Introduction to Computational Psychiatry

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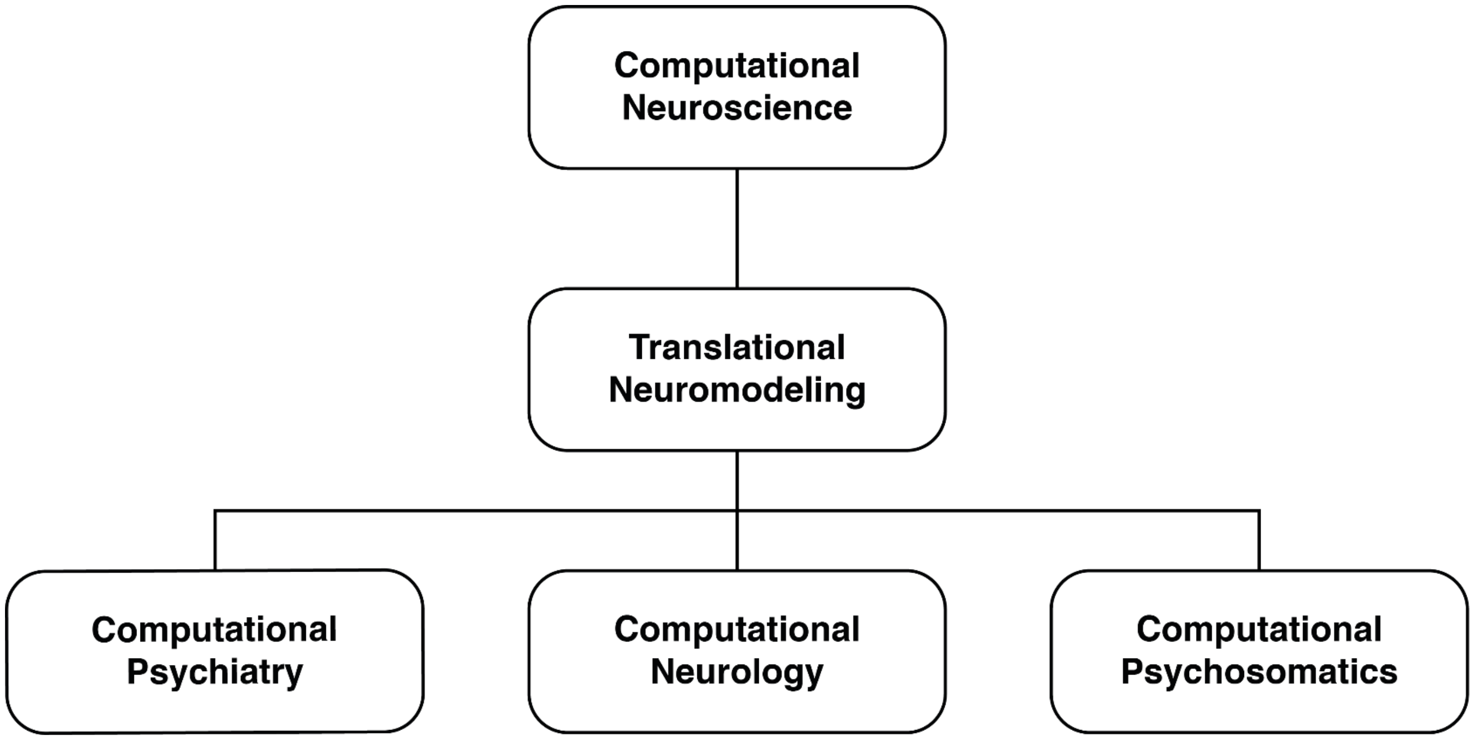
What is Computational Psychiatry?

Understanding how/what the brain computes

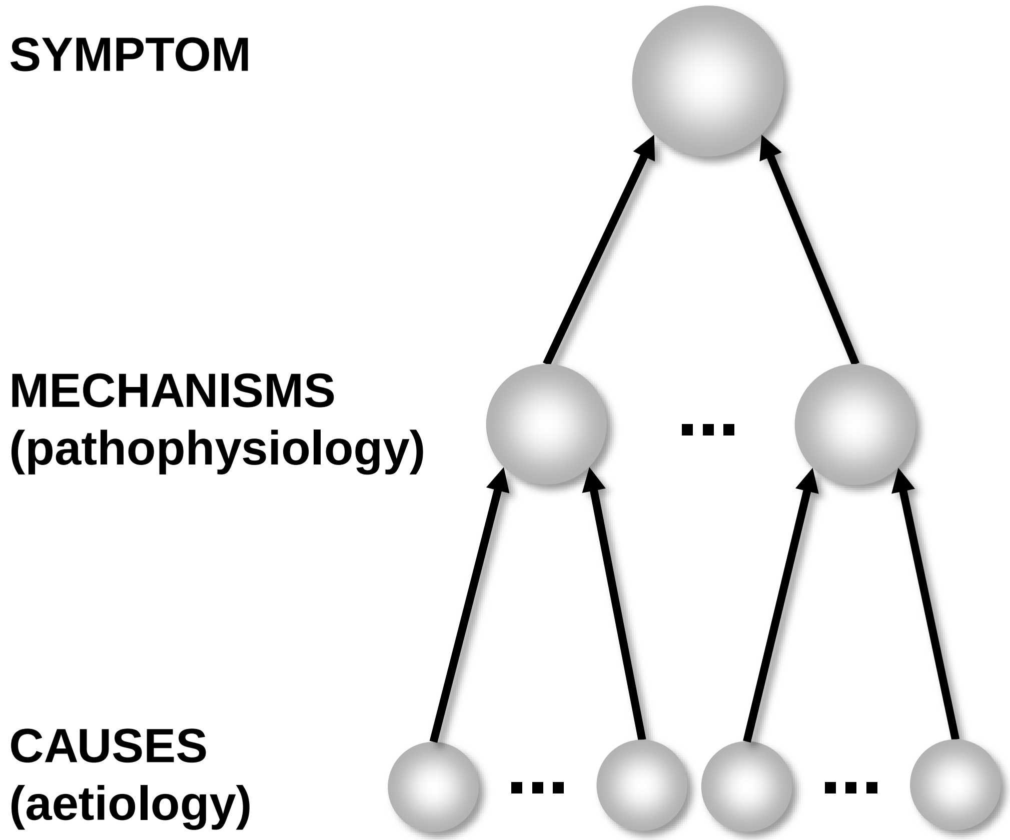
Develops/validates mathematical models for solving clinical problems

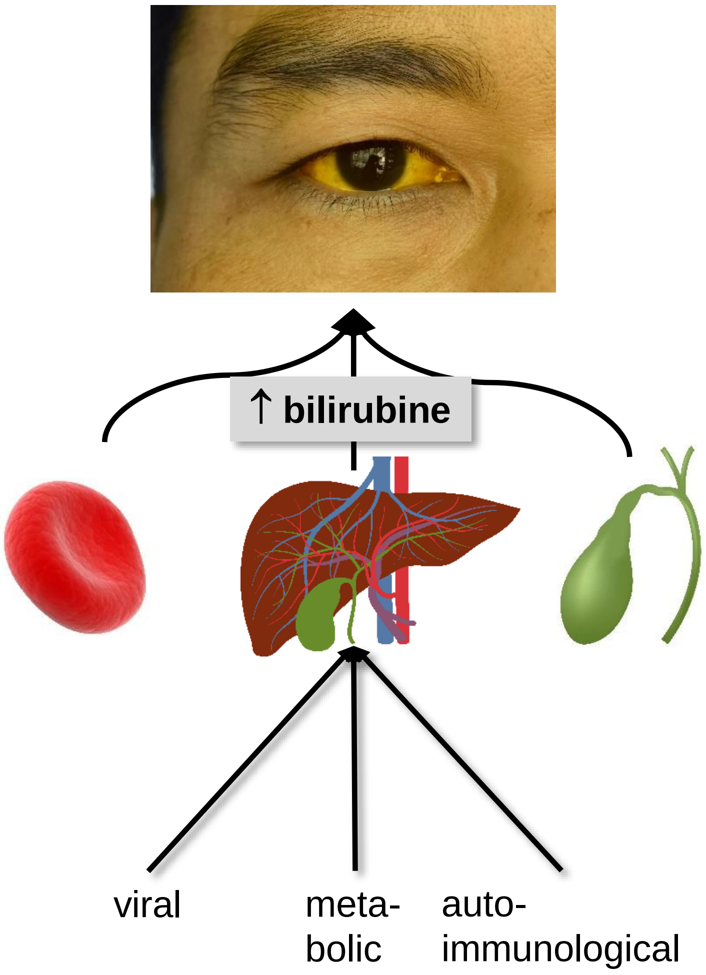
Application within specific medical fields



