Introduction to Computational Psychiatry

Klaas Enno Stephan

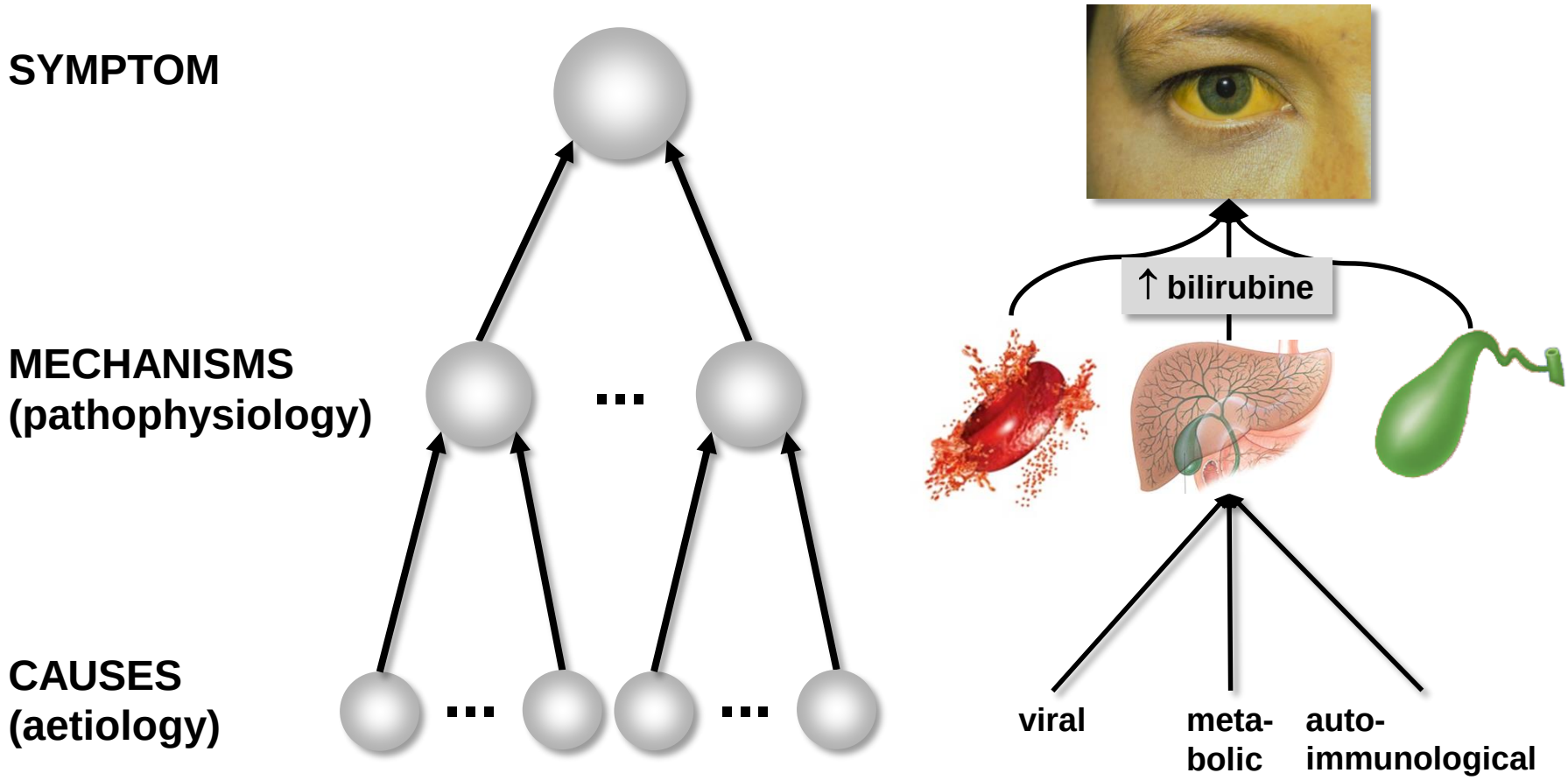
Translational Neuromodeling Unit

Universität Zürich[UZH]

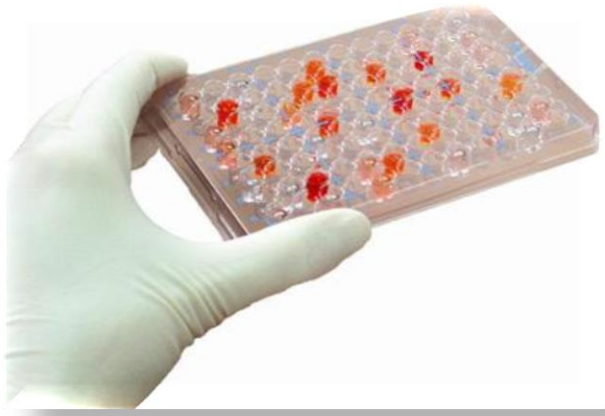
ETH

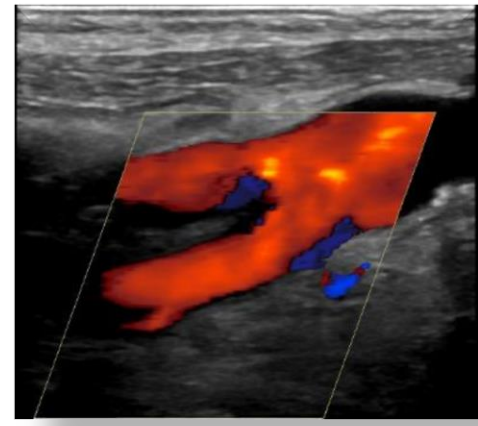
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

