

Introduction to Computational Psychiatry

Klaas Enno Stephan



Translational Neuromodeling Unit



**Universität
Zürich**^{UZH}



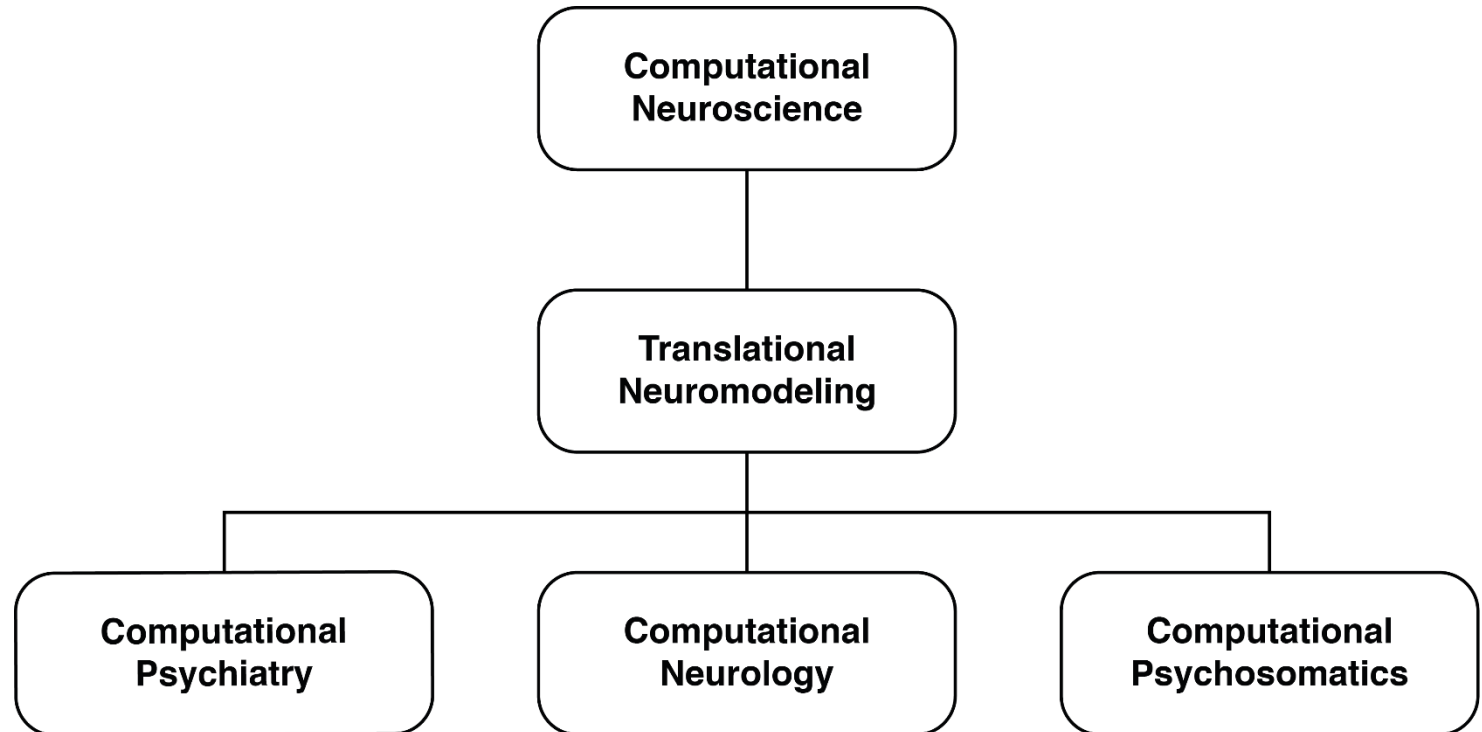
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

What is Computational Psychiatry?

Understanding how/what
the brain computes

Develops/validates
mathematical models for
solving clinical problems

Application within
specific medical fields

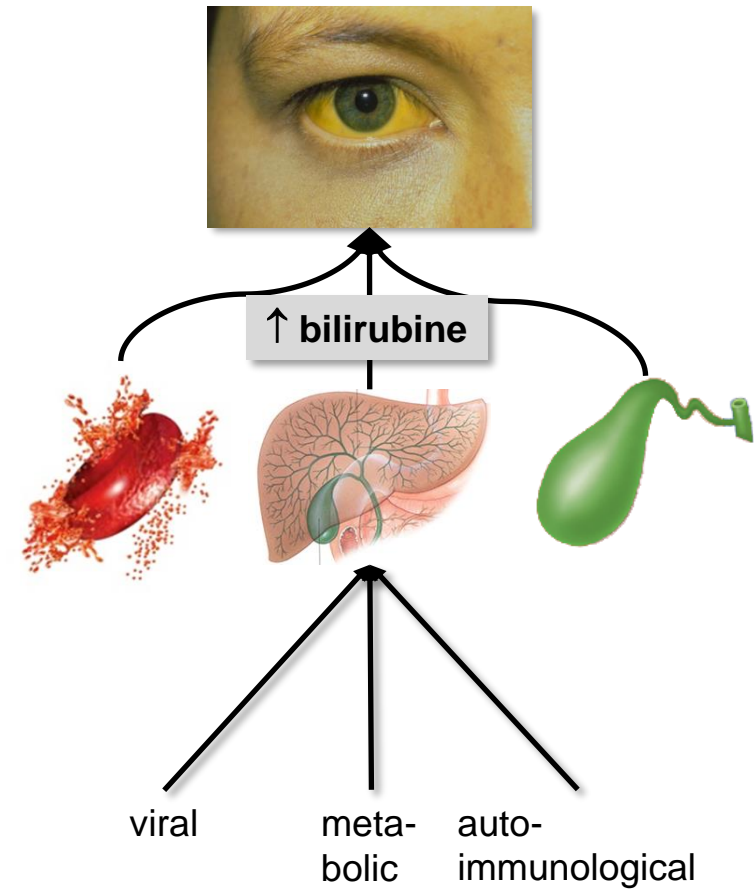
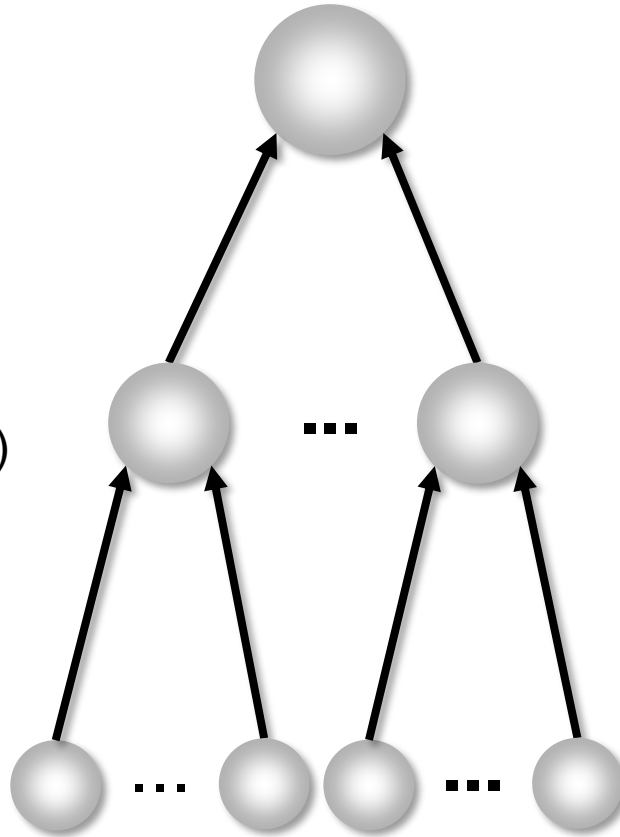


From differential diagnosis to nosology

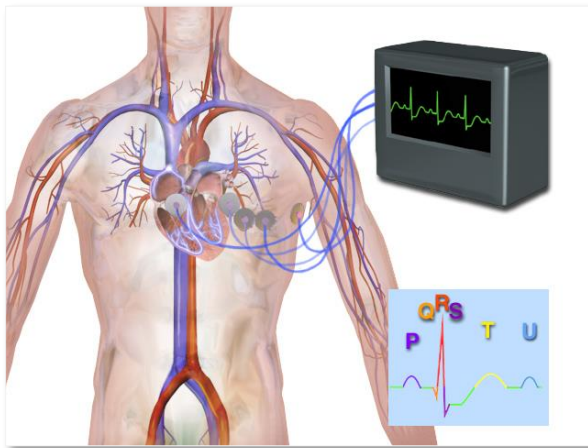
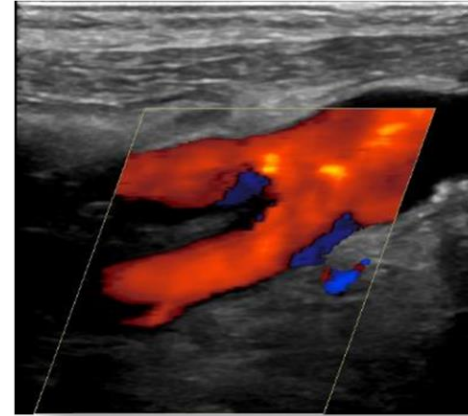
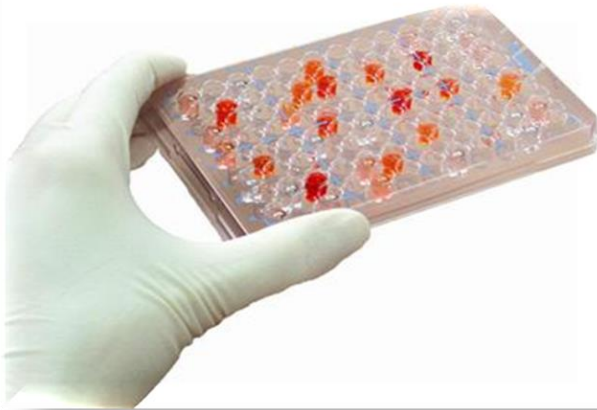
SYMPTOM

MECHANISMS
(pathophysiology)