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

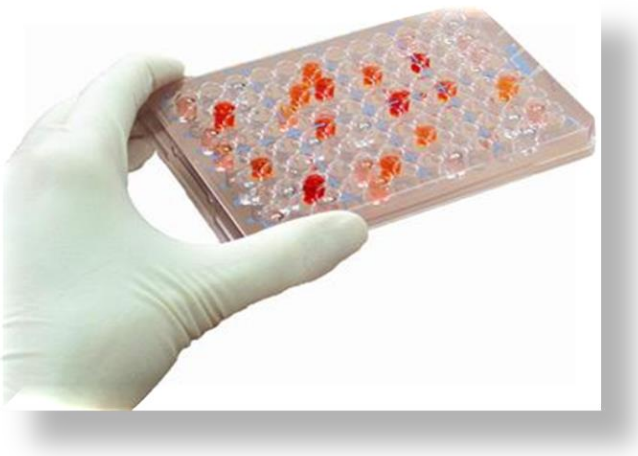
From differential diagnosis to nosology

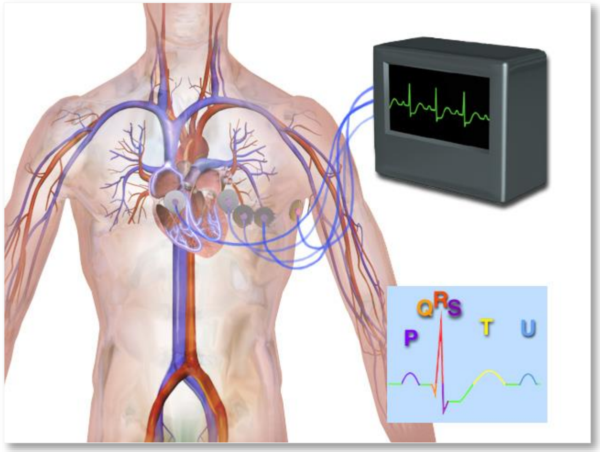




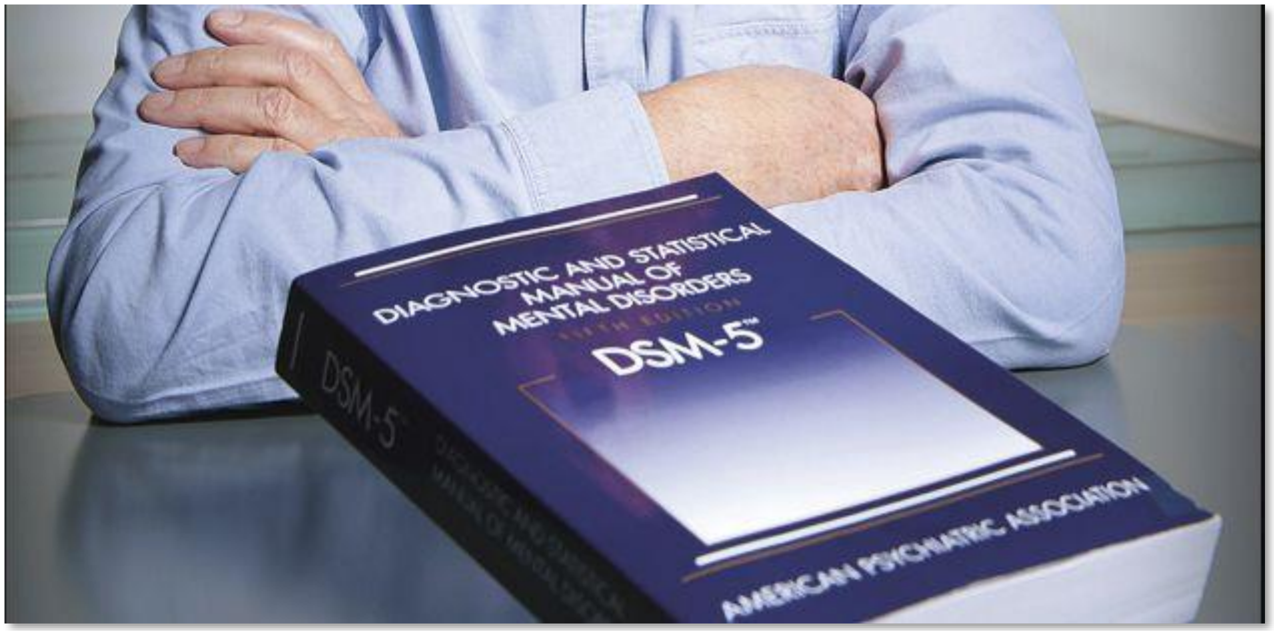
Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

>3,000 clinical tests in medicine



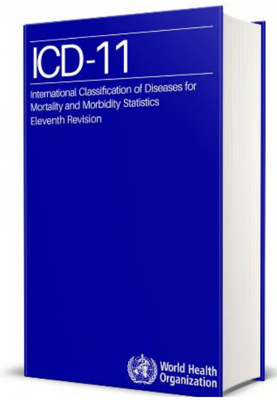


1 diagnostic instrument in psychiatry

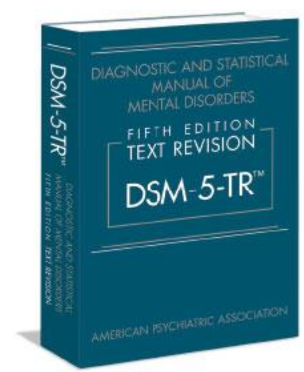


Contemporary psychiatric classifications: ICD and DSM

- **International Classification of Diseases (ICD):**
  - curated by the World Health Organization (WHO)
  - 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
  - $138.63 (Amazon, 07 Sept. 2024)



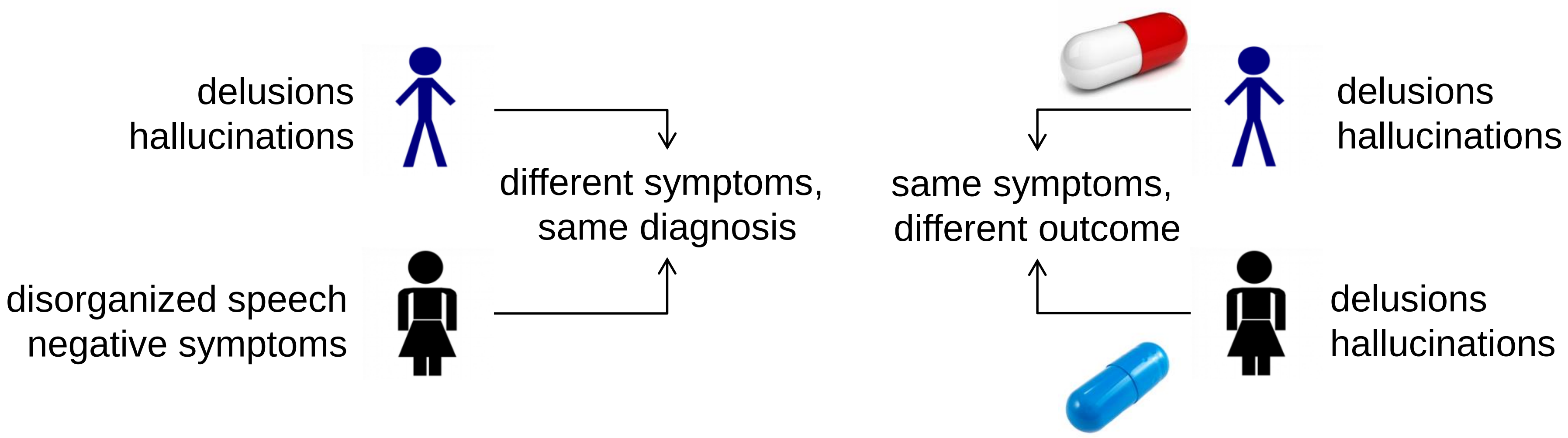
- **both schemes**
  - define mental disorders as syndromes
  - reflect the consensus (or compromise) of expert committees
  - are descriptive (without reference to mechanisms)

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

$\geq$ 2 symptoms
(at least one pos. symptom)
over $\geq$ 1 month



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Heterogeneity of psychiatric disorders

polygenetic basis

gene-environment interactions

environmental variation

variability in clinical trajectory and treatment response

multiple disease mechanisms

PERSPECTIVE

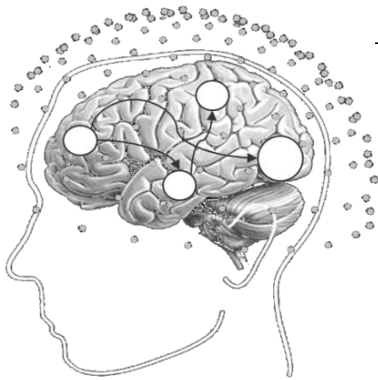
Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

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

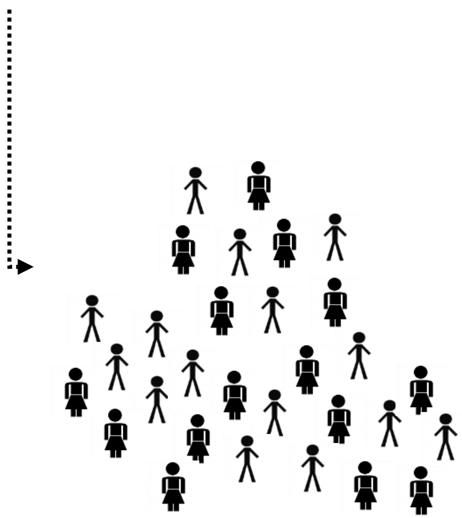
Kapur et al. 2012, *Molecular Psychiatry*

Translational Neuromodeling & Computational Psychiatry (TN/CP)

❶ **Computational assays**

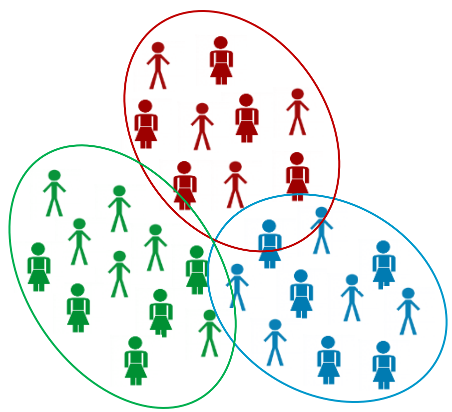


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



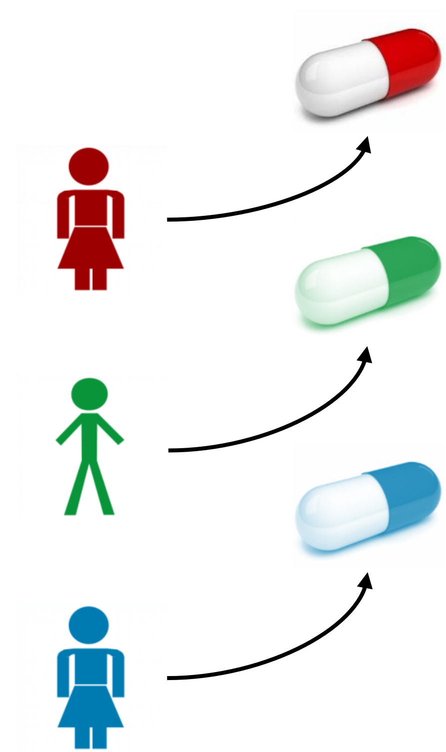
❷ **Application to individual patients**

❸ **Differentiating patients based on inferred mechanisms**



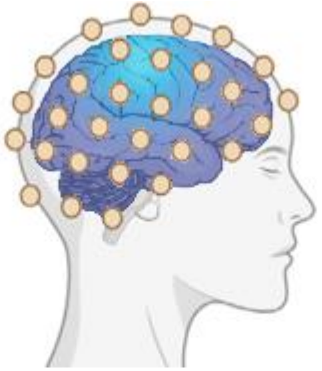
- disease mechanism A
- disease mechanism B
- disease mechanism C

❹ **Individual prediction**



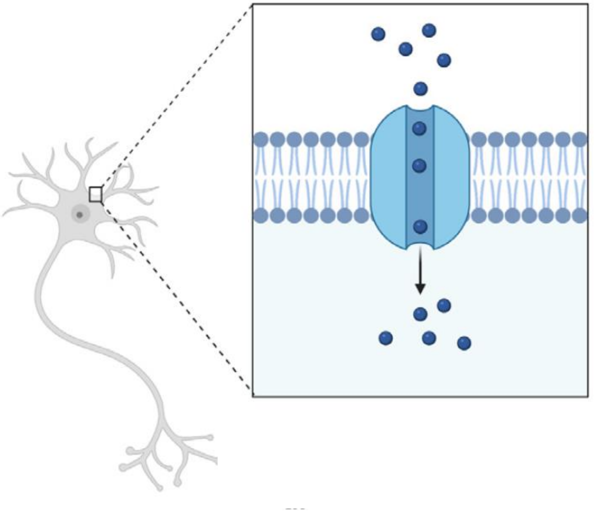
Stephan et al. 2015, *Neuron*

Generative models and "computational assays"



