COMPUTATIONAL PSYCHIATRY COURSE 2016

SCHIZOPHRENIA

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OVERVIEW

1. Clinical perspective
2. Etiology
3. Challenges for computational psychiatry
4. Summary

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CLINICAL PERSPECTIVE

Example: Hallucinations

The White Sound
directed by Weingartner & Amann, 2001

Symptoms

Example: Delusions

"I then referred to the ministry of internal affairs, because it is very difficult to get in touch with the secret service. I asked them: Hey, what do you want from me? I don't have any money, I'm not an activist, I'm not a terrorist. I don't understand why you are following and observing me, believe me, this is a waste of time and effort... I don't have any idea about technology, but I sought advice, and I found out that the chip that was implanted into my head cannot be a simple RFID chip, because the range would be far too small. Hence, it must be an implantable GPS chip, and machines that are able to detect such GPS sources cost approximately 25000 Euro."

Patient diagnosed with schizophrenia, 23 years

Symptom Dimensions

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Positive = Psychotic

- Delusions
- Hallucinations
- Ego disorders

Negative

- Blunted Affect
- Avolition/Anhedonia
- Social withdrawal

Disorganization

- Incoherent Thoughts
- Incoherent Behavior

BUT: Inconclusive evidence about dimension number and structure

Further reading

Peralta V, Cuesta MJ (2001) How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. Schizophr Res 49:269–285.

Other Signs and Symptoms

Catatonic Symptoms

Mannierism

Stereotypies

Motor immobility

Affective Symptoms

Depression

Mania

Cognitive Deficits

Working Memory

Executive Function

Attention

Neurological „Soft Signs“

Motor coordination

Sensory integration

Eye movements

Further reading

Dazzan P, Murray RM (2002) Neurological soft signs in first-episode psychosis: a systematic review. Br J Psychiatry Suppl 43:s50-57.

Epidemiology

- Lifetime prevalence ~ 0,7%
  - ♂ = ♀
  - regional variation
- Age of onset in late adolescence/early adulthood
  - ♂ earlier than ♀
- Mortality and disability
  - suicide lifetime risk ~ 10%
  - persisting disability in 40% ♂ and 25% ♀

Further reading

Saha S, Chant D, Welham J, McGrath J (2005) A systematic review of the prevalence of schizophrenia. PLoS Med 2:e141.
WHO Schizophrenia and Public Health. Geneva, World Health Organization.

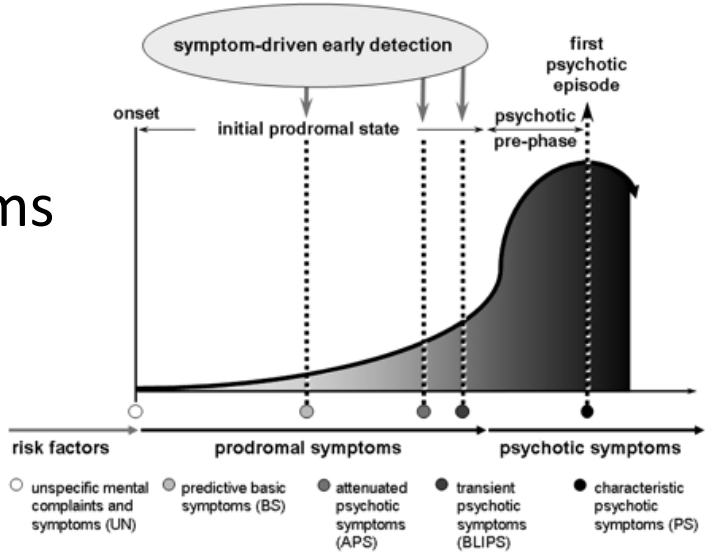
Diagnosis

categorical decision based on symptoms

- ICD-10 or DSM-IV

early recognition based on subtle symptoms

- beneficial for treatment response



Further reading

Fusar-Poli P et al. (2013) The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70:107–120.

Treatment

Antipsychotic drugs

D2 receptor blockade

efficient symptom reduction

considerable side effects

Psychosocial interventions

CBT, social skills training, family interventions, cognitive training

efficient symptom reduction

Sources

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382:951–962.

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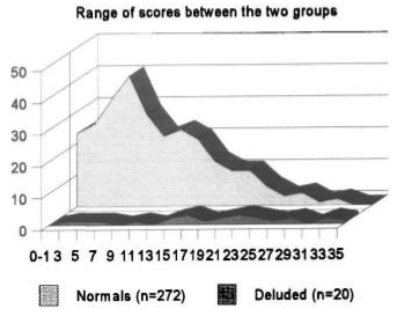
Pfammatter M, Junghan UM, Brenner HD (2006) Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. Schizophr Bull 32 Suppl 1:S64-80.

Continuity view

Psychosis-like experiences



- found in general population
- measurable by questionnaires (e.g. PDI-40, CAPS)
- similar underlying mechanisms as schizophrenia
  - relatives of schizophrenia patients
  - similar epidemiological factors as schizophrenia
  - increased schizophrenia risk
- study of schizophrenia without illness-related confounders

Sources

Peters ER, Joseph SA, Garety PA (1999) Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). Schizophr Bull 25:553–576.

