Why is fMRI important for medicine?

Klaas Enno Stephan

Translational Neuromodeling Unit

Universität Zürich[UZH]

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Overview

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

The "human circulation balance"

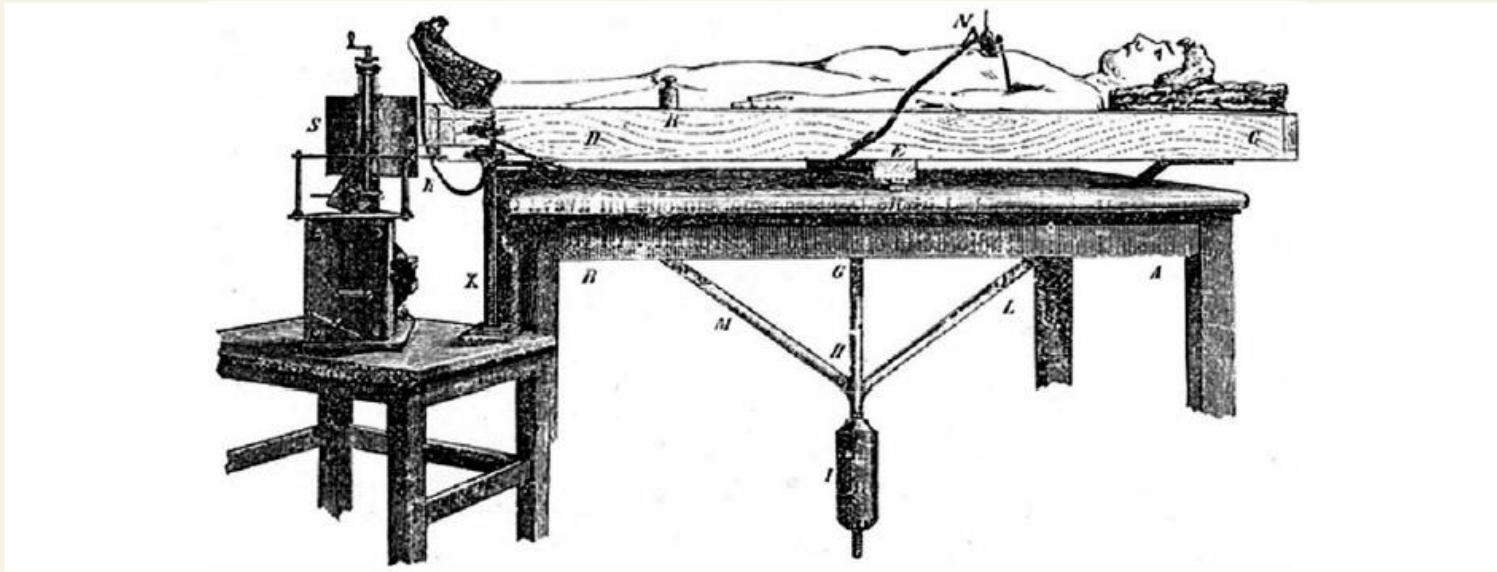
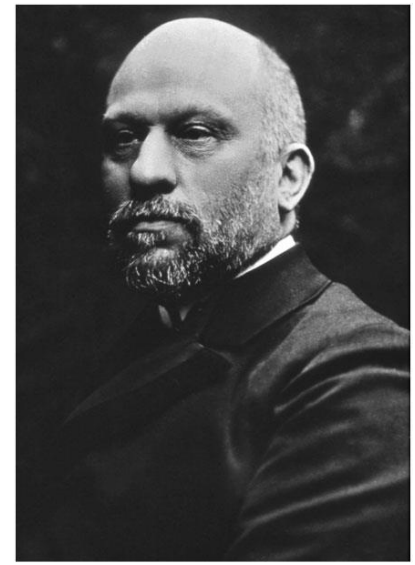


Figure 3 Mosso's 'human circulation balance', used to measure cerebral activity during resting and cognitive states. A and B = wooden table with three apertures on its top; C and D = tilting bed; E = pivot with steel knife fulcrum; G and H = 1 m long iron rod bearing the counterweight; I = cast iron 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).

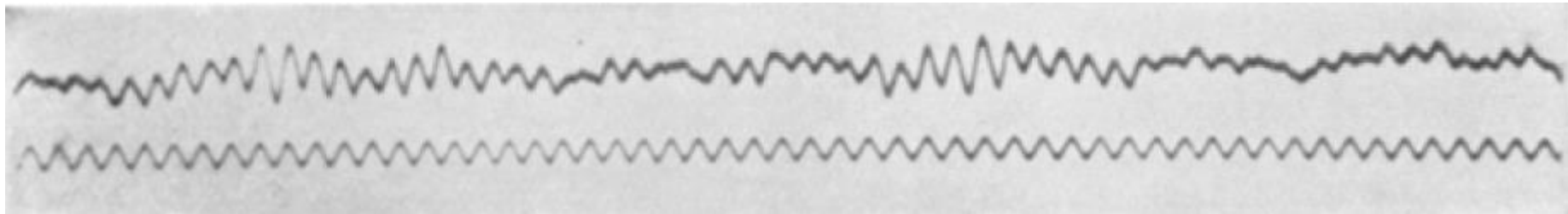


Angelo Mosso (1846-1910)

Sandrone et al. (2014) *Brain*

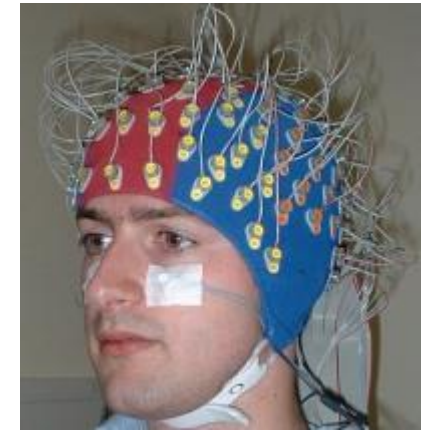
Electroencephalography (EEG)

Hans Berger (1873–1941)

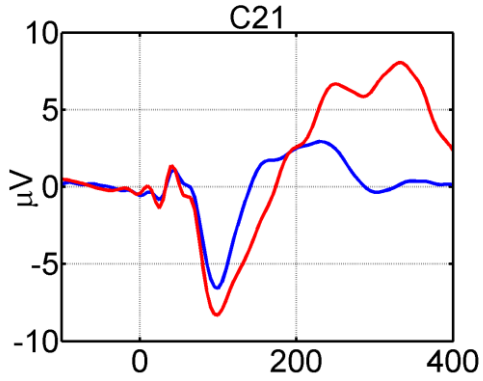


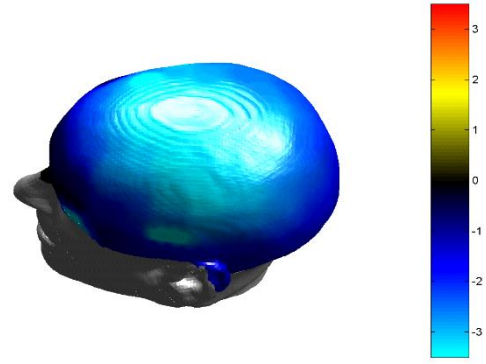
Berger H. Über das Elektrenkephalogramm des Menchen. Archive für Psychiatrie. 1929; 87:527-70., Public Domain, https://commons.wikimedia.org/w/index.php?curid=2900591

EEG & MEG

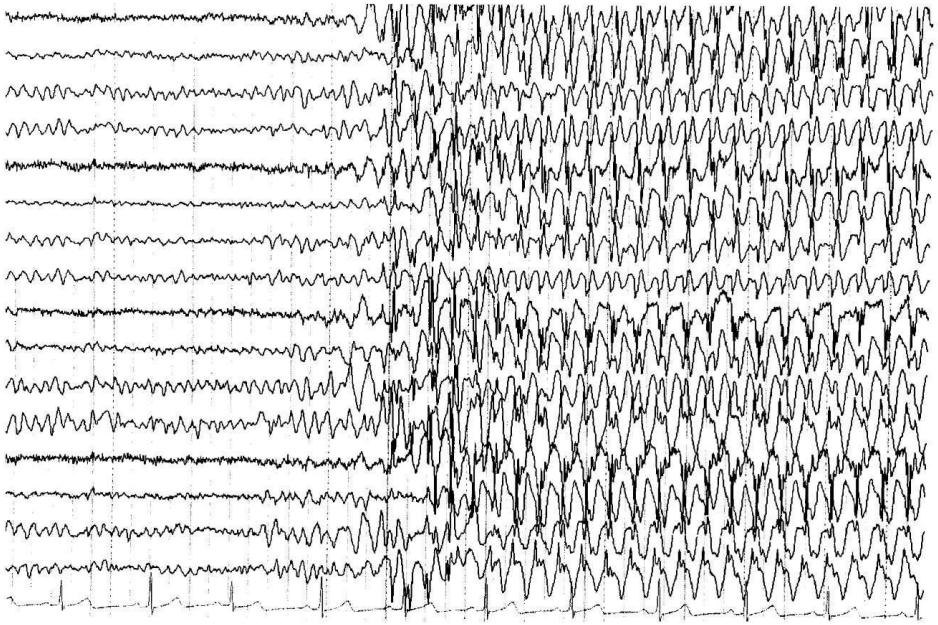


- alignment of dendritic trees of pyramidal cell allow measurements of
  - electric potentials (EEG)
  - magnetic fields (MEG)
- excellent temporal resolution (< 1 millisecond)
- limited spatial resolution (≈ 1 cm)



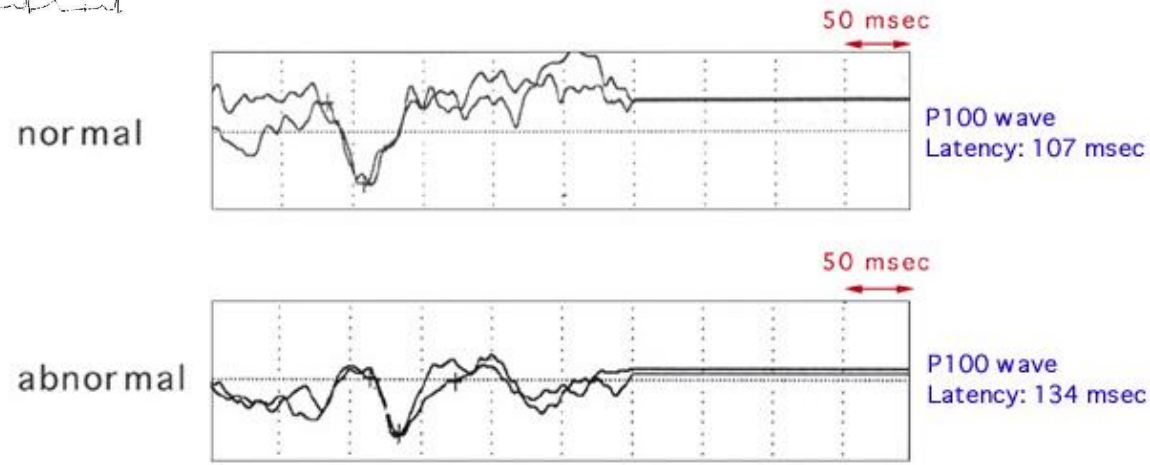


Clinical use of EEG & MEG



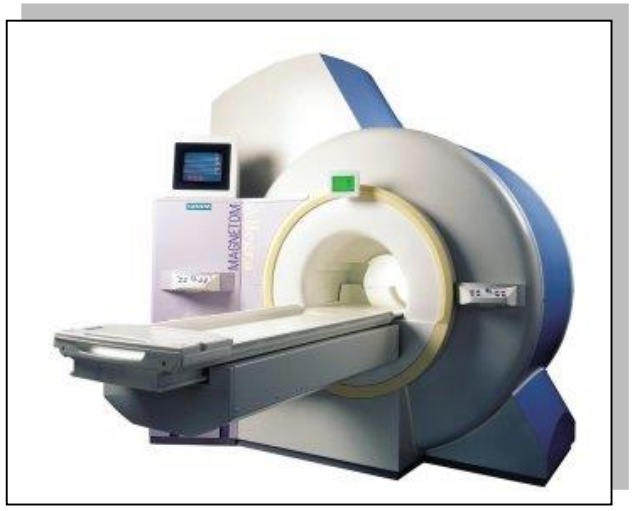
Childhood absence epilepsy

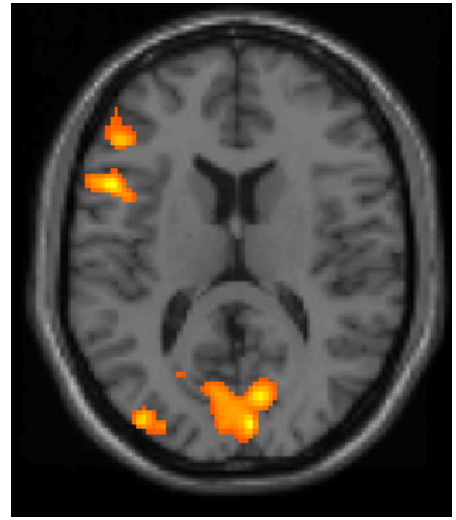
Reduced latency of a visual evoked potential due to demyelination in MS

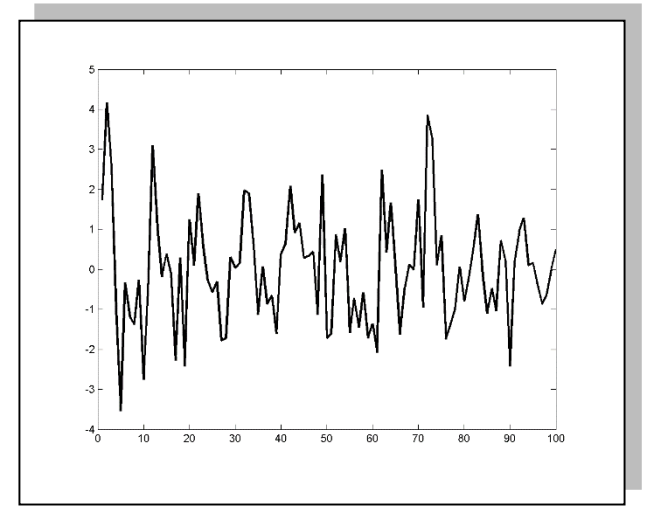


Functional magnetic resonance imaging (fMRI)

- 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



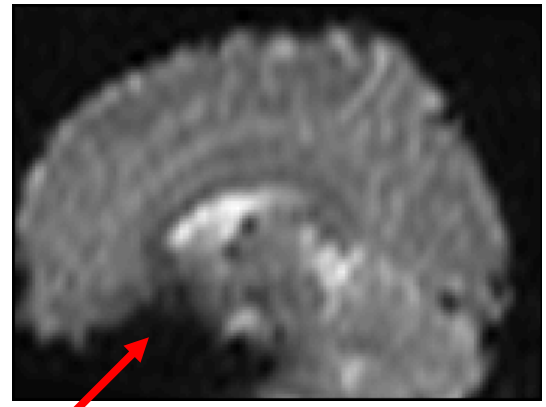




Functional MRI (fMRI)

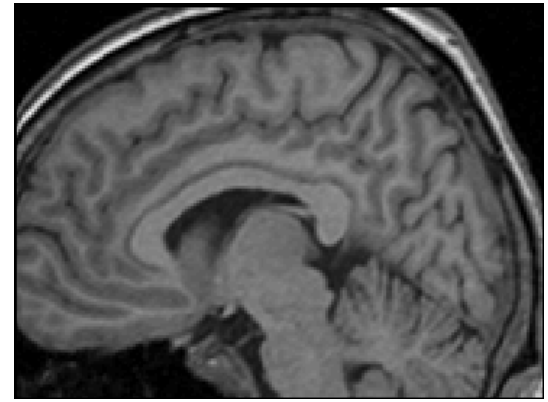
- Uses *echo planar imaging* (EPI) for fast acquisition of T2*-weighted images.
- Spatial resolution:
  - 3 mm (standard 1.5 T scanner)
  - < 200 µm (high-field systems)
- Sampling speed:
  - 1 slice: 50-100 ms
- Problems:
  - distortion and signal dropouts in certain regions
  - sensitive to head motion of subjects during scanning
- Requires spatial pre-processing and statistical analysis.

EPI ($T2^*$)



dropout

T1



What is it that makes T2* weighted images “functional”?

The BOLD contrast

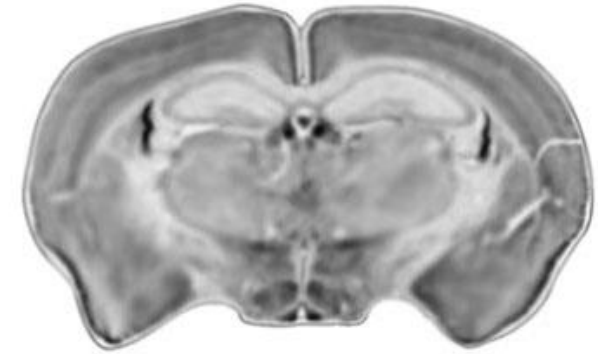
BOLD (Blood Oxygenation Level Dependent) contrast =

measures inhomogeneities in the magnetic field due to changes in the level of O_2 in the blood

Oxygenated hemoglobine:

Diamagnetic (non-magnetic)

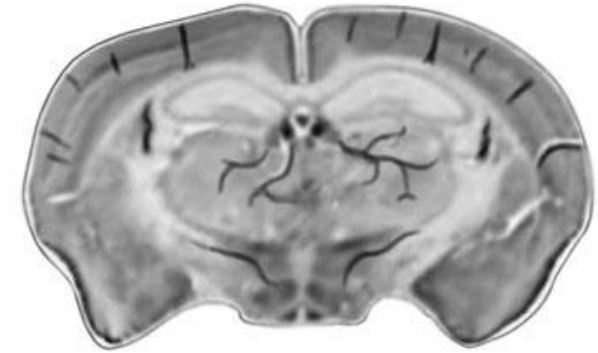
→ No signal loss…



<u>De</u>oxygenated hemoglobine:

Paramagnetic (magnetic)

→ signal loss !

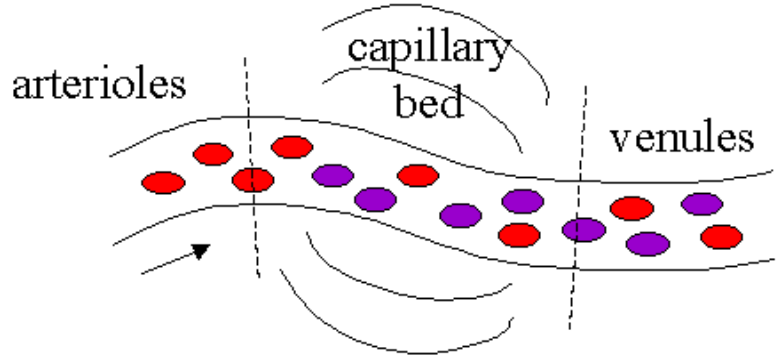


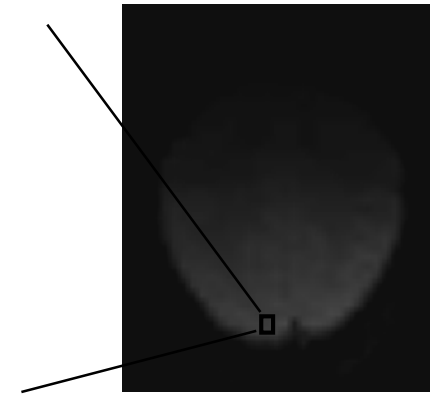
Images: Huettel, Song & McCarthy 2004, Functional Magnetic Resonance Imaging

= HbO_2
= Hbr

The BOLD contrast

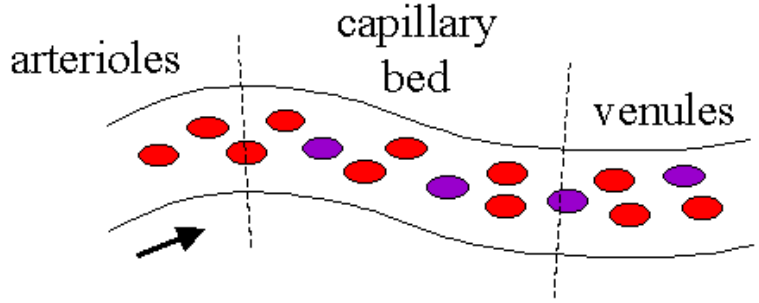
REST

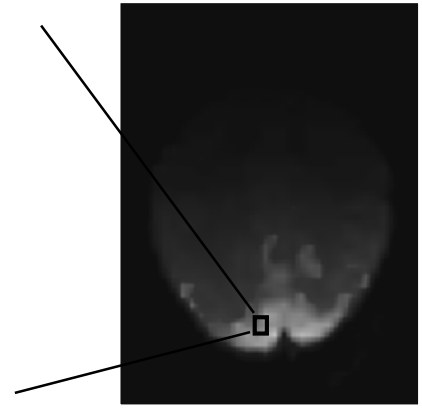




↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

ACTIVITY

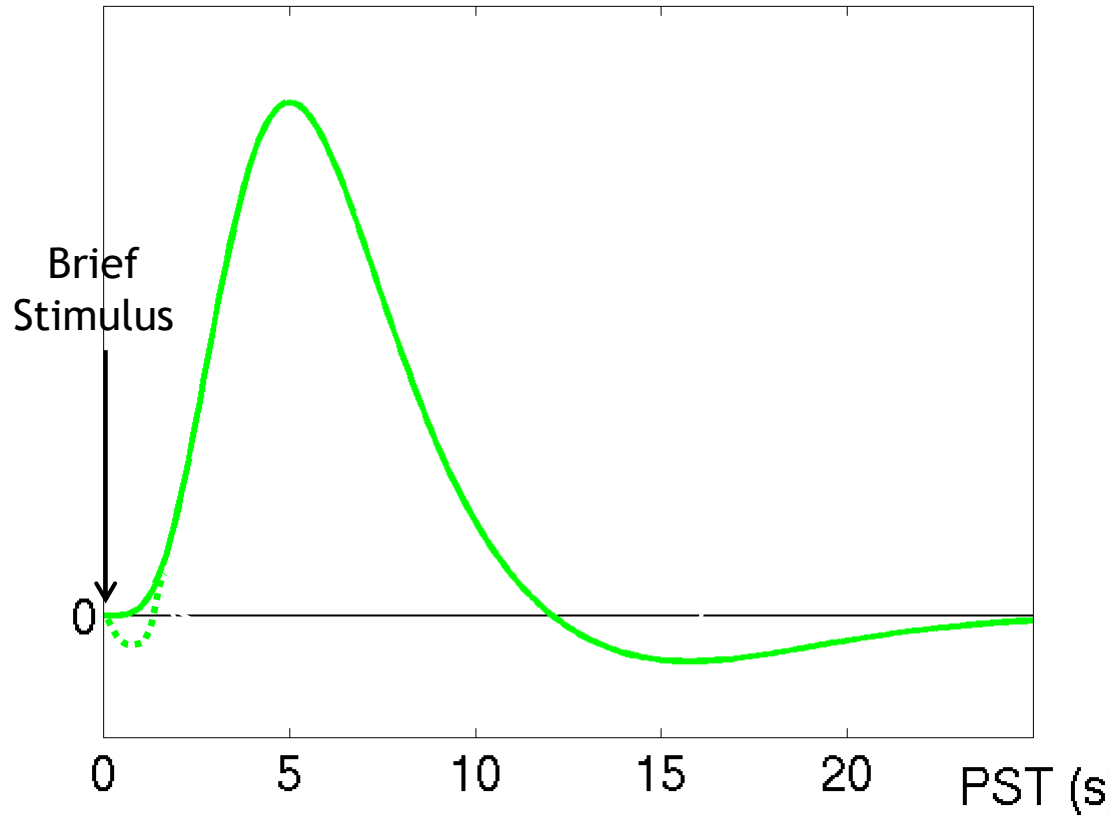




Source: Jorge Jovicich, [fMRIB Brief Introduction to fMRI]

The temporal properties of the BOLD signal

- sometimes shows initial undershoot
- peaks after 4-6 secs
- back to baseline after approx. 30 secs
- can vary between regions and subjects



Where do you think is functional MRI used in neurology?

