CPC 2018:
Introduction to Computational Psychiatry

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ETH

Eidgenössische Technische Hochschule Zürich
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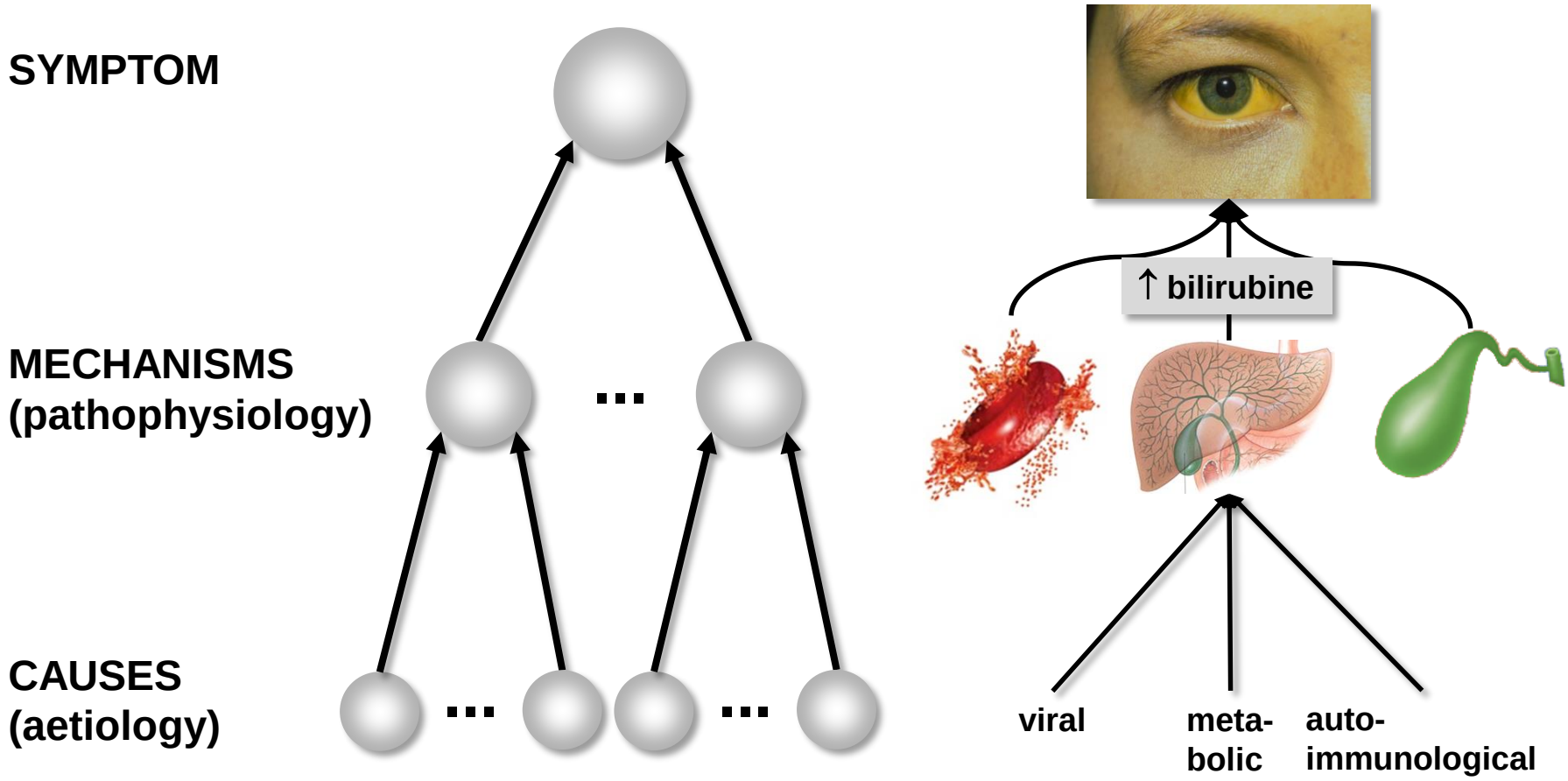
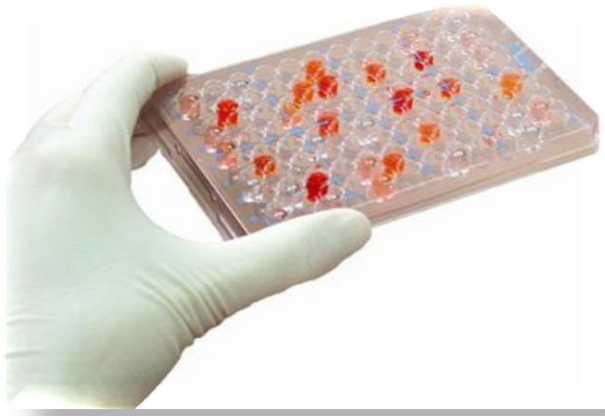
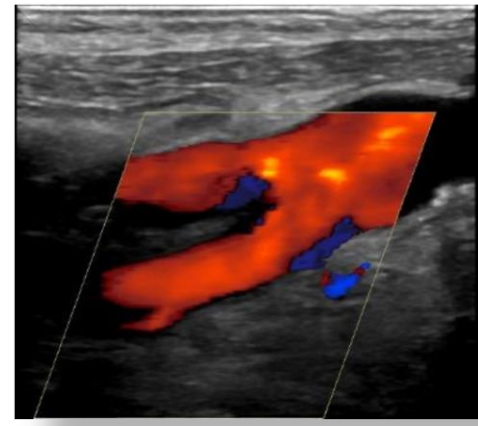
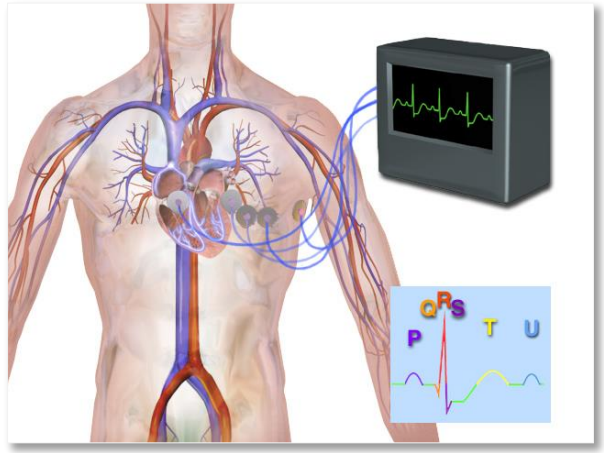
From differential diagnosis to nosology



