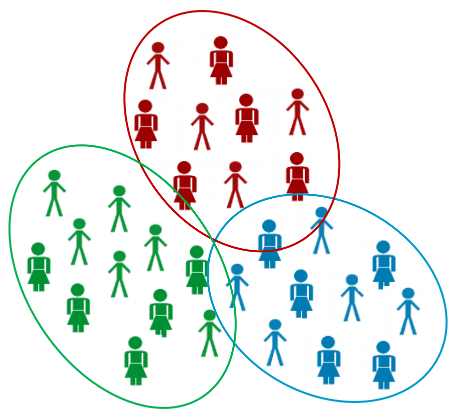


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



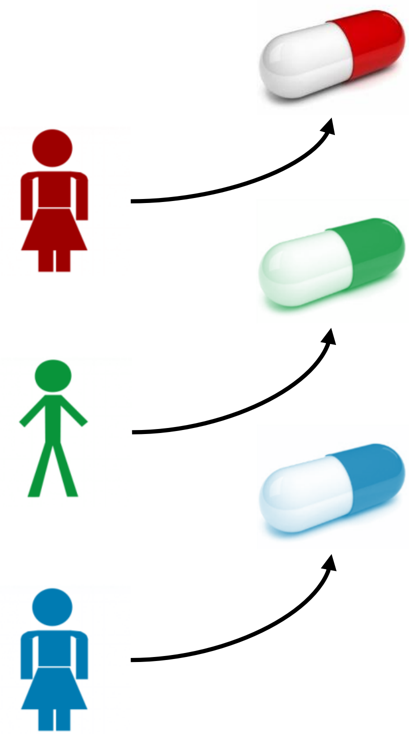
❷ **Application to brain activity and behaviour of individual patients**

❸ **Detecting physiological subgroups (based on inferred mechanisms)**



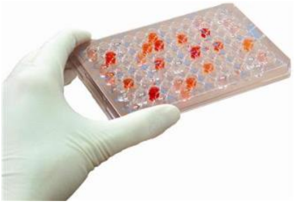
• disease mechanism A
• disease mechanism B
• disease mechanism C

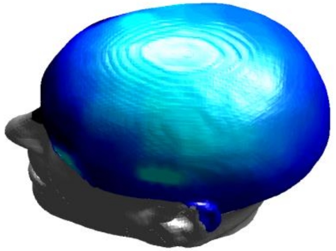
❹ **Individual treatment prediction**



Stephan et al. 2015, *Neuron*

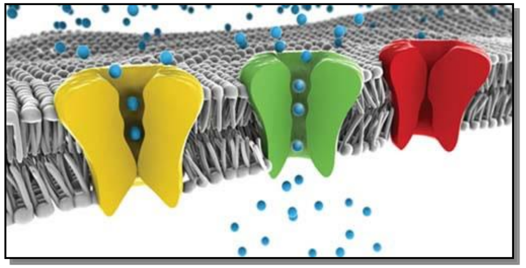
Generative models as "computational assays"



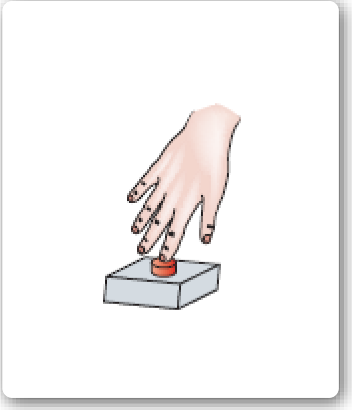


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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

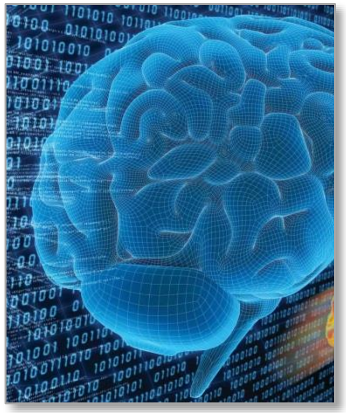


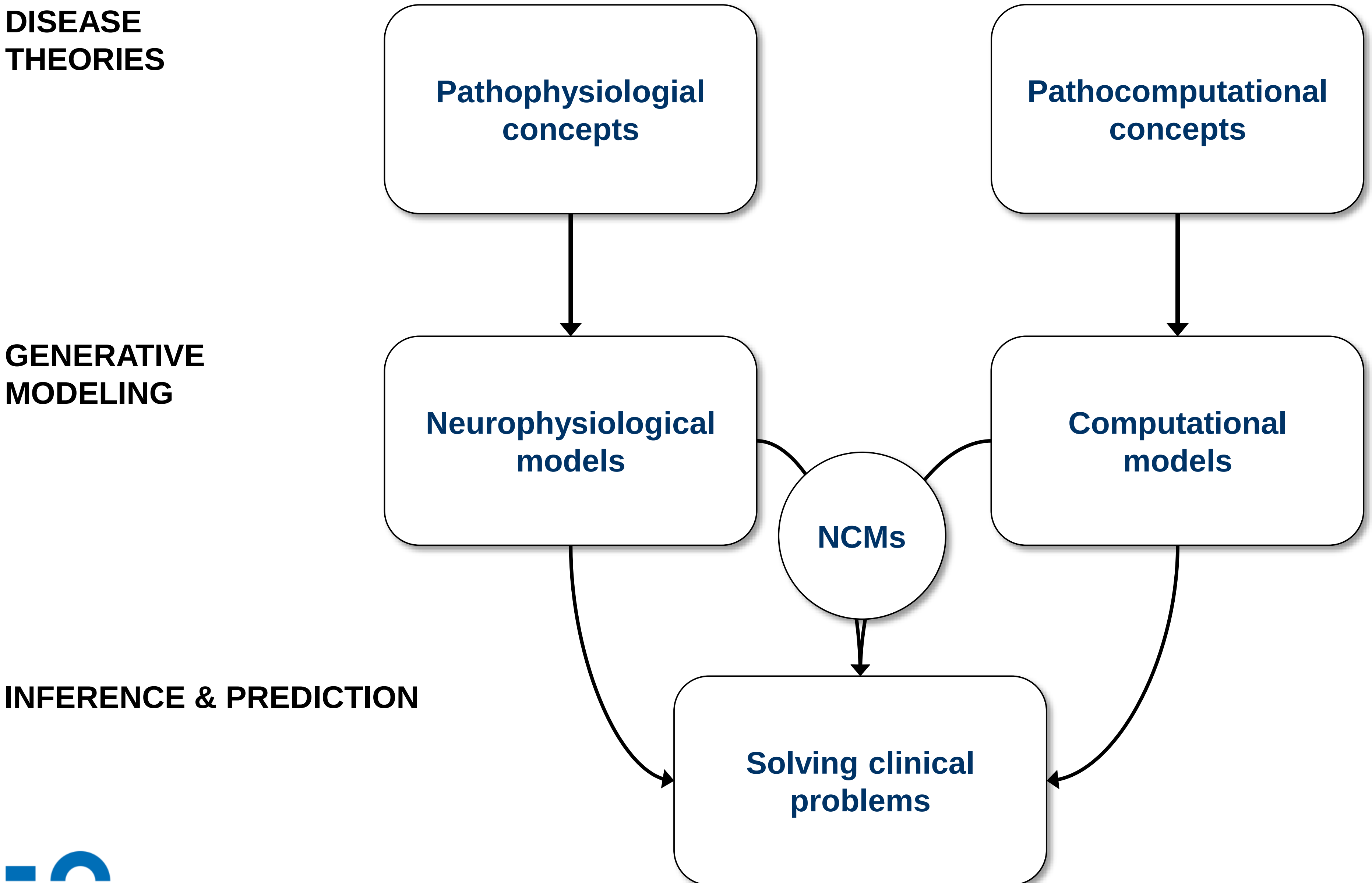
y = data, θ = parameters, m = model



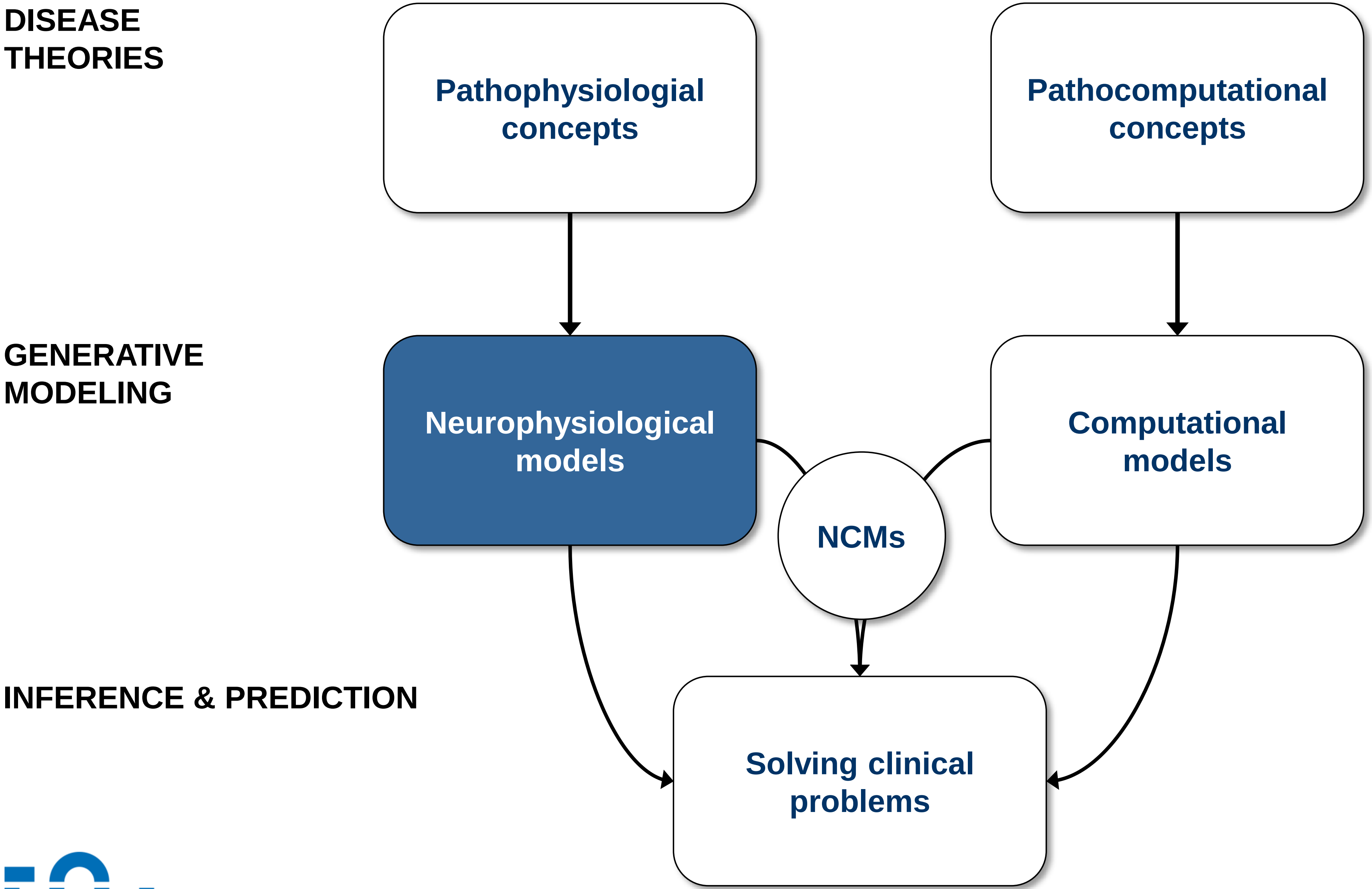
$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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





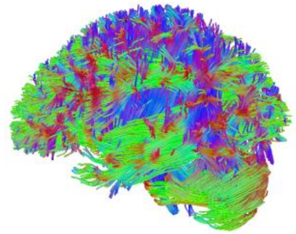
Translational Neuromodeling Unit



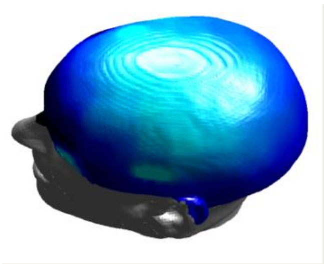
Translational Neuromodeling Unit

Dynamic causal modeling (DCM)

dwMRI



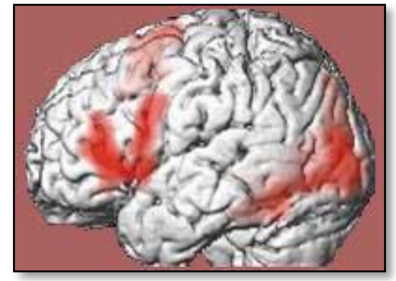
EEG, MEG

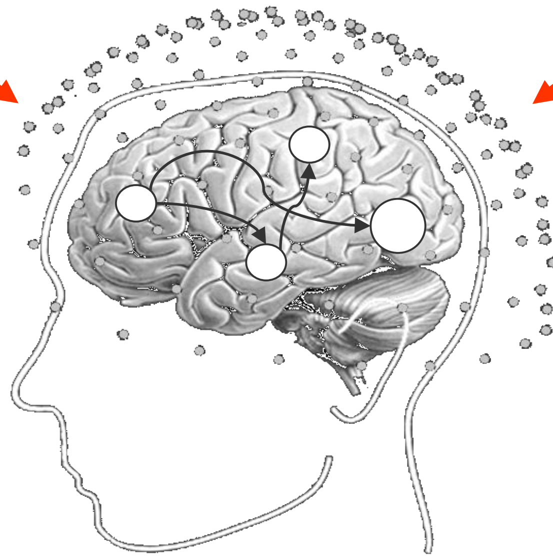


structural priors

structural priors

fMRI





Forward model:
Predicting measured activity

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

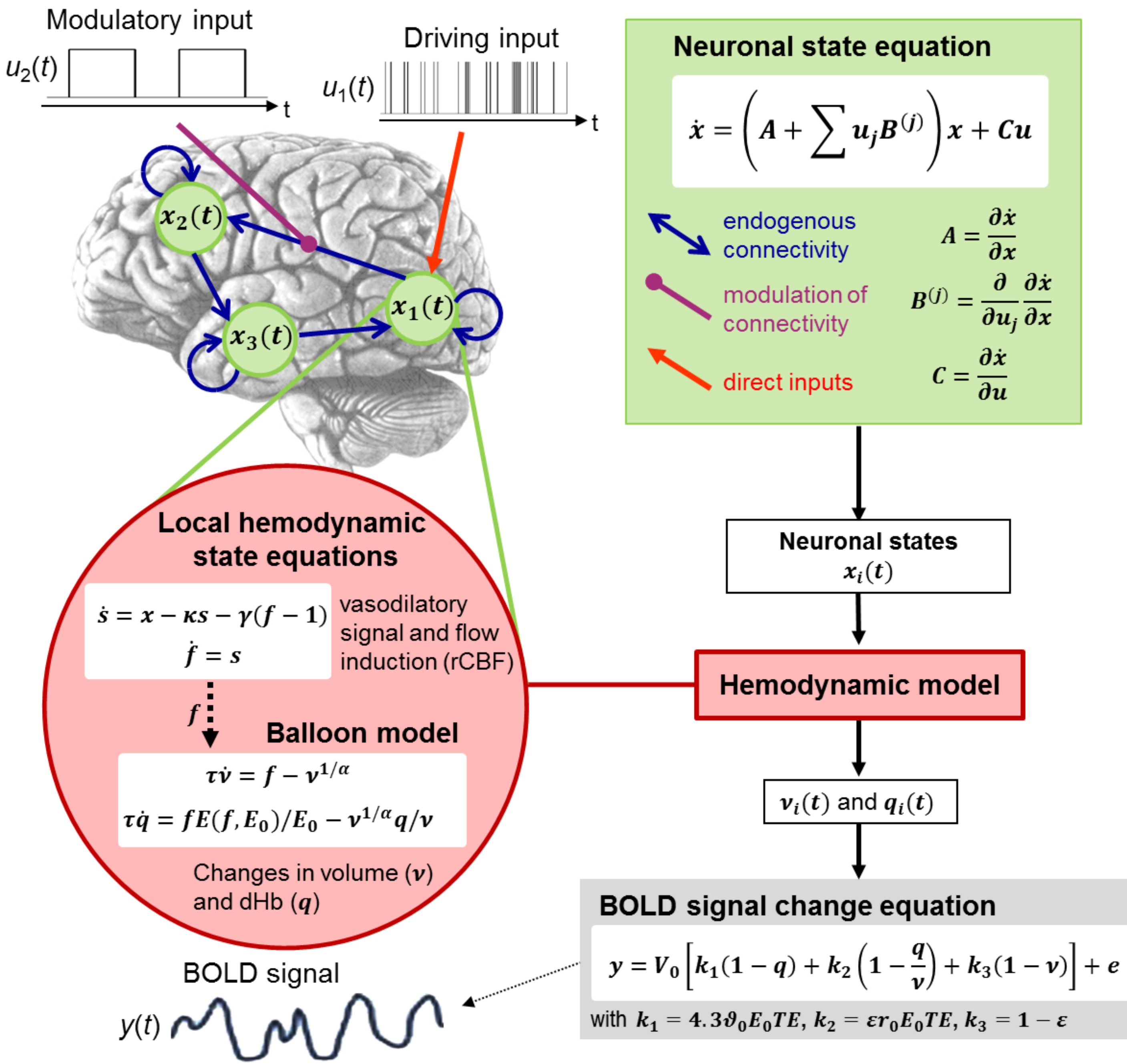
Model inversion:
Estimating neuronal mechanisms