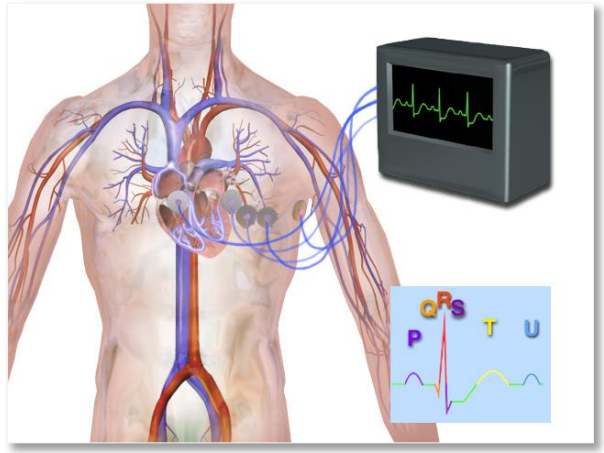
From differential diagnosis to nosology



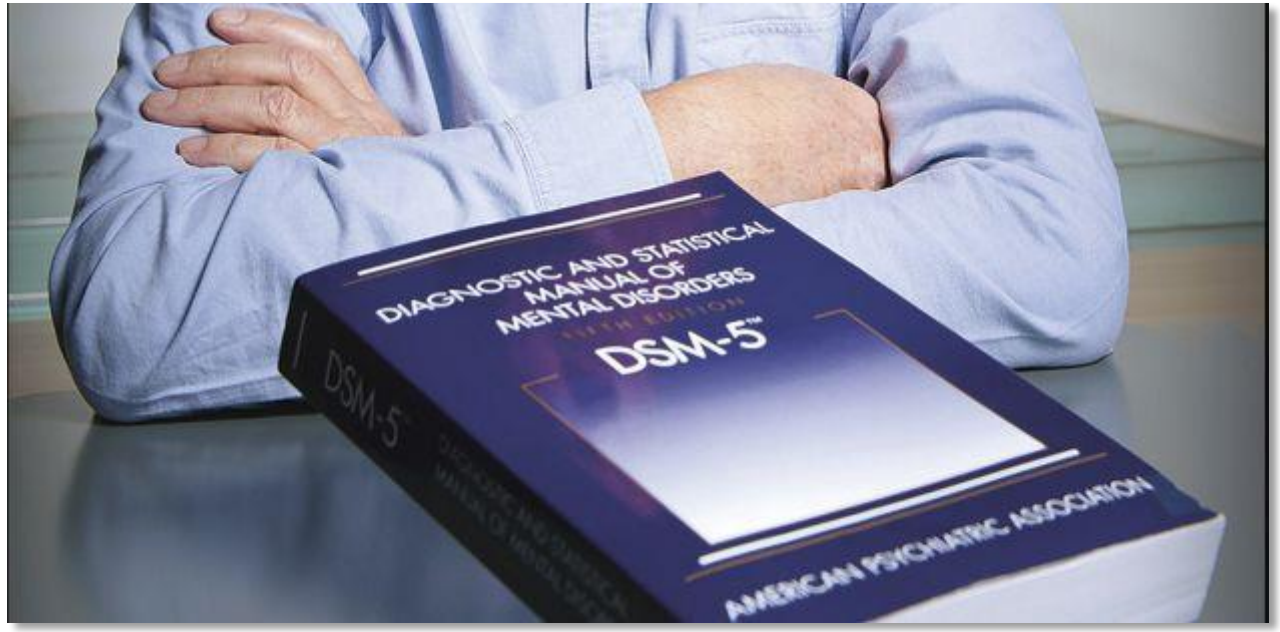
>3,000 FDA-approved clinical tests in medicine







1 diagnostic instrument in psychiatry



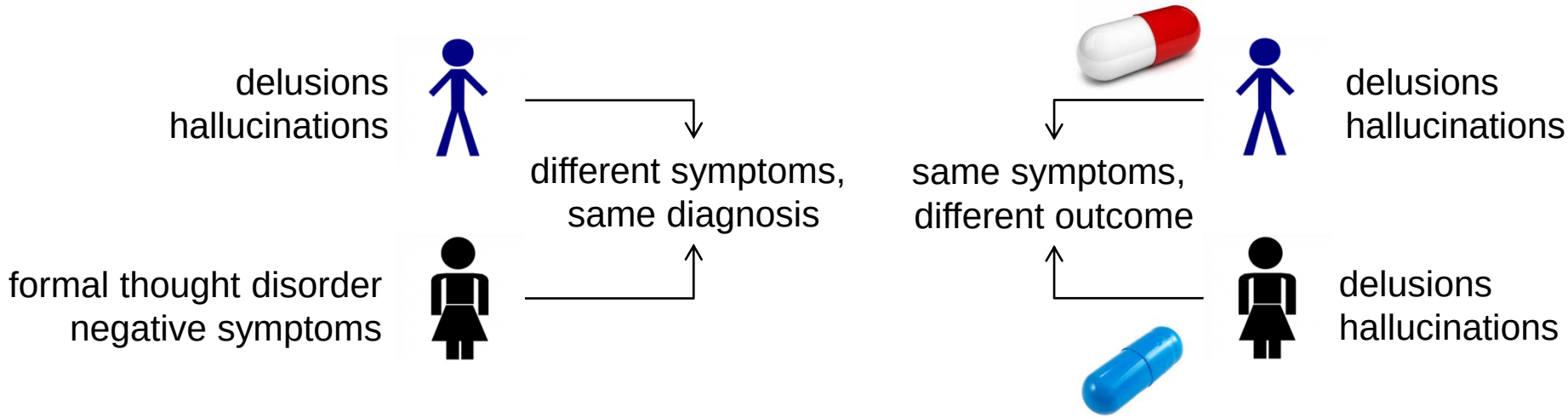
Diagnostic and Statistical Manual of Mental Disorders (DSM)

