



Schizophrenia

(for non-clinicians)

2022 Computational Psychiatry Course



Translational Neuromodeling Unit



Universität
Zürich

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Jakob Siemerkus
University of Zurich & ETH Zurich

Schizophrenia



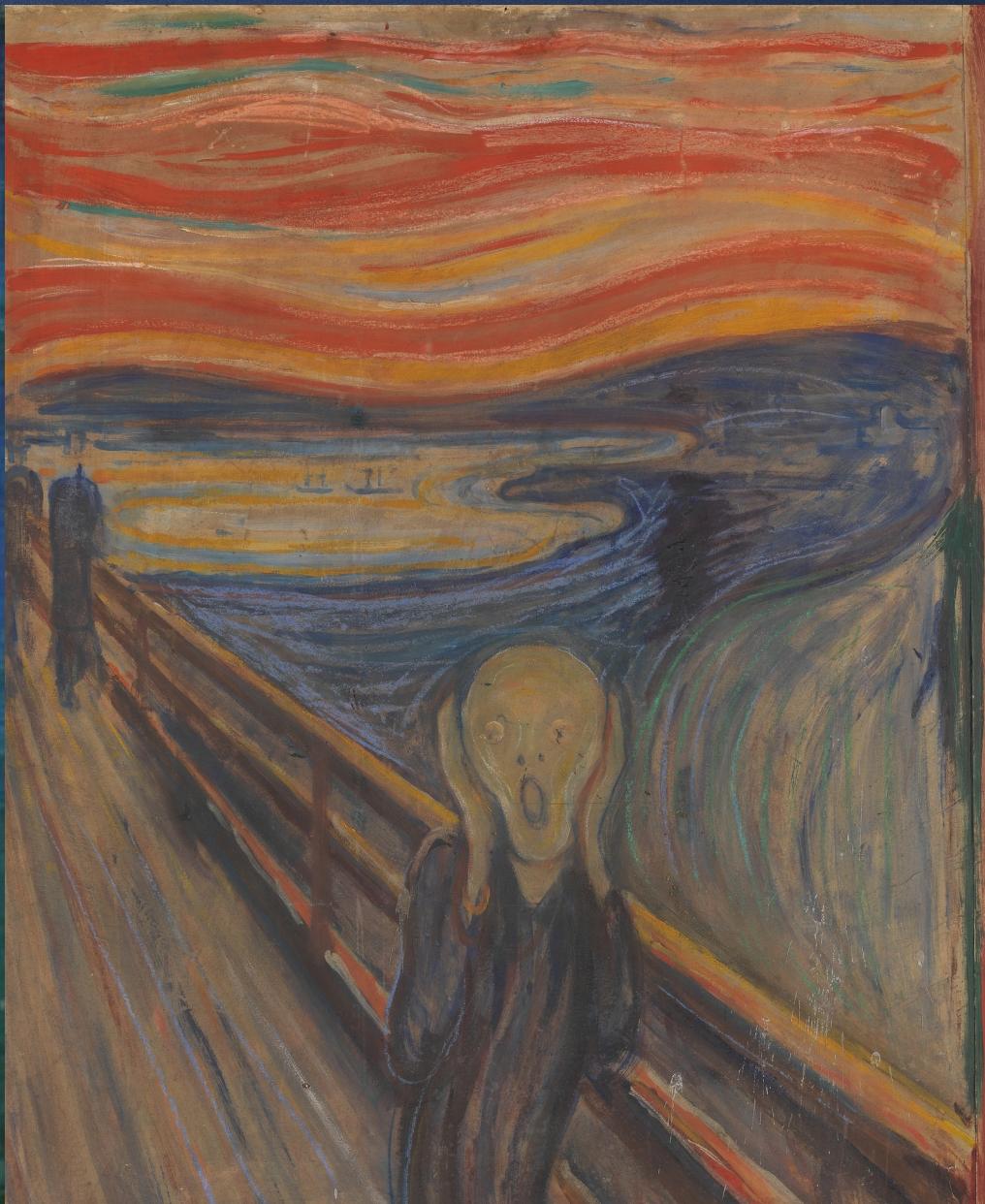
Schizophrenia

- One of the “major” psychiatric disorders
- 0.5% prevalence (Saha, 2005)
- Severe mental disorder
- Functional impairment
- Social dimension
- Many unsolved questions

