CPC 2023:
Introduction to Computational Psychiatry

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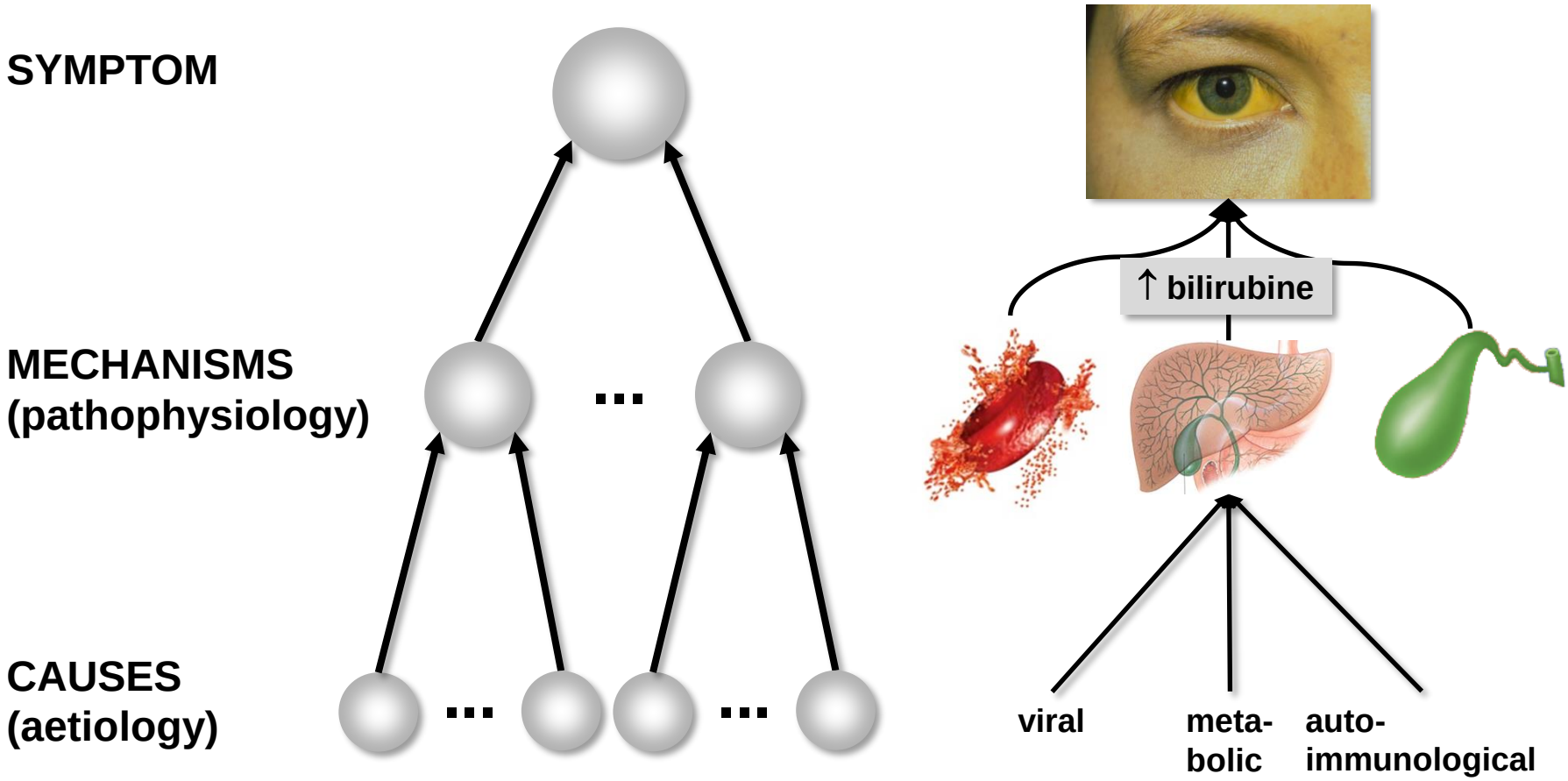
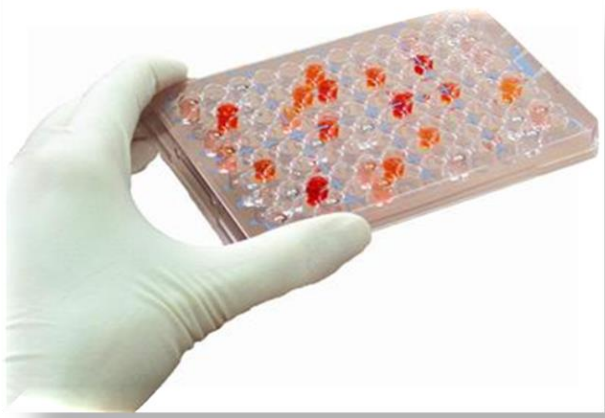
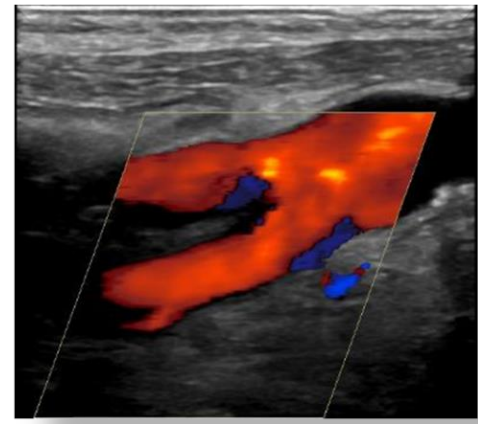
From differential diagnosis to nosology

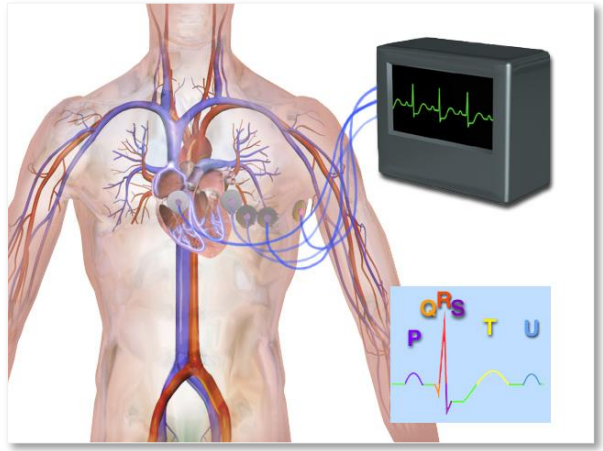


Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

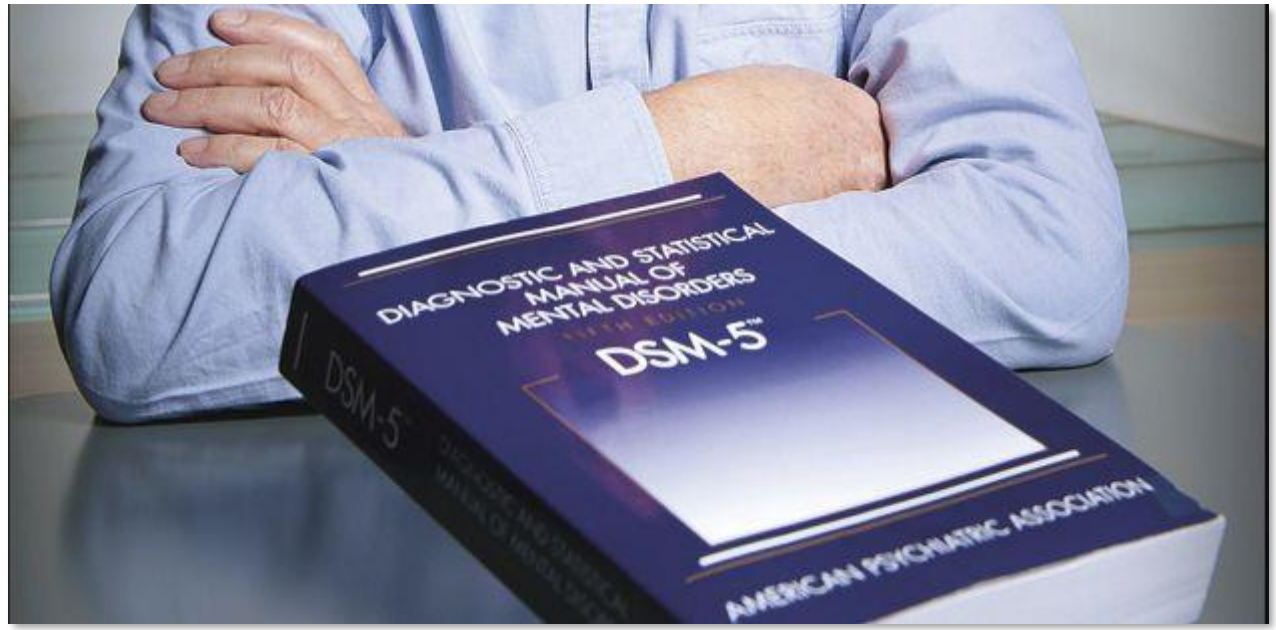
>3,000 clinical tests in medicine



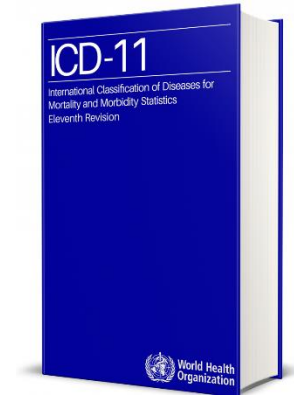




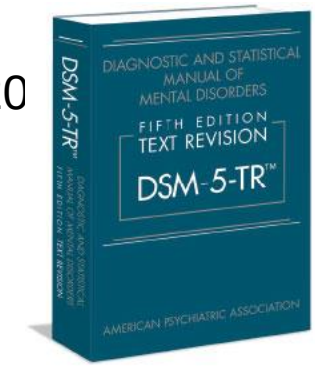
1 diagnostic instrument in psychiatry



Contemporary psychiatric classifications: ICD and DSM



- **International Classification of Diseases (ICD):**
  - curated by the World Health Organization (WHO)
  - freely available
  - presently in its 11th revision (ICD-11)
- **Diagnostic and Statistical Manual of Mental Disorders (DSM)**
  - published by the American Psychiatric Association (APA)
  - approx. $90 (September 2023)
  - presently: fifth edition (DSM-5; 2013); text revision (TR) published in 20