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

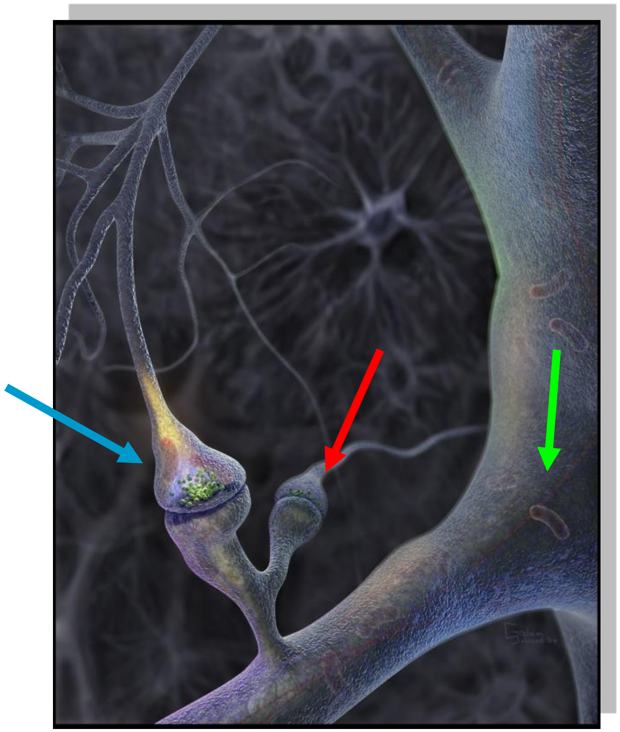
Friston et al. 2003, *NeuroImage*

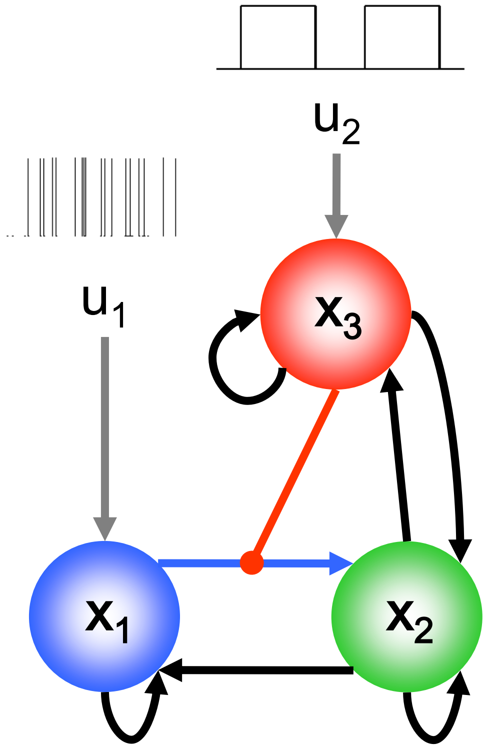
Stephan et al. 2009, *NeuroImage*

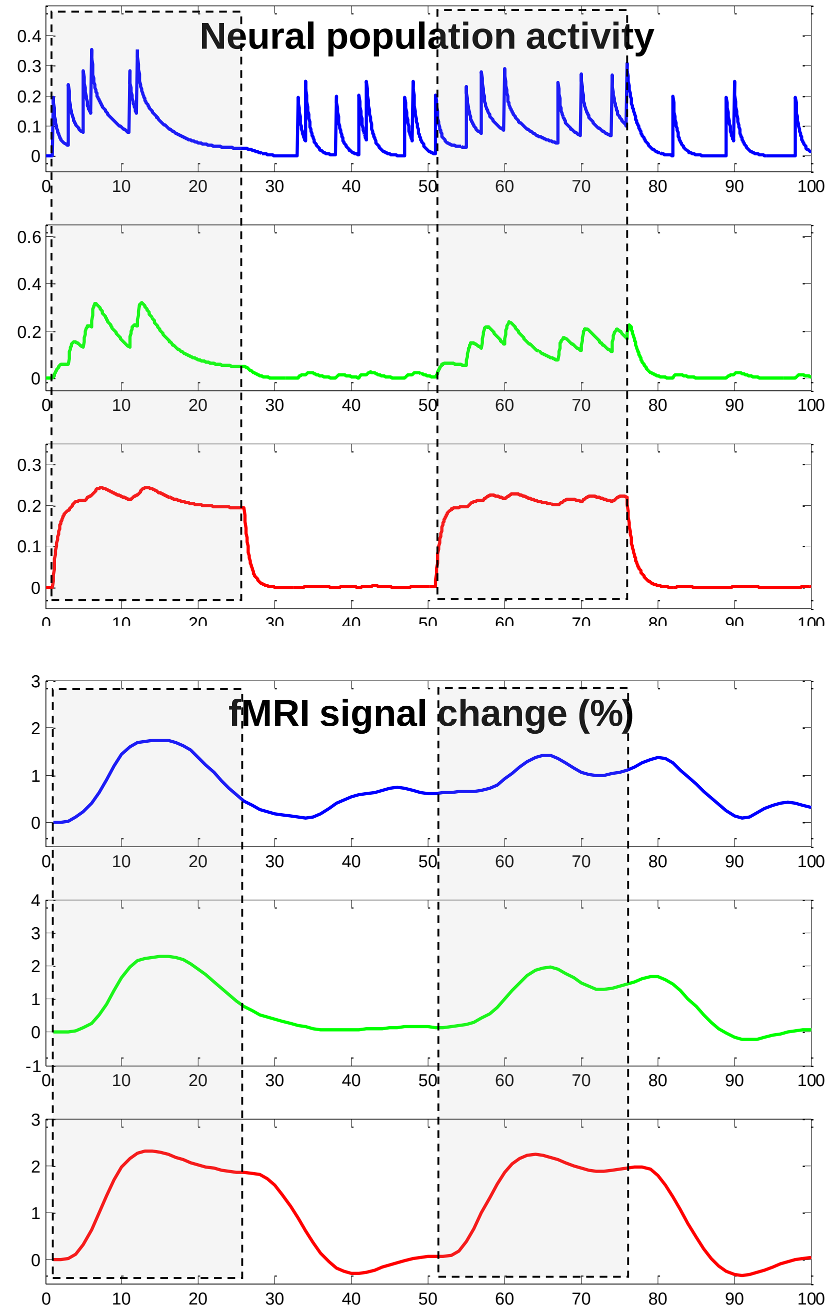
DCM for fMRI



Stephan et al. 2015, *Neuron*







Nonlinear Dynamic Causal Model for fMRI

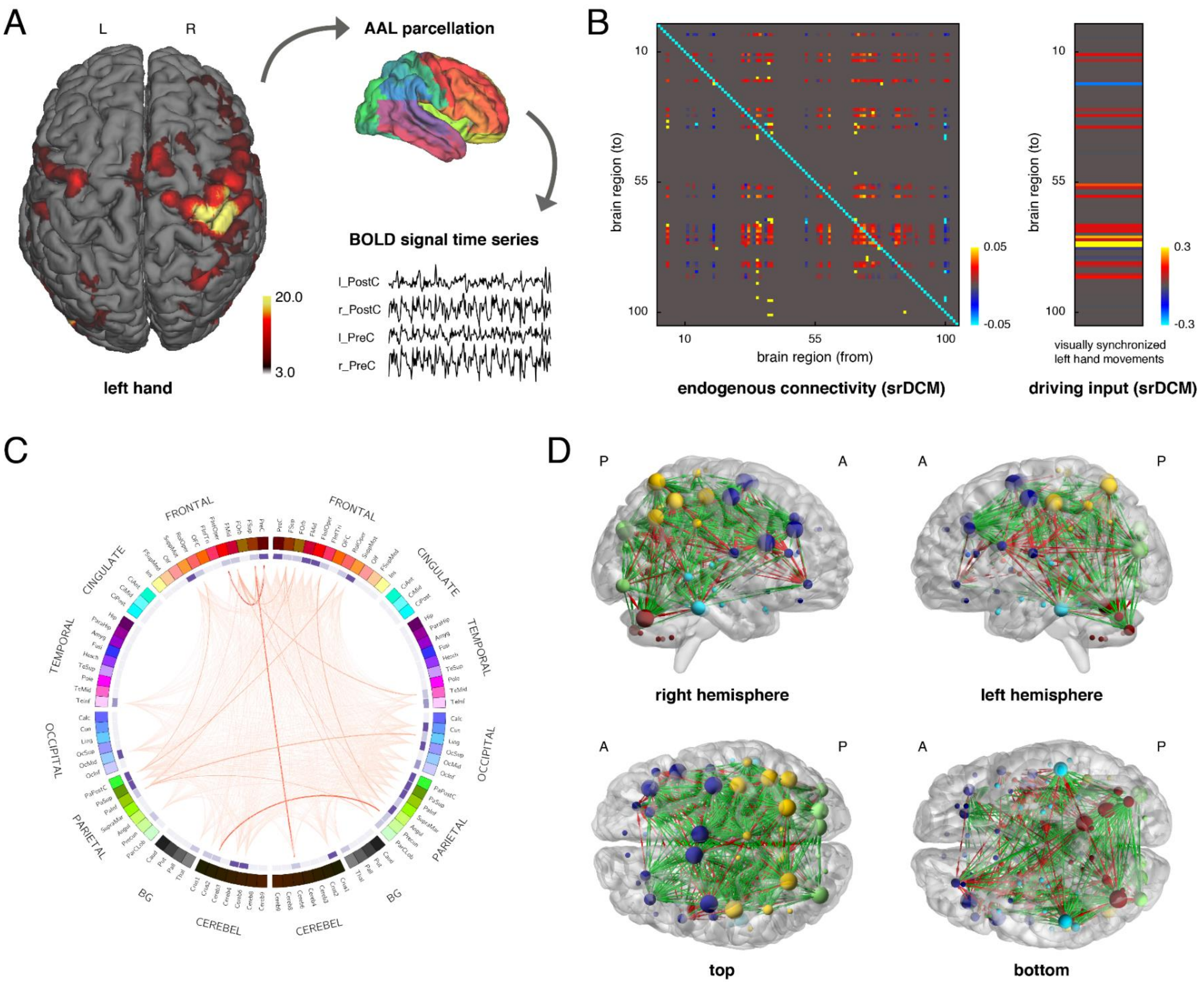
$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} x_j D^{(j)} \right) x + Cu$$