Clinical Manifestation



Schizophrenia



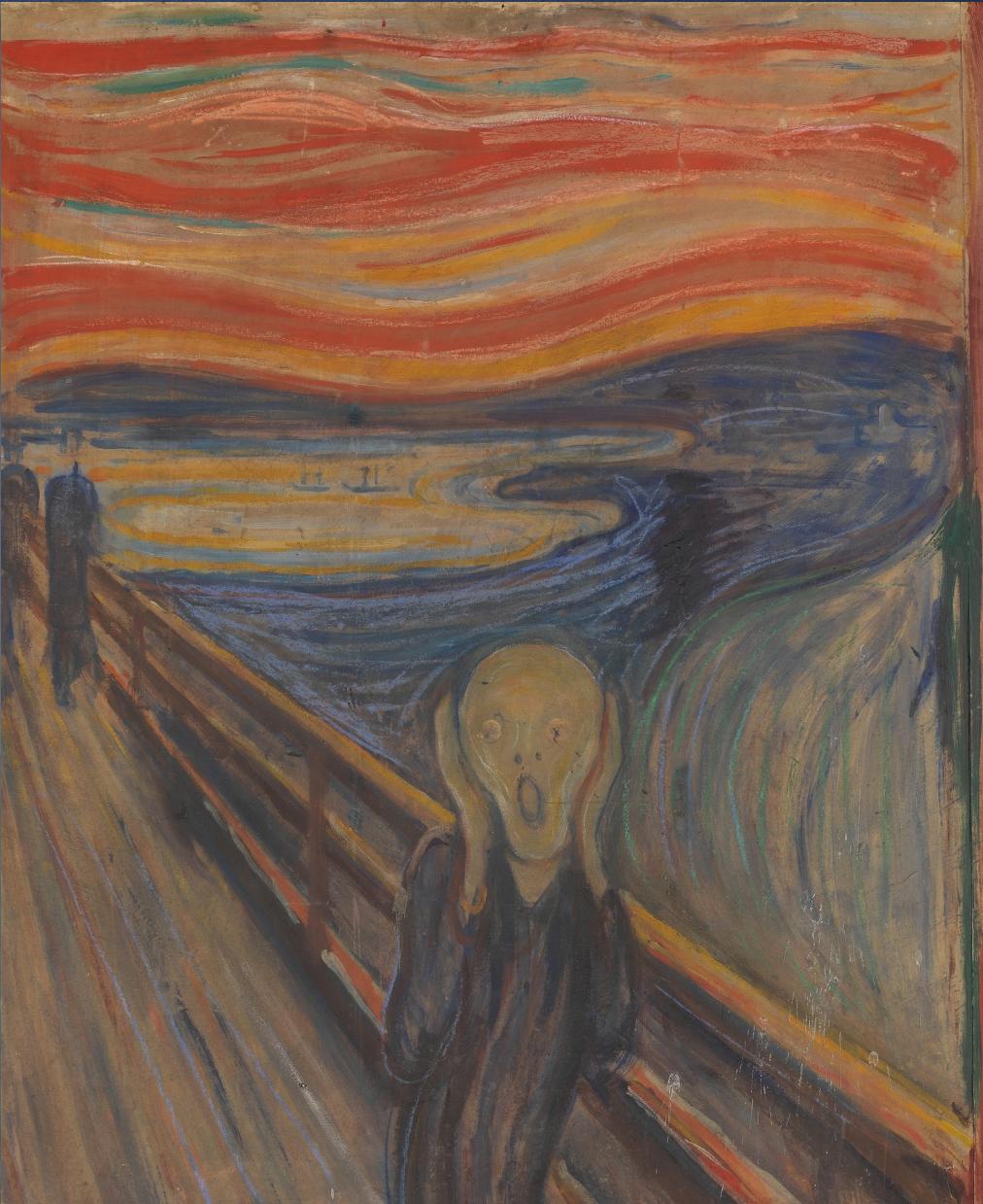
Schizophrenia



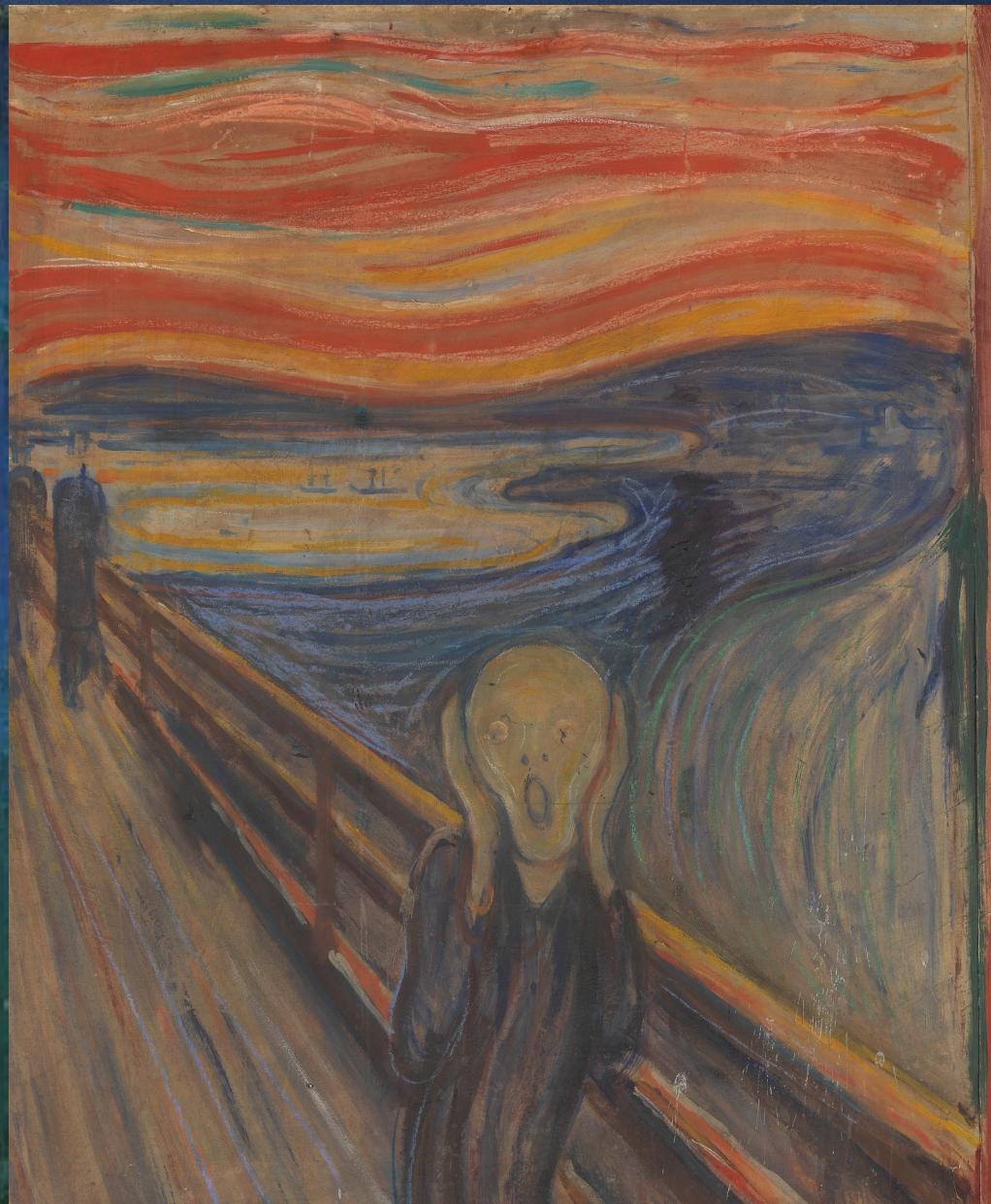
- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
- Apathy
- Slowed down
- Lost her job months ago

Schizophrenia

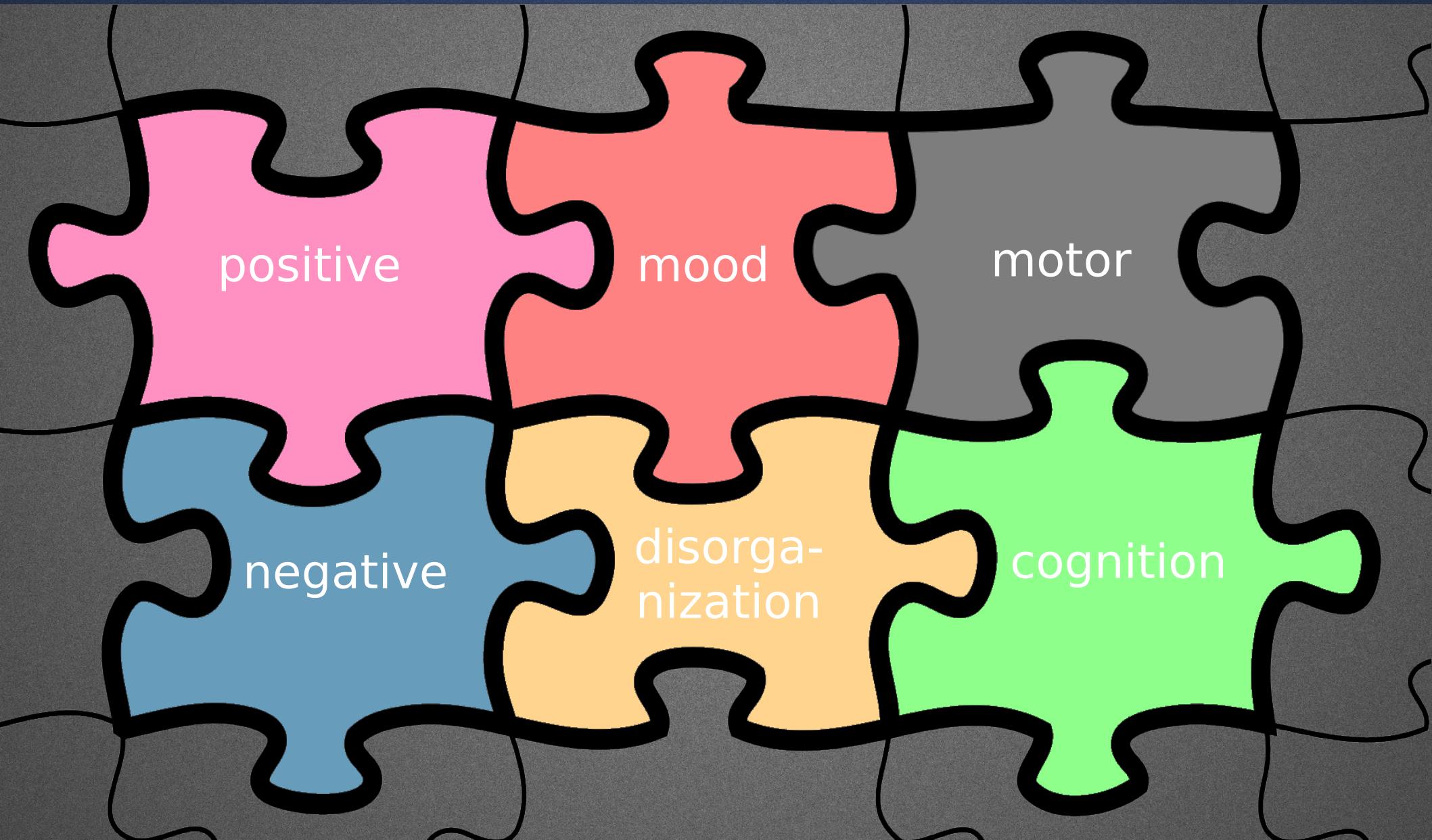
- 19yo student of physics
- Neighbor:
 - Spying on him
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 - Hears N.'s voice
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 - Started six weeks ago
- Did not attend classes for $\frac{1}{2}$ year