DSM IV: Schizophrenia

- Delusions
- Hallucinations
- Formal thought disorder
- Grossly disorganized or catatonic behavior
- Negative symptoms: flat affect, anhedonia, avolition, alogia, asociality

≥ 2 symptoms
over ≥ 1 month

+ social or occupational dysfunction
+ continuous signs of the disturbance persist 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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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”

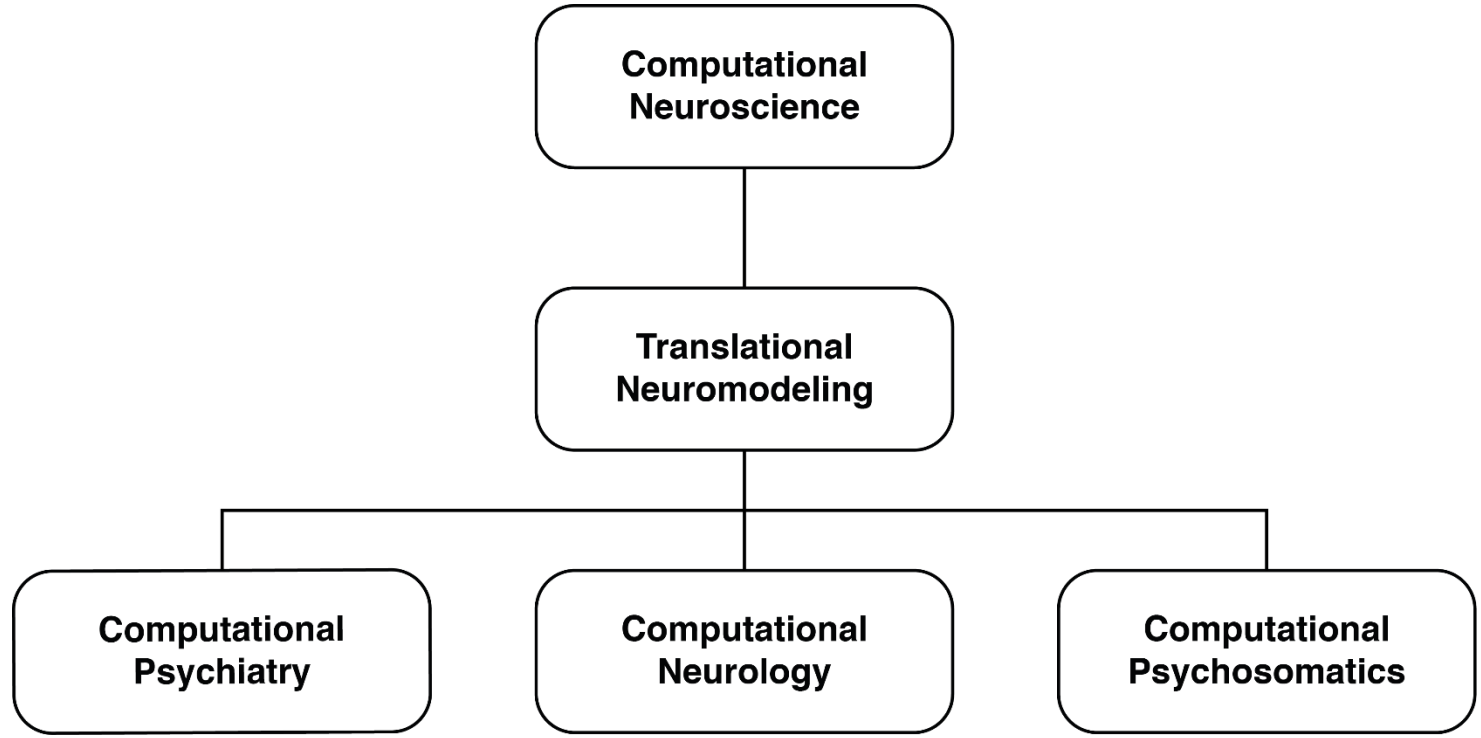
  - *information processing* (Marr's “algorithmic level”)
    - as opposed to physiological implementation

A taxonomy of computational clinical neuroscience

Understanding how/what the brain computes

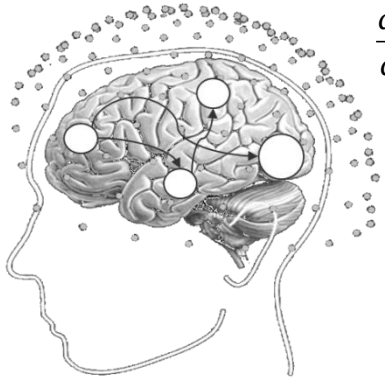
Develops/validates mathematical models for solving clinical problems