Stephan et al. 2008, *NeuroImage*

Sparse rDCM

automatically prune network as part of model inversion

fast whole-brain connectograms: >10'000 connections in <1 min

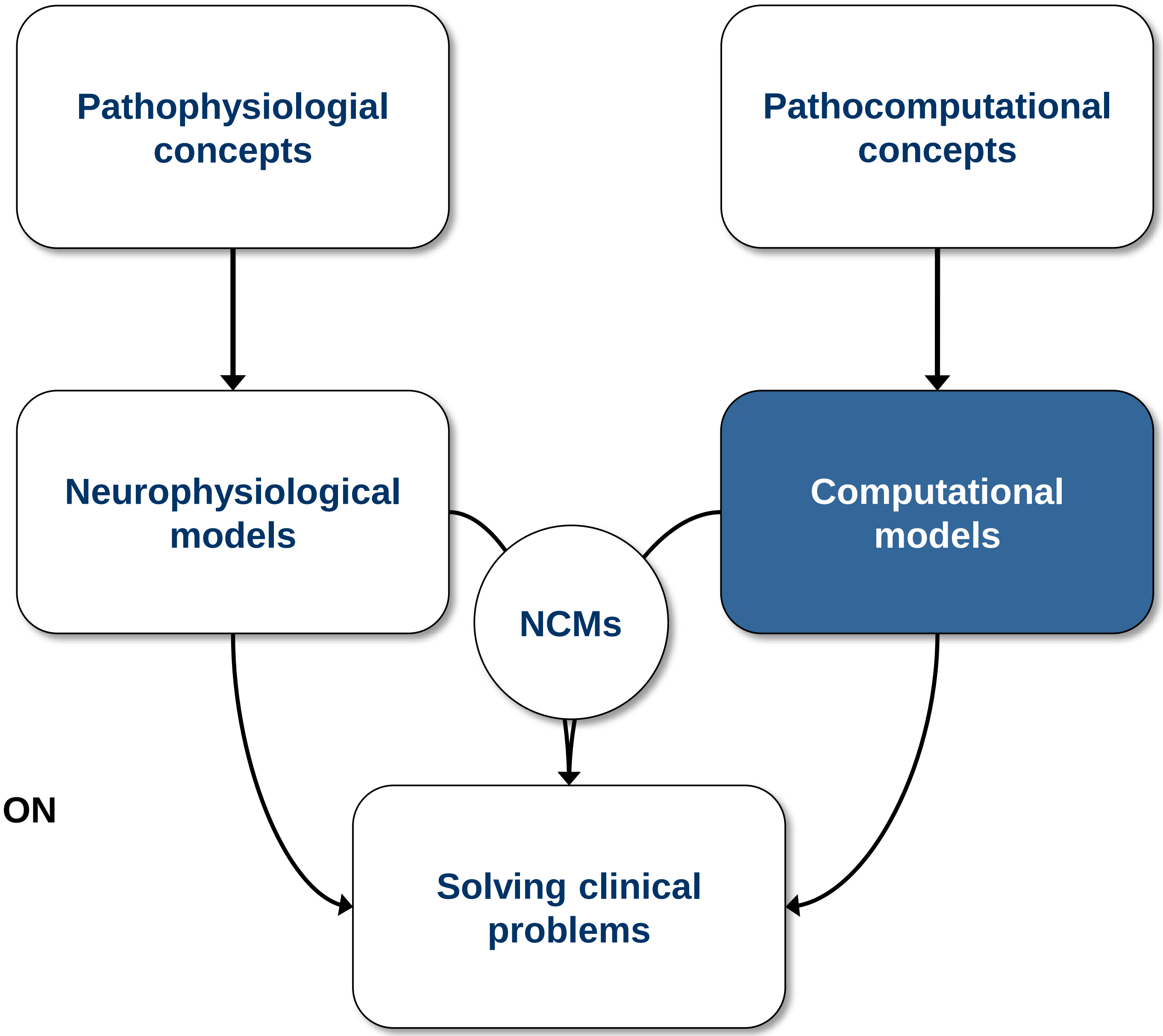


Frässle et al., 2018, NeuroImage

DISEASE THEORIES

GENERATIVE MODELING

INFERENCE & PREDICTION

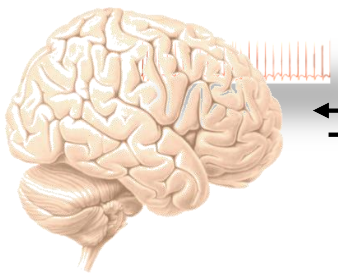


Translational Neuromodeling Unit

Perception = hierarchical Bayesian inference

neuronal states

environm. states
others' mental states
bodily states

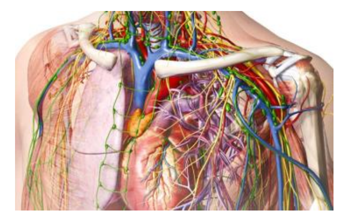


forward model

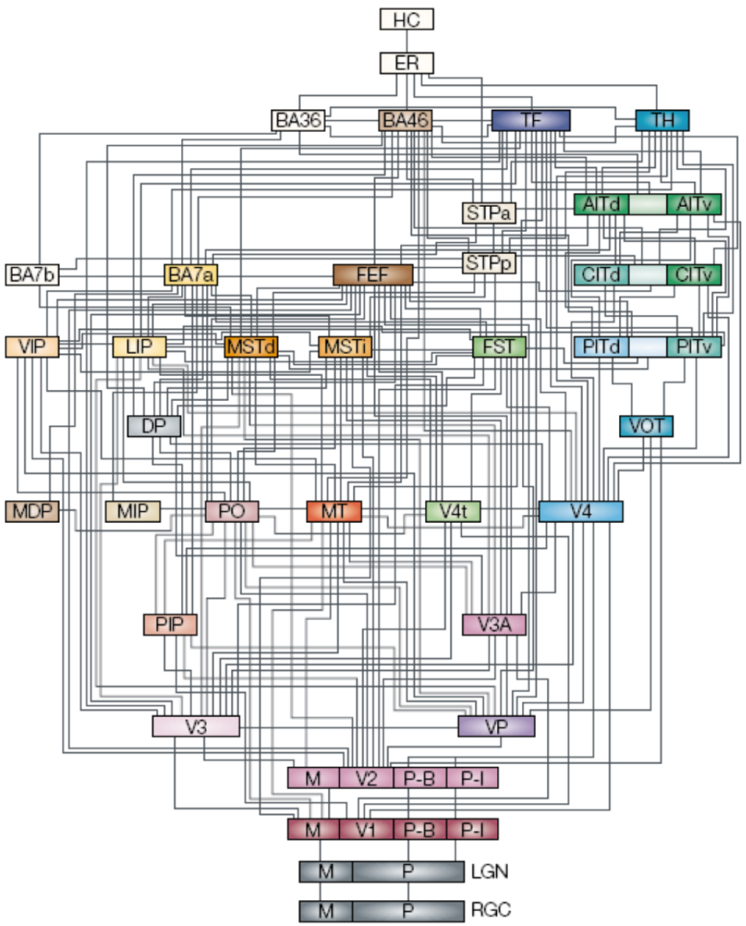
$$p(y \mid x, m) \cdot p(x \mid m)$$

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

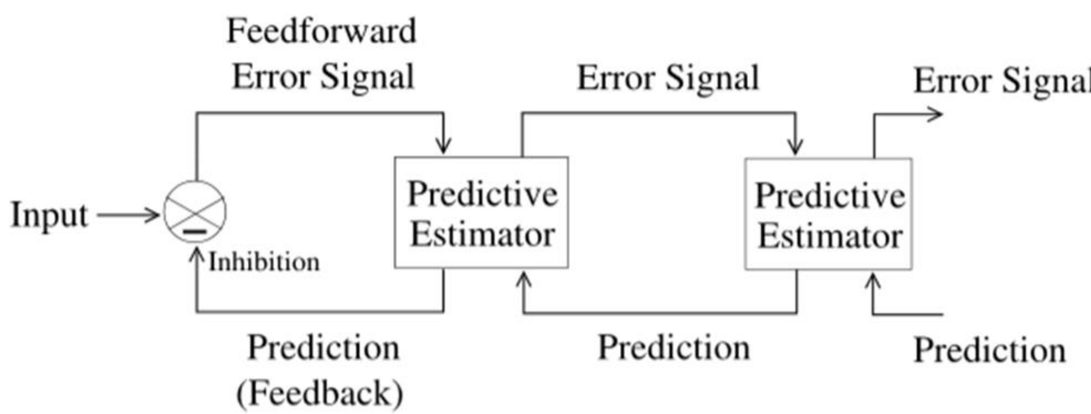
perception



Anatomical hierarchies & hierarchical Bayesian inference



predictive coding



Felleman & Van Essen 1991, *Cerebral Cortex*

Rao & Ballard 1999, *Nat. Neurosci.*

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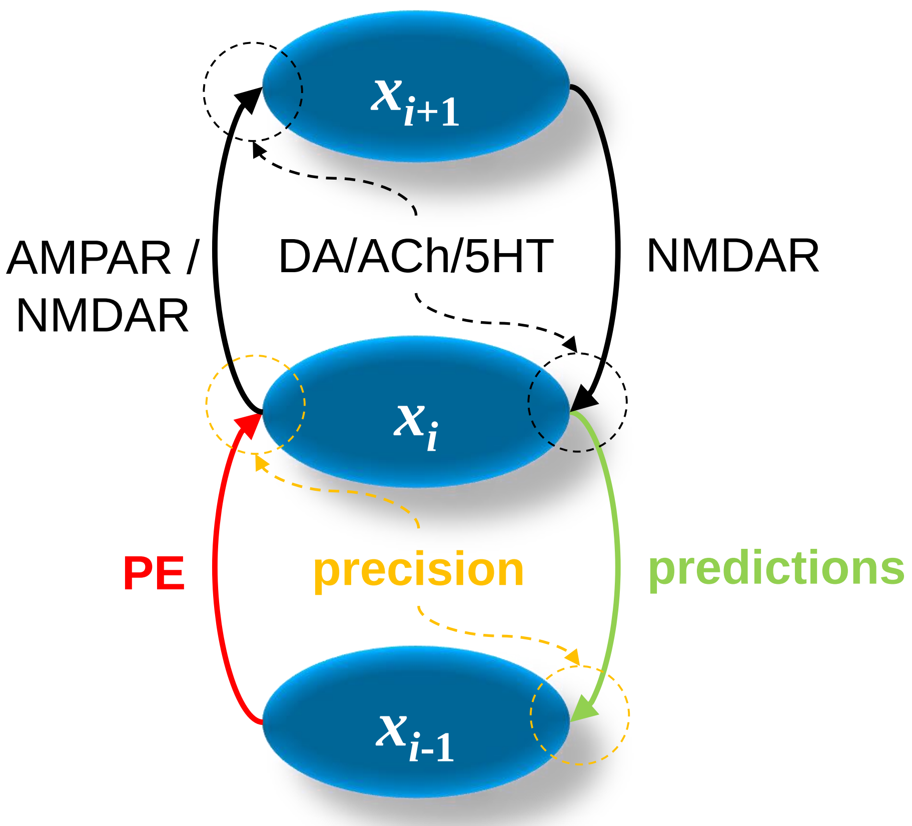
Computational and physiological components of hierarchical Bayesian inference

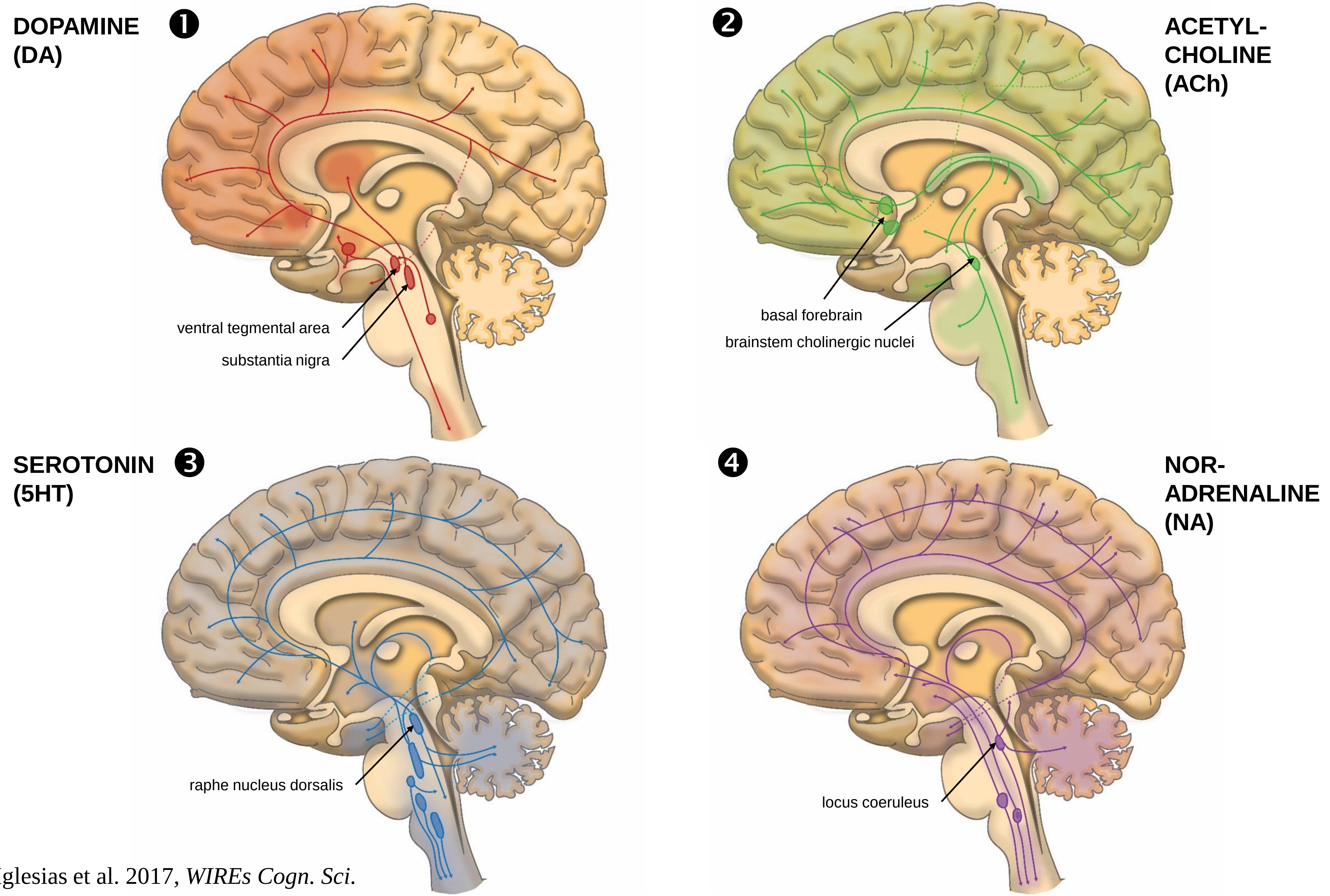


$$\Delta belief \propto precision \times PE$$

PEs	→ AMPAR & NMDAR
predictions	→ NMDAR
precisions	→ neuromodulation / GABA

physiological & computational inference targets for computational assays

Stephan et al. 2016, *Brain*



Iglesias et al. 2017, *WIREs Cogn. Sci.*

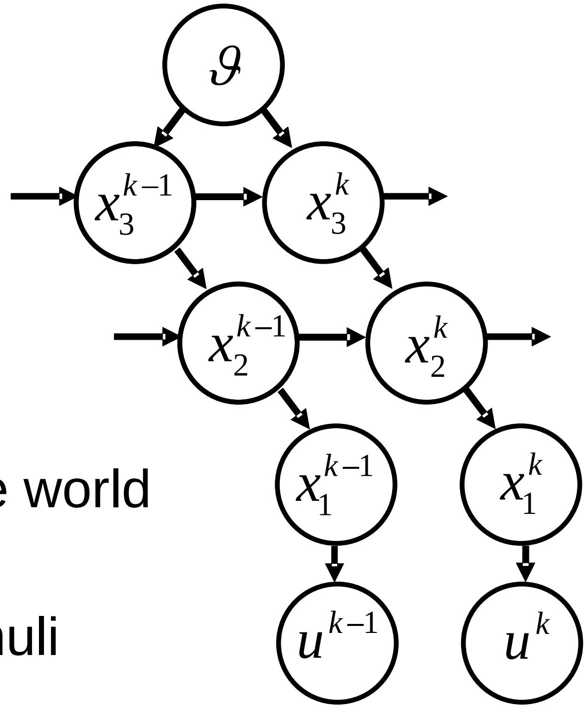
Hierarchical Gaussian Filter (HGF)

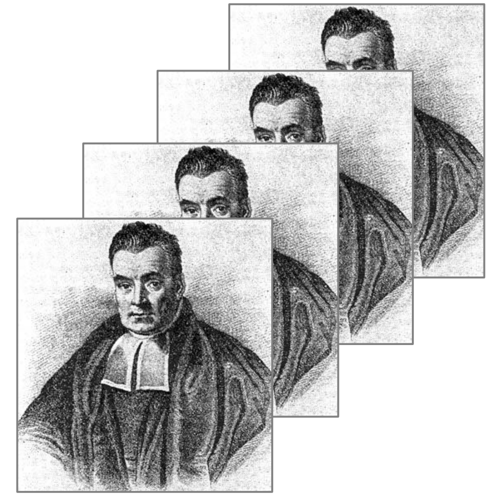
volatility

association

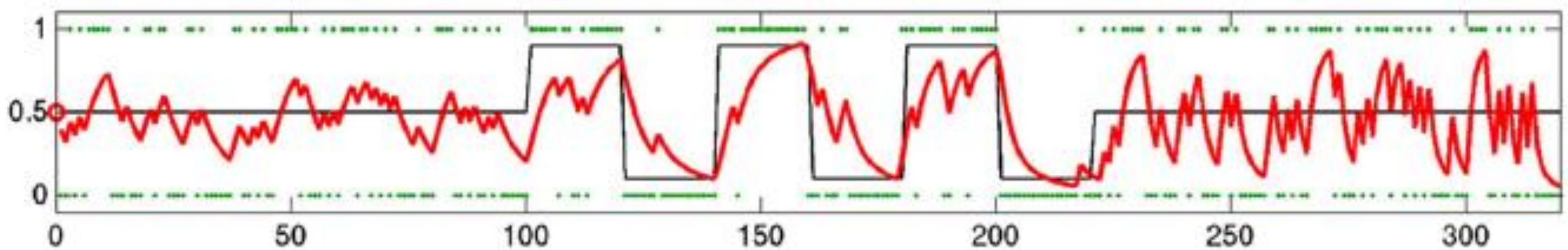
events in the world

sensory stimuli





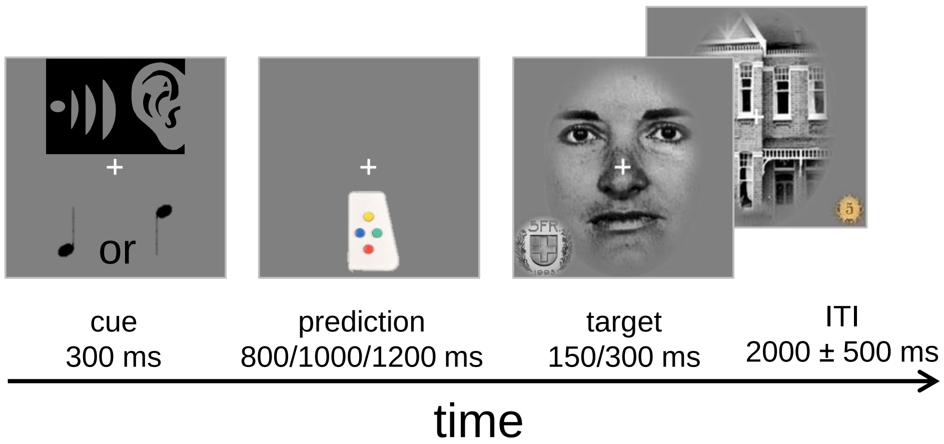
Δbelief $\propto$ precision × PE

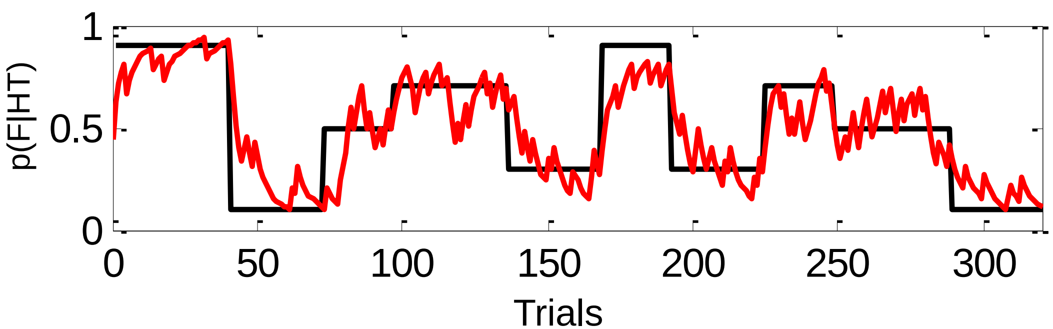


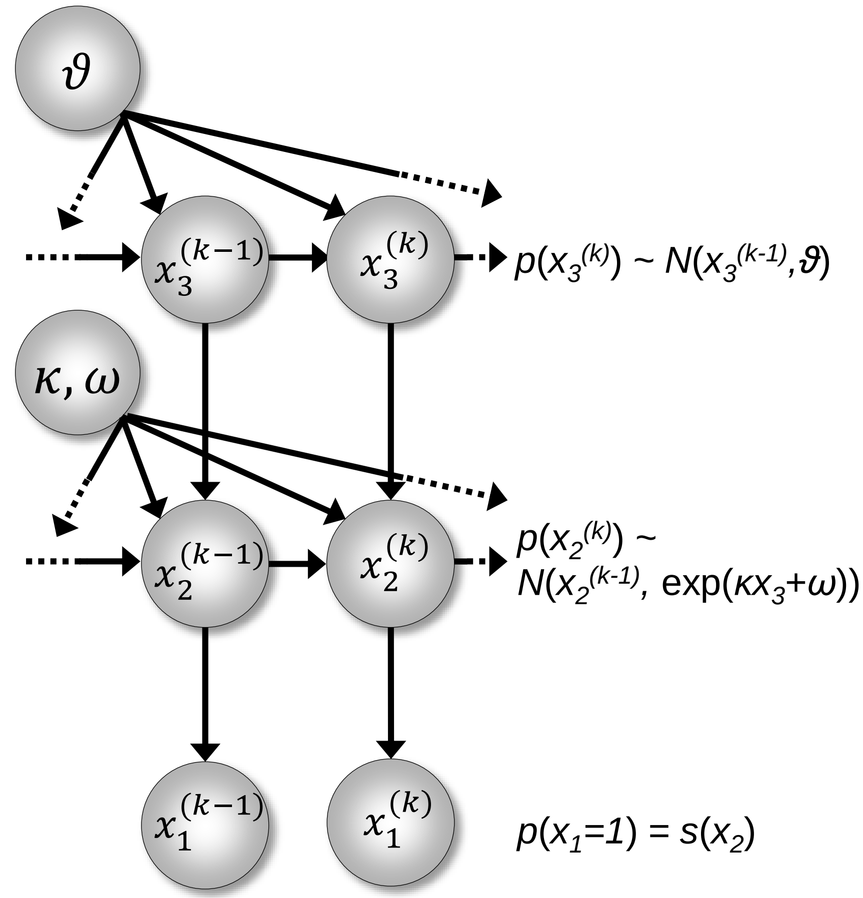
Mathys et al. 2014, *Front. Hum. Neurosci.*