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

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



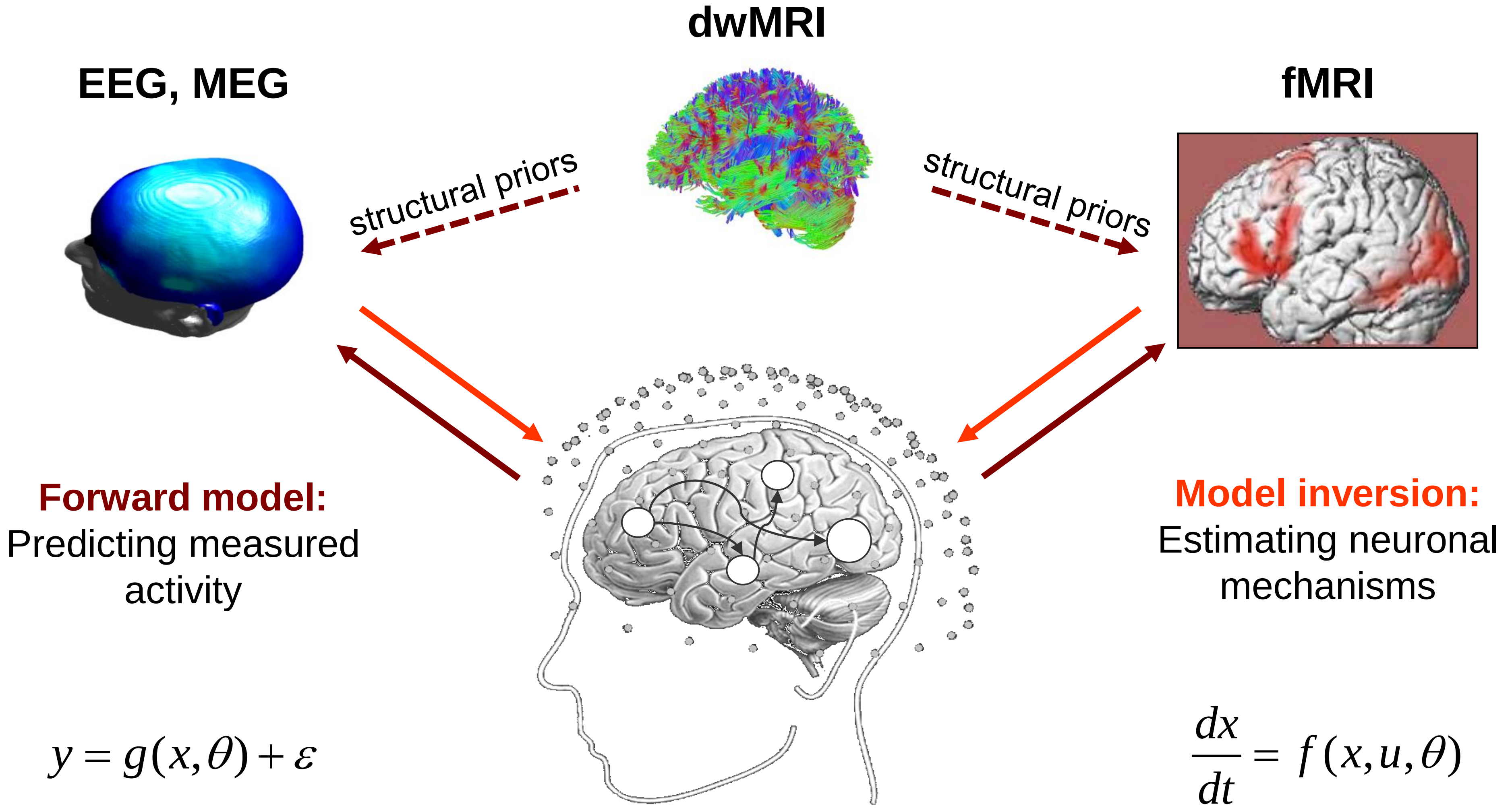
measured brain
activity y

generative
model m

hidden neuronal
parameters θ

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

Example: Dynamic causal models (DCMs)



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"

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

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

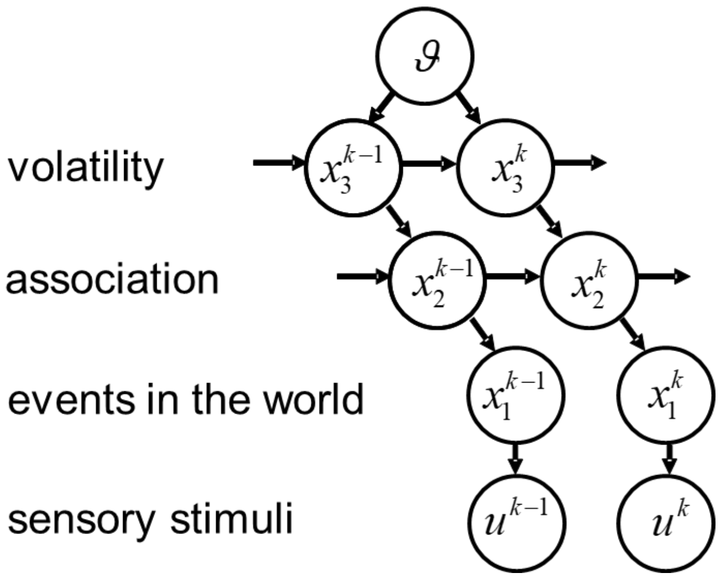
observed symptoms or behaviour y

generative model m

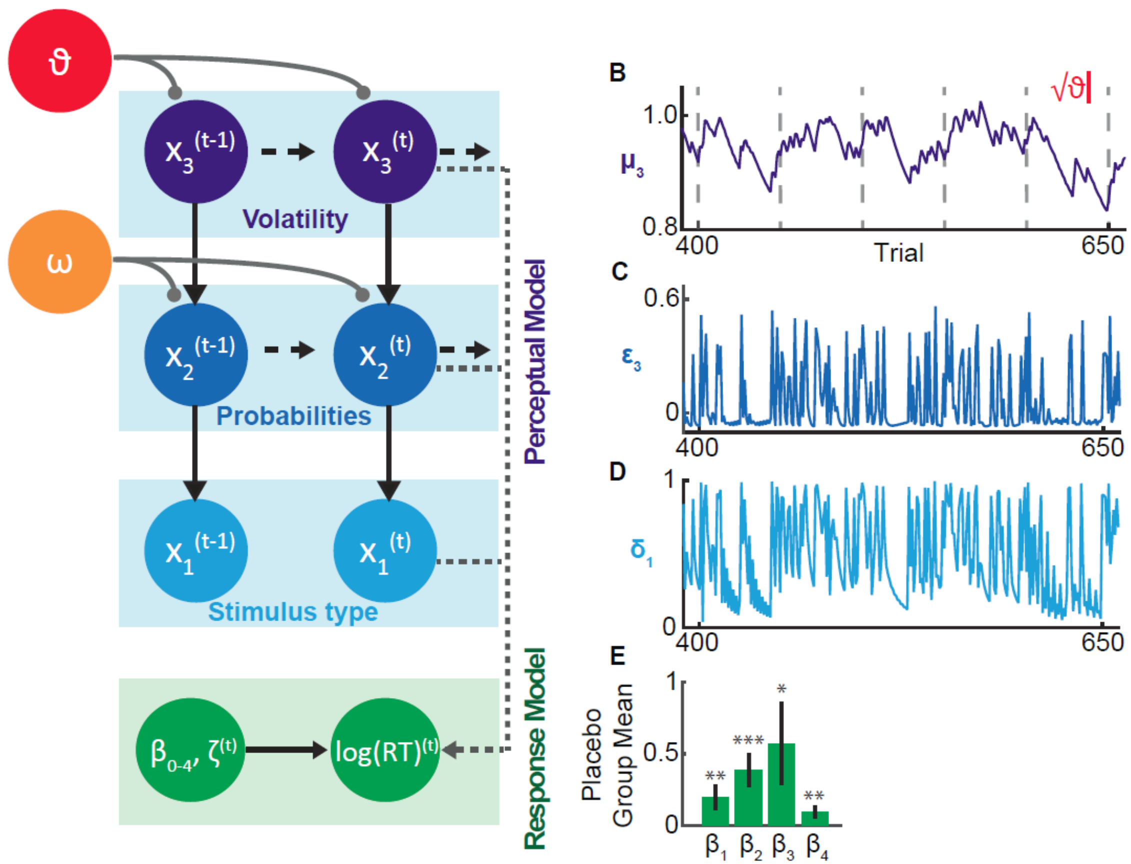
hidden algorithmic parameters θ

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

Example: Hierarchical Gaussian Filter (HGF)



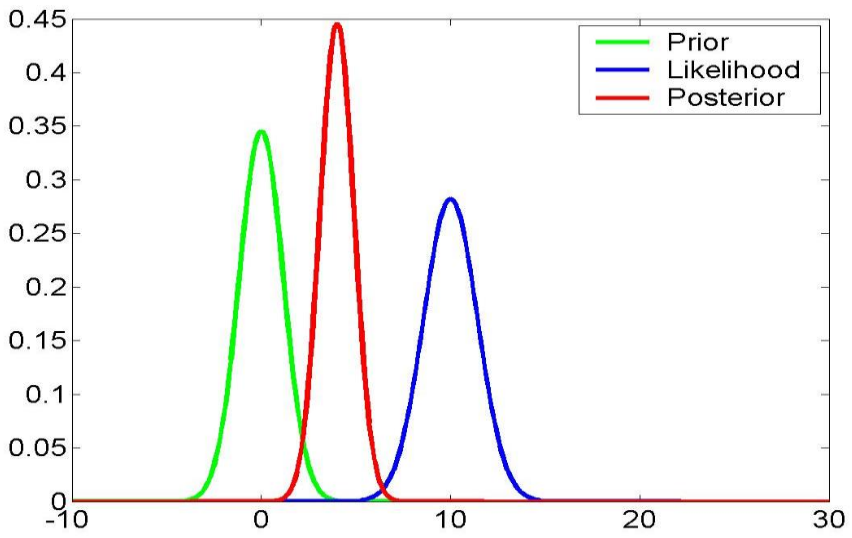
$$\Delta\text{belief} \propto \frac{\text{precision}_{\text{input}}}{\text{precision}_{\text{pred}}} \times \text{PE}$$



