CPC 2022:
Introduction to Computational Psychiatry

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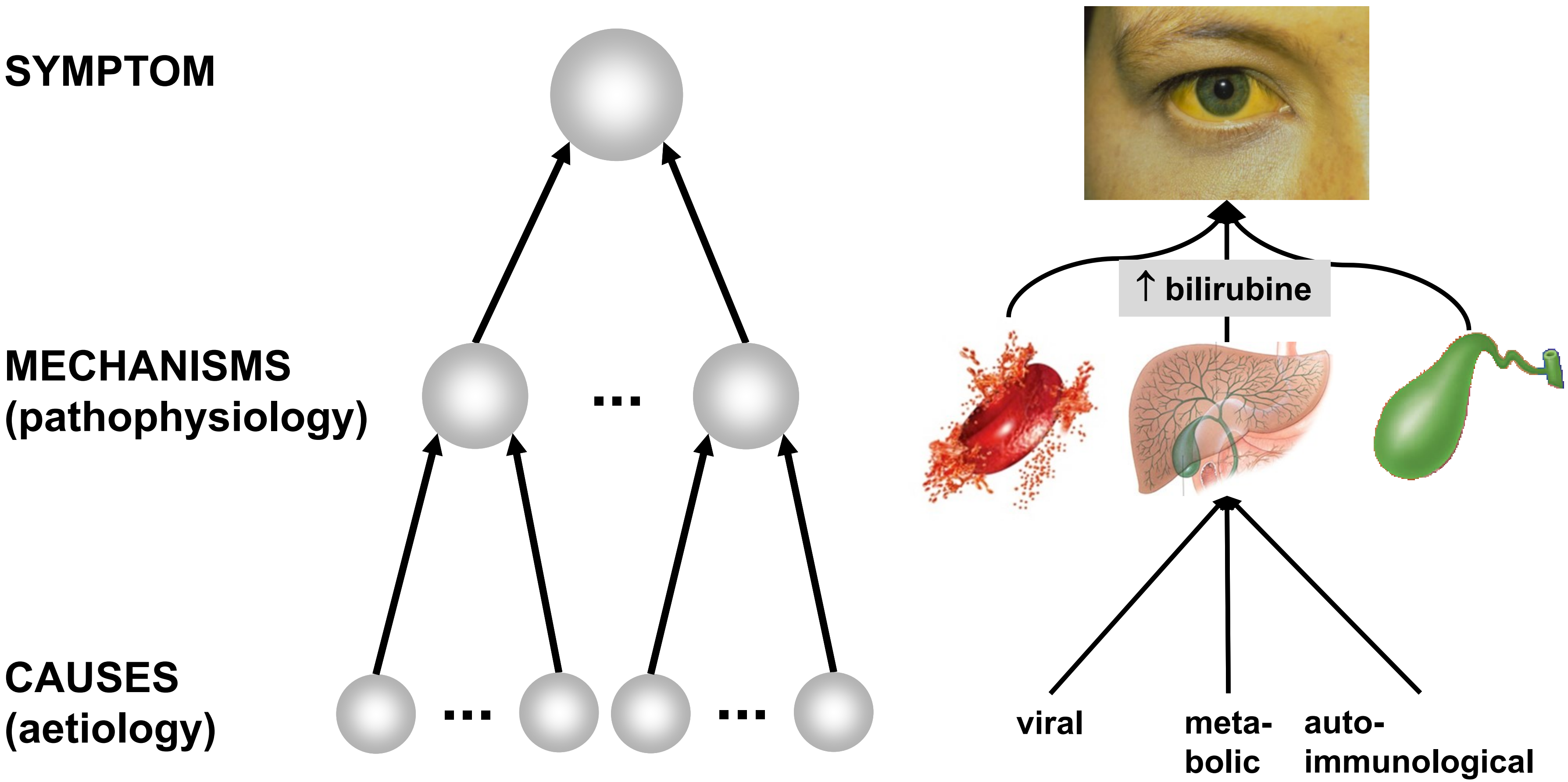
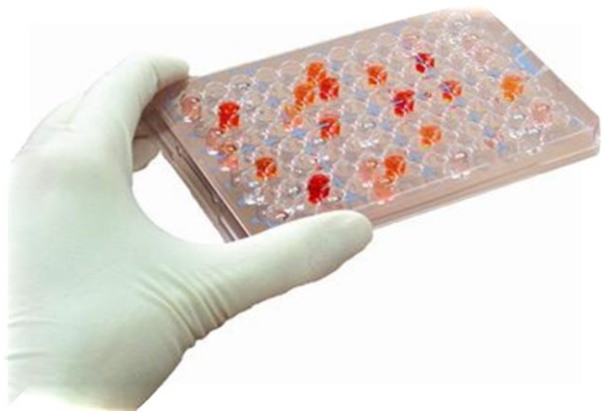
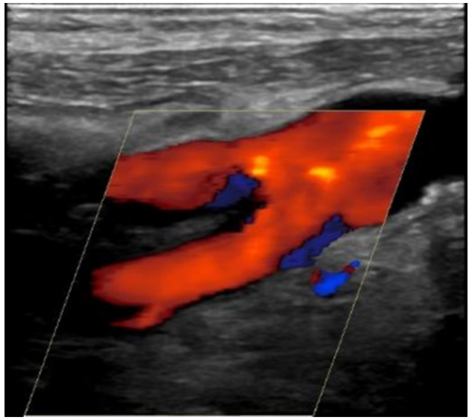
From differential diagnosis to nosology

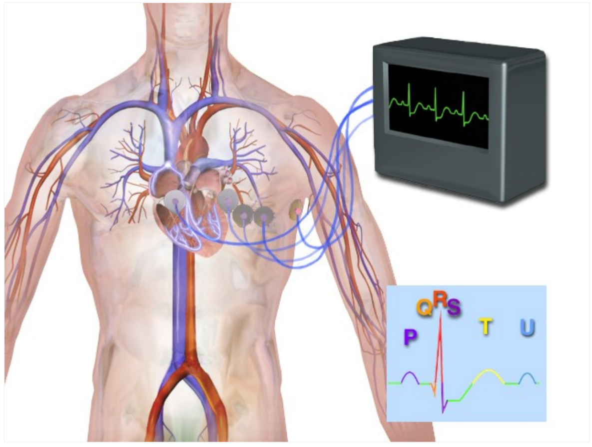


Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

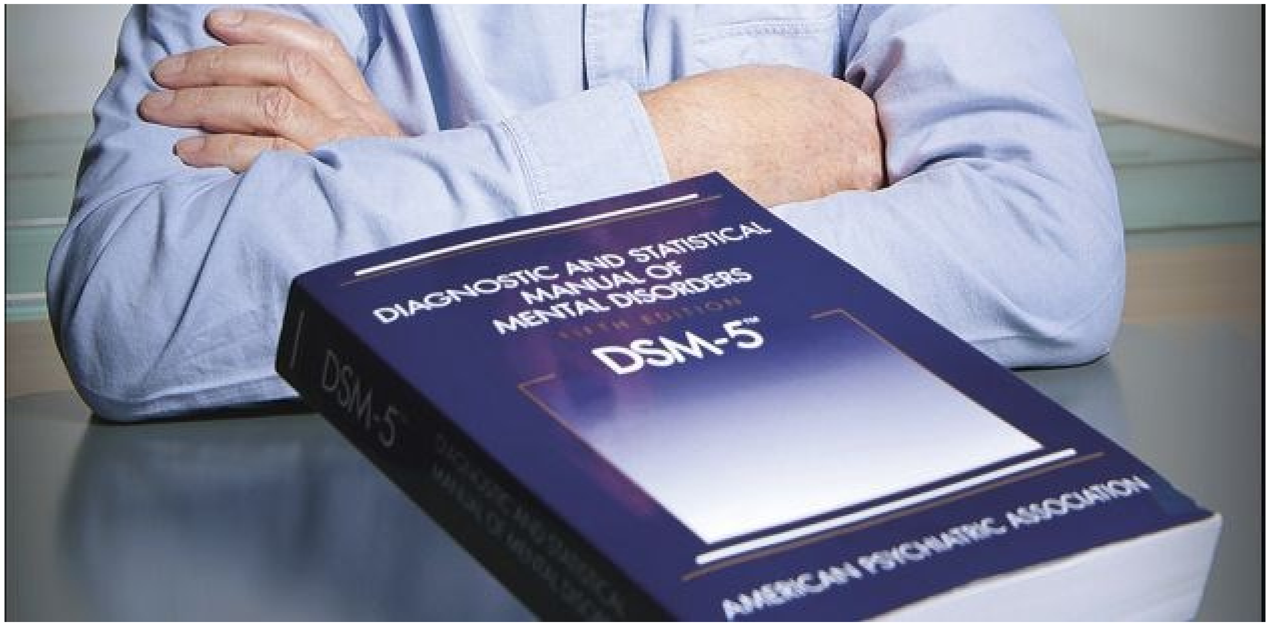
>3,000 clinical tests in medicine



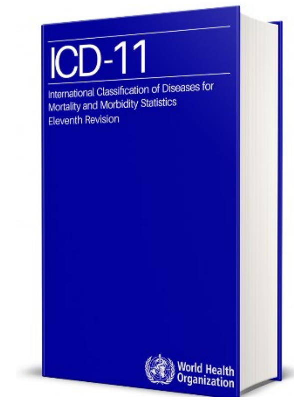




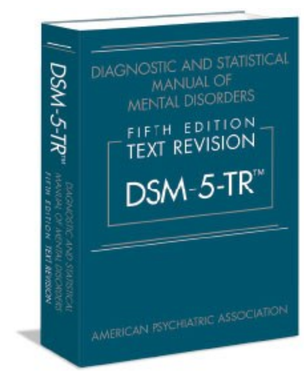
1 diagnostic instrument in psychiatry



Contemporary psychiatric classifications: ICD and DSM



- **International Classification of Diseases (ICD):**
  - curated by the World Health Organization (WHO)
  - freely available
  - presently in its 10th revision (ICD-10);
    ICD-11 will come into effect in 2022