Clinical case: Preoperative lanuage mapping in epilepsy

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

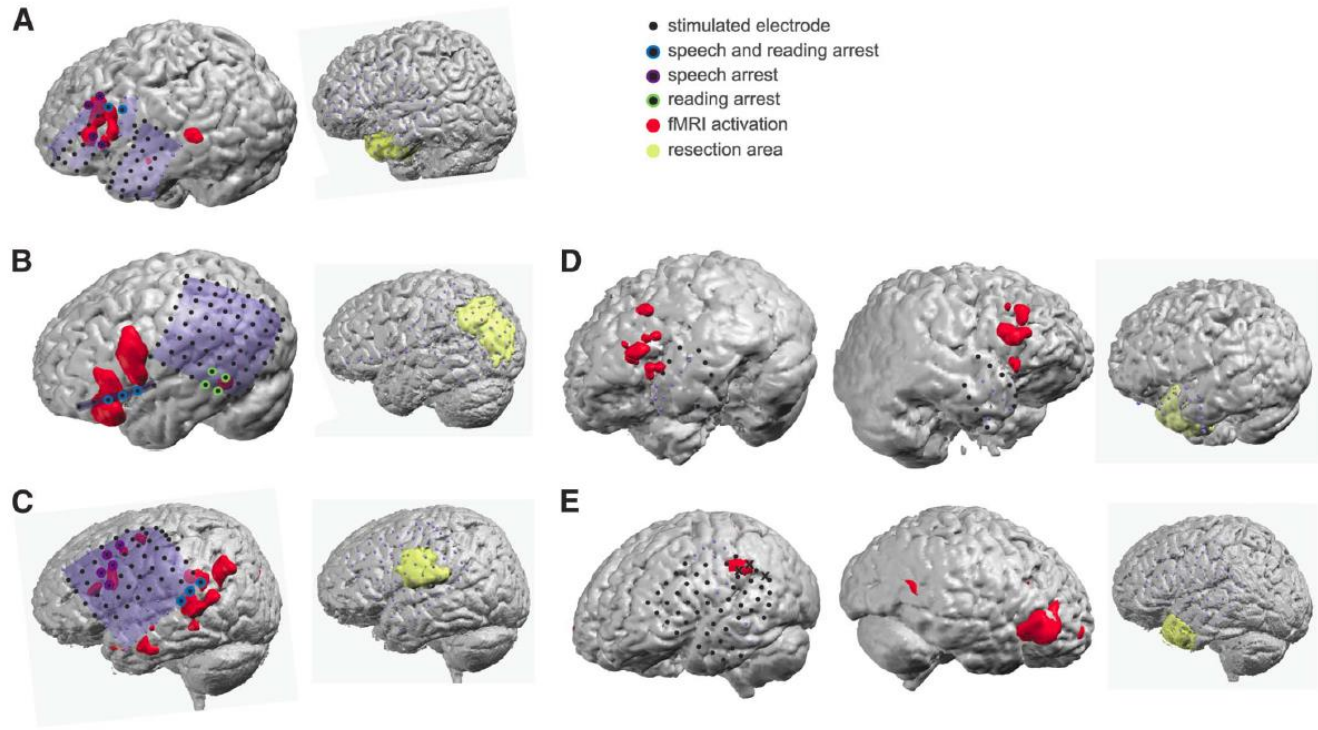
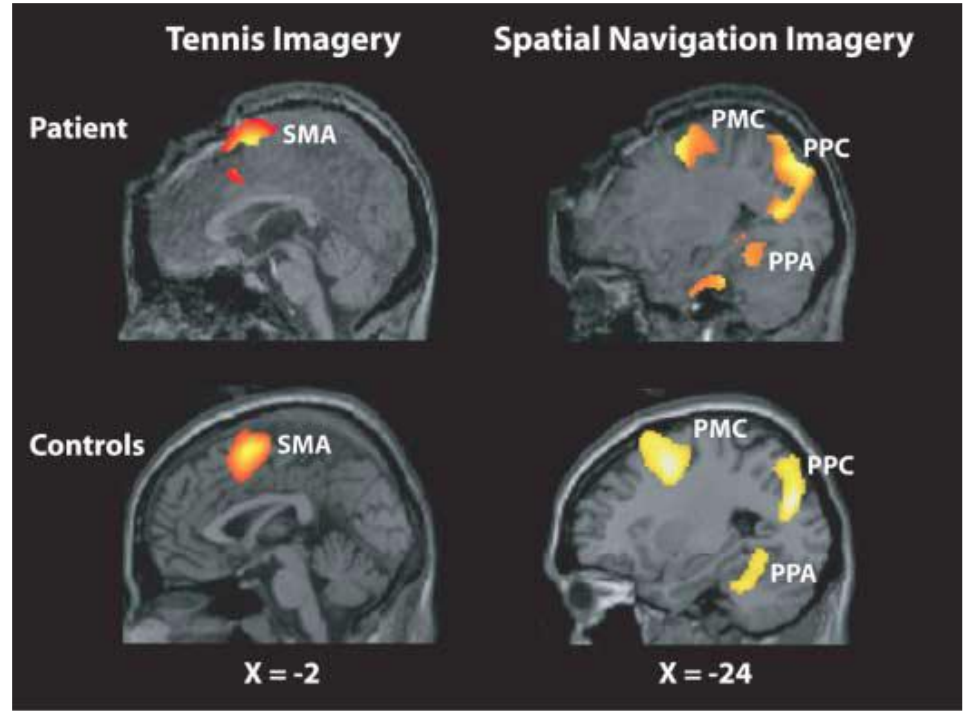


FIGURE 4. *Coregistration of fMRI activations and ECS in patient 1 (fMRI activations: P < .05, FWE-corrected) (A), patient 4 (P < .001, uncorrected) (B), patient 10 (P < .001, uncorrected) (C), patient 3 (P < .001, uncorrected) (D), and patient 8 (P < .001, uncorrected) (E). × indicates the dysfunctional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

Genetti et al. 2013, *Neurosurgery*

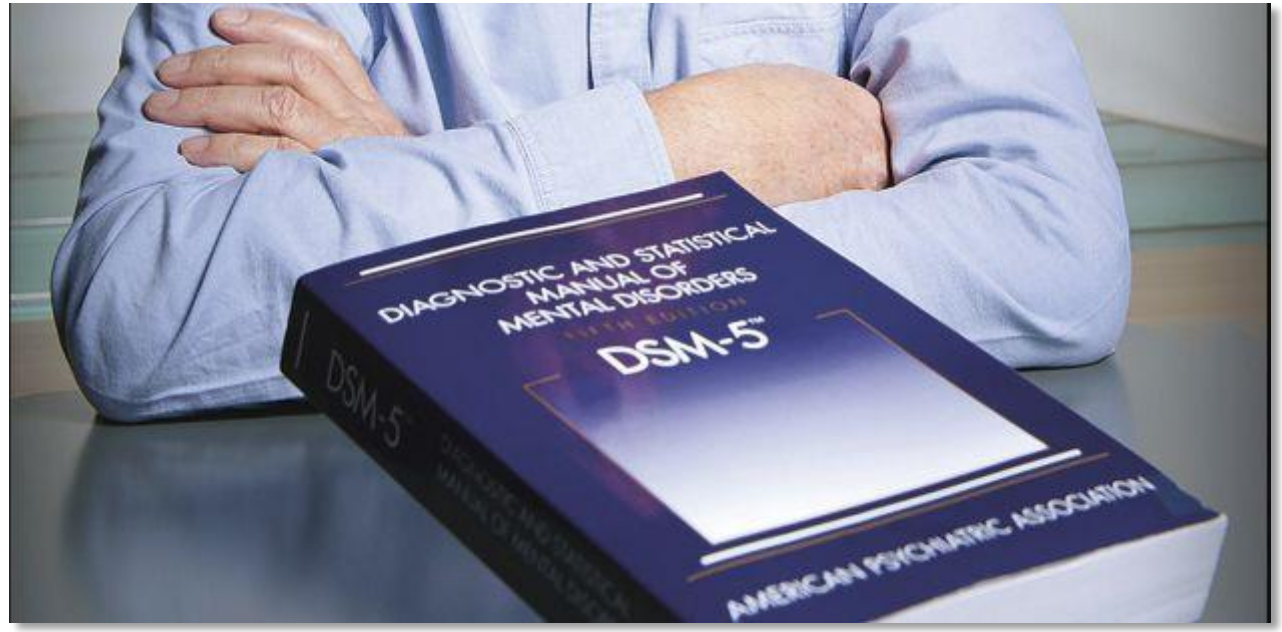
Clinical case: Detecting awareness in disorders of consciousness

- 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*

DSM/ICD

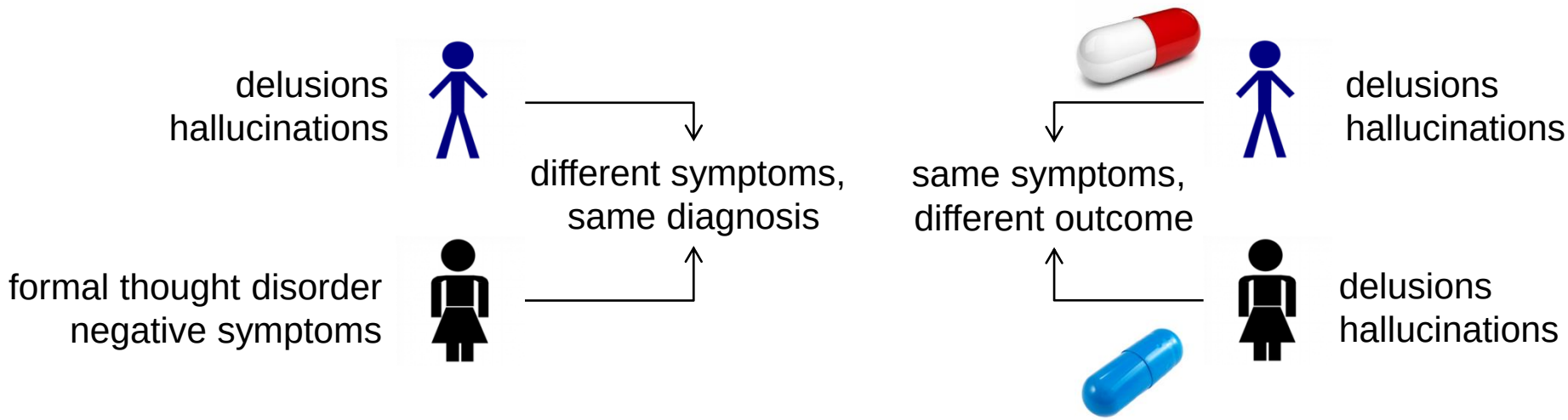

DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS
DSM-5™
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION

DSM-IV: Schizophrenia

- Delusions
- Hallucinations
- Formal thought disorder
- Grossly disorganized or catatonic behavior
- Negative symptoms: flat affect, anhedonia, avolition, alogia, asociality

≥ 2 symptoms
over ≥ 1 month

+ social or occupational dysfunction
+ continuous signs of the disturbance persist for at least six months



Psychiatric disorders = spectrum diseases

polygenetic basis

gene-environment interactions

environmental variation

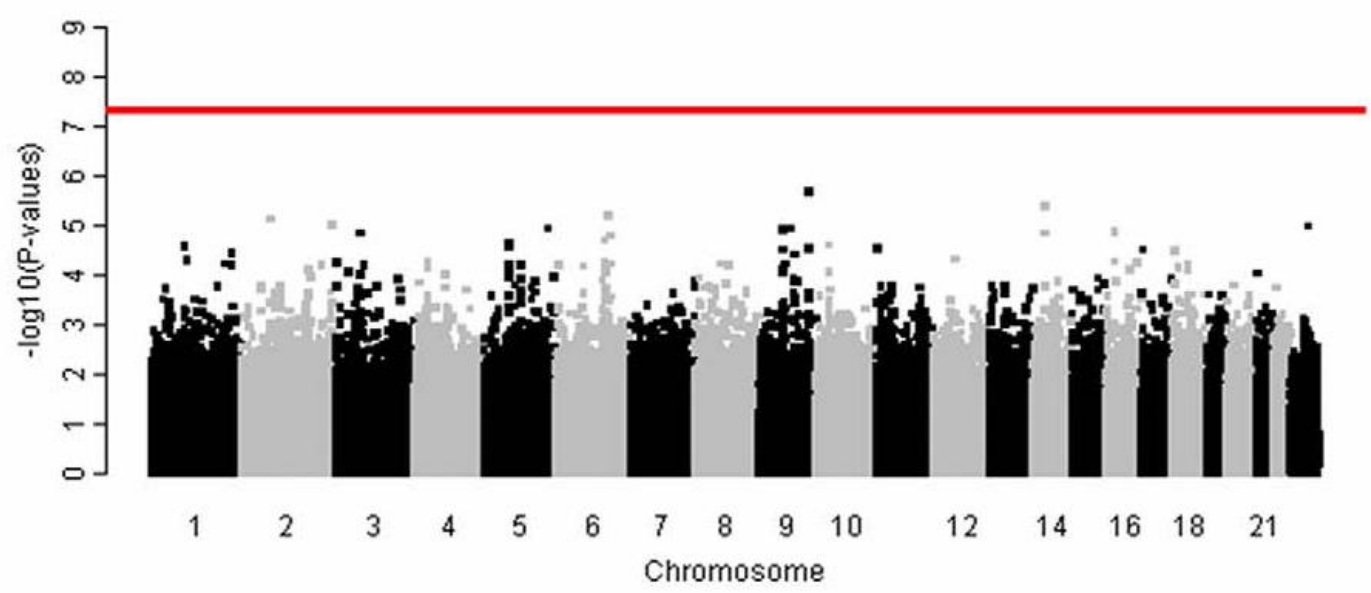
variability in clinical trajectory and treatment response

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



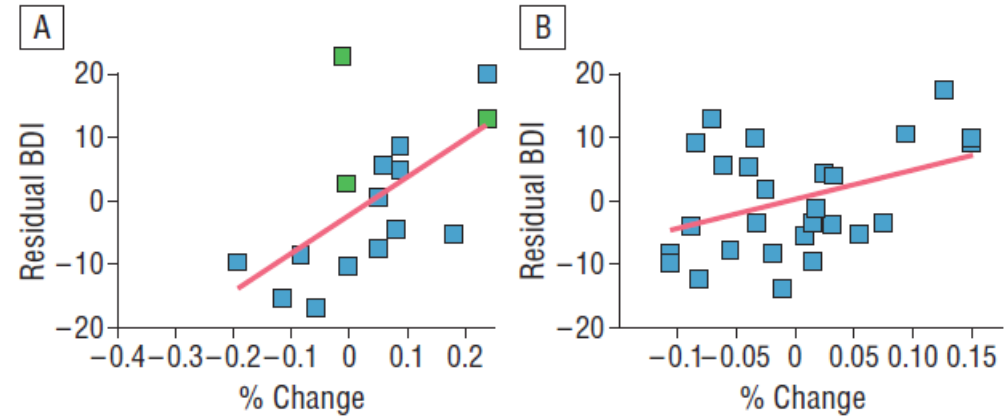
Tansey et al. 2012, *PLoS Med.* 9: e1001326

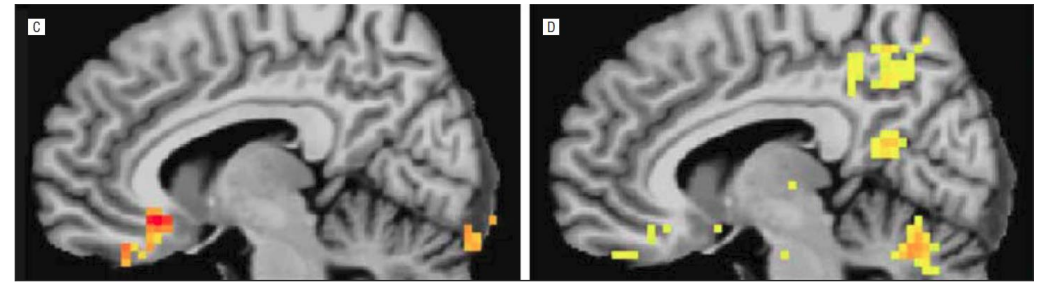
Using neuroimaging to predict treatment response

- 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%

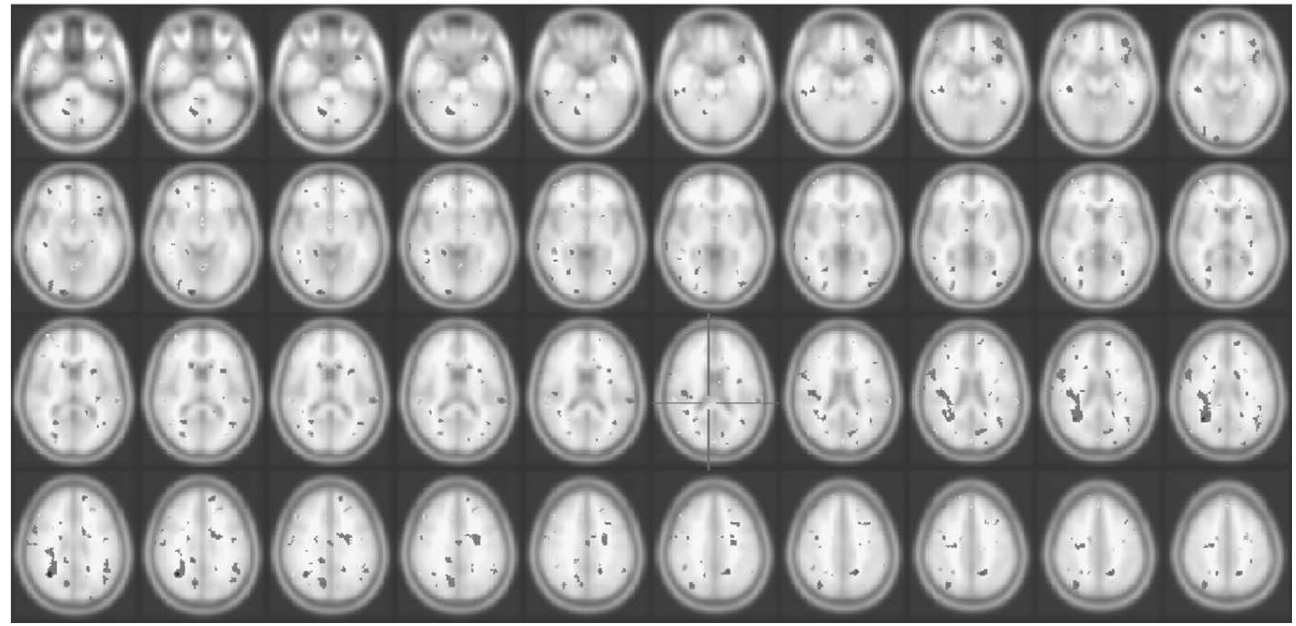




Siegle et al. 2012, *Arch. Gen. Psychiatry*

Differences in patterns of activity?