Bell V, Halligan PW, Ellis HD (2006) The Cardiff Anomalous Perceptions Scale (CAPS): a new validated measure of anomalous perceptual experience. Schizophr Bull 32:366–377.

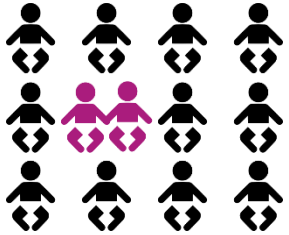
Further reading

Linscott RJ, van Os J (2013) An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults. Psychol Med 43:1133–1149.

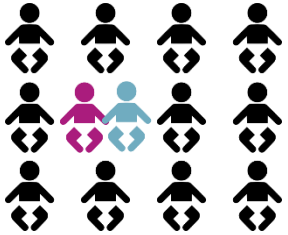
ETIOLOGY

Genetic Risk

Twin concordance rates



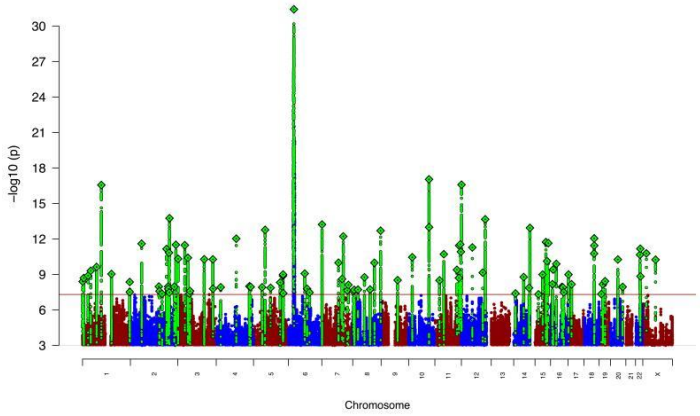
50%



15%

Genetic heterogeneity

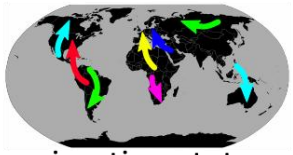
- Rare variations with large effects (CNVs)
- Frequent variations with small effects (SNPs)



Overlap with bipolar and schizoaffective disorder

Further reading
Rees E et al. (2014) Analysis of copy number variations at 15 schizophrenia-associated loci. Br J Psychiatry 204:108–114.
Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.

Environmental Risk

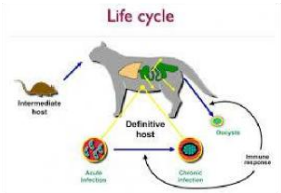


migration status

OR 4.6

older fathers

OR 3.8



Toxoplasmosis gondii antibodies

OR 2.7

winter/spring birth

OR 1.1

lifetime cannabis use

OR 2.1

urban rearing

OR 1.7

obstetrical complications

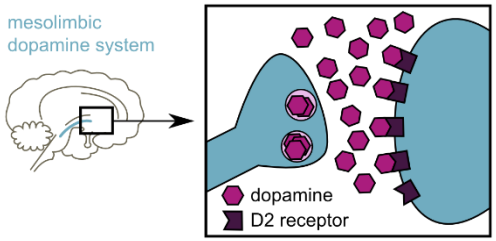
OR 1.8

prenatal famine

OR 2.3

Sources
McGrath J et al. (2004) BMC Med 2:13.
Zammit S et al. (2003) *Br J Psychiatry 1*83:405-8.
Torrey EF et al. (2007) *Schizophr Bull* 33(3):729-36.
Henquet C et al. (2005) *Schizophr Bull* 31(3):608-12.
Krabbendam L, van Os J (2005) *Schizophr Bull* 31(4):795-9
Davies G et al. (2003) *Schizophr Bull* 29(3):587-93.
St Clair D et al (2005) *JAMA* 294(5):557-62.

Dopamine hypothesis



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1. D2 antagonists reduce symptoms of schizophrenia
   immediate effect? similar effects on positive and negative symptoms?
2. Dopamine agonists lead to symptoms similar to schizophrenia
   BUT rather after chronic use or after previous schizophrenia episodes
3. Increased F-DOPA uptake in schizophrenia in PET studies
   and related conditions
4. Association of D2 receptor gene to schizophrenia in GWAS

➢ **Sensitized dopamine system is the „final common pathway“.**

Further reading
Howes OD, Murray RM (2014) Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet 383:1677–1687.

Glutamate hypothesis

1. glutamate (NMDA) antagonists induce symptoms similar to schizophrenia immediate effect and both positive and negative symptoms
2. BUT controversial whether glutamate agonists (mGluR and NMDA) reduce schizophrenia symptoms
3. Decreased glutamate signals in schizophrenia in ^{1}H-MRS studies
4. Association of gluatamtergic genes to schizophrenia in GWAS

➢ **Glutamate/NMDA hypofunction is involved in schizophrenia.**

Furhter reading

Aleman A, Lincoln TM, Bruggeman R, Melle I, Arends J, Arango C, Knegtering H (2016) Treatment of negative symptoms: Where do we stand, and where do we go? Schizophr Res.

Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE (2013) Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies. Schizophr Bull 39:120–129.

Inflammation & immunity

1. Increased inflammatory cytokines in schizophrenia

   cause or consequence? confounders?