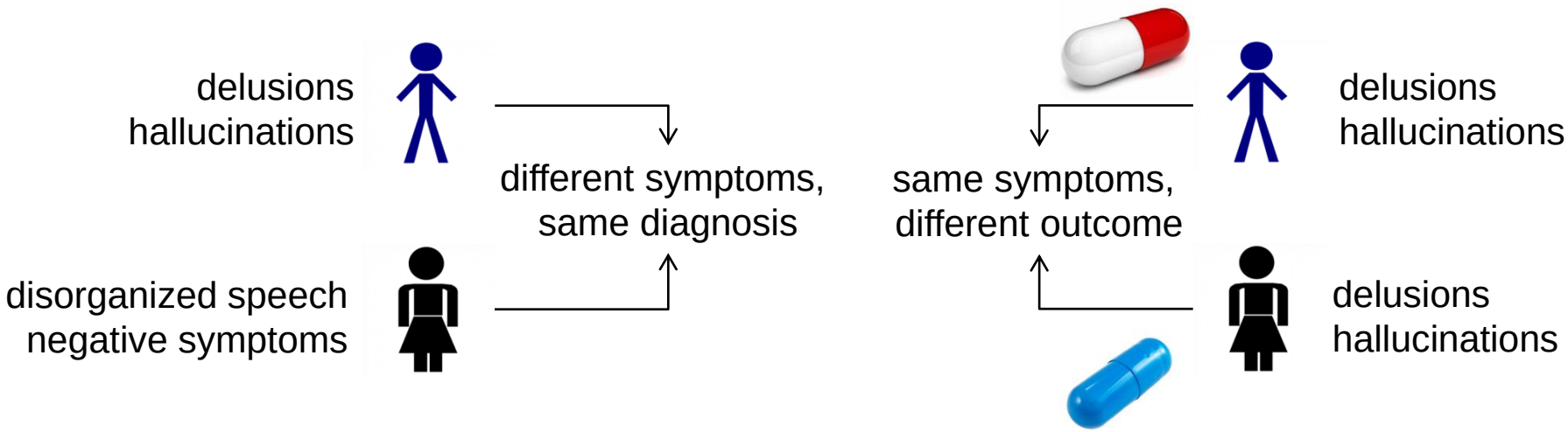
- **both schemes**
  - define mental disorders as syndromes
  - reflect the consensus (or compromise) of expert committees
  - are descriptive (without reference to mechanisms)

DSM-5: Schizophrenia

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

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

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



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

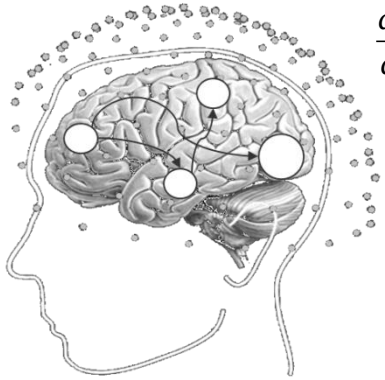
Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

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

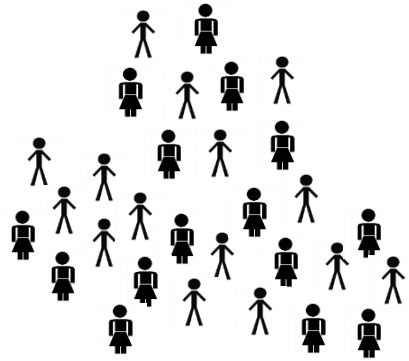
Kapur et al. 2012, *Molecular Psychiatry*

Translational Neuromodeling & Computational Psychiatry

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

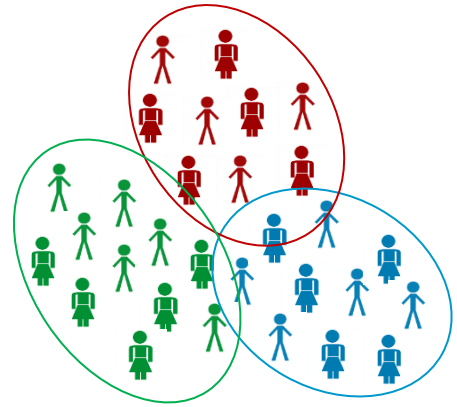


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



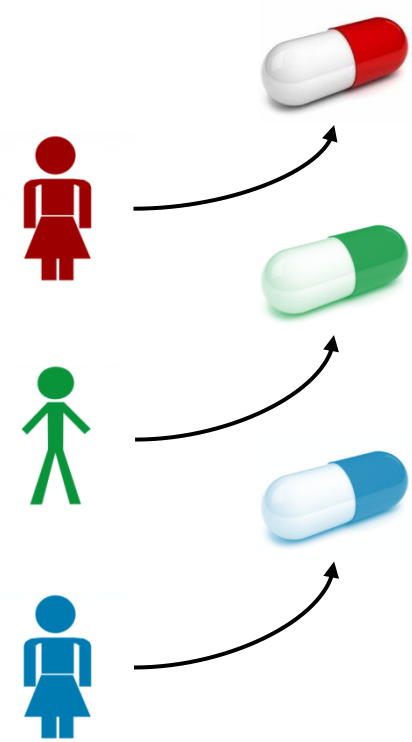
❷ **Application to brain activity and behaviour of individual patients**

❸ **Differentiating patients based on inferred mechanisms**



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

❹ **Individual prediction**



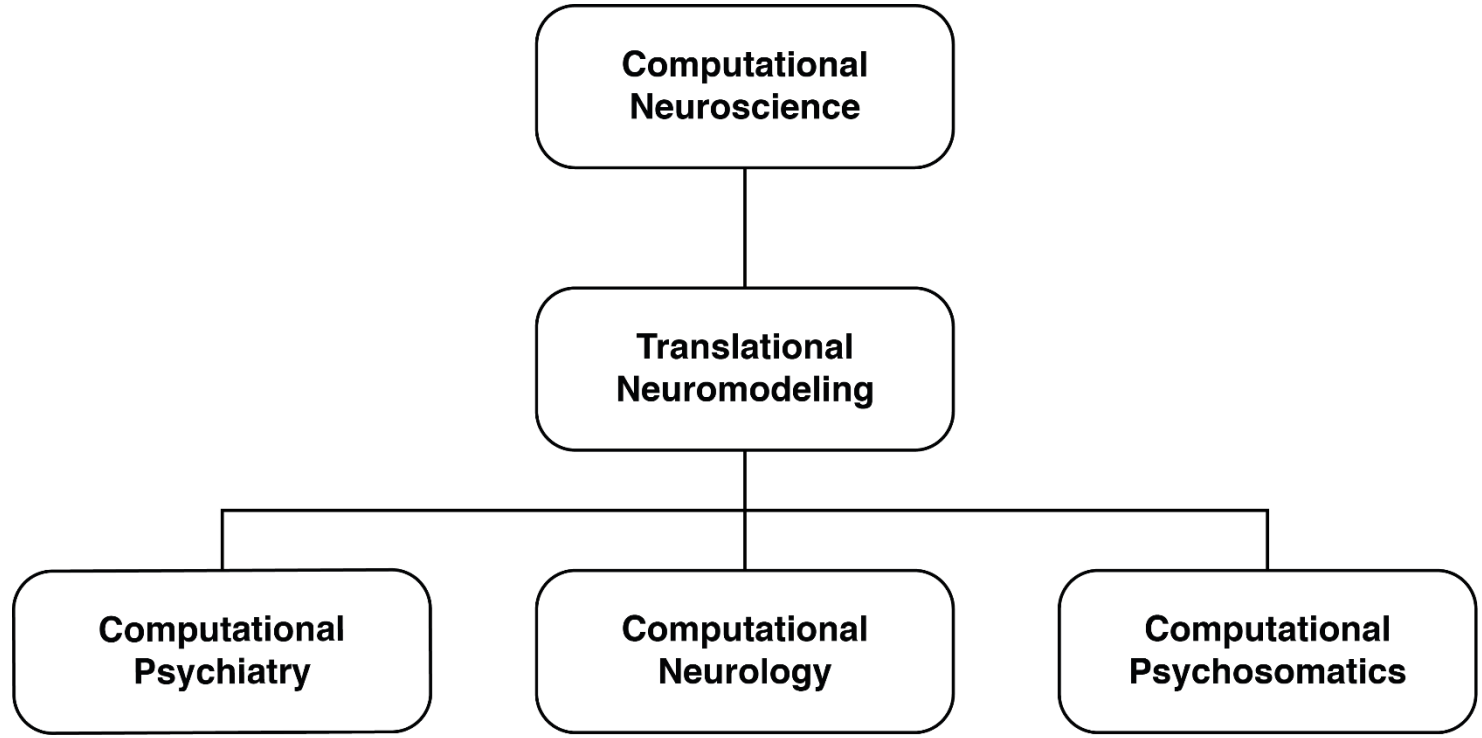
Stephan et al. 2015, *Neuron*

A taxonomy of computational clinical neuroscience

Understanding how/what the brain computes

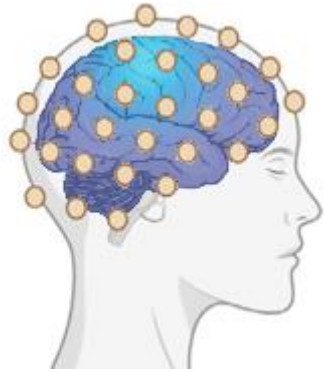
Develops/validates mathematical models for solving clinical problems

Application within specific medical fields



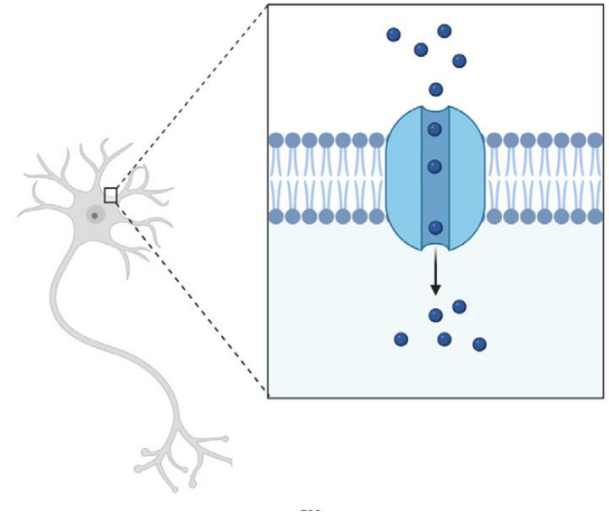
Frässle et al. 2018, *WIREs Cogn. Sci.*

Generative models and "computational assays"



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

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



measured brain activity y

generative model m

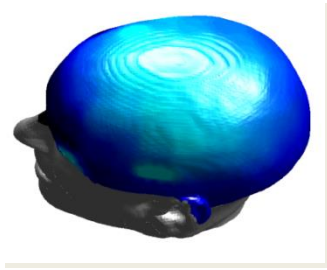
hidden neuronal parameters θ

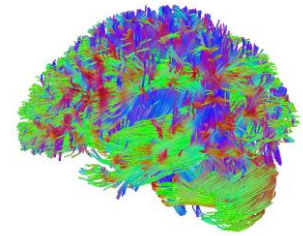
Images: Biorender, Pereira et al. (2021) *NeuroImage*