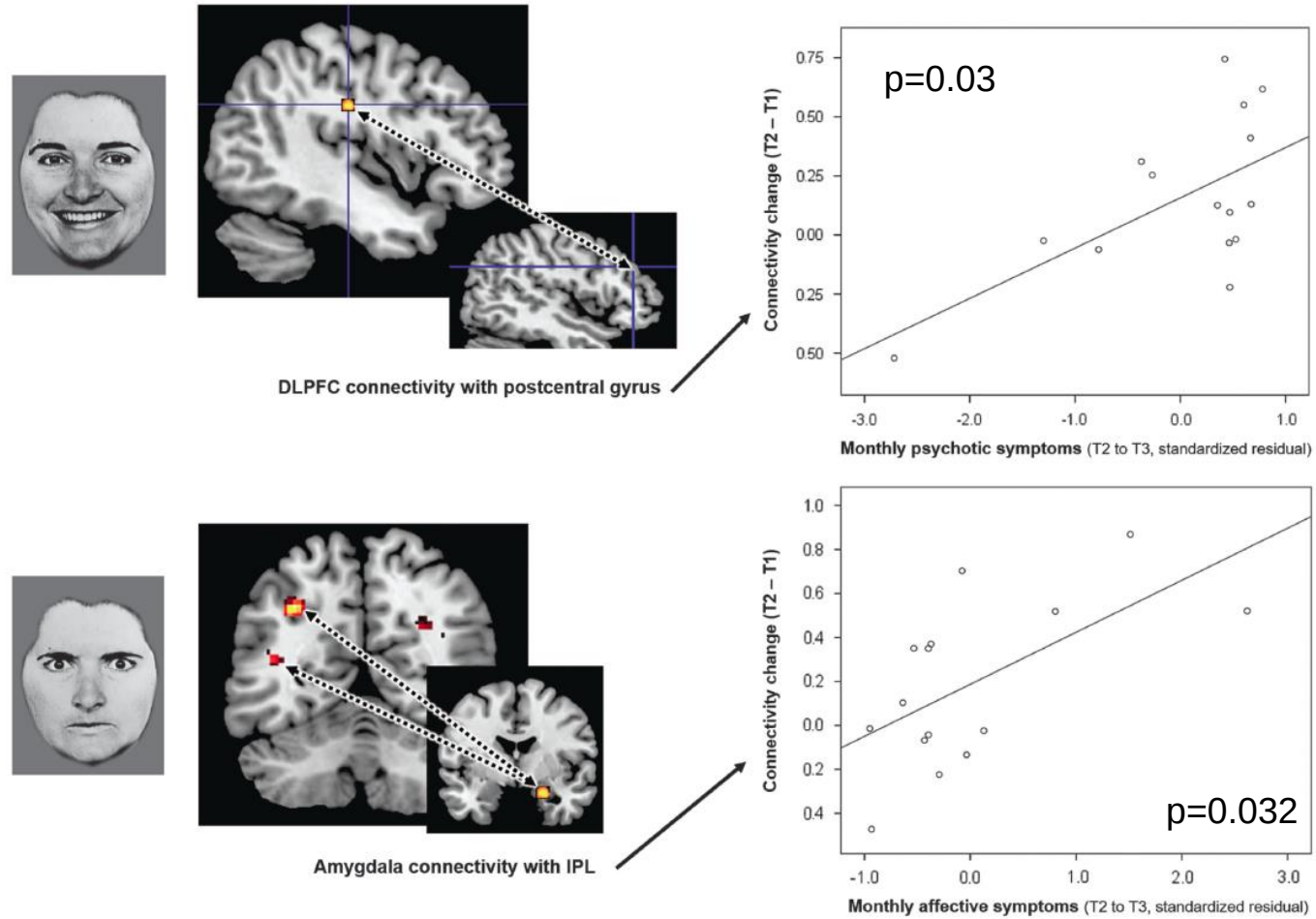
- visual presentation of sad facial expressions
- 16 medication-free patients in an acute episode of major depression, before beginning treatment with CBT
- PCA of whole-brain activity predicts clinical response to CBT (SVM, sensitivity 71%, specificity 86%)



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



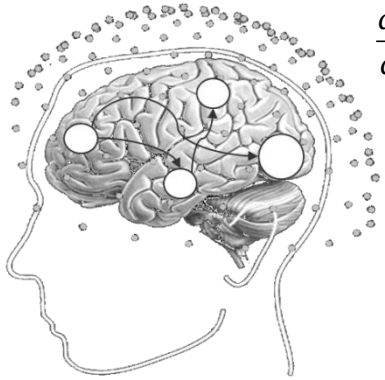
Mason et al. 2017, *Transl. Psychiatry*

But...

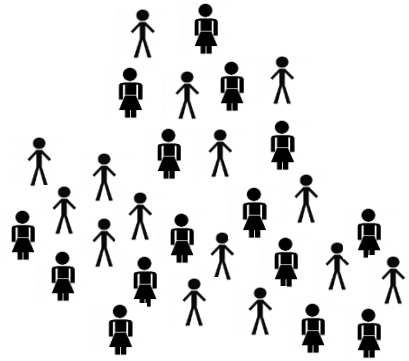
- predictions far from perfect
- no mechanistic interpretability
- no view of an emerging nosology that maps onto(patho)physiology
- how would one derive a new therapy from a demonstrated prediction of treatment response?

Translational Neuromodeling

❶ Computational assays: Models of disease mechanisms

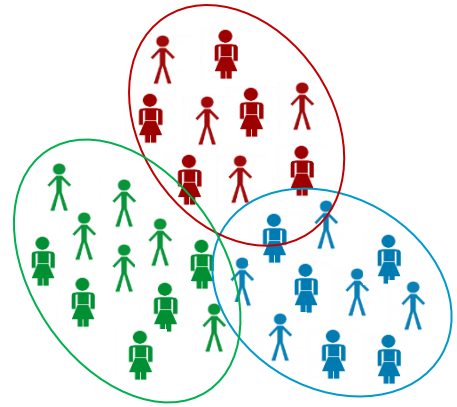


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



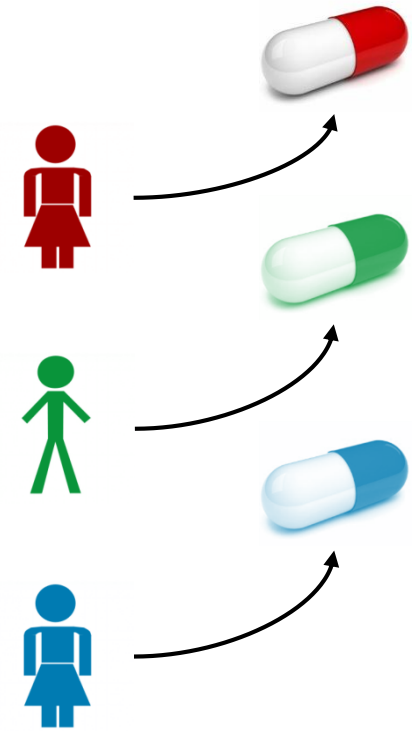
❷ Application to brain activity and behaviour of individual patients

❸ Detecting physiological subgroups (based on inferred mechanisms)



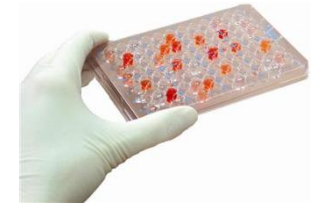
- disease mechanism A
- disease mechanism B
- disease mechanism C

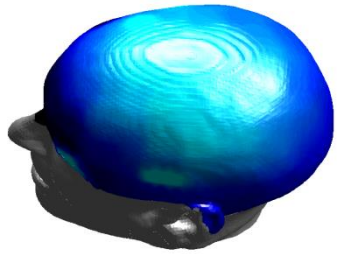
❹ Individual treatment prediction



Stephan et al. 2015, *Neuron*

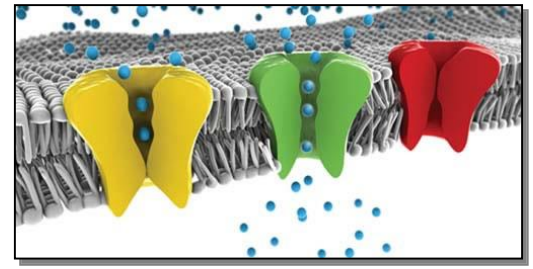
Generative models as "computational assays"

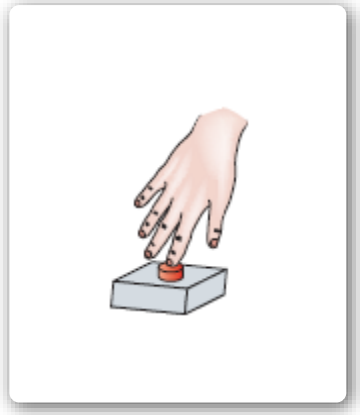




$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

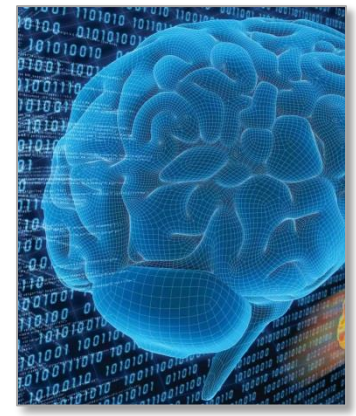
$$p(\theta \mid y, m)$$

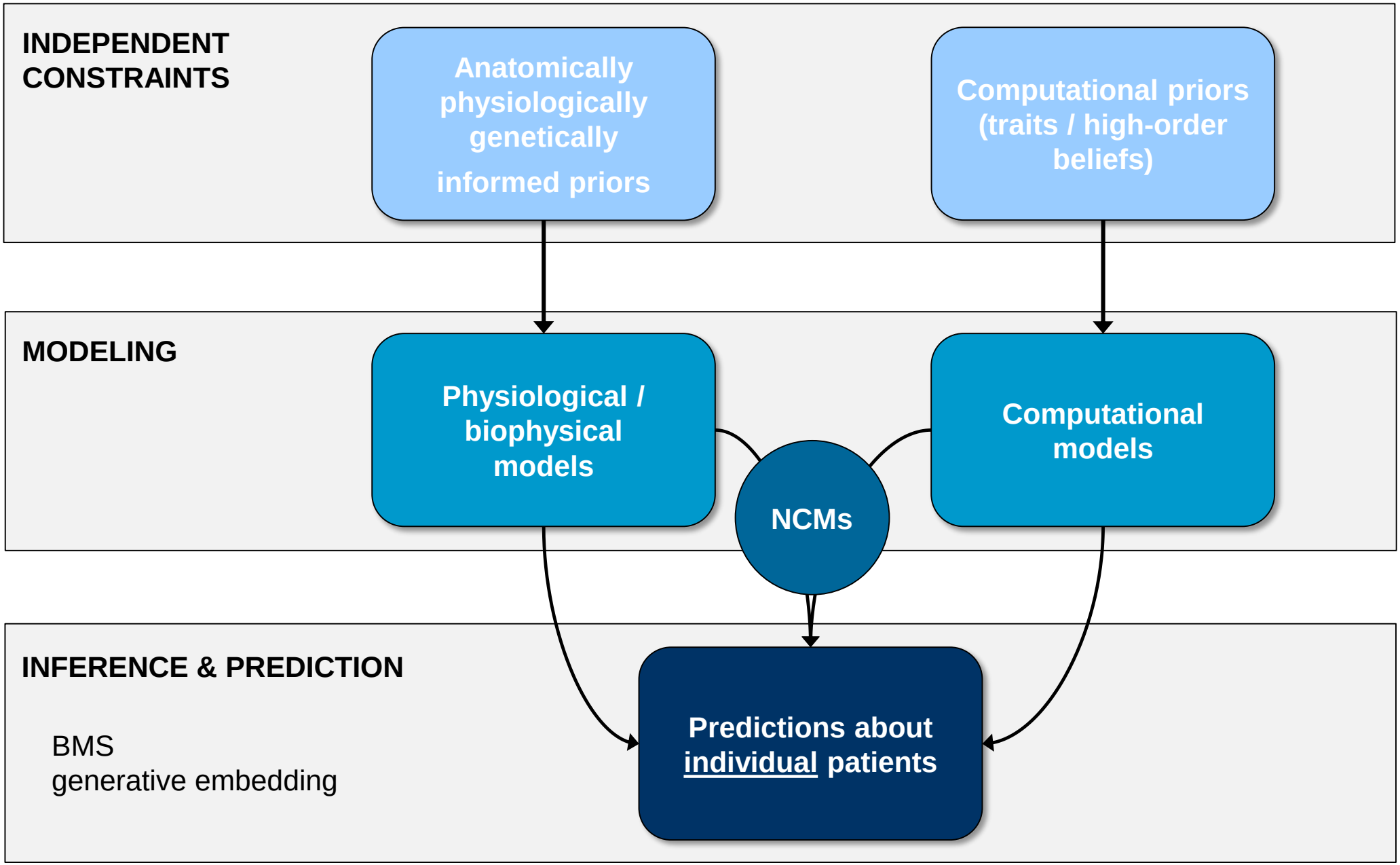


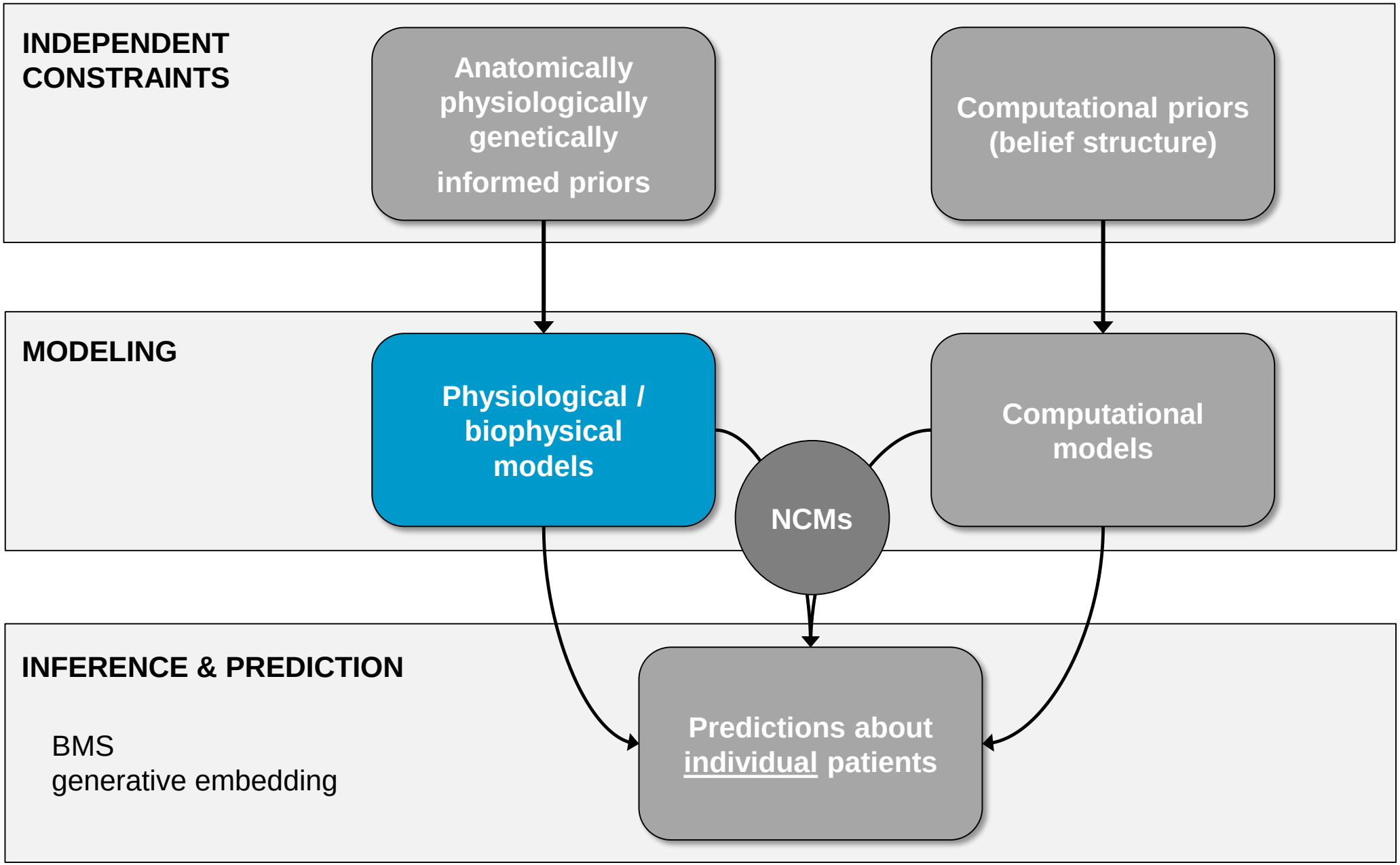


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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



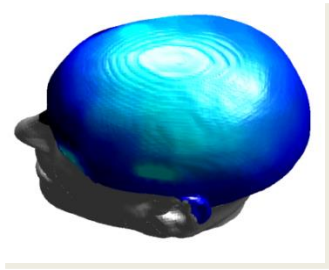

INDEPENDENT CONSTRAINTS
Anatomically physiologically genetically informed priors
Computational priors (traits / high-order beliefs)
MODELING
Physiological / biophysical models
NCMs
Computational models
INFERENCE & PREDICTION
BMS
generative embedding
Predictions about individual patients

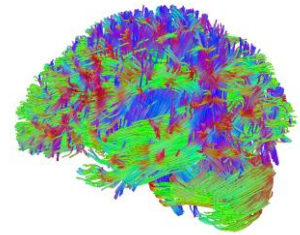

INDEPENDENT CONSTRAINTS
Anatomically physiologically genetically informed priors
Computational priors (belief structure)
MODELING
Physiological / biophysical models
NCMs
Computational models
INFERENCE & PREDICTION
BMS
generative embedding
Predictions about individual patients

Dynamic causal modeling (DCM)

dwMRI

EEG, MEG

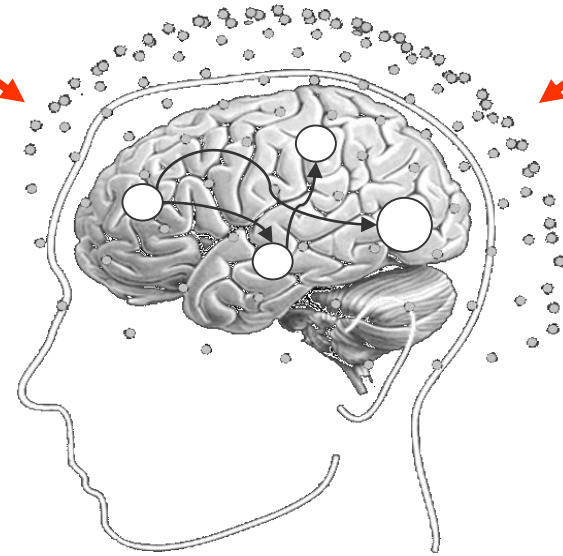




fMRI

structural priors

structural priors



Forward model:
Predicting measured activity

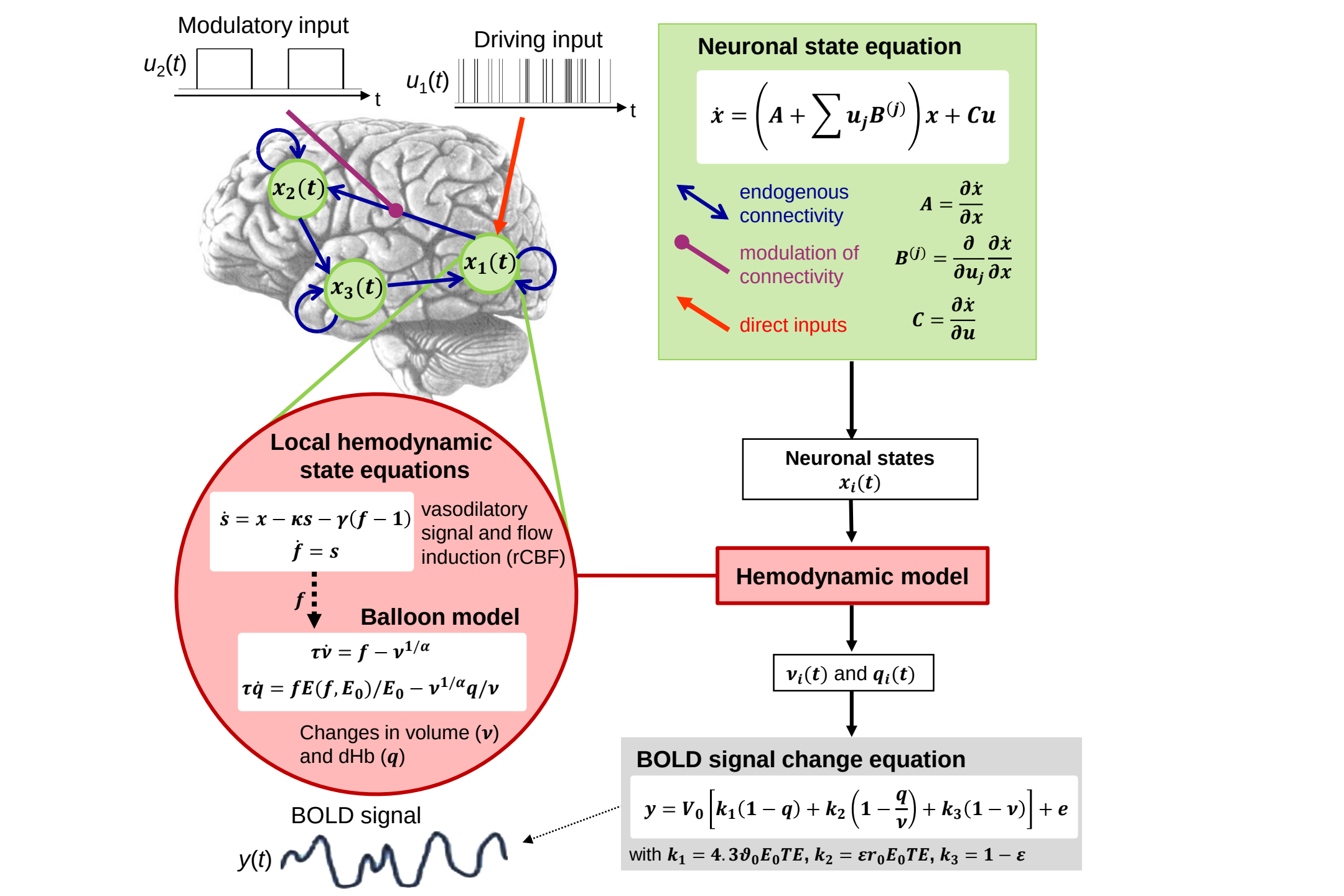
$$y = g(x,\theta) + \varepsilon$$

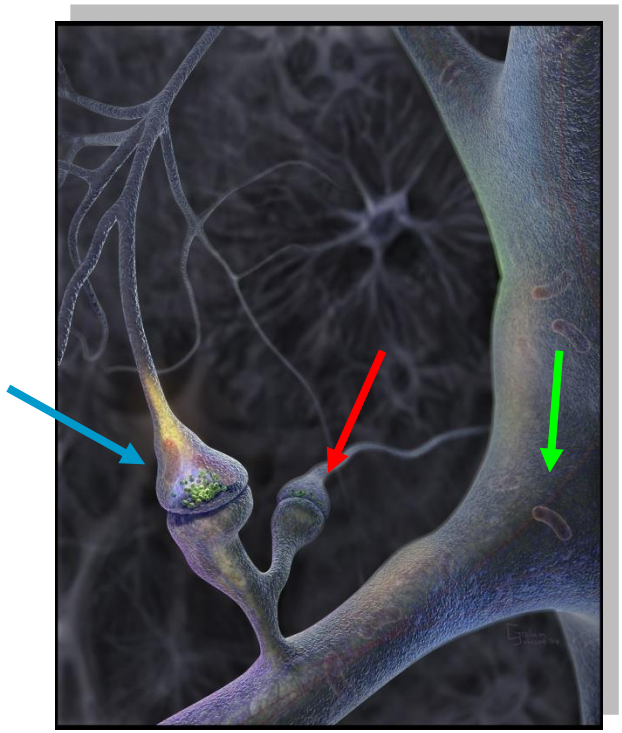
Model inversion:
Estimating neuronal mechanisms