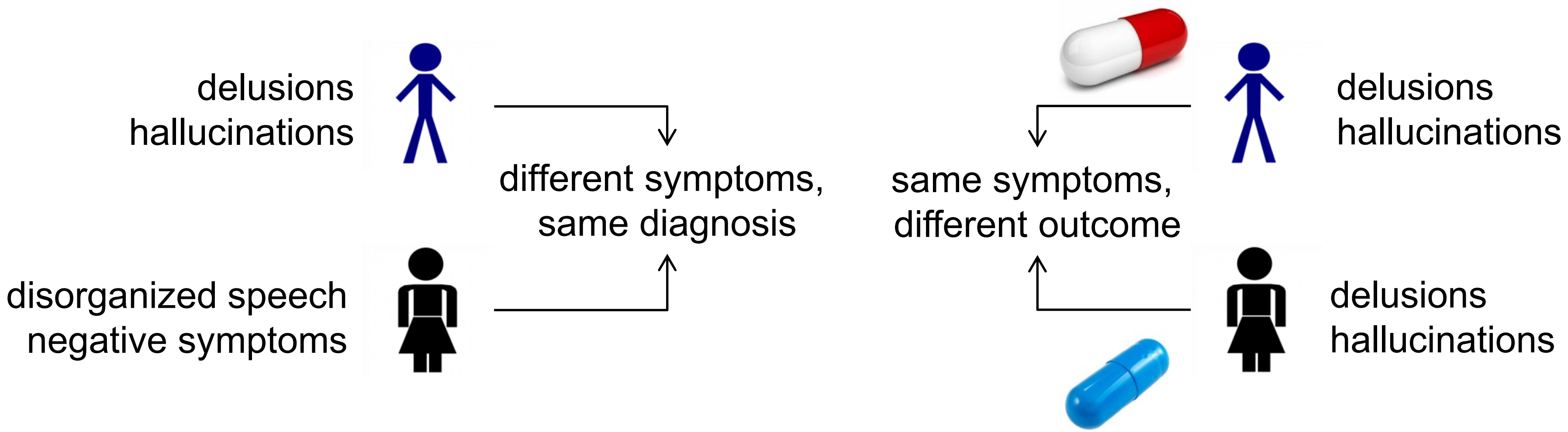
- **Diagnostic and Statistical Manual of Mental Disorders (DSM)**
  - published by the American Psychiatric Association (APA)
  - not free
  - presently: fifth edition (DSM-5); text revision (TR) published in 2022
- **both schemes**
  - define mental disorders as syndromes
  - reflect the consensus (or compromise) of expert committees
  - are descriptive (without reference to mechanisms)

DSM-5: Schizophrenia

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

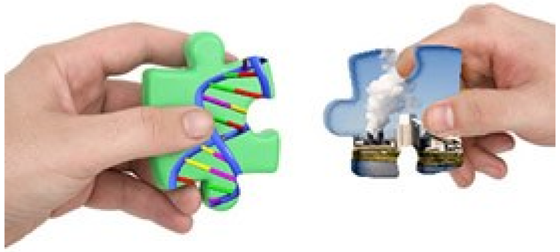
+ social or occupational dysfunction
+ continuous signs of the disturbance for at least six months

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



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

Heterogeneity of psychiatric disorders



polygenetic basis

gene-environment interactions

environmental variation

variability in clinical trajectory and treatment response

multiple disease mechanisms

PERSPECTIVE

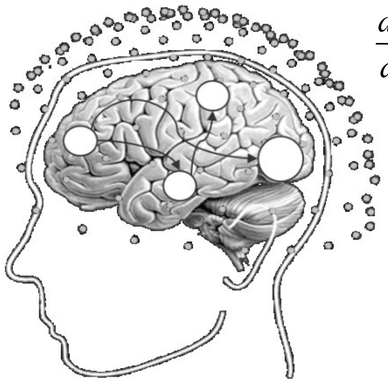
Why has it taken so long for biological psychiatry to develop clinical tests and [redacted]

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

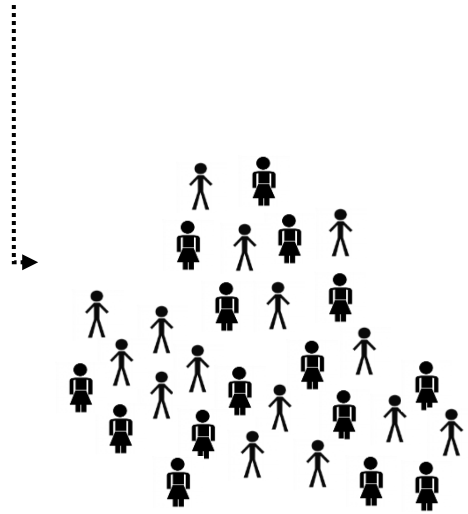
Kapur et al. 2012, *Molecular Psychiatry*

Translational Neuromodeling & Computational Psychiatry

❶ **Developing computational assays of neuronal and cognitive processes**

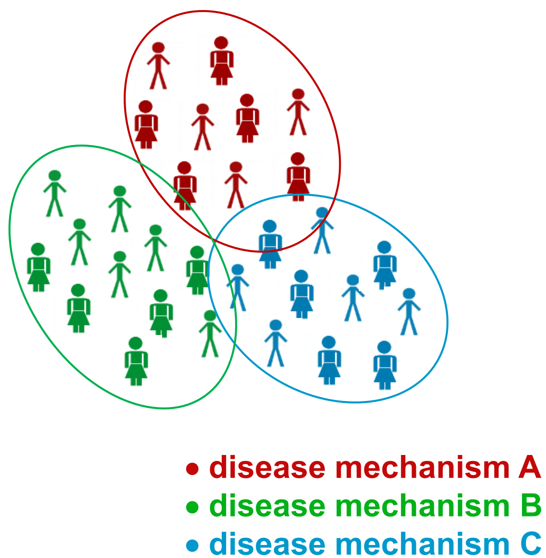


$$\frac{dx}{dt} = f(x,u,\theta)+\omega$$

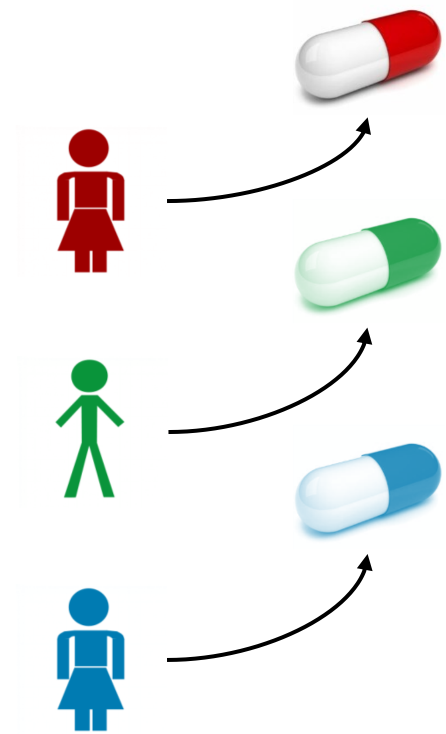


❷ **Application to brain activity and behaviour of individual patients**

❸ **Differentiating patients based on inferred mechanisms**



❹ **Individual treatment prediction**



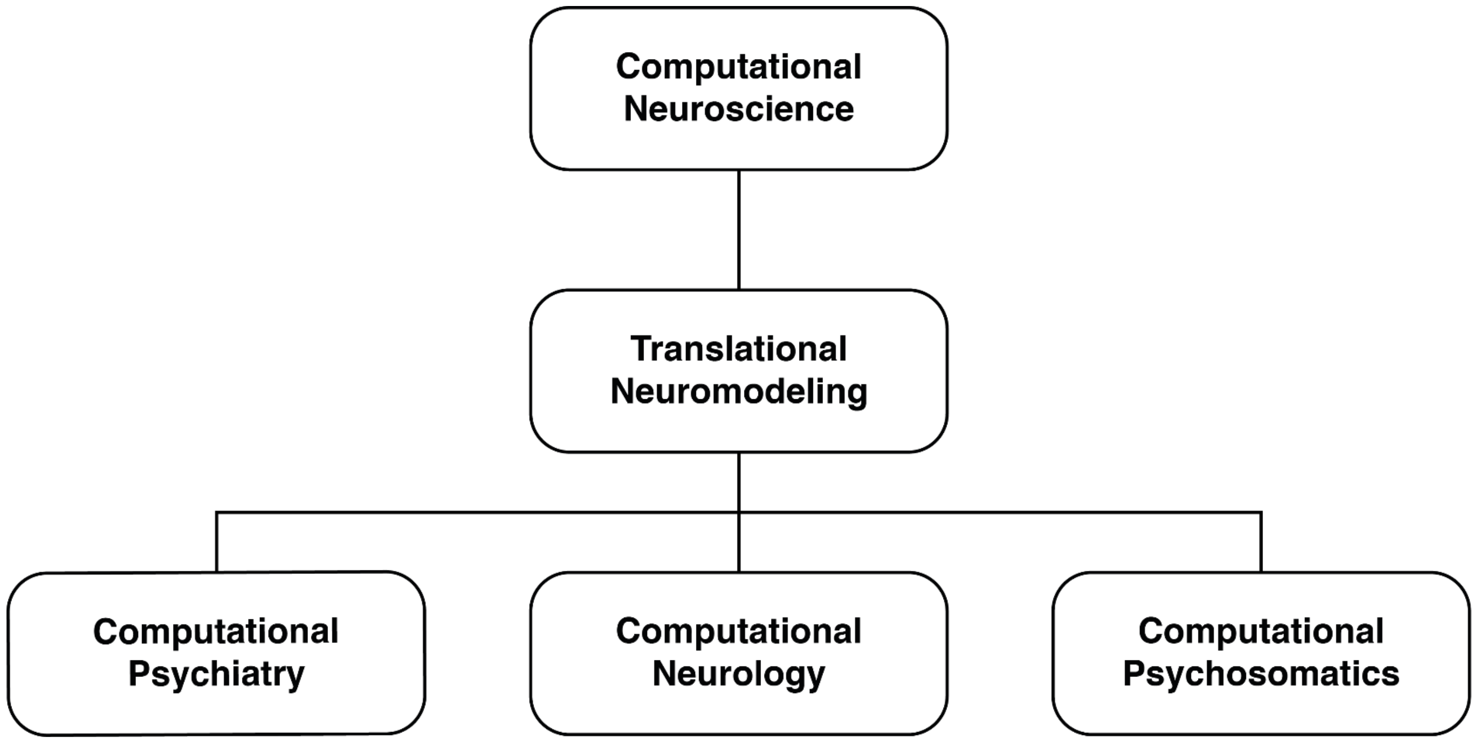
Stephan et al. 2015, *Neuron*

A taxonomy of computational clinical neuroscience

Understanding how/what the brain computes

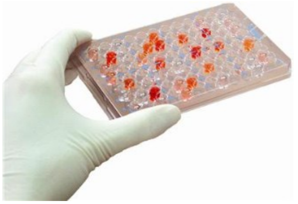
Develops/validates mathematical models for solving clinical problems