Application within specific medical fields

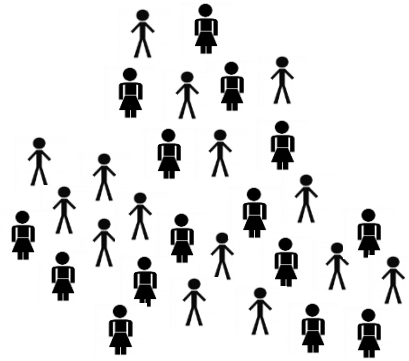


A clinical neuromodeling strategy

❶ Computational assays:
Models of disease mechanisms

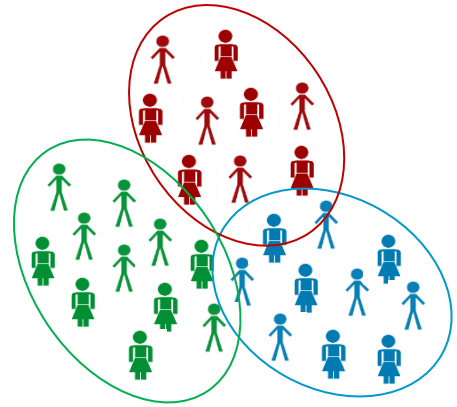


$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$



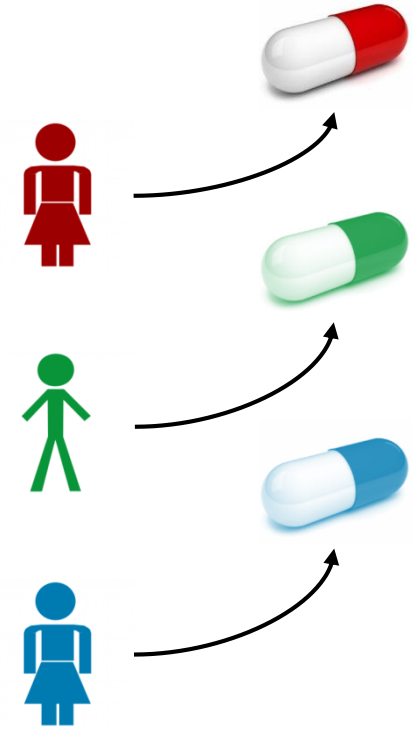
❷ Application to brain activity and behaviour of individual patients

❸ Detecting physiological subgroups (based on inferred mechanisms)



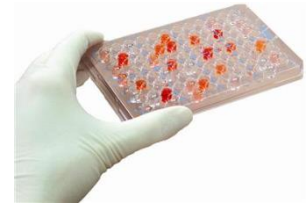
- disease mechanism A
- disease mechanism B
- disease mechanism C

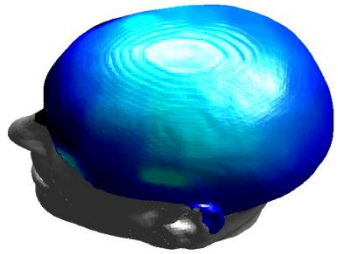
❹ Individual treatment prediction



Stephan et al. 2015, *Neuron*

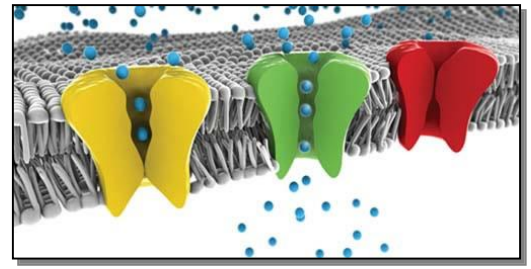
Generative models as "computational assays"

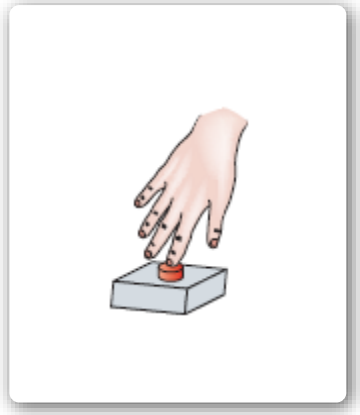




$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

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





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

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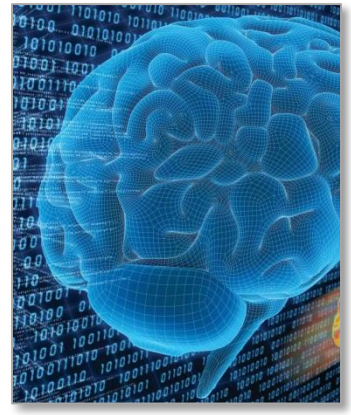
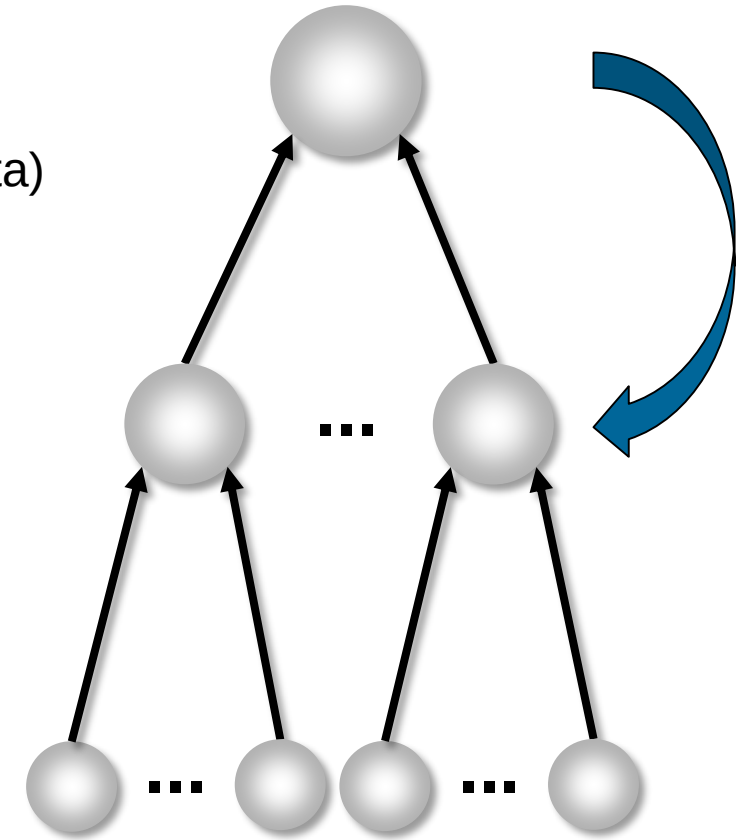