2. Activation of brain immune cells in schizophrenia in PET studies

   valid methodology? only 2 studies

3. Anti-inflammatory treatment reduces symptoms of schizophrenia

4. Association of immune-related genes to schizophrenia in GWAS

   role in inflammation or in pruning?

➢ **Immune processes play a role in schizophrenia (at least in some cases).**

Further reading

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2:258–270.

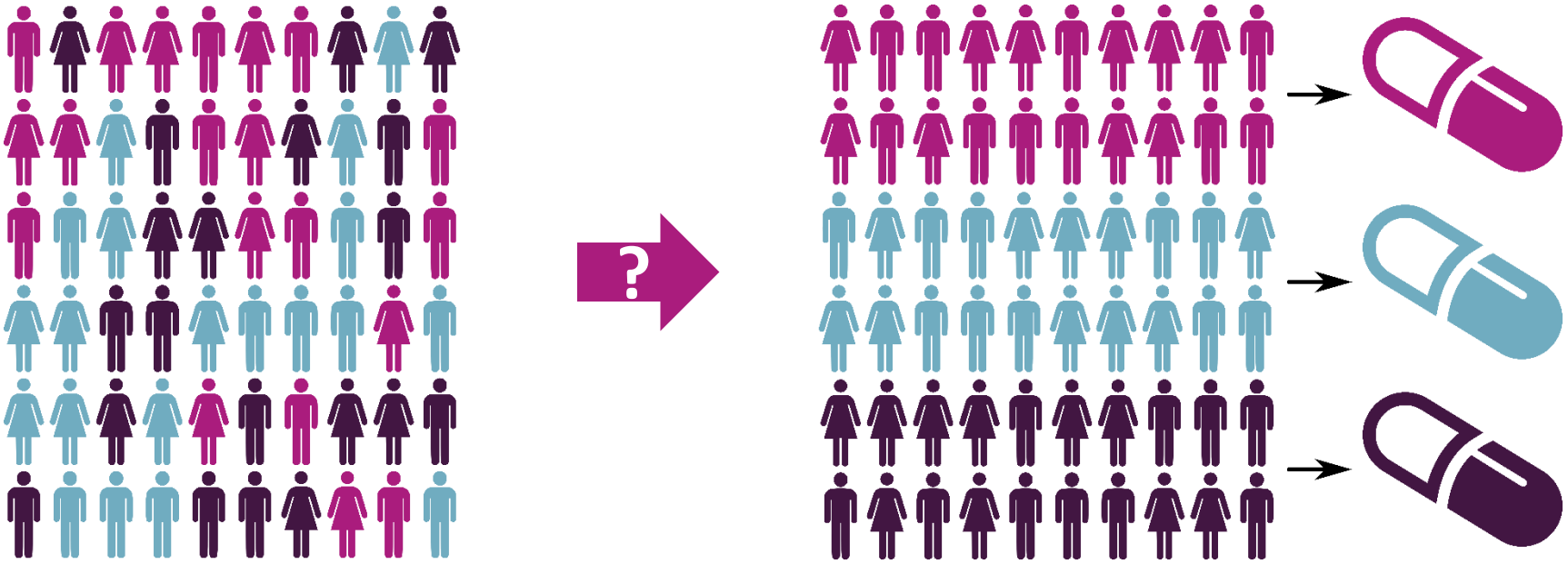
Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly MJ, Carroll MC, Stevens B, McCarroll SA (2016) Schizophrenia risk from complex variation of complement component 4. Nature 530:177–183.