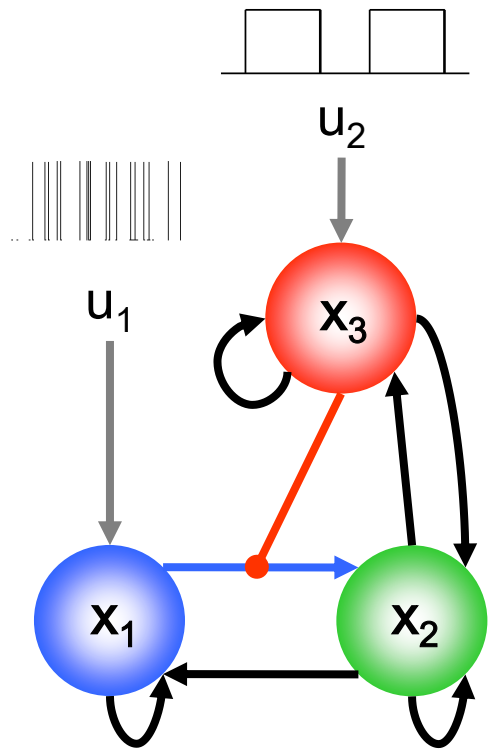
$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$

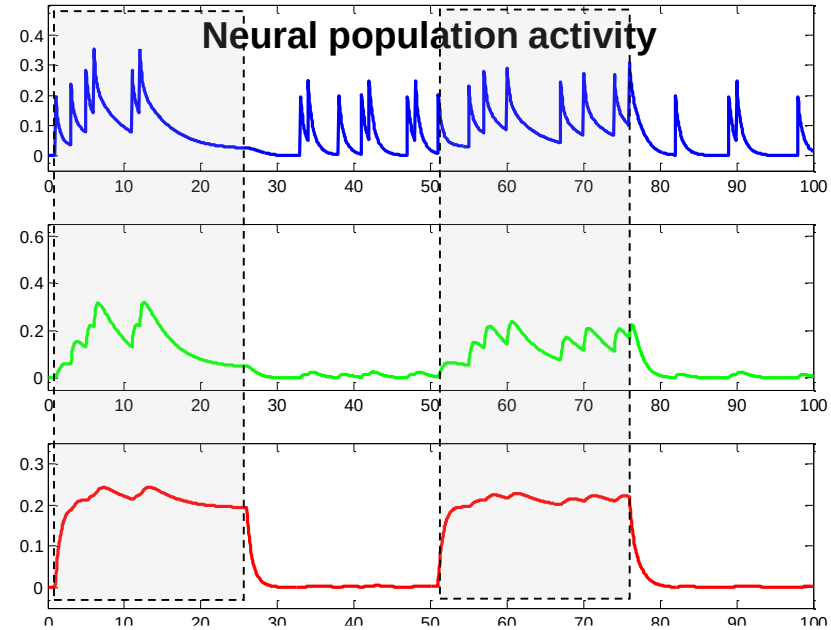
Friston et al. 2003, *NeuroImage*

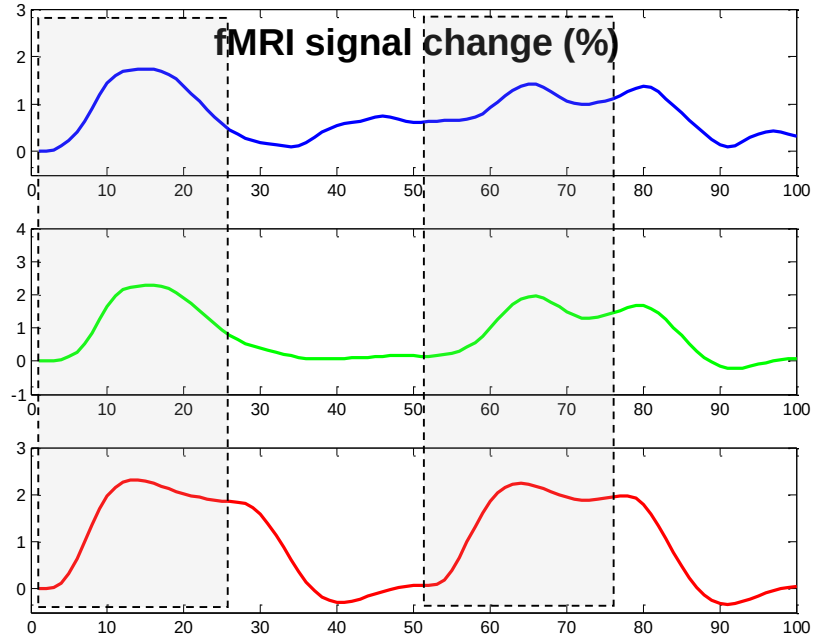
Stephan et al. 2009, *NeuroImage*


Modulatory input
$u_2(t)$
t
Driving input
$u_1(t)$
t
$x_2(t)$
$x_3(t)$
$x_1(t)$
Neuronal state equation
$\dot{x} = \left(A + \sum u_j B^{(j)}\right) x + Cu$
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
$C = \frac{\partial \dot{x}}{\partial u}$
Local hemodynamic state equations
$\dot{s} = x - \kappa s - \gamma(f - 1)$
$\dot{f} = s$
vasodilatory signal and flow induction (rCBF)
f
Balloon model
$\tau \dot{v} = f - v^{1/\alpha}$
$\tau \dot{q} = fE(f, E_0)/E_0 - v^{1/\alpha} q/v$
Changes in volume (v) and dHb (q)
Neuronal states $x_i(t)$
Hemodynamic model
$v_i(t)$ and $q_i(t)$
BOLD signal change equation
$y = V_0 \left[k_1(1 - q) + k_2\left(1 - \frac{q}{v}\right) + k_3(1 - v)\right] + e$
with $k_1 = 4.3\vartheta_0 E_0 TE$, $k_2 = \varepsilon r_0 E_0 TE$, $k_3 = 1 - \varepsilon$
BOLD signal
$y(t)$





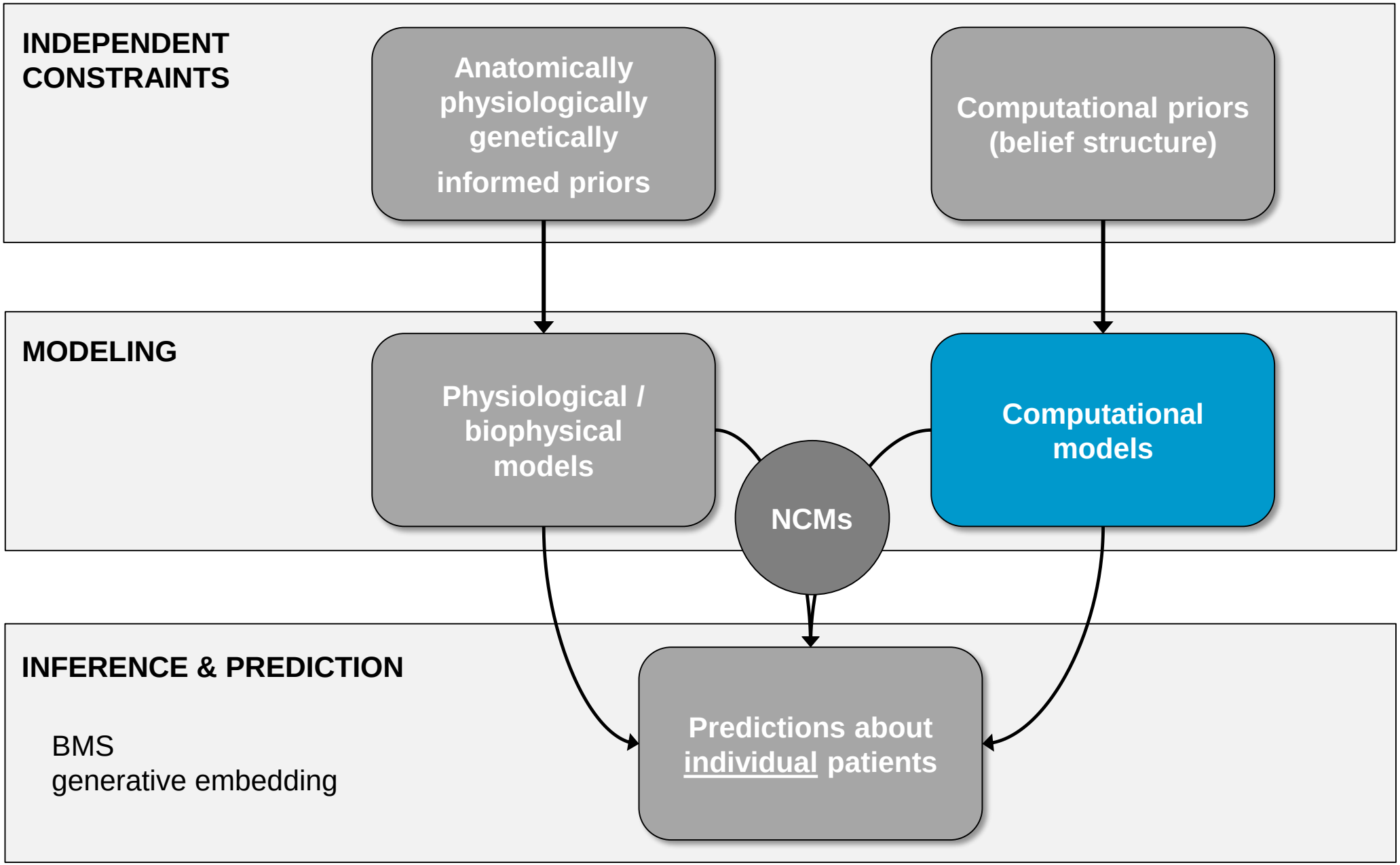




Nonlinear Dynamic Causal Model for fMRI

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

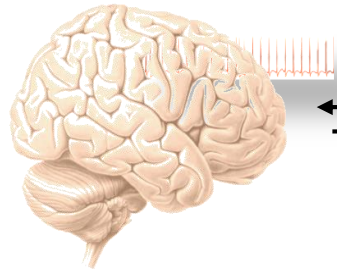
Stephan et al. 2008, *NeuroImage*


INDEPENDENT CONSTRAINTS
Anatomically physiologically genetically informed priors
Computational priors (belief structure)
MODELING
Physiological / biophysical models
NCMs
Computational models
INFERENCE & PREDICTION
BMS
generative embedding
Predictions about individual patients

Perception = inversion of a hierarchical generative model

neuronal states

environm. states
others' mental states
bodily states



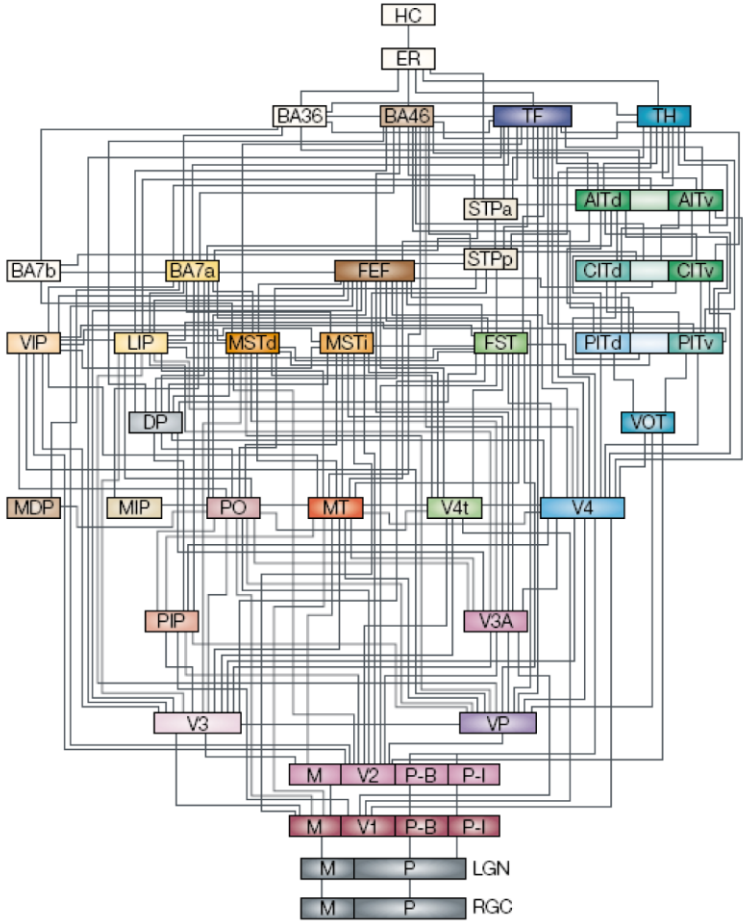
forward model

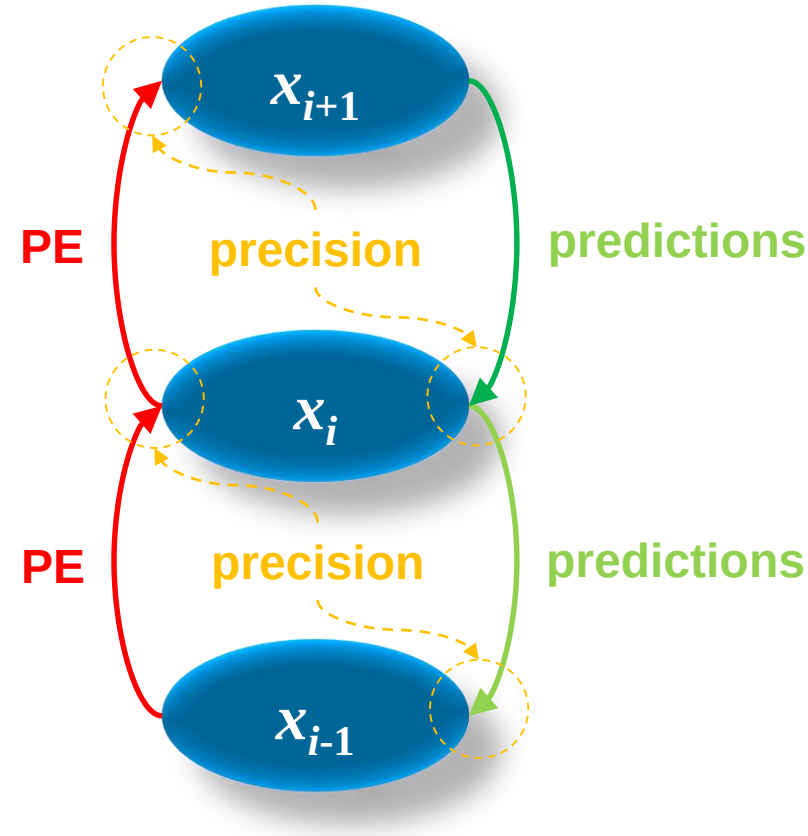
$$p(y \mid x, m) \cdot p(x \mid m)$$

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

perception

Anatomical hierarchies and predictive coding

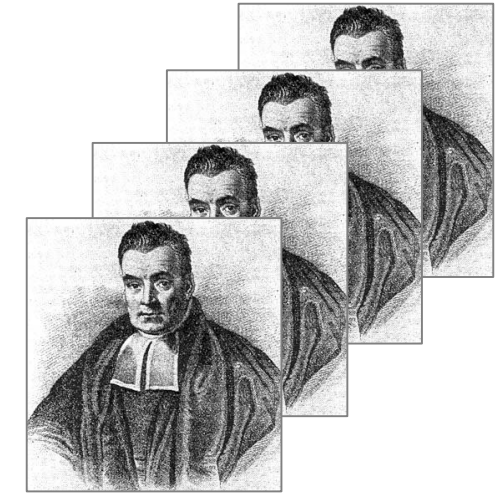




Felleman & Van Essen 1991, *Cerebral Cortex*

.