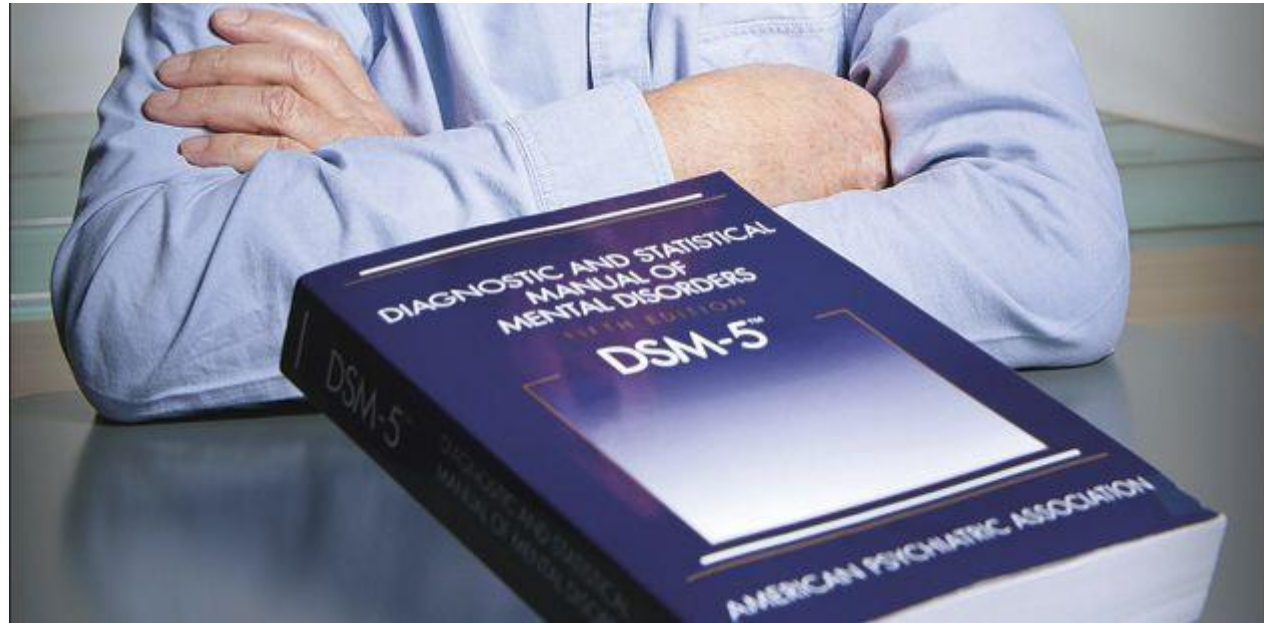
CAUSES
(aetiology)



>3,000 clinical tests in medicine

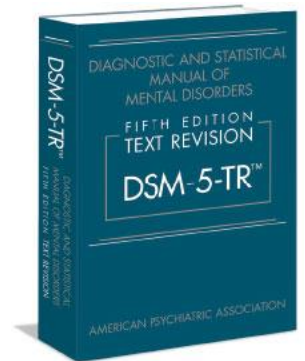
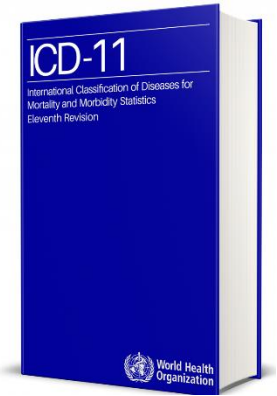


1 diagnostic instrument in psychiatry



Contemporary psychiatric classifications: ICD and DSM

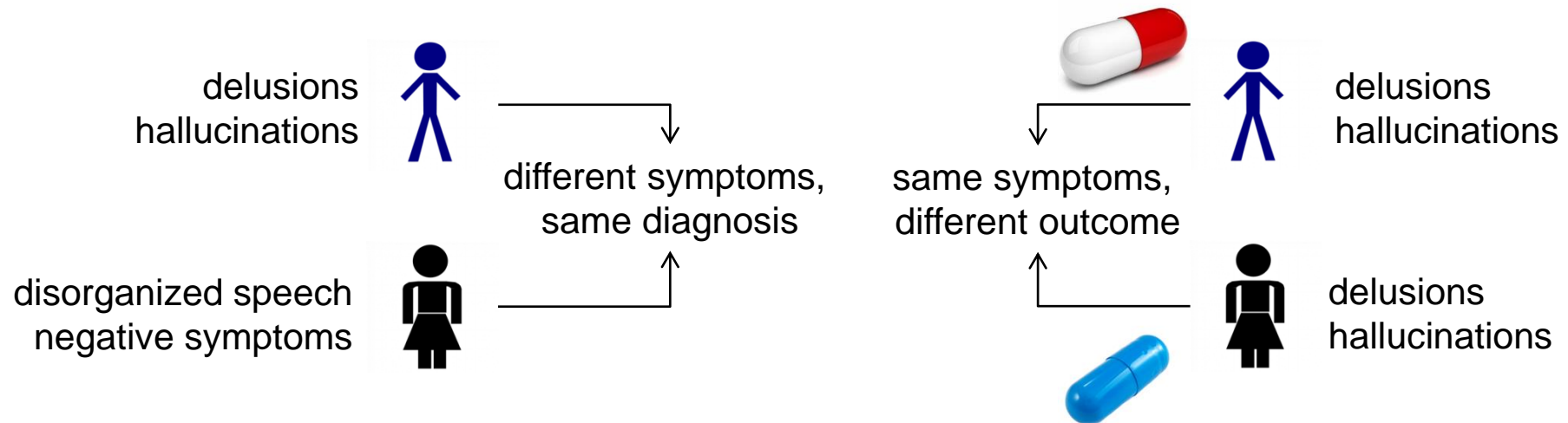
- **International Classification of Diseases (ICD):**
 - curated by the World Health Organization (WHO)
 - presently in its 11th revision (ICD-11)
 - freely available
- **Diagnostic and Statistical Manual of Mental Disorders (DSM)**
 - published by the American Psychiatric Association (APA)
 - presently: 5th edition (DSM-5; 2013); text revision (TR) in 2022
 - not free
- **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



Heterogeneity of psychiatric disorders



polygenetic basis
gene-environment interactions
environmental variation

**variability in clinical
trajectory and treatment
response**

multiple disease mechanisms

PERSPECTIVE

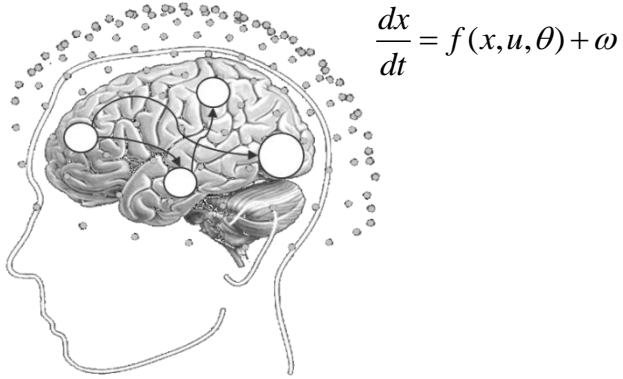
Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

S Kapur¹, AG Phillips² and TR Insel³

The computational proposal

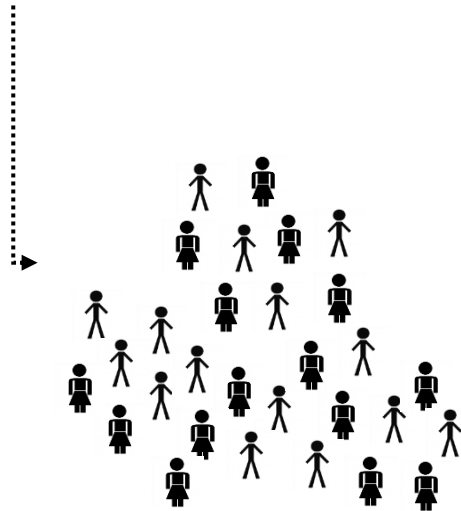
Developing & validating computational assays (Translational Neuromodeling) and applying them to clinical problems (Computational Psychiatry).

1 Computational assays

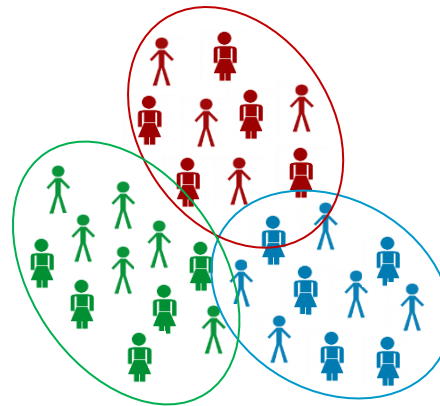


Translational Neuromodeling & Computational Psychiatry

2 Application to individual patients

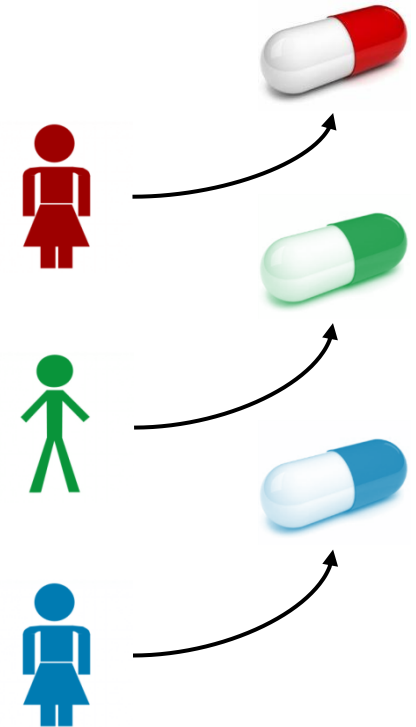


3 Mechanistic differentiation

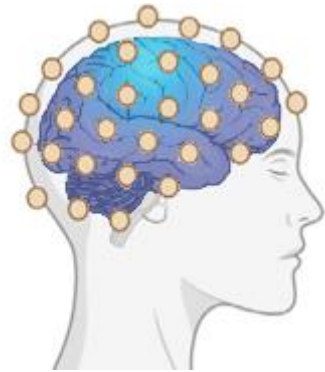


- disease mechanism A
- disease mechanism B
- disease mechanism C

4 Individual prediction



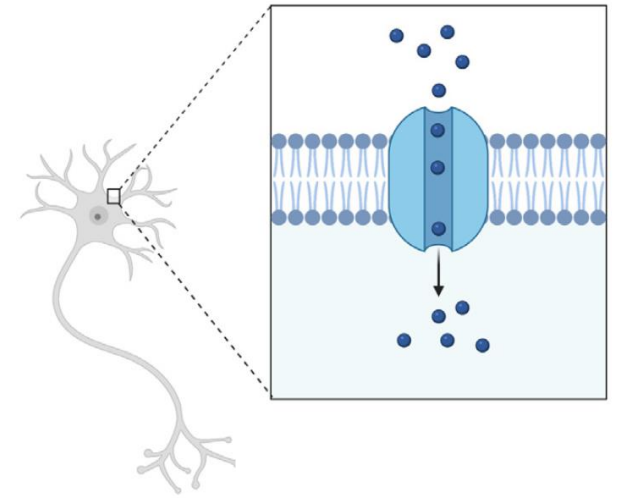
Generative models and "computational assays"