CHALLENGES & COMPUTATIONAL PSYCHIATRY

Heterogeneity

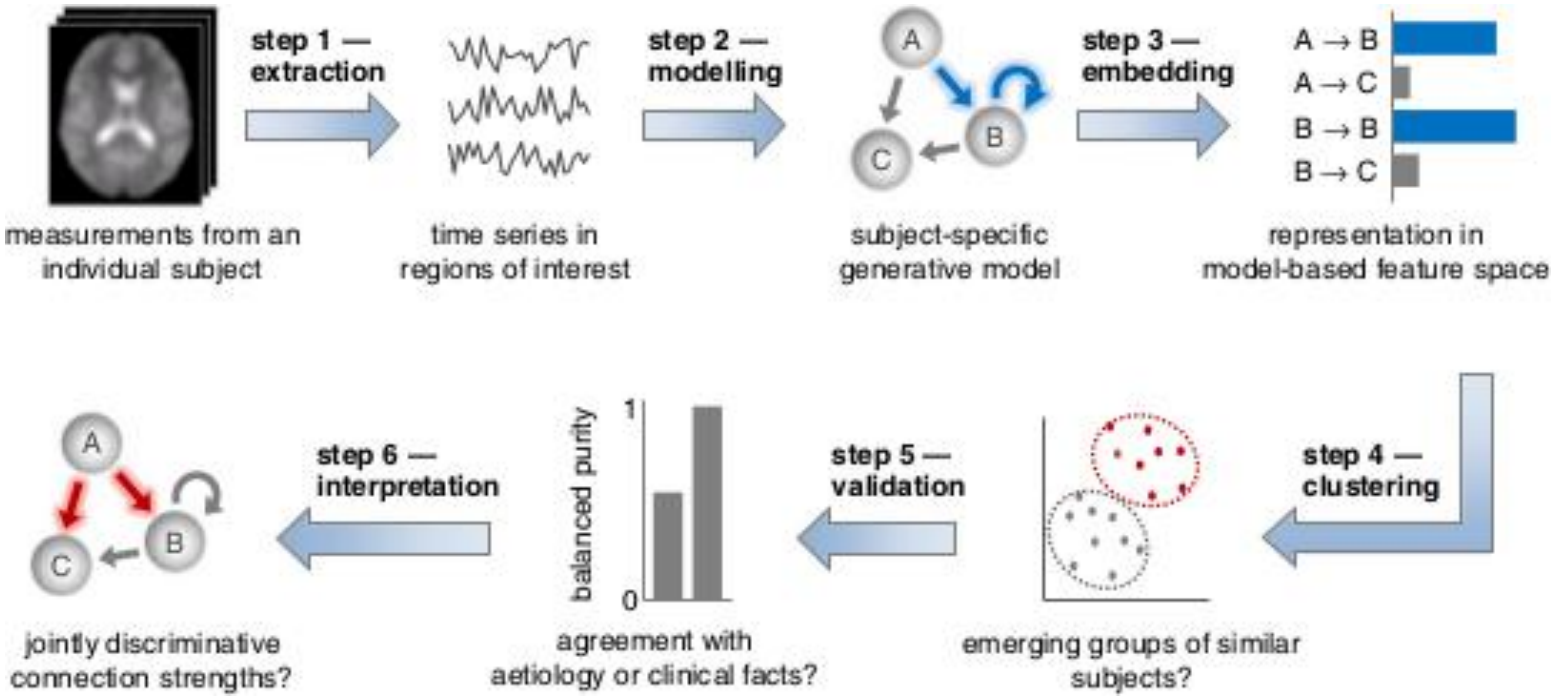
heterogenous pathogenesis

targeted treatment



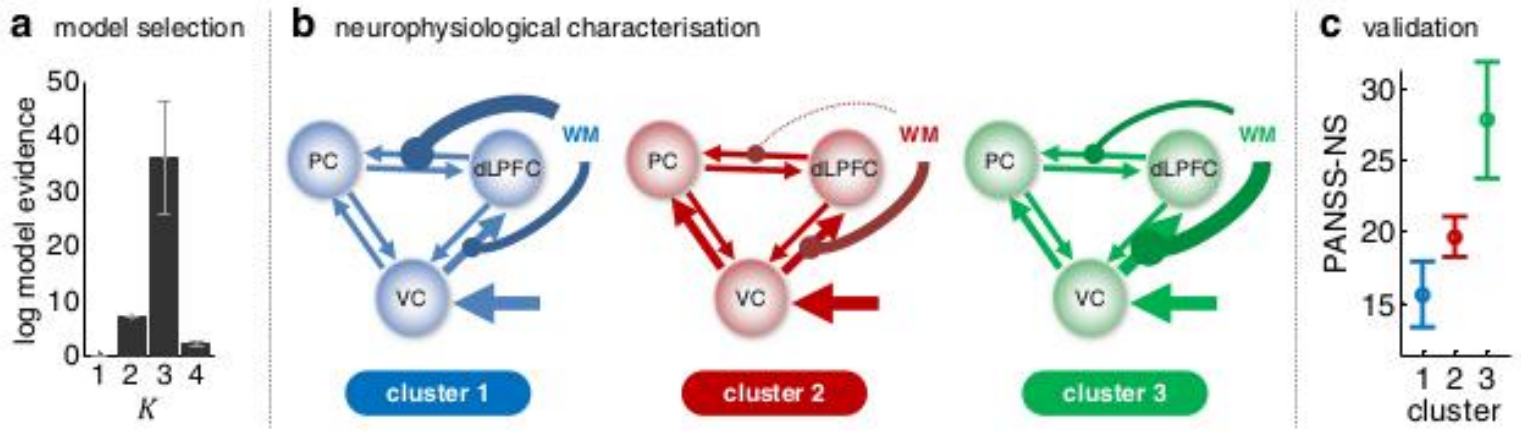
- computational algorithms for sorting individuals into neurophysiologically interpretable clusters

Example: Generative embedding



Brodersen KH, Deserno L, Schlagenhauf F, Lin Z, Penny WD, Buhmann JM, Stephan KE (2014) Dissecting psychiatric spectrum disorders by generative embedding. Neuroimage Clin 4:98–111.

Example: Generative embedding



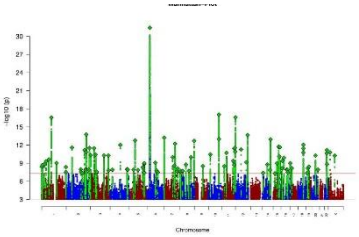
- clustering of schizophrenia patients that differ in neural circuit architecture
- mapping onto differences in clinical presentation

Brodersen KH, Deserno L, Schlagenhauf F, Lin Z, Penny WD, Buhmann JM, Stephan KE (2014) Dissecting psychiatric spectrum disorders by generative embedding. Neuroimage Clin 4:98–111.