Example: Dynamic causal models (DCMs)

dwMRI

EEG, MEG

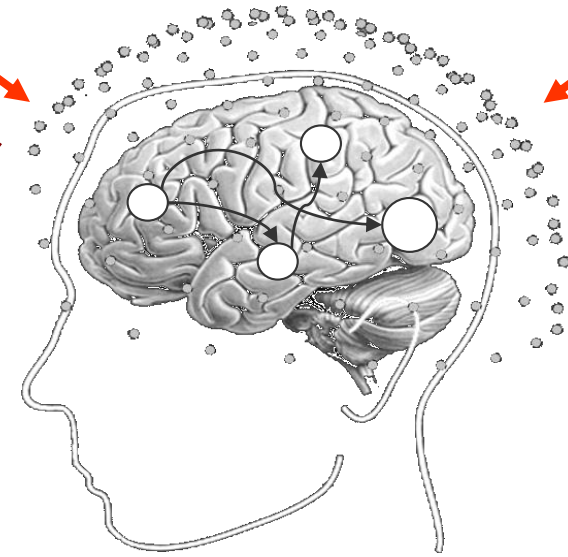




fMRI

structural priors

structural priors



Forward model:
Predicting measured activity

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

Model inversion:
Estimating neuronal mechanisms

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

Adapted from Stephan al. 2017, *NeuroImage* (DWI image: http://dsi-studio.labsolver.org/Manual/use-image-data-from-human-connectome-project)

Generative models and "computational assays"

observed symptoms or behaviour y

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

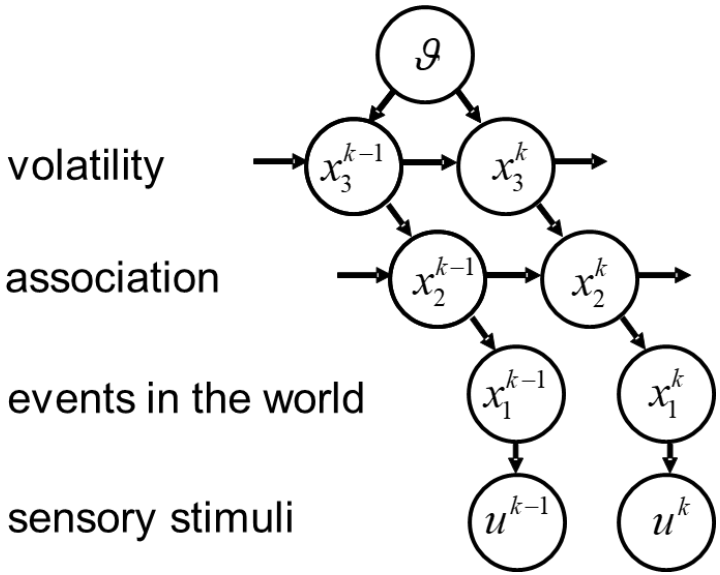
$$p(\theta \mid y, m)$$

generative model m

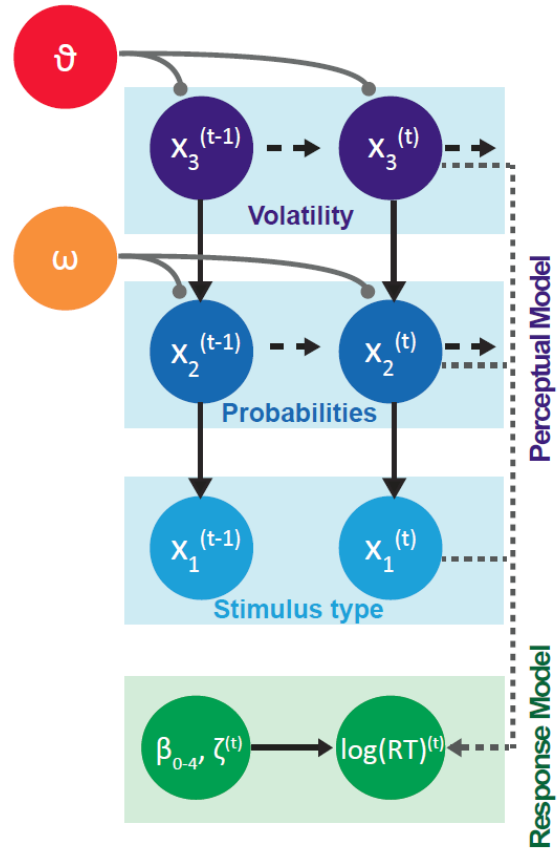
hidden algorithmic parameters θ

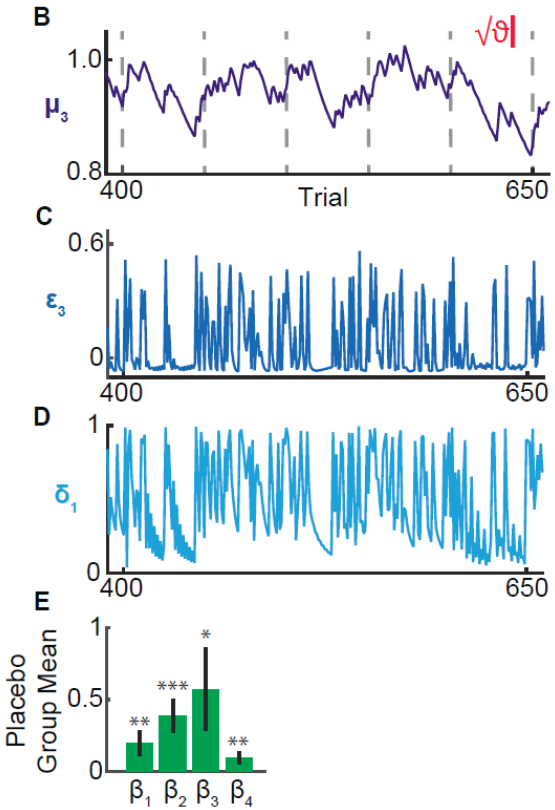
Images: https://www.health.harvard.edu/mind-and-mood/six-common-depression-types (left), Adobe Stock (right)

Example: Hierarchical Gaussian Filter (HGF)



$$\Delta\text{belief} \propto \frac{\text{precision}_{\text{input}}}{\text{precision}_{\text{pred}}} \times \text{PE}$$

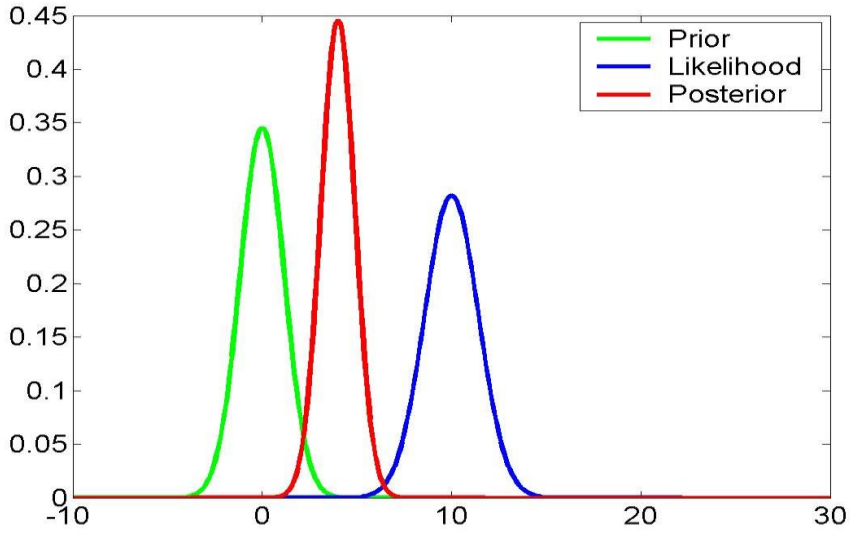


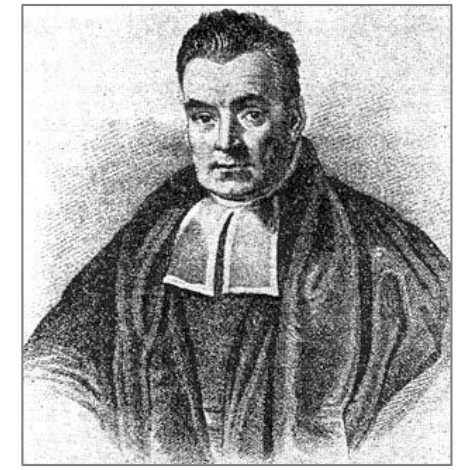


Mathys et al. 2011, 2014, *Front. Hum. Neurosci.*

Marshall et al. 2016, *PLoS Biology*

The basis of generative modeling: Bayes' rule





The Reverend Thomas Bayes
(1702-1761)

Likelihood
(data)

Prior
(prediction)

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

Posterior
(inference)

Evidence
(normalisation term)

θ: parameters
y: data

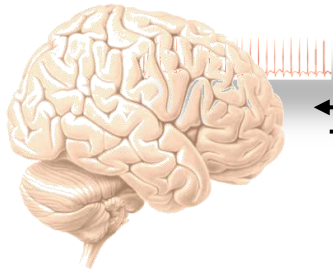
"... the theorem expresses how a degree of belief, expressed as a probability, should rationally change to account for the availability of related evidence."

Wikipedia

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

neuronal states

environm. states
others' mental states
bodily states

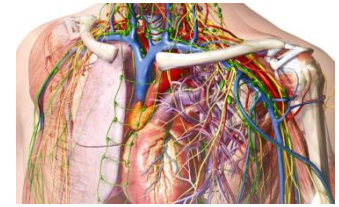


forward model

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

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

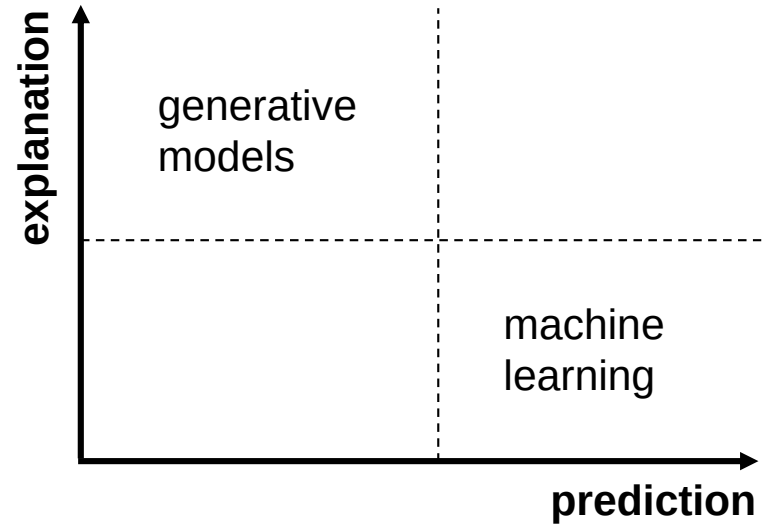
perception



perception = inference = inversion of a generative model

The “Two Cultures of Computational Psychiatry”