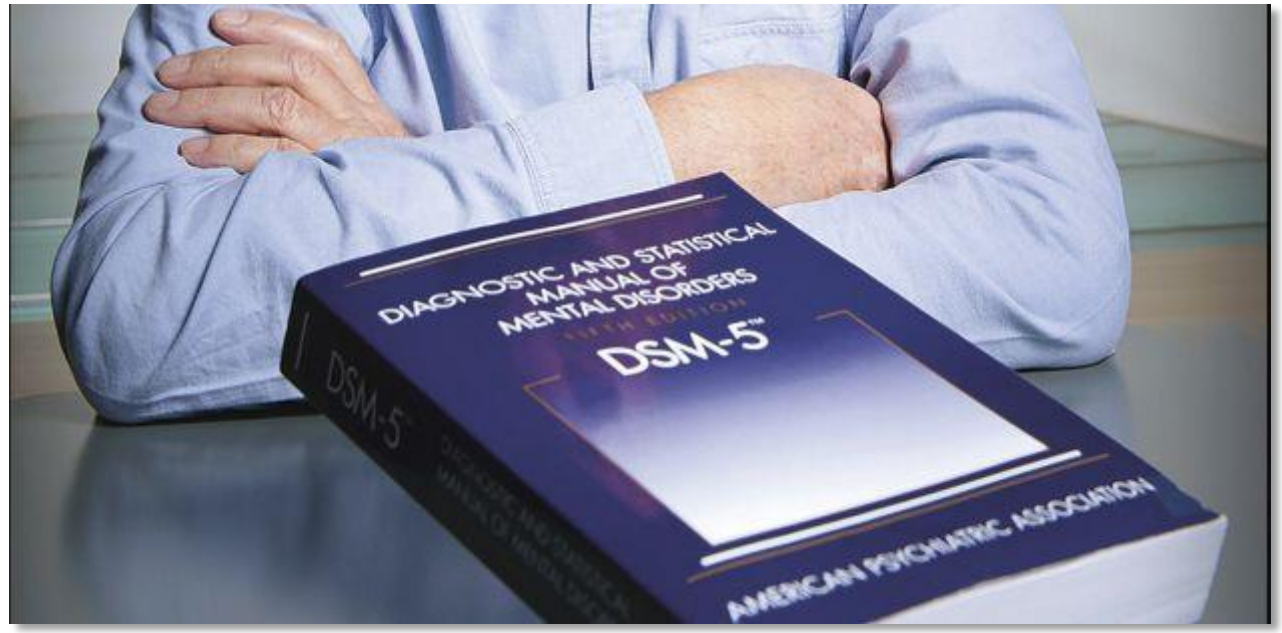
>3,000 FDA-approved clinical tests in medicine







1 diagnostic instrument in psychiatry



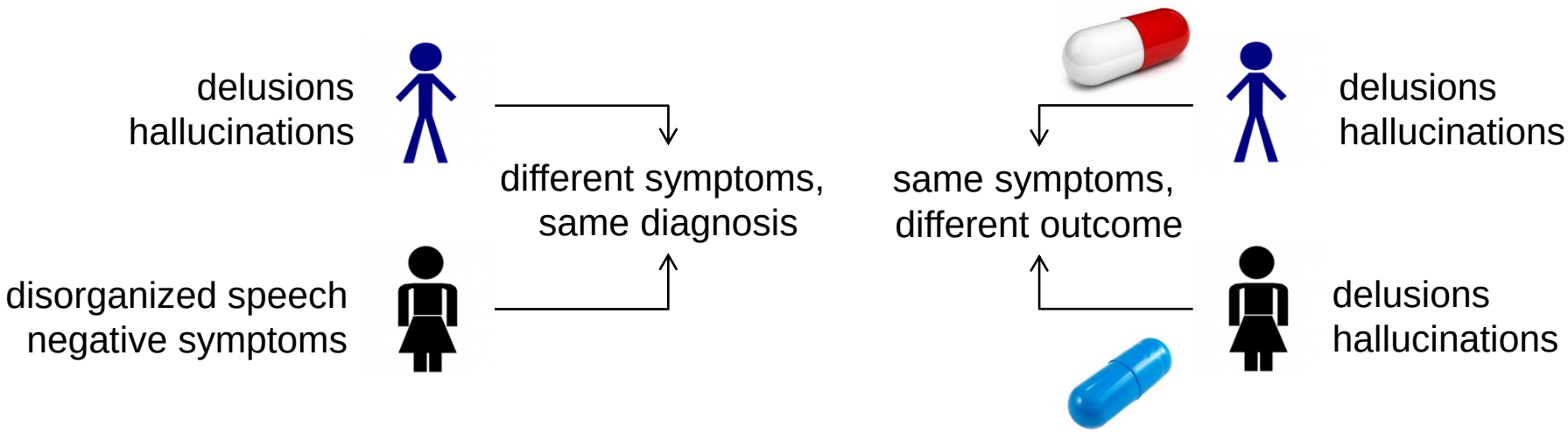
Diagnostic and Statistical Manual of Mental Disorders (DSM)

DSM-5: Schizophrenia

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

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

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



Psychiatric disorders = 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
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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.

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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]

Translational Perspectives for Computational Neuroimaging

Klaas E. Stephan,[1,2,3,*] Sandra Iglesias,[1] Jakob Heinzle,[1] and Andreea O. Diaconescu[1]

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]

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**: two common usages

  - *methodological approach*
    - investigations of neural or cognitive systems by algorithmic, as opposed to analytical, approaches
      → “computational neuroscience”

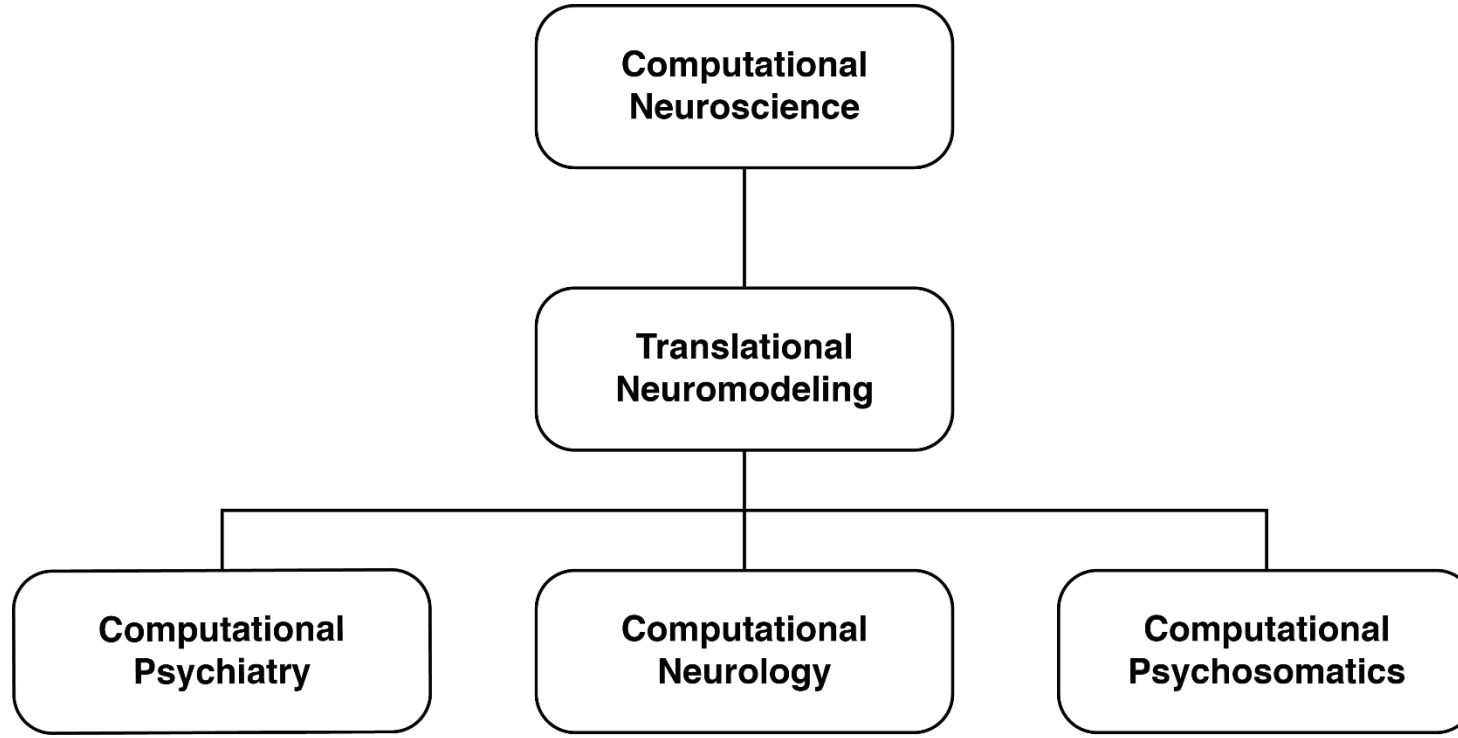
  - *information processing* (Marr's “algorithmic level”)
    - as opposed to physiological implementation