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

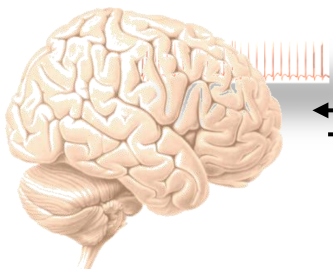
Generative models as a concept for brain function: the "Bayesian brain" hypothesis

neuronal states

environm. states
others' mental states
bodily states

forward model

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



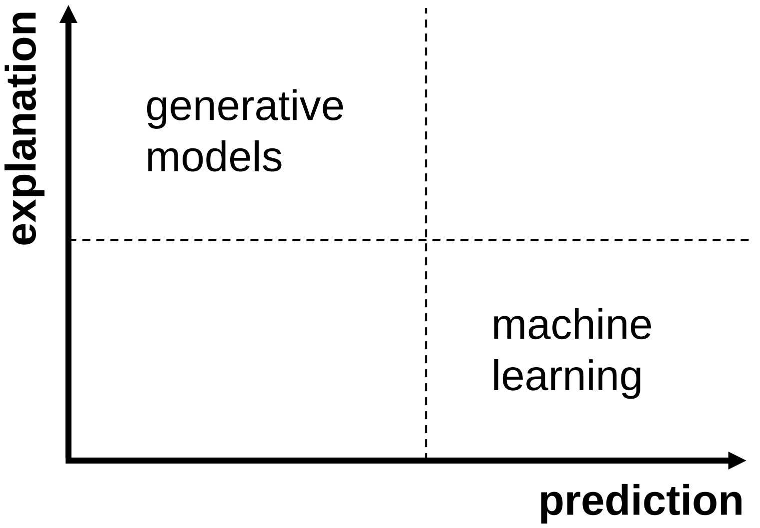
$$p(x \mid y, m)$$

perception

perception = inference = inversion of a generative model

The “Two Cultures of Computational Psychiatry”

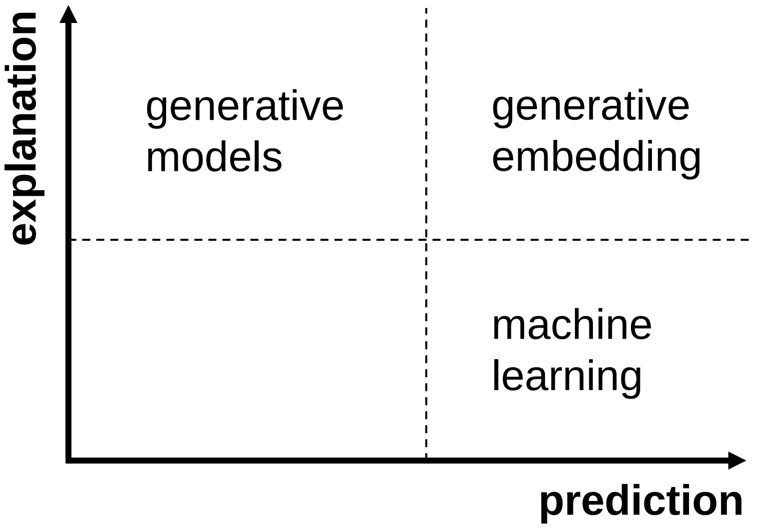
- **explanation:** generative models
  - data-generating process is of central interest
  - goal: identify the mechanisms underlying observations (e.g. clinical symptoms, brain activity)
- **prediction:** machine learning (ML)
  - data-generating process is treated as a black box
  - goal: prediction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



Bennett et al. 2019, *JAMA Psychiatry*

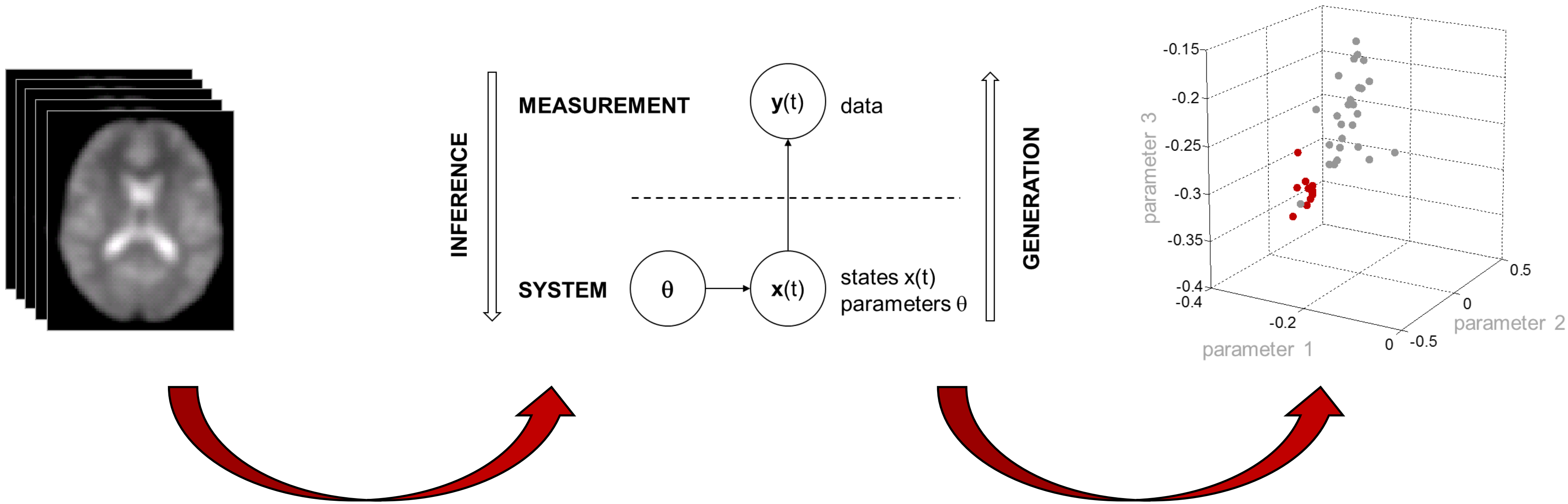
The “Two Cultures of Computational Psychiatry” ... and Generative Embedding as their bridge

- **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**



GM = theory-driven
dimensionality reduction

posterior densities → selecting
explainable parts of the data

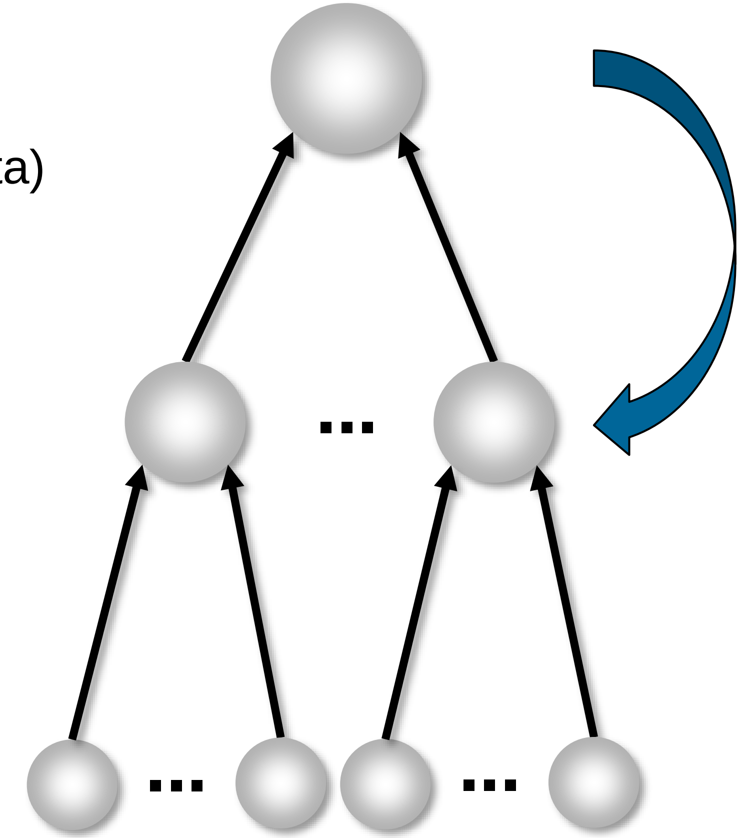
Brodersen et al. 2011, *PLoS Comp. Biol.;* Brodersen et al. 2014, *NeuroImage Clinical*

Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



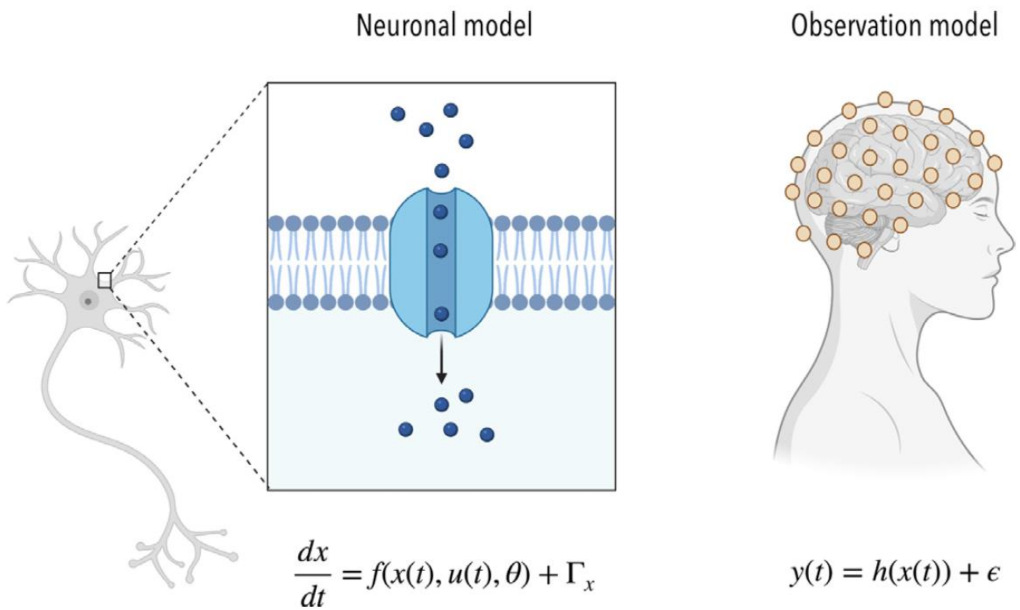
❶ **differential diagnosis:** deciding between alternative disease mechanisms

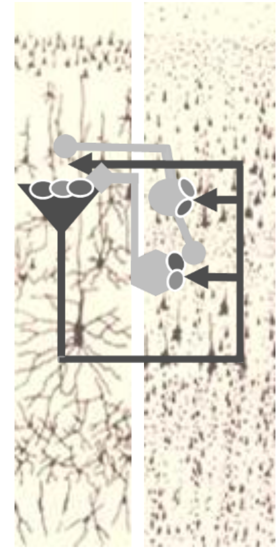
❷ **stratification / subgroup detection** into mechanistically distinct subgroups

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

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

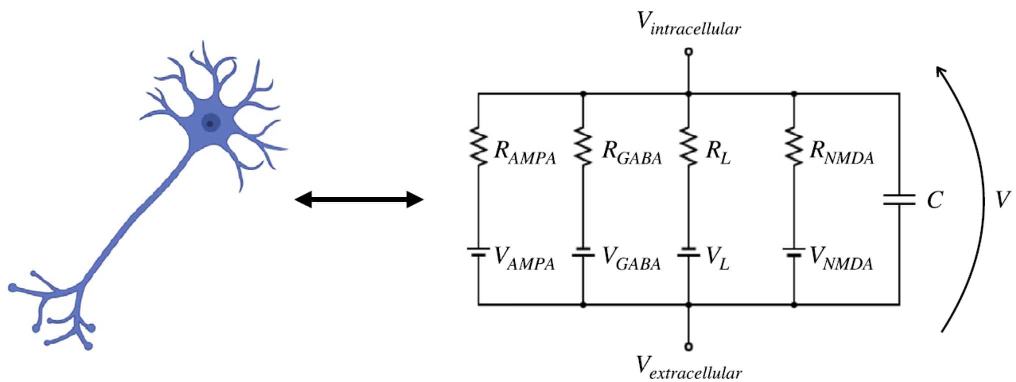
❶ Differential diagnosis: inferring synaptic processes