Computational assays: key clinical questions

SYMPTOMS
(behavioural or physiological data)

MECHANISMS
(computational, physiological)

CAUSES
(aetiology)



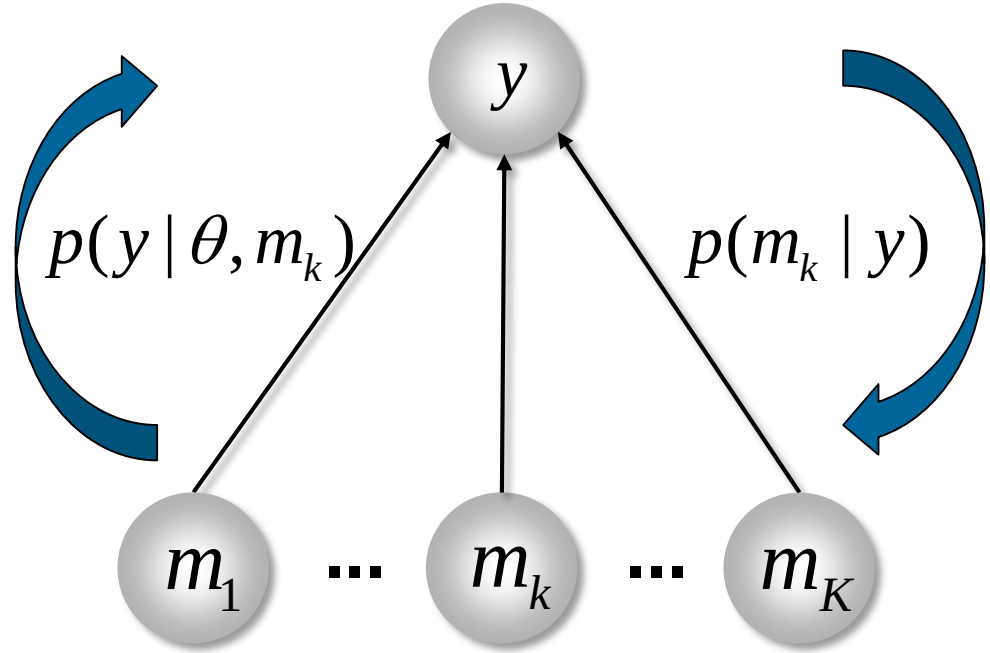
differential diagnosis of alternative disease mechanisms

spectrum dissection into mechanistically distinct subgroups

prediction of clinical trajectories and treatment response

Differential diagnosis by model selection

SYMPTOM
(behaviour
or physiology)