A taxonomy of computational clinical neuroscience

Understanding how/what the brain computes

Develops/validates mathematical models for solving clinical problems

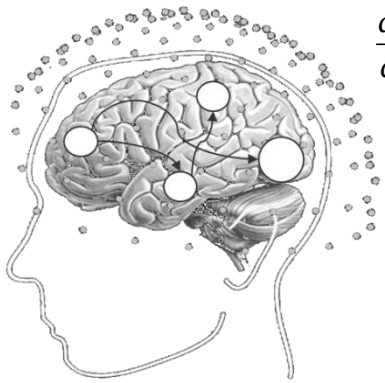
Application within specific medical fields



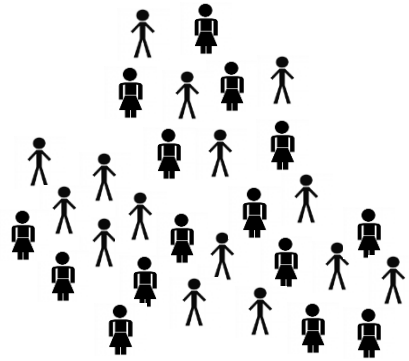
Frässle et al. 2018, *WIREs Cogn. Sci.*

Translational Neuromodeling

❶ Computational assays: Models of disease mechanisms

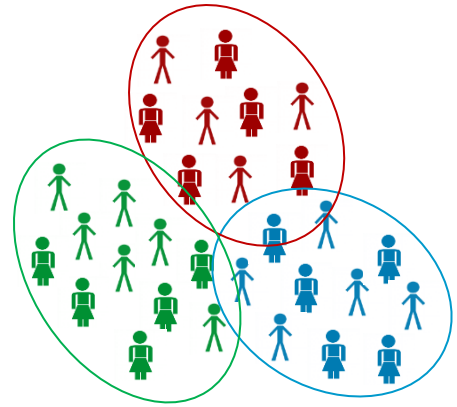


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



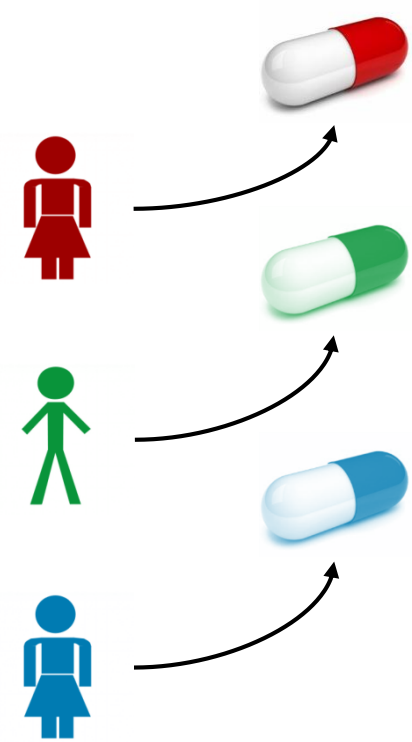
❷ Application to brain activity and behaviour of individual patients

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



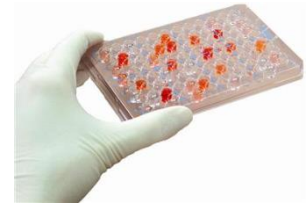
- disease mechanism A
- disease mechanism B
- disease mechanism C

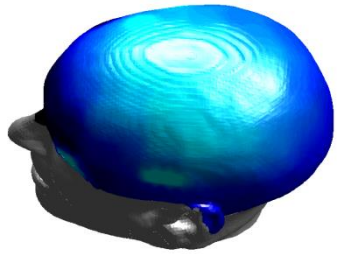
❹ Individual treatment prediction



Stephan et al. 2015, *Neuron*

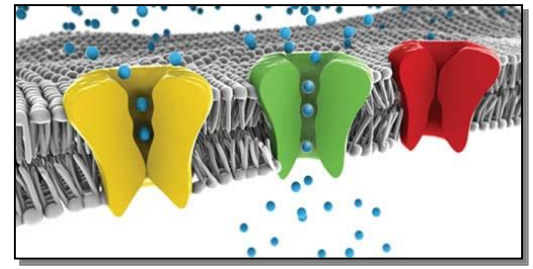
Generative models as "computational assays"



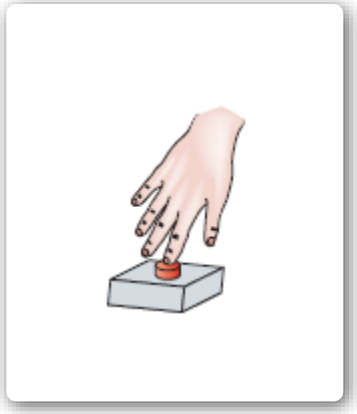


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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



y = data, θ = parameters, m = model



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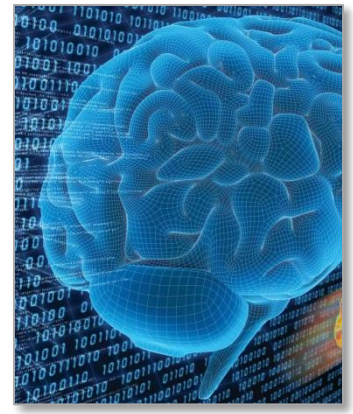
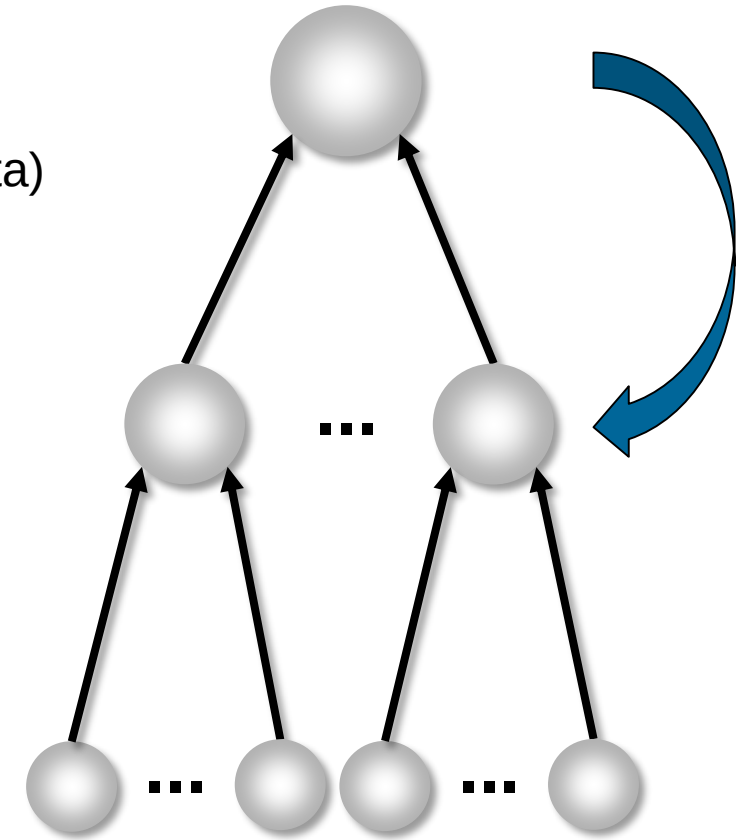


Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



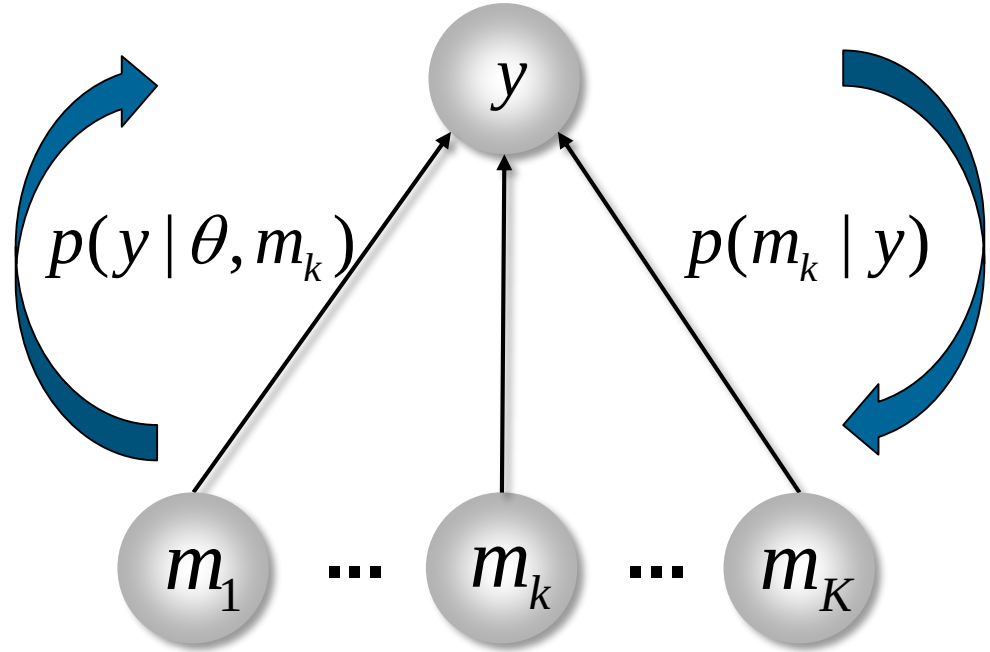
❶ **differential diagnosis** of alternative disease mechanisms

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

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

❶ Differential diagnosis: model selection

SYMPTOM
(behaviour
or physiology)



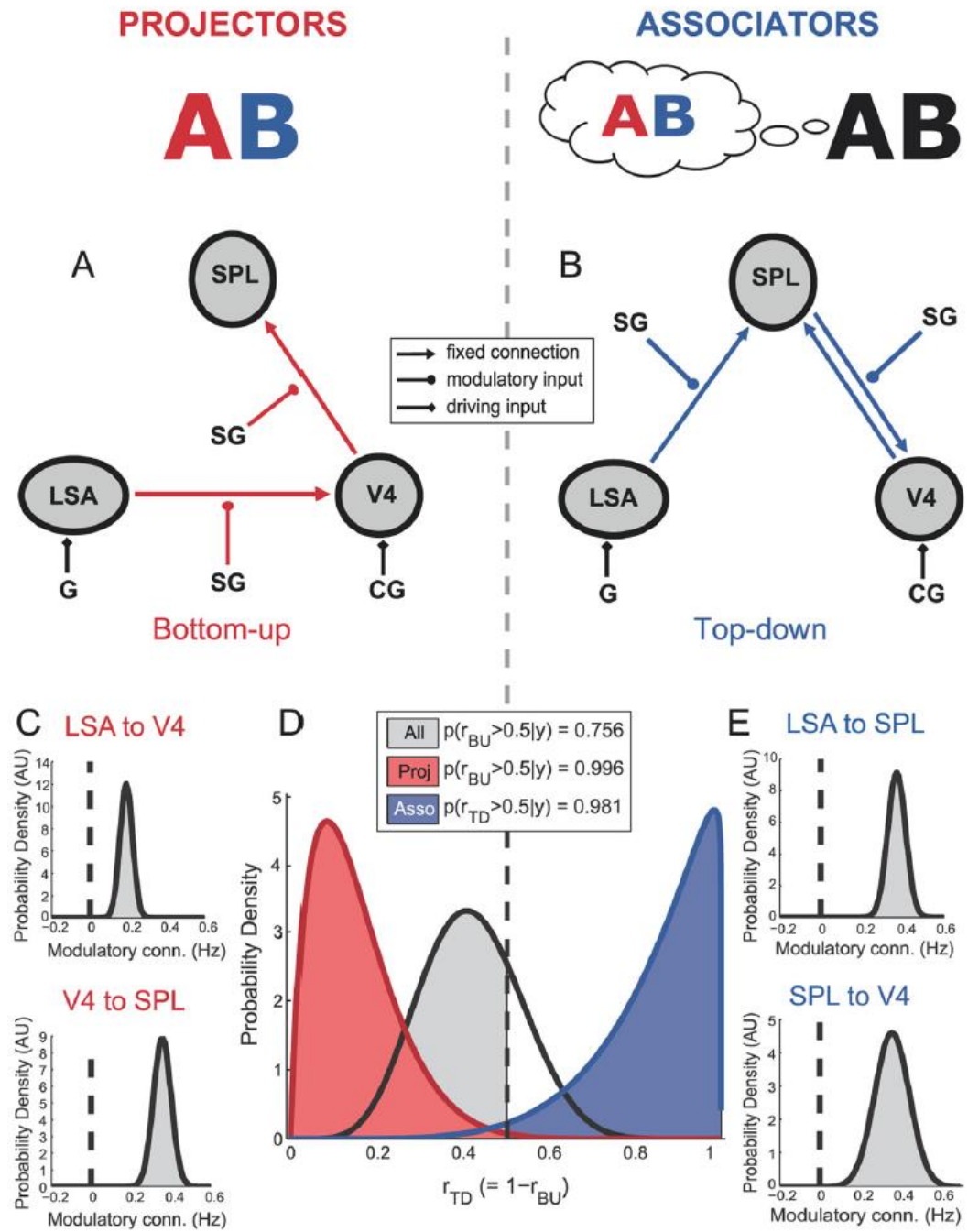
**HYPOTHETICAL
MECHANISM**

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

Stephan et al. 2017, *NeuroImage*

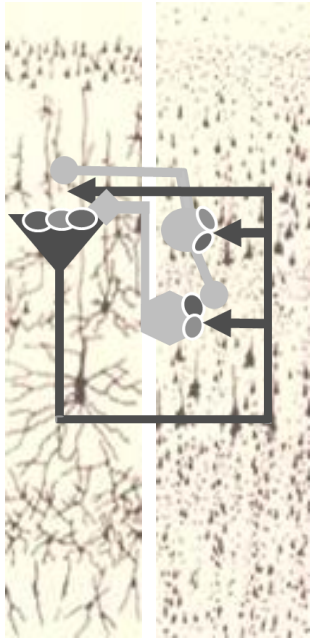
Synaesthesia

- “projectors” experience color externally colocalized with a presented grapheme
- “associators” report an internally evoked association
- Bayesian model selection of competing DCMs separates projectors (bottom-up mechanisms) and associators (top-down)