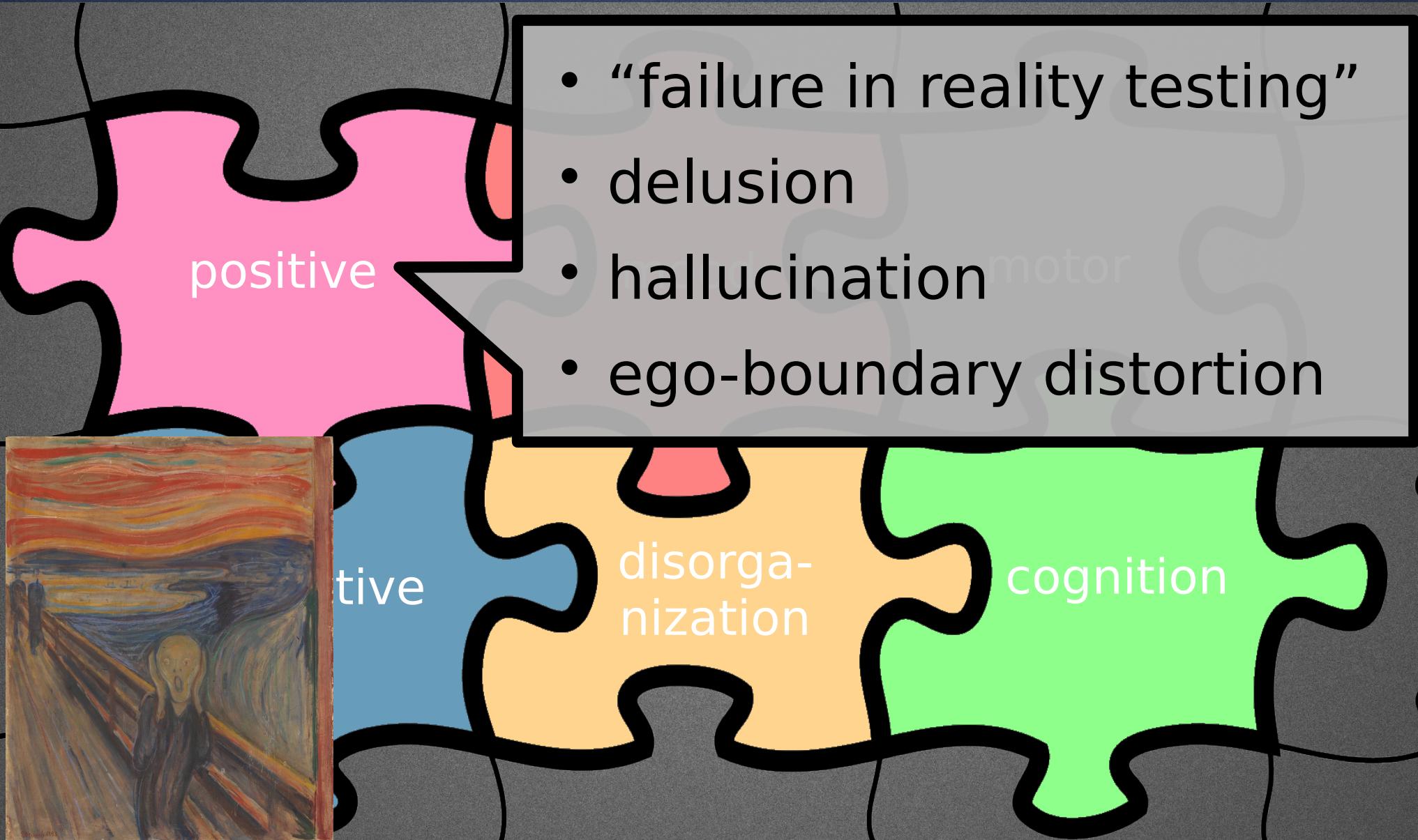
Schizophrenia(s?)