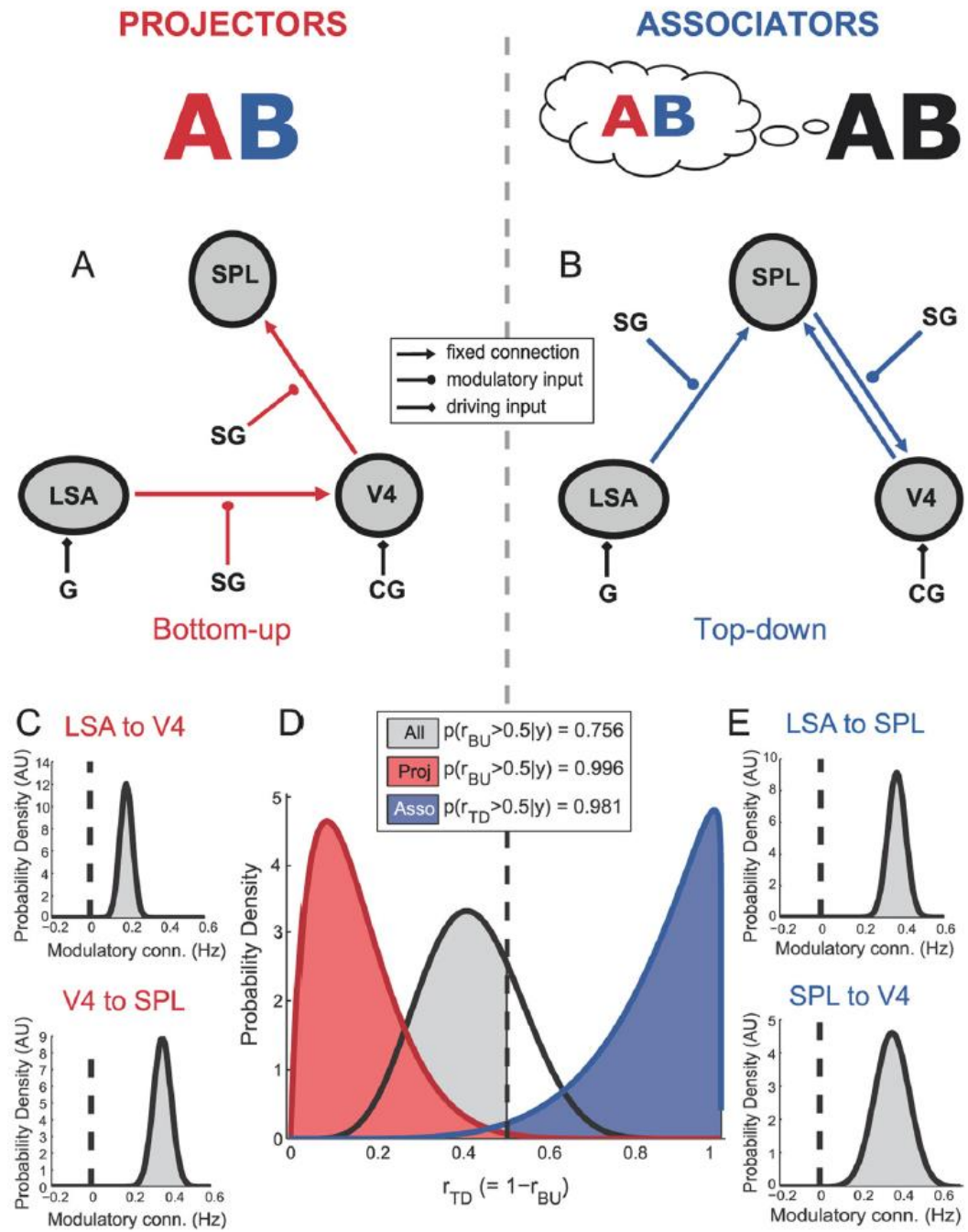
HYPOTHETICAL MECHANISM

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

Stephan et al. 2017, *NeuroImage*

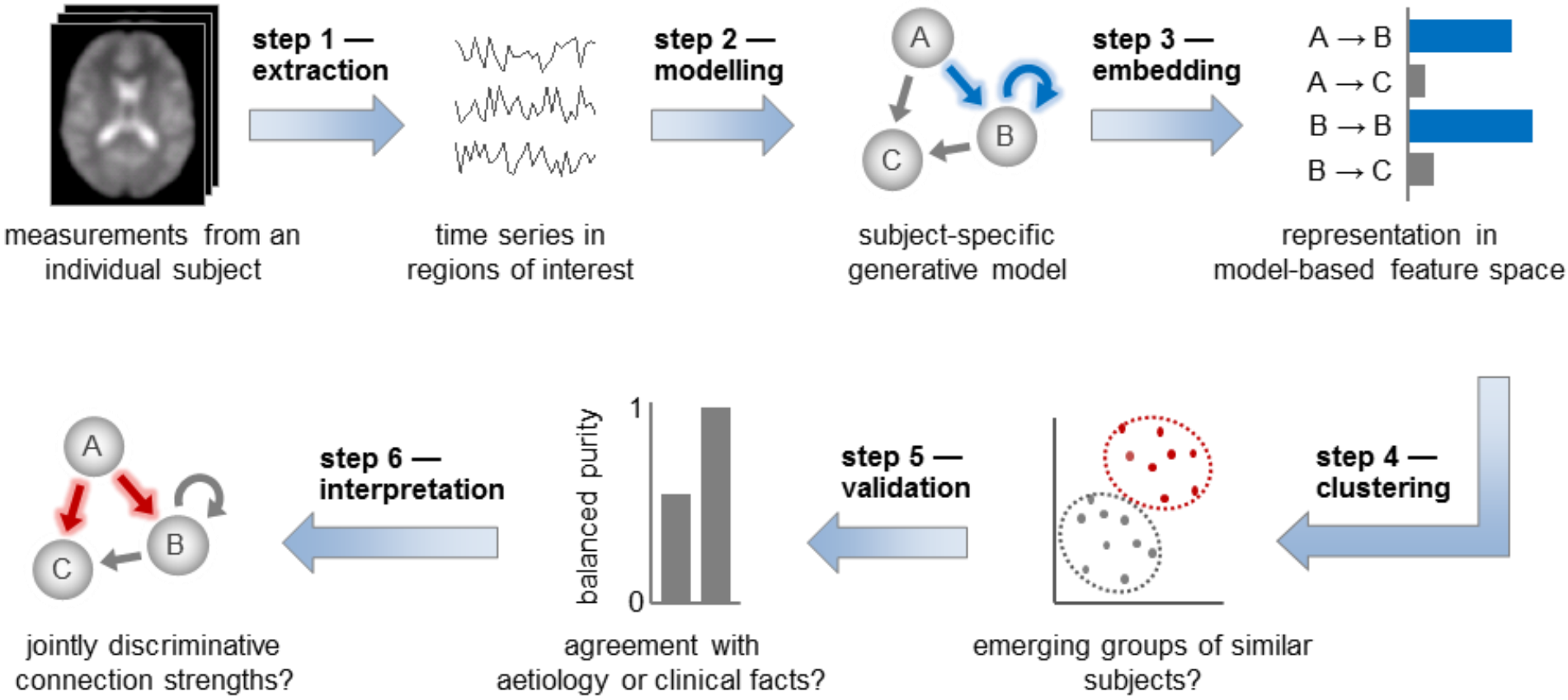
Synaesthesia

- “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.*

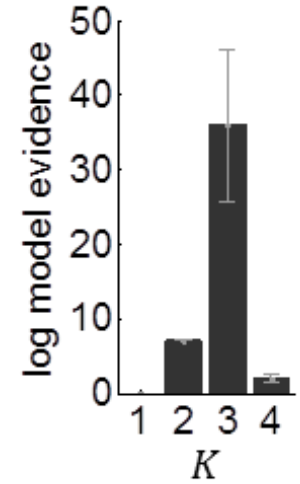
Generative embedding (unsupervised)