measured brain
activity y

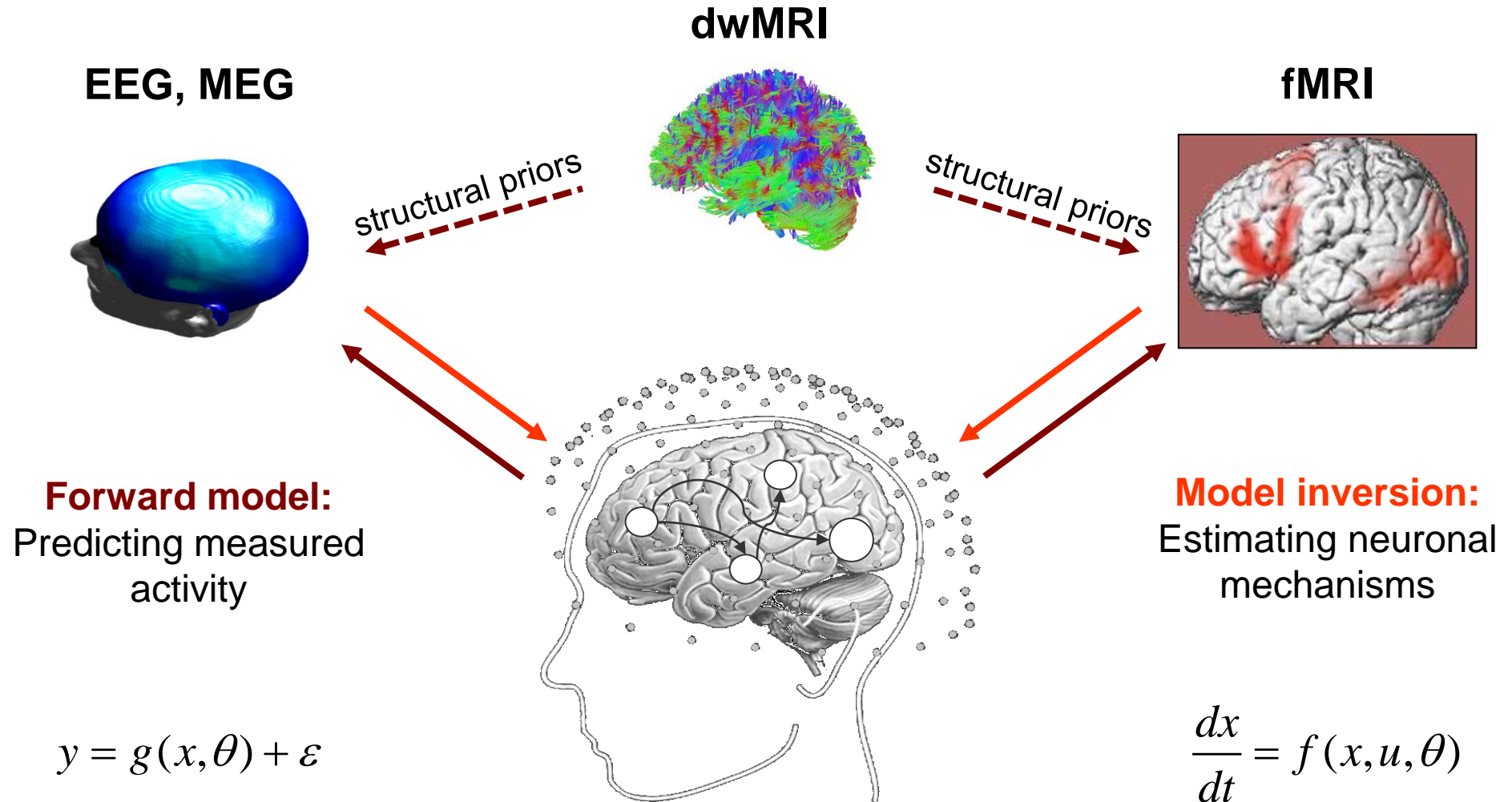
$$\begin{array}{c} \xleftarrow{p(y | \theta, m) \cdot p(\theta | m)} \\ \xrightarrow{p(\theta | y, m)} \end{array}$$

generative
model m



hidden neuronal
parameters θ

Example: Dynamic causal models (DCMs)



Generative models and "computational assays"



observed symptoms or
behaviour y

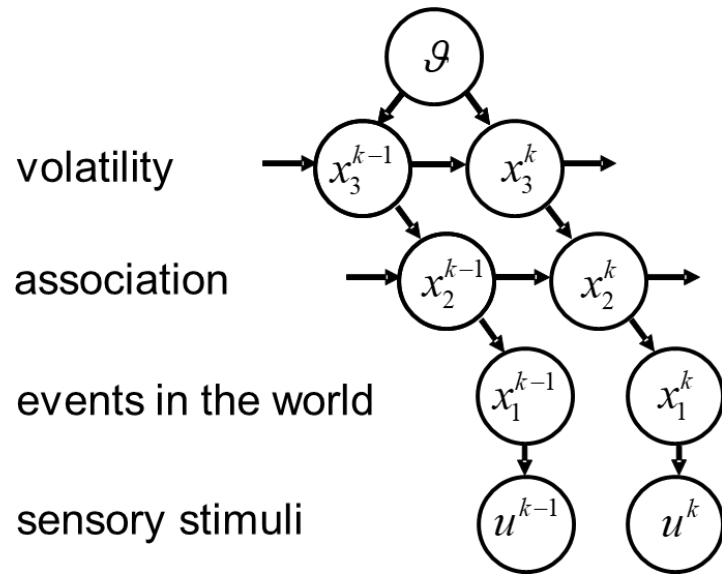
$$\begin{array}{c} \xleftarrow{p(y \mid \theta, m) \cdot p(\theta \mid m)} \\ \xrightarrow{p(\theta \mid y, m)} \end{array}$$

generative
model m

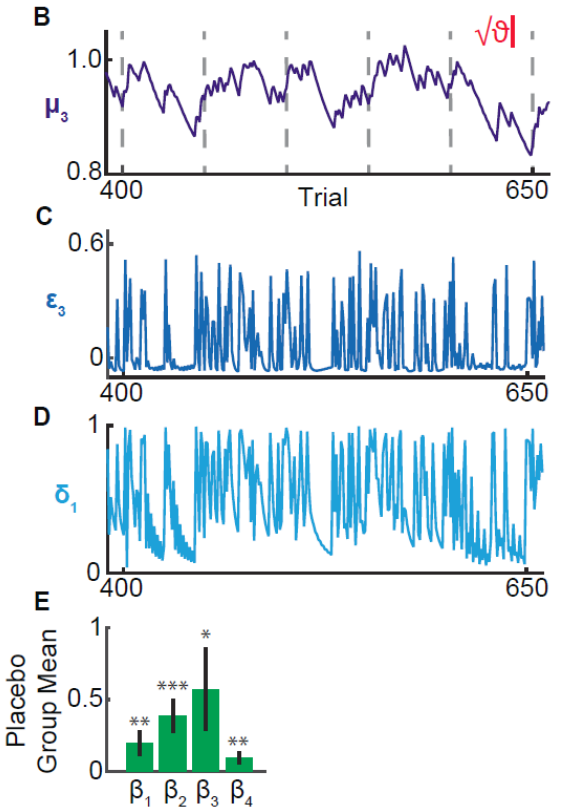
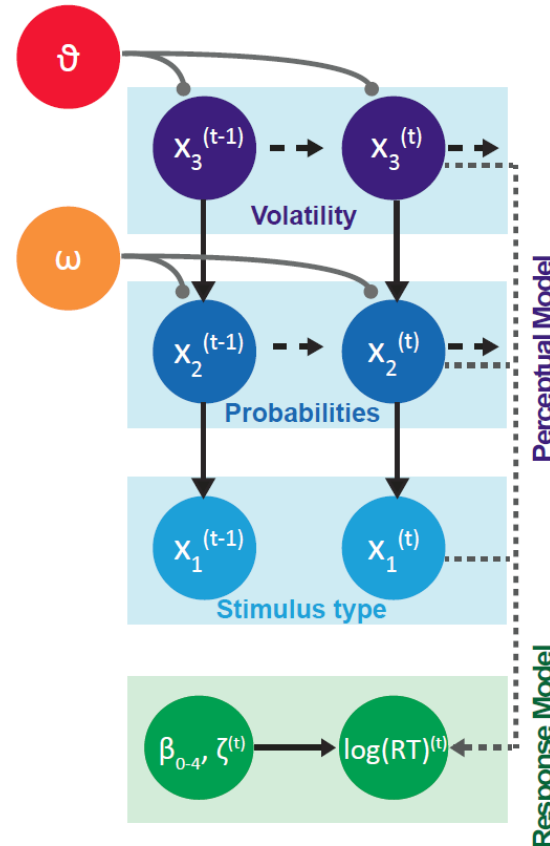


hidden algorithmic
parameters θ

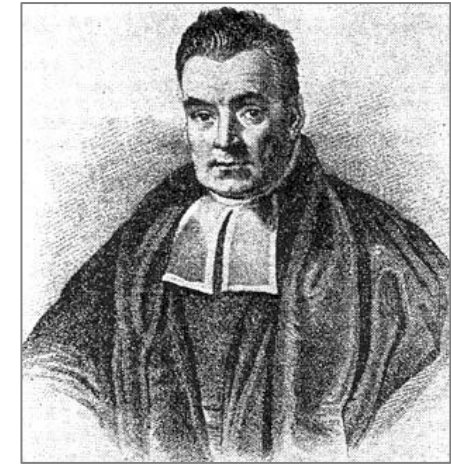
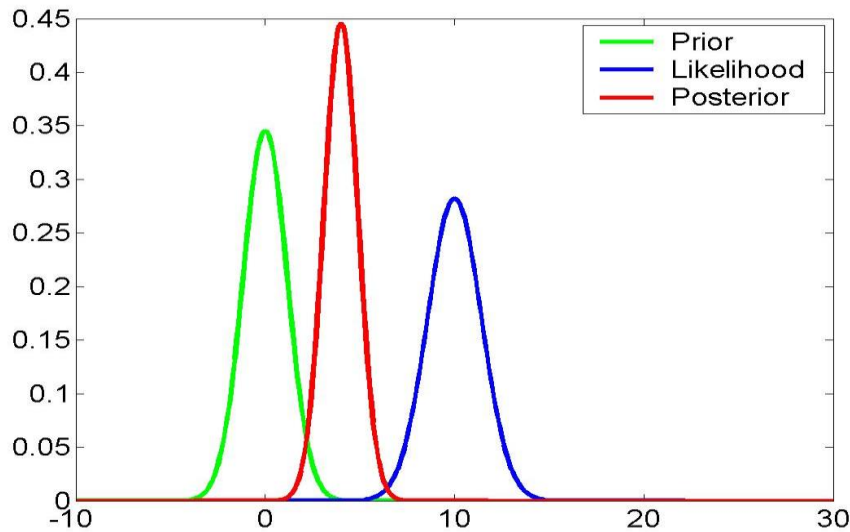
Example: Hierarchical Gaussian Filter (HGF)



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



The basis of generative modeling: Bayes' rule



The Reverend Thomas Bayes
(1702-1761)