Main Symptom Categories



Main Symptom Categories



Main Symptom Categories



negative

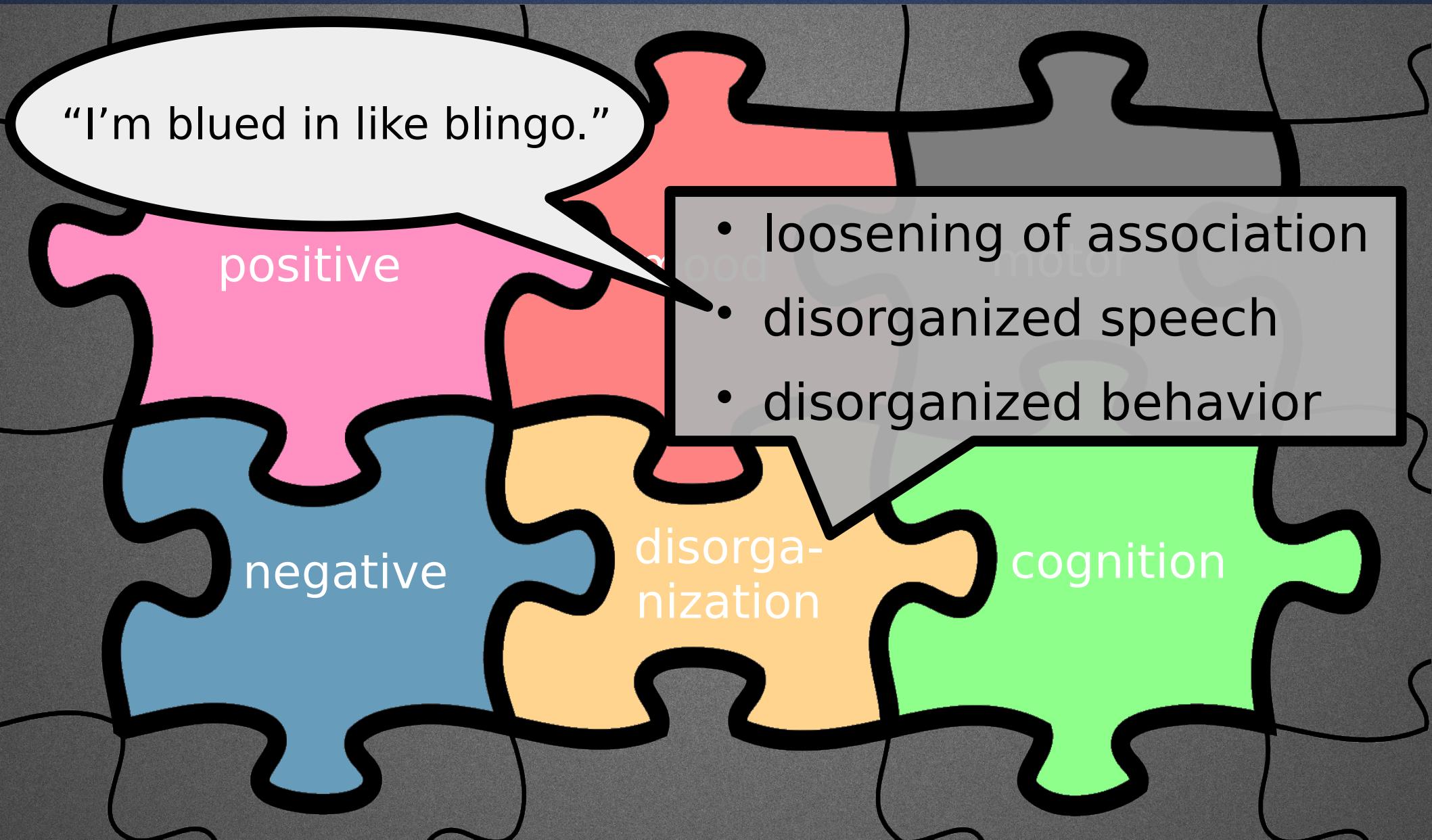
- loss of affective and driving functions
- impaired affective experience/expression
- loss of motivation & initiative
- reduced social drive
- slowed thinking

Main Symptom Categories



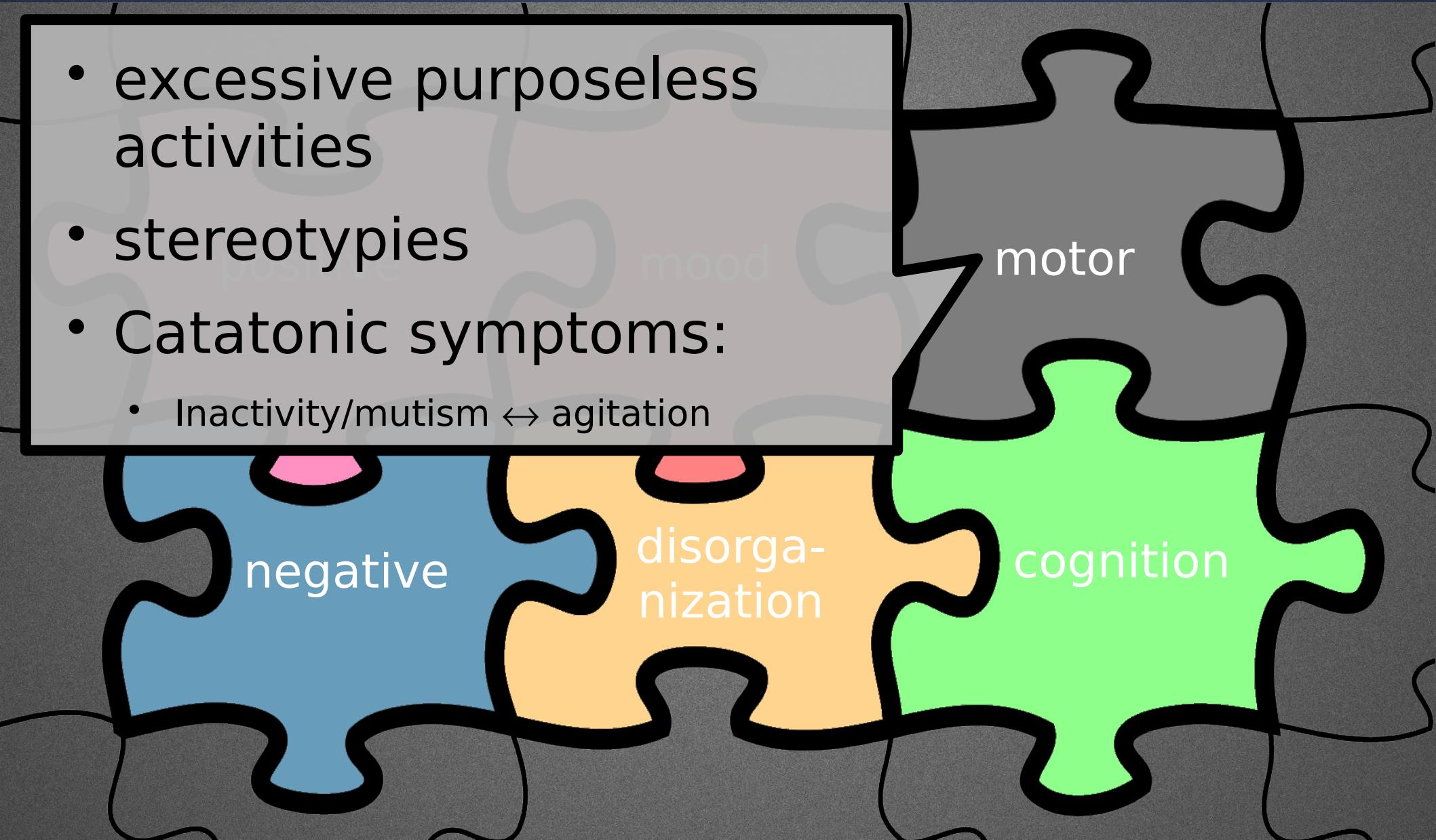
- overlap with negative symptoms
- anxiety, emotional arousal, and depression very frequent