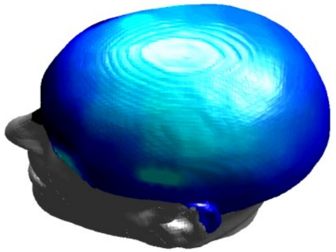
Application within specific medical fields



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

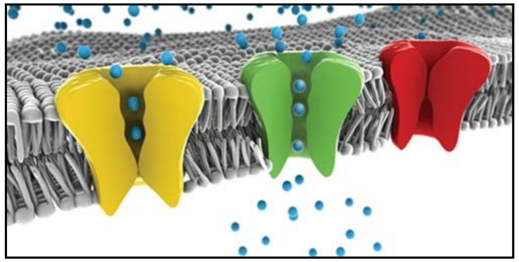
Generative models as "computational assays"



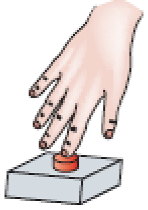


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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

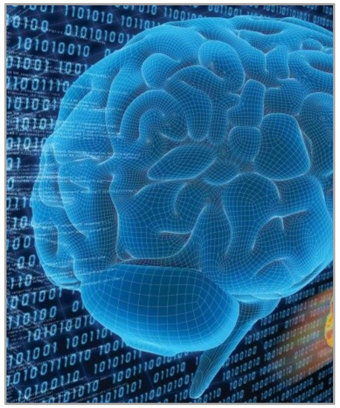


y = data, θ = parameters, m = model

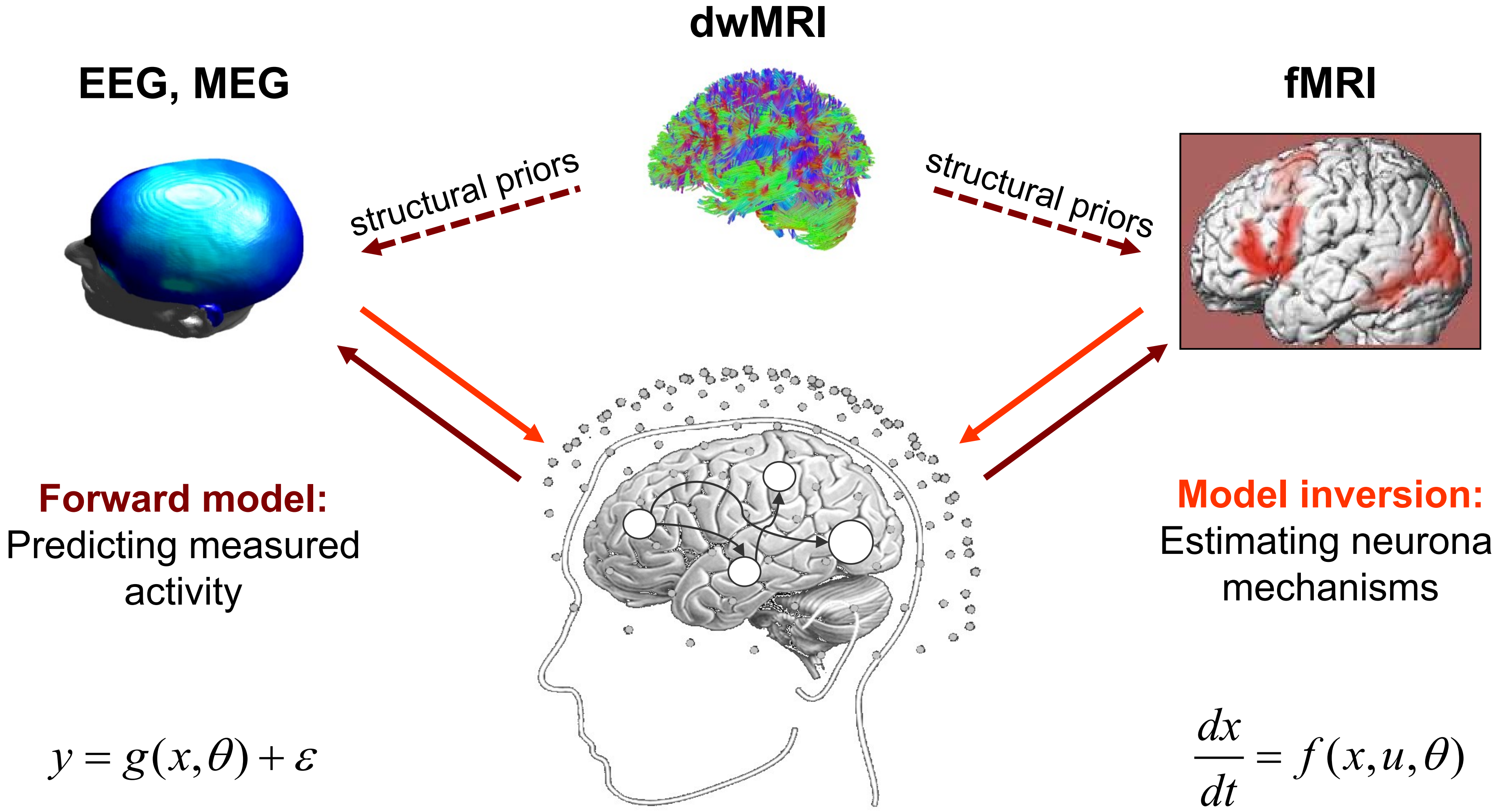


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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

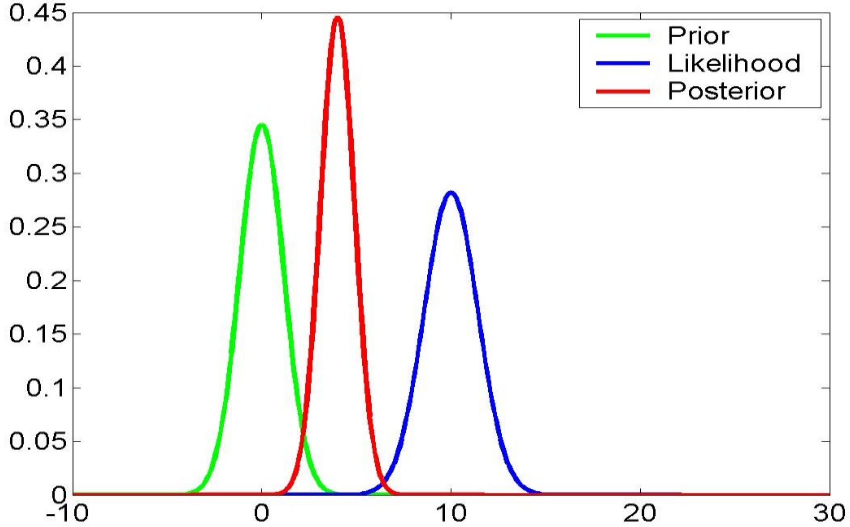


Example: Dynamic causal models (DCMs)



Adapted from Stephan al. 2017, *NeuroImage*

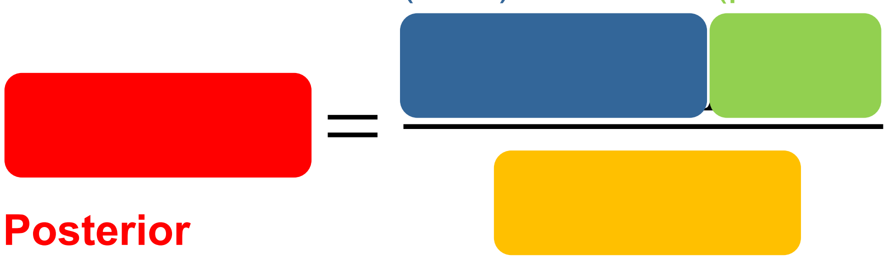
Bayes' rule



The Reverend Thomas Bayes
(1702-1761)

Likelihood
(data)

Prior
(prediction)



Posterior
(inference)

Evidence
(normalisation term)