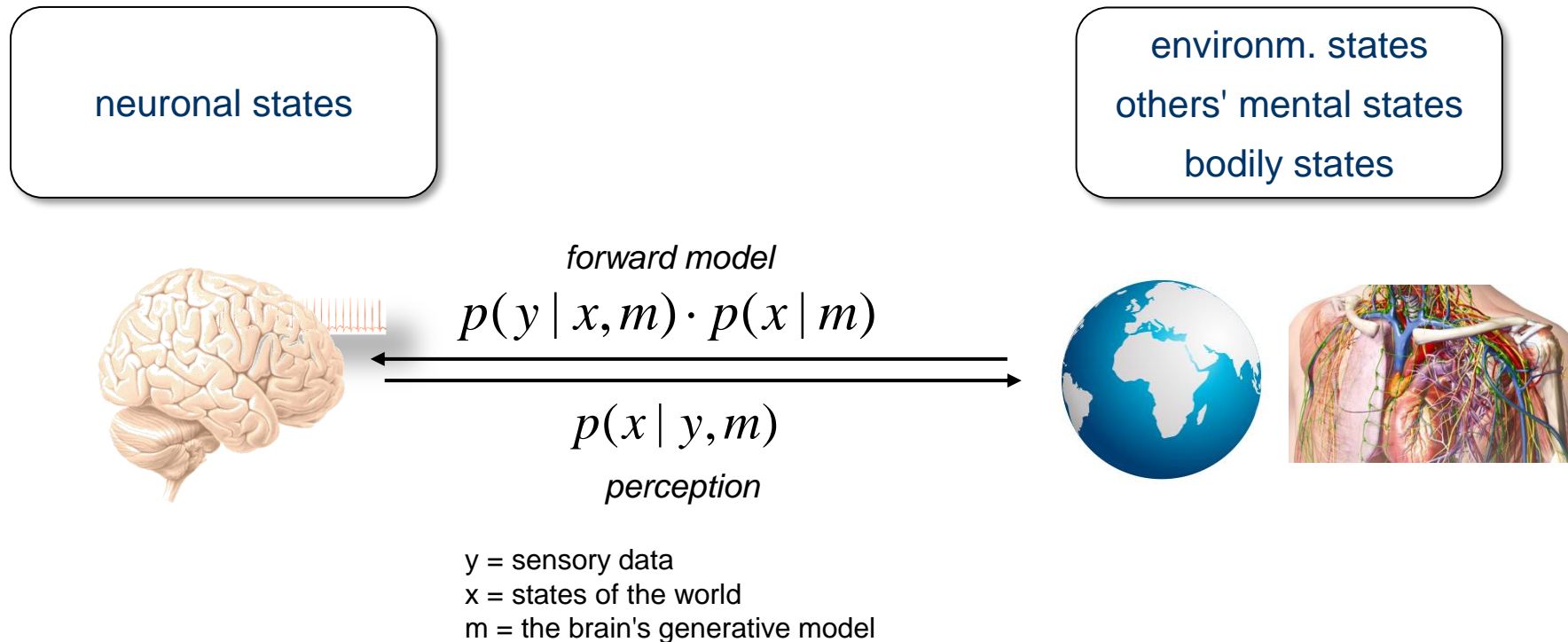
$$\text{Posterior (inference)} \quad p(\theta | y) = \frac{\text{Likelihood (data)} \quad p(y | \theta) \quad \text{Prior (prediction)} \quad p(\theta)}{\text{Evidence (normalisation term)} \quad p(y)}$$

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

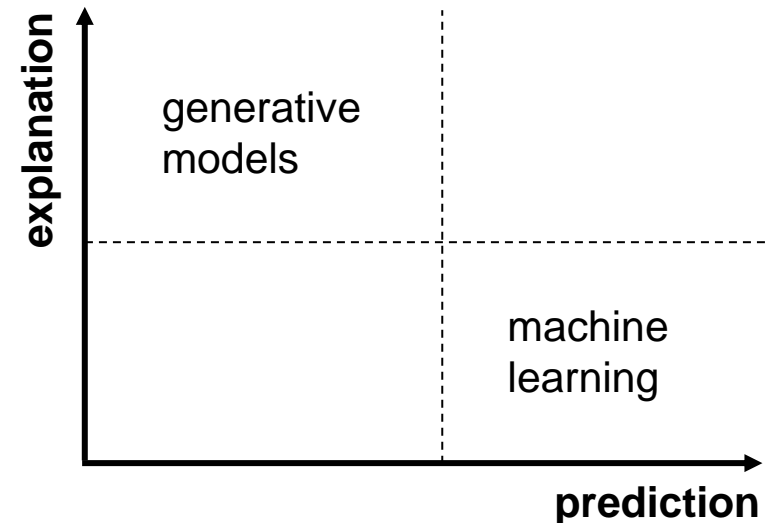
Generative models as a concept for brain function: the "Bayesian brain" hypothesis



perception = inference = inversion of a generative model

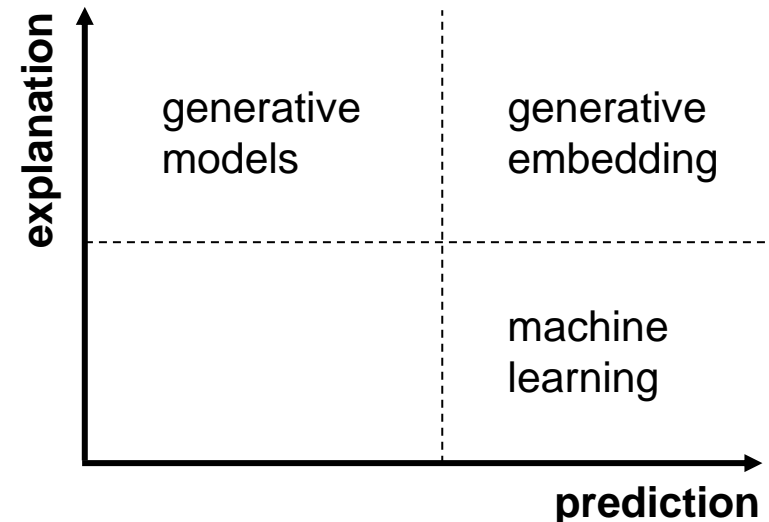
The “Two Cultures of Computational Psychiatry”

- **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



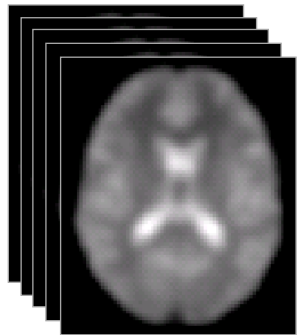
The “Two Cultures of Computational Psychiatry” ... and Generative Embedding as their bridge

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- **generative embedding:**
 - applies ML to estimated quantities from generative models

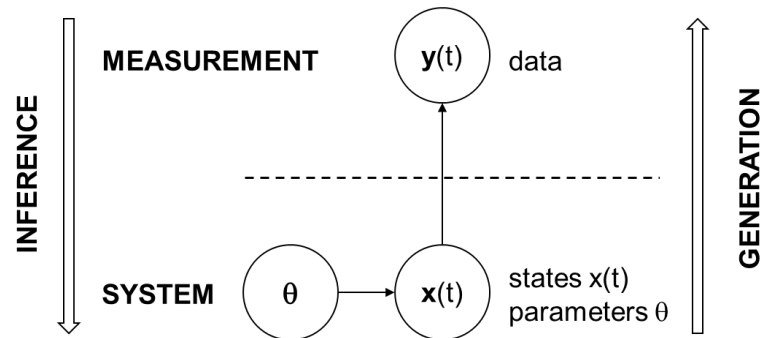


Generative embedding

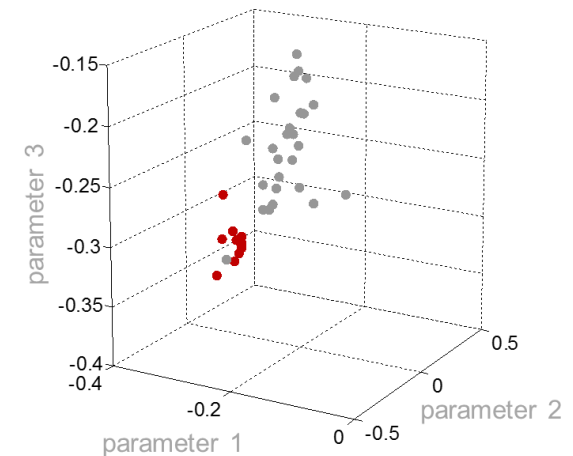
high-dimensional data



generative model



mechanistic interpretation



GM \rightarrow theory-driven
dimensionality reduction

posterior densities \rightarrow denoised, low-
dimensional, explainable features for ML

Computational assays: key clinical questions

SYMPTOMS

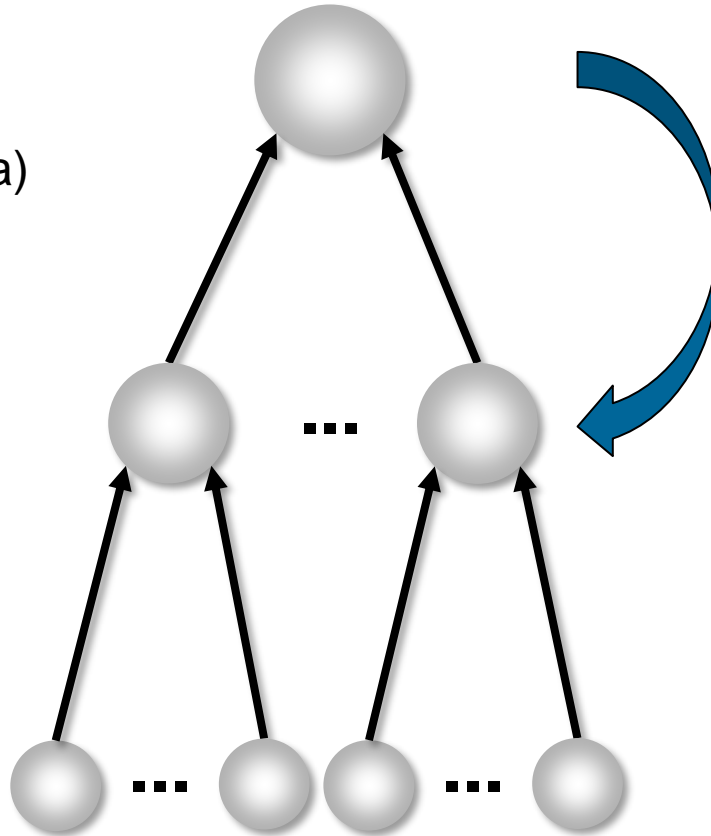
(behavioural or physiological data)

MECHANISMS

(computational, physiological)

CAUSES

(aetiology)



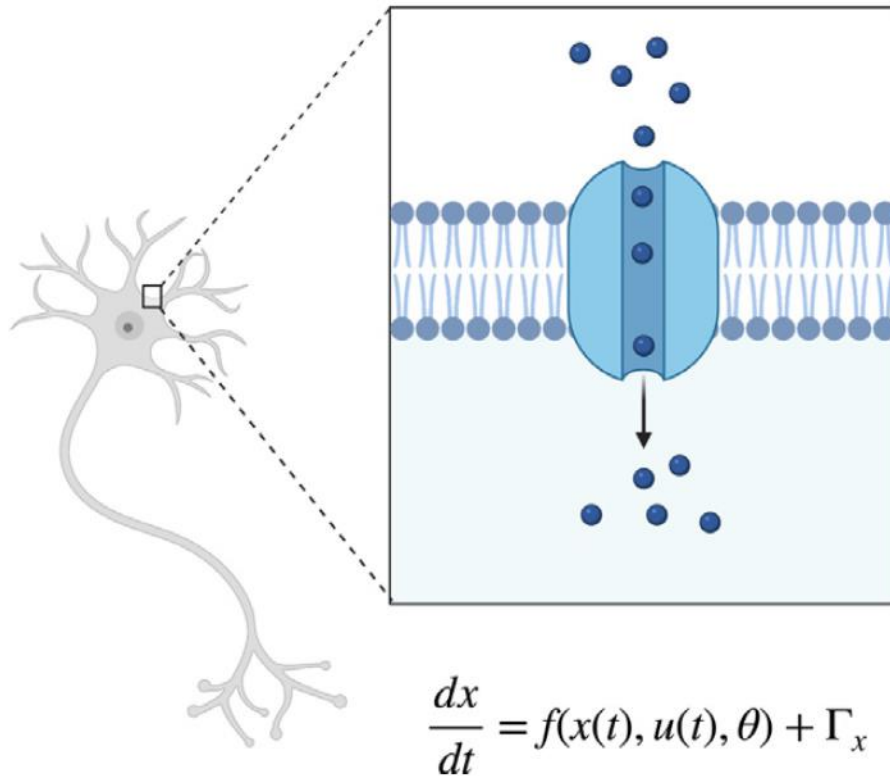
① detecting and differentiating disease mechanisms