Main Symptom Categories

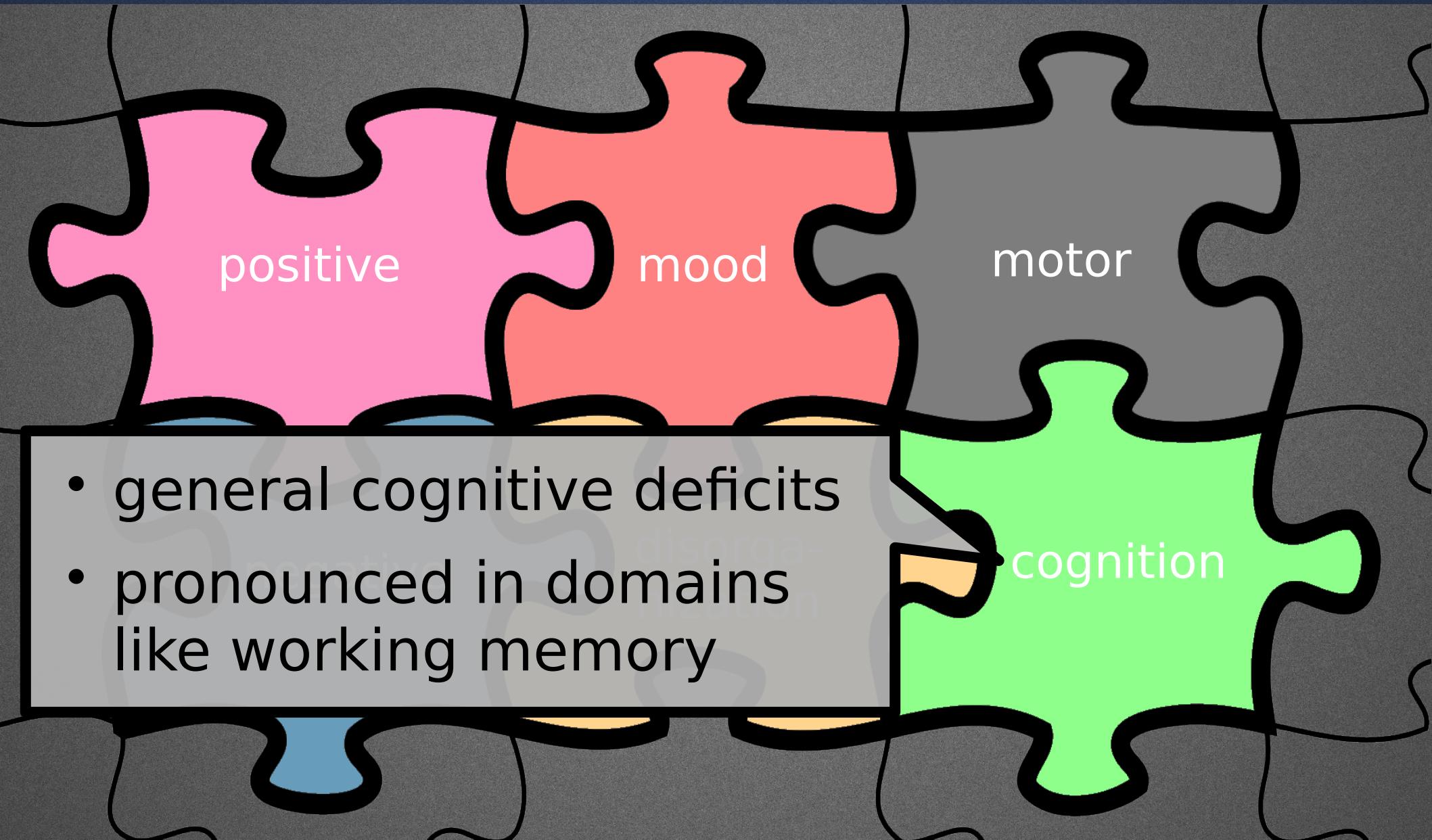


Main Symptom Categories

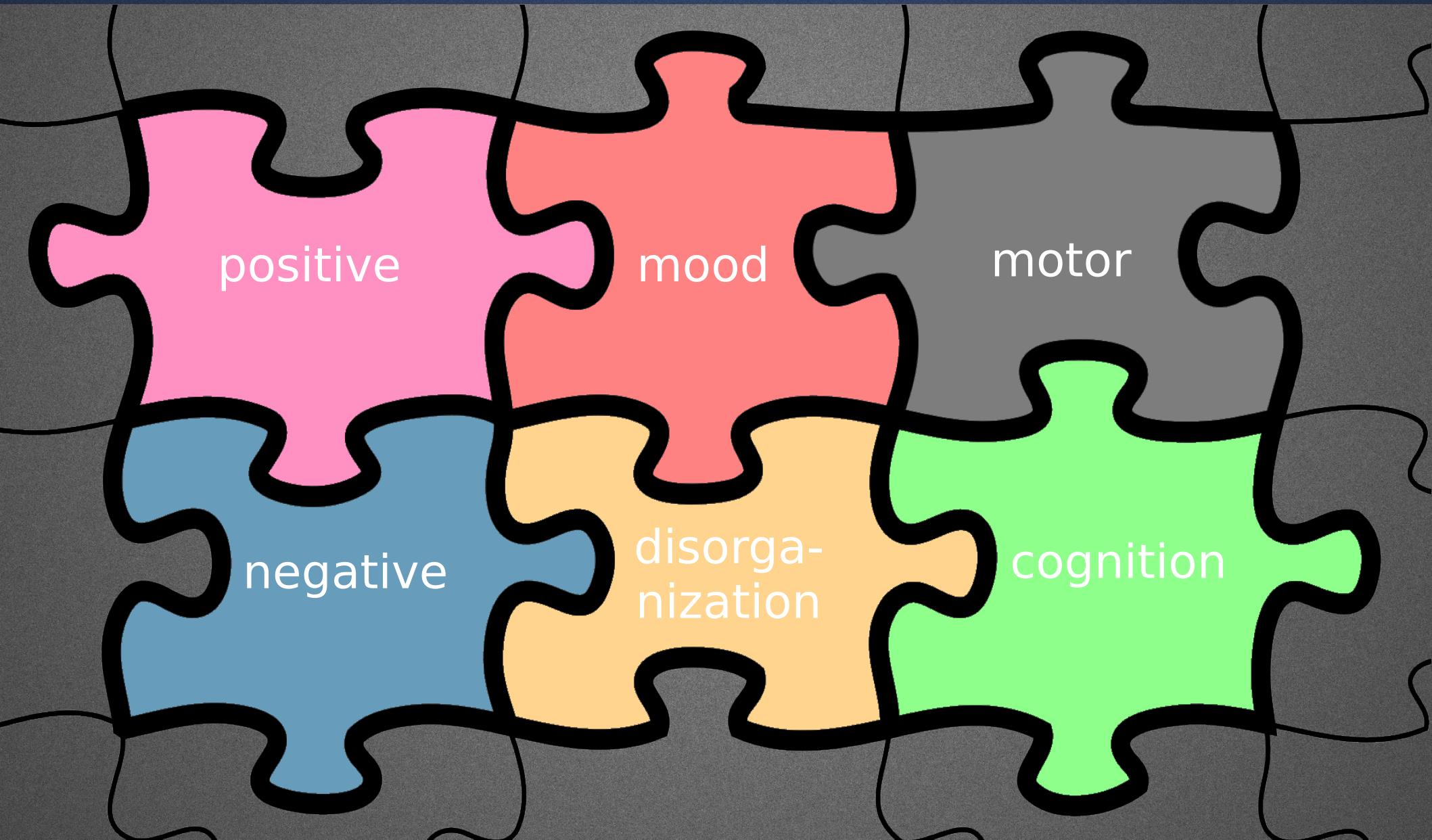
- excessive purposeless activities
- stereotypies
- Catatonic symptoms:
 - Inactivity/mutism ↔ agitation