θ: parameters
y: data

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

Wikipedia

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

neuronal states

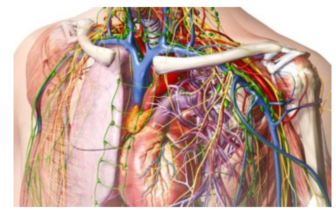
environm. states
others' mental states
bodily states

forward model

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

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

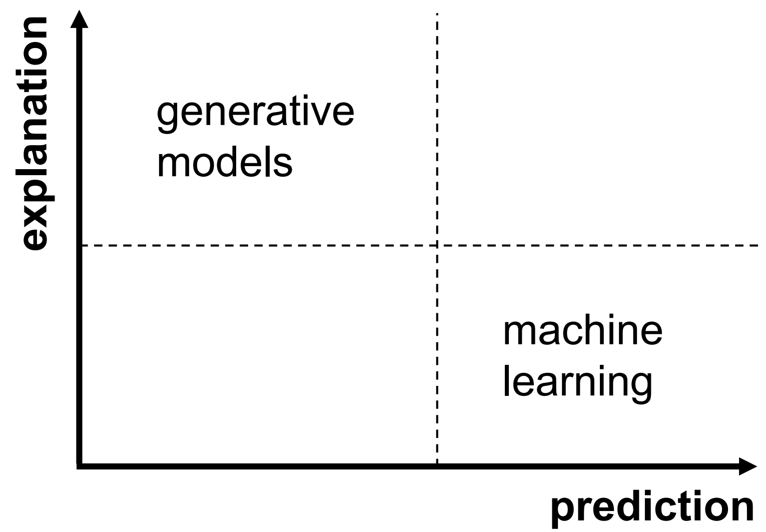
perception



perception = inference = inversion of a generative model

The “Two Cultures of Computational Psychiatry”

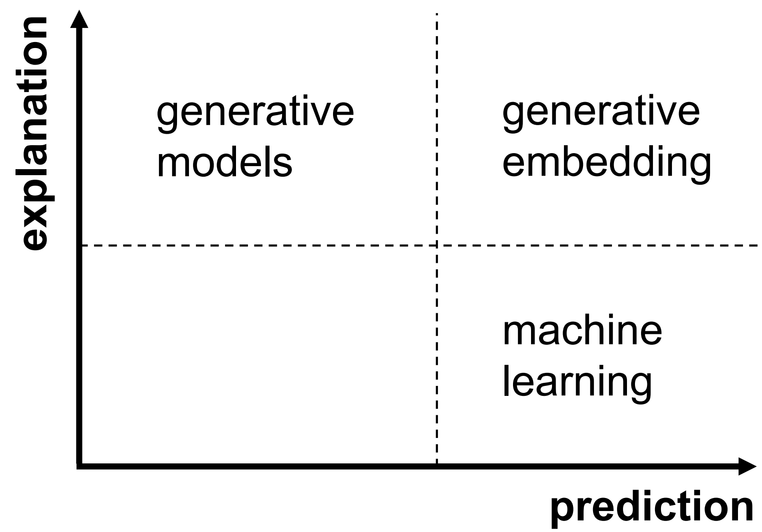
- **explanation:** generative models
  - data-generating process is of central interest
  - goal: identify the mechanisms underlying clinical symptoms
- **prediction:** machine learning (ML)
  - data-generating process is treated as a black box
  - goal: prediction of clinical relevant outcomes, e.g. treatment response, remission, relapse



Bennett et al. 2019, *JAMA Psychiatry*

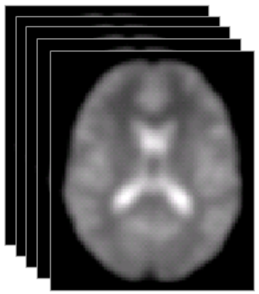
The “Two Cultures of Computational Psychiatry” ... and Generative Embedding as their bridge

- **explanation:** generative models
  - data-generating process is of central interest
  - goal: identify the mechanisms underlying clinical symptoms
- **prediction:** machine learning (ML)
  - data-generating process is treated as a black box
  - goal: prediction of clinically relevant outcomes, e.g. treatment response, remission, relapse
- **generative embedding:**
  - applies ML to estimated quantities from generative models

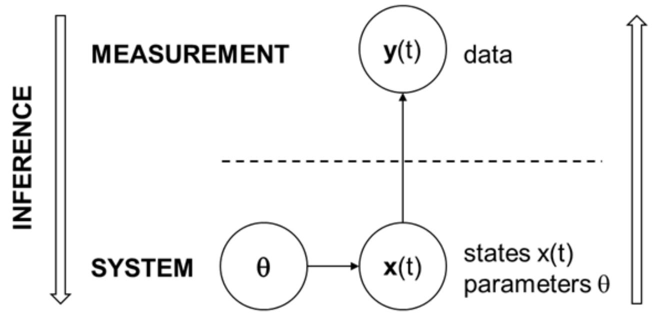


Generative embedding

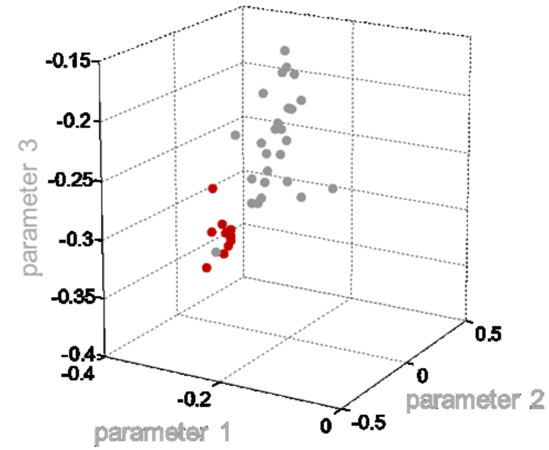
high-dimensional data



generative model



mechanistic interpretation



theory-driven
dimensionality reduction

posterior densities →
features for machine learning

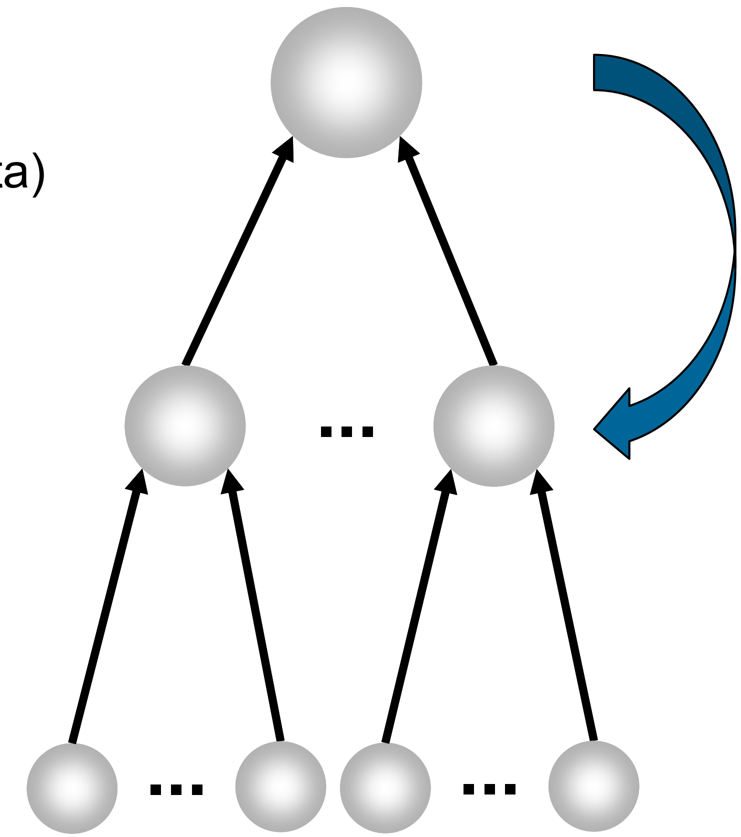
Brodersen et al. 2011, *PLoS Comp. Biol.*
Brodersen et al. 2014, *NeuroImage Clinical*

Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



➊ **differential diagnosis** of alternative disease mechanisms

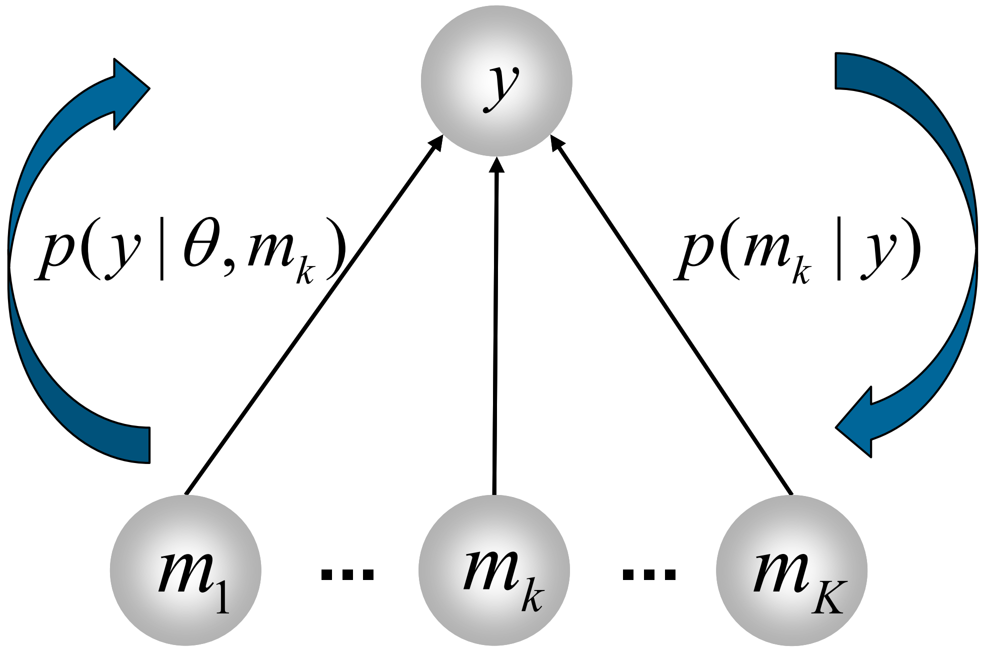
➋ **stratification / subgroup detection** into mechanistically distinct subgroups

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

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

❶ Differential diagnosis: model selection

SYMPTOM
(behaviour
or physiology)