② identifying mechanistically distinct **subgroups**

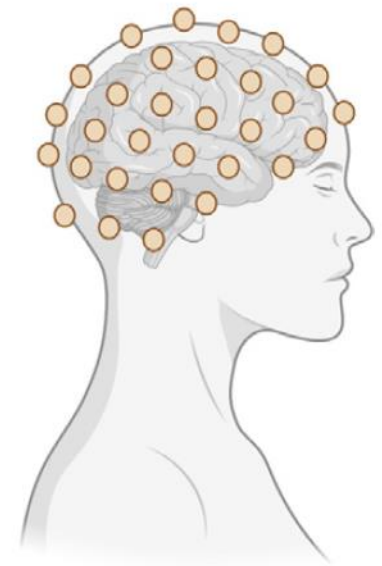
③ prediction of clinical trajectories and treatment response

① Detecting mechanisms: inferring synaptic processes

neuronal circuit model

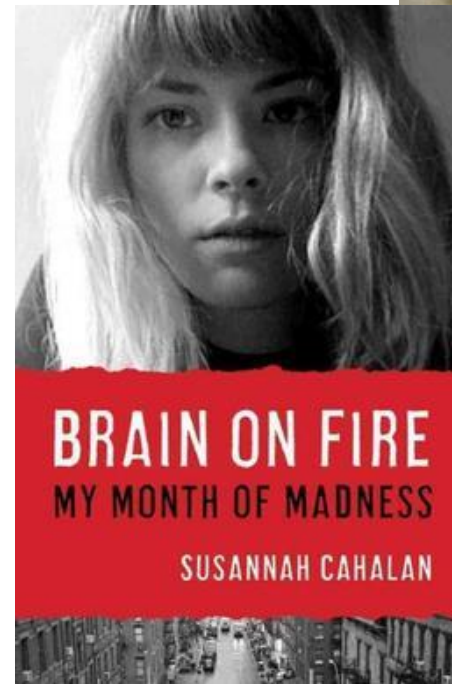
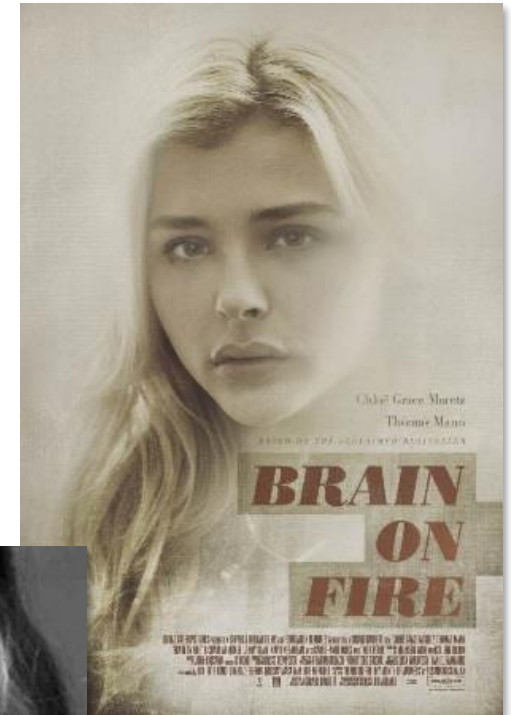
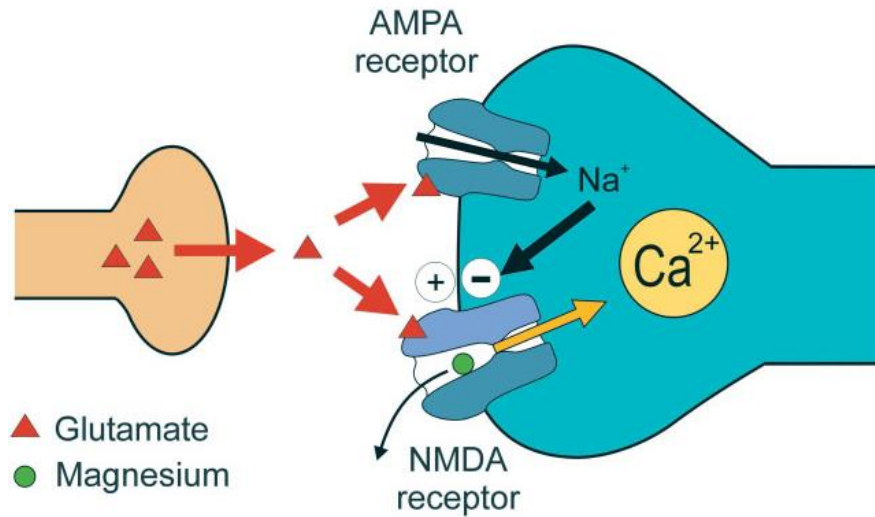


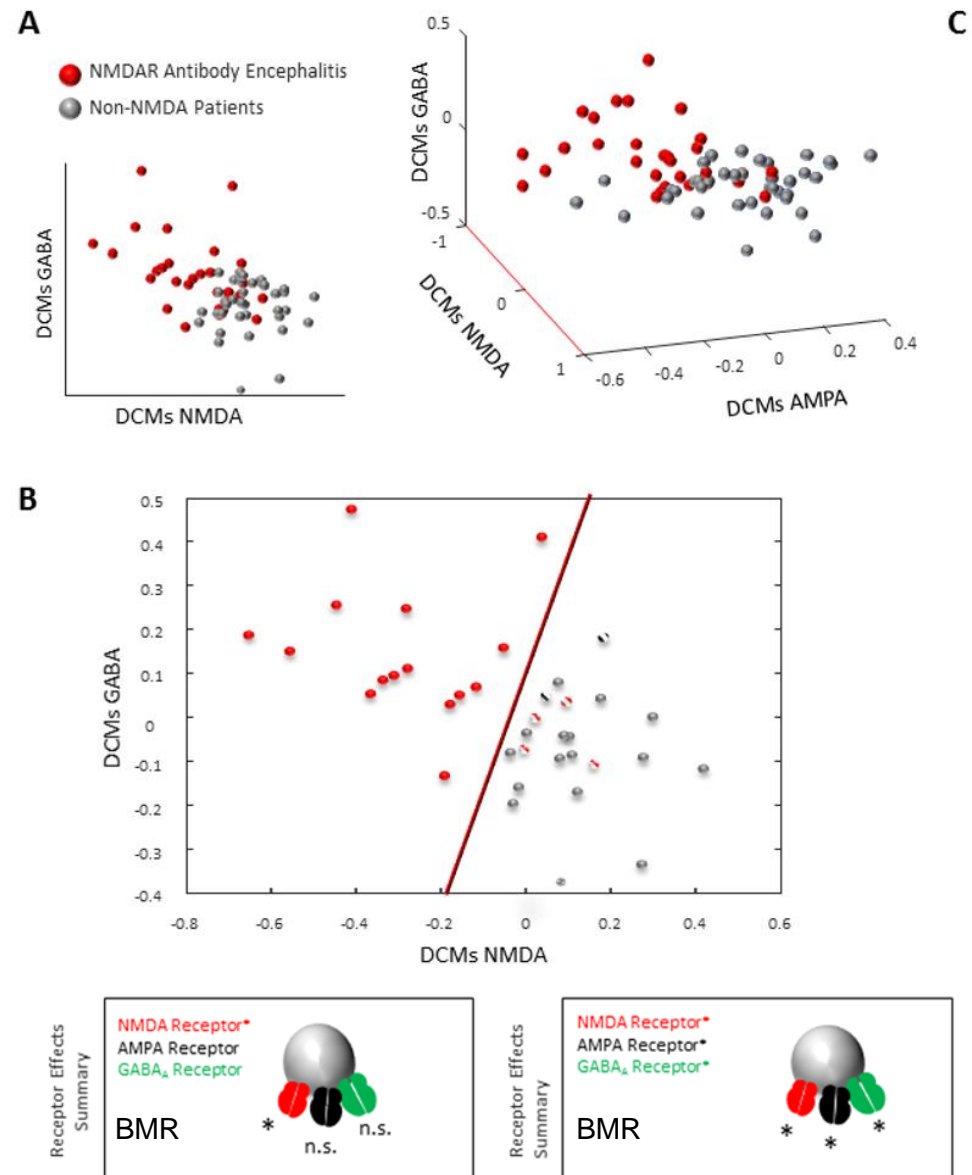
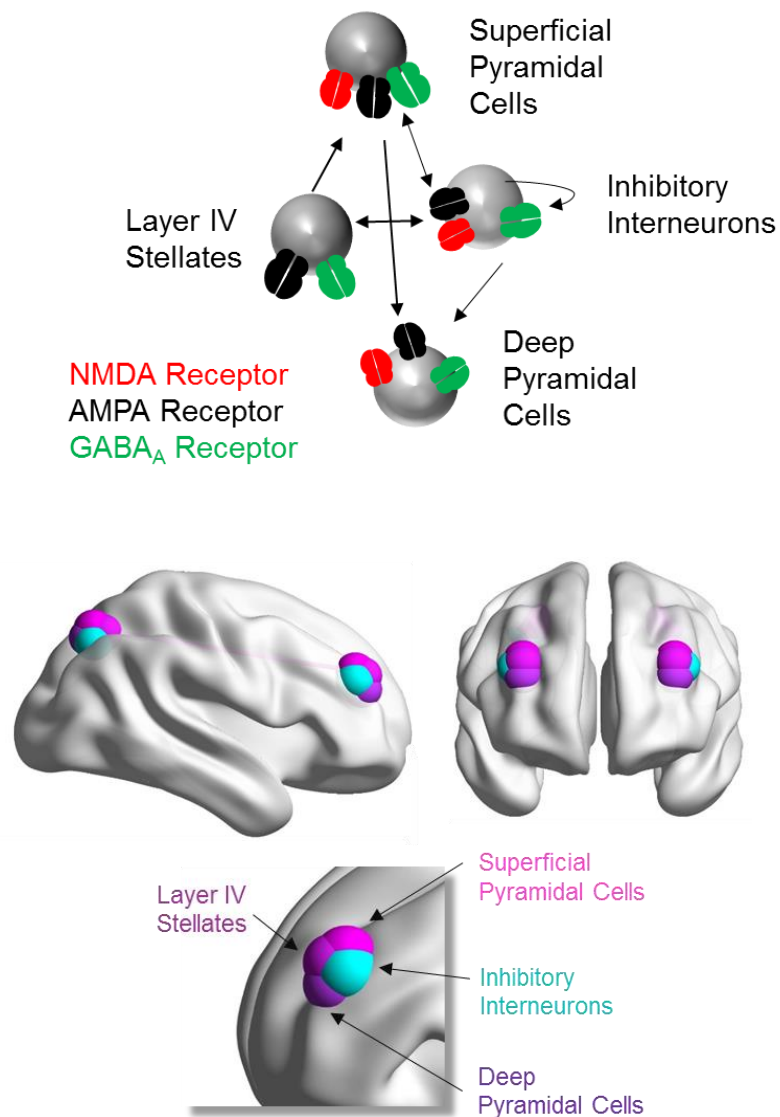
observation model