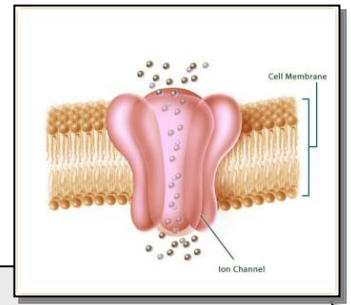
van Leeuwen et al. 2011, *J. Neurosci.*

❶ Differential diagnosis: inferring synaptic processes



- inhibitory interneurons
- excitatory interneurons
- pyramidal cells

AMPA, NMDA,$GABA_A$ receptors



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

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

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

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

II

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

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

EI

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

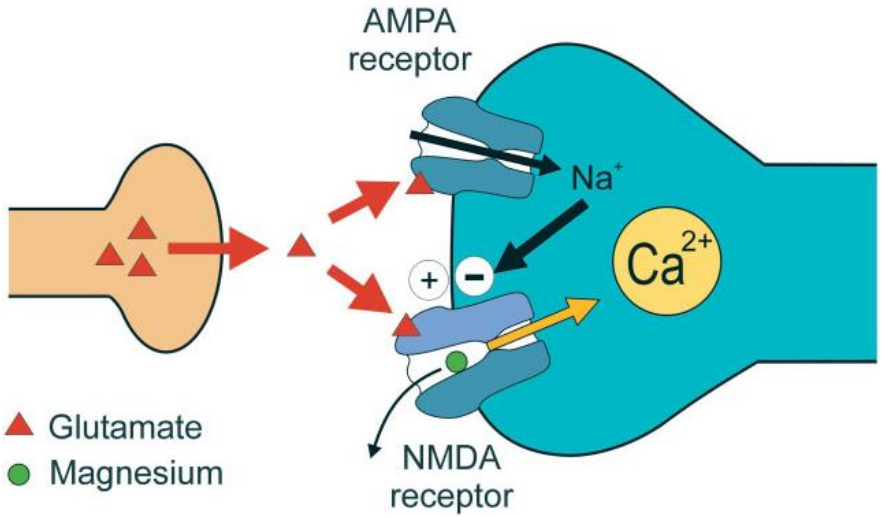
$$C\dot{V}^{(3)} = g_L(V_L - V^{(3)}) + g_E^{(3)}(V_E - V^{(3)}) + g_I^{(3)}(V_I - V^{(3)}) + g_{NMDA} f_{Mg}(V^{(3)})(V_E - V^{(3)}) + \Gamma_V$$
$$\dot{g}_E^{(3)} = \kappa_E(\gamma_{3,1}^{(E)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_E^{(3)}) + \Gamma_E$$
$$\dot{g}_I^{(3)} = \kappa_I(\gamma_{3,2}^{(I)}\sigma(\mu_V^{(2)}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

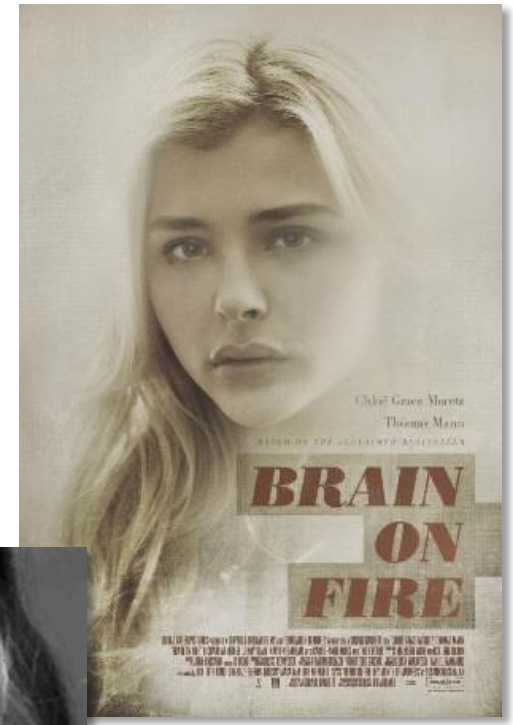
PC

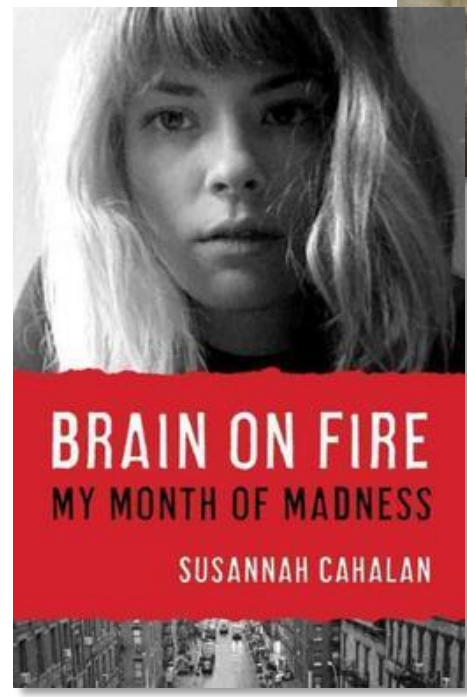
u_{ij} = presynaptic input from ensemble j to i
σ = CDF of presynaptic depolarization density around threshold potential V_R

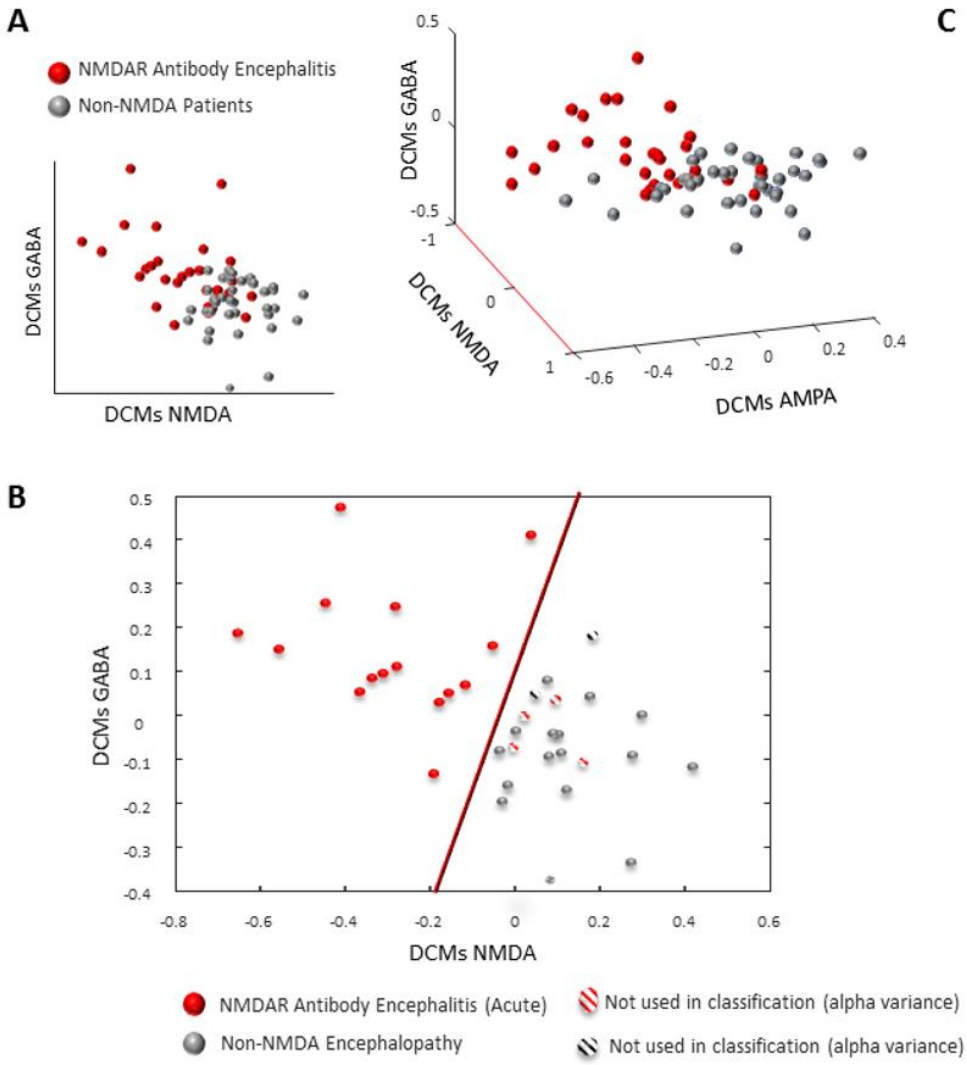
Marreiros et al. 2010, *NeuroImage*
Moran et al. 2011, *NeuroImage*