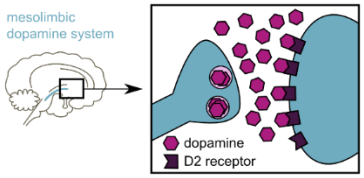
Explanatory gaps

environment

genes



neurotransmitter alterations

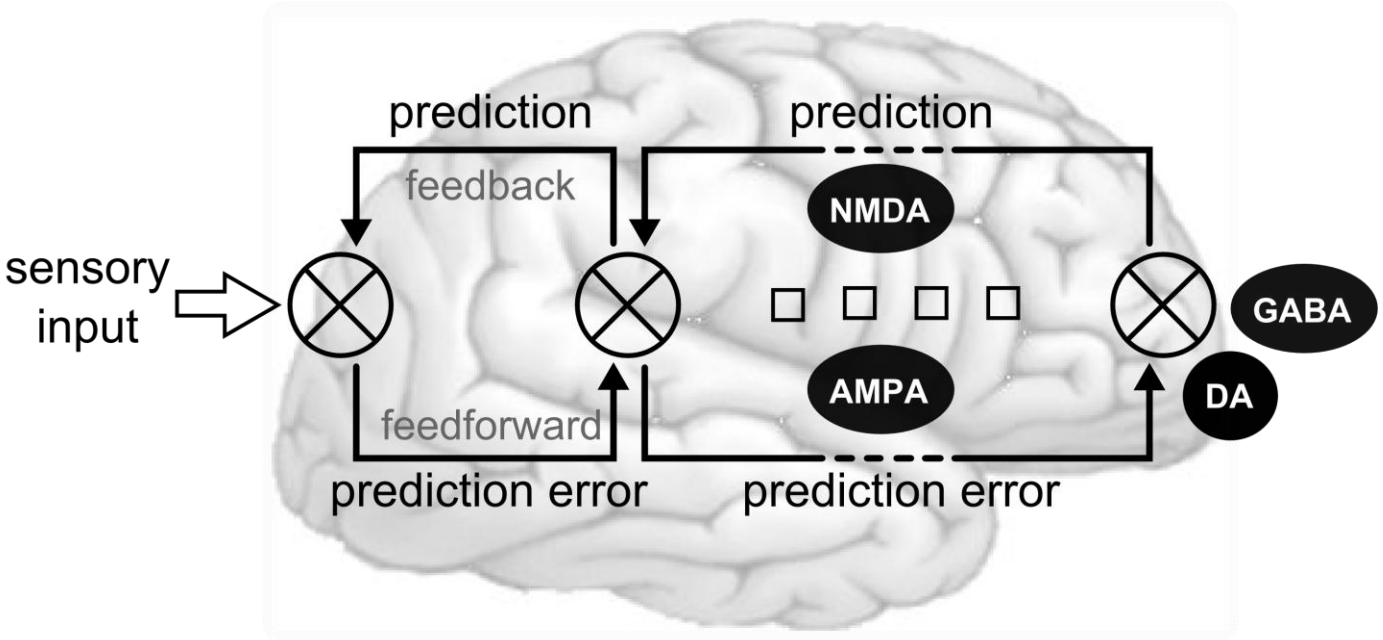


symptoms

- computational models for linking clinical symptoms with neurophysiologically plausible models of neural circuitry

