CPC 2020:
Introduction to Computational Psychiatry

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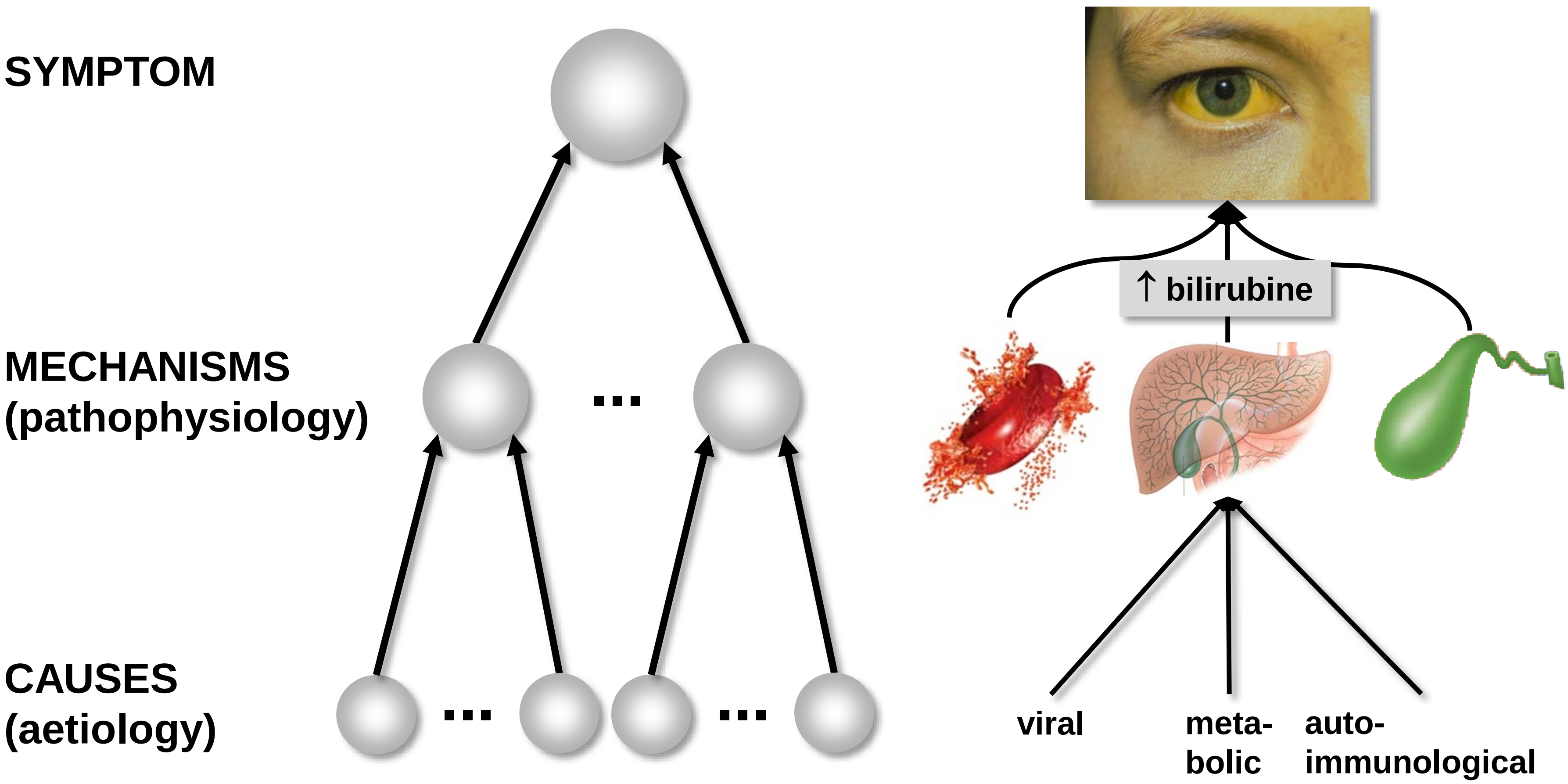
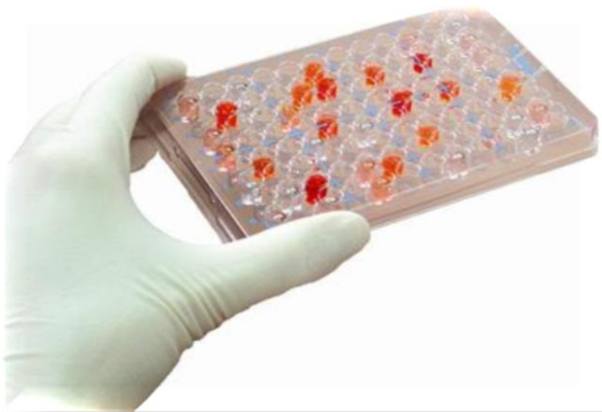
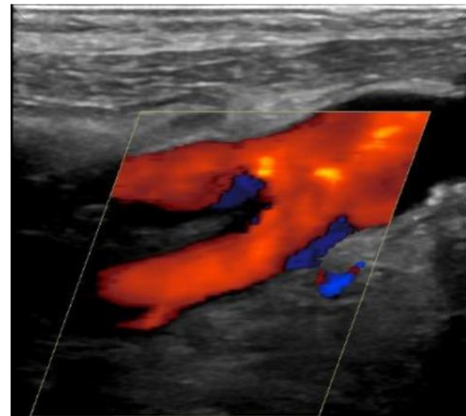
From differential diagnosis to nosology

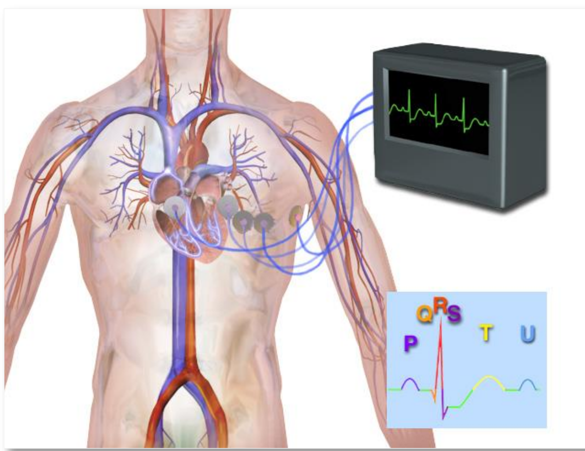


Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

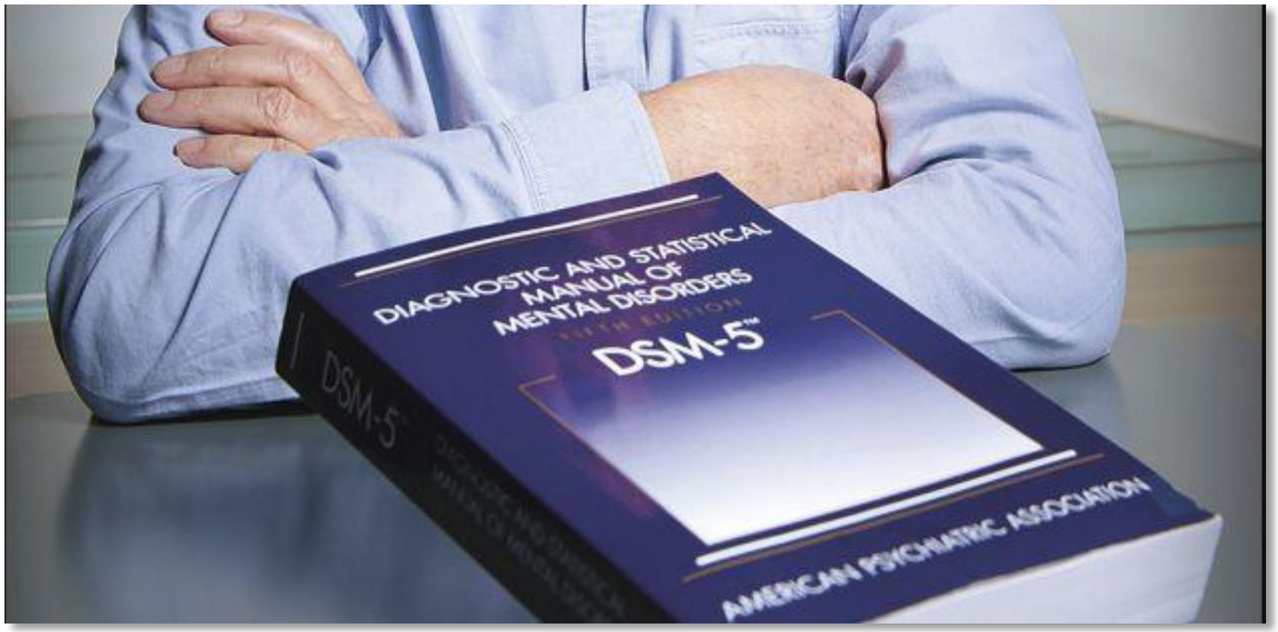
>3,000 FDA-approved clinical tests in medicine