- inhibitory interneurons
- excitatory interneurons
- pyramidal cells

AMPA, NMDA,GABA$_A$ receptors

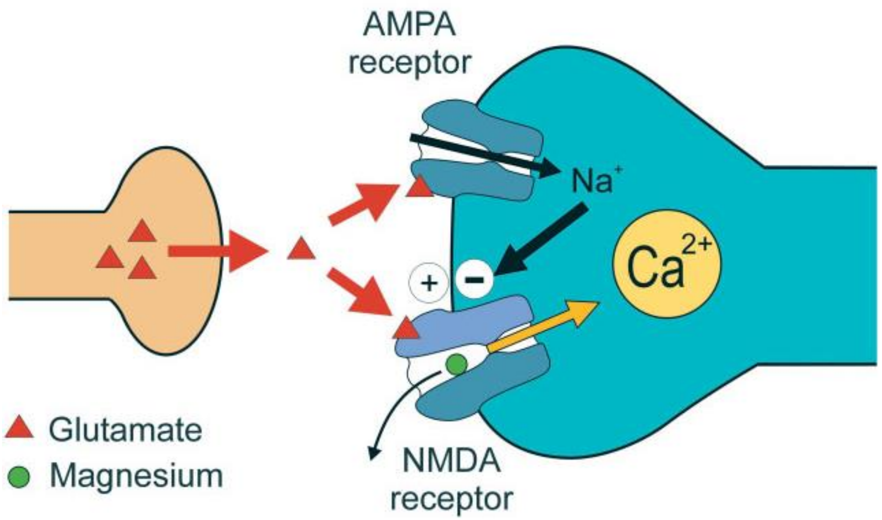


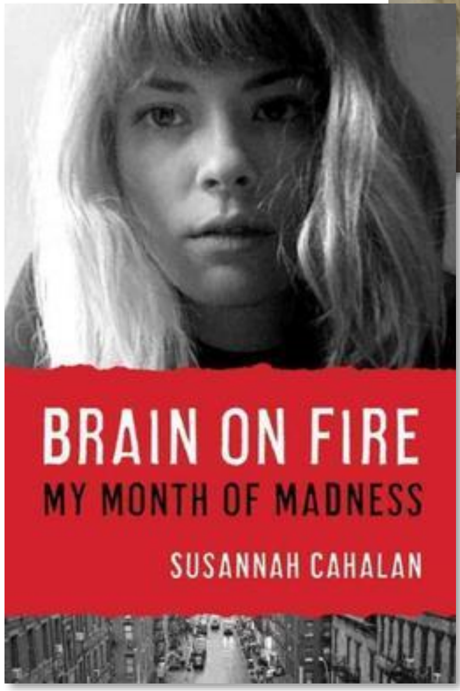
$$C\dot{V} = \sum g_i \left(V_i^0 - V\right)$$
$$\dot{g}_k = \kappa\left(u_{ij} - g_k\right)$$
$$u_{ij} = \gamma_{ij}\sigma\left(\mu_V^{(j)} - V_R, \Sigma^{(j)}\right)$$

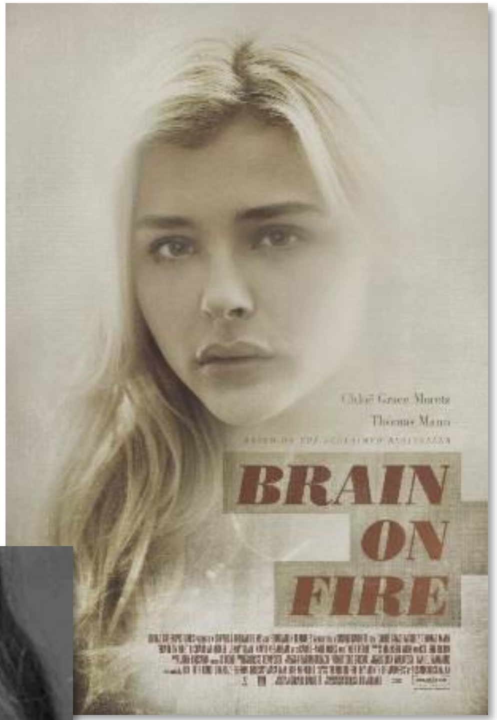
u_{ij} = presynaptic input from ensemble j to i
σ = CDF of presynaptic depolarization density around threshold potential V_R

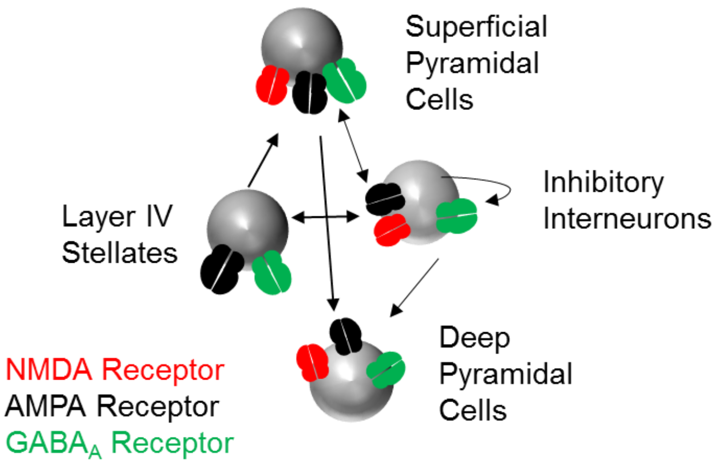
Images: Pereira et al. 2021, *NeuroImage*

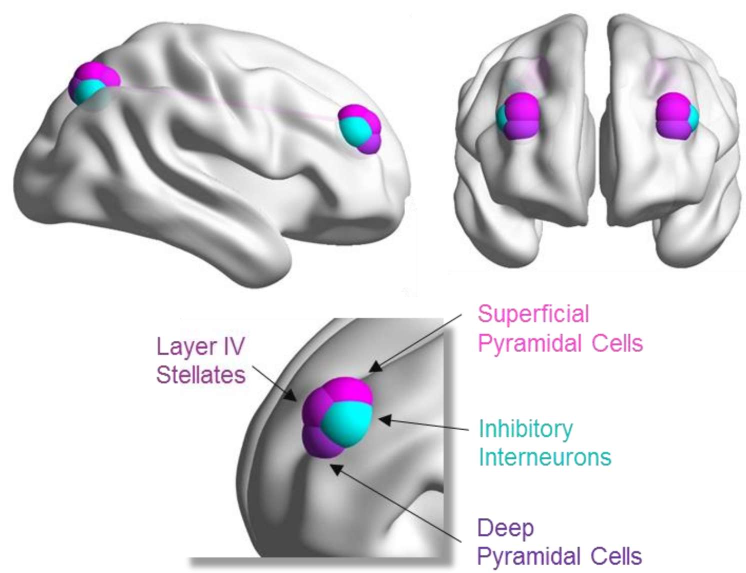
NMDA receptor antibody encephalitis

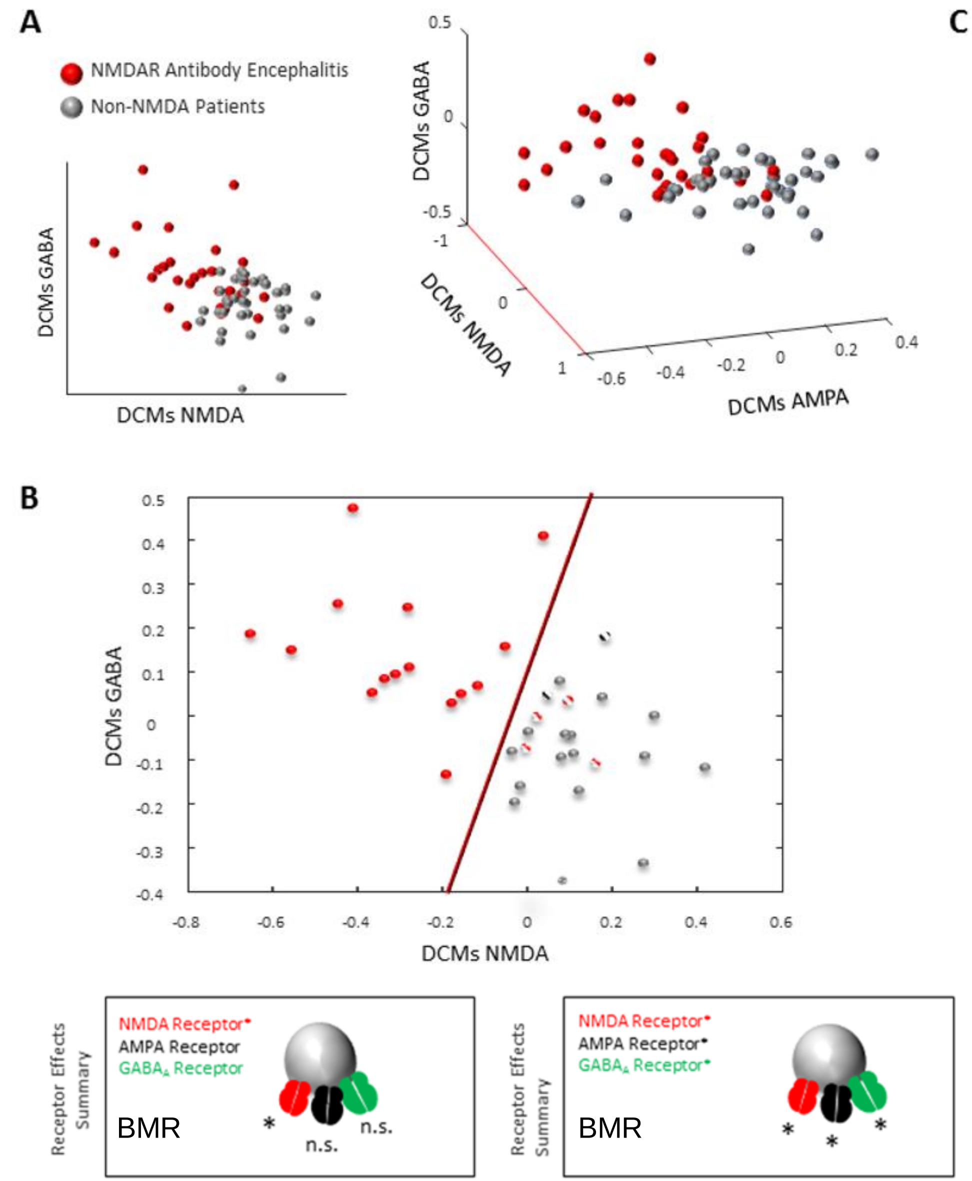












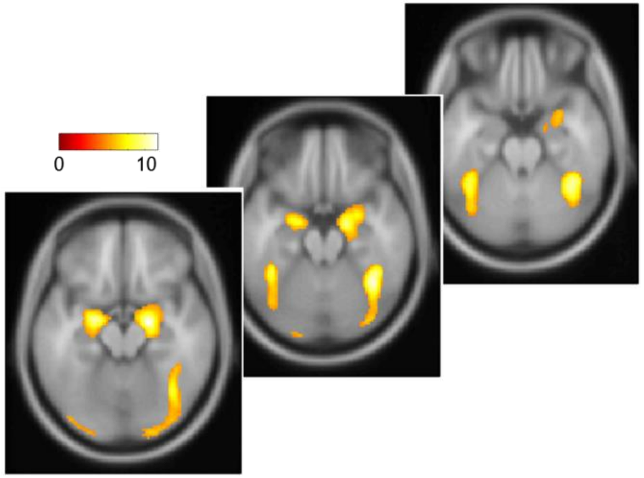
29 patients with NMDAR-antibody encephalitis
18 control patients (with inflammatory/metabolic encephalopathy)