Example:
Non-linear learning

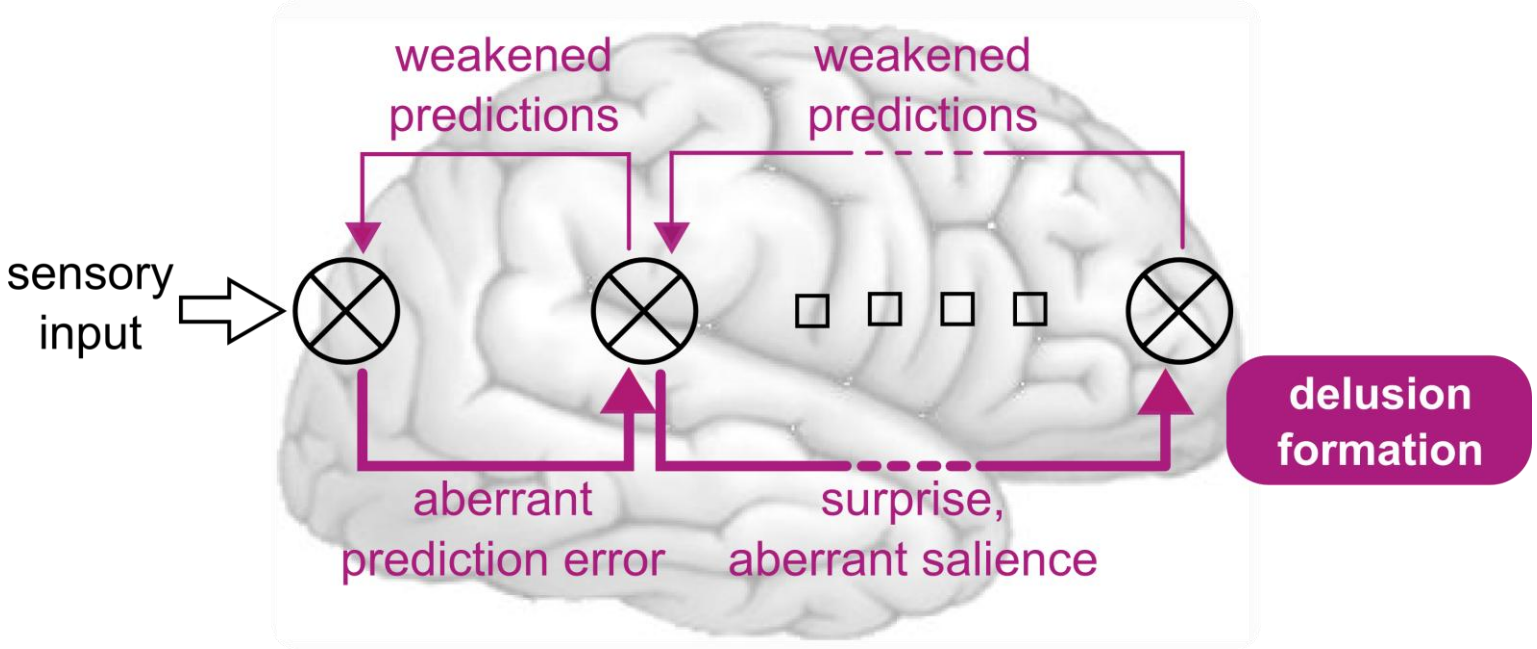
Predictive coding



Rao & Ballard 1998, Nat Neurosci; Friston 2005, Philos Trans Roy Soc London

Example: Non-linear learning

Predictive coding and psychosis



Heinz 2002, Eur Pscyhiatry
Kapur 2005, Am J Psychiatry
Fletcher & Frith 2008, Nat Rev Neurosci

Example: Non-linear learning

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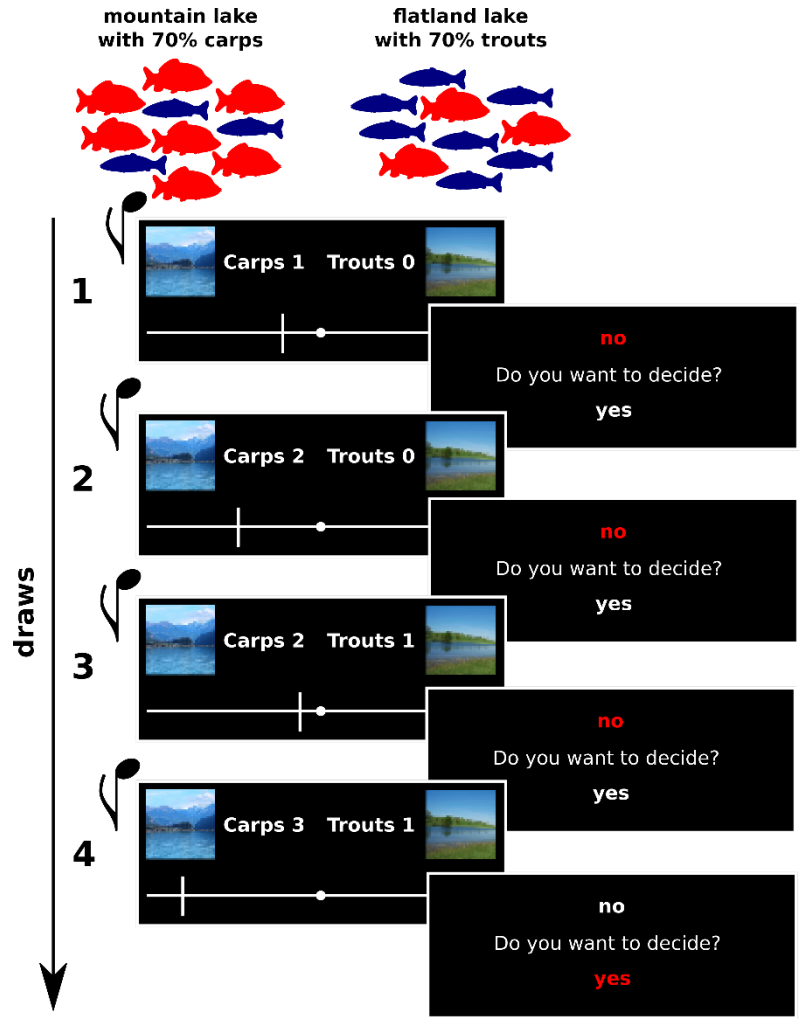