1 diagnostic instrument in psychiatry



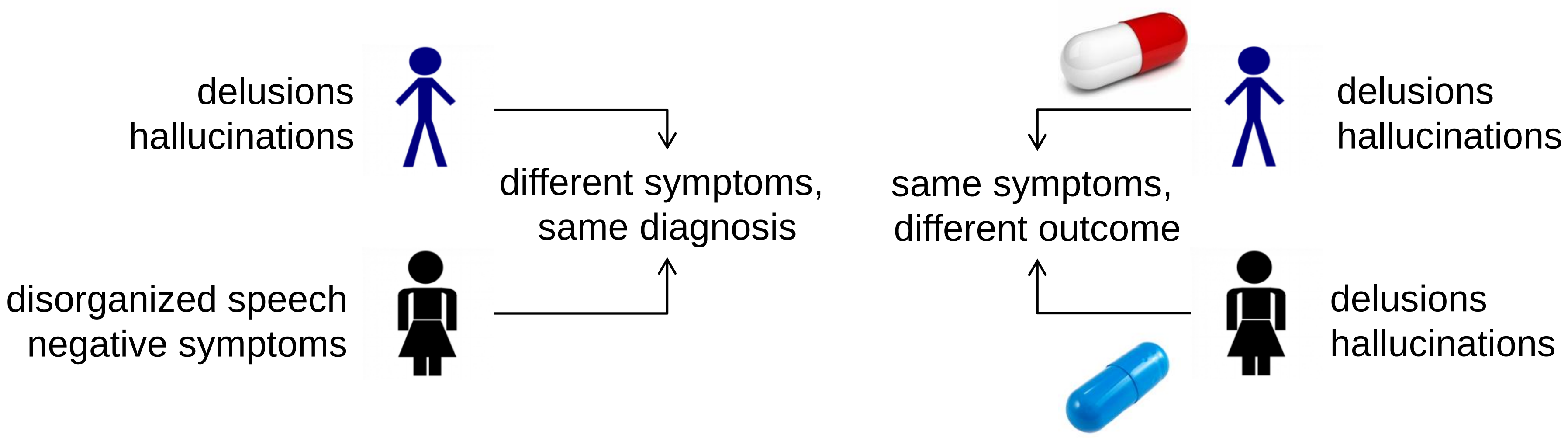
Diagnostic and Statistical Manual of Mental Disorders (DSM)

DSM-5: Schizophrenia

- Positive symptoms:
  - Delusions
  - Hallucinations
  - Disorganized speech
- Grossly disorganized or catatonic behavior
- Negative symptoms (e.g., flat affect, anhedonia, avolition, asociality)

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

≥ 2 symptoms
(at least one pos. symptom)
over ≥ 1 month



Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

Psychiatric disorders = heterogeneous spectrum diseases

polygenetic basis
gene-environment interactions
environmental variation

variability in clinical trajectory and treatment response

multiple disease mechanisms

Molecular Psychiatry (2012) 17, 1174–1179

www.nature.com/mp

PERSPECTIVE

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

S Kapur[1], AG Phillips[2] and TR Insel[3]

We often take DSM too seriously
(or forget about its original purpose).

Trying to develop clinical tests based on constructs which are inherently heterogenous is not a promising strategy.

Molecular Psychiatry (2012) 17, 1174–1179

www.nature.com/mp

PERSPECTIVE

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

S Kapur[1], AG Phillips[2] and TR Insel[3]

From reinforcement learning models to psychiatric and neurological disorders

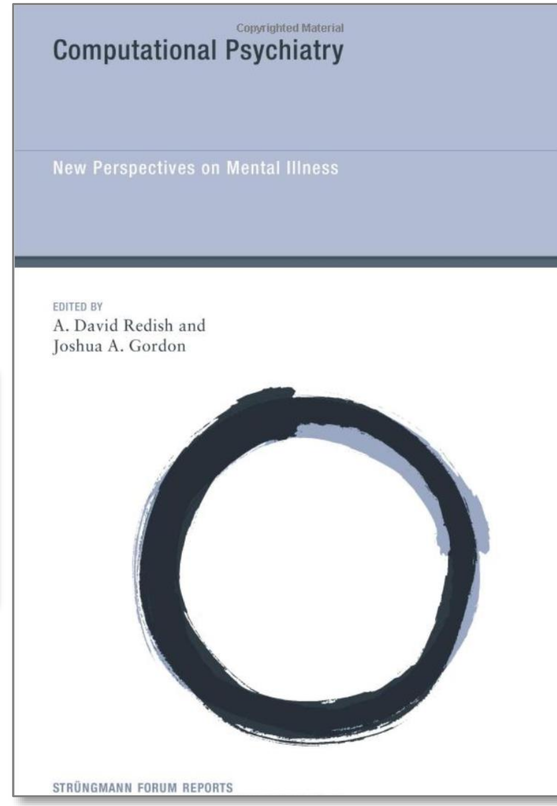
Tiago V Maia[1,2] & Michael J Frank[3,4]

Computational psychiatry

P. Read Montague[1,2], Raymond J. Dolan[2], Karl J. Friston[2] and Peter Dayan[3]

Computational approaches to psychiatry

Klaas Enno Stephan[1,2,3] and Christoph Mathys[3]



Computational psychiatry: the brain as a phantastic organ

Karl J Friston, Klaas Enno Stephan, Read Montague, Raymond J Dolan

Computational Psychiatry

Xiao-Jing Wang[1,2,3,*] and John H. Krystal[3,4,5,6]

Computational Psychiatry: towards a mathematically informed understanding of mental illness

Rick A Adams,[1,2] Quentin J M Huys,[3,4] Jonathan P Roiser[1]

Computational psychiatry as a bridge from neuroscience to clinical applications

Quentin J M Huys[1,2,5], Tiago V Maia[3,5] & Michael J Frank[4]

Computational Psychosomatics and Computational Psychiatry: Toward a Joint Framework for Differential Diagnosis

Frederike H. Petzschner, Lilian A.E. Weber, Tim Gard, and Klaas E. Stephan

What exactly do we mean by "computational"?

- in **computer science**:
  - “computation” = a well-defined process (algorithm) that transforms an input set into an output set in a finite number of steps

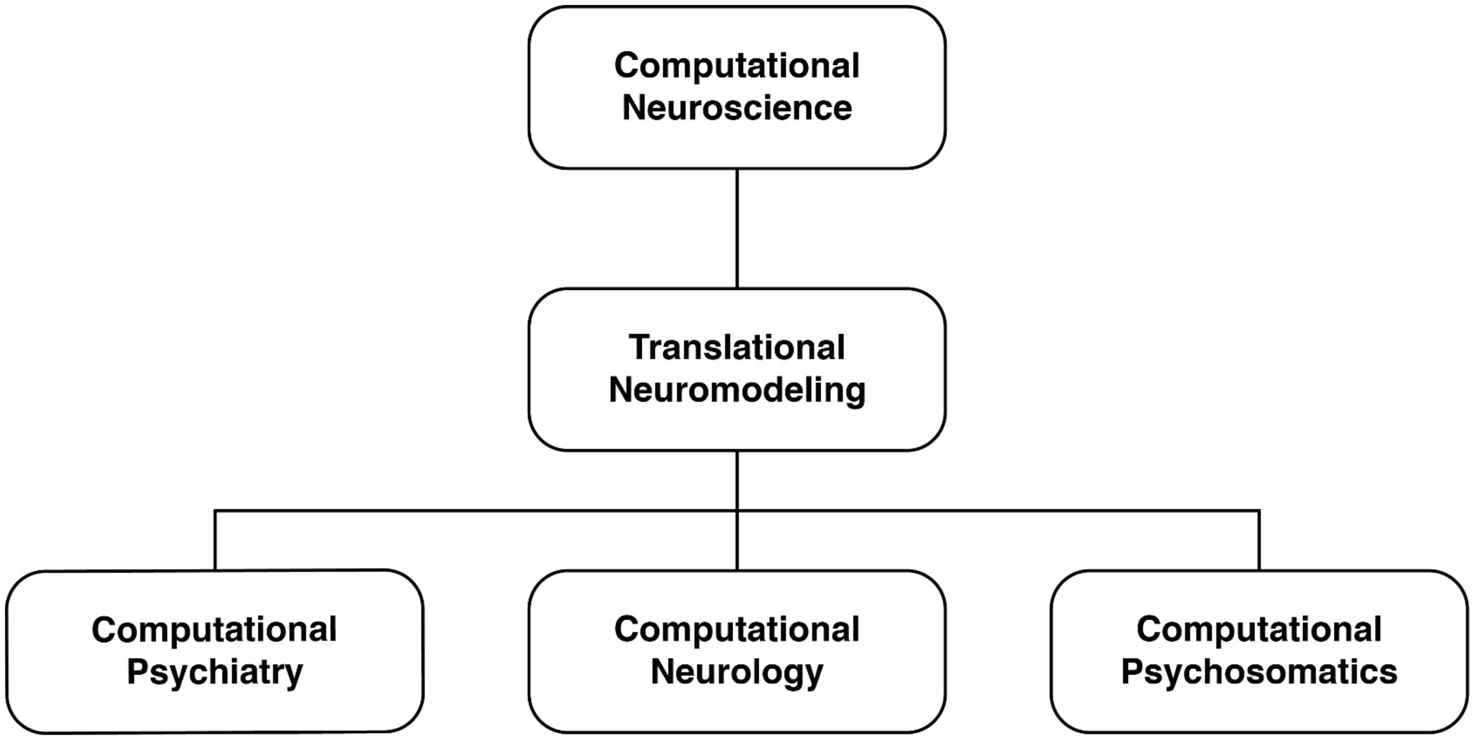
- in **neuroscience**: three common usages
  - *methodological approach*
    - investigations of neural or cognitive systems by algorithmic, as opposed to analytical (algebraic), approaches
      → “computational neuroscience”
  - *information processing*
    - as opposed to biophysical implementation
  - *unspecified*
    - any work in which computer-based analyses play a dominant role
    - e.g. machine learning analyses of clinical, behavioural, imaging data