Symmonds et al. 2018, *Brain*

❸ Prediction: two-year outcome in depression

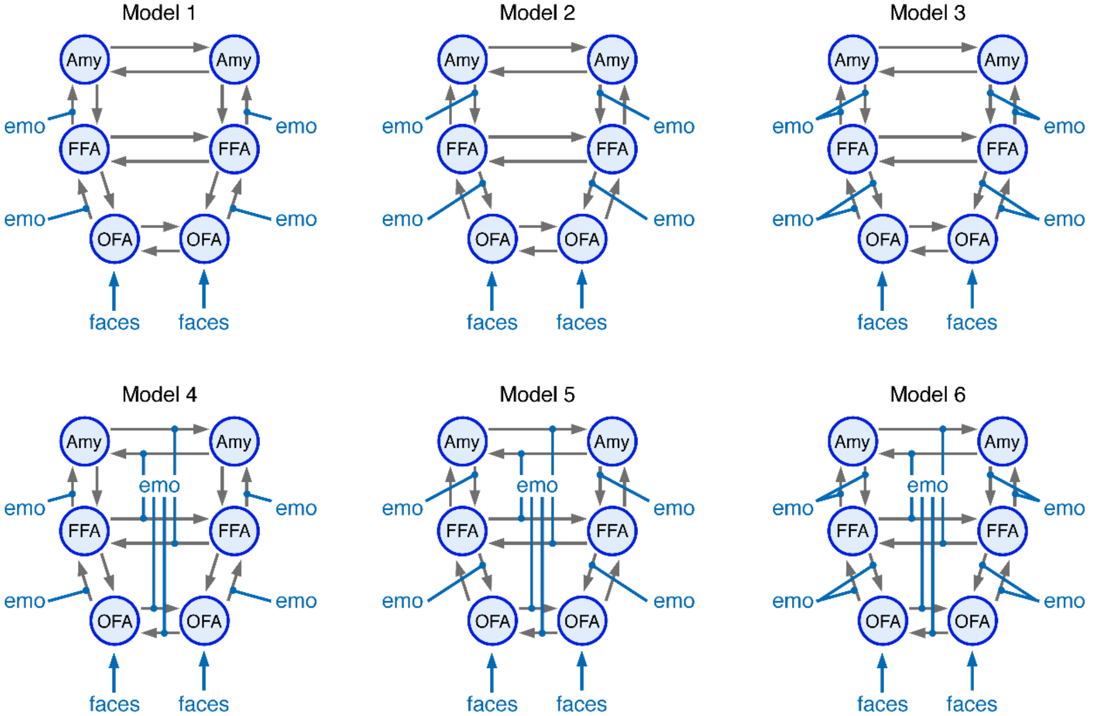
N=85 MDD patients from NESDA study (Schmaal et al. 2015, Biol. Psychiatry)

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



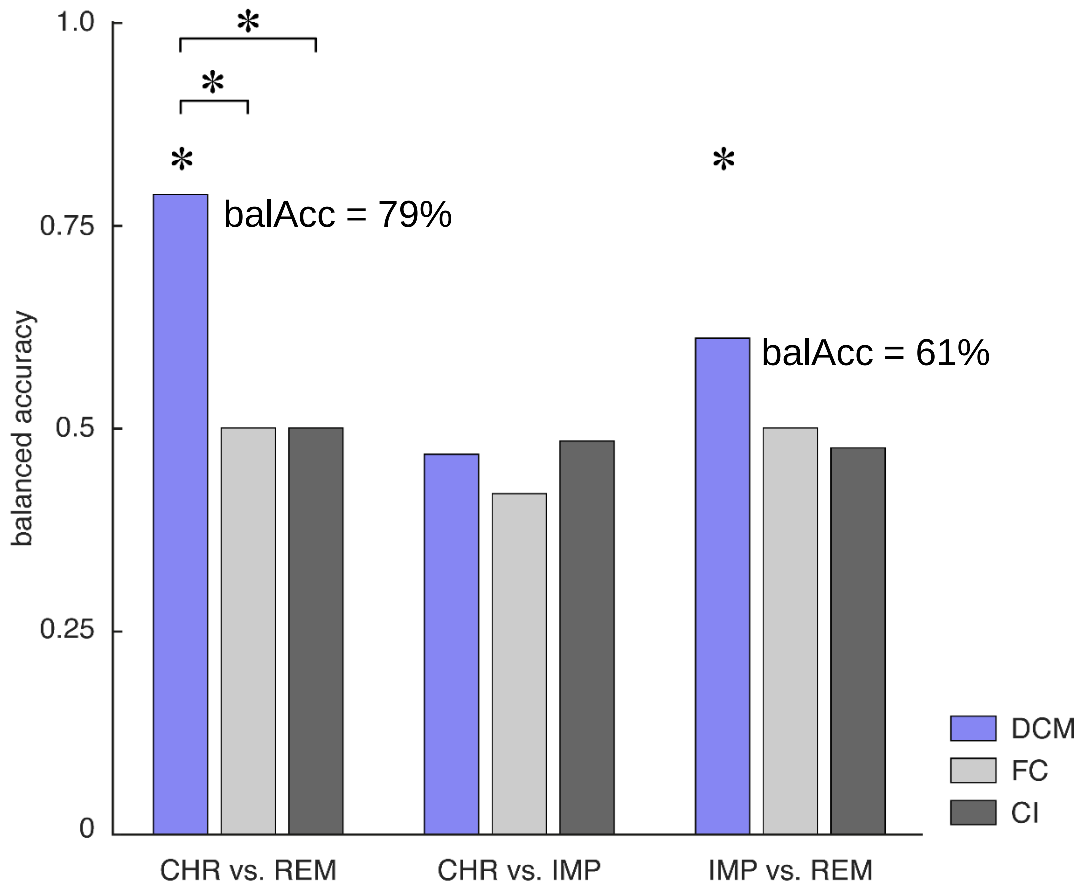
emotional faces > scrambled faces

DCM + BMA (emotional face processing)

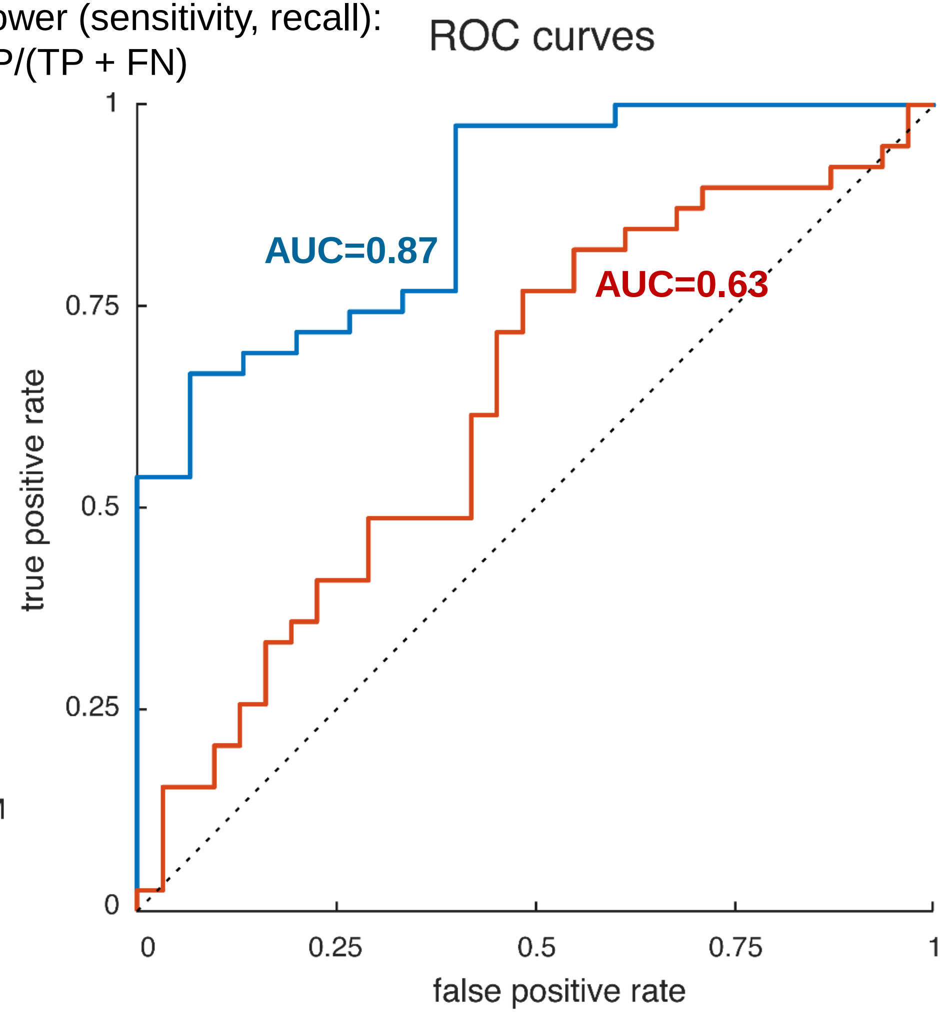


Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: two-year outcome in depression



power (sensitivity, recall):
TP/(TP + FN)