$$y(t) = h(x(t)) + \epsilon$$

NMDA receptor antibody encephalitis





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

③ Prediction: two-year outcome in depression

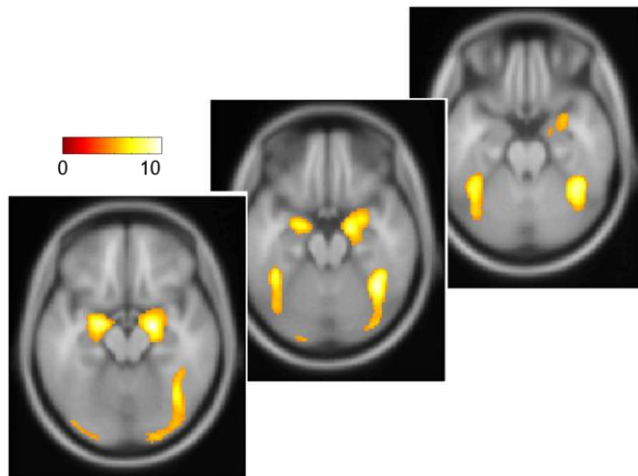
N=85 MDD patients from NESDA study (Schmaal et al. 2015, Biol. Psychiatry)

Three distinct trajectories:

chronic (CHR): n = 15

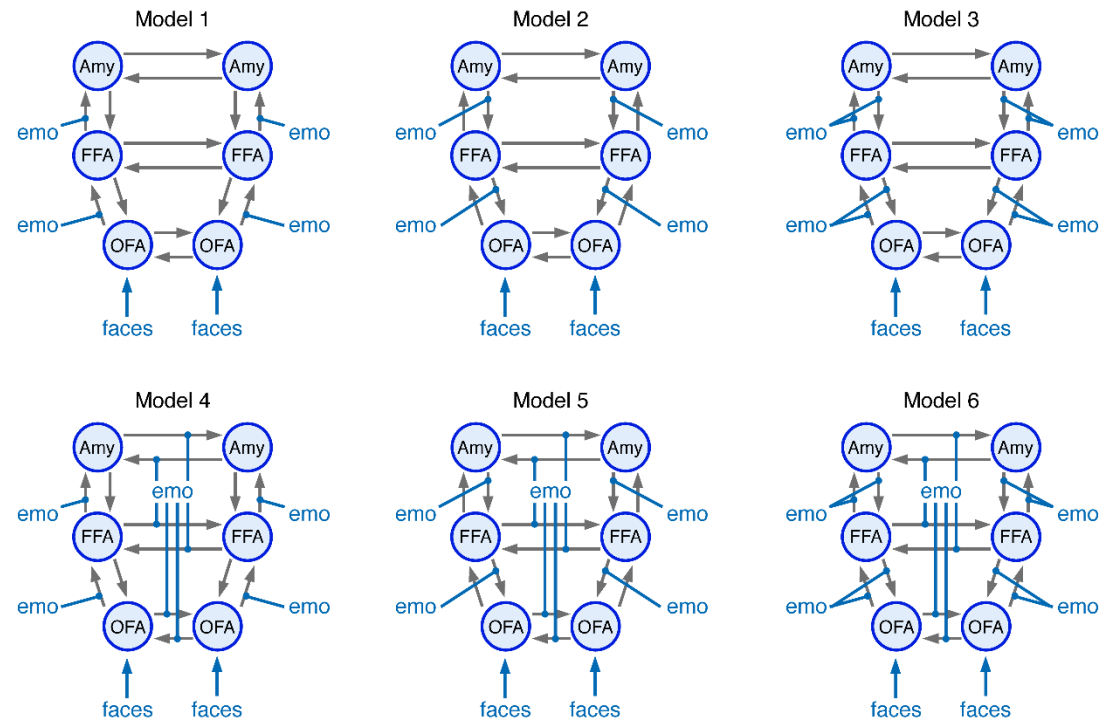
gradually improving (IMP): n = 31

remission (REM): n = 39