Marshall, Mathys et al. 2016, *PLoS Biology*

Hierarchical prediction errors (PEs) in sensory learning

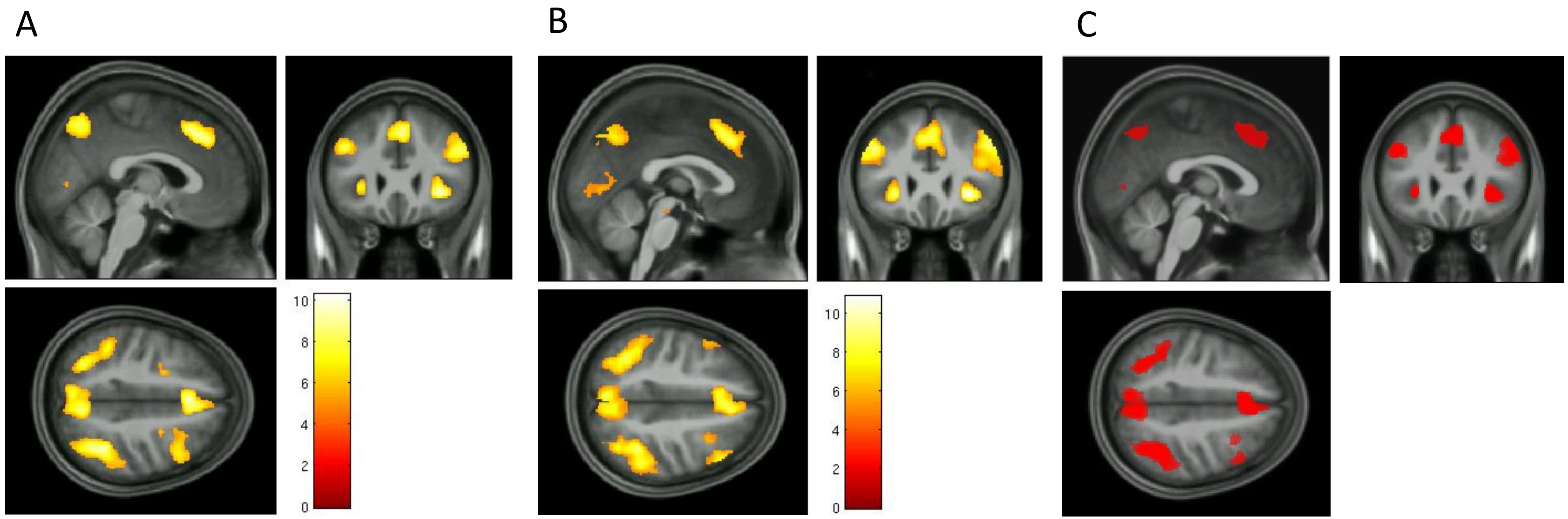






Iglesias et al. 2013, *Neuron*

Sensory precision-weighted PEs (pwPEs)



first fMRI study
(N=45)

second fMRI study
(N=27)

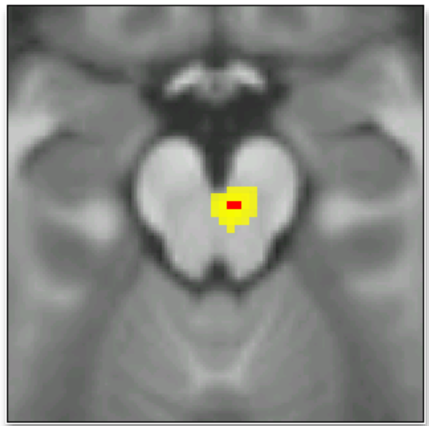
conjunction across studies

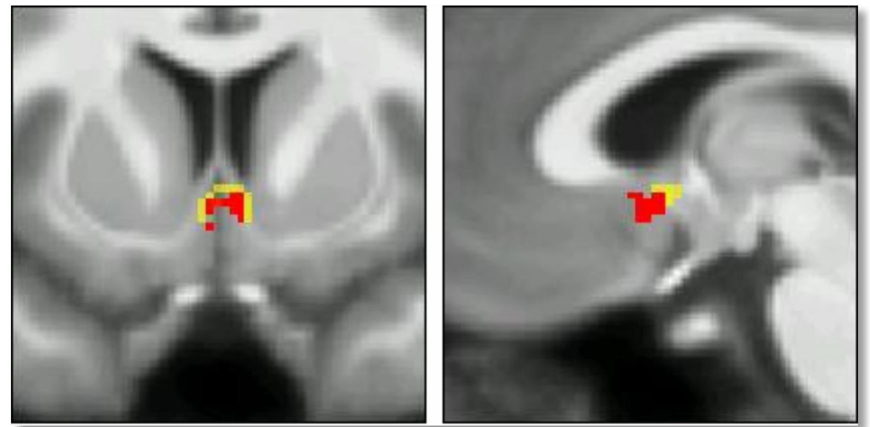
p<0.05 FWE whole-brain corrected

Iglesias et al. 2013, *Neuron*

Hierarchical precision-weighted PEs in sensory learning

Study 1: N=48

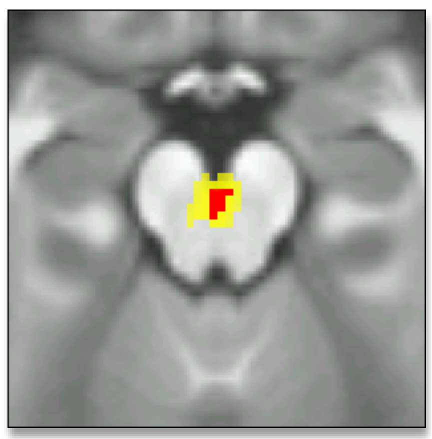


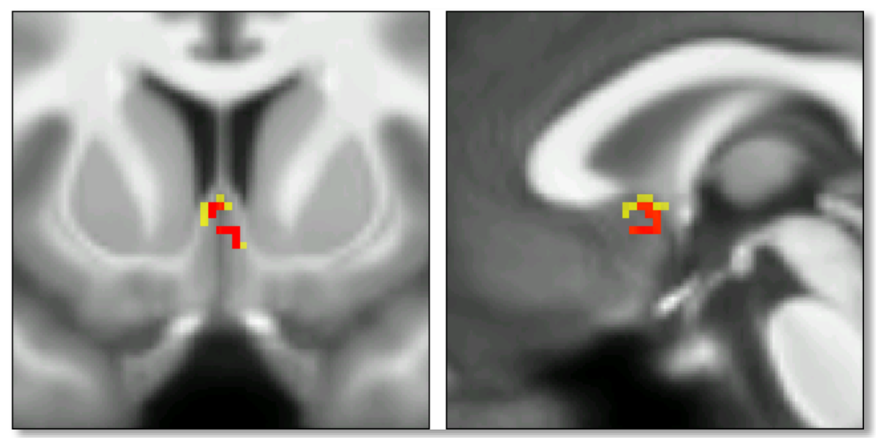


Outcome PEs in VTA/SN

Probability PEs in basal forebrain

Study 2: N=27





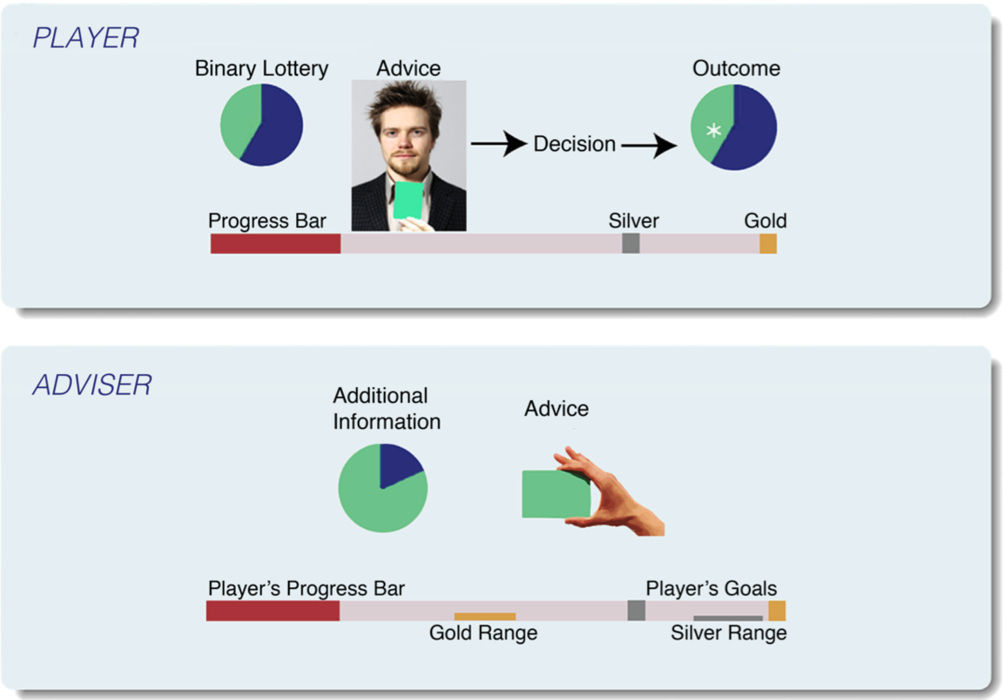
p<0.05, whole brain FWE corrected
p<0.05, SVC FWE corrected

p<0.05, SVC FWE corrected
p<0.001, uncorrected

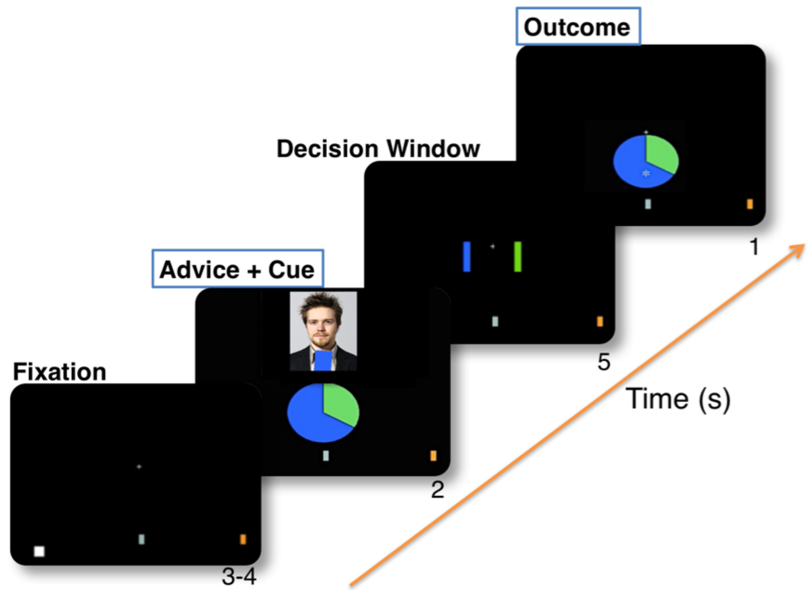
Iglesias et al. 2013, *Neuron*

Hierarchical PEs during social learning

A.

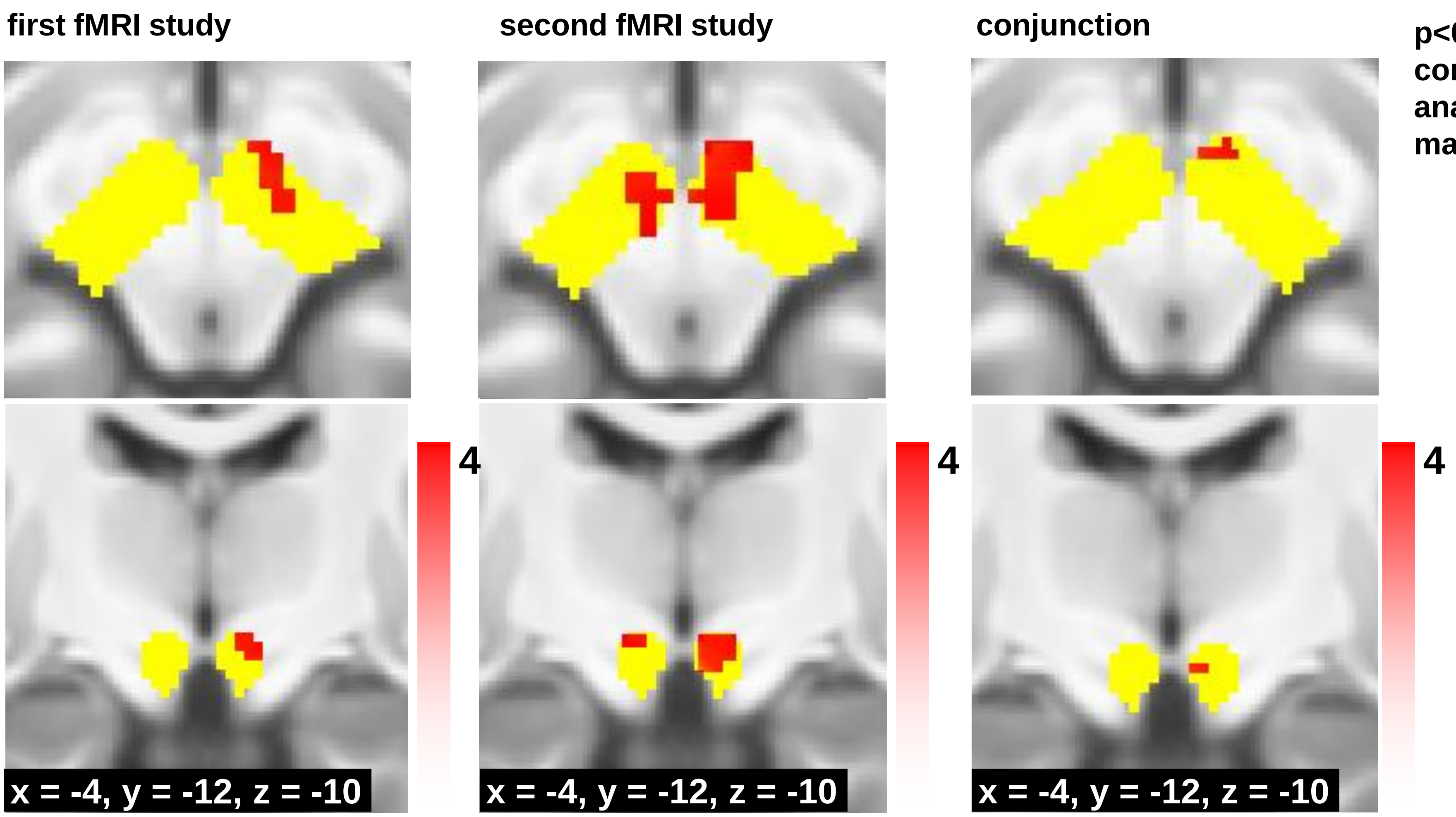


B.