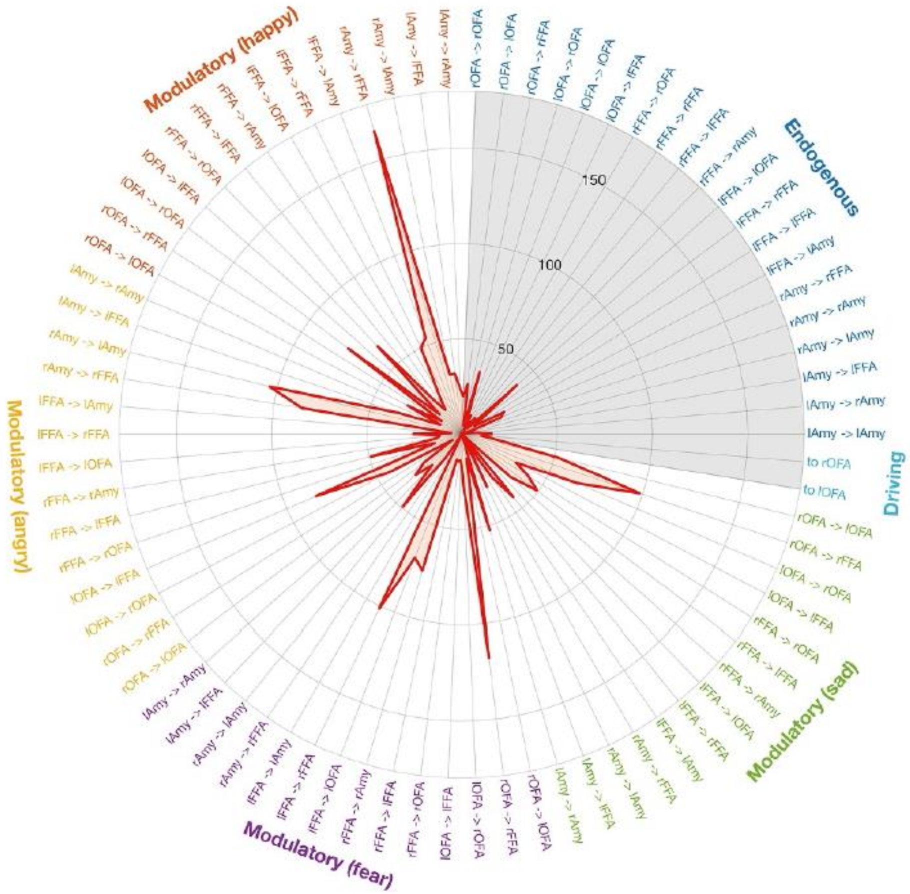


type I error (1 - specificity):
FP/(FP + TN)

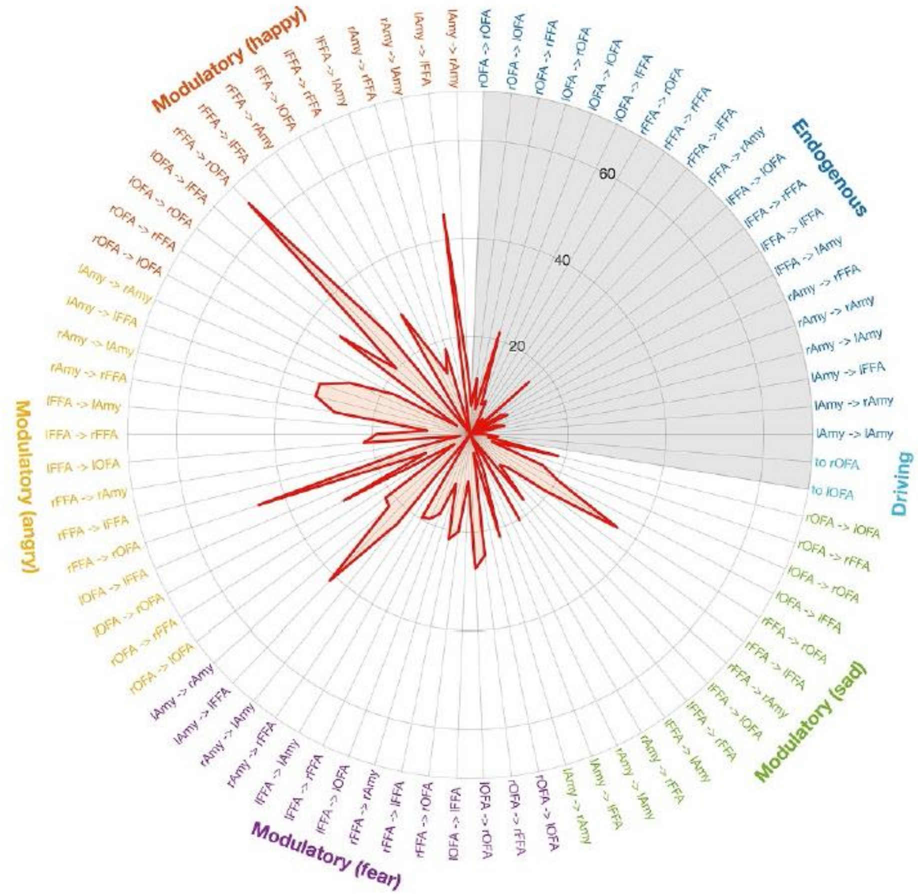
Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: two-year outcome in depression

CHR vs. REM



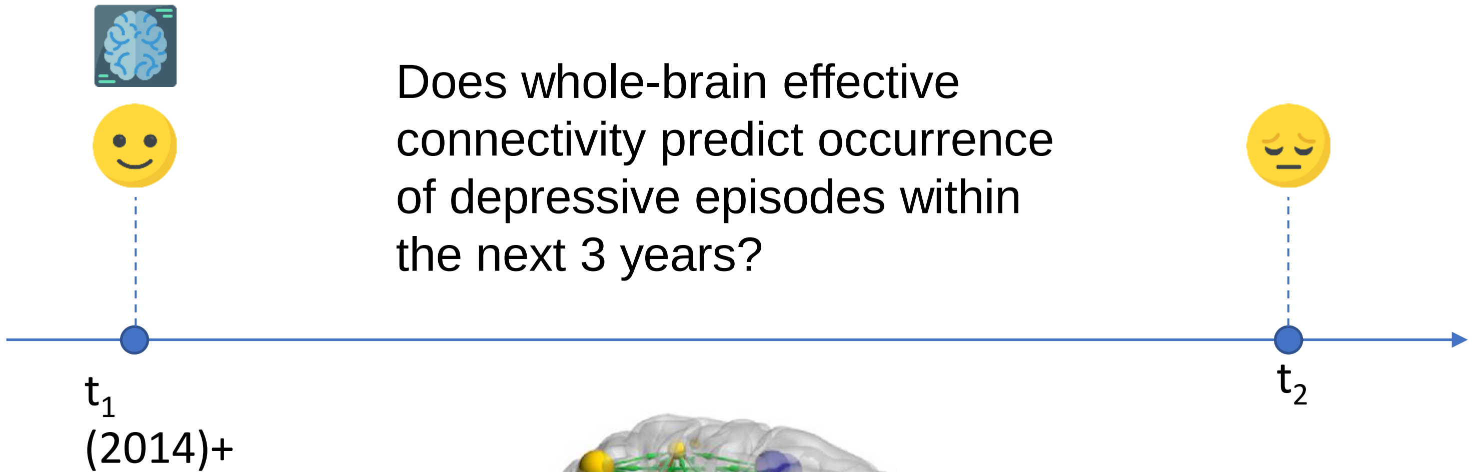
IMP vs. REM

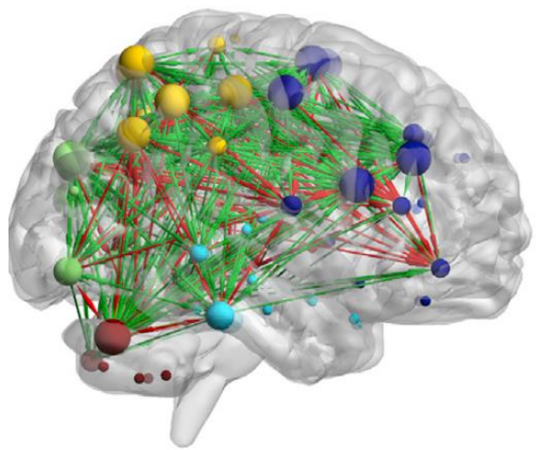


Frässle et al. 2020, *NeuroImage Clinical*

❸ Prediction: depressive symptoms within next 3 years

Does whole-brain effective connectivity predict occurrence of depressive episodes within the next 3 years?



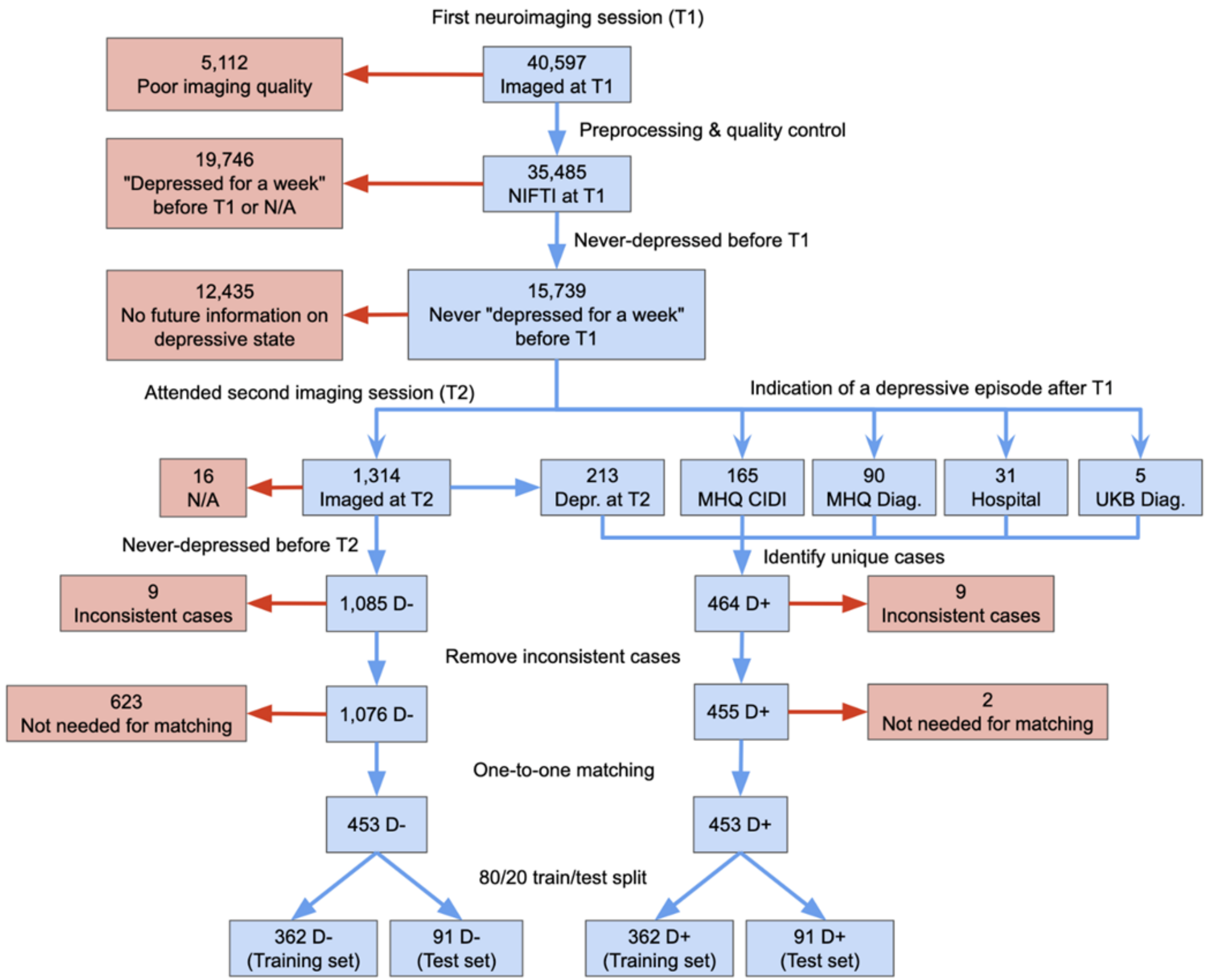


Galioulline et al. 2023, *NeuroImage*

❸ Prediction: depressive symptoms within next 3 years

rsfMRI data from UKB (N=906):