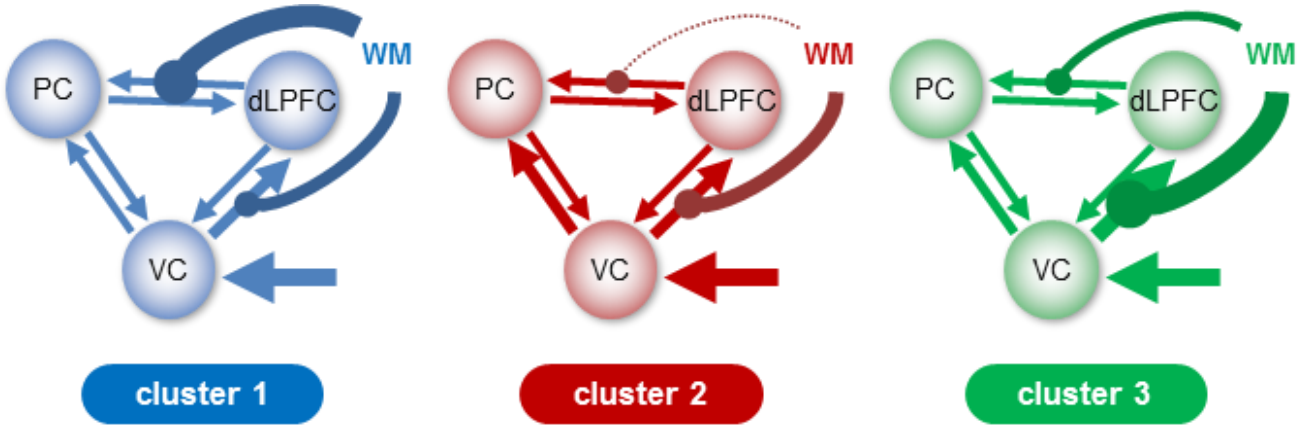
Brodersen et al. 2014, *NeuroImage Clinical*

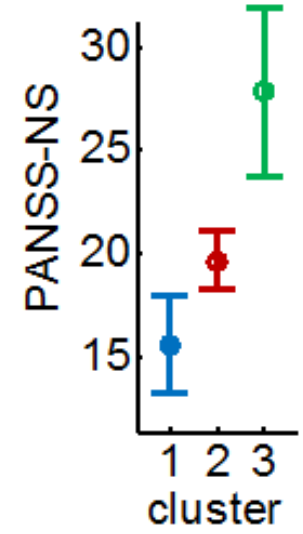
Detecting subgroups of patients in schizophrenia

Optimal cluster solution



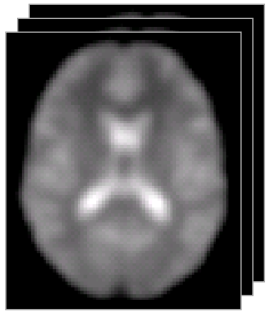
- three distinct subgroups (total N=41)
- subgroups differ ($p < 0.05$) wrt. negative symptoms on the *positive and negative symptom scale* (PANSS)





Brodersen et al. 2014, *NeuroImage Clinical*

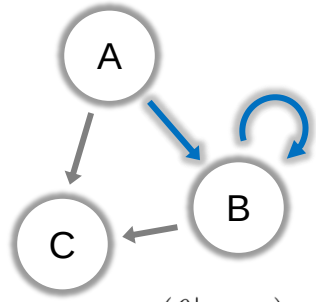
Generative embedding (supervised)



measurements from
an individual subject

**step 1 —
model inversion**

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



$p(\theta|x, m)$

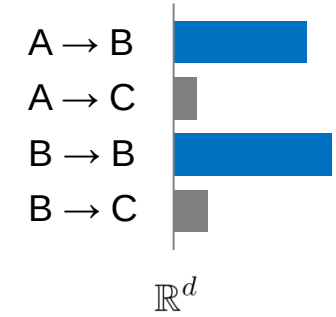
subject-specific
inverted generative model

**step 2 —
kernel construction**

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

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

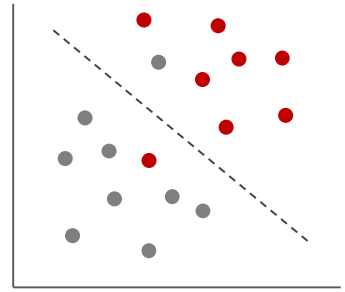
$k_\mathcal{M} : \mathcal{M}_\Theta \times \mathcal{M}_\Theta \to \mathbb{R}$



subject representation in the
generative score space

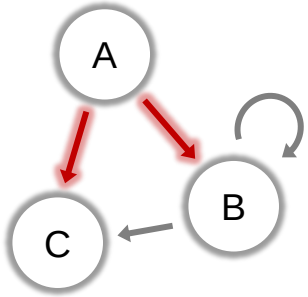
**step 3 —
support vector classification**