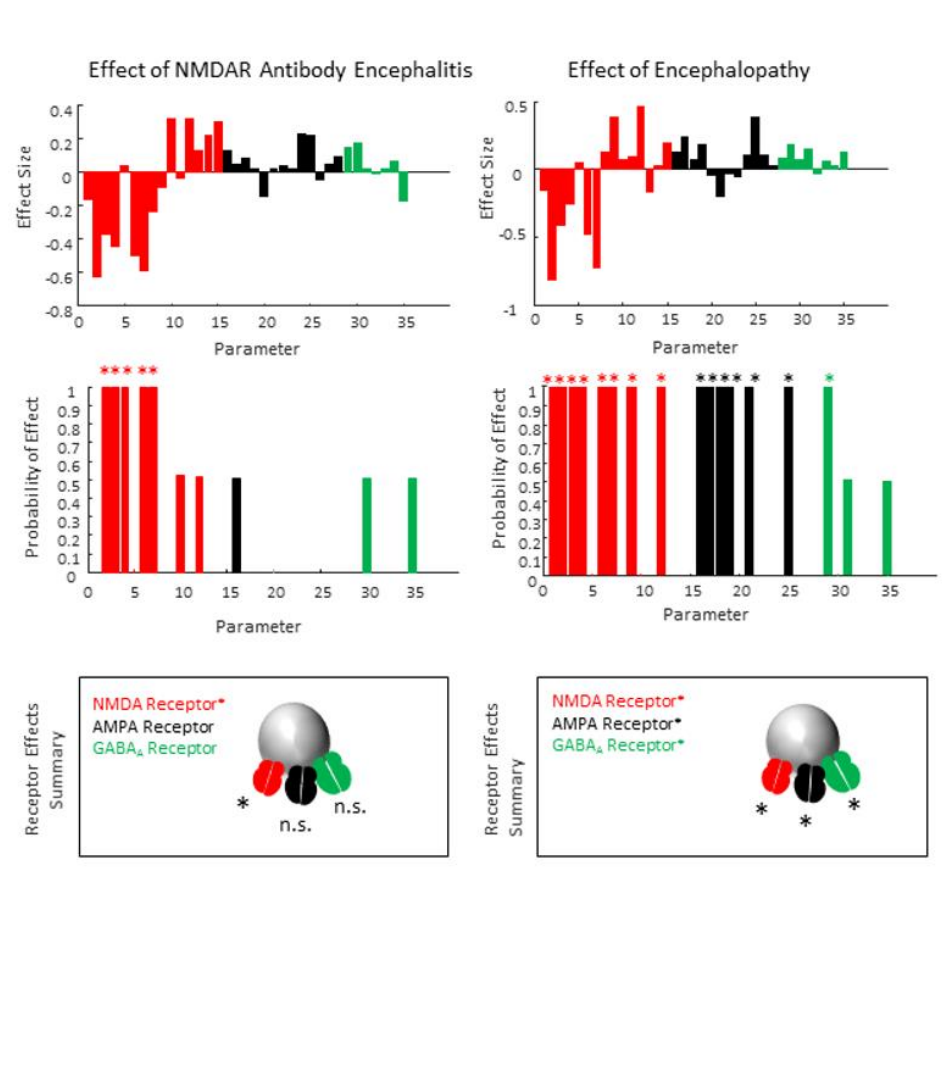
NMDA receptor antibody encephalitis





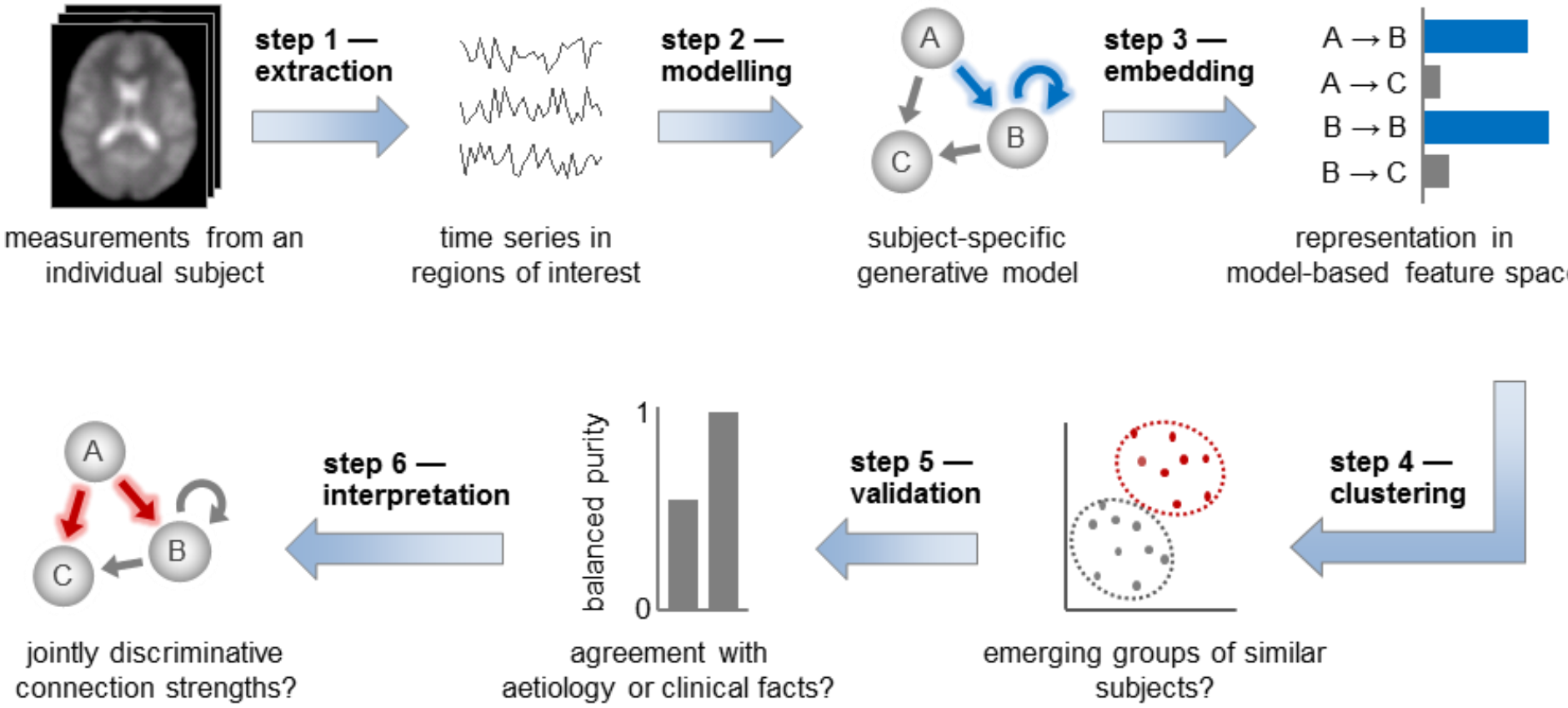






Symmonds et al. 2018, *Brain*

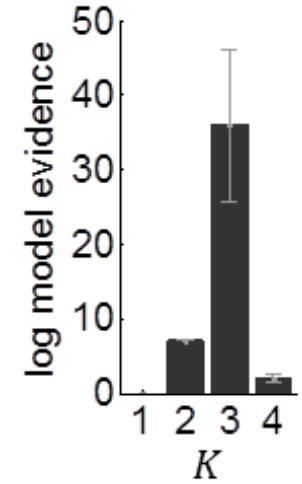
❷ Stratification / subgroup detection: Generative embedding (unsupervised)