Main Symptom Categories



Main Symptom Categories



Diagnostic Criteria

DSM 5

MAIN CRITERIA	<ul style="list-style-type: none">• ≥ 2 symptom (categories) present• AND ≥ 1 core symptom• no other cause
TIME	<ul style="list-style-type: none">• ≥ 1 month main criteria• ≥ 6 months symptoms/functional impairment
SYMPTOMS	<ul style="list-style-type: none">• (core) delusions• (core) hallucinations• (core) disorganized speech• negative symptoms (especially avolition, diminished emotional expression)• disorganized or catatonic behaviour

Schizophrenia



- 37yo librarian
 - Messy apartment
 - Has been talking “weirdly” for weeks, but now unable to talk
 - Apathy
 - Slowed down
 - Lost her job months ago
-
- Exam&lab results ok
 - Starts talking, uses “blue” in many contexts like “I’m blued in like blingo.”
→ Schizophrenia

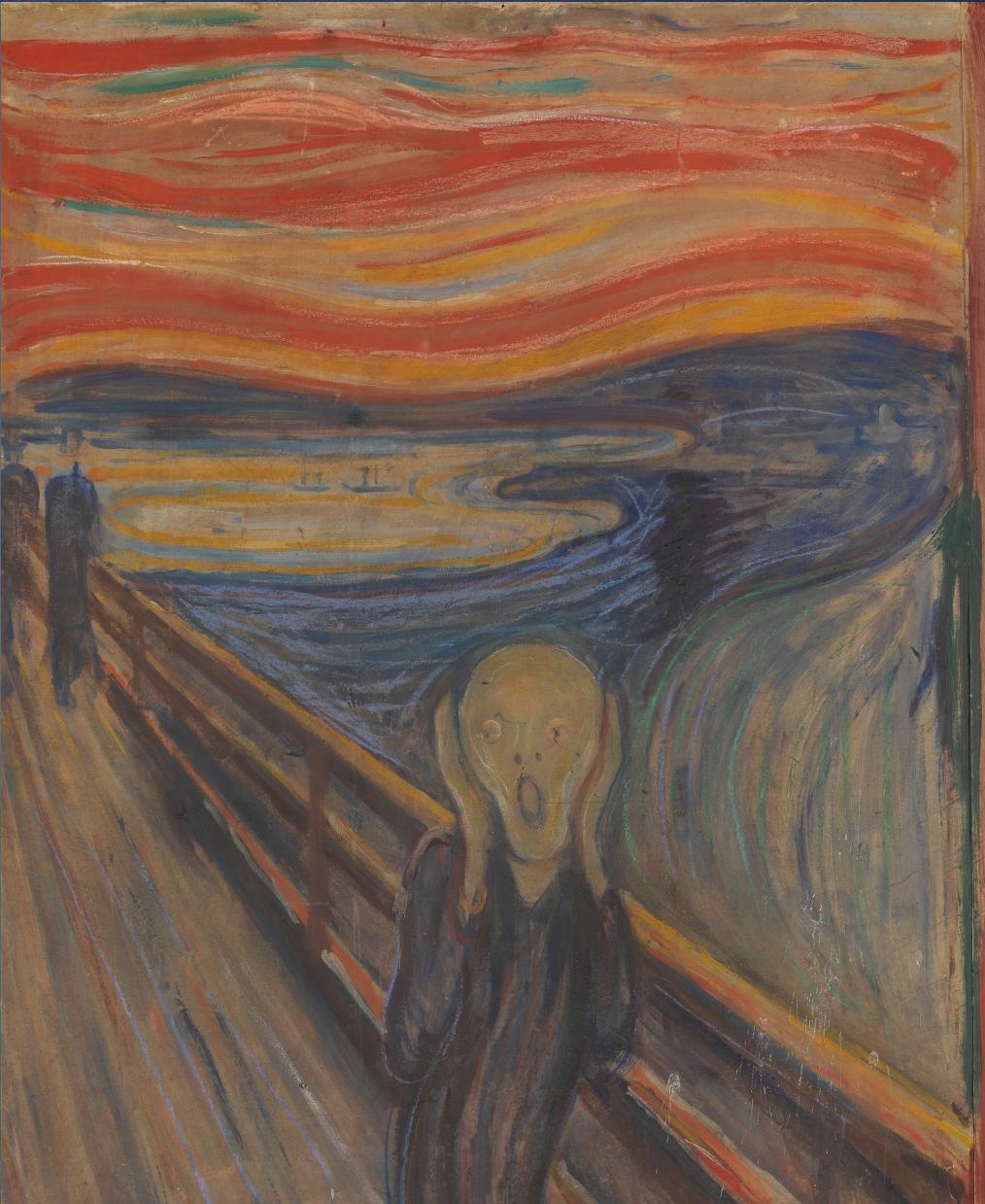
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Schizophrenia