„Jumping-to-conclusions“

Correlation draws to decisions and psychotic experiences

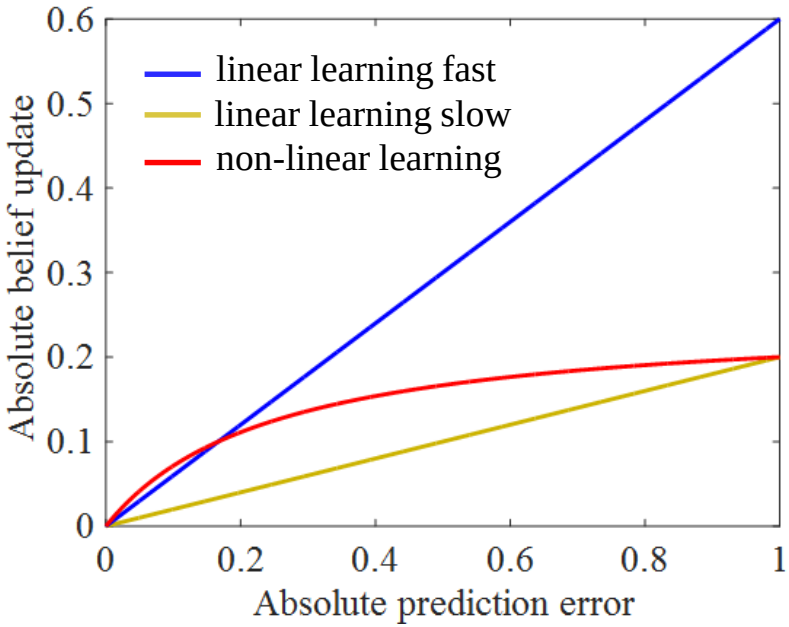
delusions: r=-0.18, p=0.04*

hallucinations: r=-0.15, p=0.06

n=94 healthy individuals

Stuke H, Stuke H, Weilnhammer V, Schmack K (under review) Psychotic experiences and overhasty inferences are related to maladaptive learning.

Example: Non-linear learning



non-linear learning model

$$b_i = b_{i-1} \pm \alpha * \frac{1}{\zeta + \frac{1}{|b_{i-1} - o_i|}}$$

resilience against irrelevant information

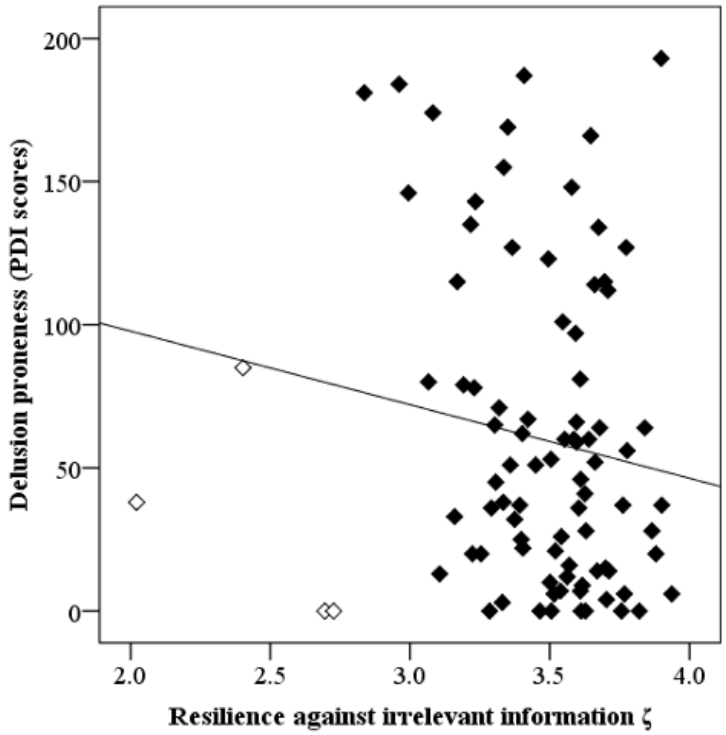
exceedance probability 100%

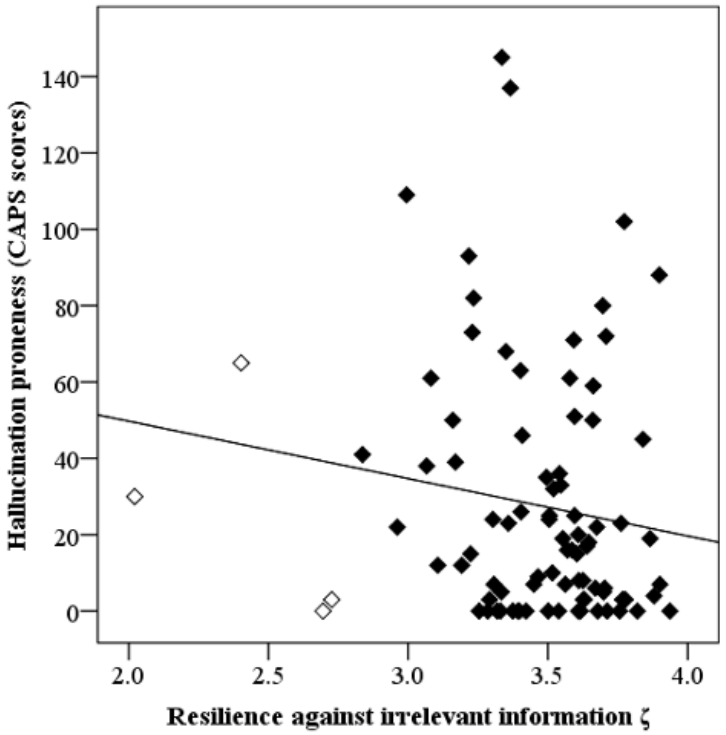
explained variance R^2=0.70

ζ * draws to decision: r=-0.77, p<0.001

Stuke H, Stuke H, Weilnhammer V, Schmack K (under review) Psychotic experiences and overhasty inferences are related to maladaptive learning.