Diaconescu et al. 2017, *SCAN*

Precision-weighted advice PEs (ε_2)

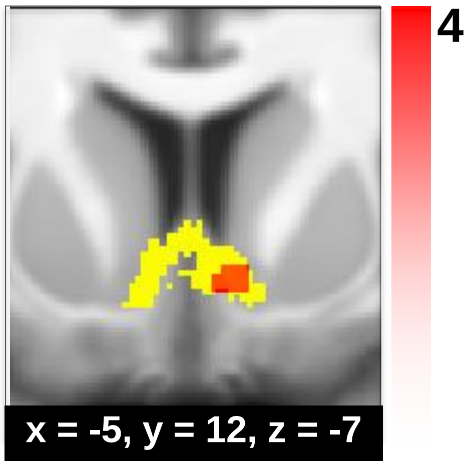


p<0.05, FWE corrected for anatomical mask

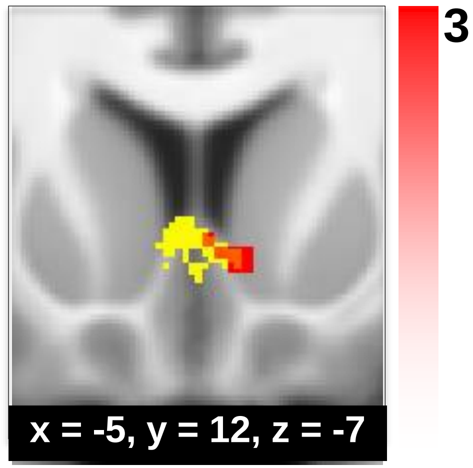
Diaconescu et al. 2017, *SCAN*

Precision-weighted PEs about adviser fidelity (ε_3)

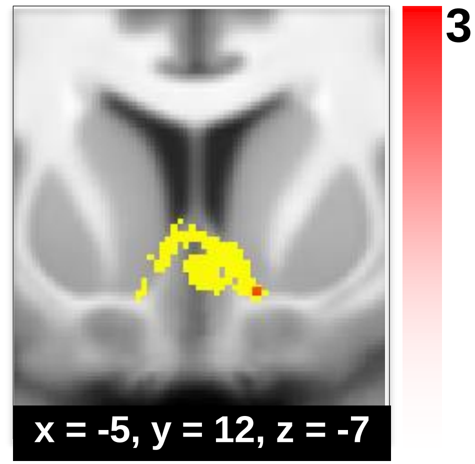
first fMRI study



second fMRI study



conjunction



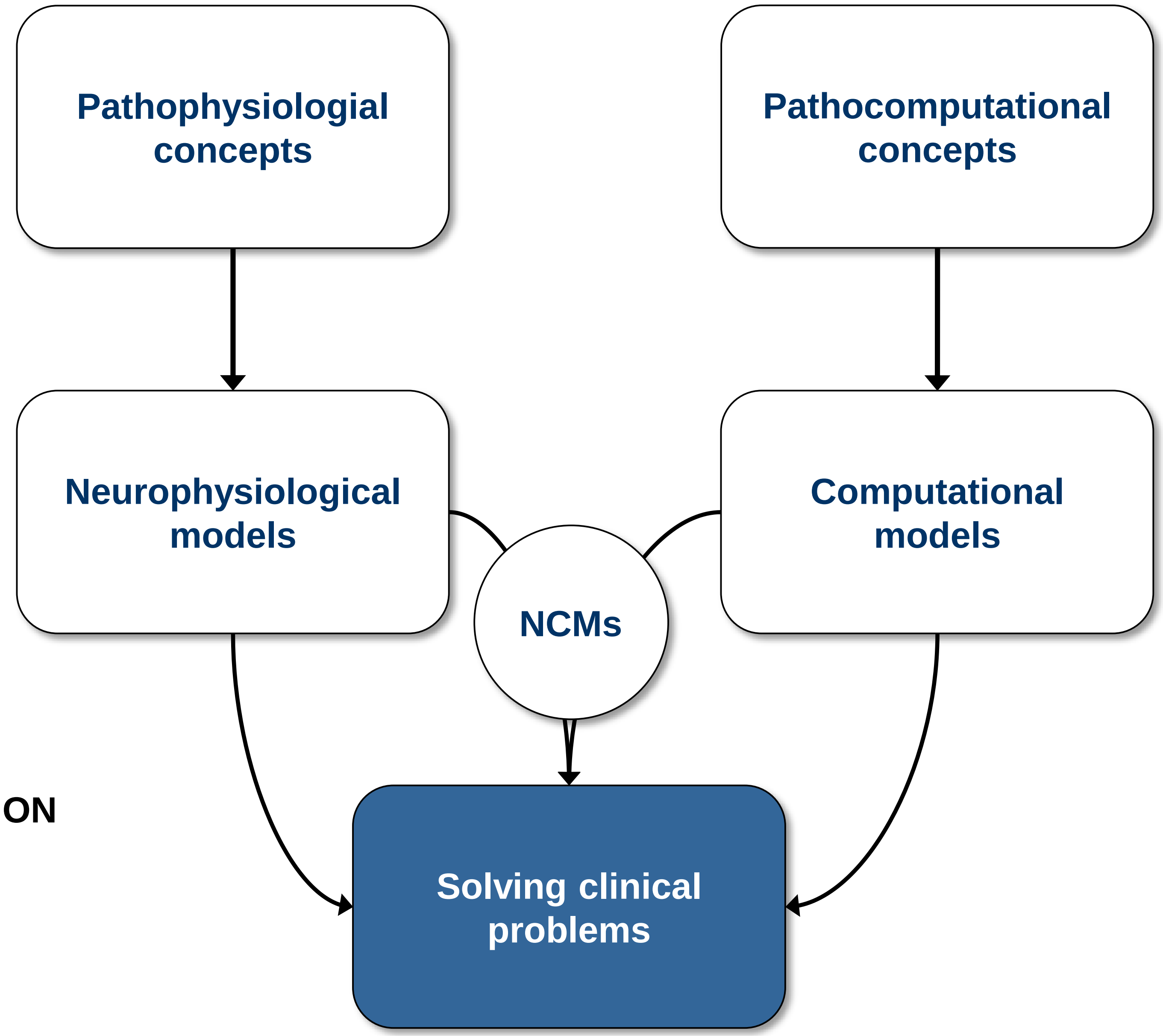
p<0.05, FWE corrected for anatomical mask

Diaconescu et al. 2017, *SCAN*

DISEASE THEORIES

GENERATIVE MODELING

INFERENCE & PREDICTION



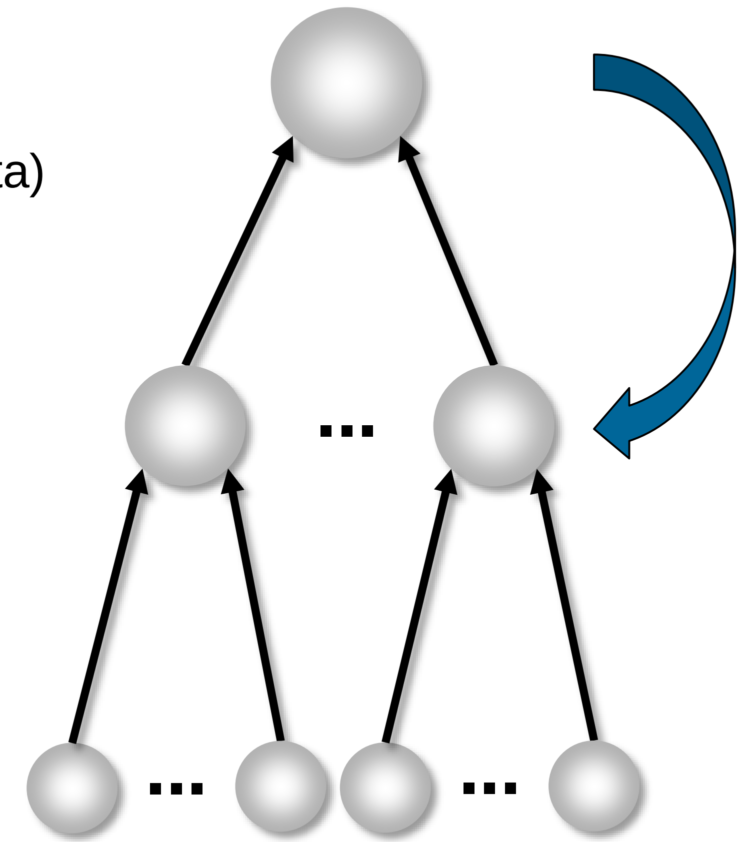
Translational Neuromodeling Unit

Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



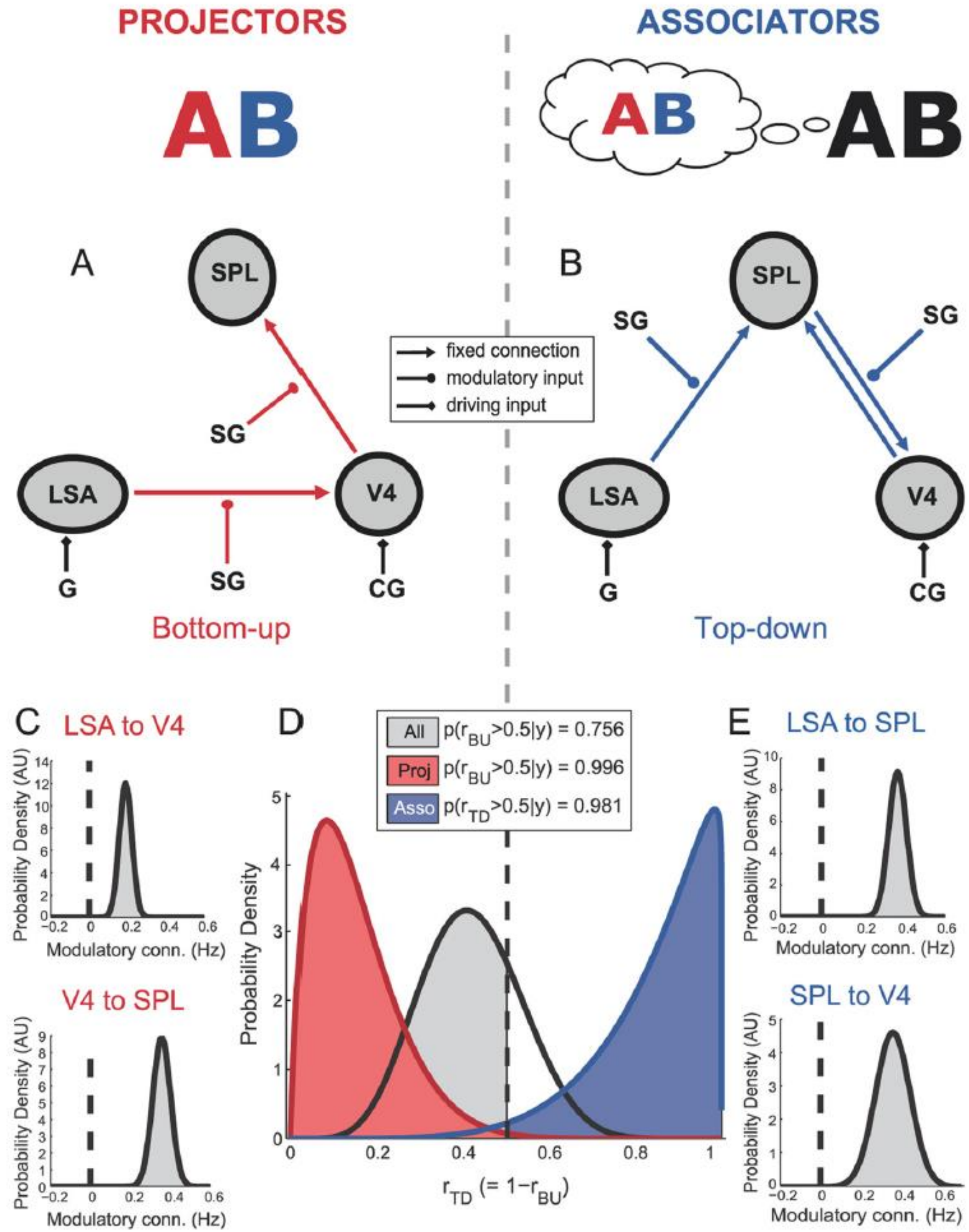
❶ **differential diagnosis** of alternative disease mechanisms

❷ **stratification / subgroup detection** into mechanistically distinct subgroups

❸ **prediction** of clinical trajectories and treatment response

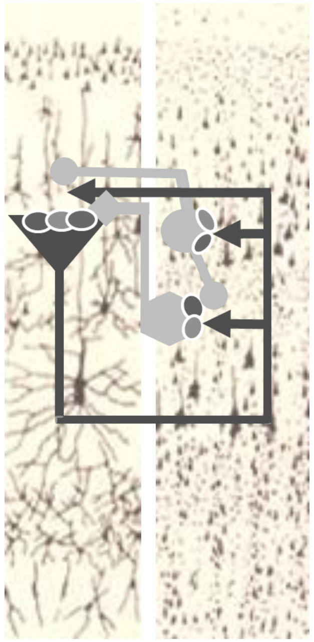
Synaesthesia

- “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)



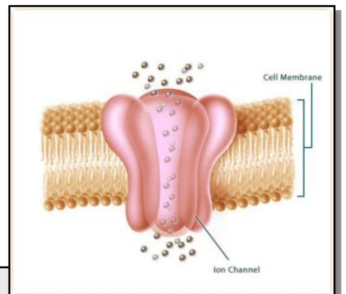
van Leeuwen et al. 2011, *J. Neurosci.*

❶ Differential diagnosis: inferring synaptic processes



- inhibitory interneurons
- excitatory interneurons
- pyramidal cells

AMPA, NMDA,$GABA_A$ receptors



$$C\dot{V} = \sum g_i \left(V_i^0 - V\right)$$

$$\dot{g}_k = \kappa\left(u_{ij} - g_k\right)$$

$$u_{ij} = \gamma_{ij}\sigma\left(\mu_V^{(j)} - V_R, \Sigma^{(j)}\right)$$

II

$$C\dot{V}^{(2)} = g_L(V_L - V^{(2)}) + g_E^{(2)}(V_E - V^{(2)}) + g_{NMDA} f_{Mg}(V^{(2)})(V_E - V^{(2)}) + \Gamma_V$$
$$\dot{g}_E^{(2)} = \kappa_E(\gamma_{2,3}^{(E)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_E^{(2)}) + \Gamma_E$$
$$\dot{g}_{NMDA}^{(2)} = \kappa_{NMDA}(\gamma_{2,3}^{(I)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_{NMDA}^{(2)}) + \Gamma_{NMDA}$$

$\gamma_{1,2}^{(I)}$ $\gamma_{2,3}^{(E)}$

EI

$$C\dot{V}^{(1)} = g_L(V_L - V^{(1)}) + g_E^{(1)}(V_E - V^{(1)}) + g_I^{(1)}(V_I - V^{(1)}) + u + \Gamma_V$$
$$\dot{g}_E^{(1)} = \kappa_E(\gamma_{1,3}^{(E)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_E^{(1)}) + \Gamma_E$$
$$\dot{g}_I^{(1)} = \kappa_I(\gamma_{1,2}^{(E)}\sigma(\mu_V^{(2)} - V_R, \Sigma^{(2)}) - g_I^{(1)}) + \Gamma_I$$

$\gamma_{3,2}^{(I)}$ $\gamma_{1,3}^{(E)}$ $\gamma_{3,1}^{(E)}$

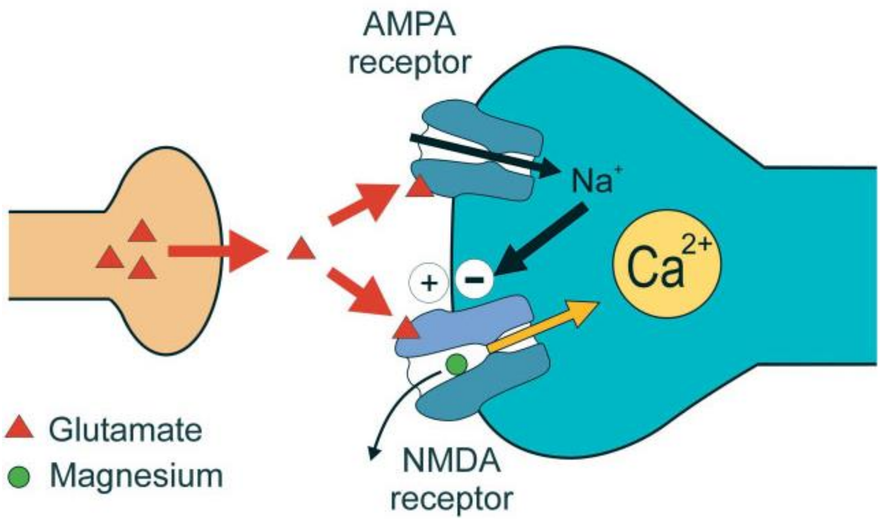
PC

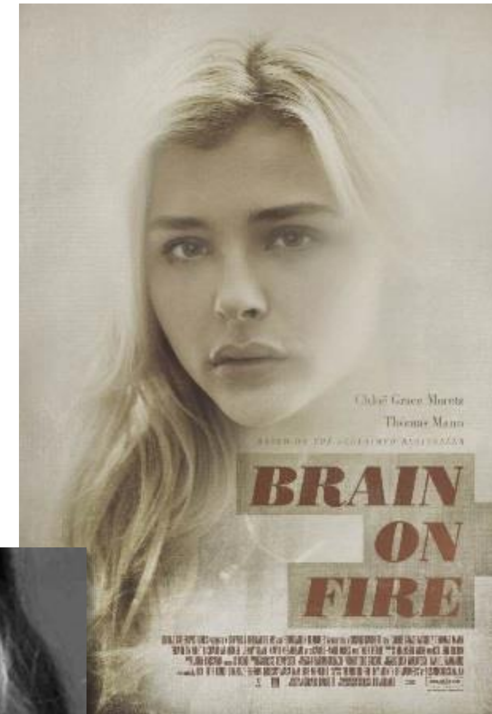
$$C\dot{V}^{(3)} = g_L(V_L - V^{(3)}) + g_E^{(3)}(V_E - V^{(3)}) + g_I^{(3)}(V_I - V^{(3)}) + g_{NMDA} f_{Mg}(V^{(3)})(V_E - V^{(3)}) + \Gamma_V$$
$$\dot{g}_E^{(3)} = \kappa_E(\gamma_{3,1}^{(E)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_E^{(3)}) + \Gamma_E$$
$$\dot{g}_I^{(3)} = \kappa_I(\gamma_{3,2}^{(I)}\sigma(\mu_V^{(2)} - V_R, \Sigma^{(2)}) - g_I^{(3)}) + \Gamma_I$$
$$\dot{g}_{NMDA}^{(3)} = \kappa_{NMDA}(\gamma_{3,1}^{(I)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_{NMDA}^{(3)}) + \Gamma_{NMDA}$$