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Diagnostic Criteria

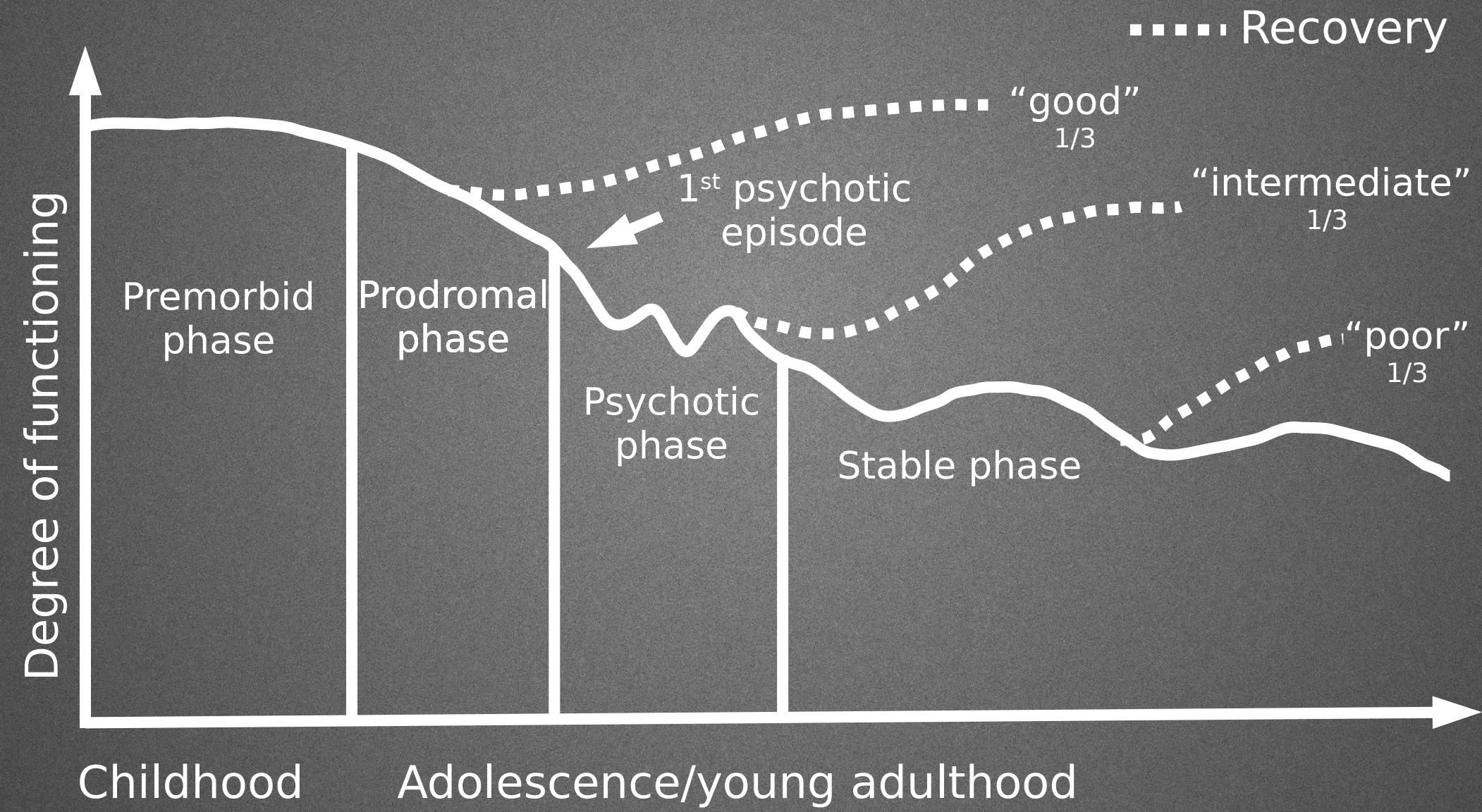
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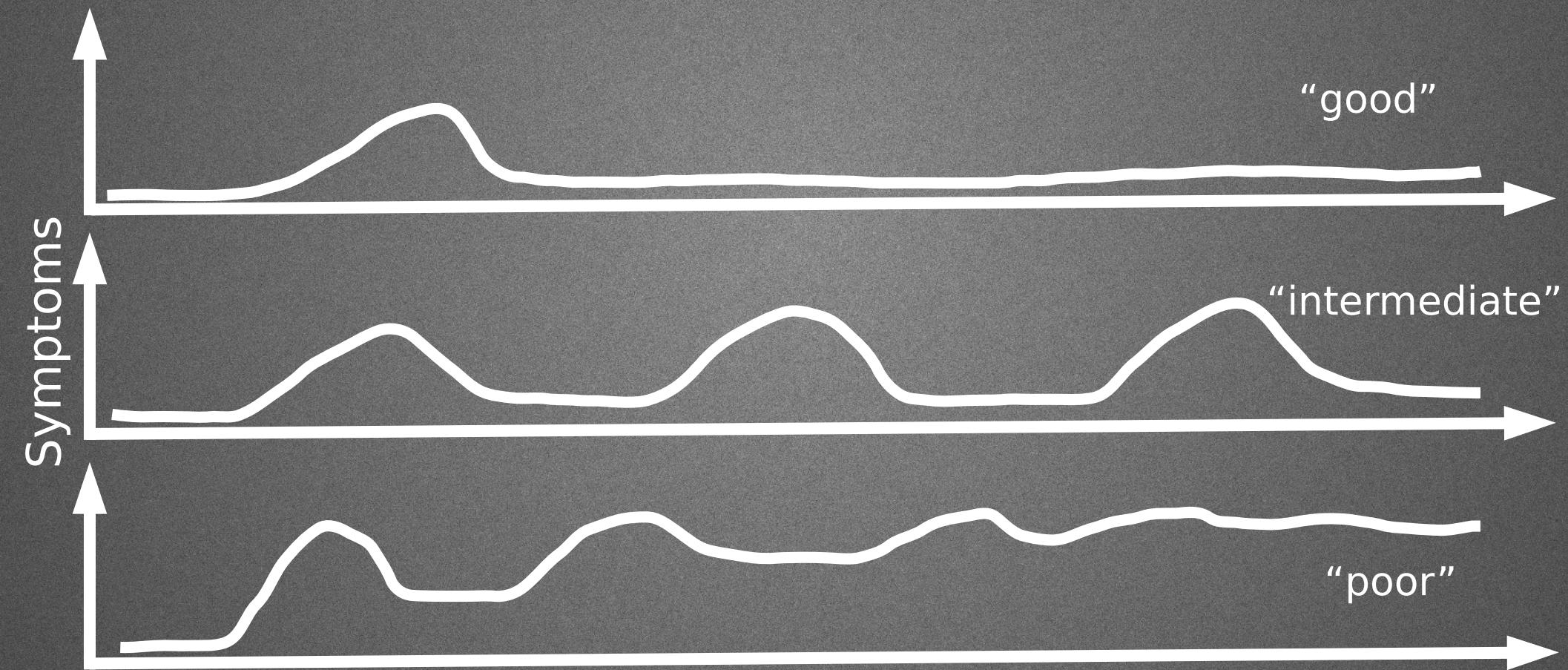