A taxonomy of computational clinical neuroscience

Understanding how/what the brain computes

Develops/validates mathematical models for solving clinical problems

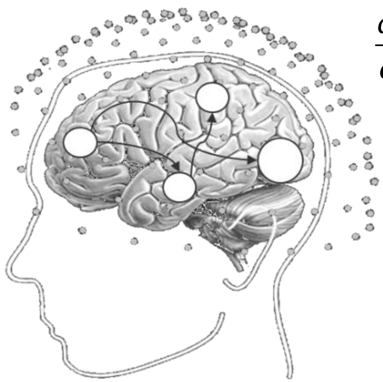
Application within specific medical fields



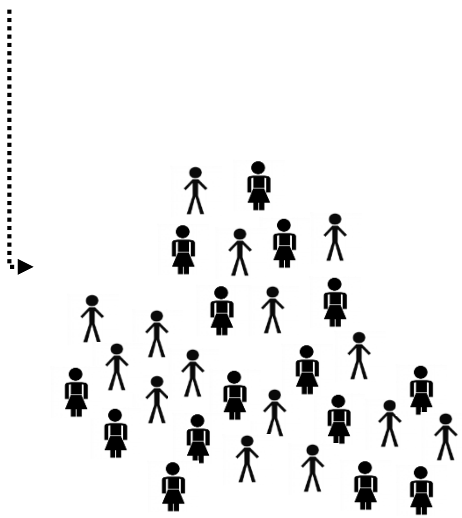
Frässle et al. 2018, *WIREs Cogn. Sci.*

Translational Neuromodeling and Computational Psychiatry

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

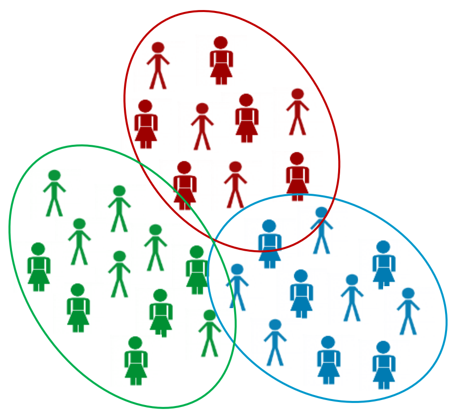


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



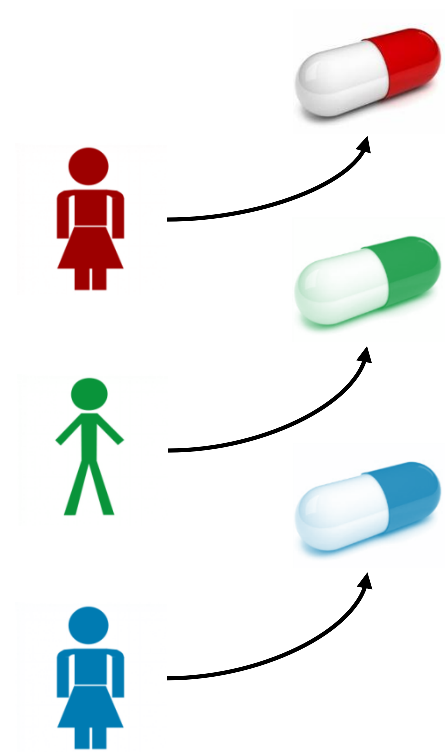
❷ **Application to brain activity and behaviour of individual patients**

❸ **Detecting subgroups/-dimensions (based on inferred mechanisms)**



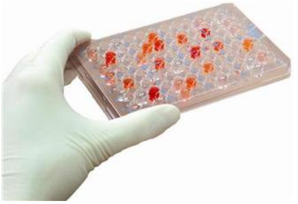
• disease mechanism A
• disease mechanism B
• disease mechanism C

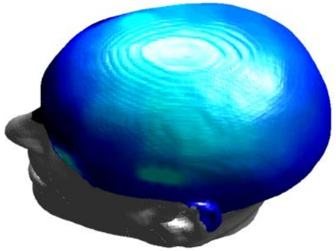
❹ **Individual treatment prediction**



Stephan et al. 2015, *Neuron*

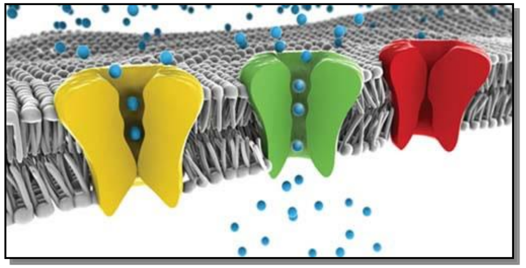
Generative models as "computational assays"



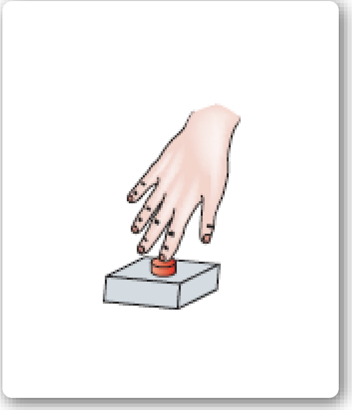


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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

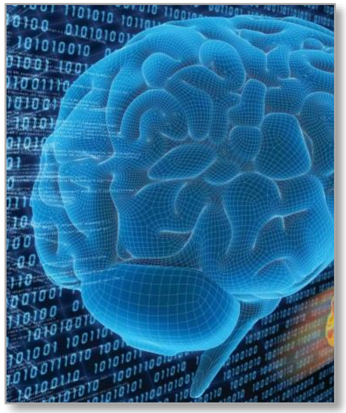


y = data, θ = parameters, m = model

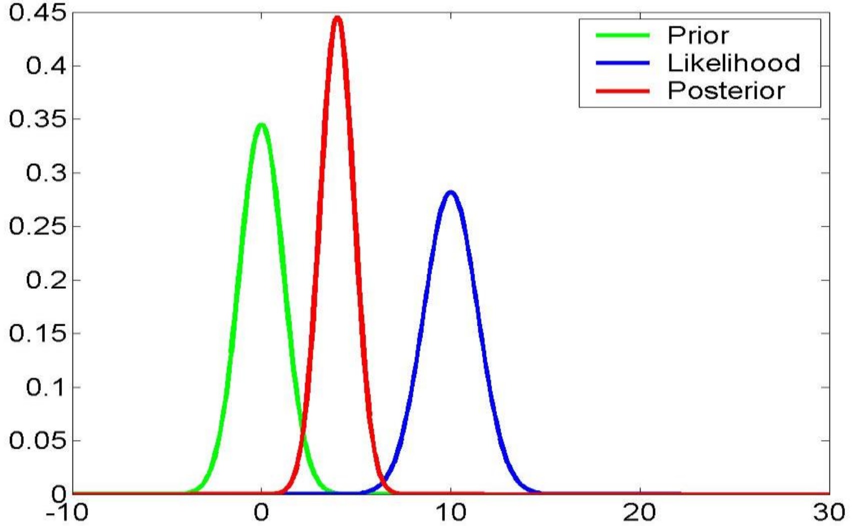


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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



Bayes' rule



The Reverend Thomas Bayes
(1702-1761)

Likelihood × **prior**: generative model

$$p(\boldsymbol{\theta} \mid \mathbf{y}) = \frac{\boxed{p(\mathbf{y} \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta})}}{\boxed{p(\mathbf{y})}}$$

θ: parameters
y: data

Model evidence: normalisation term and index for model goodness

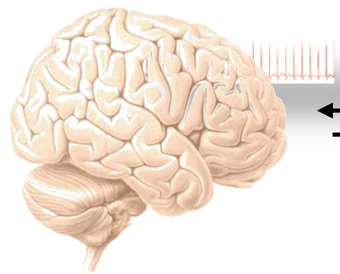
"... the theorem expresses how a degree of belief, expressed as a probability, should rationally change to account for the availability of related evidence."