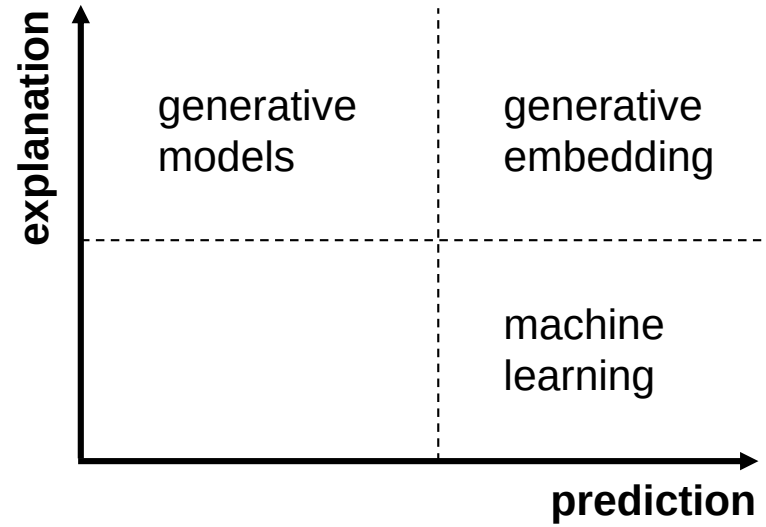
- **explanation:** generative models
  - data-generating process is of central interest
  - goal: identify the mechanisms underlying observations (e.g. clinical symptoms, brain activity)
- **prediction:** machine learning (ML)
  - data-generating process is treated as a black box
  - goal: prediction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



Bennett et al. 2019, *JAMA Psychiatry*

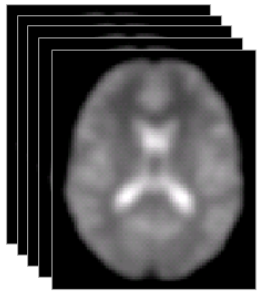
The “Two Cultures of Computational Psychiatry” ... and Generative Embedding as their bridge

- **explanation:** generative models
  - data-generating process is of central interest
  - goal: identify the mechanisms underlying observations (e.g. clinical symptoms, brain activity)
- **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

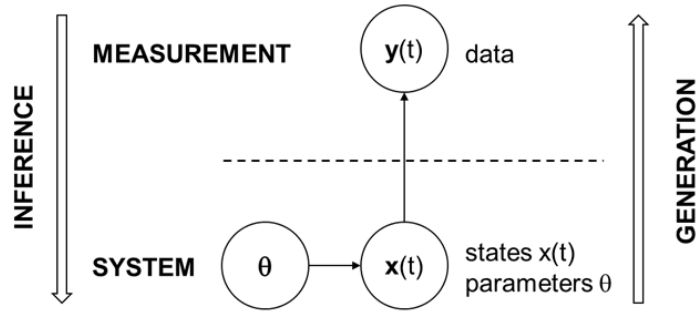


Generative embedding

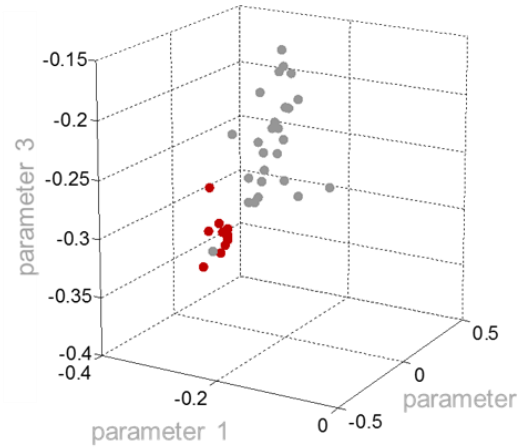
high-dimensional data



generative model



mechanistic interpretation



theory-driven
dimensionality reduction

posterior densities →
features for machine learning

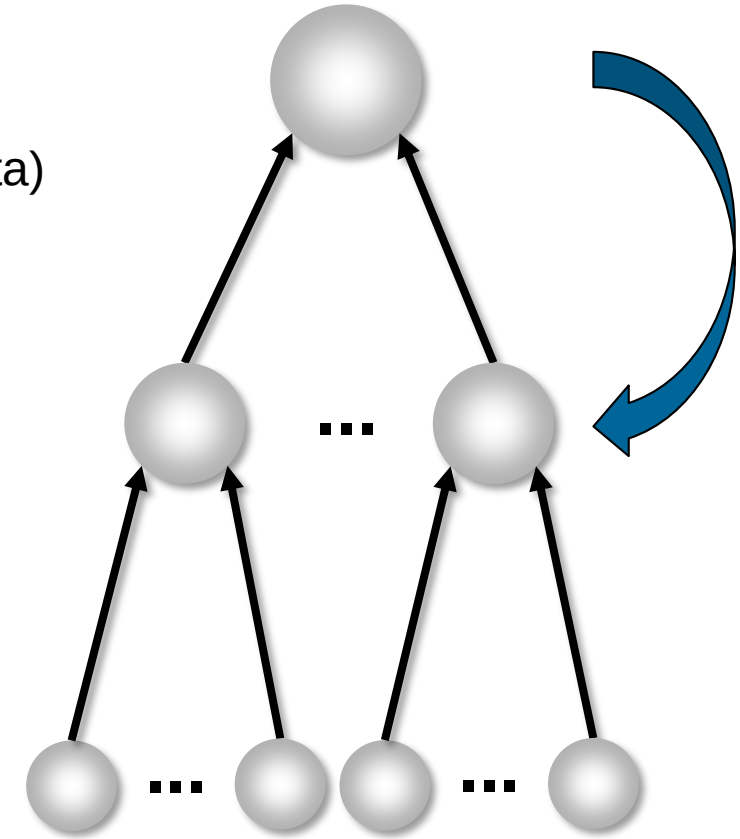
Brodersen et al. 2011, *PLoS Comp. Biol.*
Brodersen et al. 2014, *NeuroImage Clinical*

Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



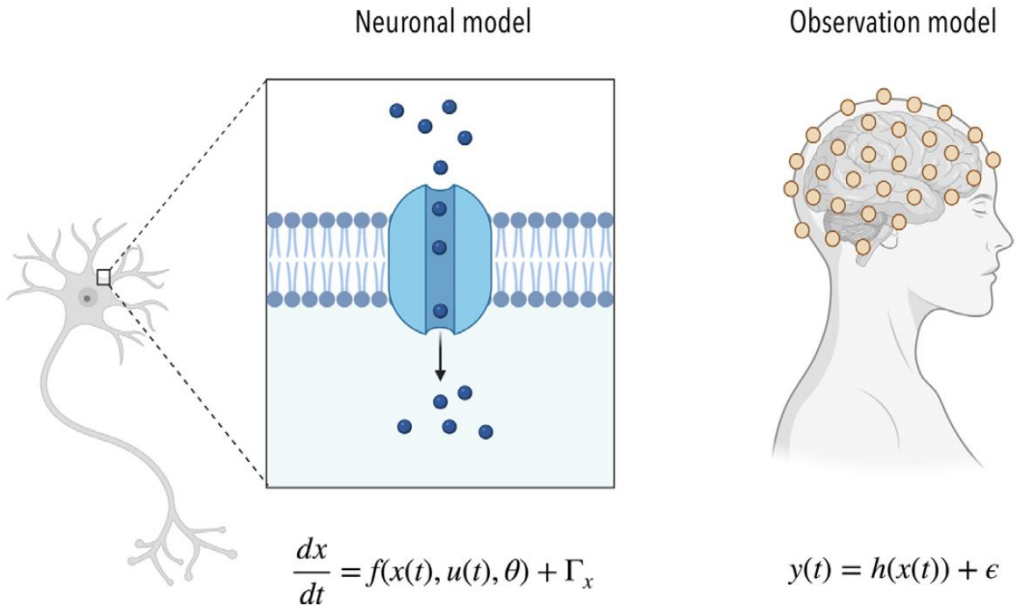
❶ **differential diagnosis:** deciding between alternative disease mechanisms

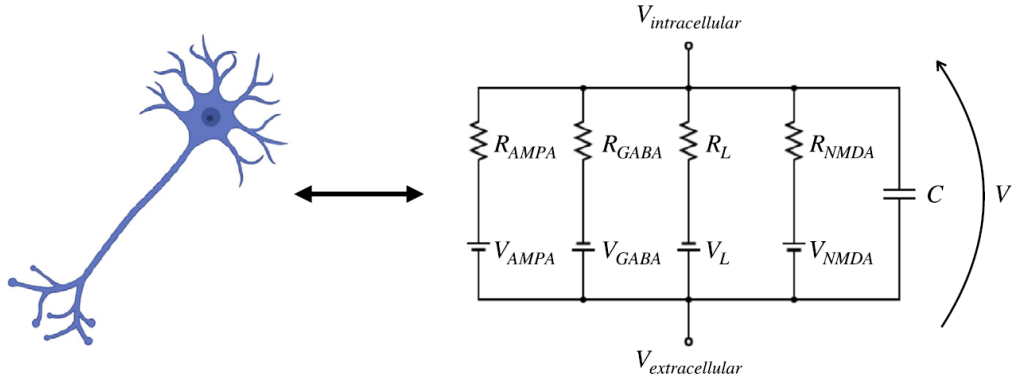
❷ **stratification / subgroup detection** into mechanistically distinct subgroups

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

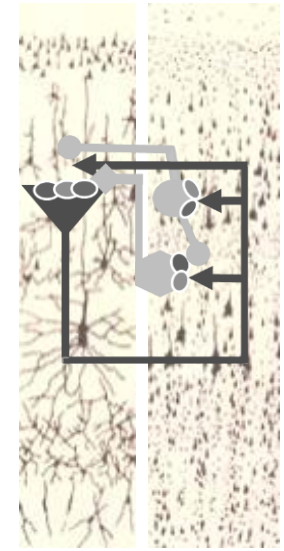
Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

❶ **Differential diagnosis:** inferring synaptic processes





Images: Pereira et al. 2021, *NeuroImage*



- inhibitory interneurons
- excitatory interneurons
- pyramidal cells

AMPA, NMDA,$GABA_A$ receptors

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

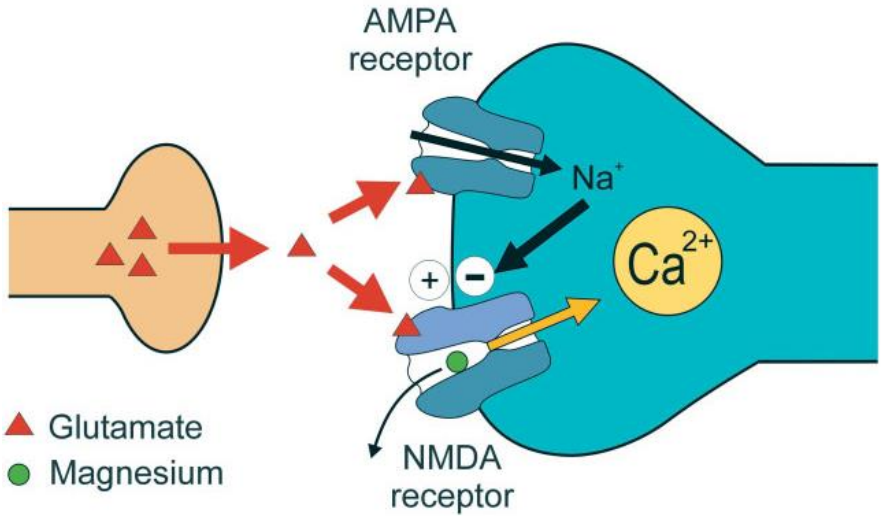
$$\dot{g}_k = \kappa\left(u_{ij} - g_k\right)$$