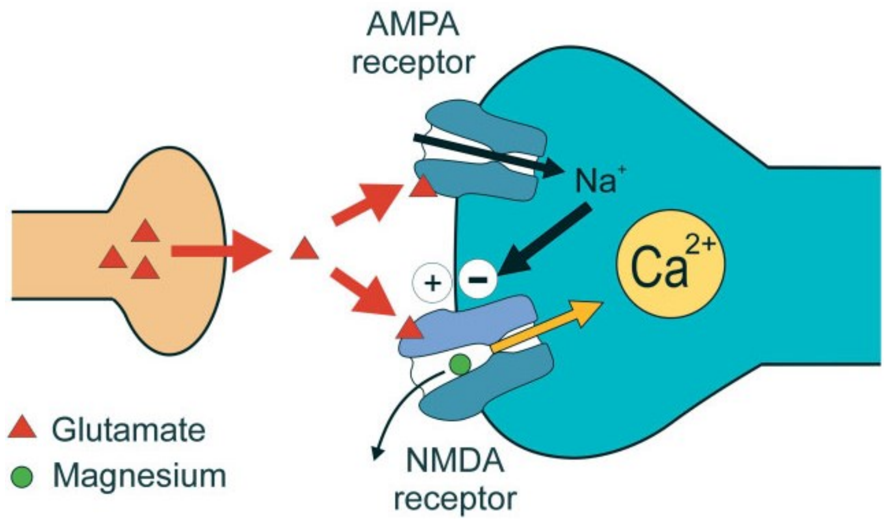


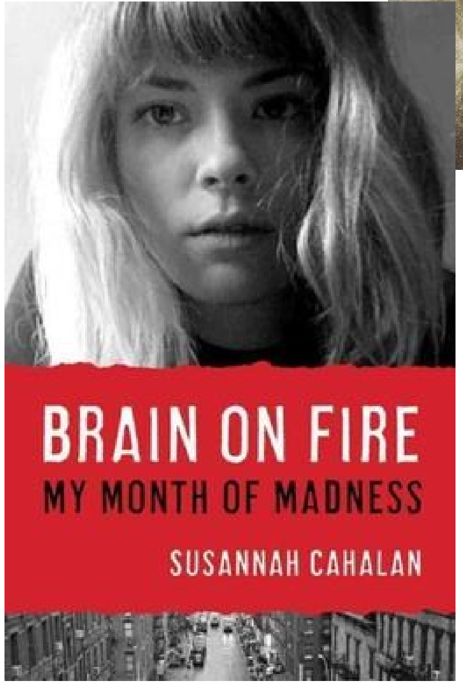
HYPOTHETICAL
MECHANISM

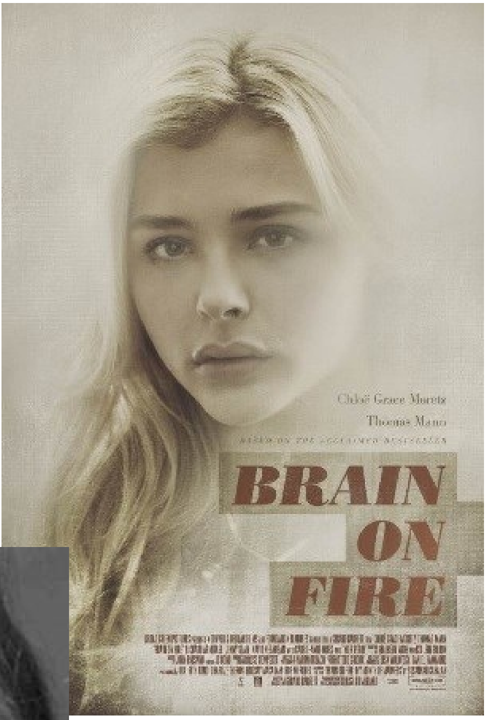
$$p(m_k \mid \mathrm{y}) = \frac{p(y \mid m_k)\, p(m_k)}{\sum_k p(y \mid m_k)\, p(m_k)}$$

Stephan et al. 2017, *NeuroImage*

NMDA receptor antibody encephalitis







Generative modeling of seizure activity in NMDAR antibody encephalitis

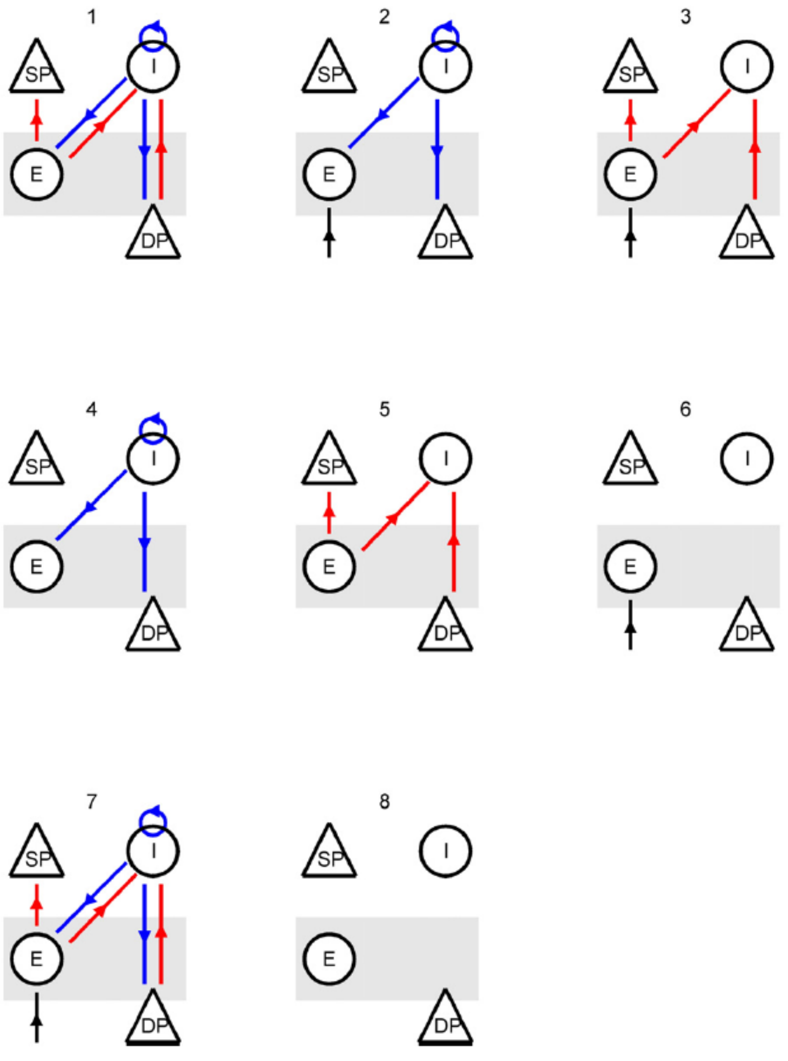


Table 2
The variance described and the free energy for the different models inverted for each patient. Note that the winning model (highest free energy) also had the best fit and these were the same models for both patients. The free energies are expressed relative to the null model.

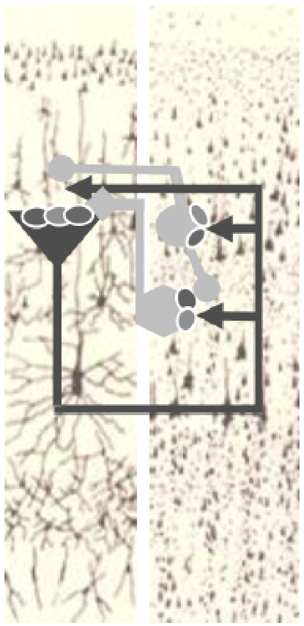
Model	Patient 1		Patient 2	
	Variance explained	Free energy	Variance explained	Free energy
Inhibitory + excitatory + endogenous	0.97	1430	0.95	1740
Inhibitory + excitatory	0.97	1380	0.94	1650
Inhibitory + endogenous	0.97	1320	0.94	1600
Excitatory + endogenous	0.96	1310	0.94	1680
Inhibitory	0.90	860	0.91	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 can serve to infer on pathophysiological processes in single patients.

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

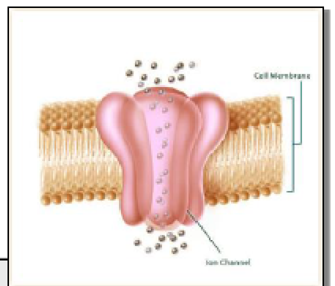
Cooray et al. 2015, *NeuroImage*

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

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

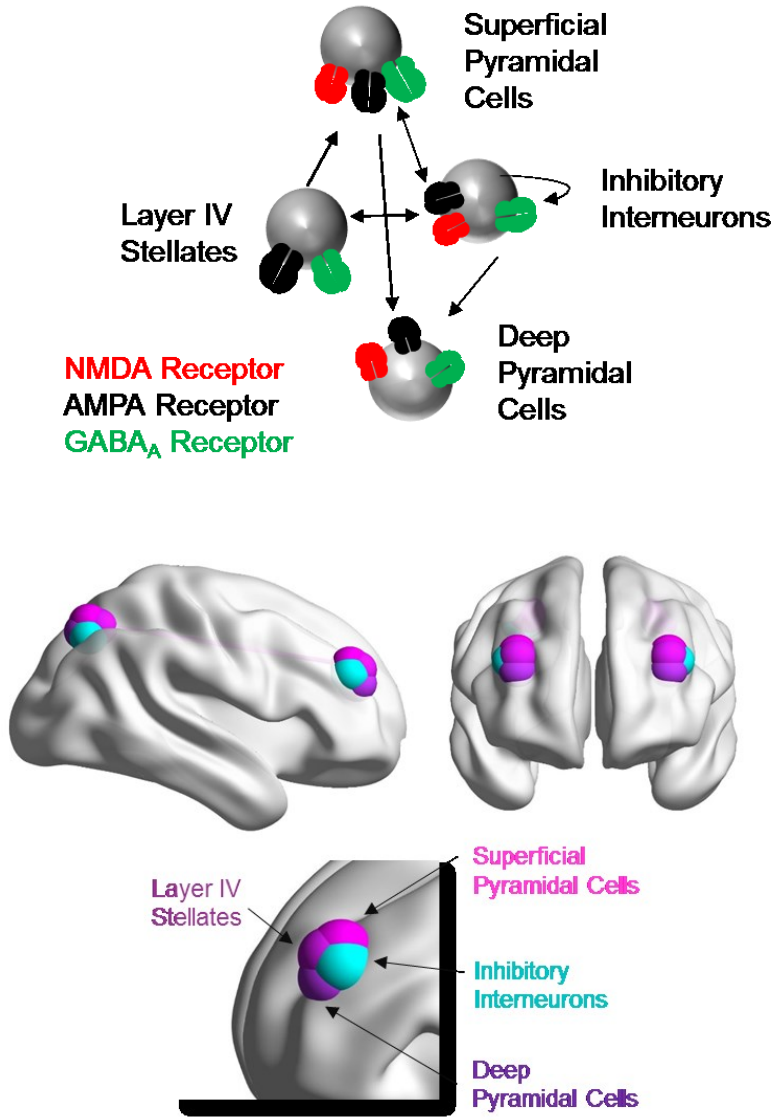
$\gamma_{3,2}^{(I)}$ $\gamma_{1,3}^{(E)}$ $\gamma_{3,1}^{(E)}$