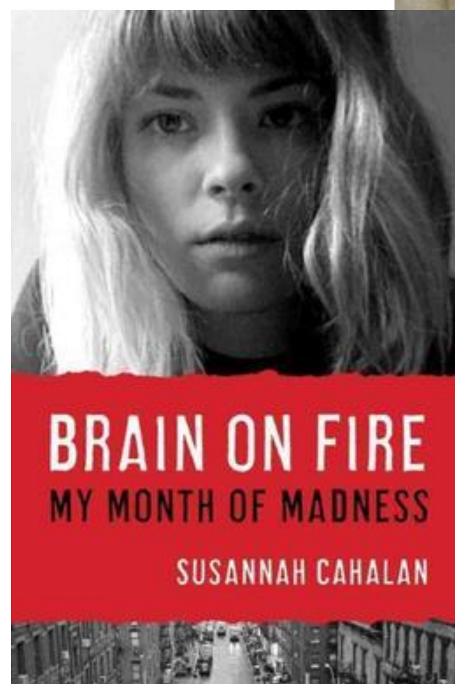
u_{ij} = presynaptic input from ensemble j to i
σ = CDF of presynaptic depolarization density around threshold potential V_R

Marreiros et al. 2010, *NeuroImage*
Moran et al. 2011, *NeuroImage*

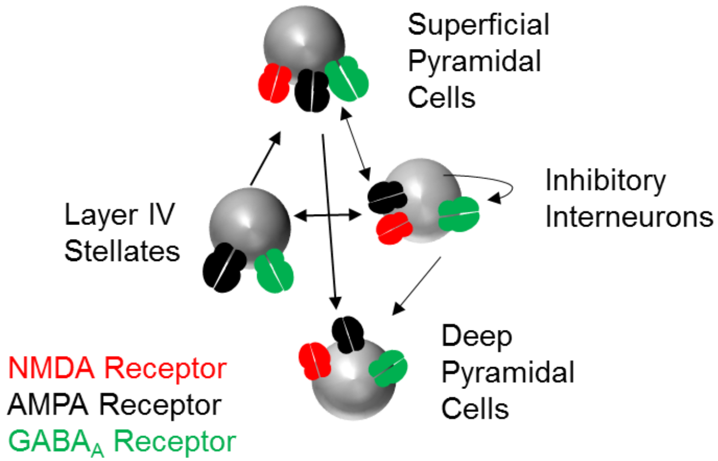
NMDA receptor antibody encephalitis

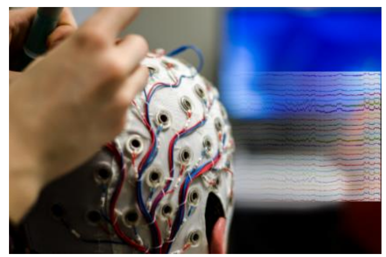


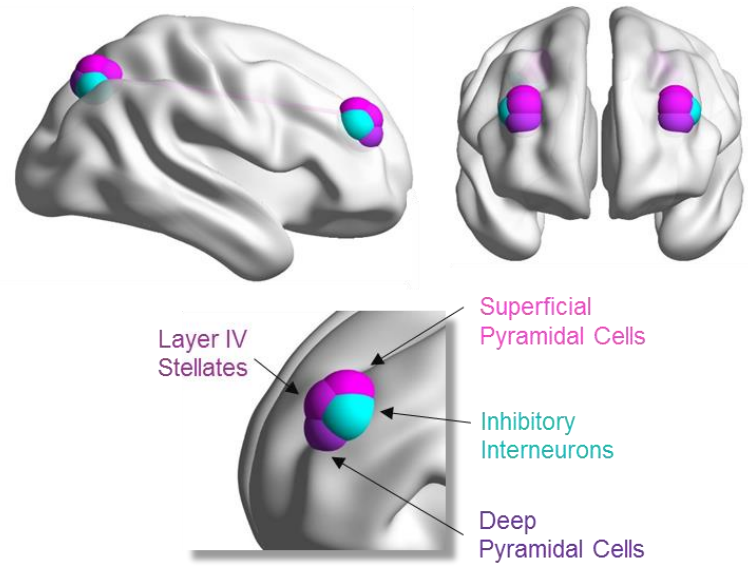


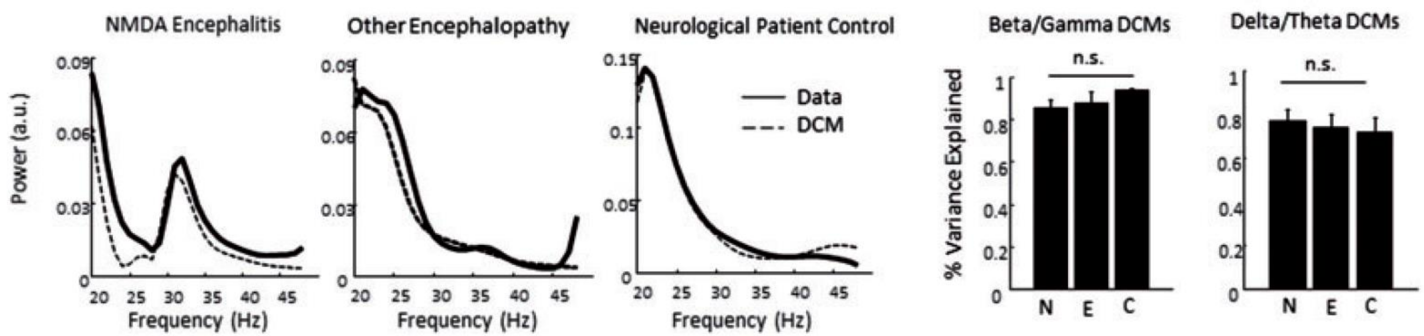


Assaying NMDA receptors

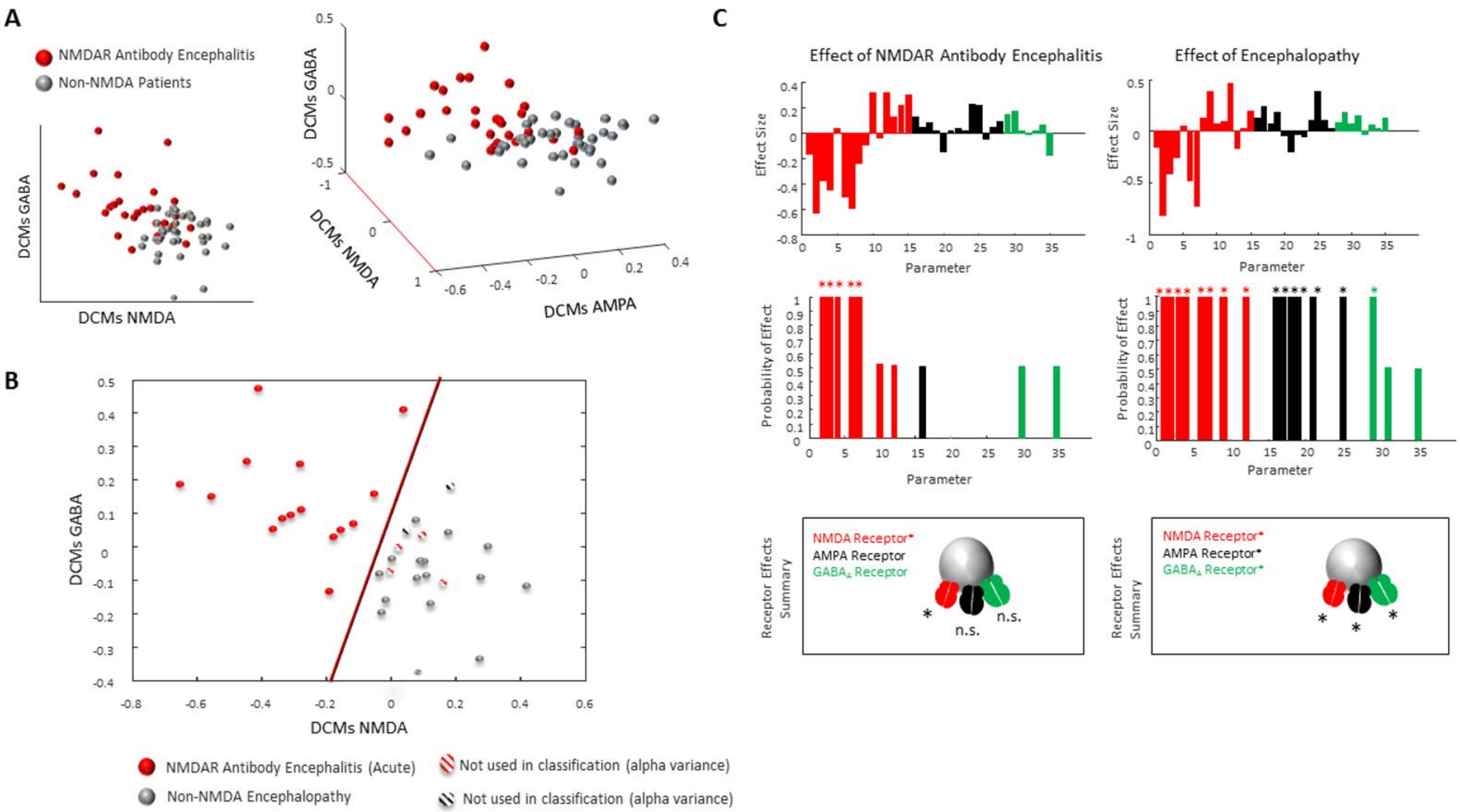






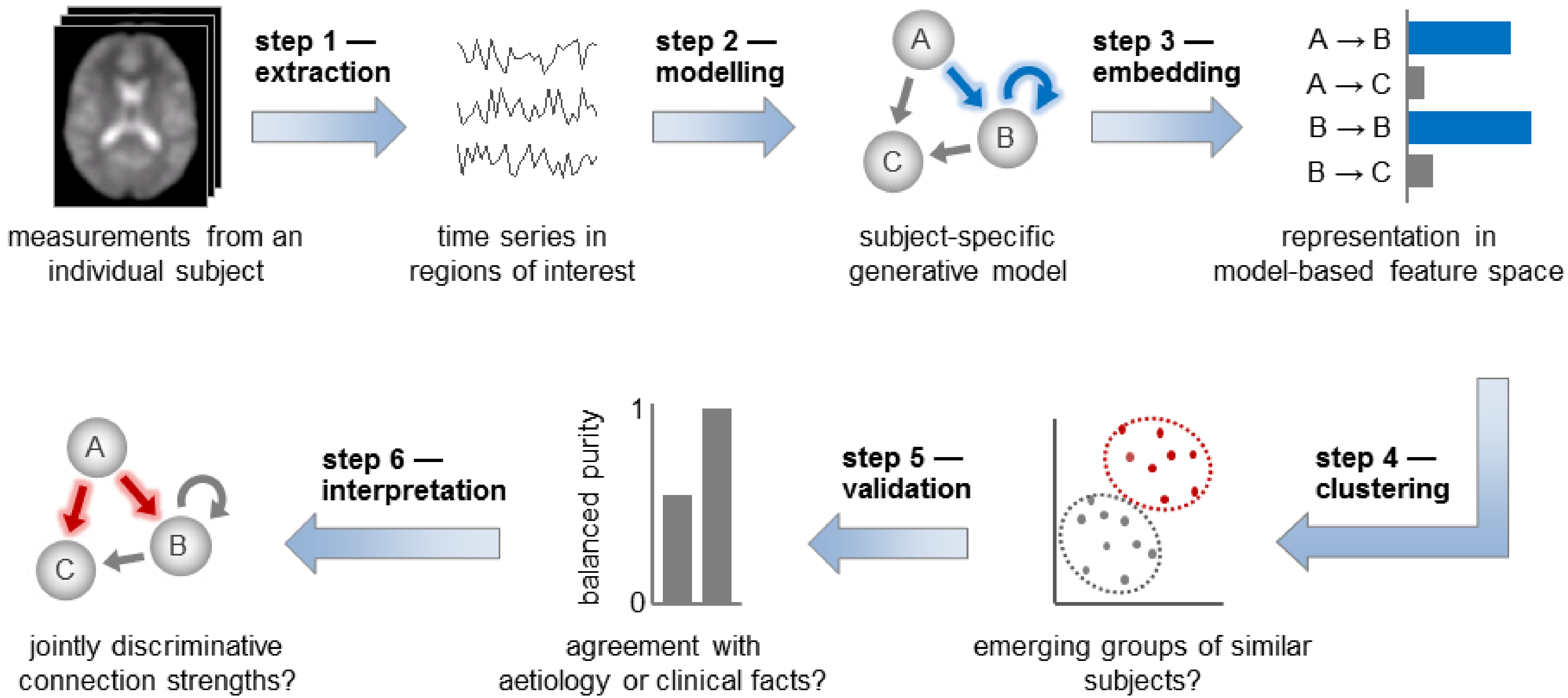


Symmonds et al. 2018, *Brain*



Symmonds et al. 2018, *Brain*

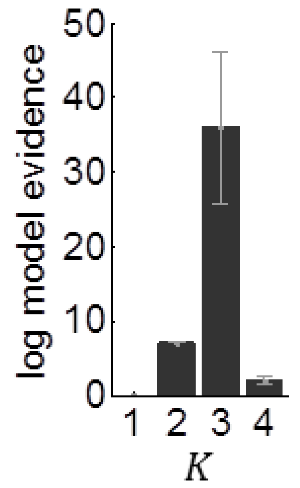
❷ Stratification / subgroup detection: Generative embedding (unsupervised)



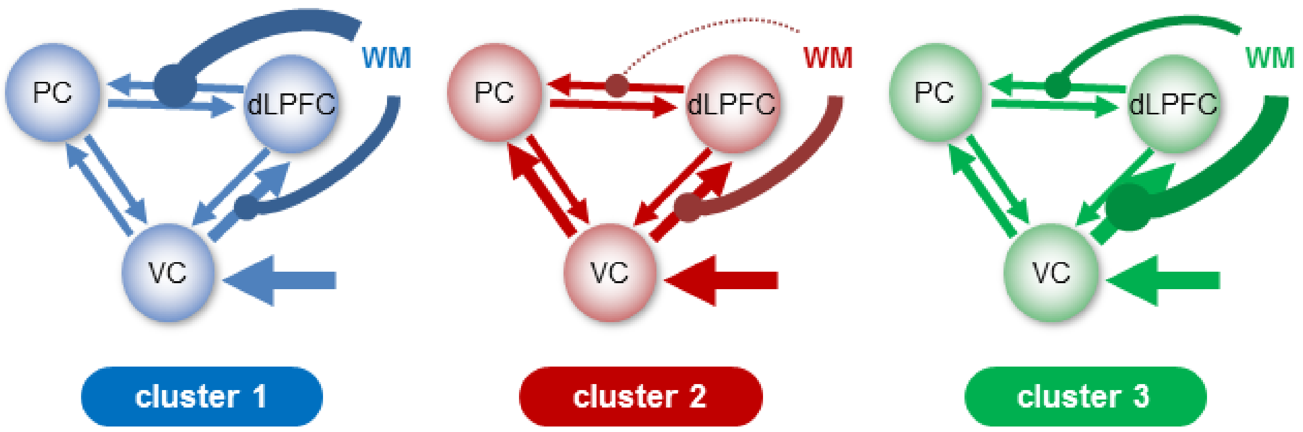
Brodersen et al. 2014, *NeuroImage Clinical*

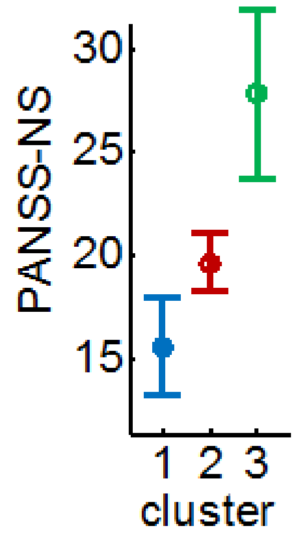
Detecting subgroups of patients in schizophrenia