Hierarchical Gaussian Filter (HGF)

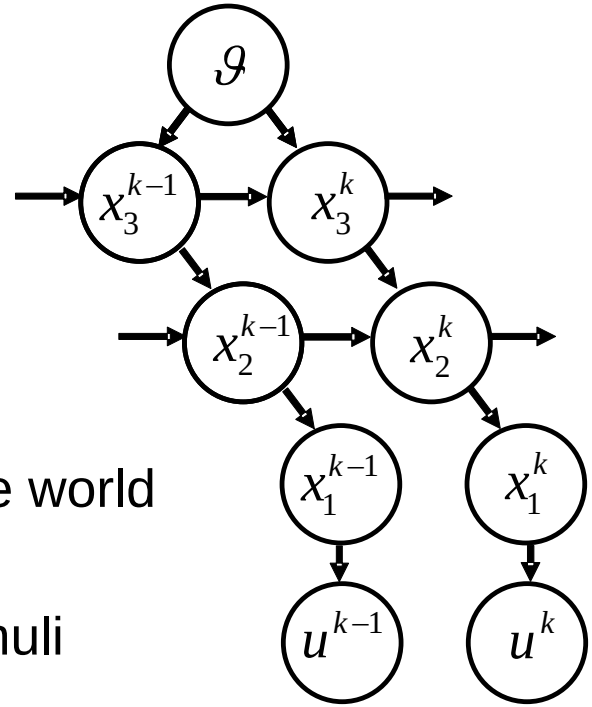


volatility

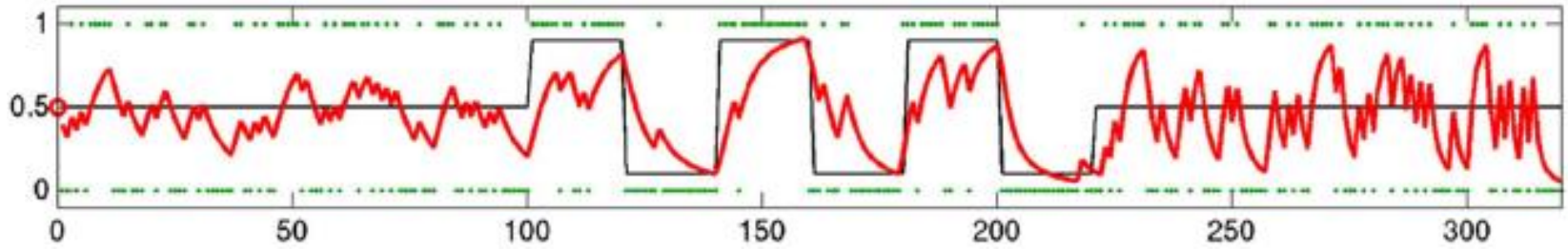
association

events in the world

sensory stimuli



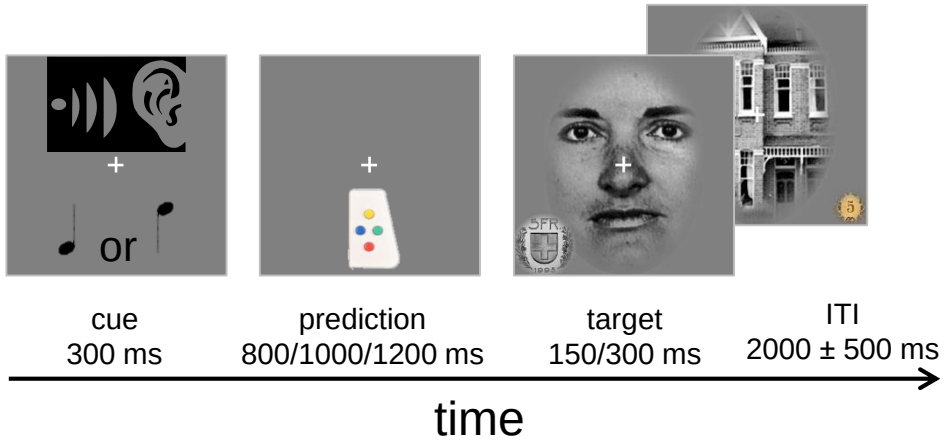
$\Delta\text{belief} \propto \text{precision} \times \text{PE}$

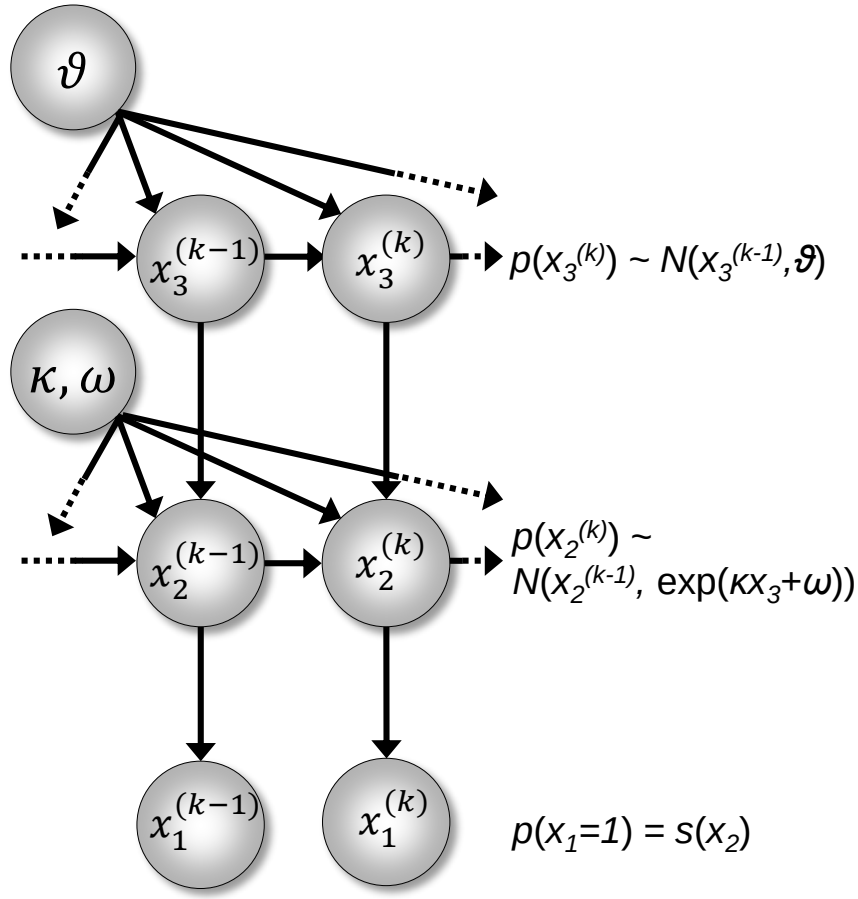


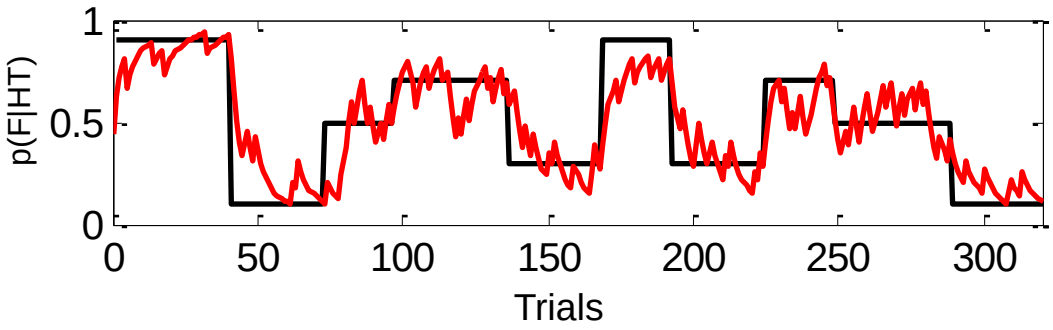
Mathys et al. 2014, *Front. Hum. Neurosci.*

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

Hierarchical prediction errors (PEs) in sensory learning

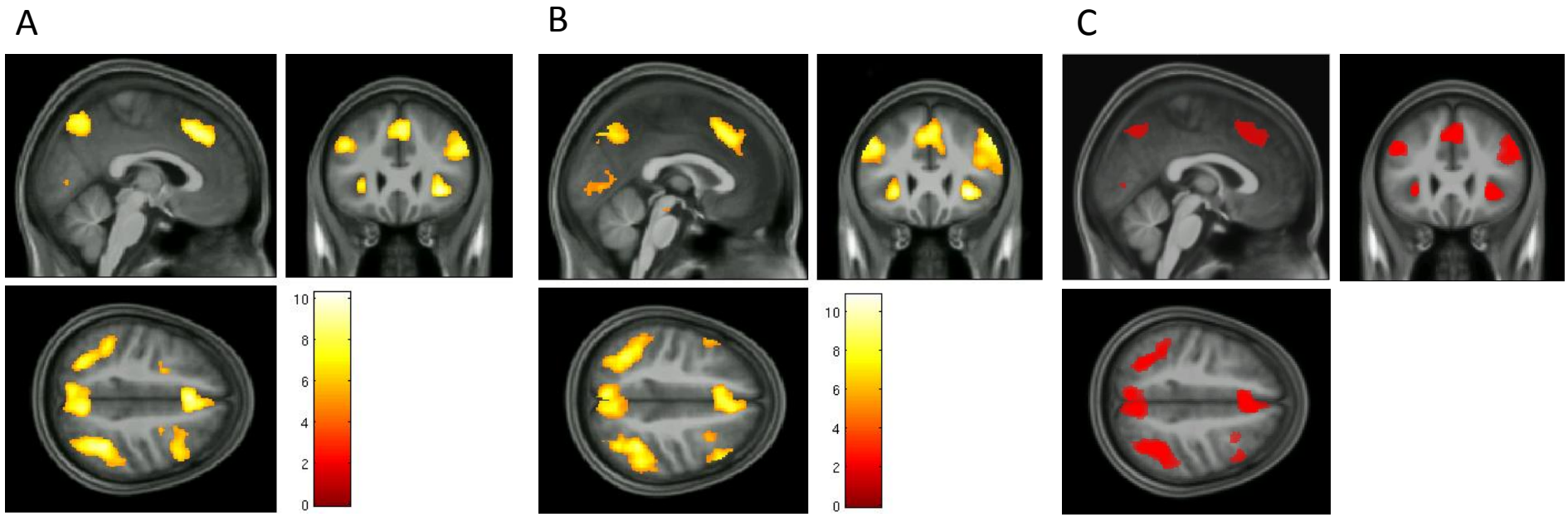






Iglesias et al. 2013, *Neuron*

Sensory precision-weighted PEs (pwPEs)



first fMRI study
(N=45)

second fMRI study
(N=27)

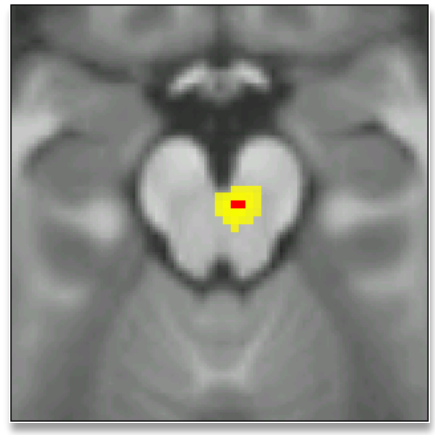
conjunction across studies

p<0.05 FWE whole-brain corrected

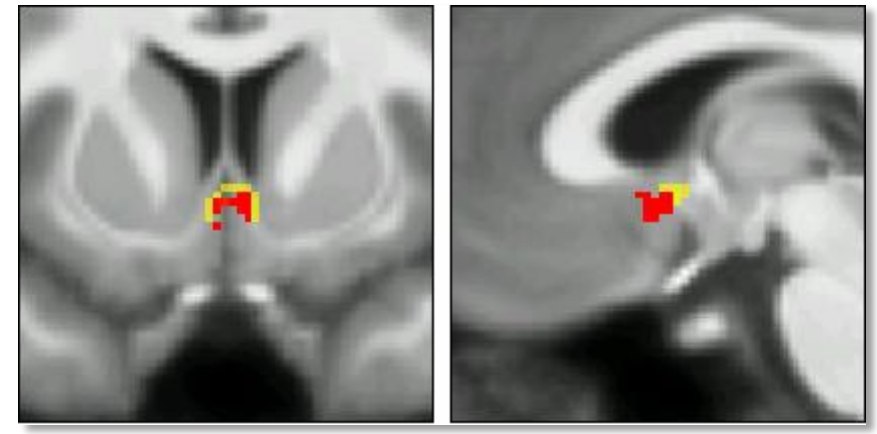
Iglesias et al. 2013, *Neuron*

Hierarchical precision-weighted PEs in sensory learning

Study 1: N=48

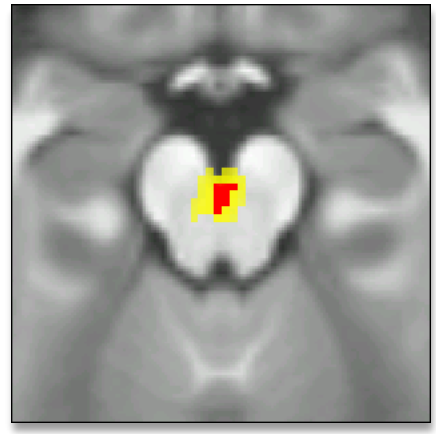


Outcome PEs in VTA/SN

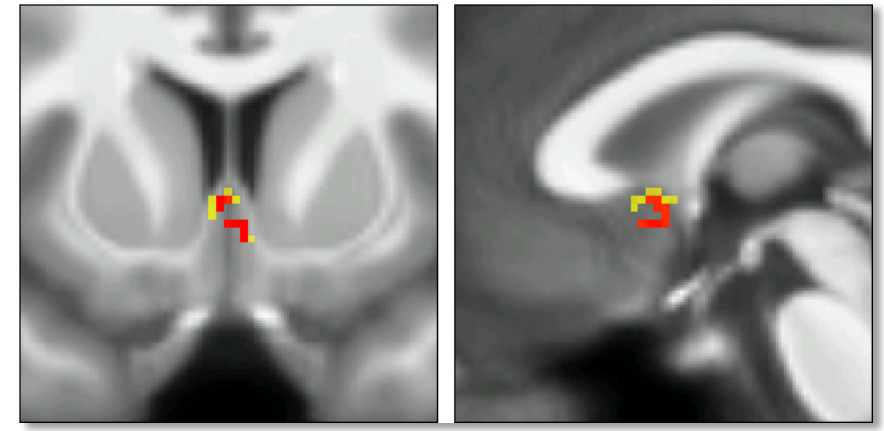


Probability PEs in basal forebrain

Study 2: N=27



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



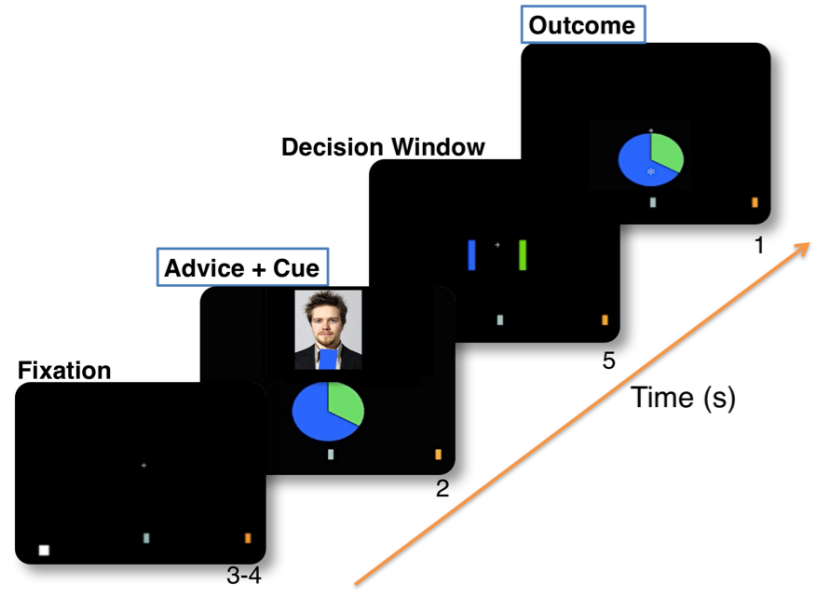
p<0.05, SVC FWE corrected
p<0.001, uncorrected

Iglesias et al. 2013, *Neuron*

Hierarchical PEs during social learning

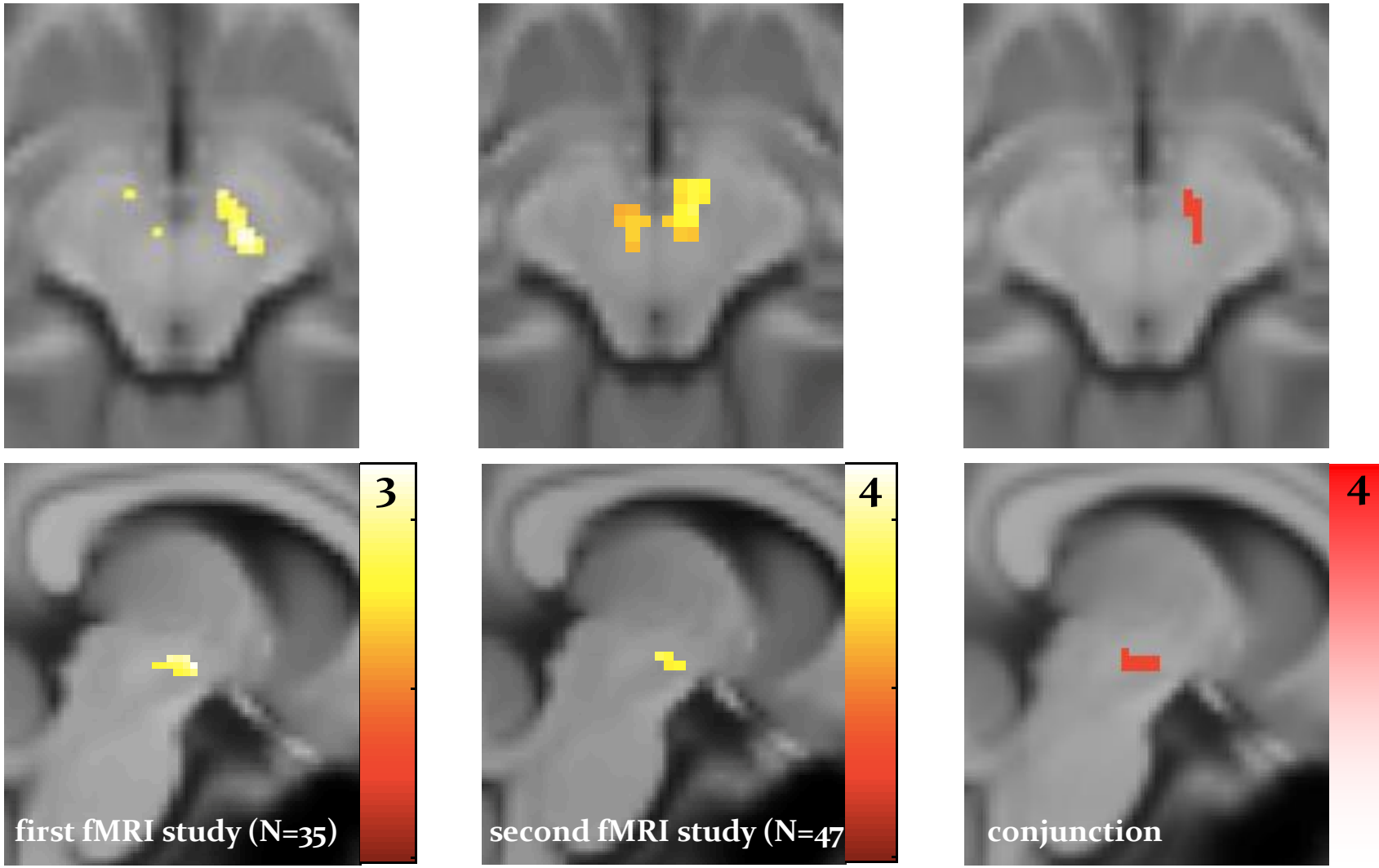
A.

B.



Diaconescu et al., *in preparation*

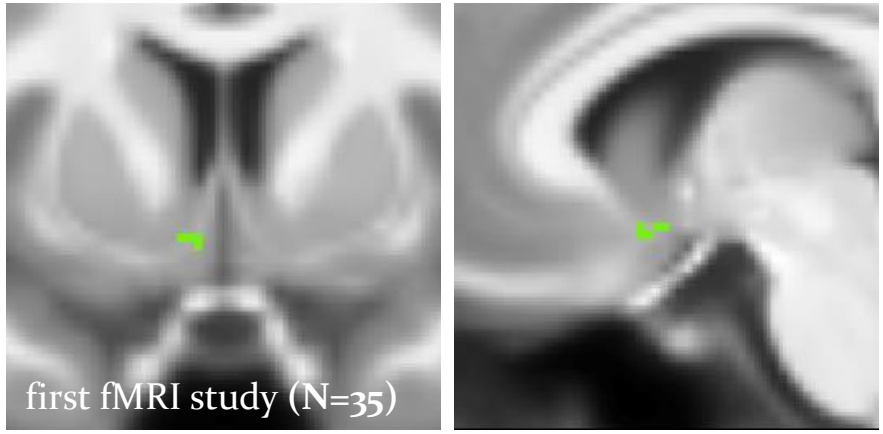
Precision-weighted advice PEs (ε_2)

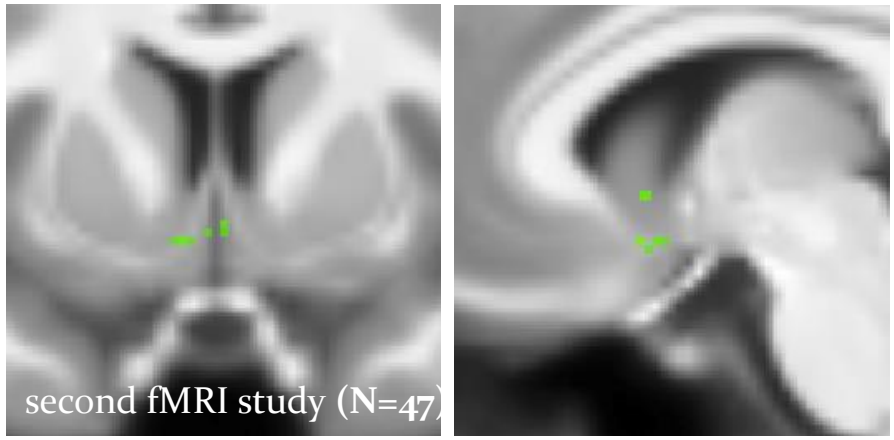


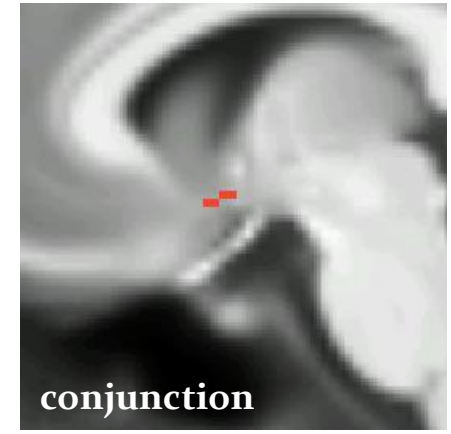
p<0.05, FWE corrected for joint midbrain/BF mask

Diaconescu et al., *in preparation*

Precision-weighted PEs about adviser fidelity (ε_3)