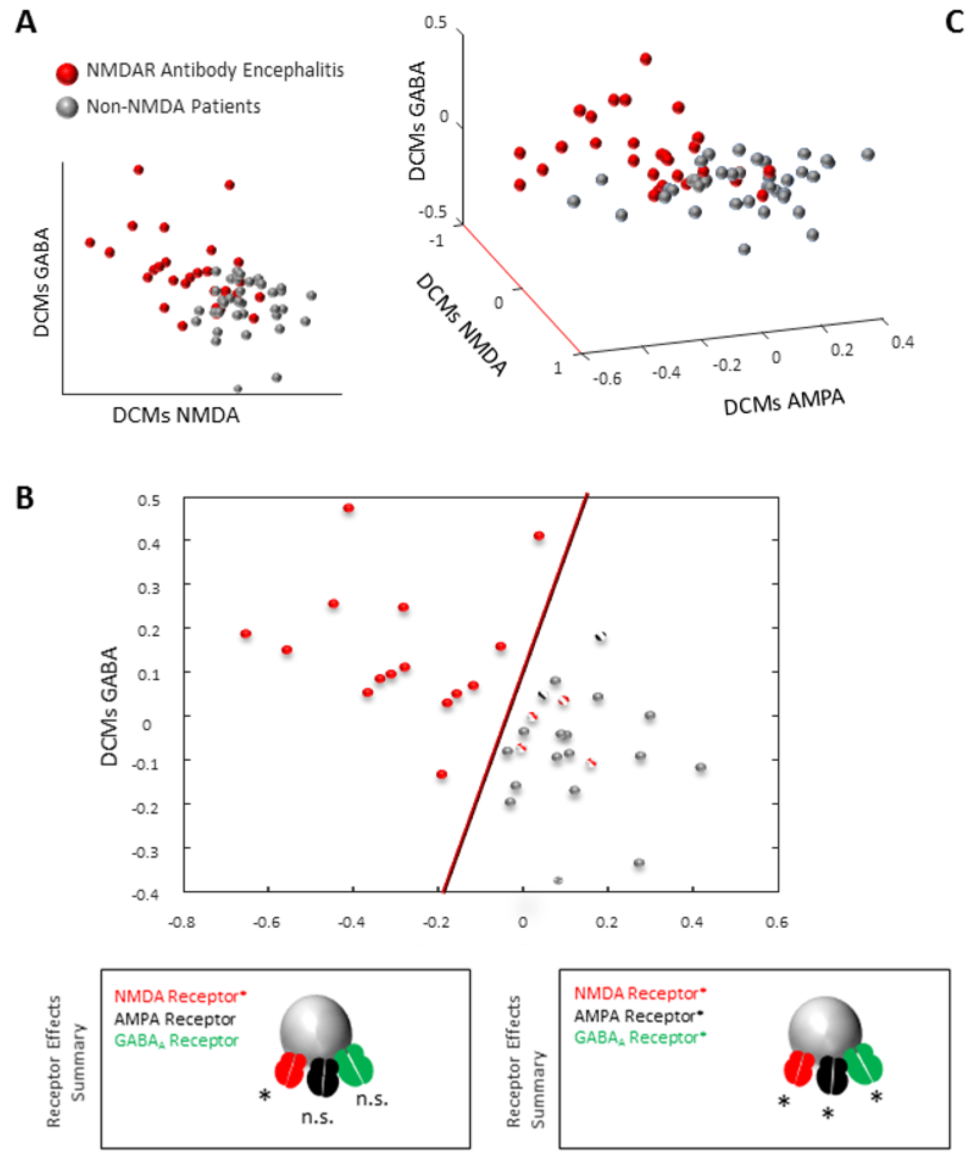
PC

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

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*





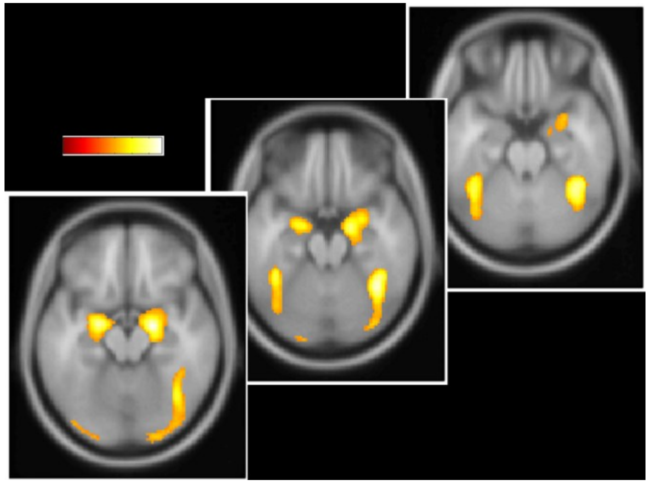
29 patients with NMDAR-antibody encephalitis
18 control patients (with inflammatory/metabolic encephalopathy)

Symmonds et al. 2018, *Brain*

❸ Prediction: Two-year outcome in depression

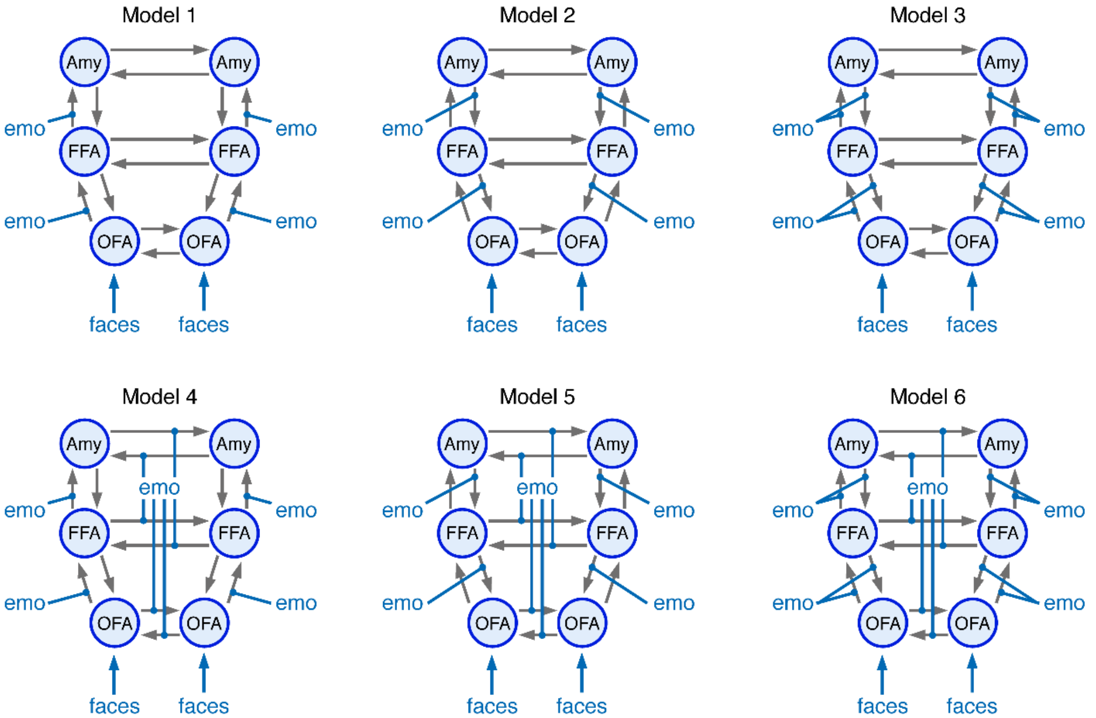
N=85 MDD patients from NESDA study (Schmaal et al. 2015, Biol. Psychiatry)