Wikipedia

Generative models as a concept for brain function: the "Bayesian brain" hypothesis

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

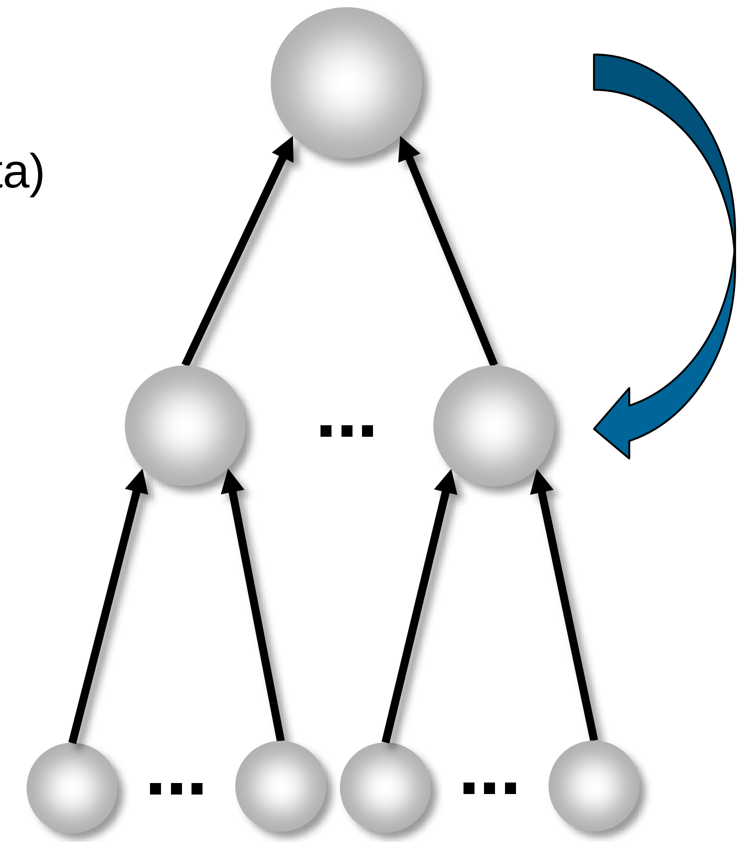
perception = inference = inversion of a generative model

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

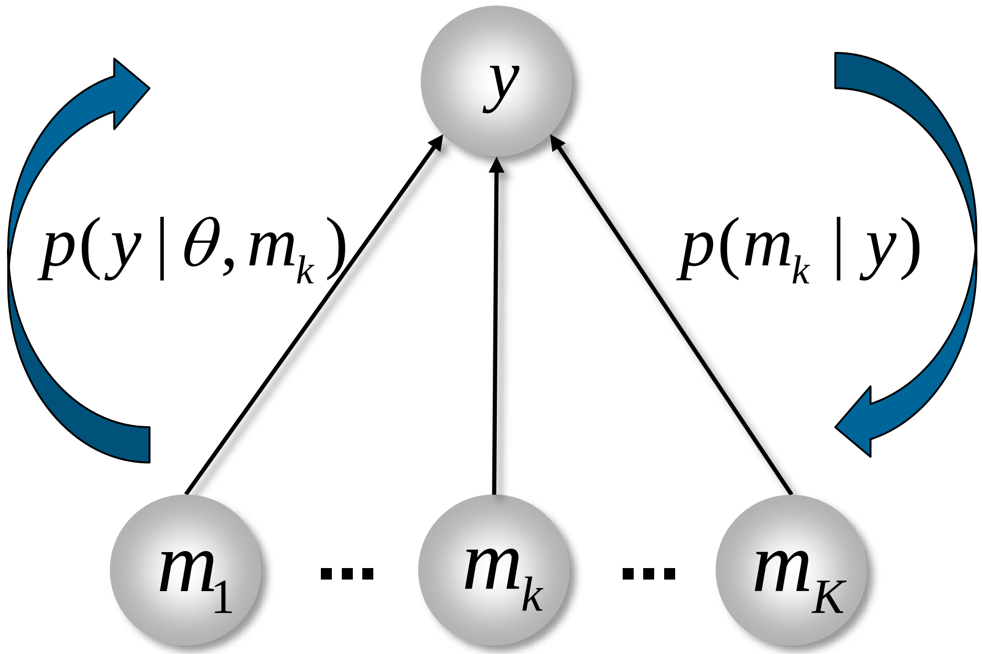
❸ **prediction** of clinical trajectories and treatment response

Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

❶ Differential diagnosis: model selection

SYMPTOM
(behaviour
or physiology)

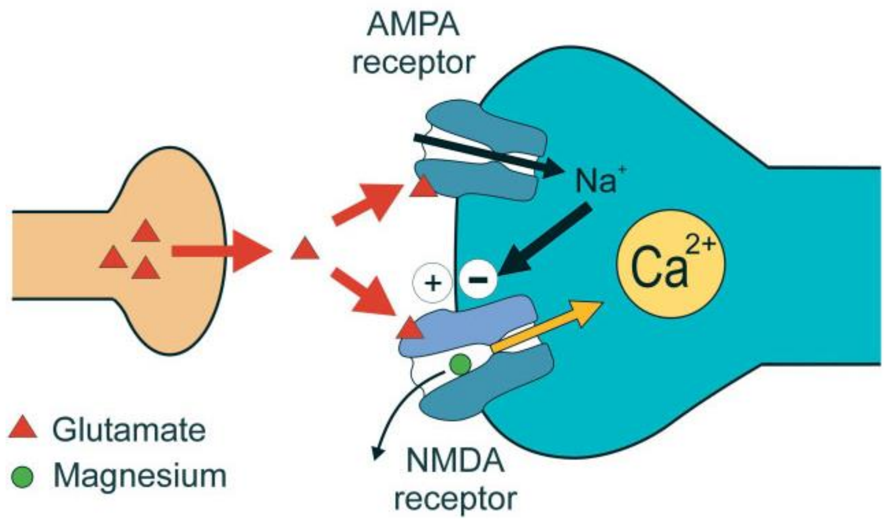
HYPOTHETICAL
MECHANISM

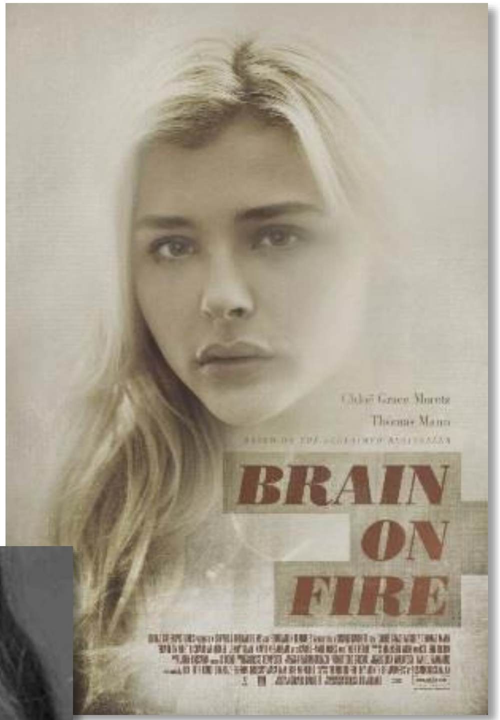


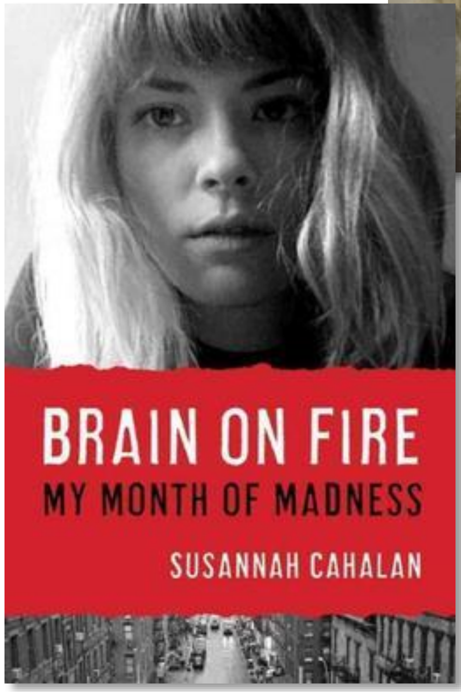
$$p(m_k \mid \mathrm{y}) = \frac{p(y \mid m_k)\, p(m_k)}{\sum_k p(y \mid m_k)\, p(m_k)}$$

Stephan et al. 2017, *NeuroImage*

NMDA receptor antibody encephalitis







Generative modeling of seizure activity in NMDAR antibody encephalitis

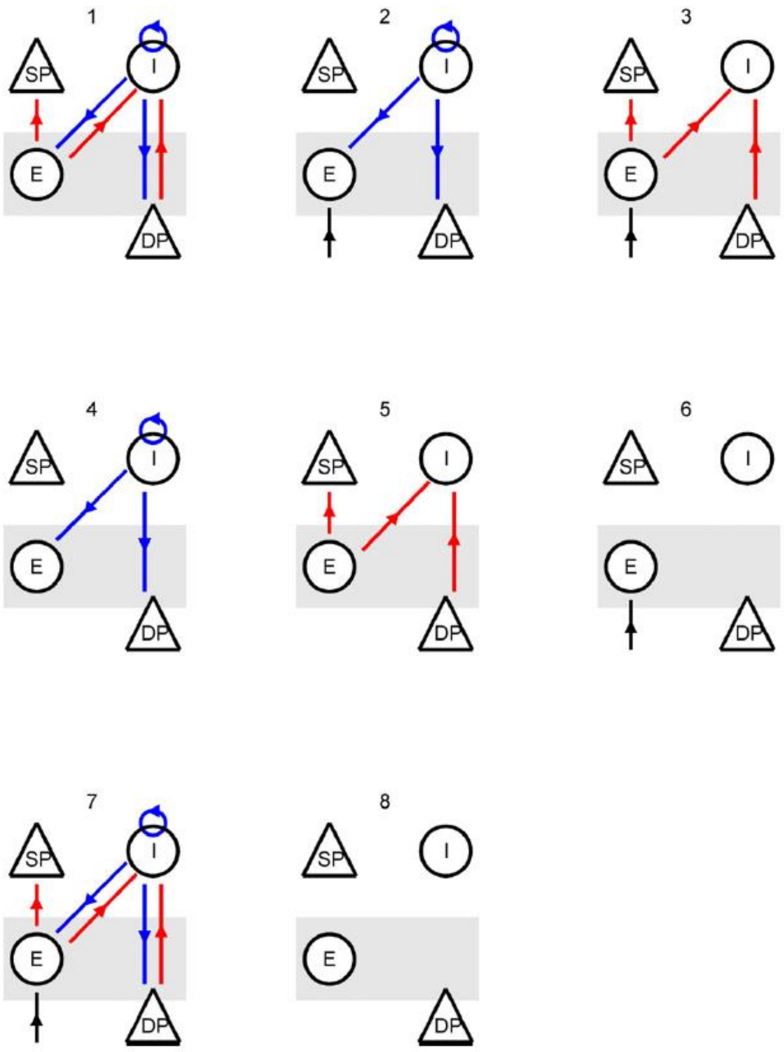


Table 2
The variance described and the free energy for the different models inverted for each patient. Note that the winning model (highest free energy) also had the best fit and these were the same models for both patients. The free energies are expressed relative to the null model.