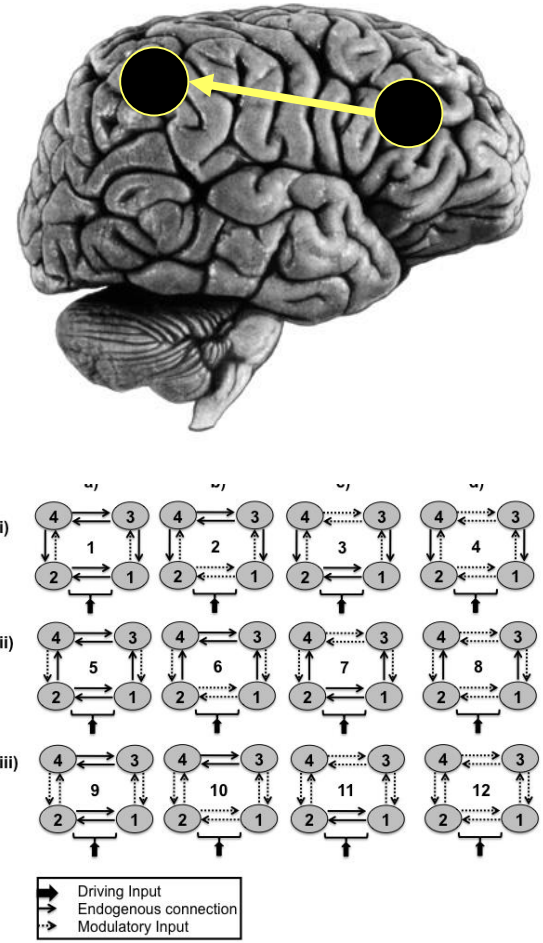
p<0.05, FWE corrected for joint midbrain/BF mask

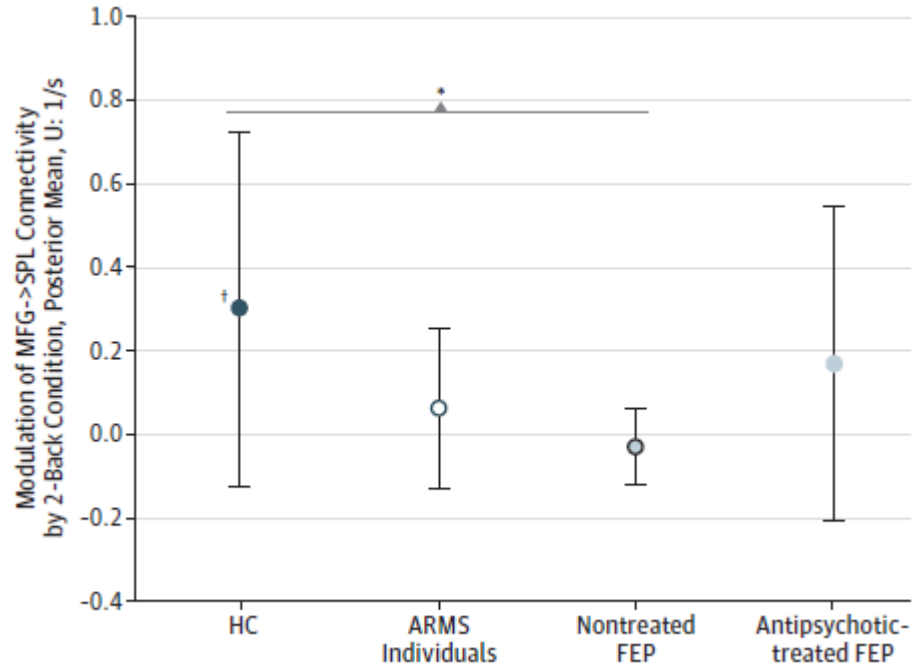
Diaconescu et al., *in preparation*

At-risk mental state (ARMS)

- construct pertaining to the pre-psychotic phase, before a formal diagnosis
- presence of either
  - attenuated psychotic symptoms,
  - brief and self-limiting psychotic symptoms (BLIPS), or
  - significant reduction of function under a family history of schizophrenia
- of major interest for clinical management ("prodromal schizophrenia")
  - early detection
  - possible prevention by early treatment?

Prefrontal-parietal connectivity during working memory in schizophrenia





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

Schmidt et al. 2013, *JAMA Psychiatry*

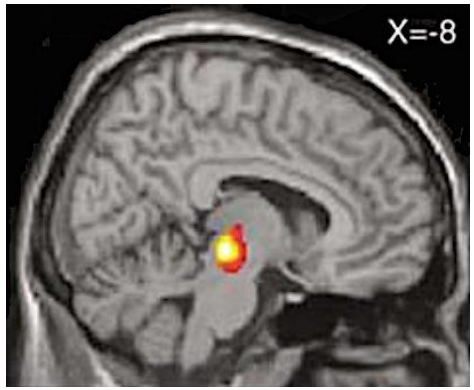
Aberrant salience

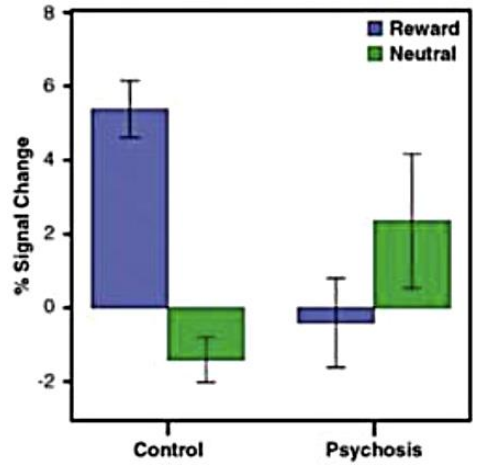
- Kapur (2003): attribution of “aberrant salience” to irrelevant events as the starting point of delusion formation

- linked to abnormal phasic dopamine (DA) release
  - "chaotic" or "mistimed" PE signals that triggers maladaptive (NMDAR) dependent plasticity and shifts high-order beliefs
  - prediction: abnormal PE responses to irrelevant/neutral events in midbrain and/or dopaminoceptive regions

Aberrant salience in schizophrenia

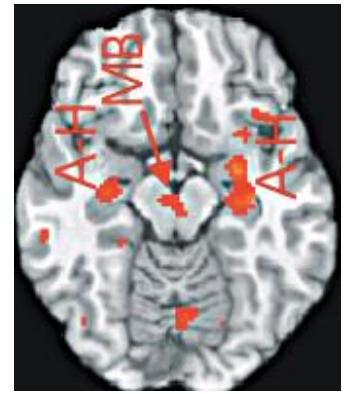
A.

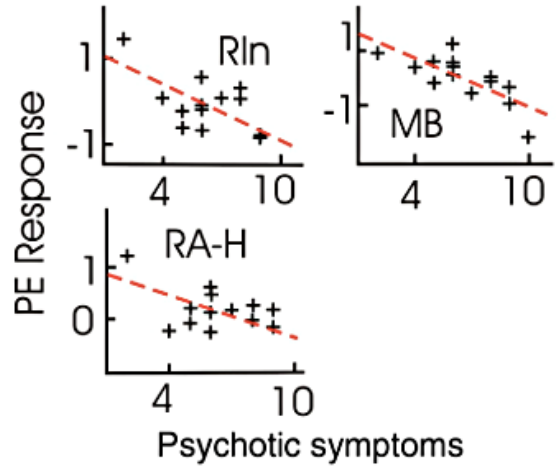




Murray et al. 2008, *Mol. Psychiatry*

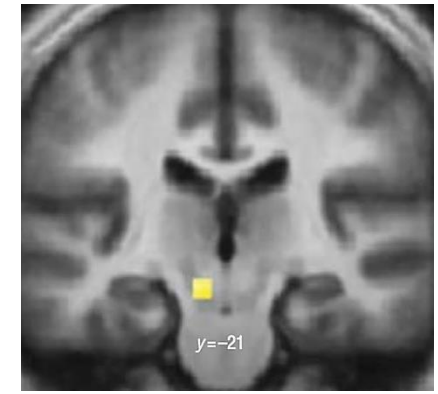
B.

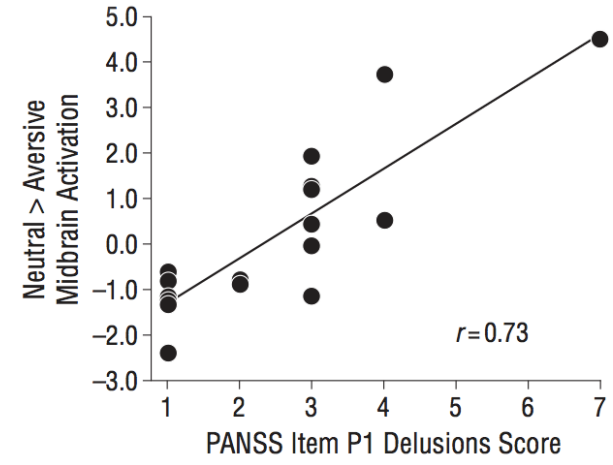




Gradin et al. 2011, *Brain*

C.





Romaniuk et al. 2008, *Archiv. Gen. Psychiatry*

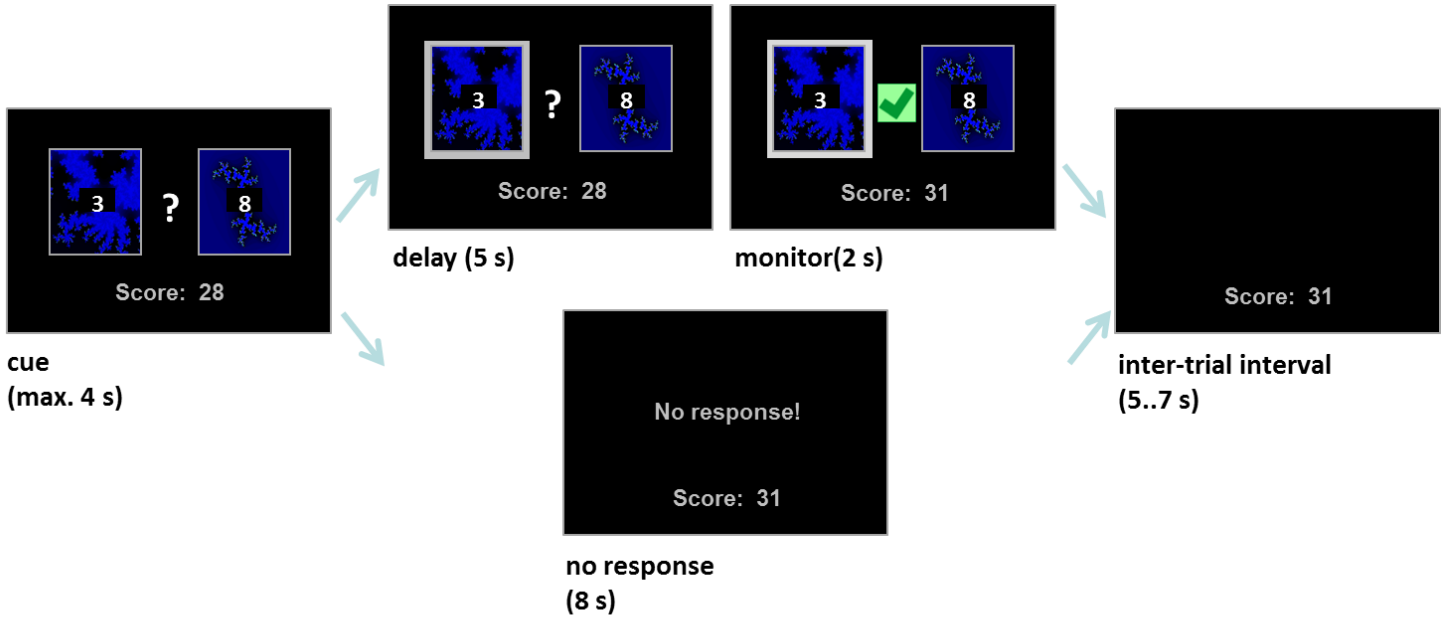
Aberrant salience

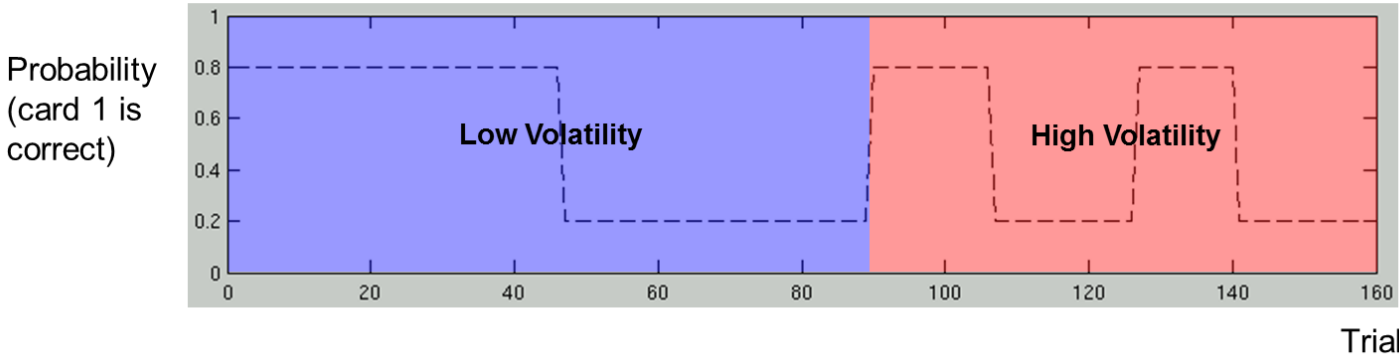
- several limitations of previous studies:
  - vague concept of “salience”, should be defined in terms of precision of PEs

$$\Delta\mu_i \propto \frac{\hat{\pi}_{i-1}}{\pi_i} PE_{i-1}$$

  - studies restricted to patients with fully developed disease (not at beginning of delusion formation)
  - "(ir)relevance" of events defined in a static experimental frame of reference

Aberrant salience and hierarchical inference in ARMS

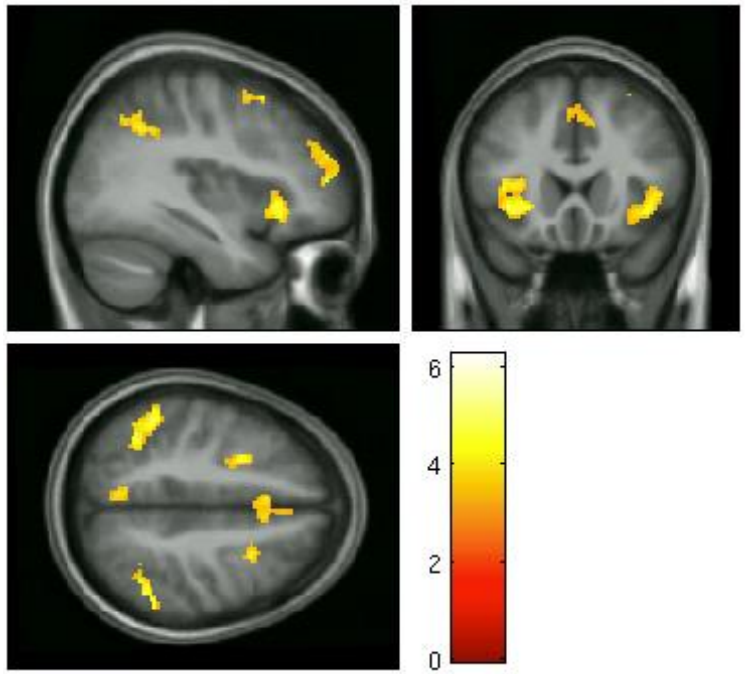




Cole et al., *in preparation*

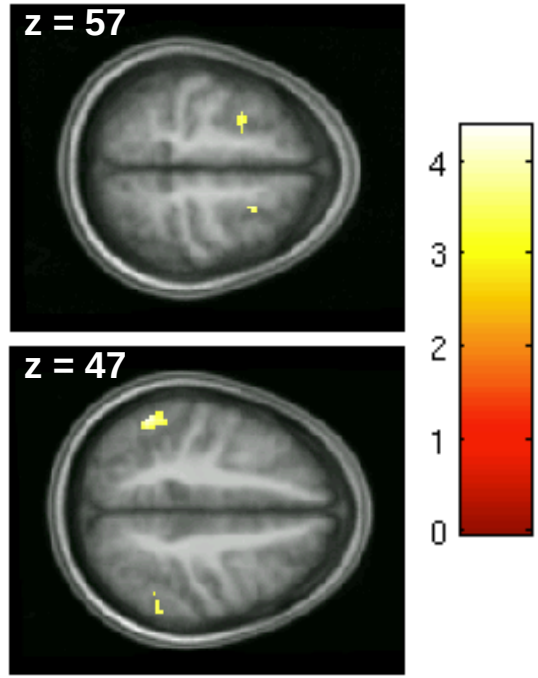
Aberrant salience (enhanced ε_2) in prodromal schizophrenia

Outcome pwPE (ε_2) pooled across groups



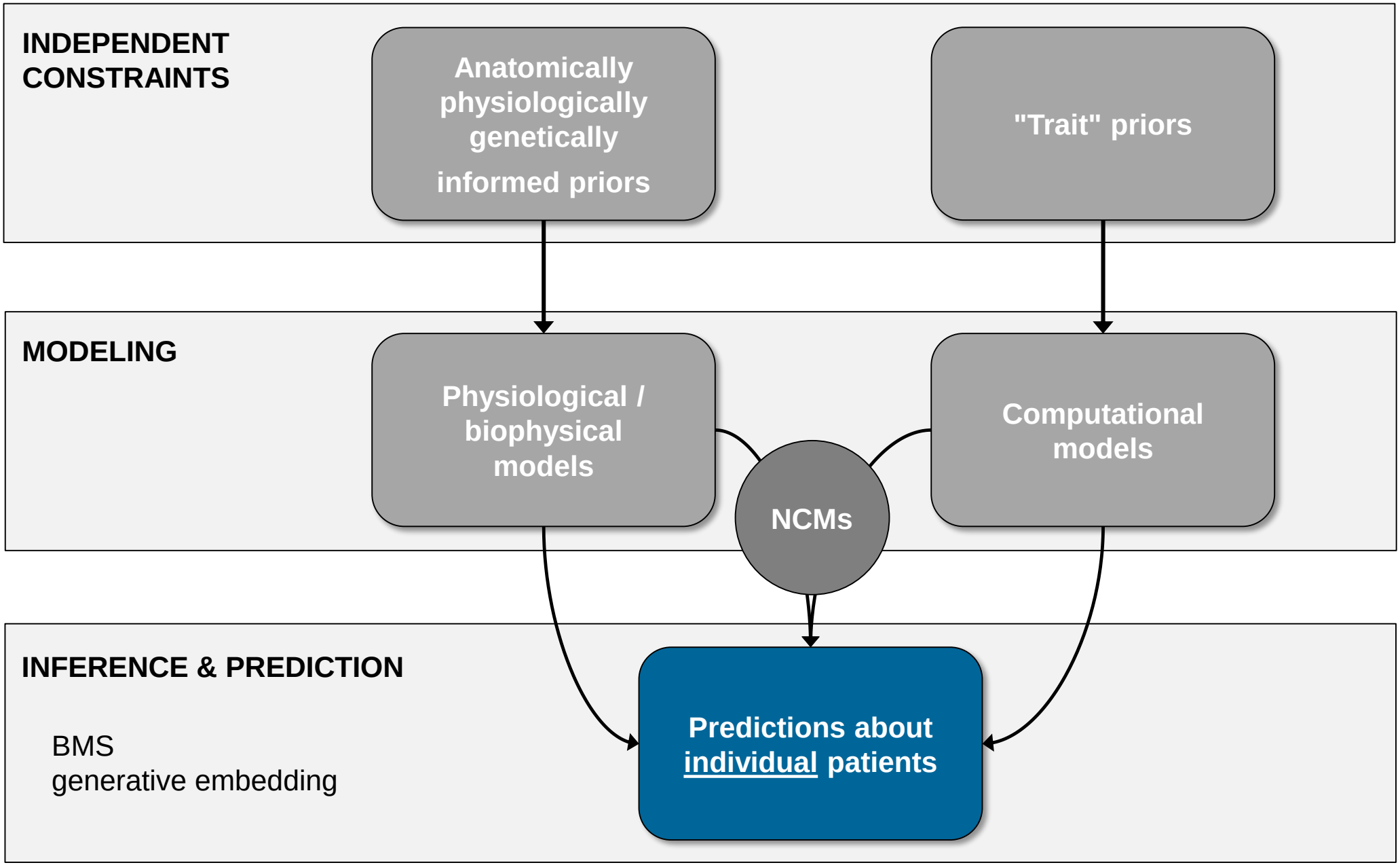
p<0.05, FWE cluster-level whole-brain corrected