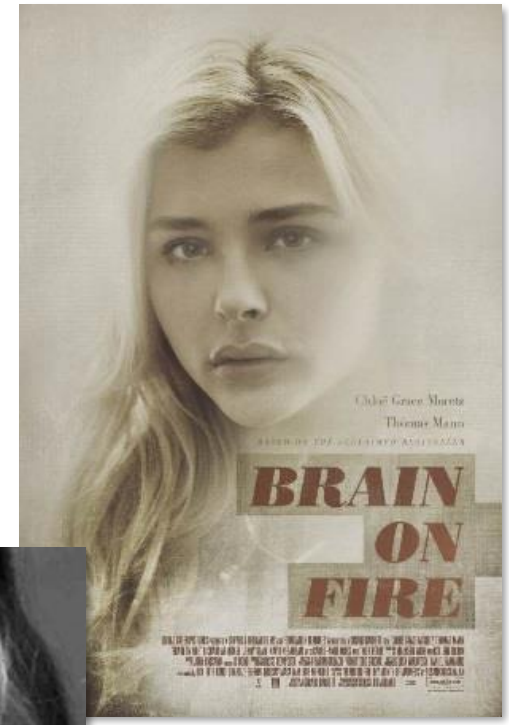
$$u_{ij} = \gamma_{ij}\sigma\left(\mu_V^{(j)} - V_R, \Sigma^{(j)}\right)$$

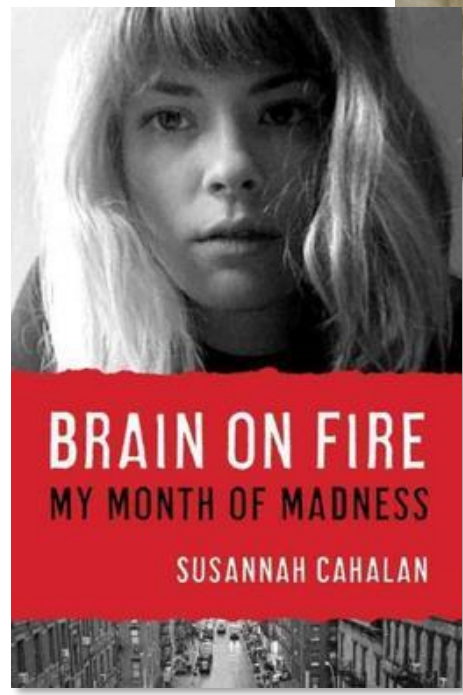
u_{ij} = presynaptic input from ensemble j to i

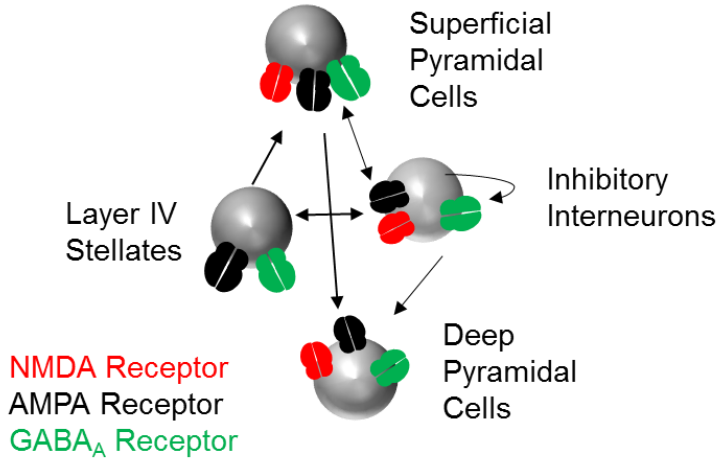
σ = CDF of presynaptic depolarization density around threshold potential V_R

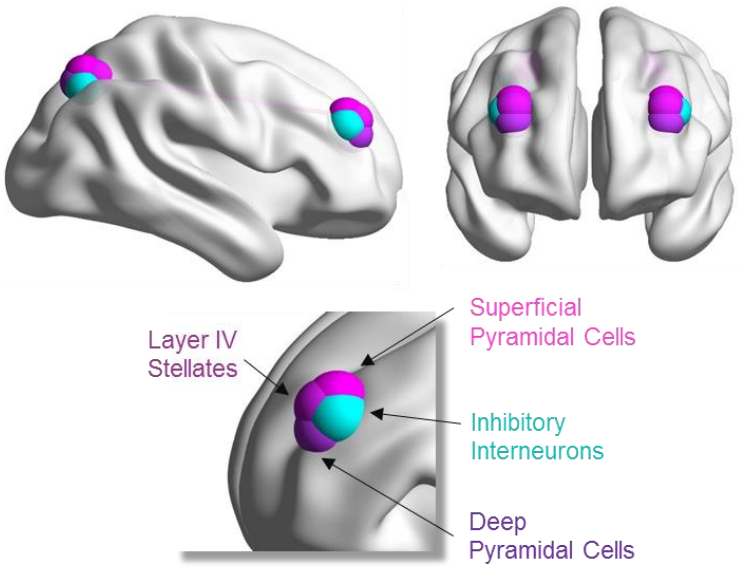
NMDA receptor antibody encephalitis

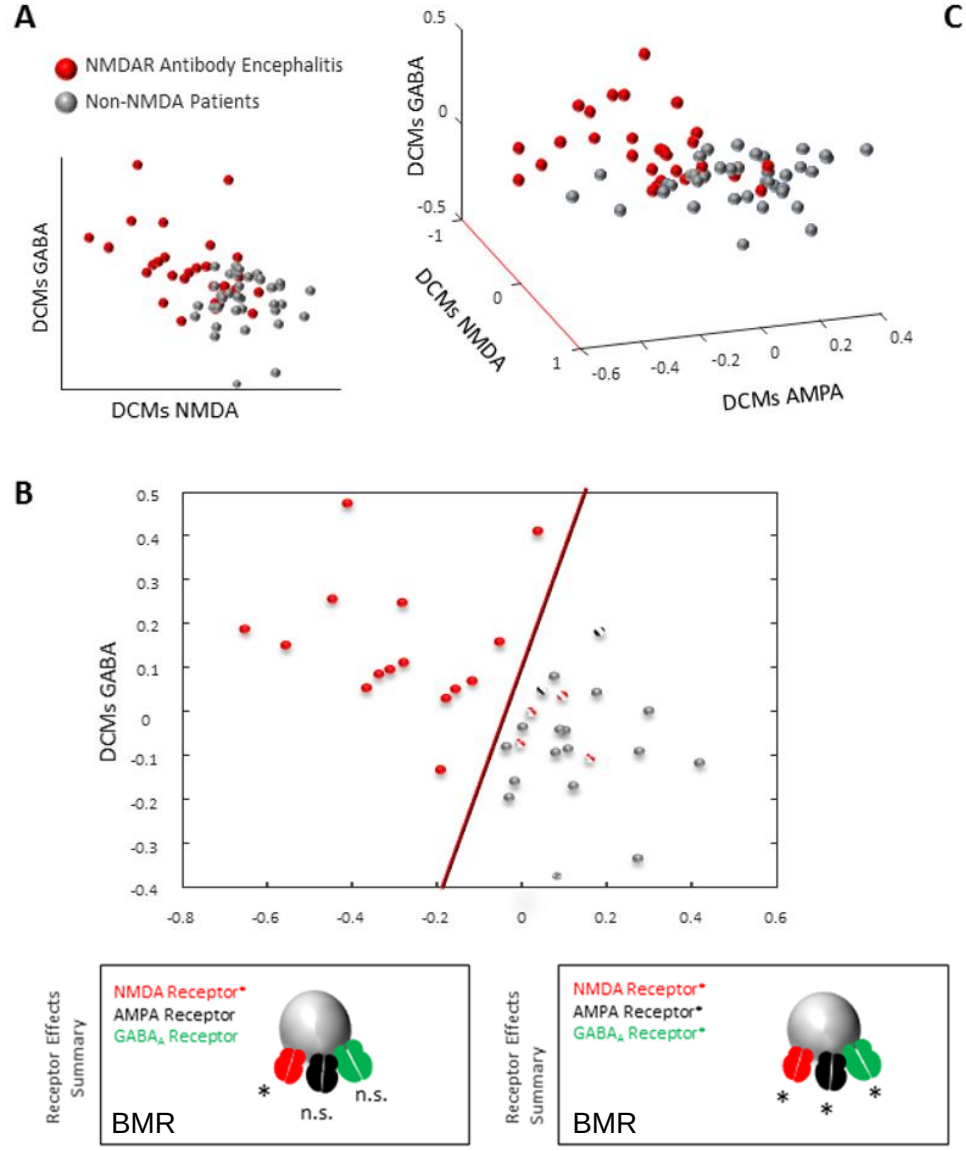












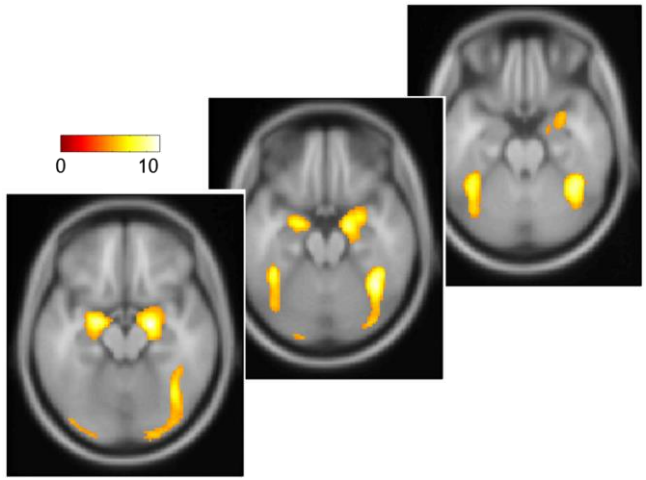
29 patients with NMDAR-antibody encephalitis
18 control patients (with inflammatory/metabolic encephalopathy)