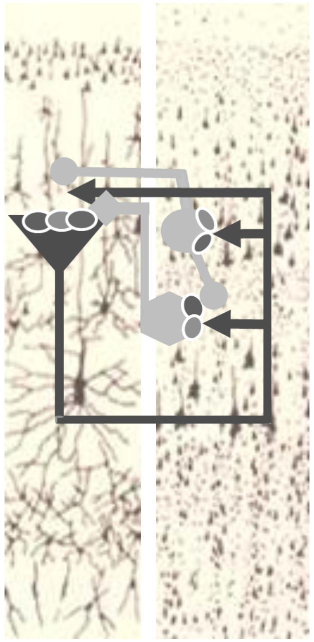
Model	Patient 1		Patient 2	
	Variance explained	Free energy	Variance explained	Free energy
Inhibitory + excitatory + endogenous	0.97	1430	0.95	1740
Inhibitory + excitatory	0.97	1380	0.94	1650
Inhibitory + endogenous	0.97	1320	0.94	1600
Excitatory + endogenous	0.96	1310	0.94	1680
Inhibitory	0.90	860	0.91	1130
Excitatory	0.91	1010	0.92	1460
Endogenous	0.91	950	0.91	1230
Null	0.50	0	0.75	0

Example of how model selection serves to infer on pathophysiological processes in single patients.

"Free energy" in table above
= negative free energy
= approximation to log model evidence

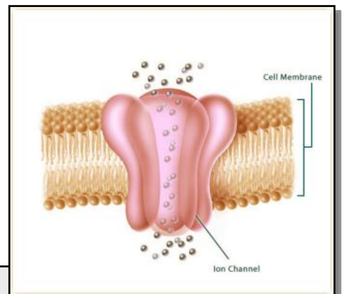
Cooray et al. 2015, *NeuroImage*

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

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

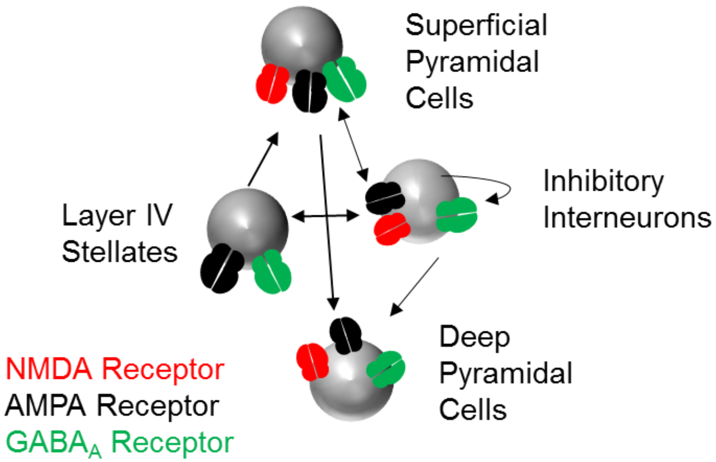
$\gamma_{3,2}^{(I)}$ $\gamma_{1,3}^{(E)}$ $\gamma_{3,1}^{(E)}$

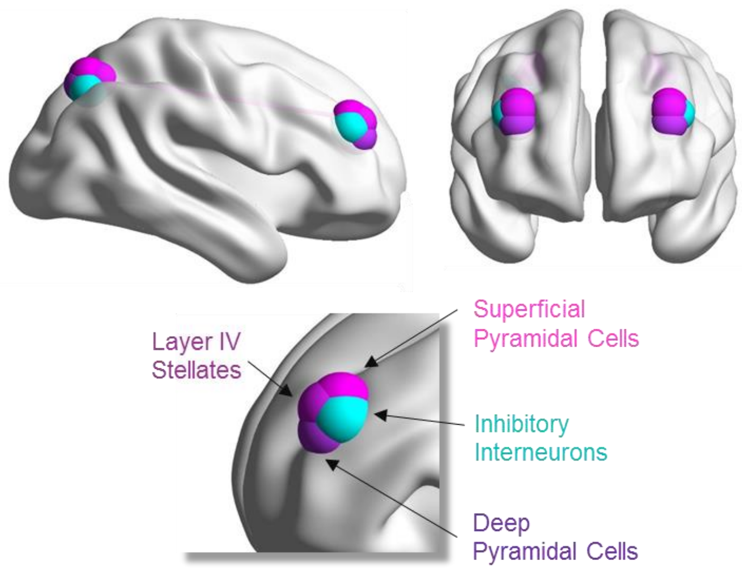
PC

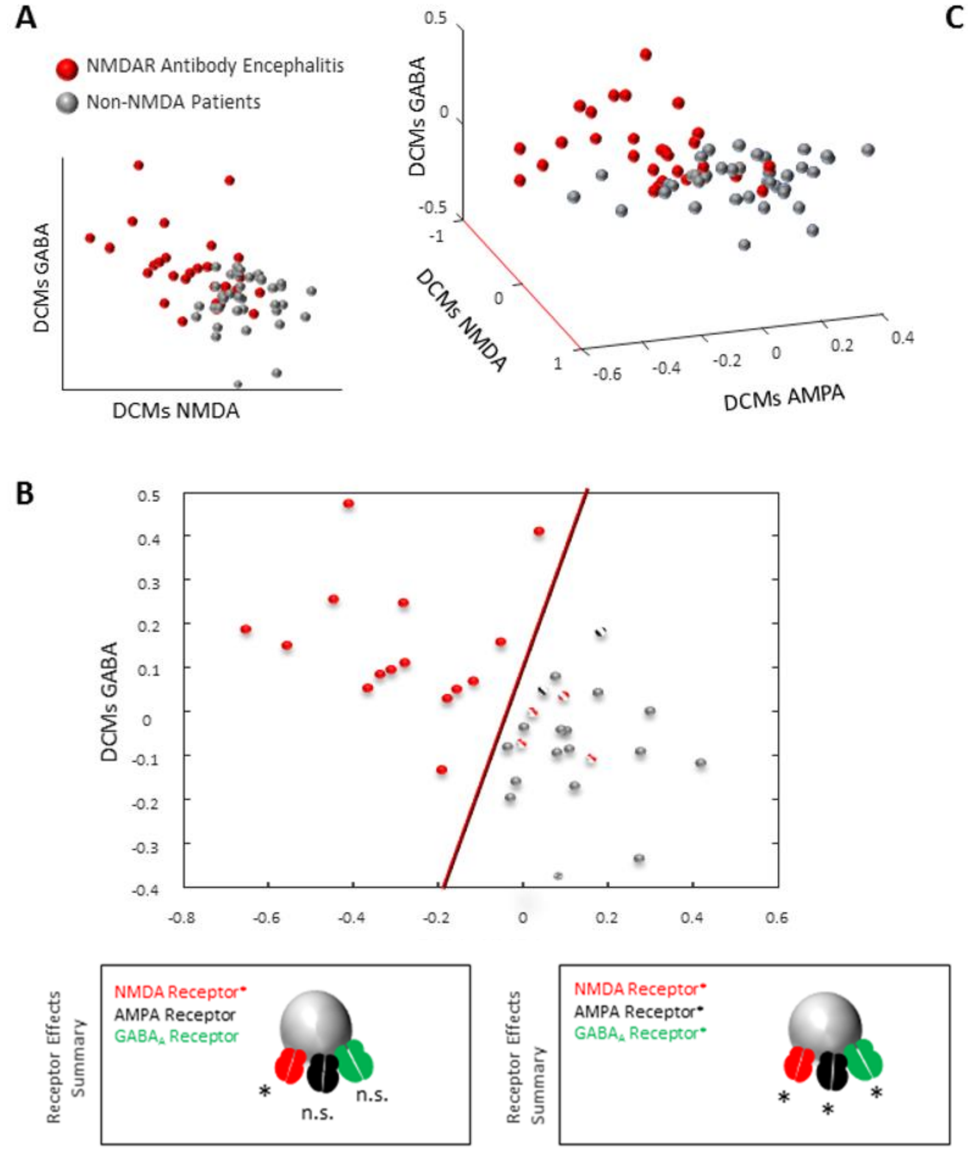
$$C\dot{V}^{(3)} = g_L(V_L - V^{(3)}) + g_E^{(3)}(V_E - V^{(3)}) + g_I^{(3)}(V_I - V^{(3)}) + g_{NMDA} f_{Mg}(V^{(3)})(V_E - V^{(3)}) + \Gamma_V$$
$$\dot{g}_E^{(3)} = \kappa_E(\gamma_{3,1}^{(E)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_E^{(3)}) + \Gamma_E$$
$$\dot{g}_I^{(3)} = \kappa_I(\gamma_{3,2}^{(I)}\sigma(\mu_V^{(2)}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