Example: Non-linear learning





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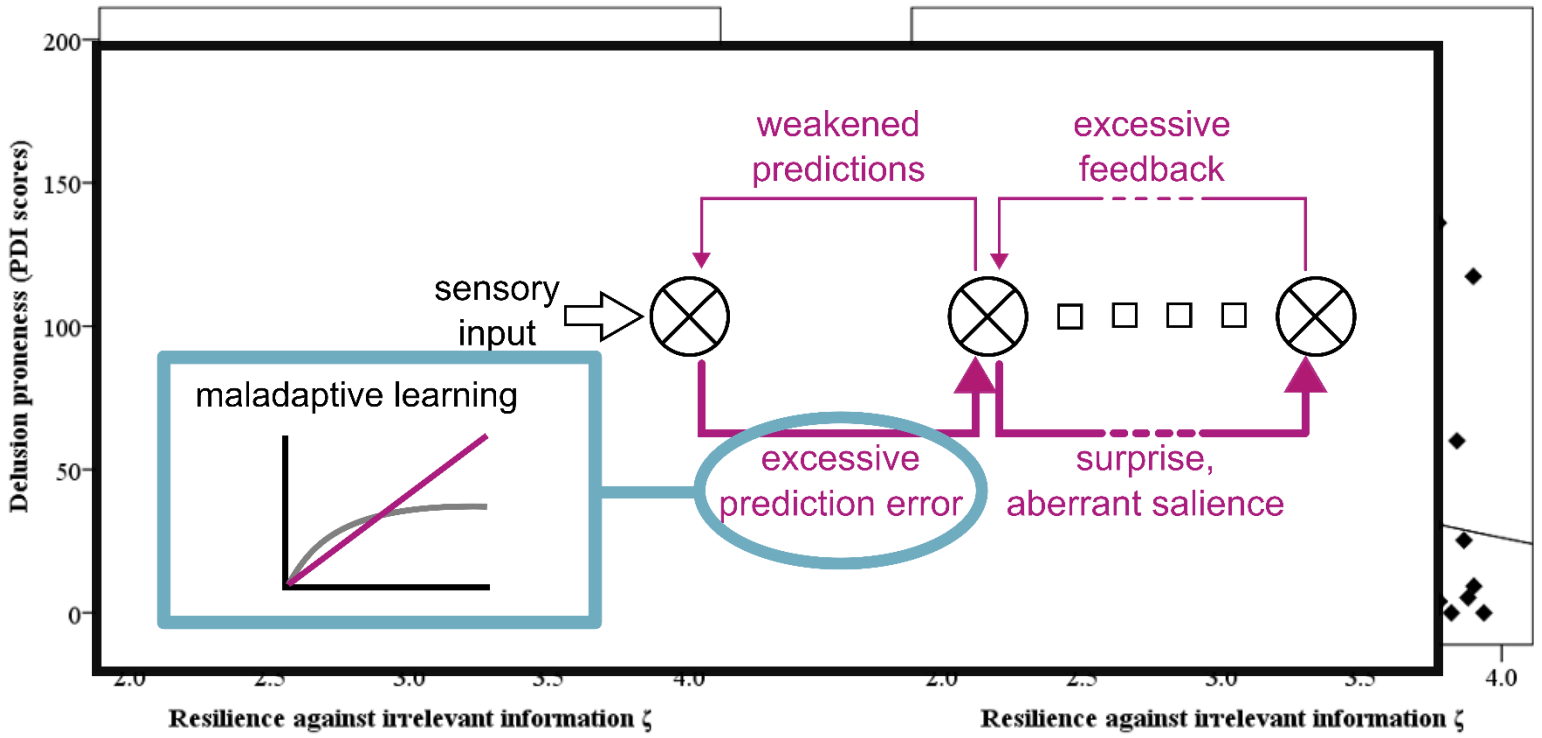


- neurophysiologically plausible description of ‚psychotic' cognition/perception
- mapping onto neurophysiological alterations

Stuke H, Stuke H, Weilnhammer V, Schmack K (under review) Psychotic experiences and overhasty inferences are related to maladaptive learning.

SUMMARY

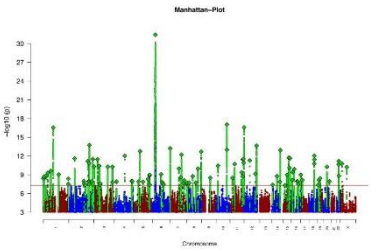
Clinical features

- positive, negative and disorganization symptoms
- purely ‚phenomenological' diagnosis
- increased mortality and often persistent disability
- pharmacological (D2 antagonists) and psychosocial treatment

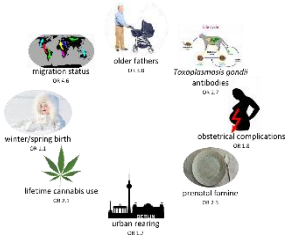
Etiology and pathogenesis

FACTS

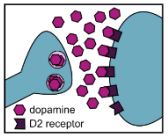
genetic risk with polygenic and/or monogenic pattern



variety of environmental risk factors



HYPOTHESES



excessive mesolimbic dopamine signaling

deficient NMDA signaling

inflammation

Challenges for computational psychiatry

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1. **HETEROGENEITY**

   - computational algorithms for sorting individuals into neurophysiologically interpretable clusters

2. **EXPLANATORY GAPS**

   - computational models for linking clinical symptoms with neurophysiologically plausible models of neural circuitry

QUESTIONS?

THANK YOU!

Psychiatry – Charité
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Matthias Guggenmos
Andreas Heinz
Marcus Rothkirch
Maria Sekutowicz
Philipp Sterzer
Heiner Stuke
Veith Weilnhammer

Goethe-Universität
Frankfurt

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