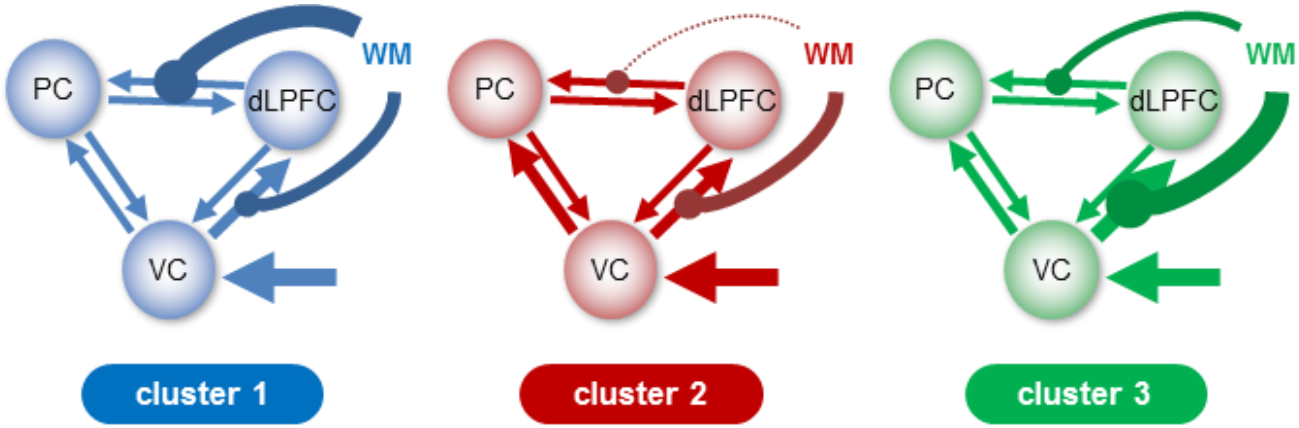
Brodersen et al. 2014, *NeuroImage Clinical*

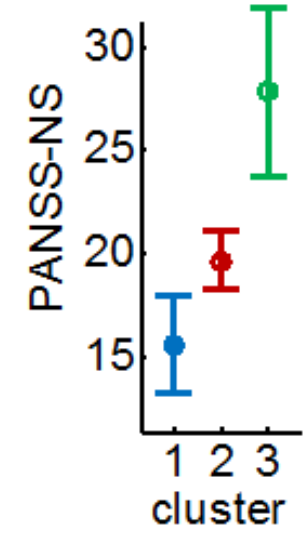
Detecting subgroups of patients in schizophrenia

Optimal cluster solution



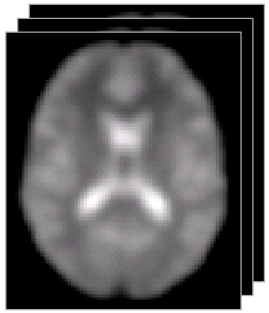
- three distinct subgroups (total N=41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)





Brodersen et al. 2014, *NeuroImage Clinical*

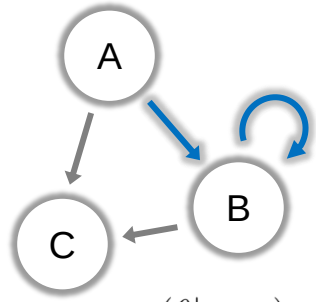
❸ Prediction: Generative embedding (supervised)



measurements from
an individual subject

**step 1 —
model inversion**

$\mathcal{X} \to \mathcal{M}_\Theta$



$p(\theta|x, m)$

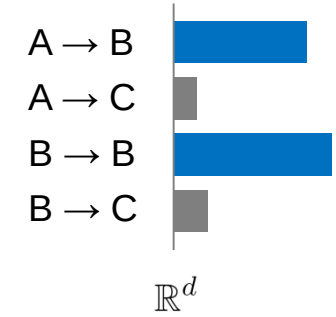
subject-specific
inverted generative model

**step 2 —
kernel construction**

$\mathcal{M}_\Theta \to \mathbb{R}^d$

$k : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$

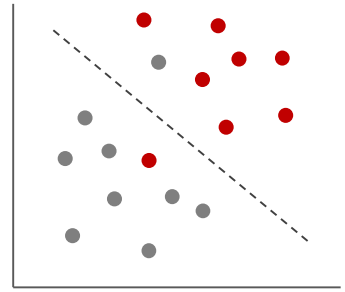
$k_\mathcal{M} : \mathcal{M}_\Theta \times \mathcal{M}_\Theta \to \mathbb{R}$



subject representation in the
generative score space

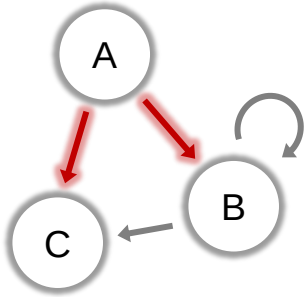
**step 3 —
support vector classification**

$$\hat{c} = \text{sgn}\left(\sum_i^n \alpha_i^* k(x_i, x) + b^*\right)$$



separating hyperplane fitted to
discriminate between groups

**step 4 —
interpretation**

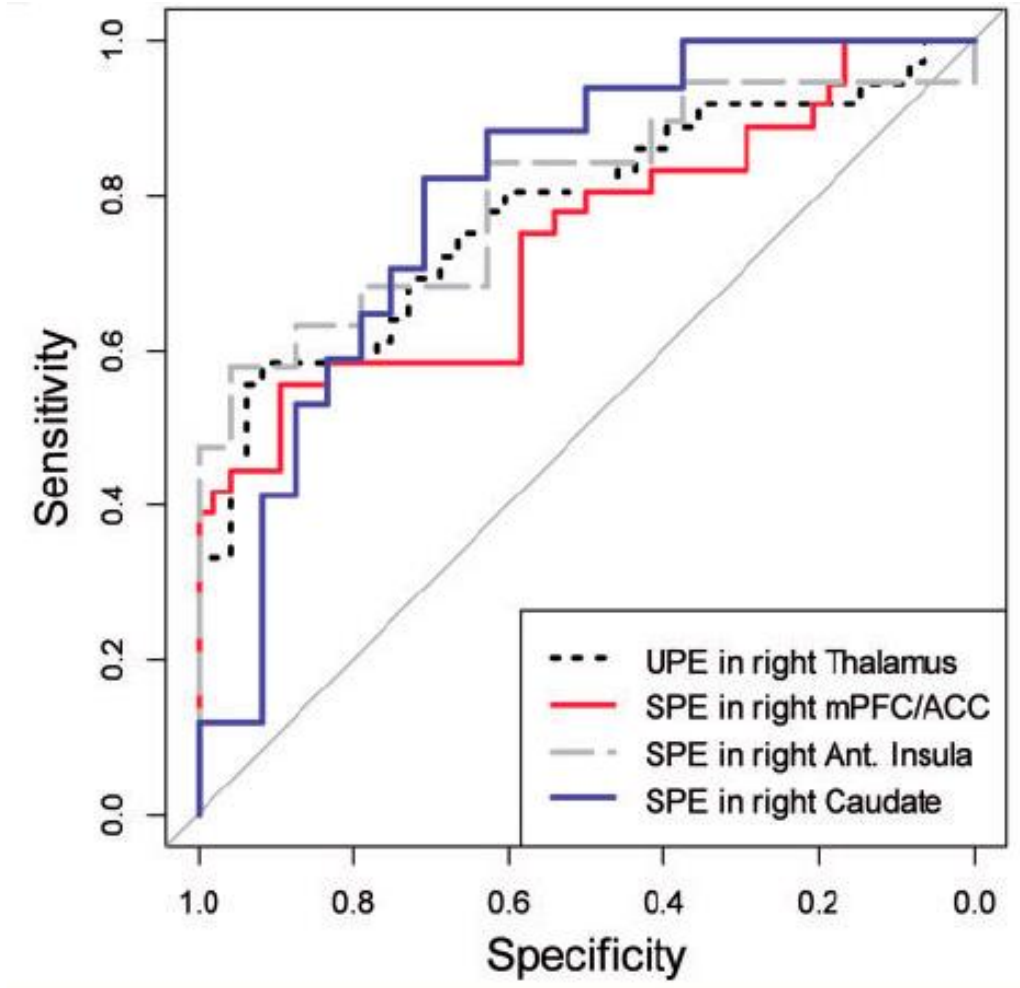


jointly discriminative
model parameters

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

Predicting future drug abuse

- 157 occasional stimulant users
- fMRI (stop-signal task), Bayesian hidden Markov model
- prediction error (PE) activity from several 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*