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*



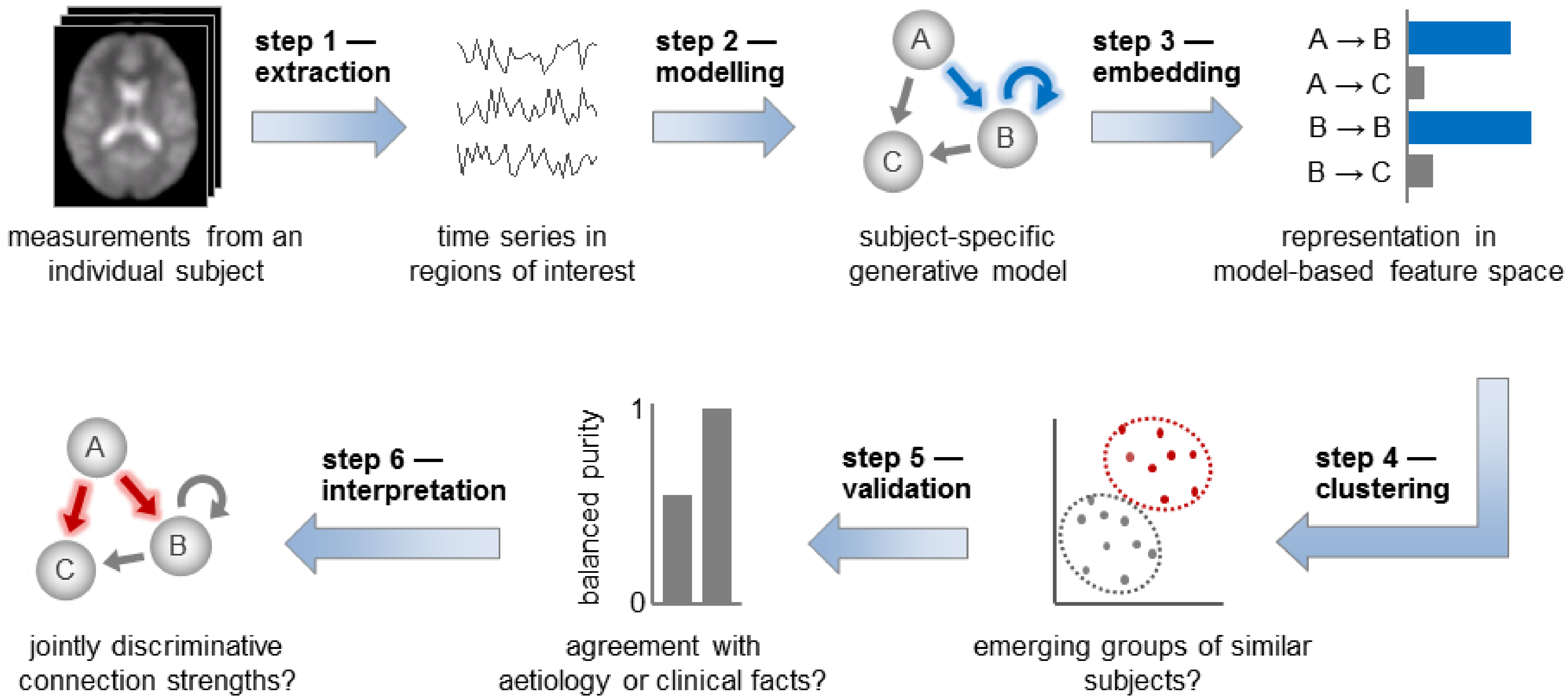




29 patients with NMDAR-antibody encephalitis
18 control patients (with inflammatory/metabolic encephalopathy)

Symmonds et al. 2018, *Brain*

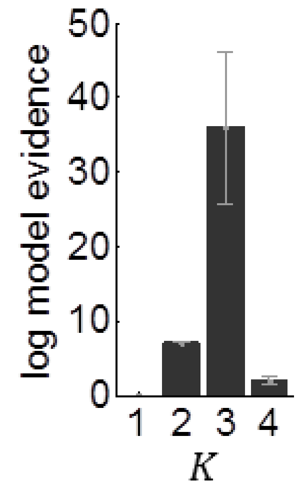
❷ Stratification / subgroup detection: Generative embedding (unsupervised)



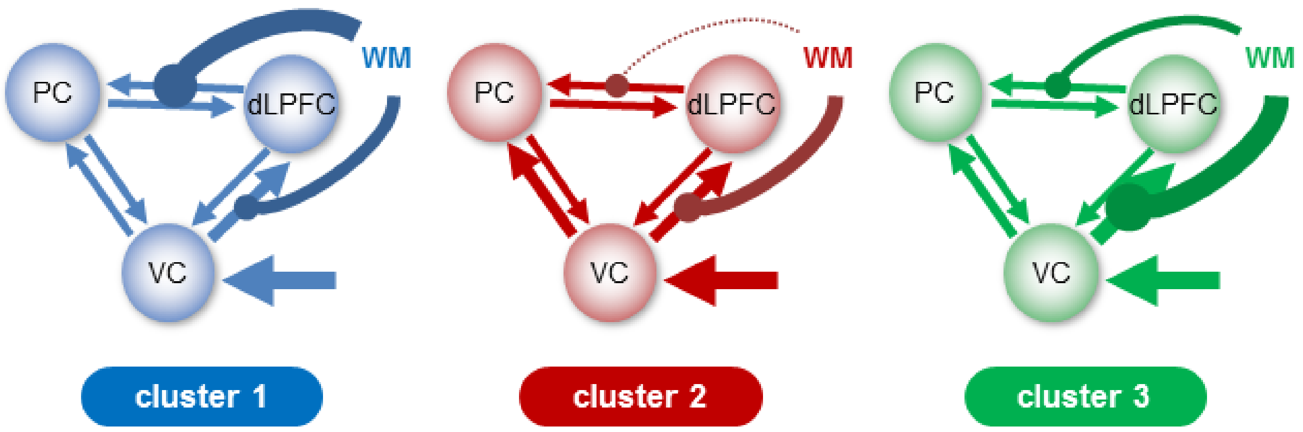
Brodersen et al. 2014, *NeuroImage Clinical*

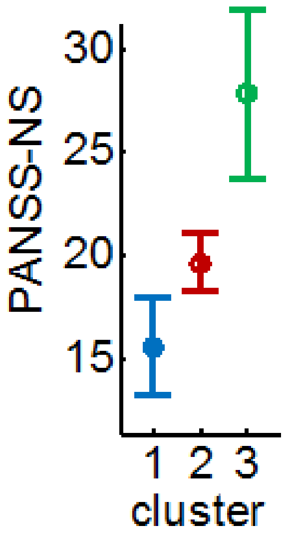
Detecting subgroups of patients in schizophrenia

Optimal cluster solution



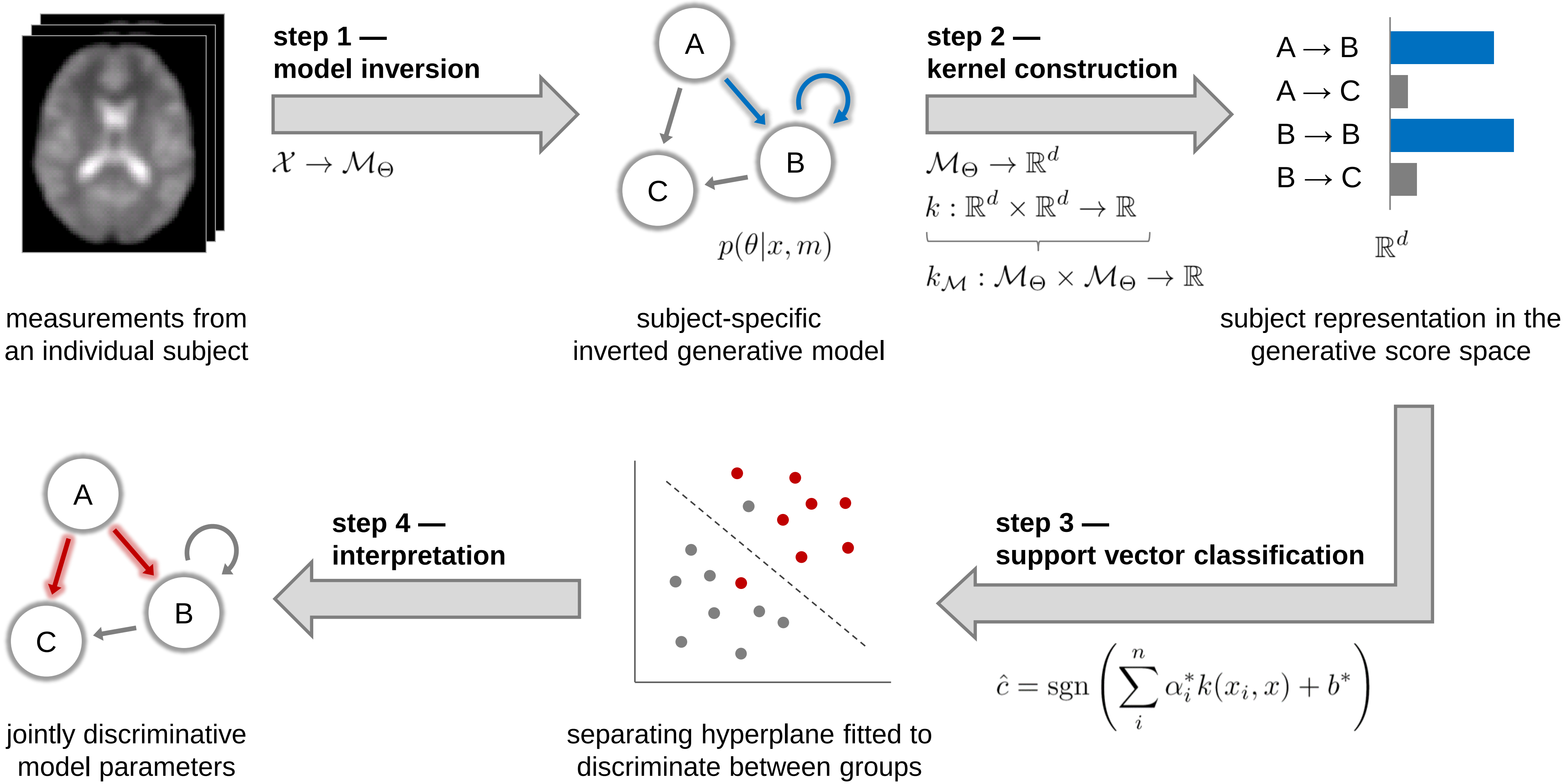
- three distinct subgroups (total N=41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)