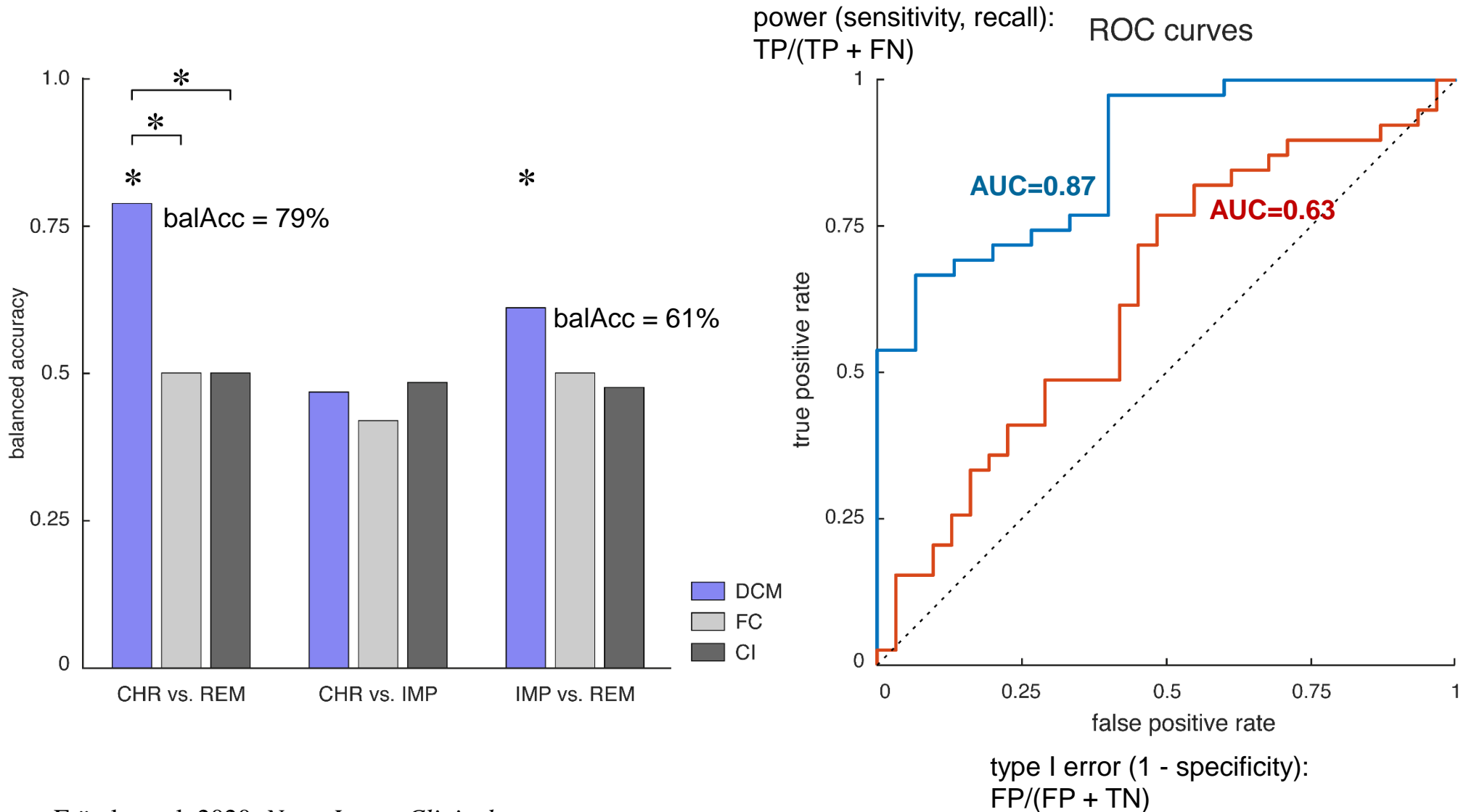


emotional faces > scrambled faces

DCM + BMA

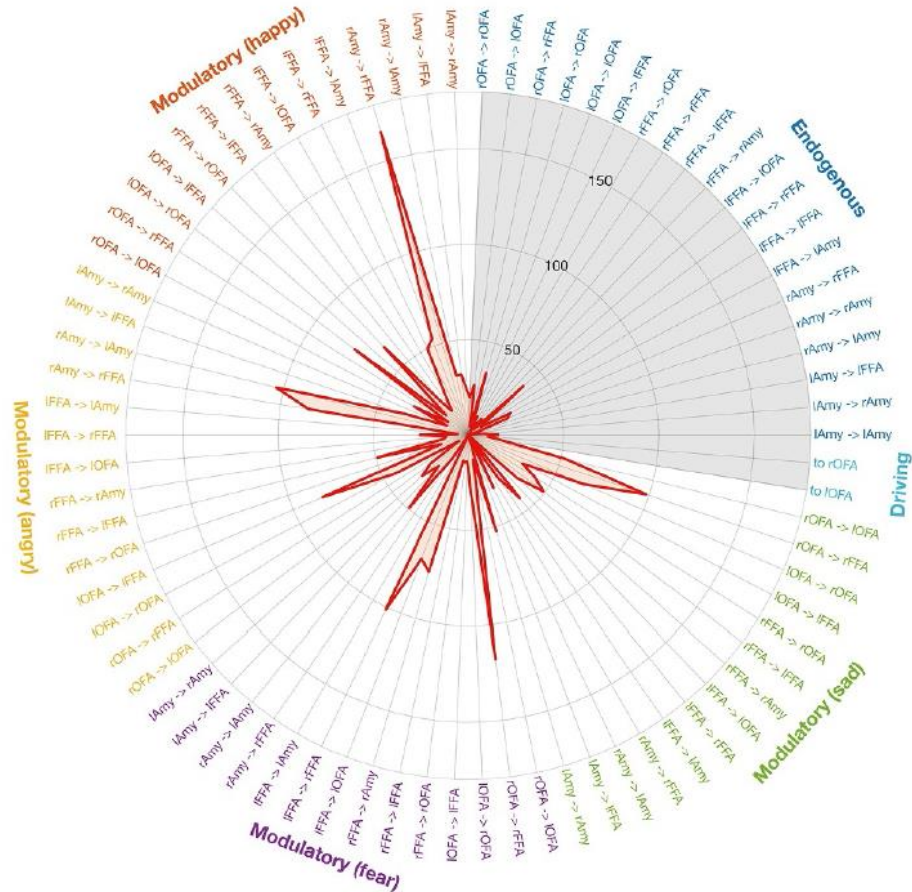


③ Prediction: two-year outcome in depression

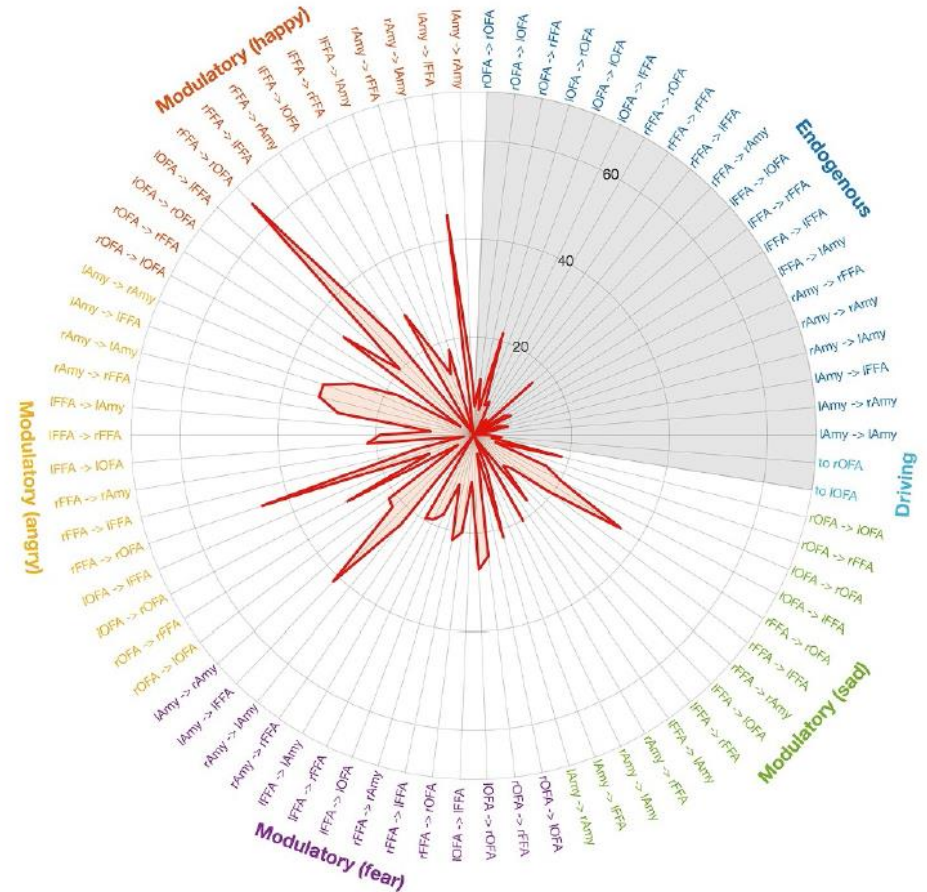


③ Prediction: two-year outcome in depression

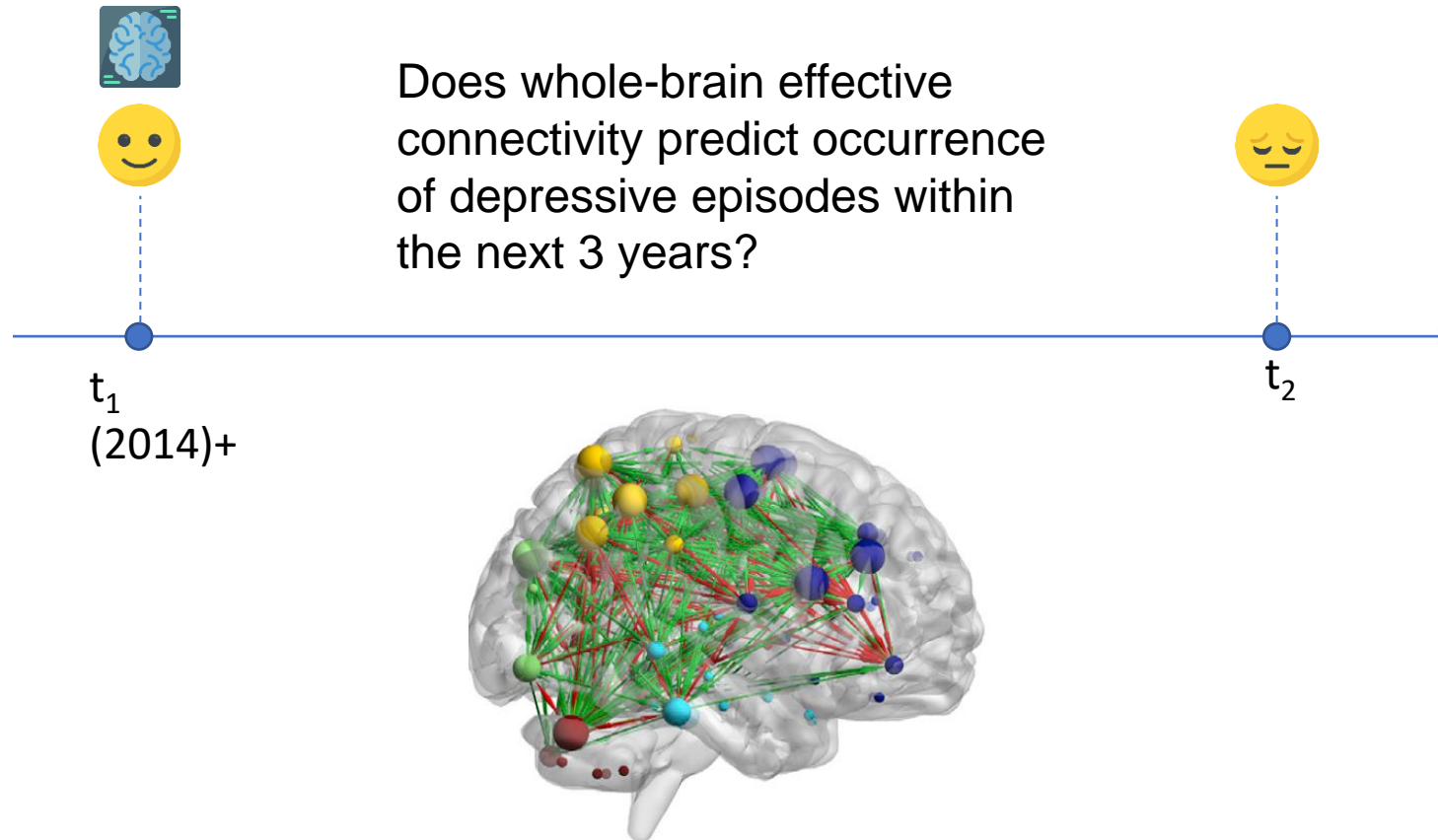
CHR vs. REM



IMP vs. REM



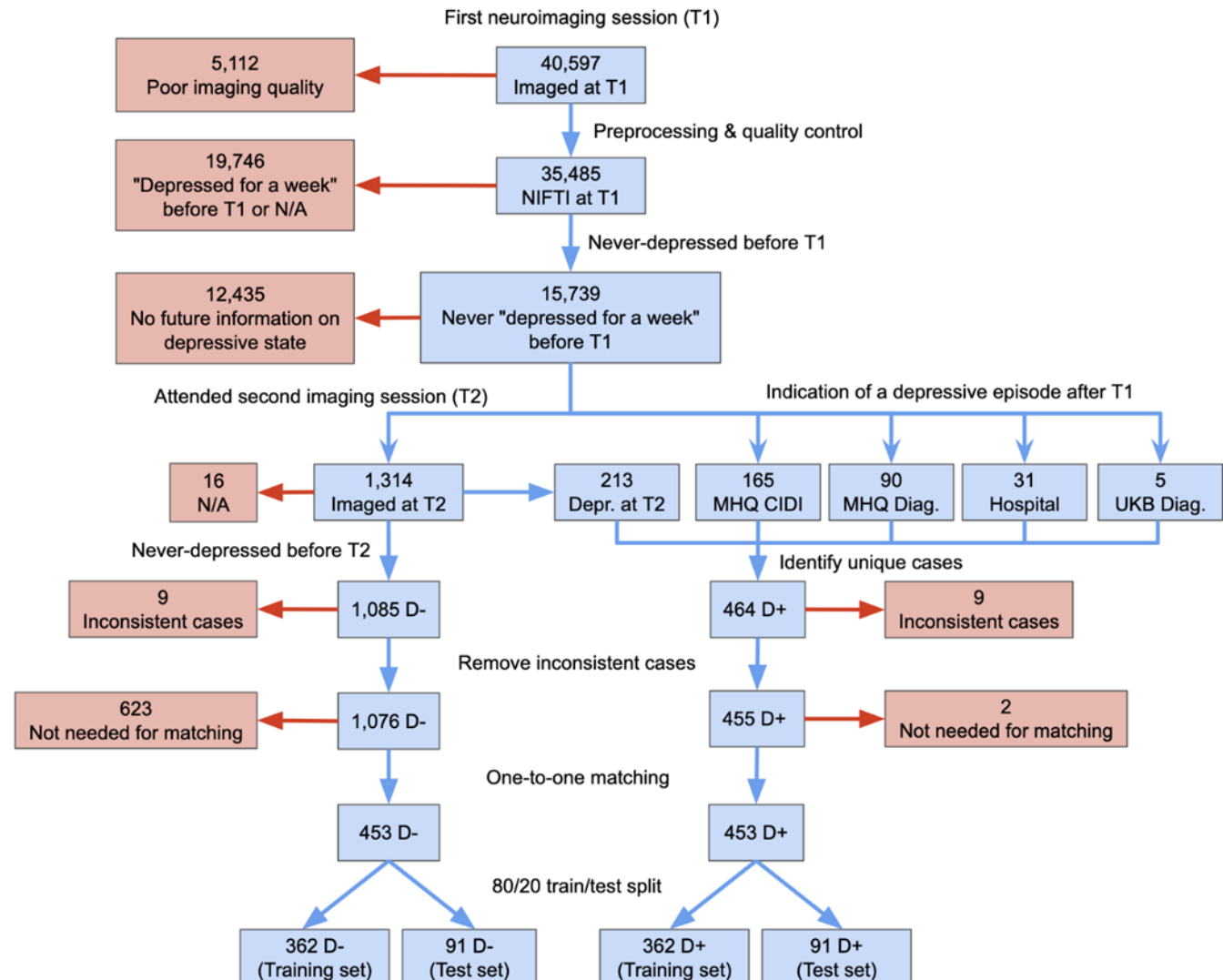
③ Prediction: depressive symptoms within next 3 years