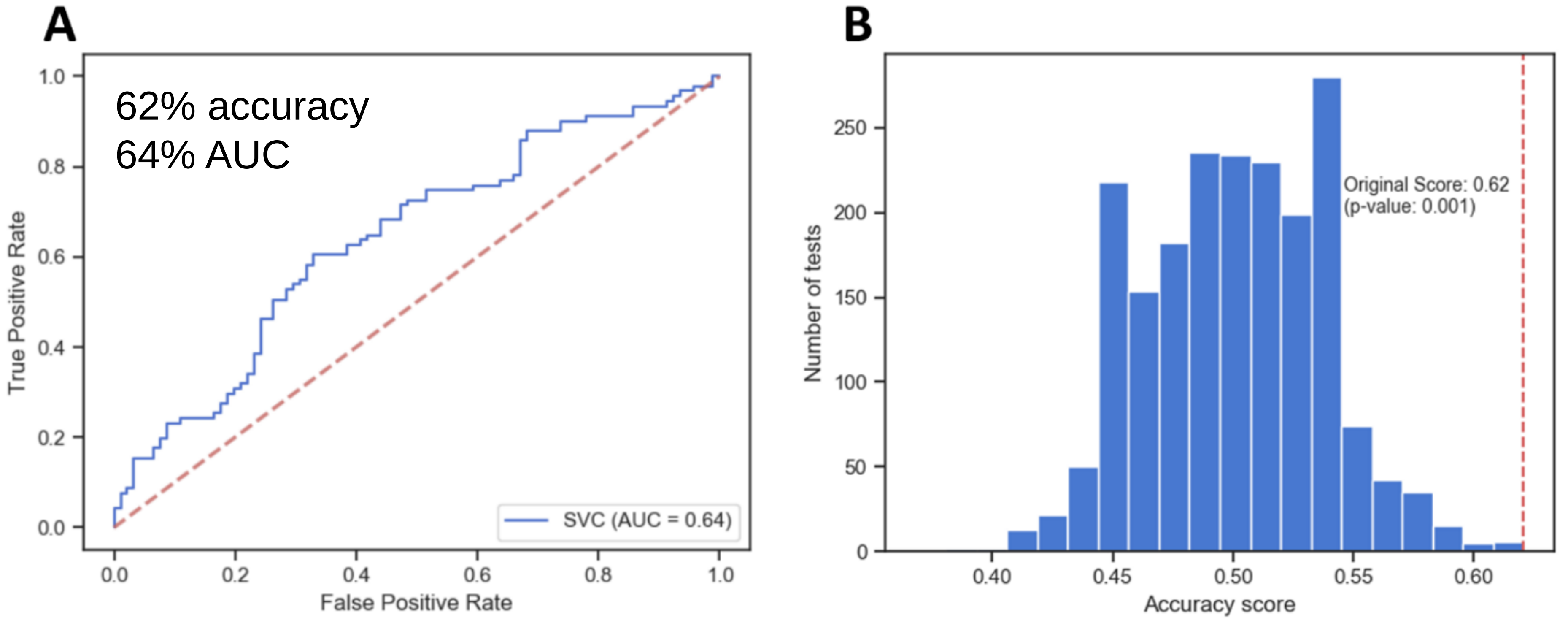
- N=453 with indication for ≥1 depressive episode
- N=453 w/o depressive episode
- 1:1 matching for 7 criteria (age, sex, comorbidities)
- 80/20 split into training and test sets



Galioulline et al. 2023, *NeuroImage*

❸ Prediction: depressive symptoms within next 3 years

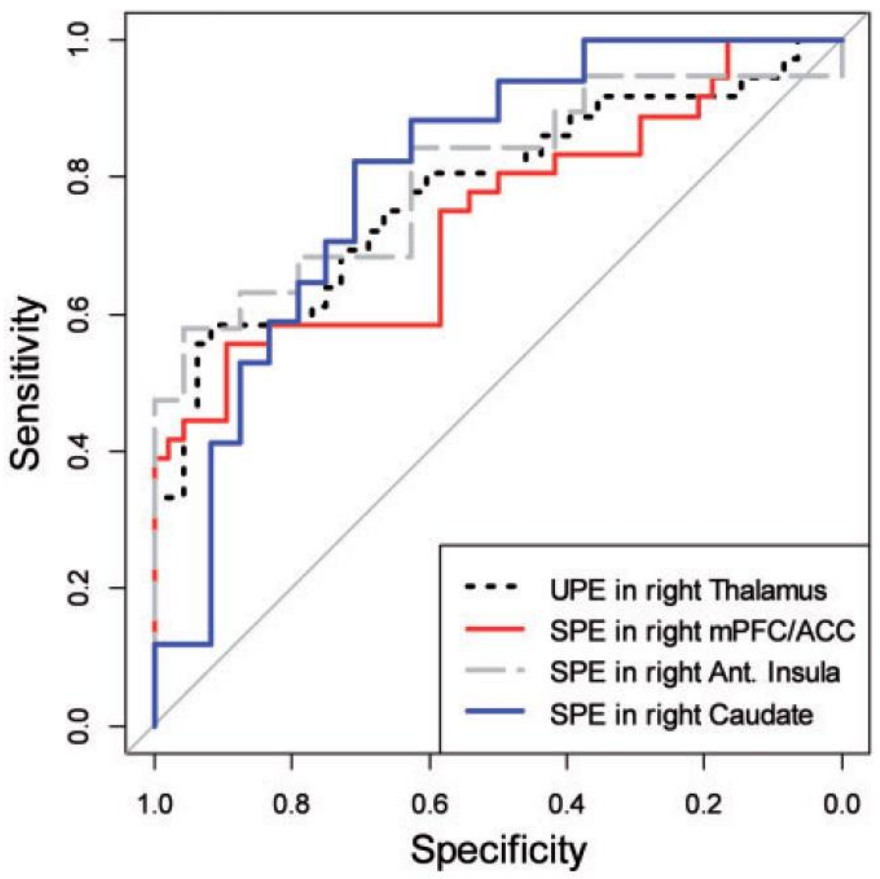
Generative embedding (55 IC rDCM + sigmoid SVM):
Predictive performance on **held-out test set**



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

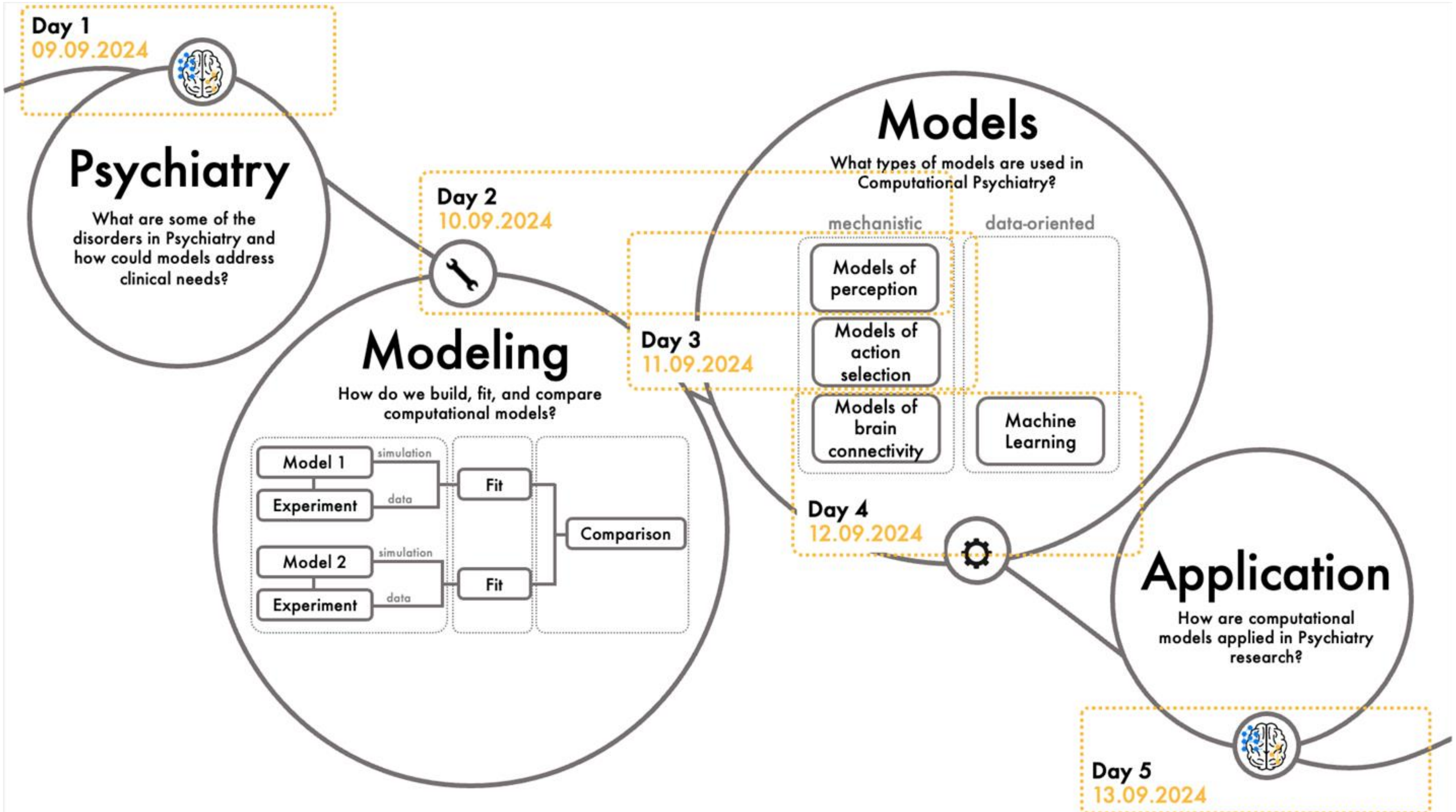
Harle et al. 2015, *Brain*

CPC 2024

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

- 10th 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 2024: thematic structure



Further reading: reviews on computational psychiatry

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Once again, a very warm welcome –
we hope you will enjoy the CPC 2024!

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