Enhanced ε_2 in ARMS



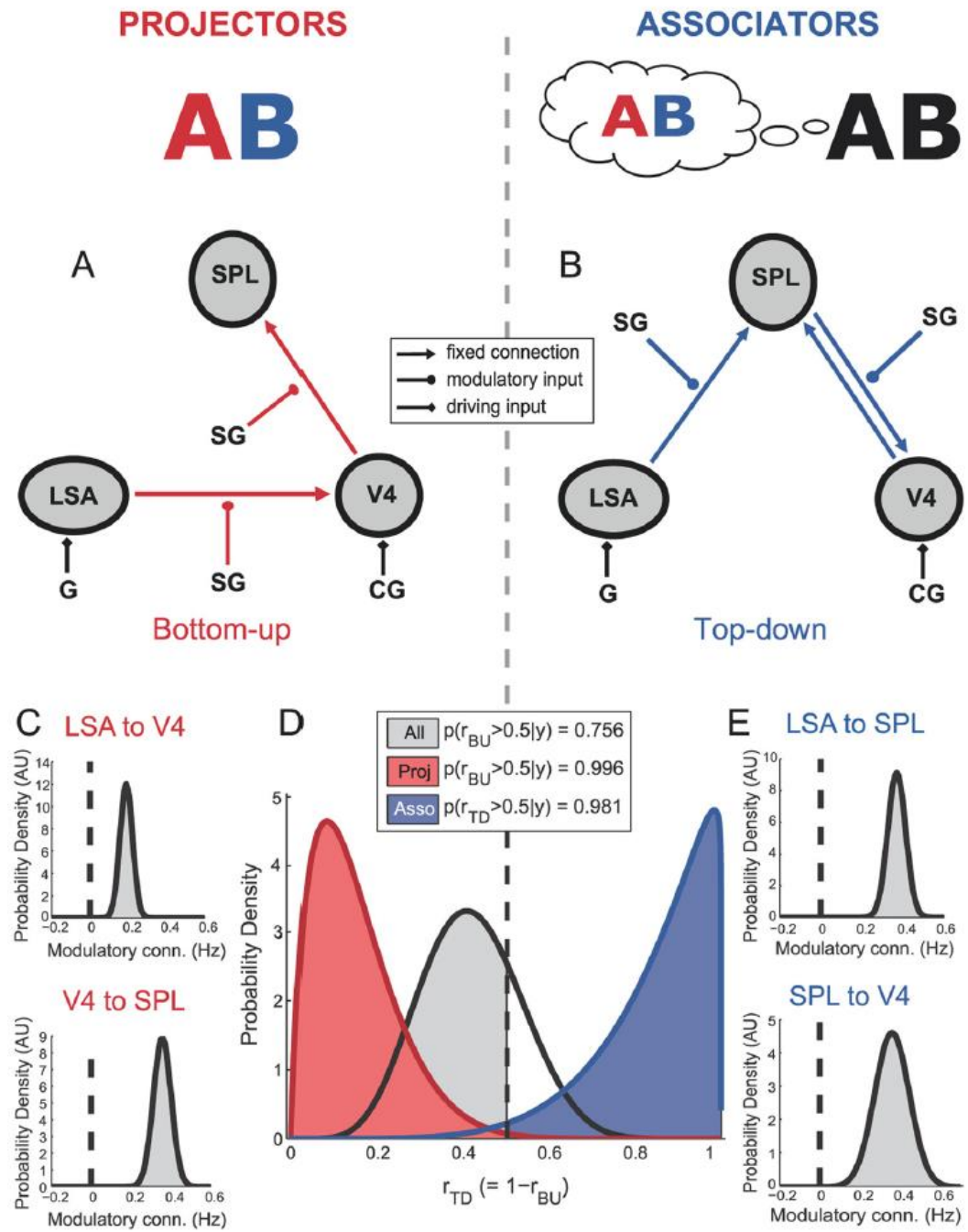
p<0.05, FWE cluster-level corrected within orthogonal functional mask

Cole et al., *in preparation*


INDEPENDENT CONSTRAINTS
Anatomically physiologically genetically informed priors
"Trait" priors
MODELING
Physiological / biophysical models
NCMs
Computational models
INFERENCE & PREDICTION
BMS
generative embedding
Predictions about individual patients

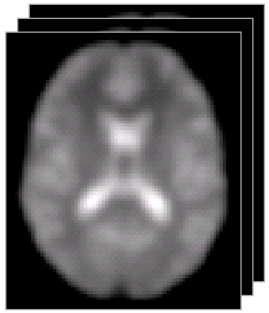
Synaesthesia

- “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.*

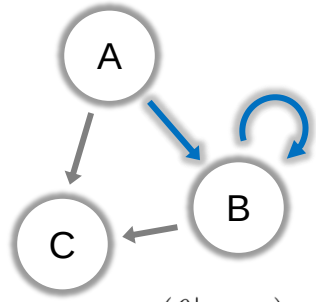
Generative embedding (supervised)



measurements from
an individual subject

**step 1 —
model inversion**

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



$p(\theta|x, m)$

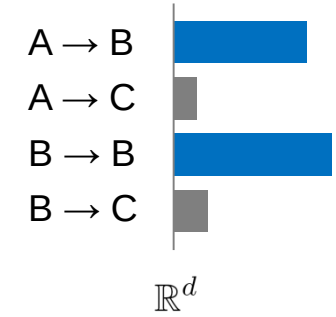
subject-specific
inverted generative model

**step 2 —
kernel construction**

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

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

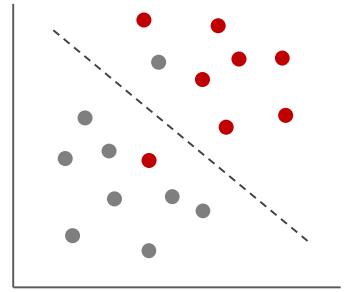
$k_\mathcal{M} : \mathcal{M}_\Theta \times \mathcal{M}_\Theta \to \mathbb{R}$



subject representation in the
generative score space

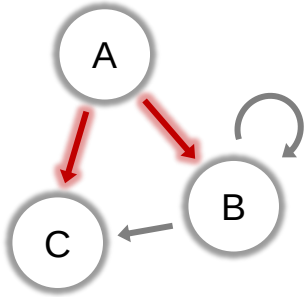
**step 3 —
support vector classification**

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



separating hyperplane fitted to
discriminate between groups

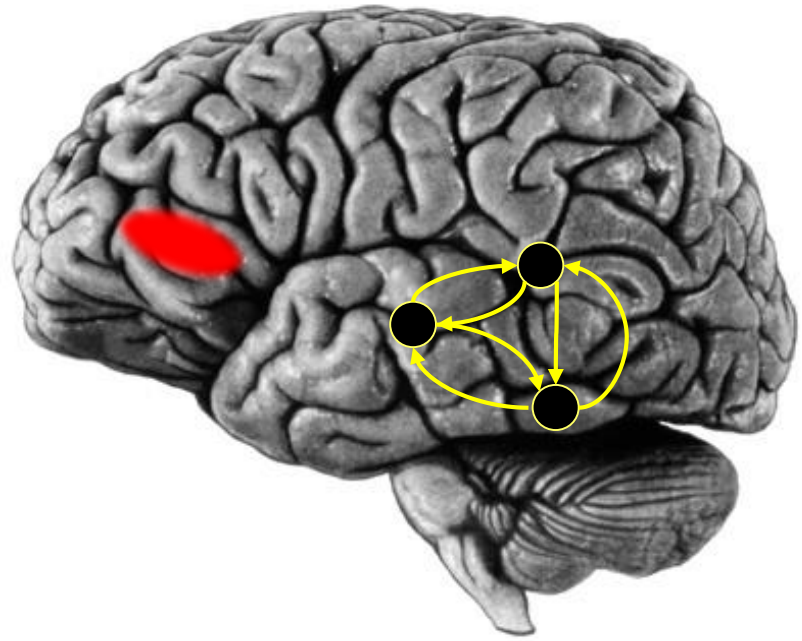
**step 4 —
interpretation**



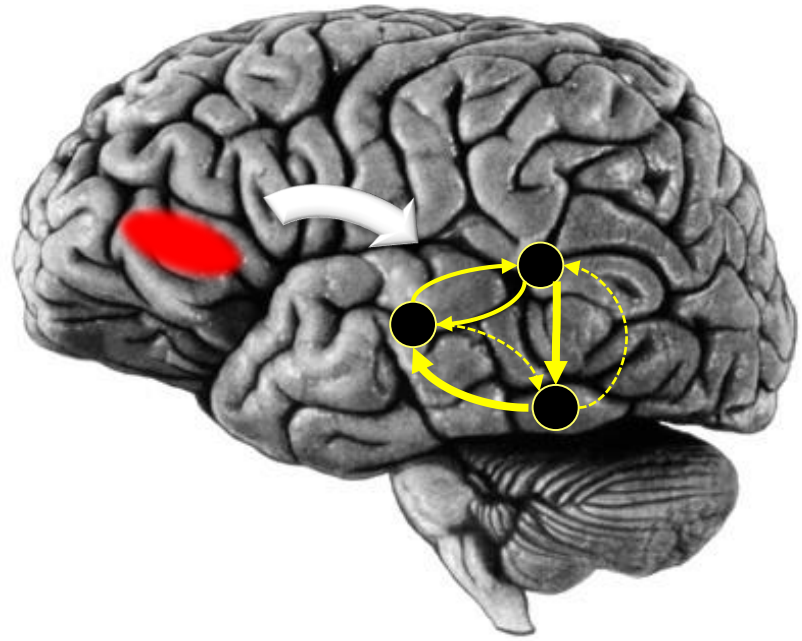
jointly discriminative
model parameters

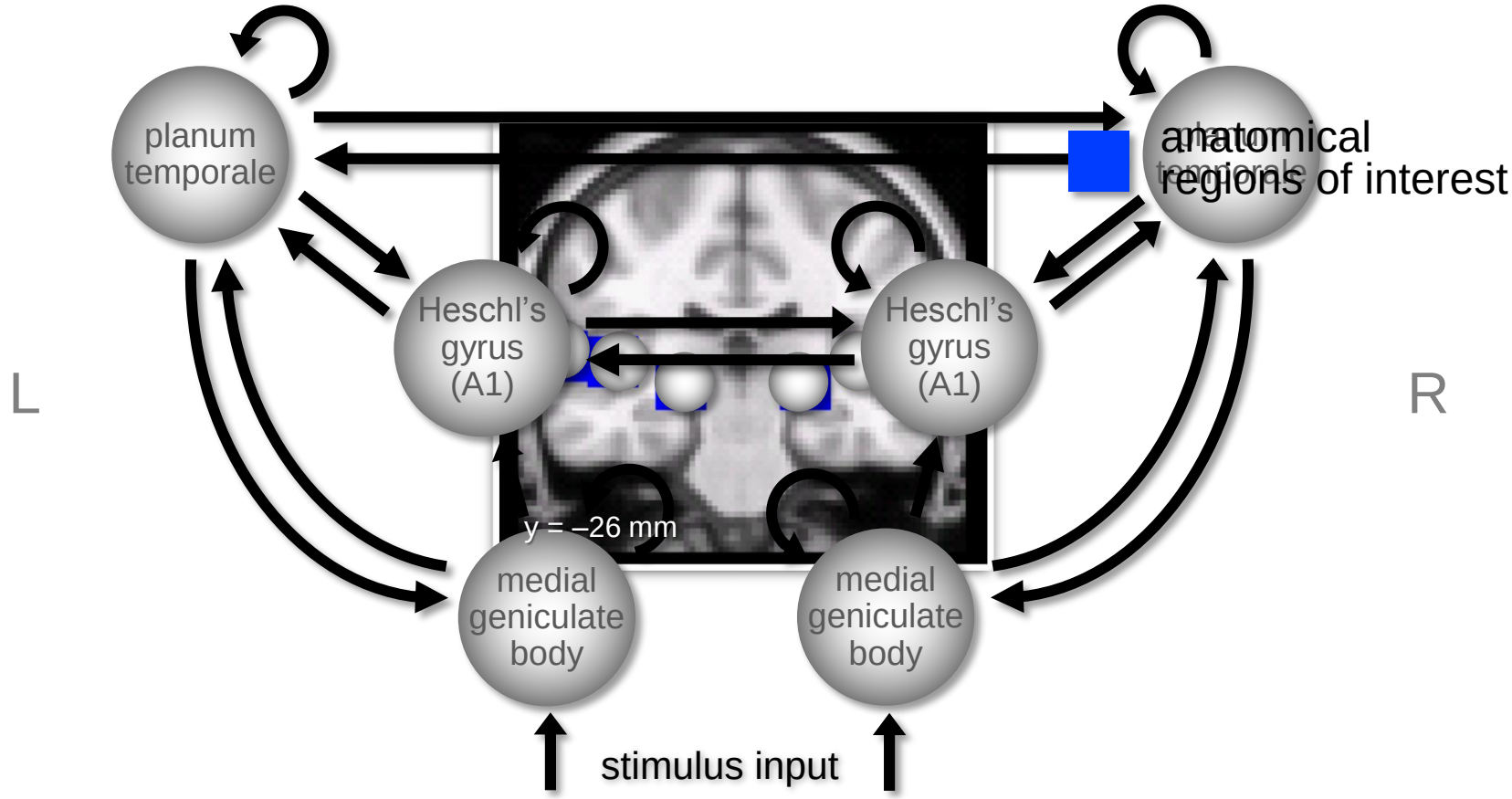
Brodersen et al. 2011, *PLoS Comput. Biol.*

Discovering remote or “hidden” brain lesions



Discovering remote or “hidden” brain lesions

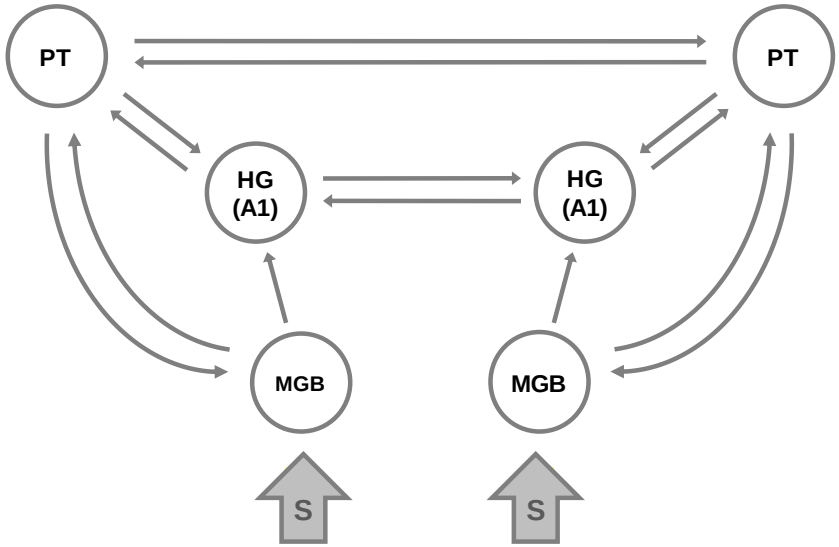


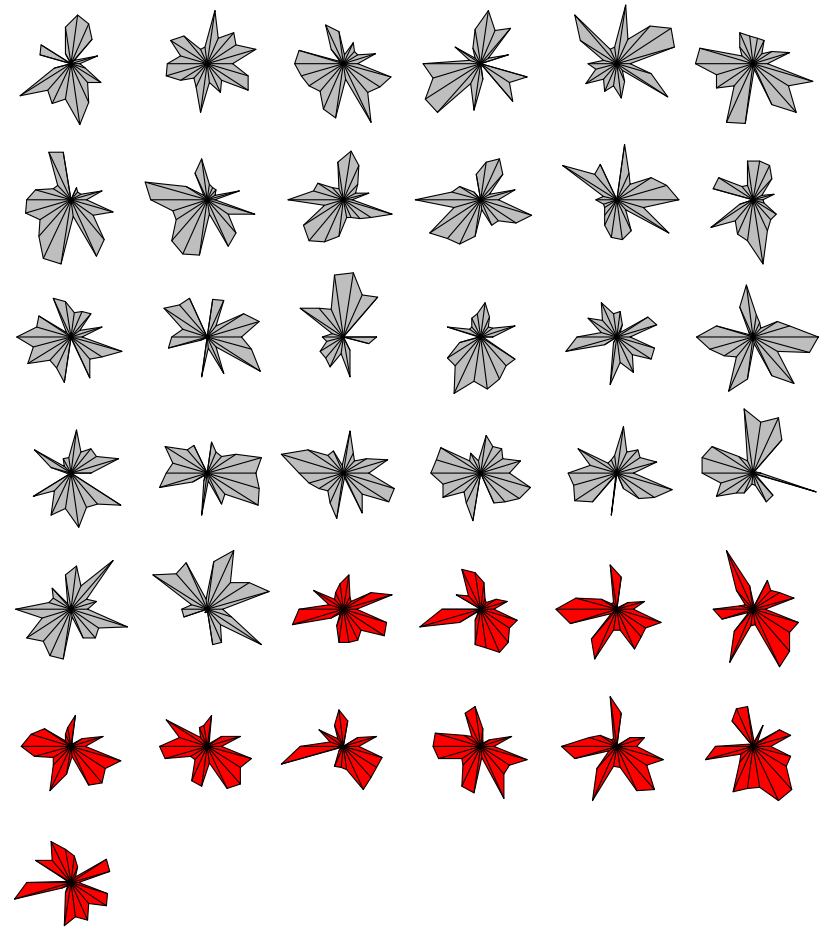


Brodersen et al. 2011, *PLoS Comput. Biol.*

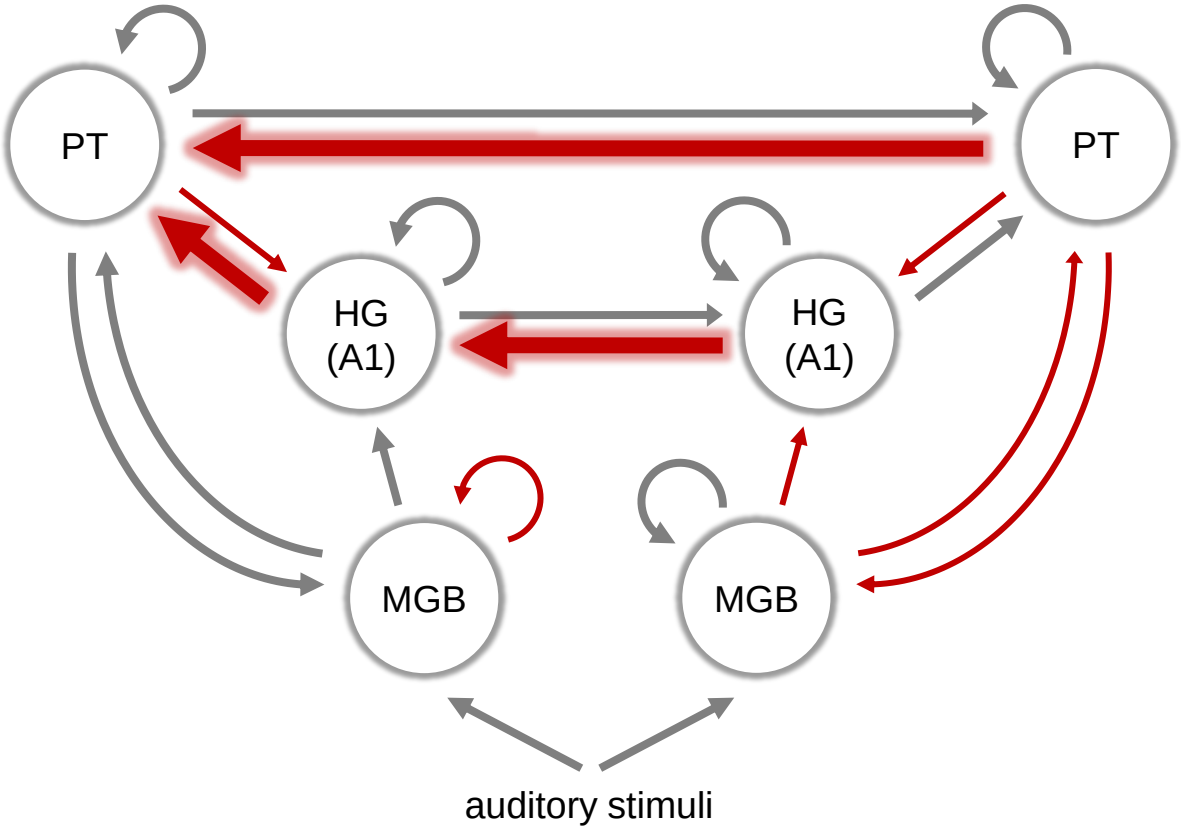
Connectional fingerprints : aphasic patients (N=11) vs. controls (N=26)

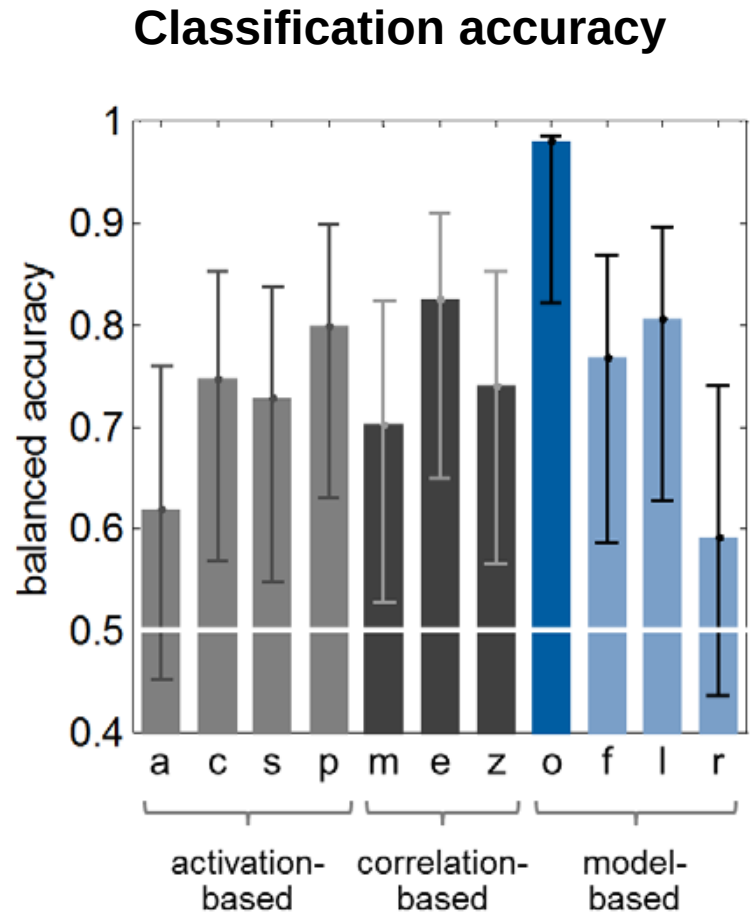
6-region DCM of auditory areas during passive speech listening





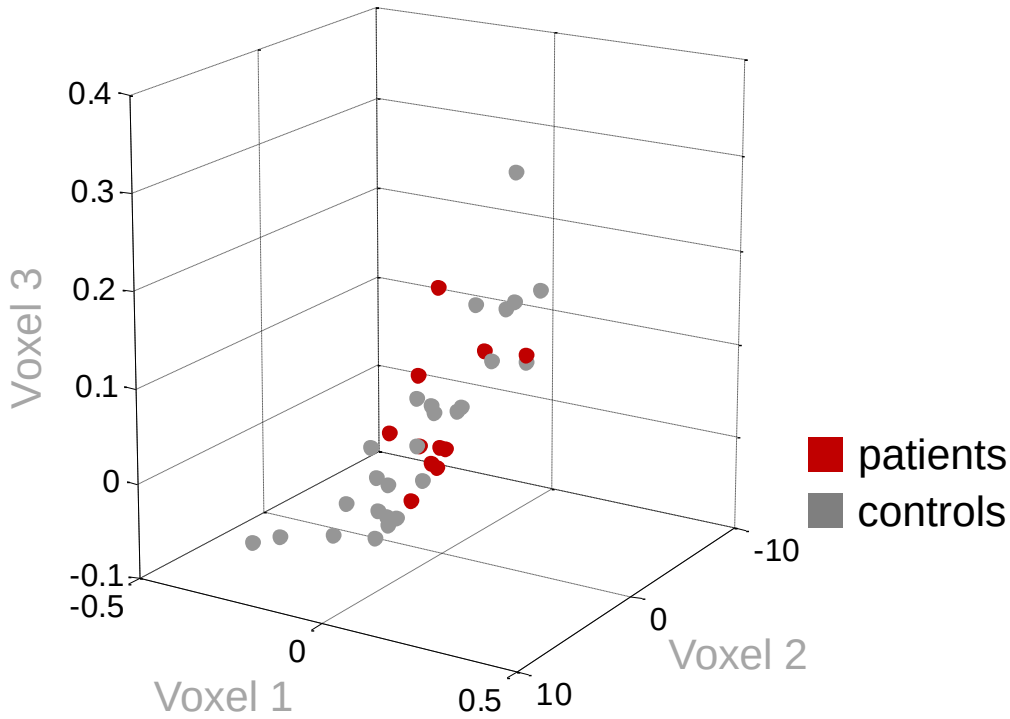
Brodersen et al. 2011, *PLoS Comput. Biol.*
Data from Schofield et al.