Symmonds et al. 2018, *Brain*

❸ **Prediction:** two-year outcome in depression

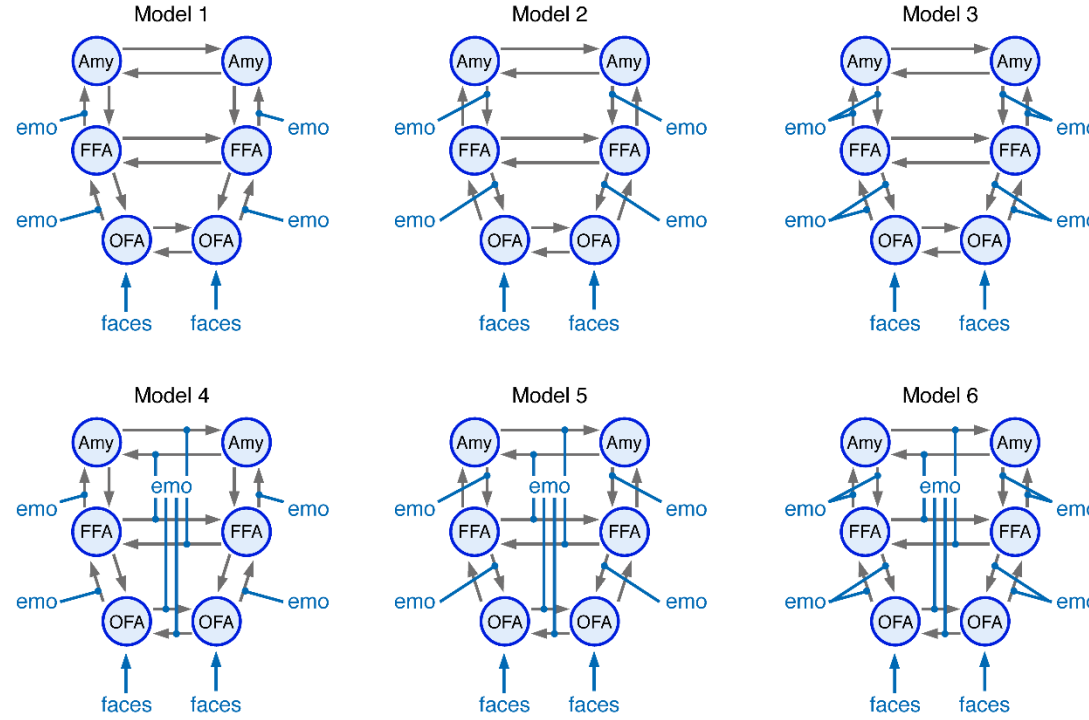
N=85 MDD patients from NESDA study (Schmaal et al. 2015, Biol. Psychiatry)

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



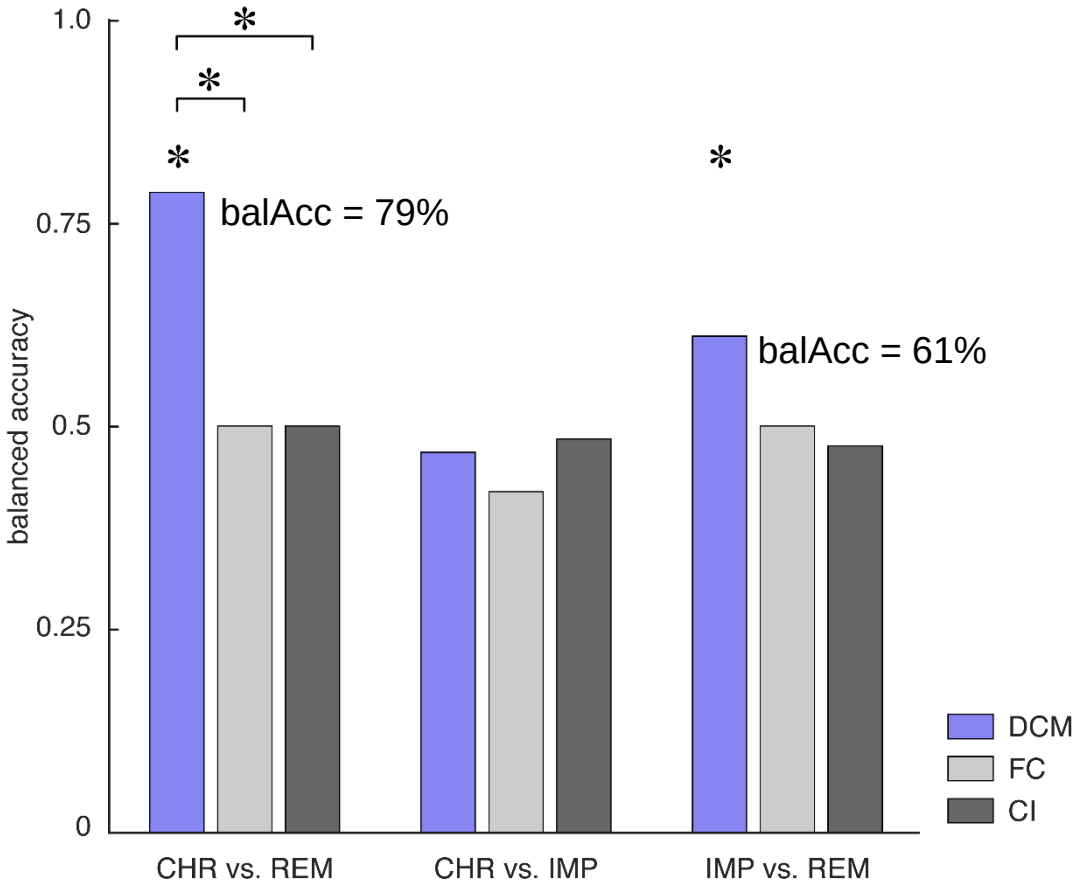
emotional faces > scrambled faces

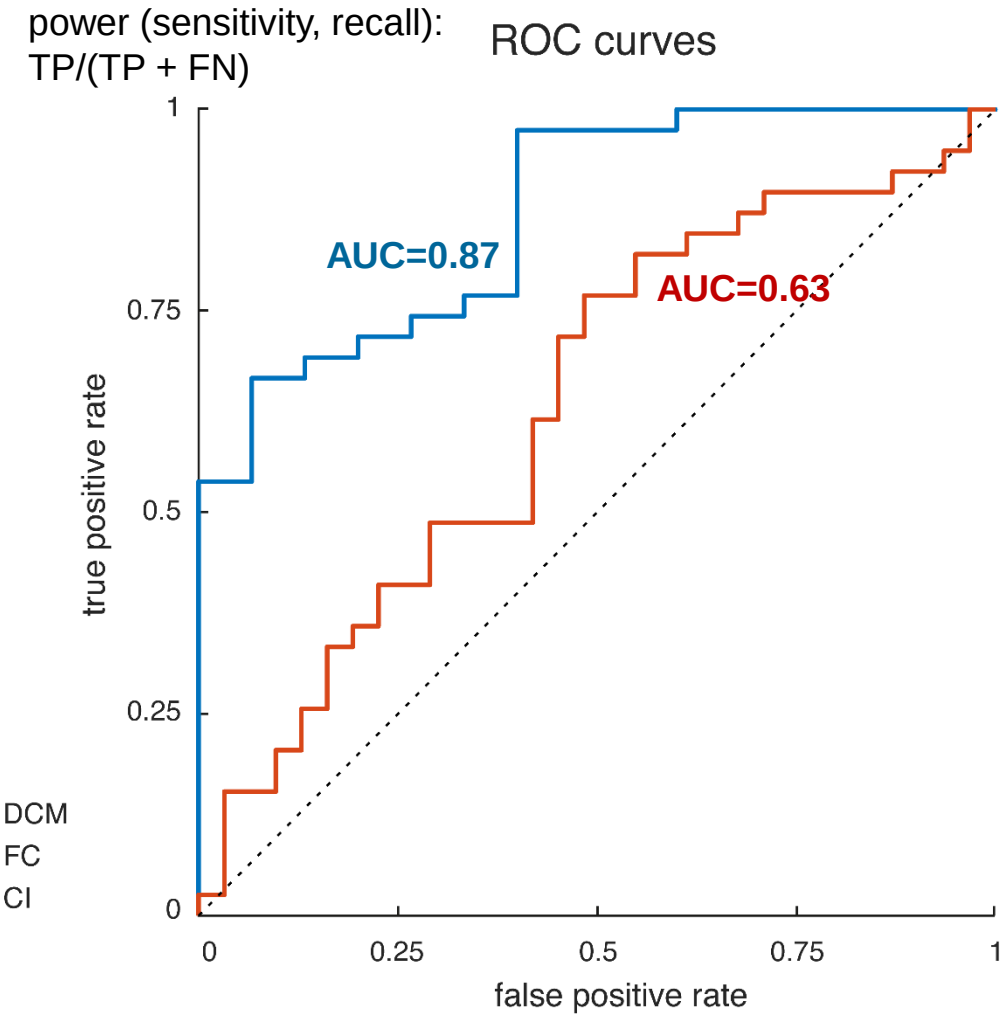
DCM + BMA (emotional face processing)