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



separating hyperplane fitted to
discriminate between groups

**step 4 —
interpretation**

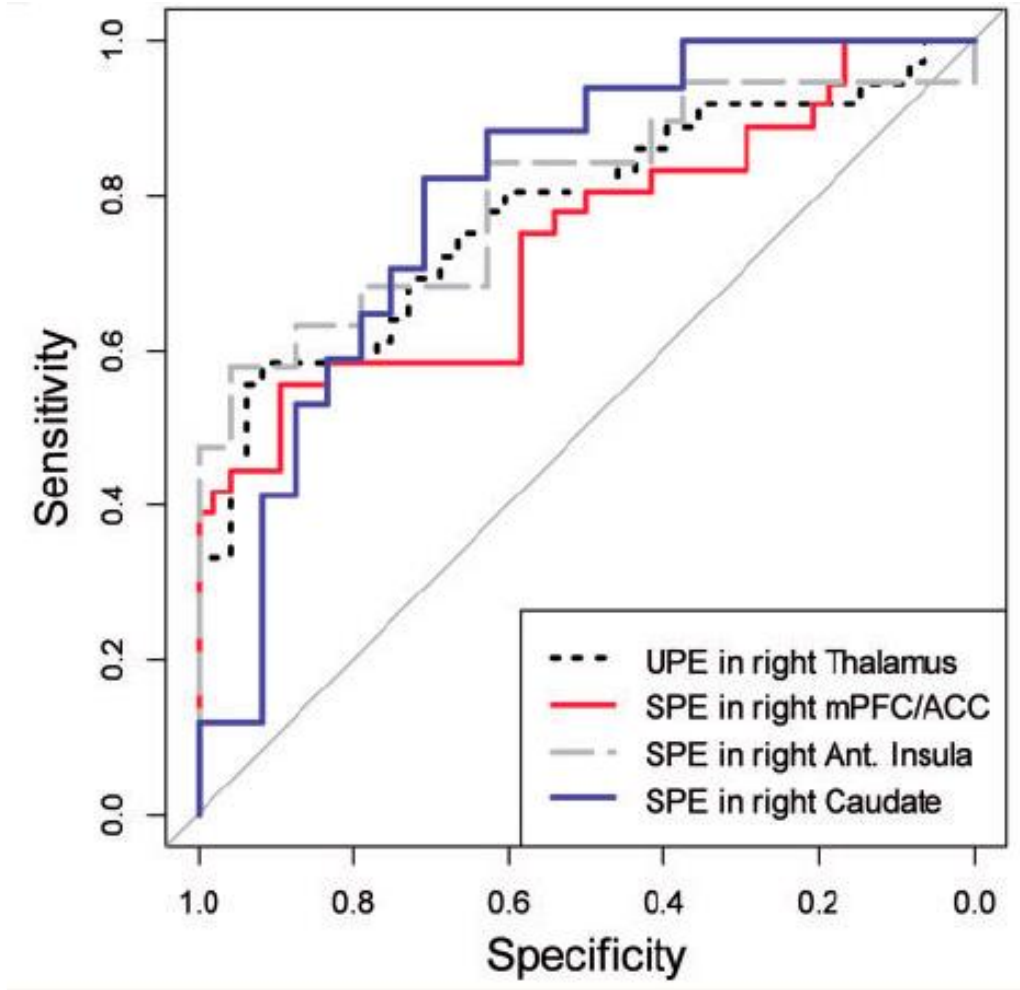


jointly discriminative
model parameters

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

Predicting future drug abuse

- fMRI of 157 occasional stimulant users (stop-signal task), Bayesian hidden Markov model
- prediction error (PE) activity from several brain regions predicted problem use 3 years later
- model-based prediction (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/TN (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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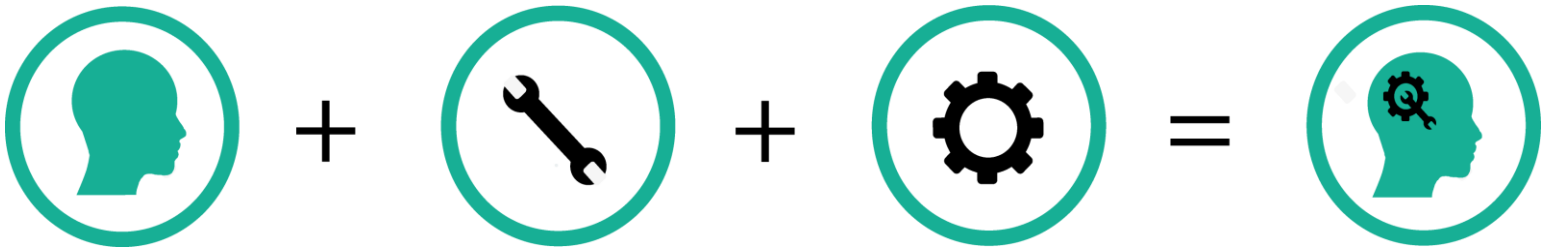
COMPUTATIONALPSYCHIATRYCOURSE



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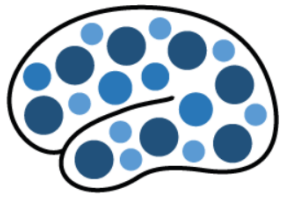

TAPAS

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Translational Neuromodeling Unit

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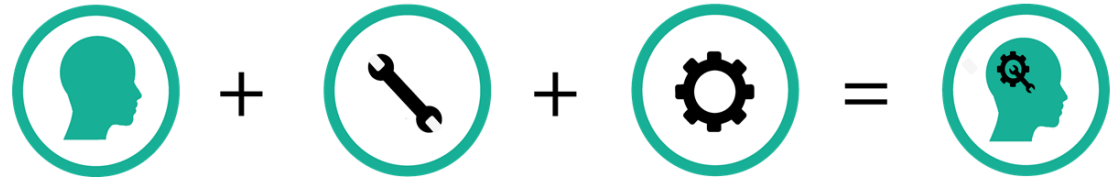
CPC 2017

- 3rd international edition
- originated from our local courses on Computational Psychiatry since 2012
- key features
  - theoretical lectures & practical demonstrations coupled
  - open source software only
  - covers models of both physiology and behaviour
  - 26 international presenters from 17 different institutions

CPC 2017

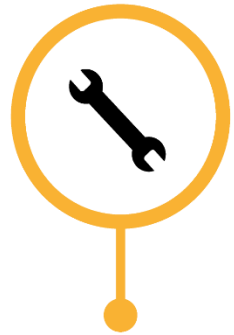
COMPUTATIONALPSYCHIATRYCOURSE



DAY 1

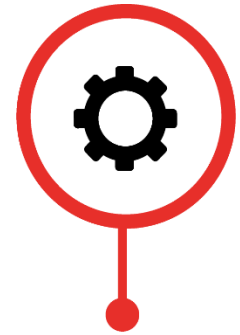
Psychiatry

DAY 2



Bayesian Inference & Machine Learning

DAY 3



Models of Planning & Decision Making

DAY 4

Biophysical Models & Model Inversion

DAY 5

Computational Psychiatry Applied

Further reading

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A very warm welcome –
we hope you will enjoy the CPC 2017!

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