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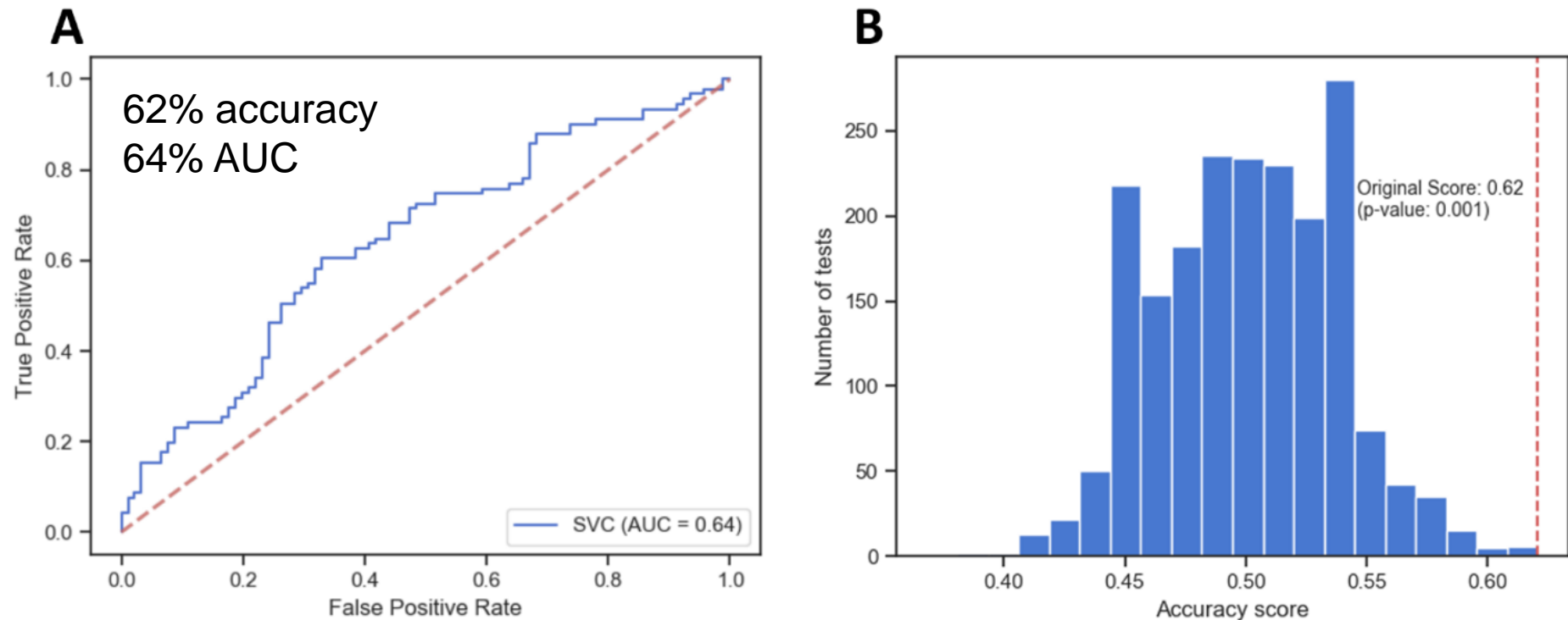
rsfMRI data from UKB (N=906):

- 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



③ Prediction: depressive symptoms within next 3 years

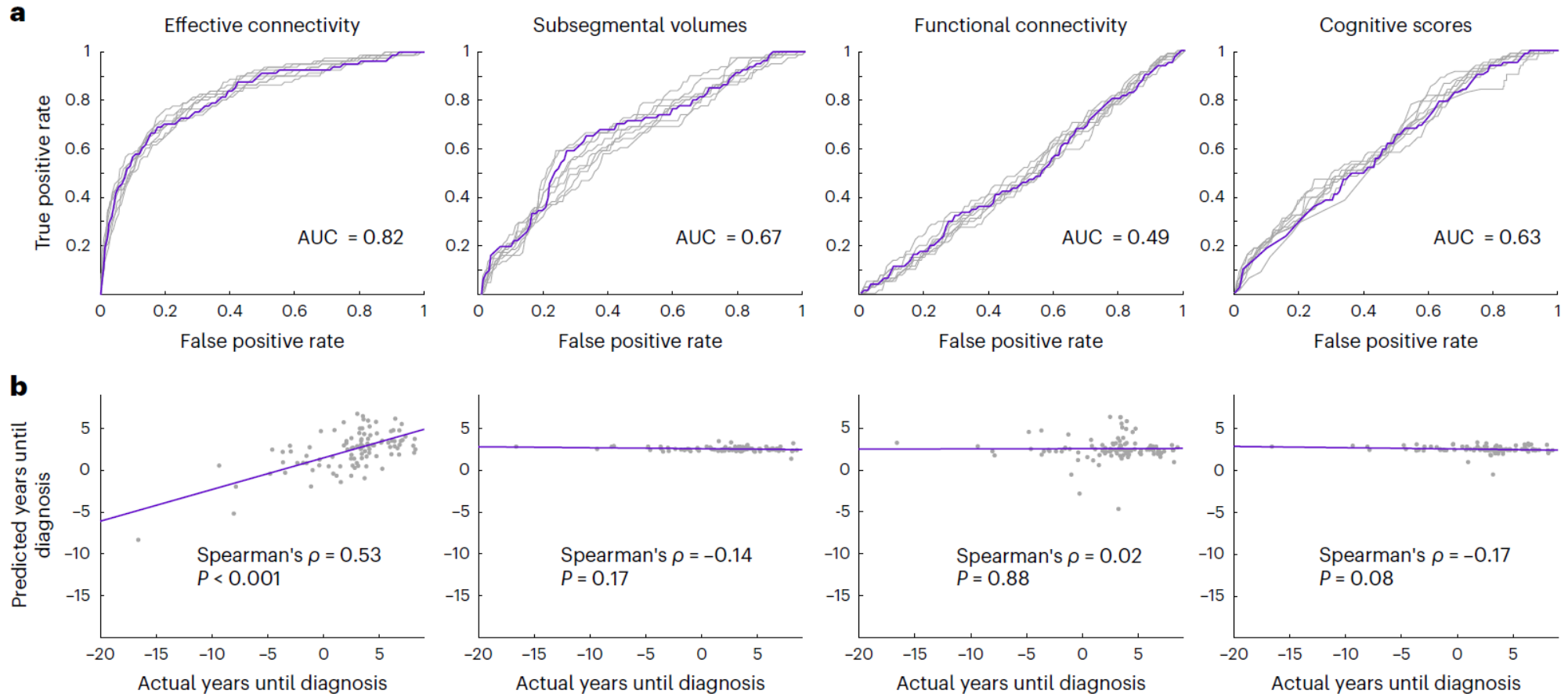
Generative embedding (55 IC rDCM + sigmoid SVM):
Predictive performance on **held-out test set**



③ Prediction: early detection of dementia

- 103 patients with dementia from UK Biobank
 - N=22 with a diagnosis of dementia at the time of the scan
 - N=81 who would later develop dementia
- generative embedding
 - spectral DCM of default mode network ("resting state" fMRI)
 - elastic net regularized logistic regression
 - nested cross-validation
- effective connectivity estimates predicted both future dementia diagnosis (AUC=0.82) and time to diagnosis ($\rho=0.53$)
- ... while other measures (functional connectivity, volumetric data from structural MRI, cognitive scores) did not

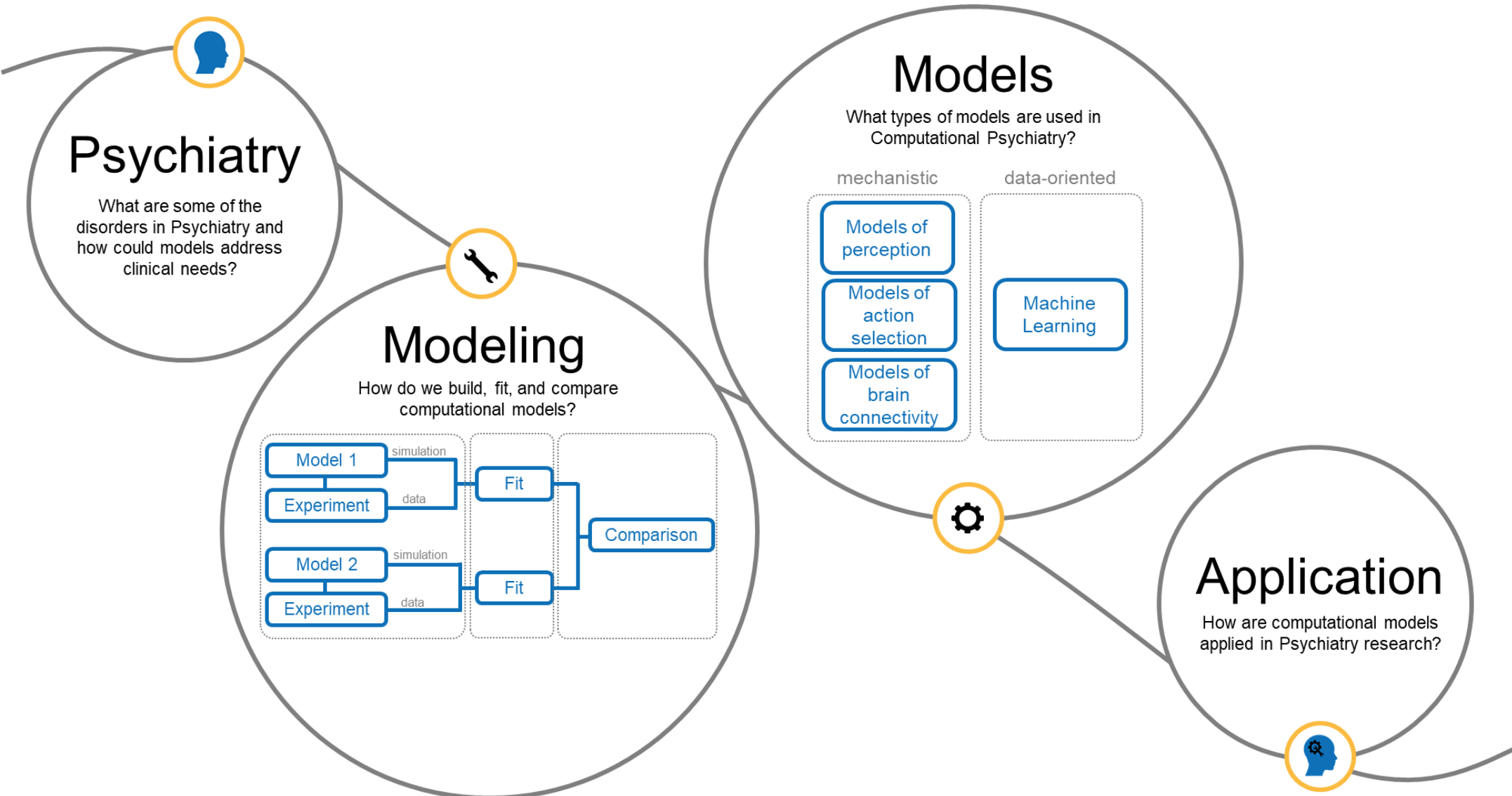
③ Prediction: early detection of dementia





- 11th 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
 - >250 registered participants

CPC 2025: thematic structure



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.
- 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
- Montague PR, Dolan RJ, Friston KJ, Dayan P (2012) Computational psychiatry. *Trends Cogn. Sci.* 16, 72–80.
- Petzschner FH, Weber LAE, Gard T, Stephan KE (2017) Computational Psychosomatics and Computational Psychiatry: Toward a joint framework for differential diagnosis. *Biological Psychiatry* 82: 421-430.
- 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 2025!



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