Optimal cluster solution



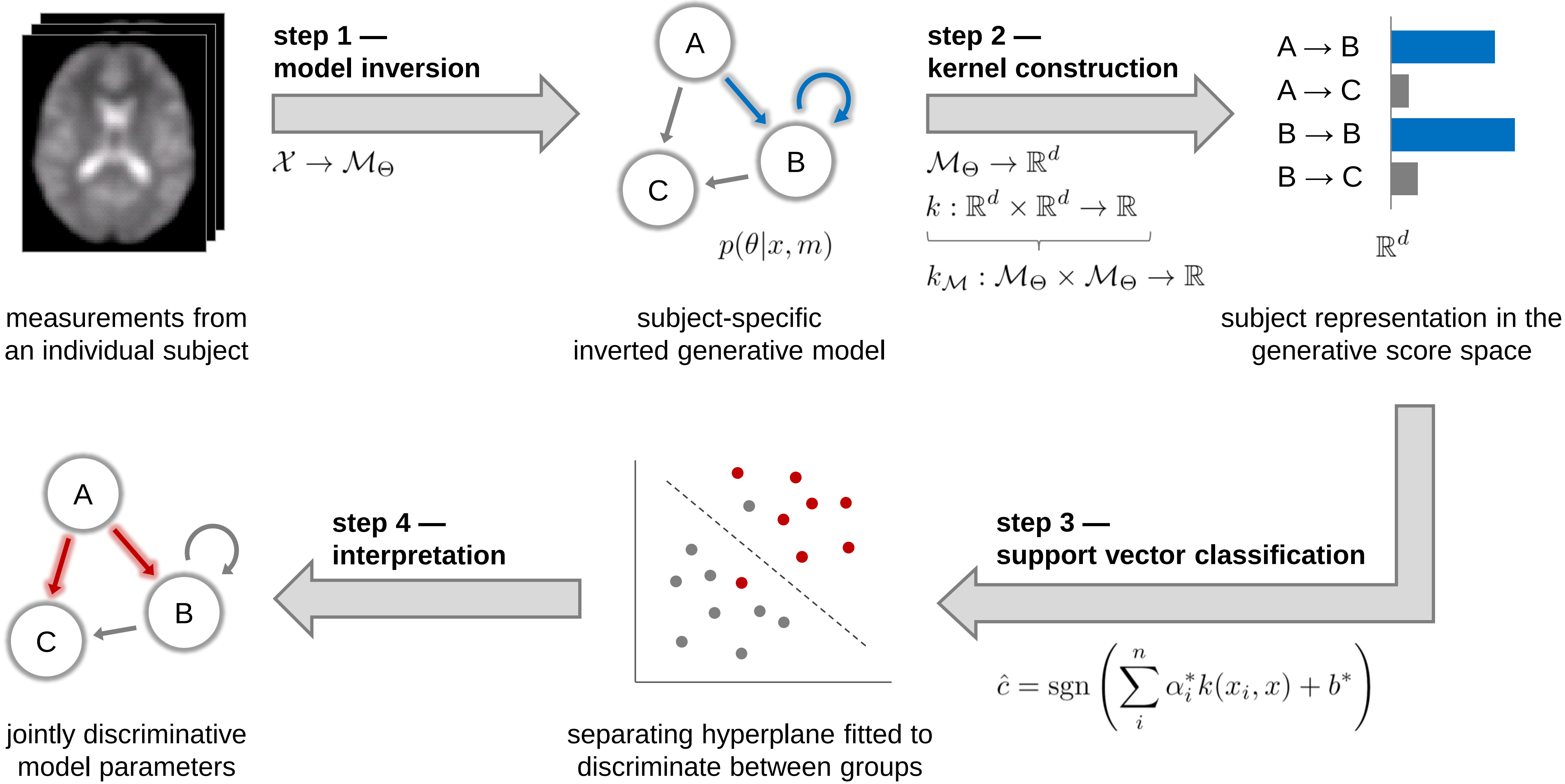
- three distinct subgroups (total N=41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)





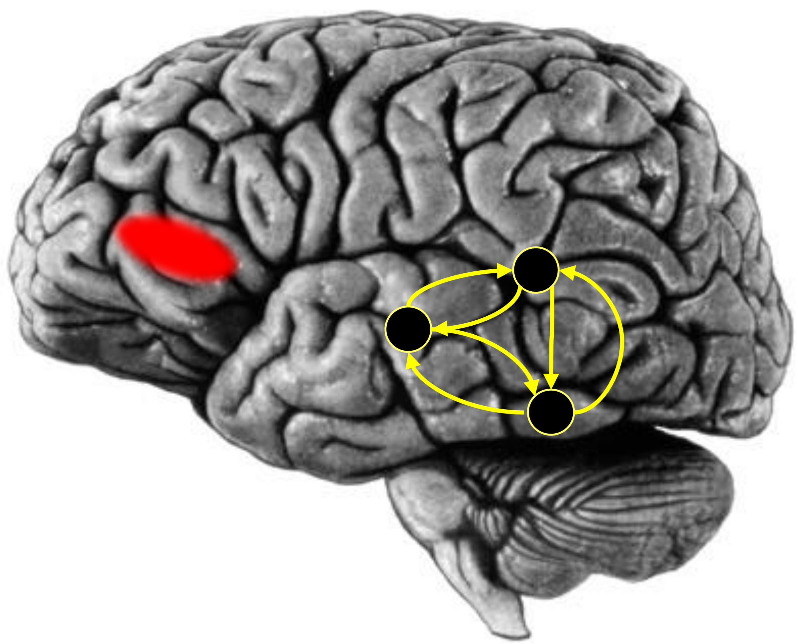
Brodersen et al. 2014, *NeuroImage Clinical*

❸ Prediction: Generative embedding (supervised)

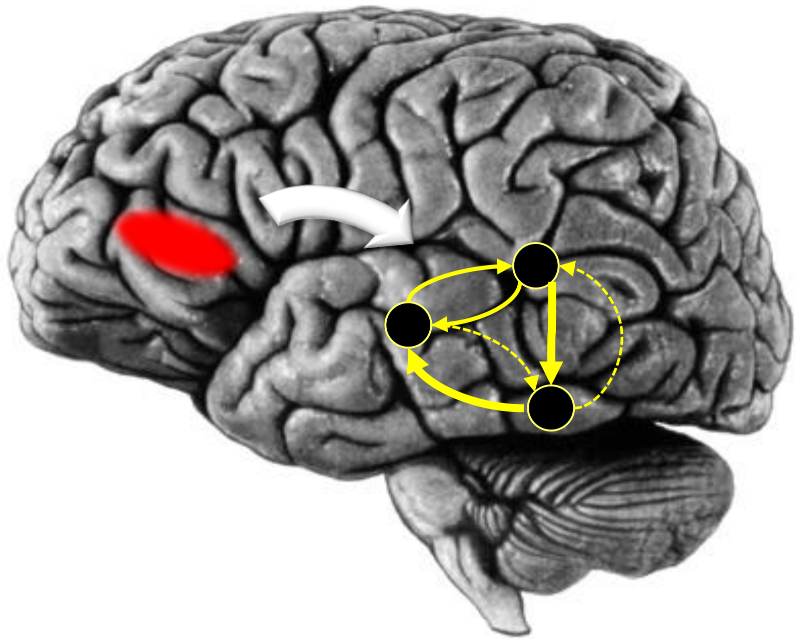


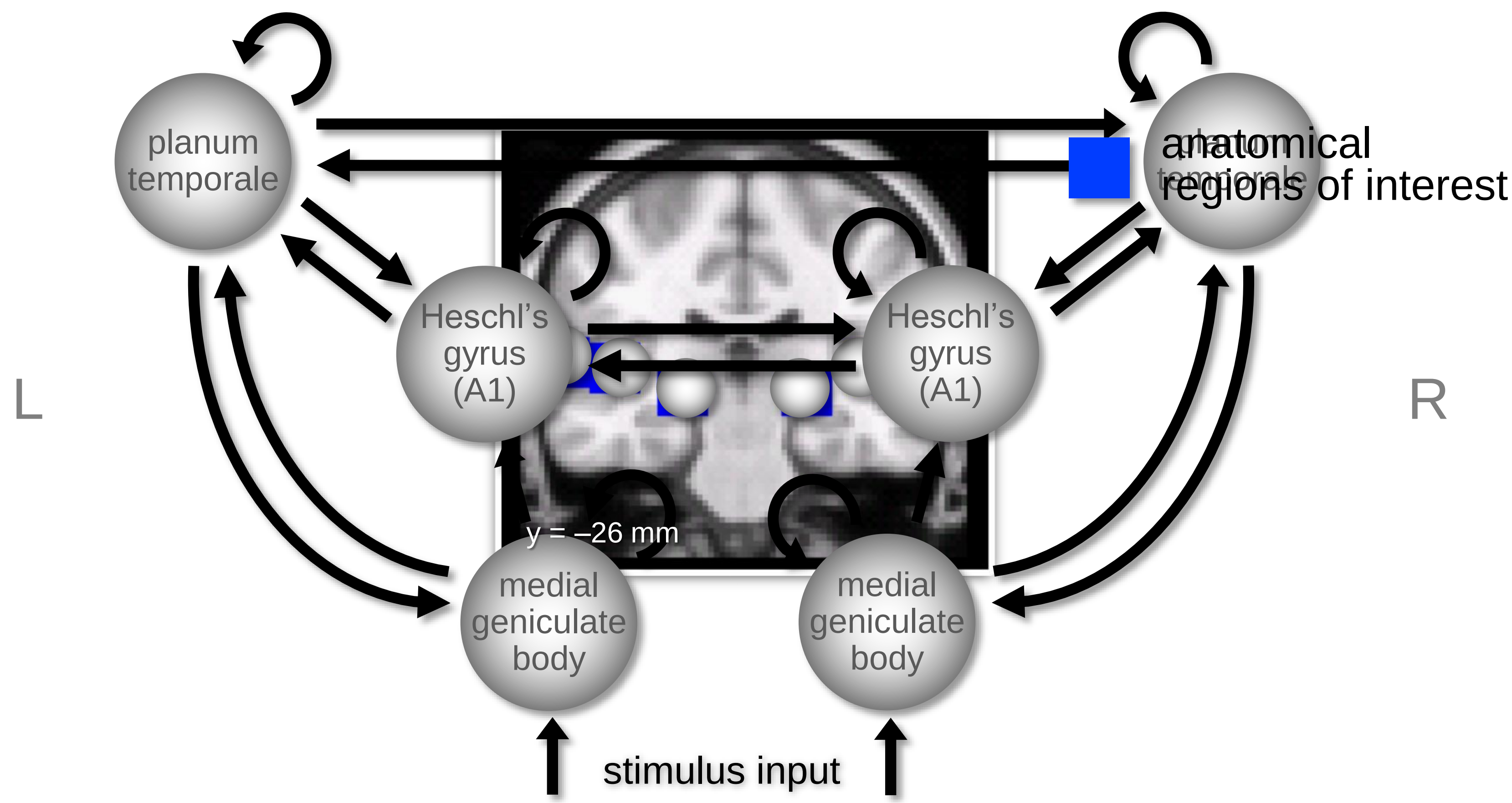
Brodersen et al. 2011, *PLoS Comput. Biol.*

Discovering remote or “hidden” brain lesions



Discovering remote or “hidden” brain lesions

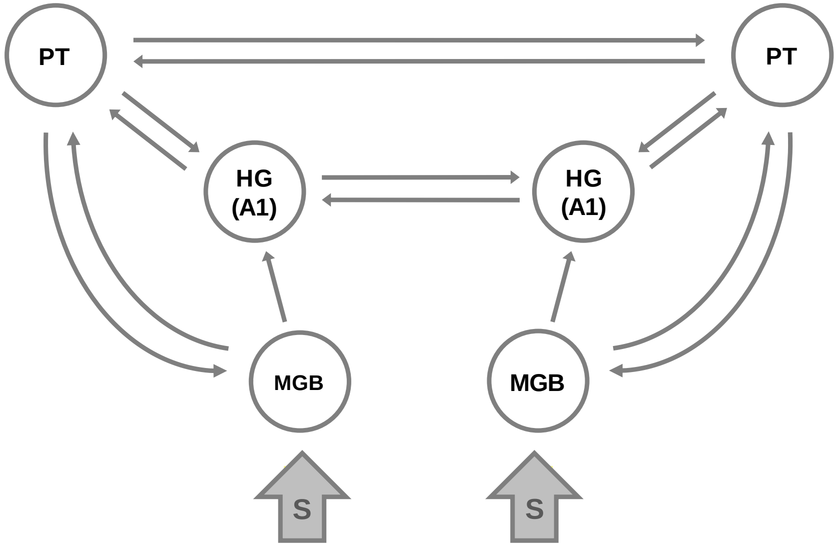


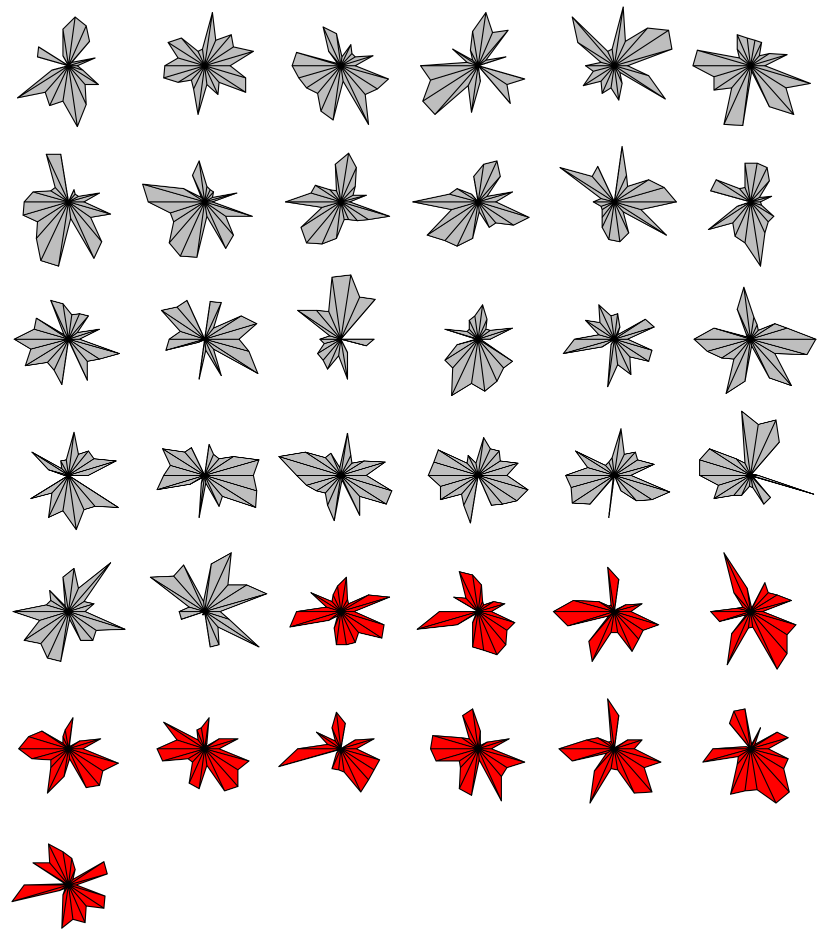


Brodersen et al. 2011, *PLoS Comput. Biol.*

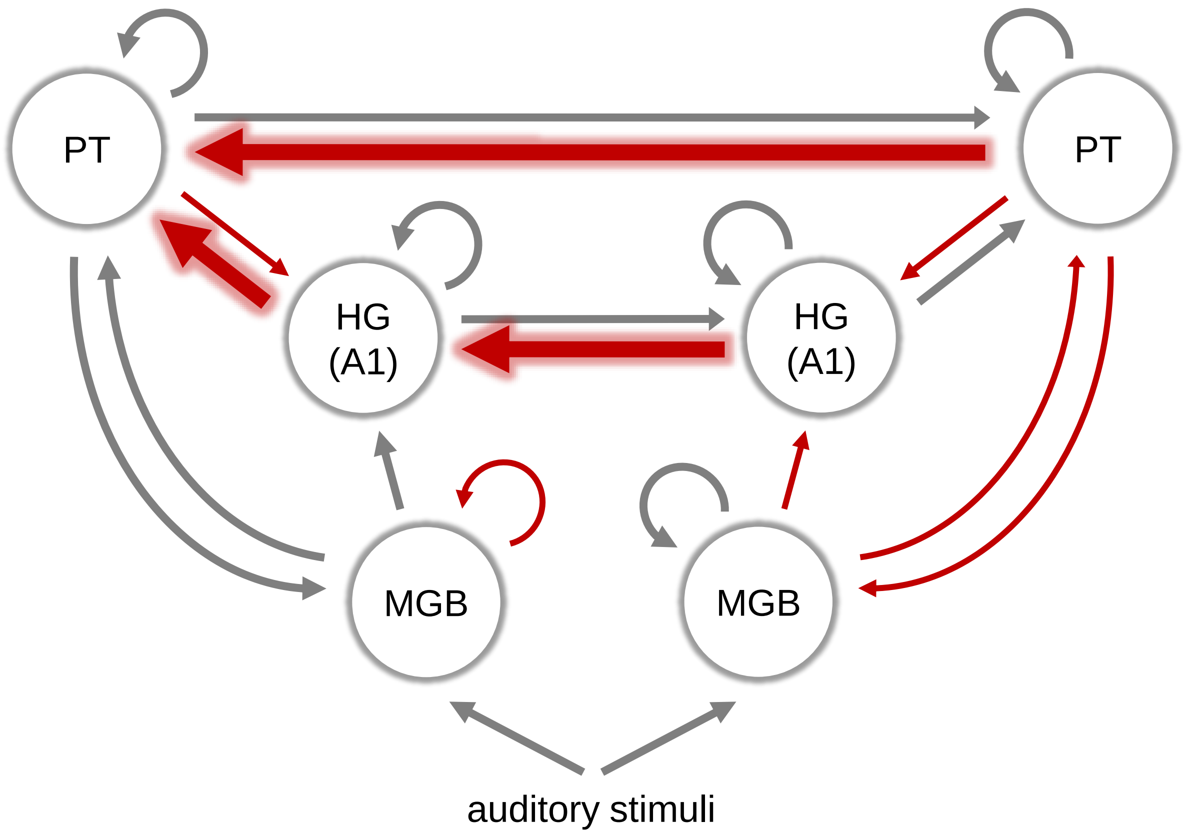
Connectional fingerprints : aphasic patients (N=11) vs. controls (N=26)

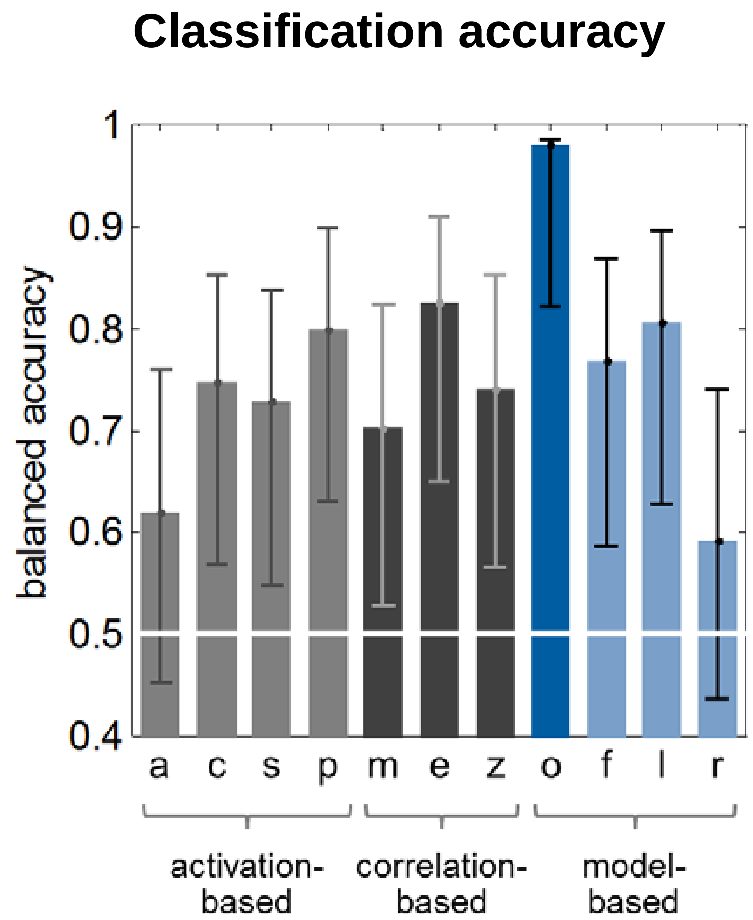
6-region DCM of auditory areas during passive speech listening





Brodersen et al. 2011, *PLoS Comput. Biol.*
Data from Schofield et al.