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



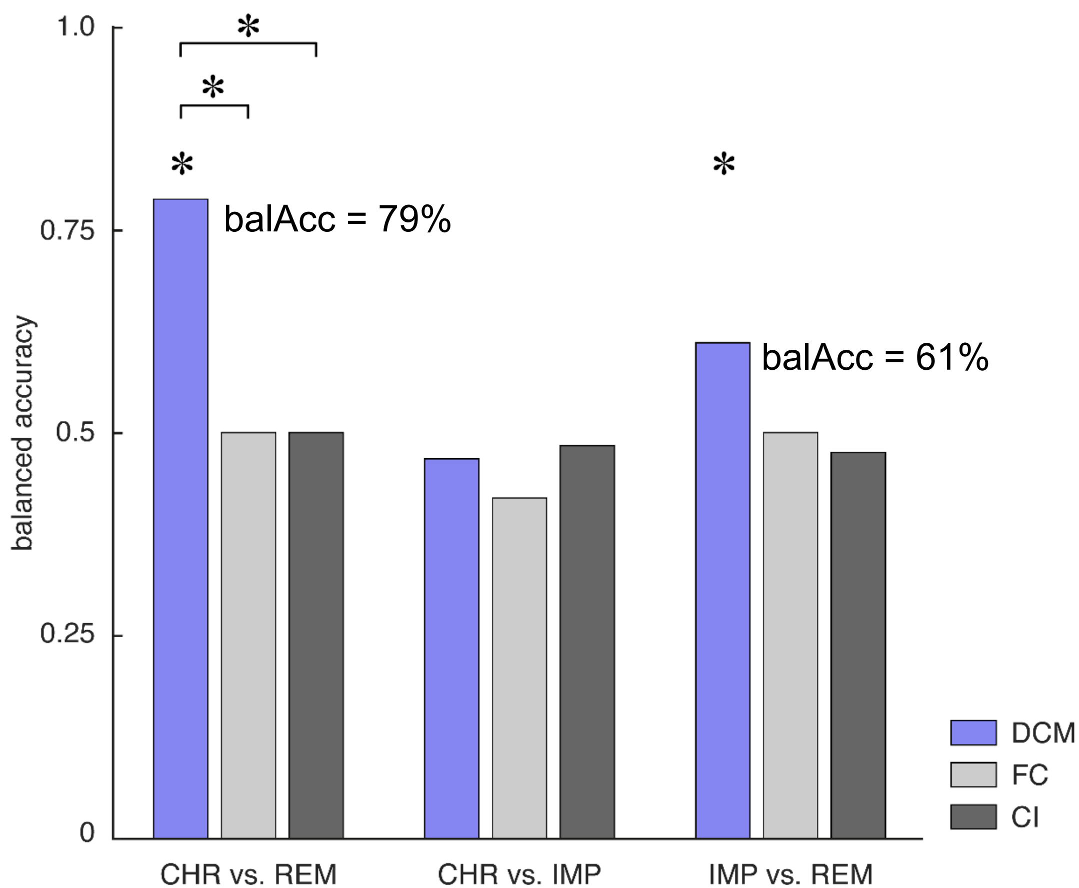
emotional faces > scrambled faces

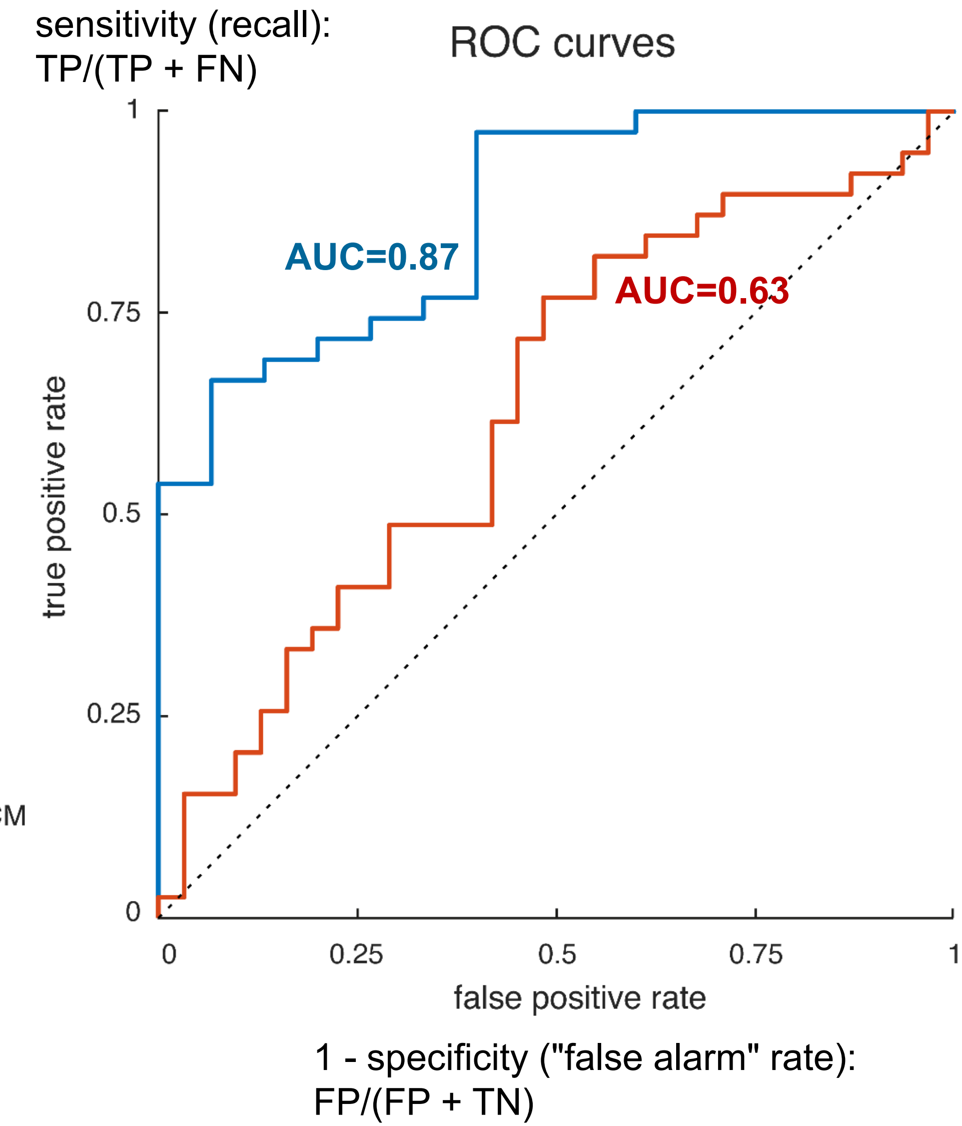
DCM + BMA (emotional face processing)



Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: Two-year outcome in depression

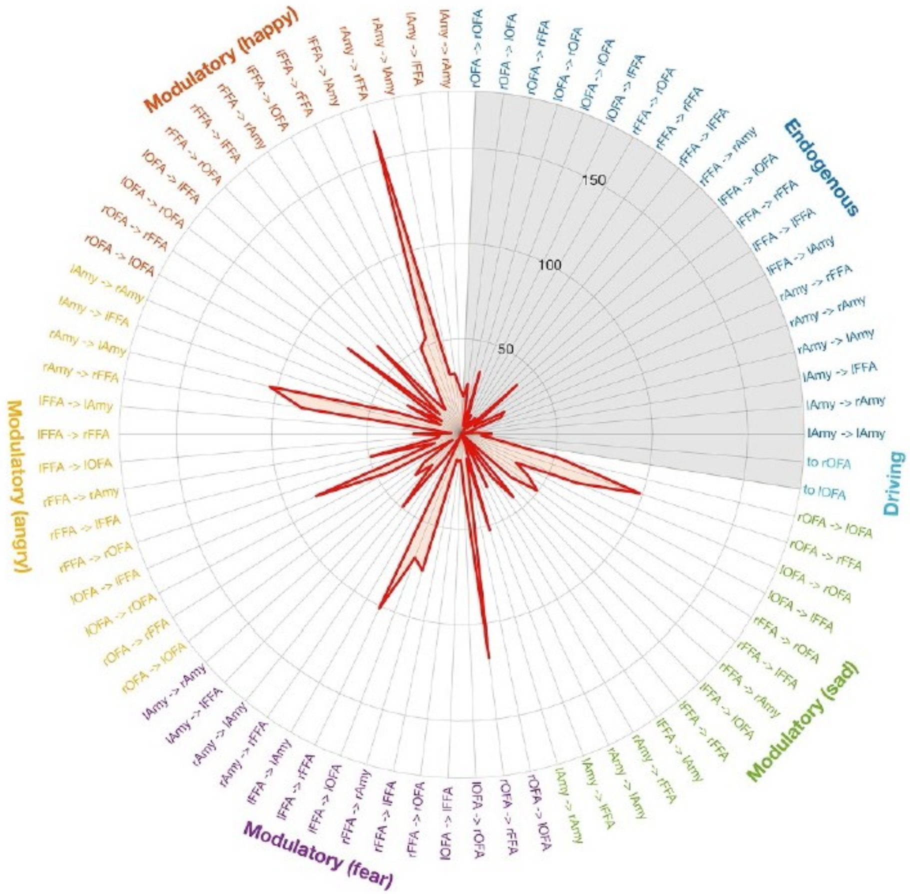




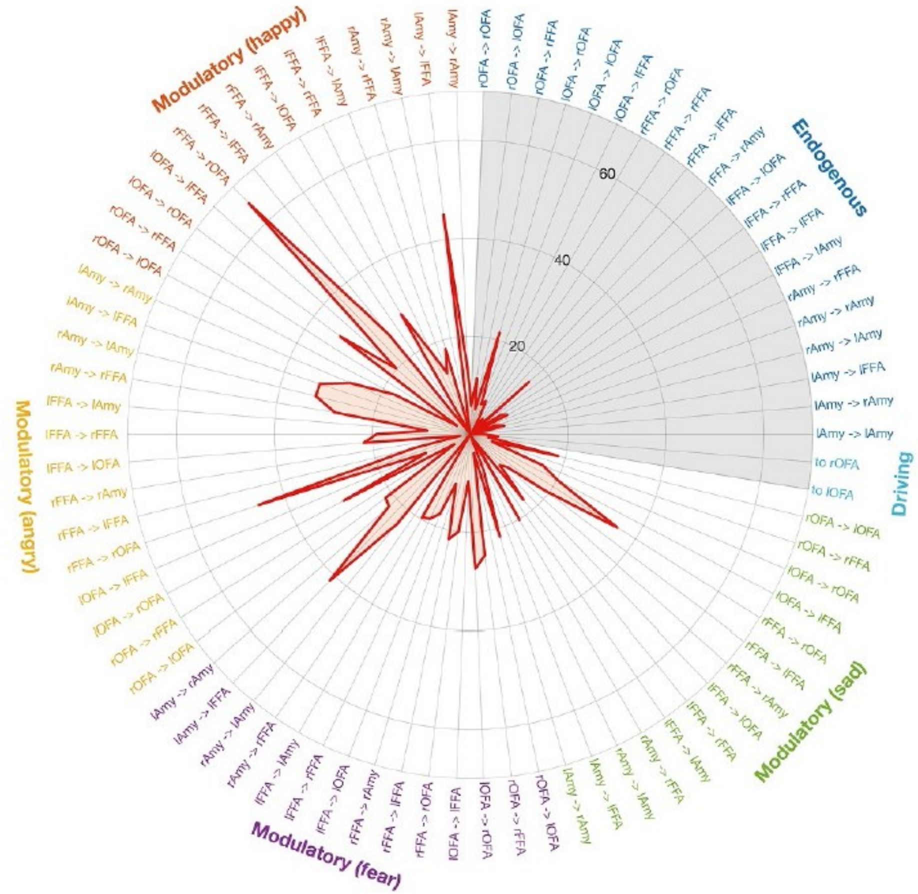
Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: Two-year outcome in depression