Brodersen et al. 2014, *NeuroImage Clinical*

❸ Prediction: Generative embedding (supervised)

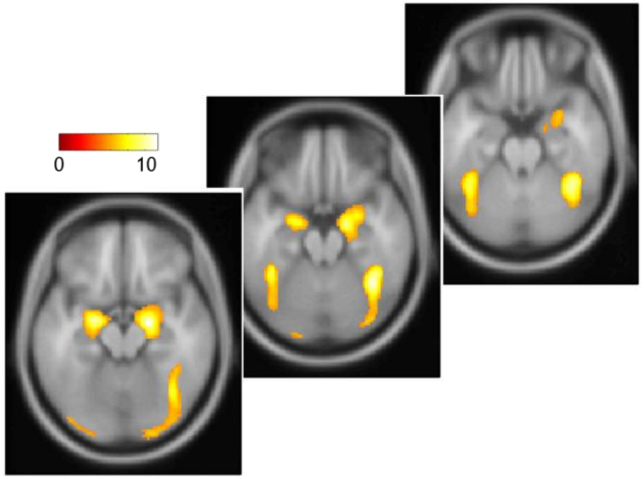


Brodersen et al. 2011, *PLoS Comput. Biol.*

❸ Prediction: Two-year outcome in depression

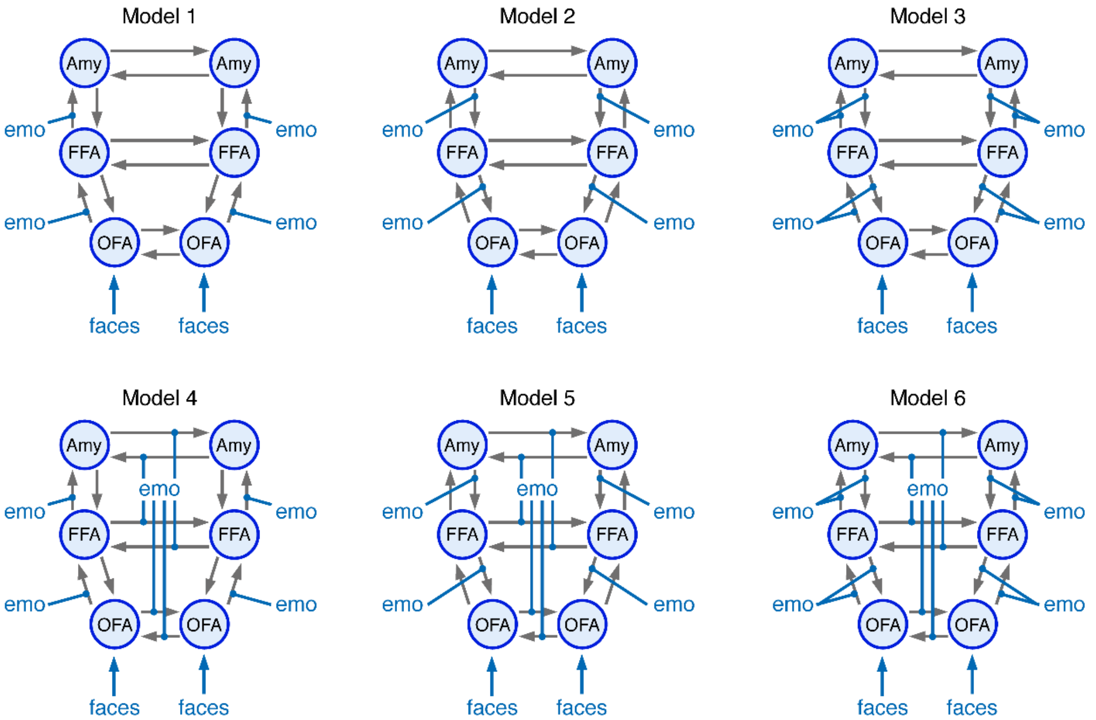
N=85 MDD patients from NESDA study (Schmaal et al. 2015, Biol. Psychiatry)

Three distinct trajectories:
chronic (CHR): n = 15
gradually improving (IMP): n = 31
remission (REM): n = 39