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

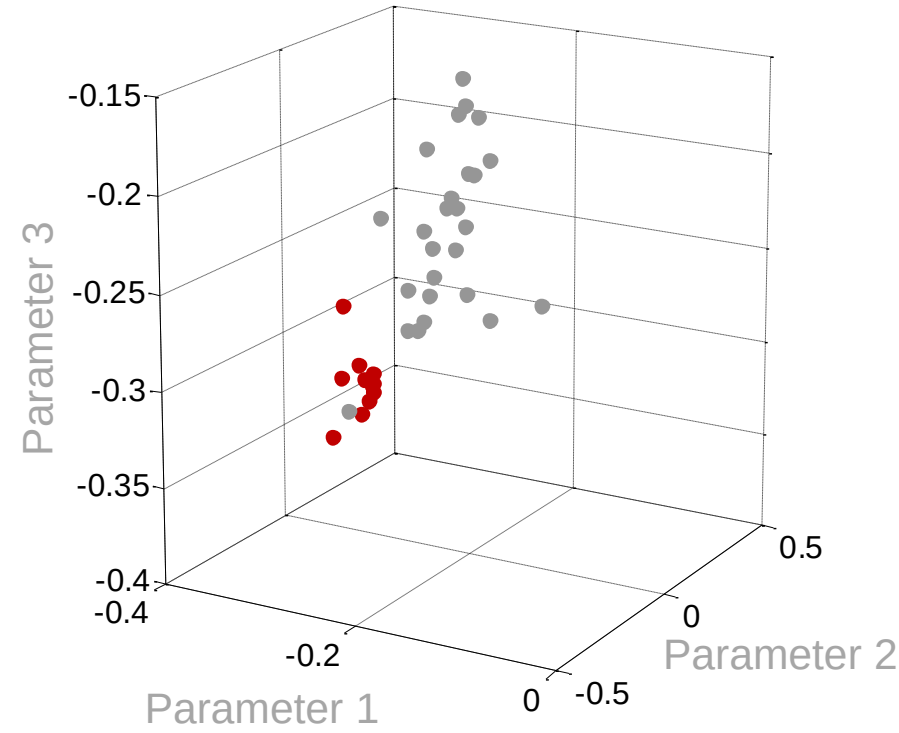
Voxel-based activity space



classification accuracy

75%

Model-based parameter space

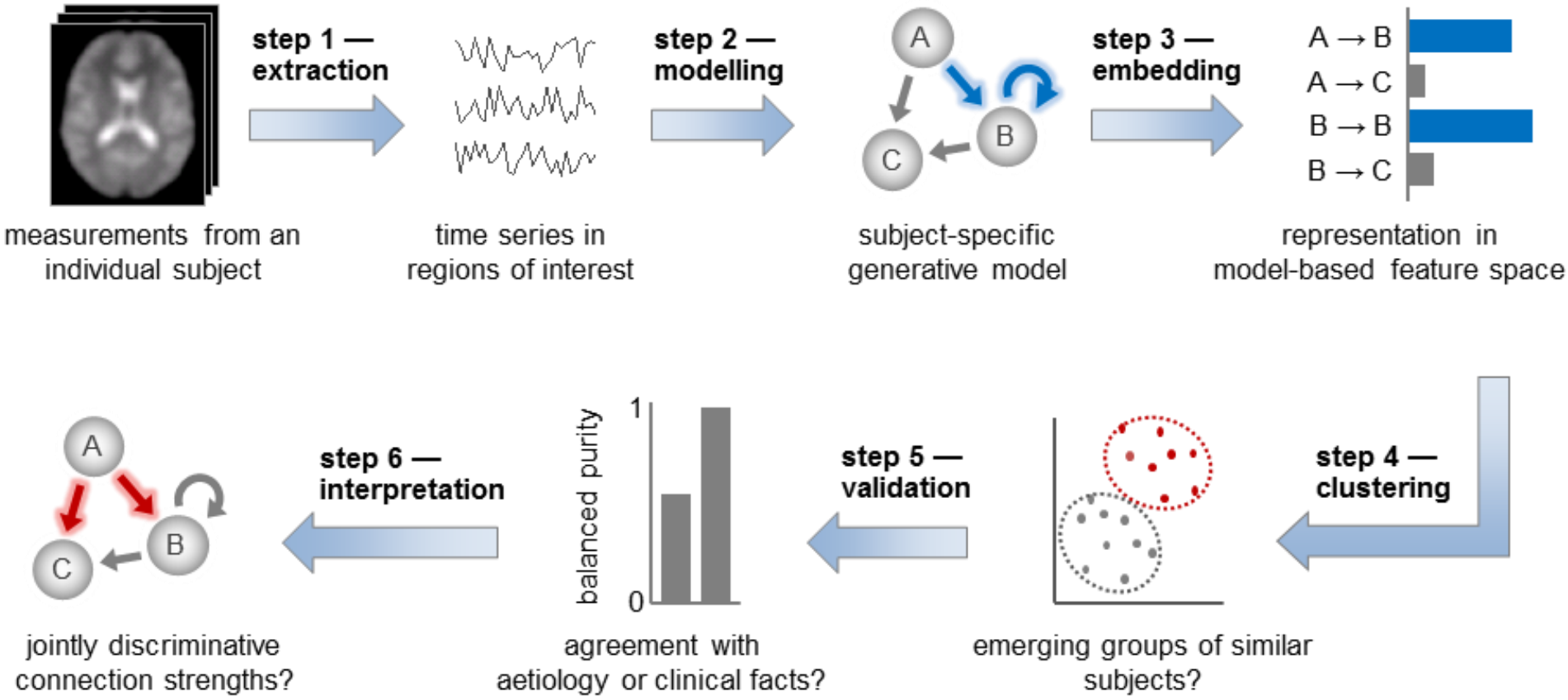


classification accuracy

98%

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

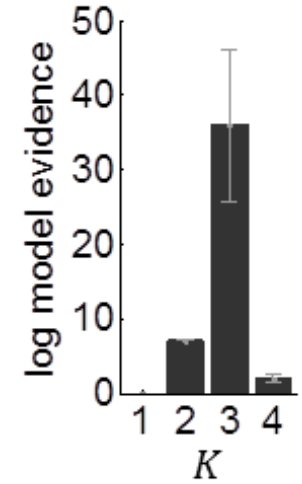
Generative embedding (unsupervised)



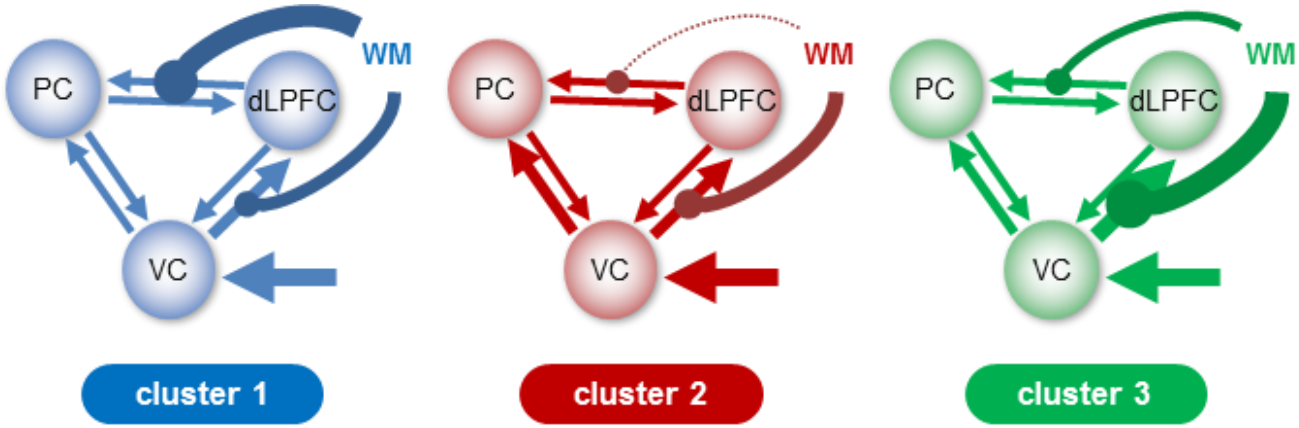
Brodersen et al. 2014, *NeuroImage Clinical*

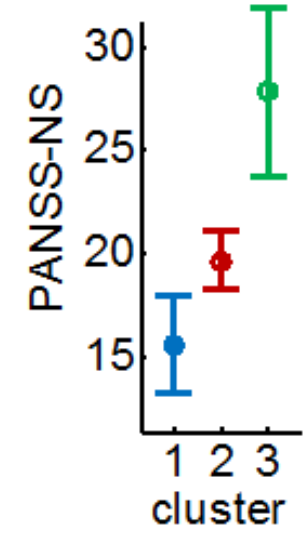
Detecting subgroups of patients in schizophrenia

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)



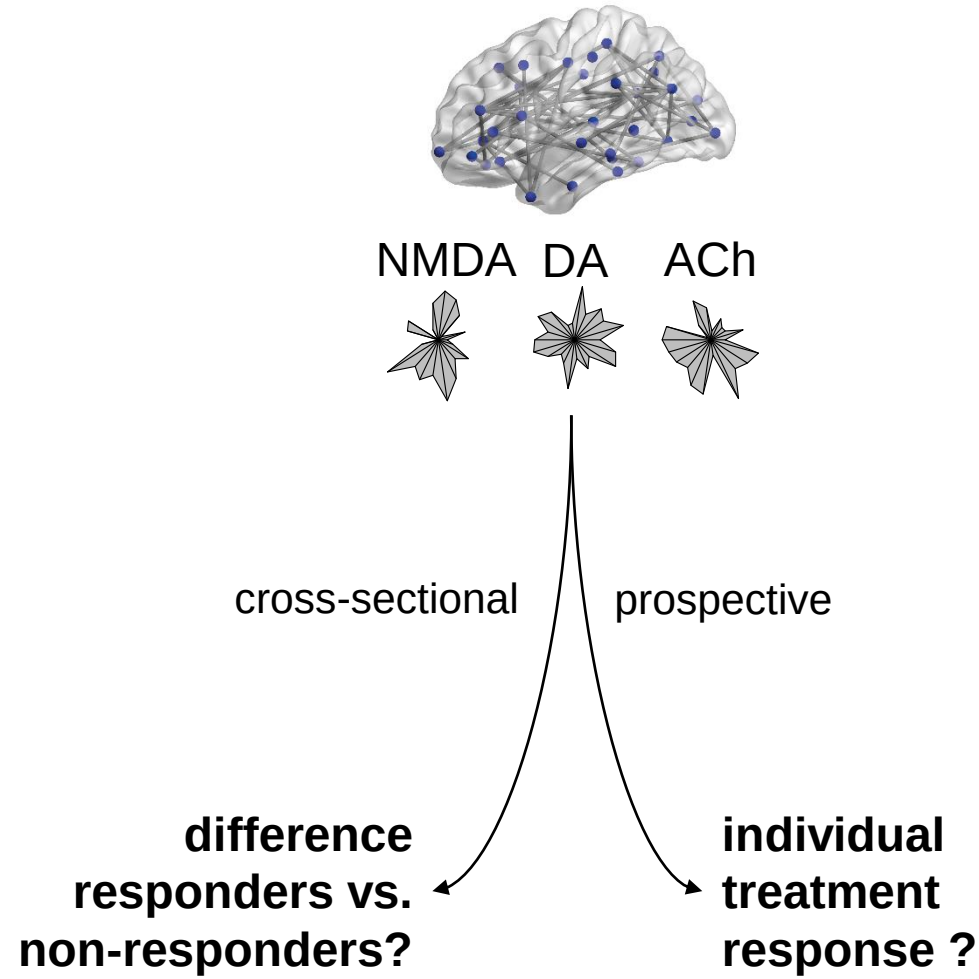


Brodersen et al. 2014, *NeuroImage Clinical*

Prospective patients studies: https://tnu-studien.ethz.ch

Ongoing studies at TNU Zurich:

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



Translational Neuromodeling Unit

Universität Zürich[UZH]

TNU Zurich

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Development of mathematical models & software

Multimodal measurements

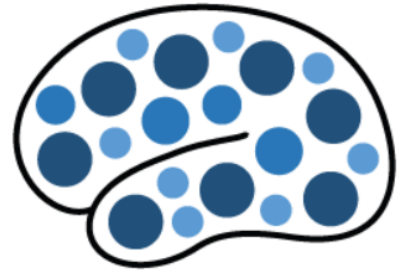
Research clinic for patient studies

Prospective studies for model validation & translation

www.tnu.ethz.ch

Twitter: @tnuzurich

Open source software TAPAS



TAPAS

www.translationalneuromodeling.org/tapas

Computational Psychiatry Course (CPC) Zurich

www.translationalneuromodeling.org/cpcourse

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.

Brodersen KH, Deserno L, Schlagenhauf F, Lin Z, Penny WD, Buhmann JM, Stephan KE (2014) Dissecting psychiatric spectrum disorders by generative embedding. NeuroImage Clinical 4: 98-111.

Iglesias S, Mathys C, Brodersen KH, Kasper L, Piccirelli M, den Ouden HEM, Stephan KE (2013) Hierarchical prediction errors in midbrain and basal forebrain during sensory learning. Neuron 80: 519-530.

Lieder F, Daunizeau J, Garrido MI, Friston KJ, Stephan KE (2013) Modelling Trial-by-Trial Changes in the Mismatch Negativity. PLoS Computational Biology 9: e1002911.

Mathys C, Daunizeau J, Friston KJ, Stephan KE (2011) A Bayesian foundation for individual learning under uncertainty. Frontiers in Human Neuroscience 5: 39.

Stephan KE, Baldeweg T, Friston KJ (2006) Synaptic plasticity and dysconnection in schizophrenia. Biological Psychiatry 59: 929-939.

Stephan KE, Kasper L, Harrison LM, Daunizeau J, den Ouen HEM, Breakspear M, Friston KJ (2008) Nonlinear dynamic causal models for fMRI. NeuroImage 42: 649-662.

Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ (2009) Bayesian model selection for group studies. NeuroImage 46: 1004-1017.

Stephan KE, Friston KJ, Frith CD (2009) Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia Bulletin 35: 509-527.

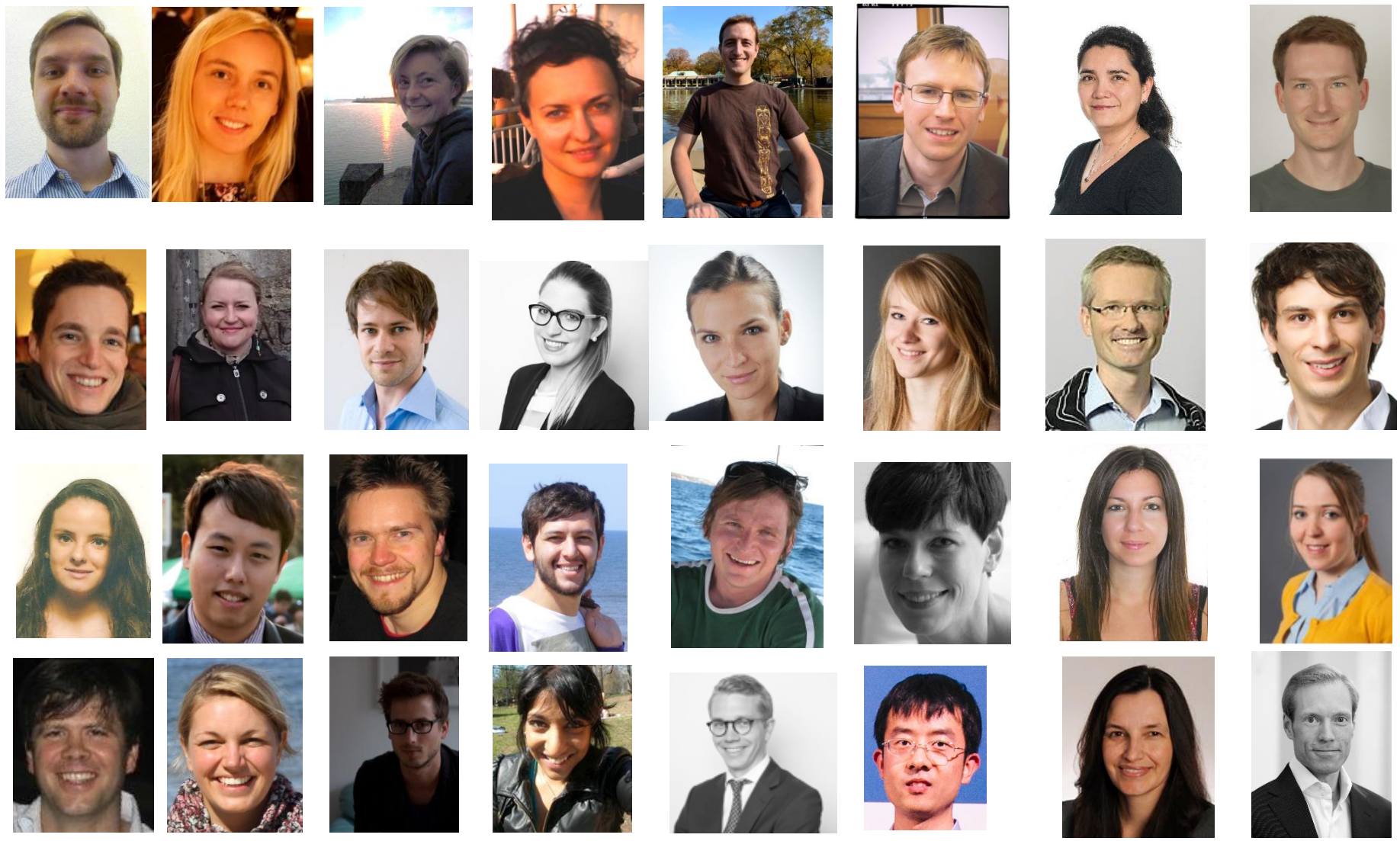
Stephan KE, Mathys C (2014) Computational Approaches to Psychiatry. Current Opinion in Neurobiology 25:85-92.

Stephan KE, Iglesias S, Heinzle J, Diaconescu AO (2015) Translational Perspectives for Computational Neuroimaging. Neuron 87: 716-732.

The TNU – 15 nationalities, from mathematics to medicine

Translational Neuromodeling Unit

E. Aponte
N. Araya
I. Berwian
M. Bischoff
H. Brunner
D. Cole
A. Diaconescu
H.C.T. Do
S. Frässle
S. Grässli
H. Haker
J. Heinzle
Q. Huys
S. Iglesias
L. Kasper
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
L. Weber
K. Wellstein
Y. Yao



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

Thank you

www.tnu.ethz.ch

@tnuzurich
@CompPsychiatry