CHR vs. REM



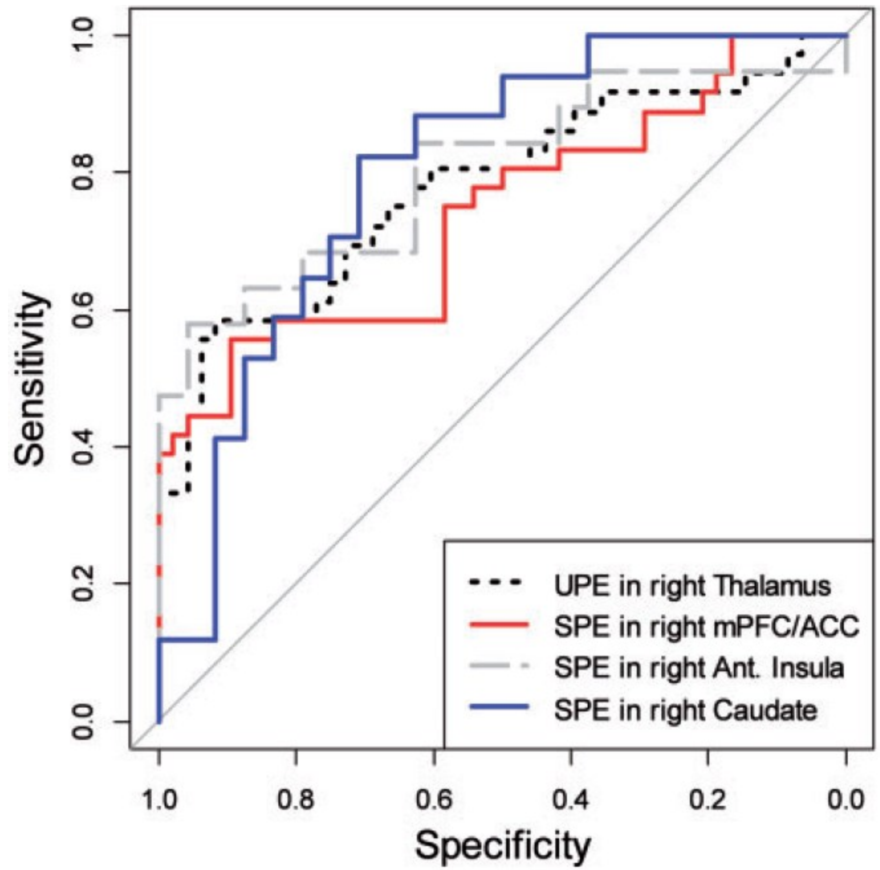
IMP vs. REM



Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: Future problem use of stimulants

- 88 occasional stimulant users
- "determine whether individual differences in the neural representation of the need to stop in an inhibitory task can predict the development of problem use (i.e. abuse or dependence)"
- fMRI (stop-signal task), Bayesian Hidden Markov Model
- prediction error (PE) activity from 4 brain regions predicted problem use 3 years later
- prediction based on computational variables: sensitivity 62%, specificity 83%
- outperformed predictions based on clinical variables and conventional fMRI analyses



UPE = unsigned PE
SPE = signed PE

Harle et al. 2015, *Brain*

Final remark:
What exactly do we mean by "computational"?

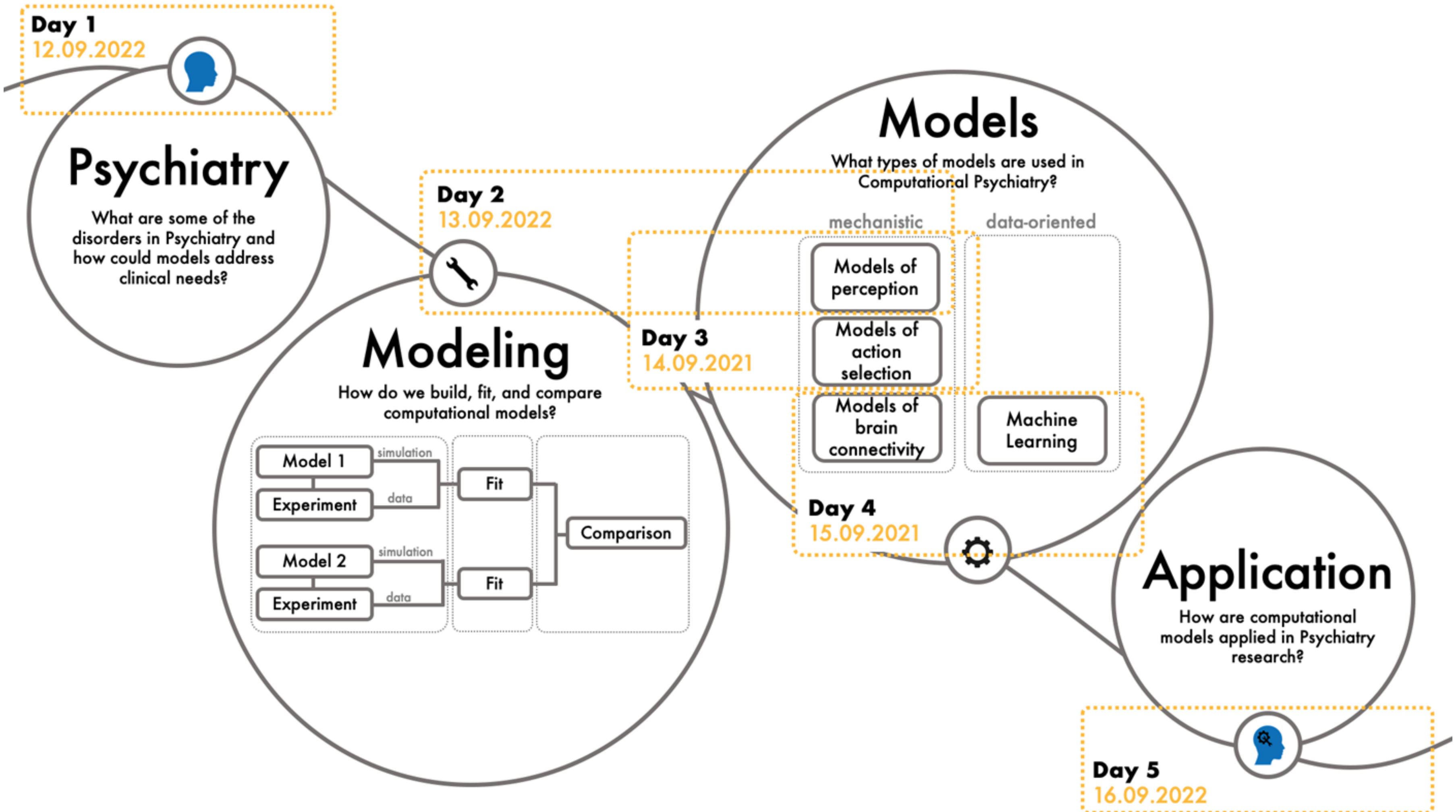
- often used in computational psychiatry:
  levels of analysis for an information-processing system (David Marr):
  - **computational level:** what problem does the system solve?
  - **algorithmic level:** which representations and operations are used?
  - **implementational level:** how is the system physically realized?
- this is in conflict with the classical concept of "computation" from computer science
  - **“computation” = finite sequence of operations (algorithm)** that transform an input set into an output set
- a better terminology might be to replace the "computational level" with "teleological" level

CPC 2022

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

- 8th international edition
- originated from our local courses on Computational Psychiatry since 2012
- 2022: first time in hybrid mode
- key features
  - clinical lectures (Monday)
  - methodological lectures (Tuesday – Thursday)
  - application talks (Friday)
  - practical exercises (Saturday) with different open source toolboxes
  - covers models of both neurophysiology and behaviour
  - 46 presenters from 22 international institutions

CPC 2022



Day 1
12.09.2022
Psychiatry
What are some of the disorders in Psychiatry and how could models address clinical needs?
Day 2
13.09.2022
Modeling
How do we build, fit, and compare computational models?
Model 1
simulation
Experiment
data
Model 2
simulation
Experiment
data
Fit
Fit
Comparison
Day 3
14.09.2021
Models
What types of models are used in Computational Psychiatry?
mechanistic
data-oriented
Models of perception
Models of action selection
Models of brain connectivity
Machine Learning
Day 4
15.09.2021
Application
How are computational models applied in Psychiatry research?
Day 5
16.09.2022

Further reading: reviews on computational psychiatry

- Bennett D, Silverstein SM, Niv Y (2019) The Two Cultures of Computational Psychiatry. JAMA Psychiatry 76: 563-564.
- 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.
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- Huys Q, Maia T, Frank M (2016) Computational psychiatry as a bridge between neuroscience and clinical applications. Nat. Neurosci. 19: 404-413
- Montague PR, Dolan RJ, Friston KJ, Dayan P (2012) Computational psychiatry. Trends Cogn. Sci. 16, 72–80.
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- 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 2022!

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