Frässle et al. 2020, *NeuroImage Clinical*

❸ **Prediction:** two-year outcome in depression

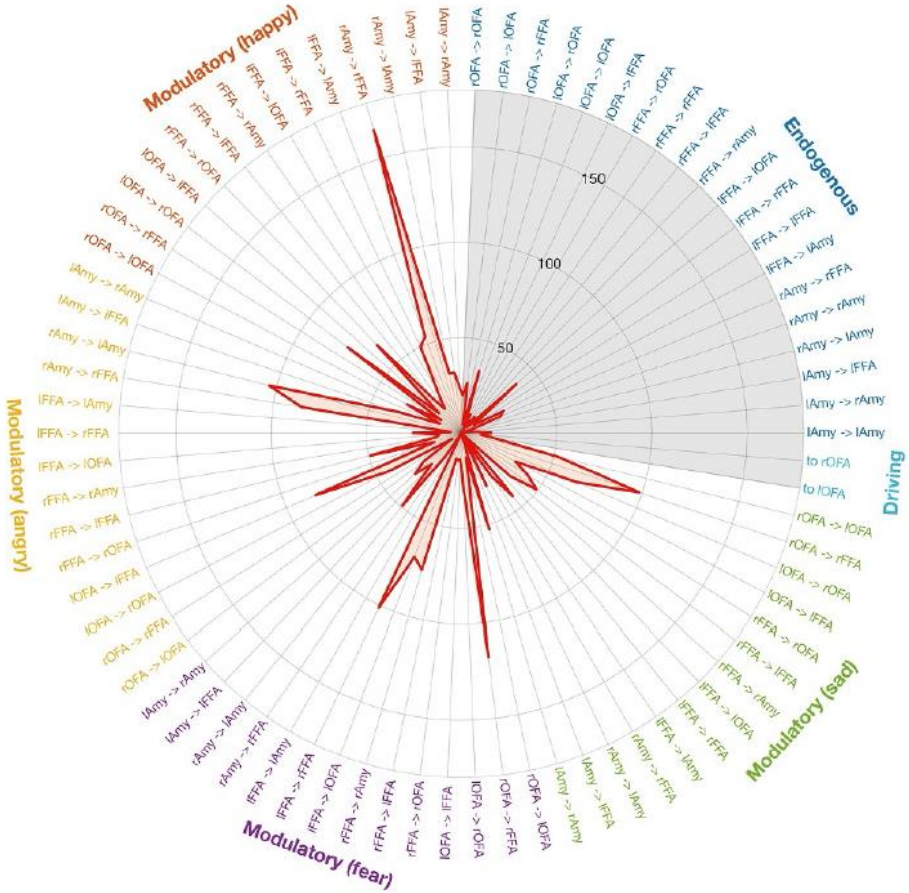




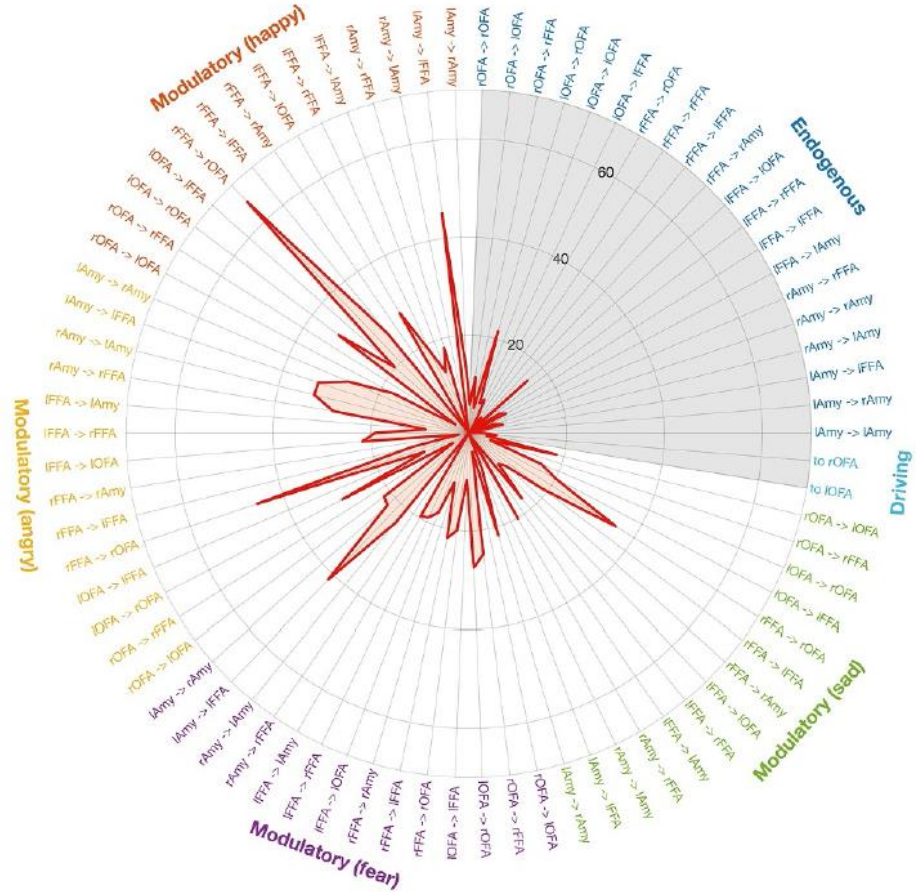
Frässle et al. 2020, *NeuroImage Clinical*

❸ **Prediction:** two-year outcome in depression

CHR vs. REM

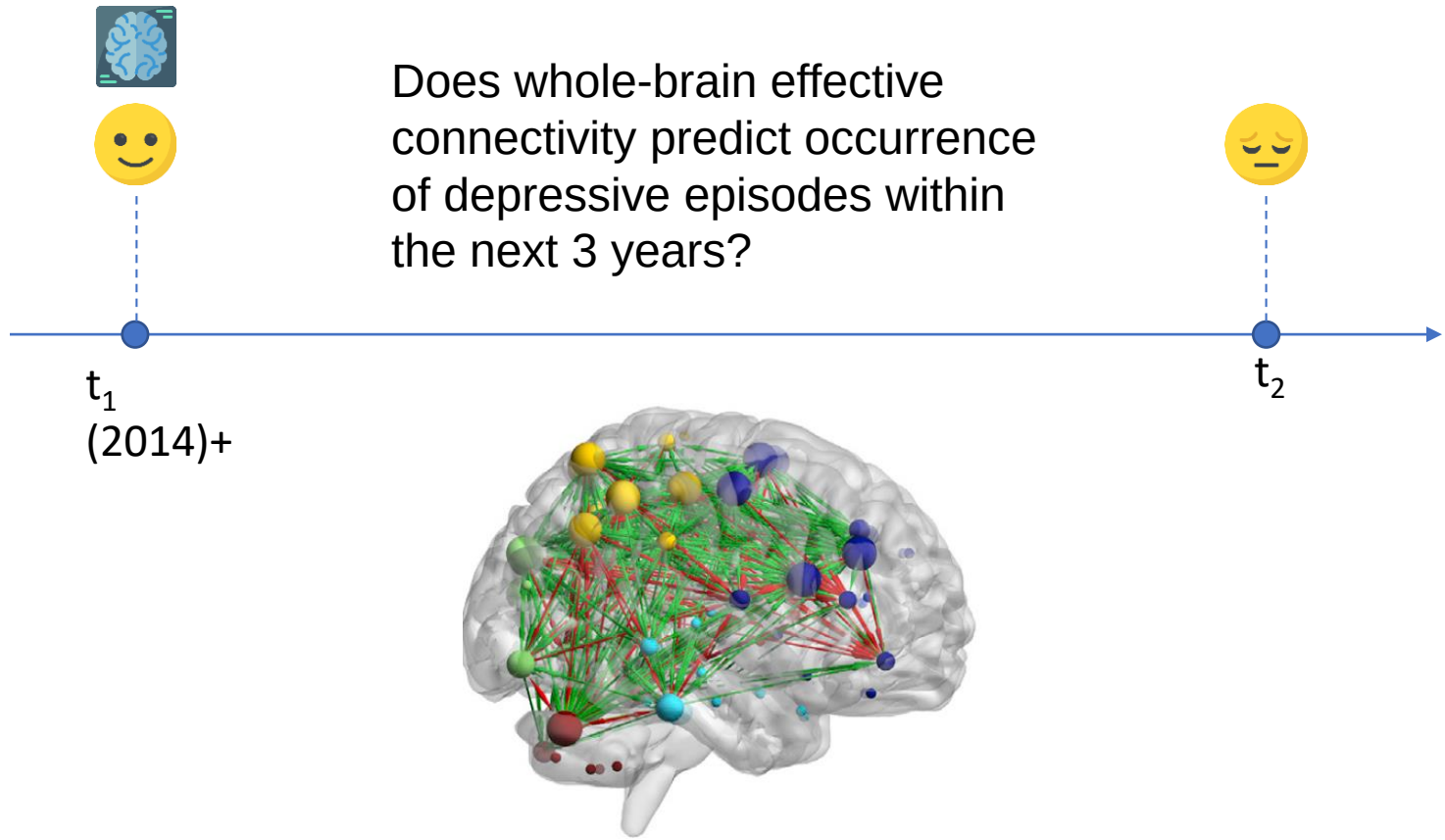


IMP vs. REM



Frässle et al. 2020, *NeuroImage Clinical*

❸ **Prediction:** depressive symptoms within next 3 years

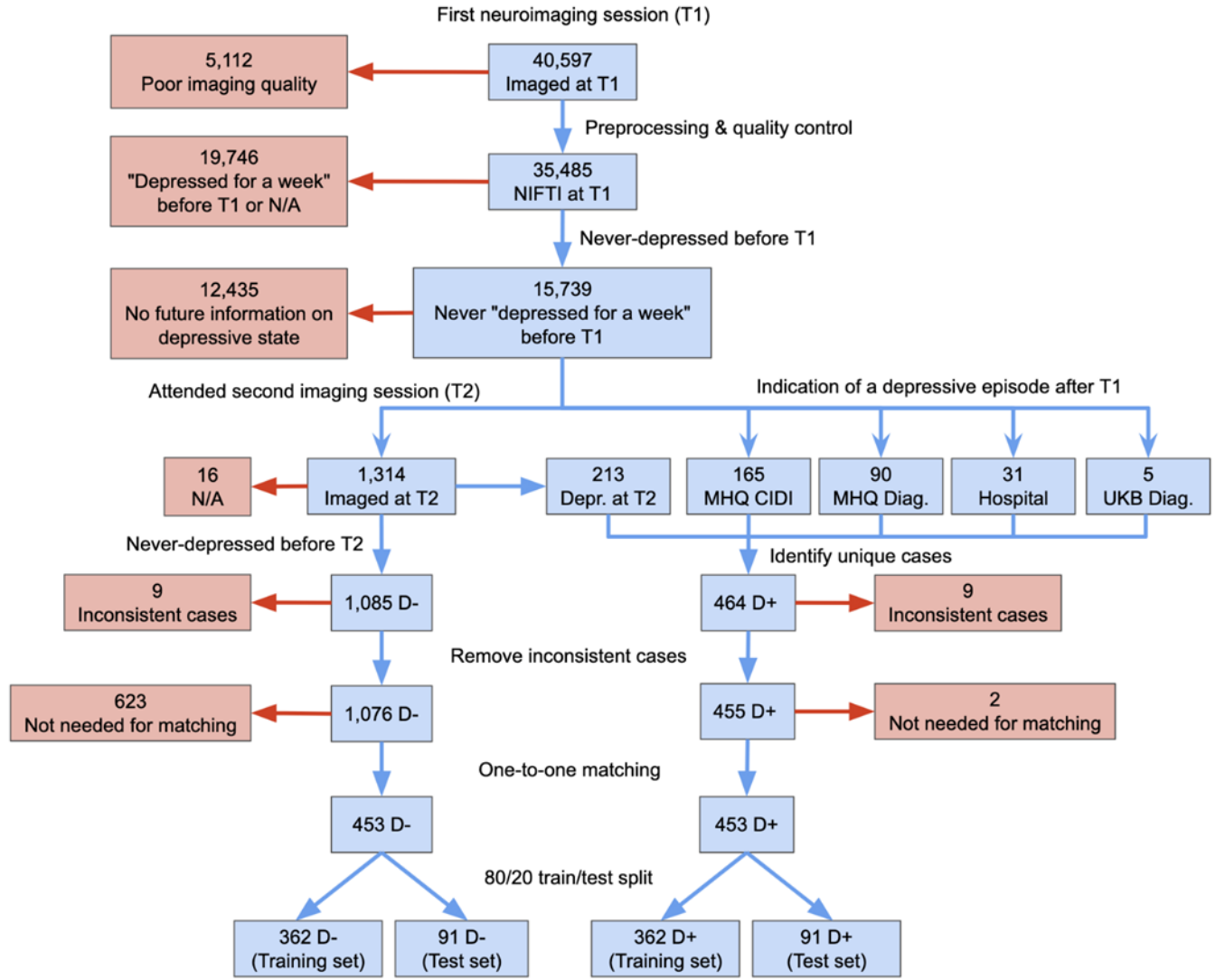


Galioulline et al. 2023, *NeuroImage*

❸ **Prediction:** depressive symptoms within next 3 years

rsfMRI data from UKB (N=906):