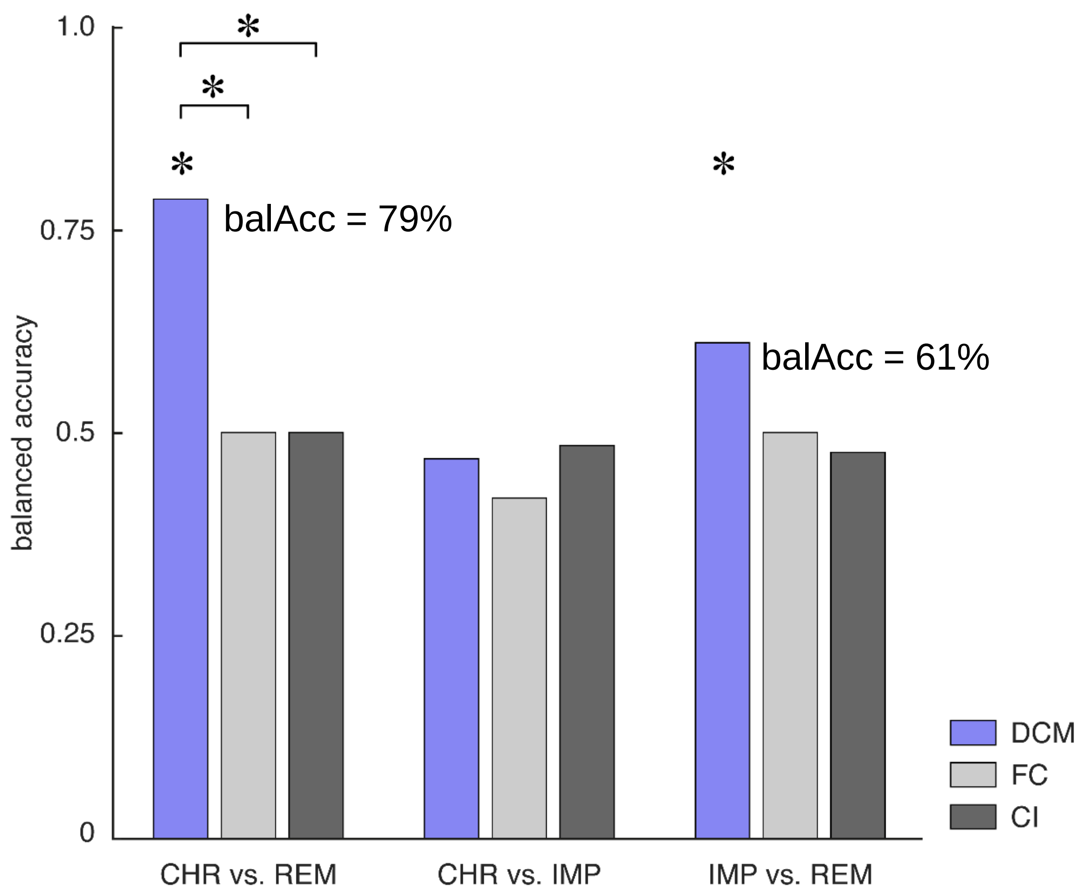
emotional faces > scrambled faces

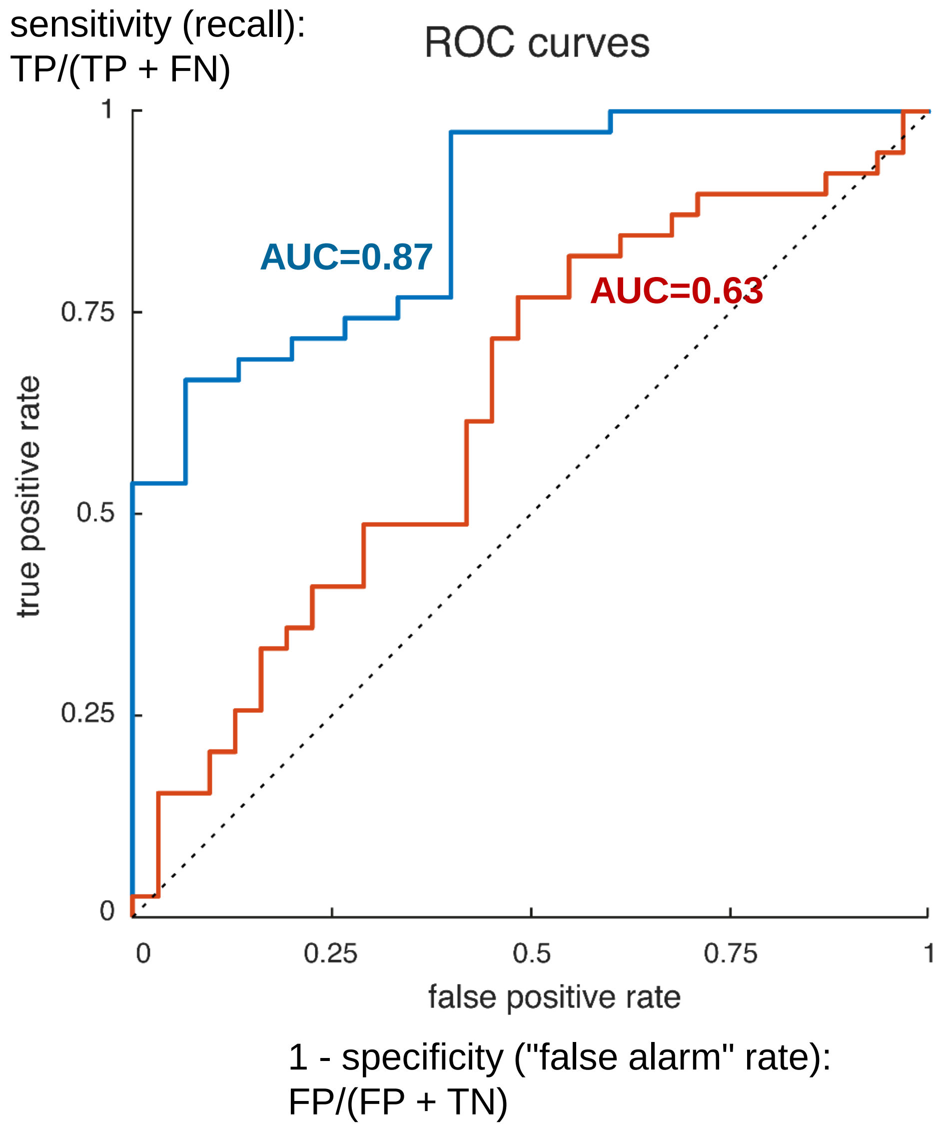
DCM + BMA (emotional face processing)



Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: Two-year outcome in depression





Frässle et al. 2020, *NeuroImage Clinical*

Key challenges for CP (and our local response)

1. **Highly interdisciplinary → mutual teaching**
2. **Methodology in its infancy → open source code and data sharing**
3. **Prospective validation studies → uniting computational & biomedical scientists in new types of organisations**

Key challenges for CP (and our local response)

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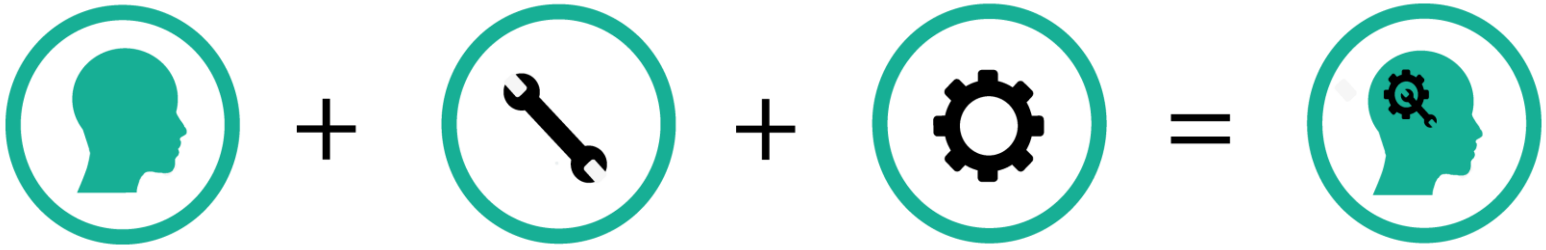
COMPUTATIONALPSYCHIATRYCOURSE



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   biomedical scientists in ne

Translational Neuromodeling Course

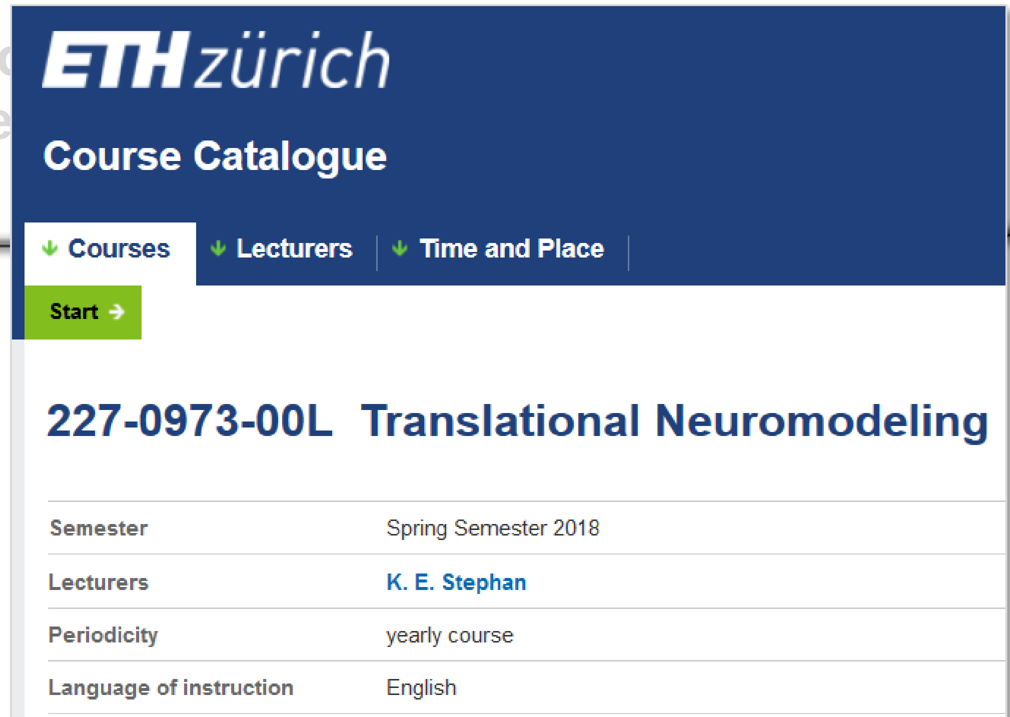
University of Zurich & ETH Zurich

3 hours lectures per week

+ 2h exercises per week

+ 2 week project

annual course (spring semester)



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TAPAS

www.translationalneuromodeling.org/tapas

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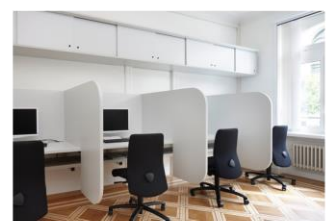
Translational Neuromodeling Unit

www.tnu.ethz.ch



CPC 2020

http://www.translationalneuromodeling.org/cpcourse/

- 6th international edition
- originated from our local courses on Computational Psychiatry since 2012
- key features
  - clinical lectures (Monday)
  - methodological lectures (Tuesday – Thursday)
  - application talks (Friday)
  - practical exercises (Saturday) with different open source toolboxes
  - covers models of both physiology and behaviour
  - 35 presenters from 20 international institutions

CPC 2020

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
Clinical Psychiatry	Bayesian modeling basics & RL	Bayesian models, active inference, HGF, MDP, DDM	Connectivity (DCM), machine learning	Computational Psychiatry in application

Further reading: reviews on computational psychiatry

- Frässle S, Yao Y, Schöbi D, Aponte EA, Heinzle J, Stephan KE (2018) Generative models for clinical applications in computational psychiatry. Wiley Interdisciplinary Reviews: Cognitive Science 9: e1460.
- Friston KJ, Stephan KE, Montague R, Dolan RJ (2014) Computational psychiatry: the brain as a phantastic organ. The Lancet Psychiatry 1: 148-158.
- Huys Q, Maia T, Frank M (2016) Computational psychiatry as a bridge between neuroscience and clinical applications. Nat. Neurosci. 19: 404-413
- Maia TV, Frank MJ (2011) From reinforcement learning models to psychiatric and neurological disorders. Nat. Neurosci. 14, 154–162.
- Montague PR, Dolan RJ, Friston KJ, Dayan P (2012) Computational psychiatry. Trends Cogn. Sci. 16, 72–80.
- 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.
- Stephan KE, Schlagenhauf F, Huys QJM, Raman S, Aponte EA, Brodersen KH, Rigoux L, Moran RJ, Daunizeau J, Dolan RJ, Friston KJ, Heinz A (2017) Computational Neuroimaging Strategies for Single Patient Predictions. NeuroImage 145:180-199
- Wang XJ, Krystal JH (2014) Computational psychiatry. Neuron 84: 638-654.

Once again, a very warm welcome – we hope you will enjoy the CPC 2020!

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http://www.translationalneuromodeling.org/cpcourse/