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**

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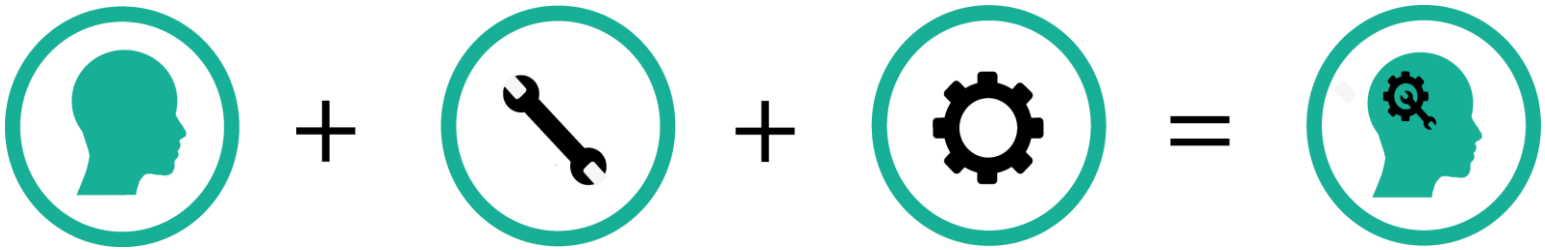
COMPUTATIONALPSYCHIATRYCOURSE



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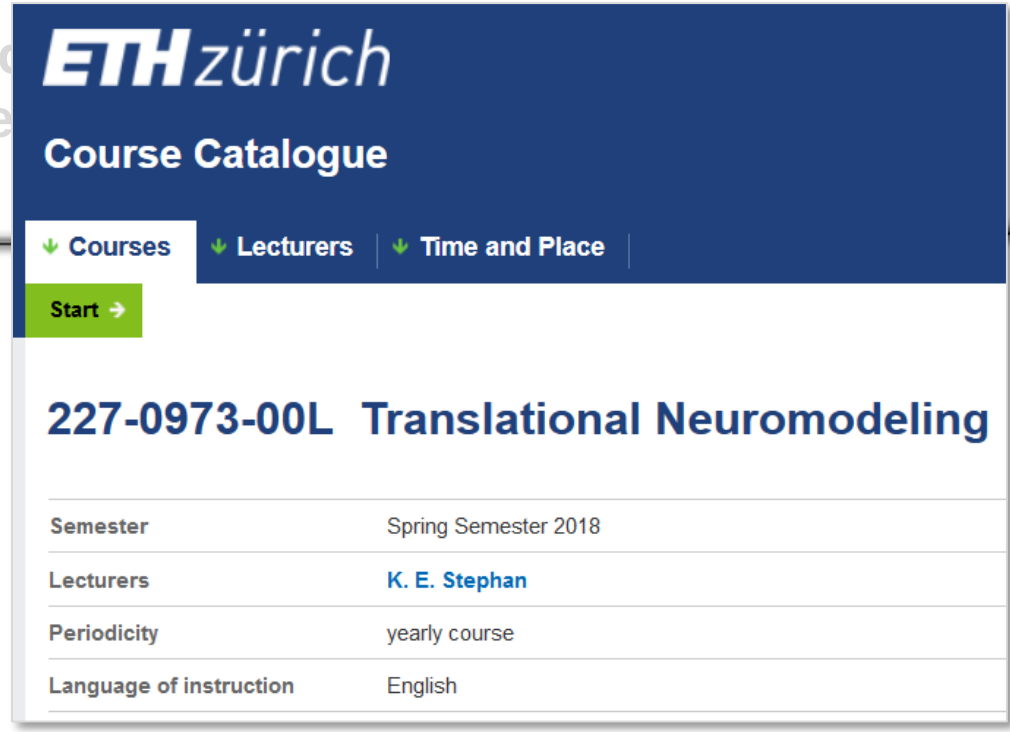
3. Prospective validation stu
   biomedical scientists in ne

Translational Neuromodeling Course
University of Zurich & ETH Zurich
3 hours lectures + 2h exercises per week
annual course (spring semester)



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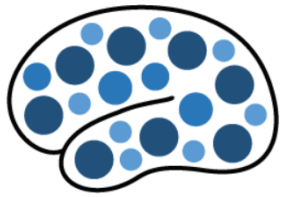

TAPAS

www.translationalneuromodeling.org/tapas

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**

Translational Neuromodeling Unit

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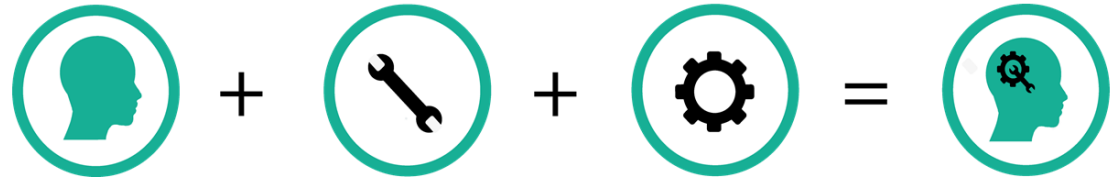
CPC 2018

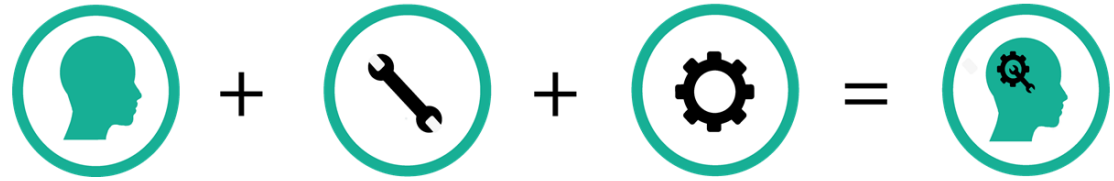
COMPUTATIONALPSYCHIATRYCOURSE



- 4th international edition
- originated from our local courses on Computational Psychiatry since 2012
- key features
  - clinical lectures (Monday)
  - methodological lectures (Tuesday – Thursday)
  - practical exercises (Friday)
  - open source software only
  - covers models of both physiology and behaviour
  - 27 international presenters from 15 different institutions

CPC 2018

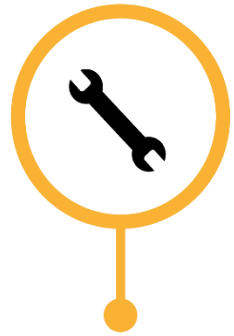
COMPUTATIONALPSYCHIATRYCOURSE



DAY 1

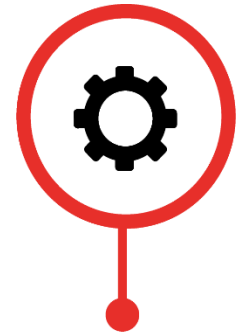
Clinical Psychiatry

DAY 2



Bayesian inference & machine learning

DAY 3



MDP, RL, biophysical models

DAY 4

Computational Psychiatry in application

DAY 5

Practical exercises

Further reading

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A very warm welcome –
we hope you will enjoy the CPC 2018!

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