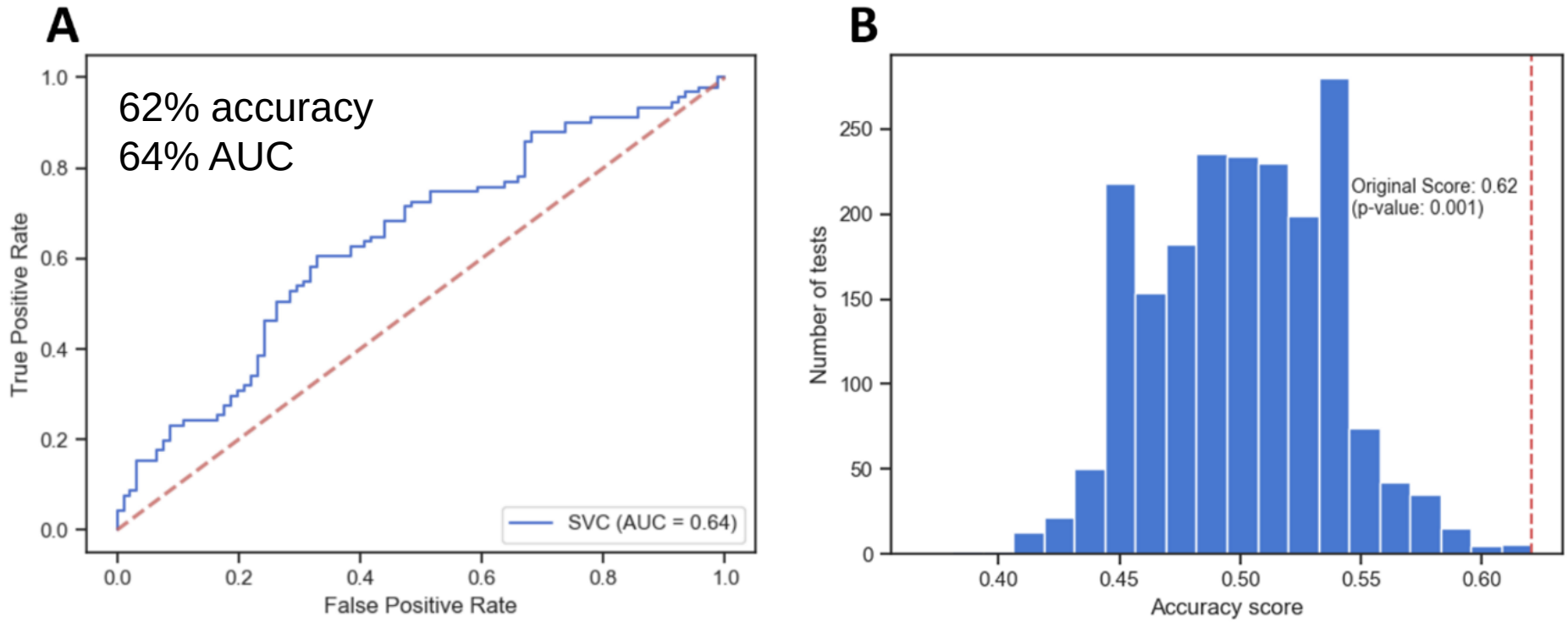
- N=453 with indication for ≥1 depressive episode
- N=453 w/o depressive episode
- 1:1 matching for 7 criteria (age, sex, comorbidities)
- 80/20 split into training and test sets



Galioulline et al. 2023, *NeuroImage*

❸ **Prediction:** depressive symptoms within next 3 years

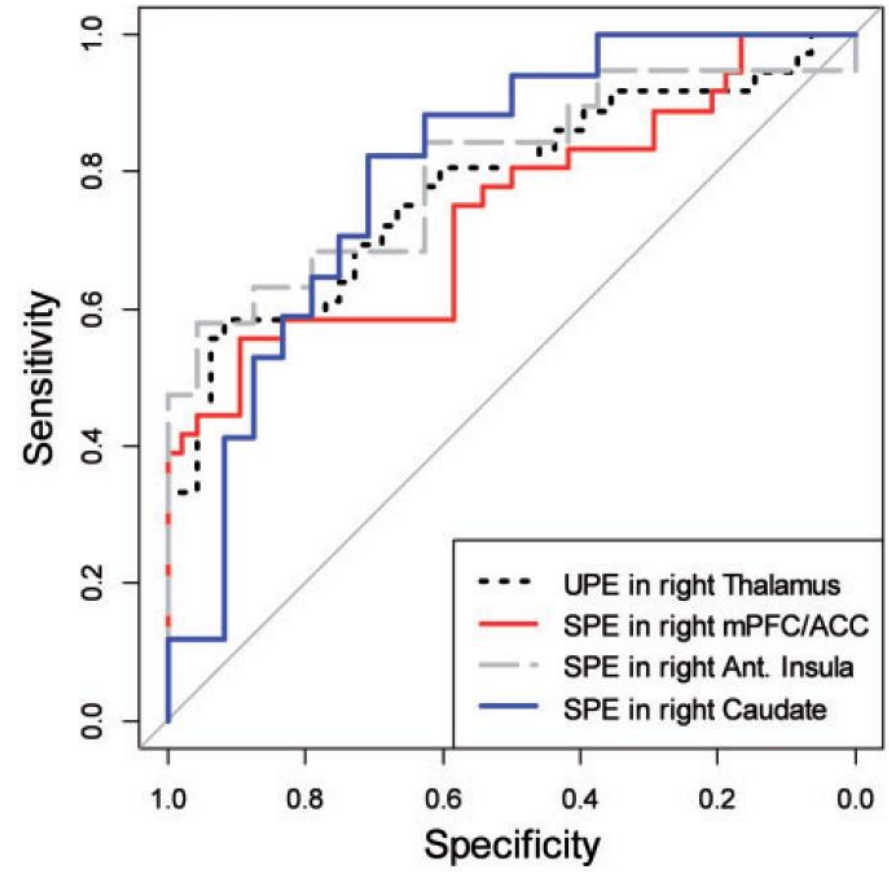
Generative embedding (55 IC rDCM + sigmoid SVM):
Predictive performance on **held-out test set**



Galioulline et al. 2023, *NeuroImage*

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*

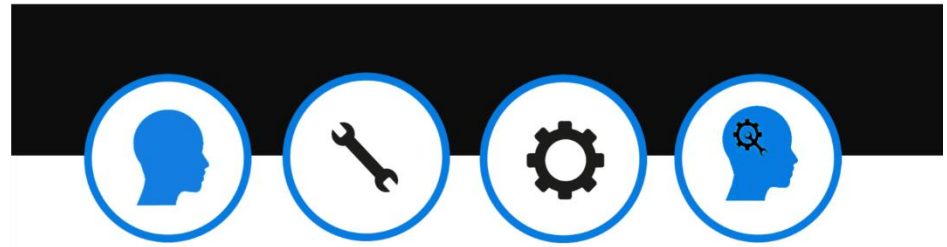
Final remark:
What exactly do we mean by "computational"?

- 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" or "purpose" level

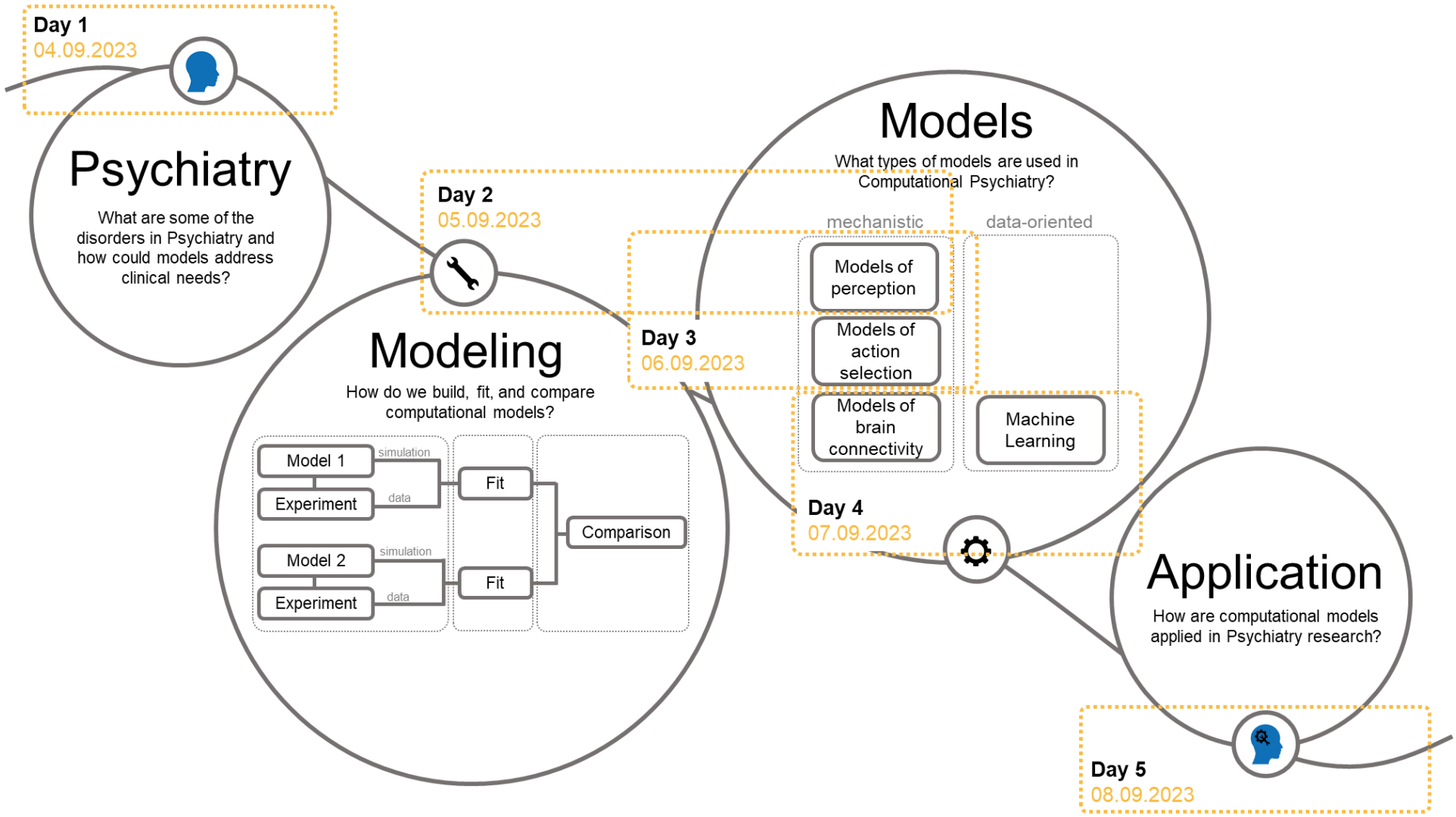
CPC 2023



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

- 9th international edition
- originated from our local courses on Computational Psychiatry since 2012
- in hybrid mode since 2022
- key features
  - clinical, methodological & application topics
  - covers models of both neurophysiology and behaviour
  - practical exercises with different open source toolboxes
  - >40 presenters from >20 international institutions
  - >350 registered participants

CPC 2023


Day 1
04.09.2023
Psychiatry
What are some of the disorders in Psychiatry and how could models address clinical needs?
Day 2
05.09.2023
Modeling
How do we build, fit, and compare computational models?
Model 1
Experiment
Model 2
Experiment
simulation
data
simulation
data
Fit
Fit
Comparison
Day 3
06.09.2023
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
07.09.2023
Application
How are computational models applied in Psychiatry research?
Day 5
08.09.2023

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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- 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 2023!

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