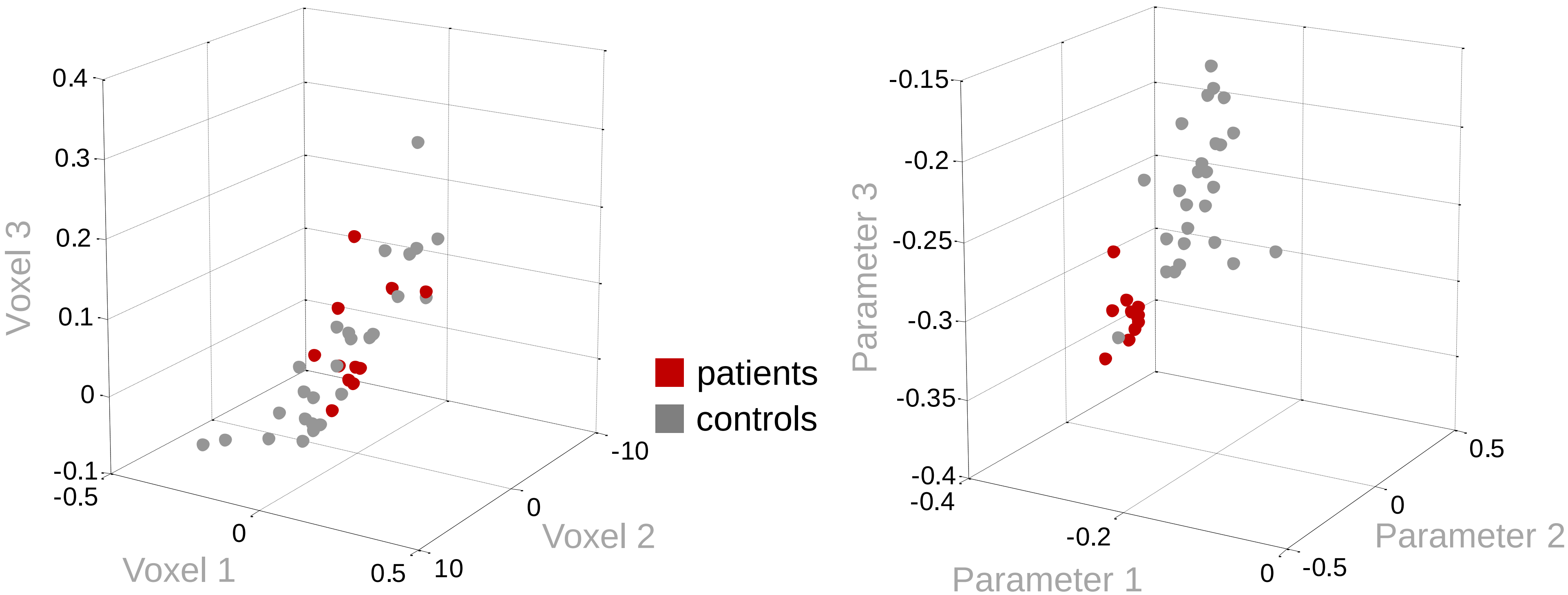




Brodersen et al. 2011, *PLoS Comput. Biol.*

Voxel-based activity space

Model-based parameter space



classification accuracy
75%

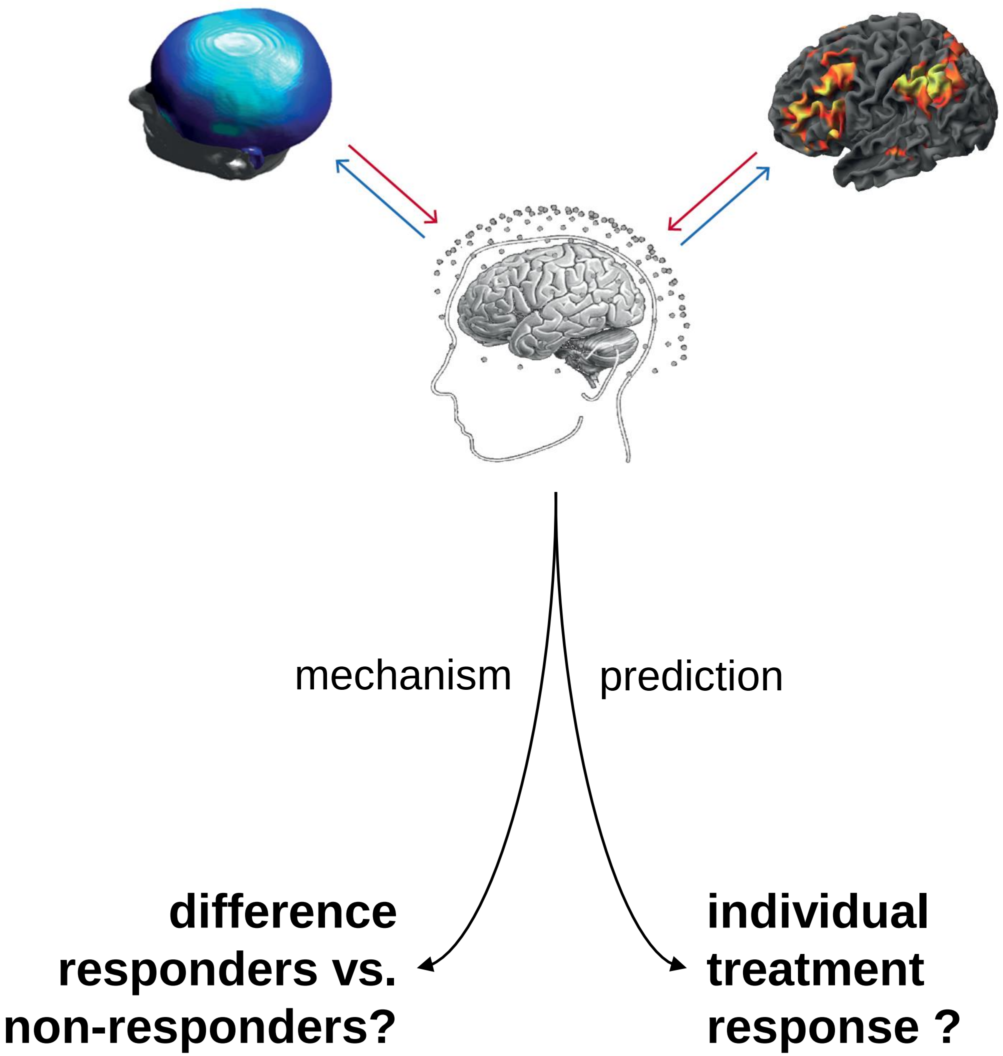
classification accuracy
98%

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

Prospective patient studies at TNU Zurich

Ongoing studies:

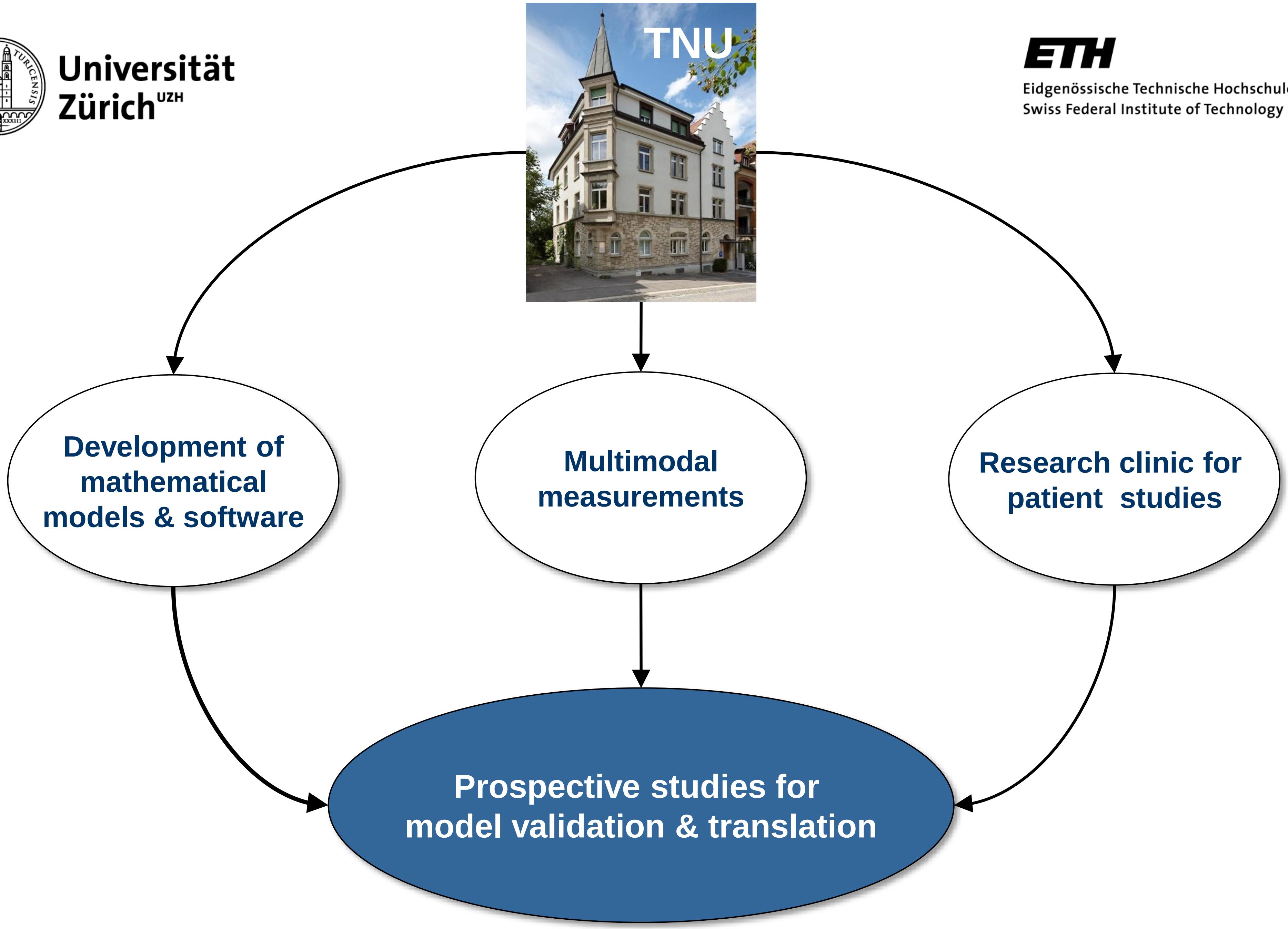
- schizophrenia (COMPASS)
- depression (AIDA)
- autism (BIASD)
- pathological gambling (CSTCG)
- multiple sclerosis (EEGMS)



Translational Neuromodeling Unit

Universität Zürich[UZH]

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich



The TNU – 16 nationalities, from mathematics to medicine

Translational Neuromodeling Unit

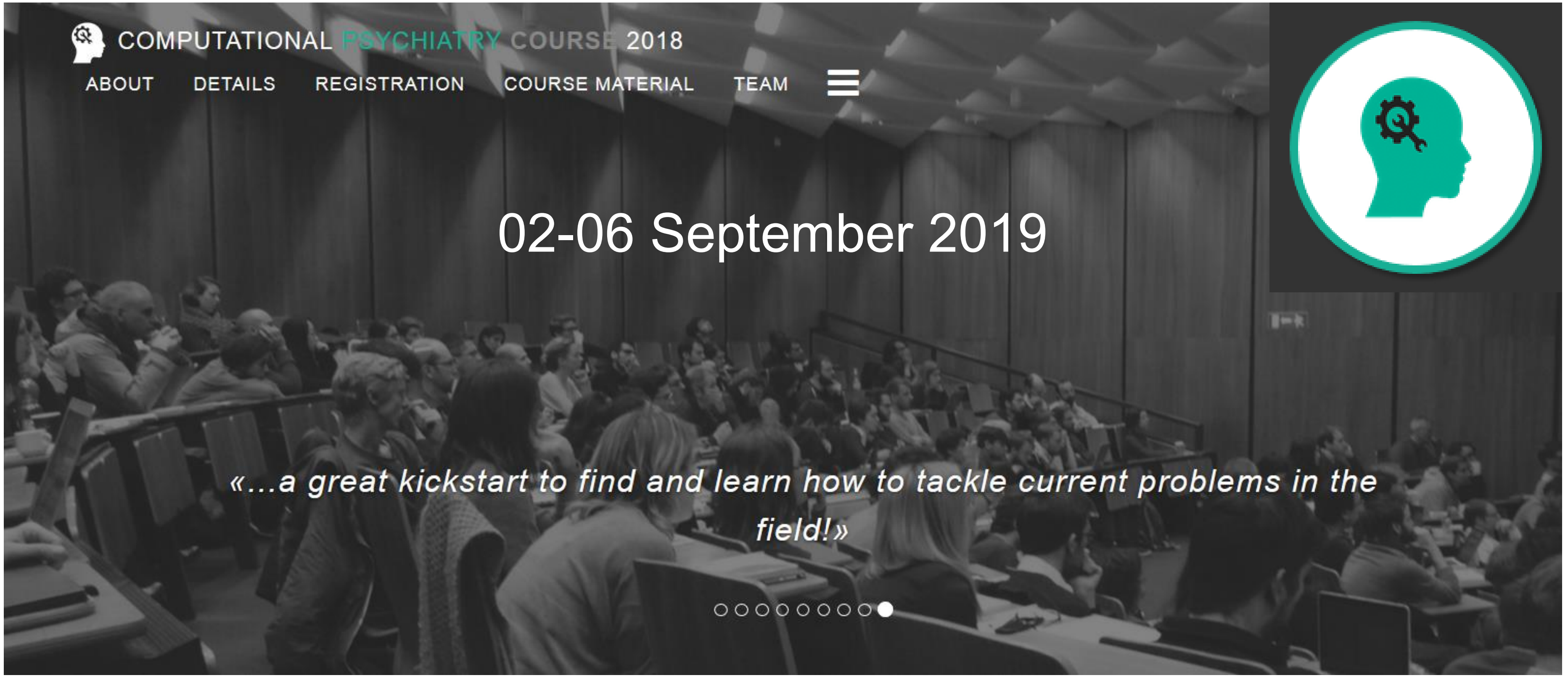
E. Aponte
N. Araya
I. Berwian
H. Brunner
D. Cole
A. Diaconescu
H.C.T. Do
I. Elbau
S. Frässle
S. Grässli
H. Haker
J. Heinzle
Q. Huys
S. Iglesias
L. Kasper
S. Maier
C. Mathys
S. Paliwal
G. Paolini
F. Petzschner
D. Renz
L. Rigoux
M. Schneebeli
I. Schnürer
D. Schöbi
J. Siemerkus
G. Stefanics
K.E. Stephan
S. Tomiello
F. Vinckier
L. Weber
K. Wellstein
Y. Yao
N. Zahnd

Open source software TAPAS

TAPAS

www.translationalneuromodeling.org/tapas

Computational Psychiatry Course (CPC) Zurich



www.translationalneuromodeling.org/cpcourse

Thank you – UZH & ETH partnership

Medical Faculty
Faculty of Science

Universität Zürich UZH

Dept. of Information Technology
& Electrical Engineering

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Further reading

Brodersen KH, Schofield TM, Leff AP, Ong CS, Lomakina EI, Buhmann M, Stephan KE (2011) Generative Embedding for Model-Based Classification of fMRI Data. PLoS Computational Biology 7: e1002079.

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Thank you

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