Trajectory Risk factors Outcome

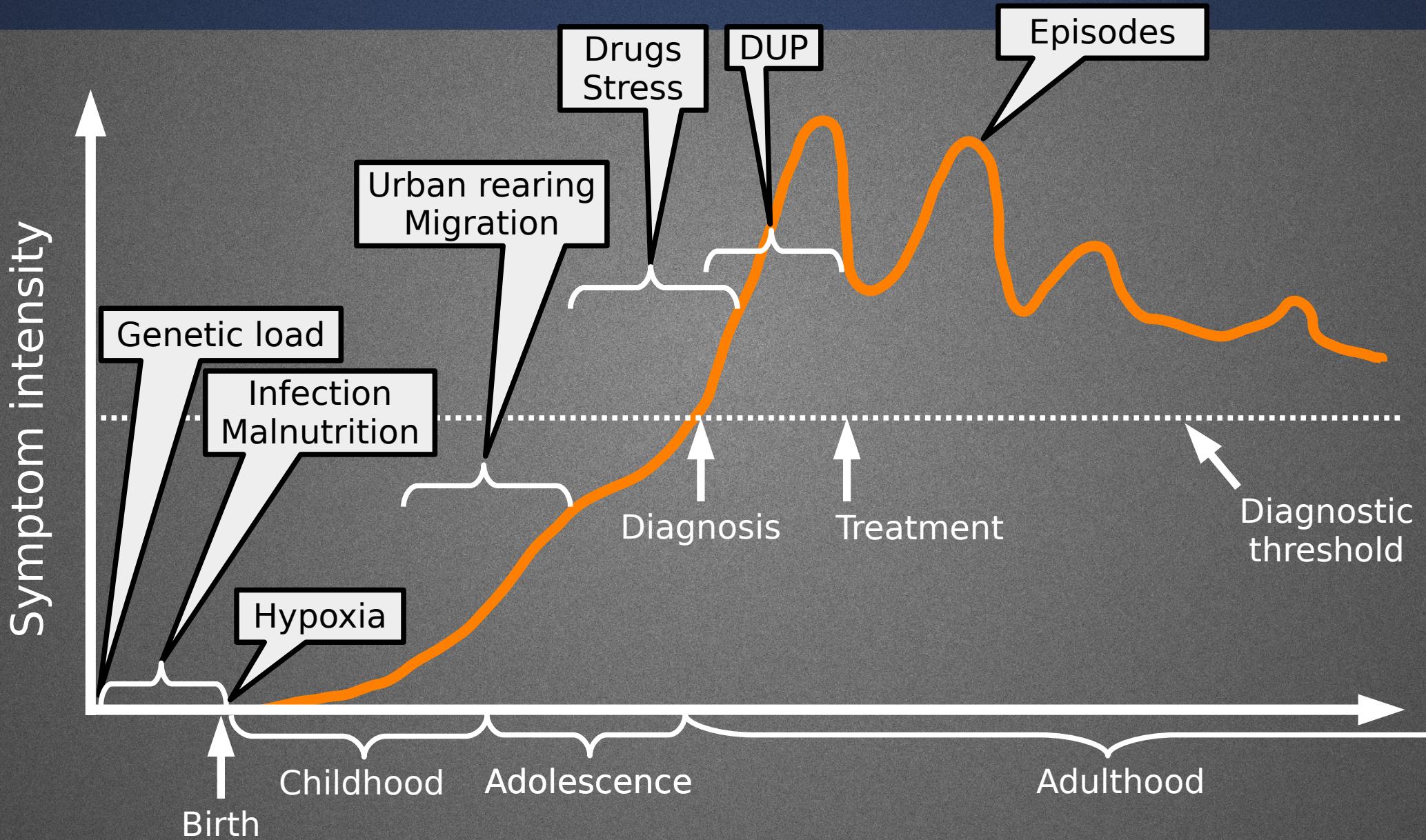
Trajectory



Trajectory



Risk Factors



Clinical Care



Schizophrenia



- Aripiprazole → no improvement
- Risperidone → improvement, but motor side-effects
- Clozapine → function improves much
- Discharge to live with parents after 3 month

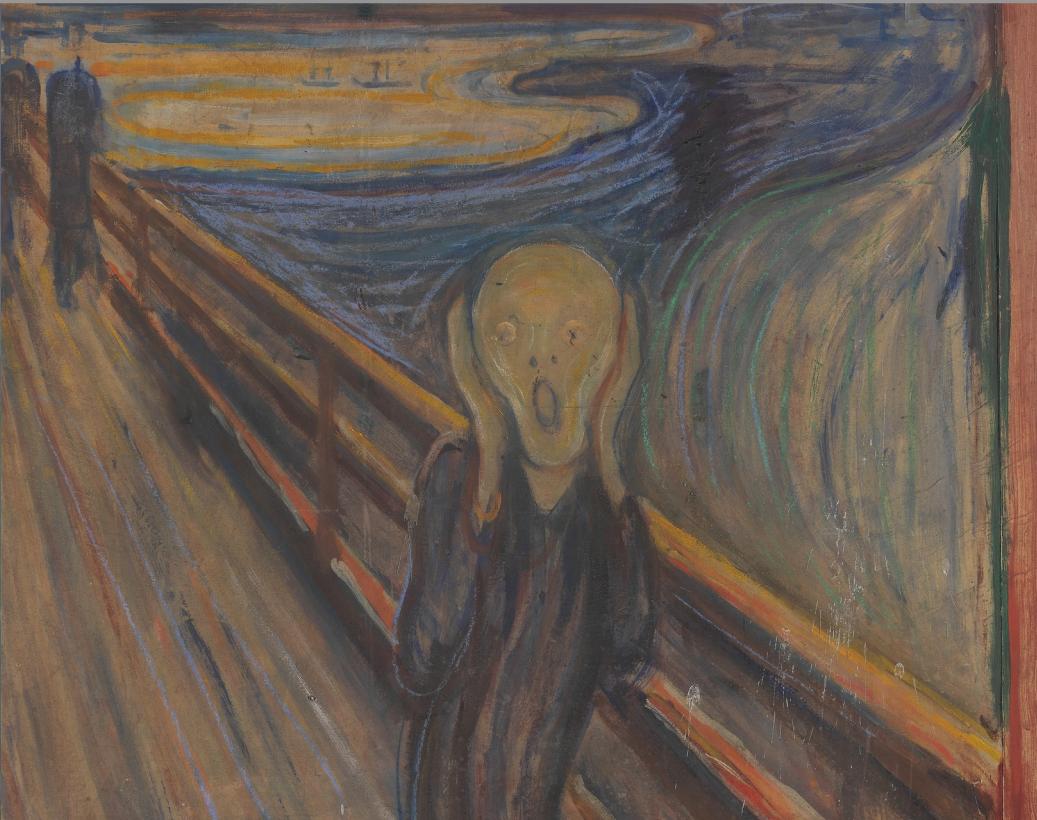
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Schizophrenia

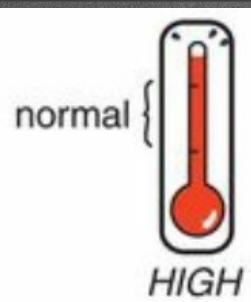
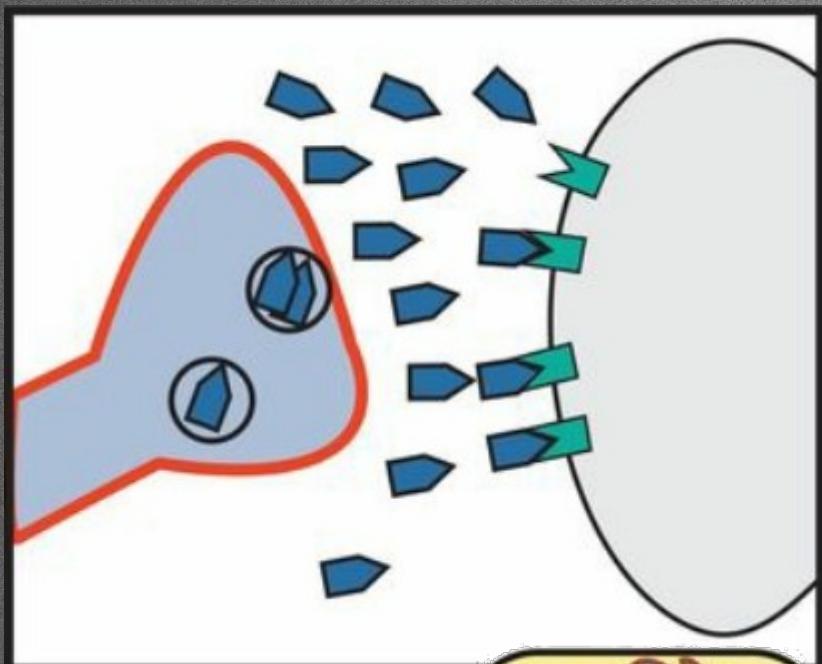
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→ Schizophrenia

- Risperidone → remission after 20d
- Day care clinic for 6wks
- Returns to uni after 9wks



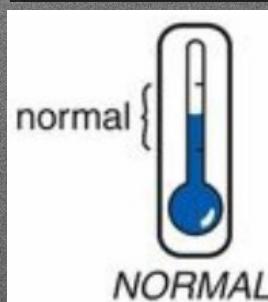
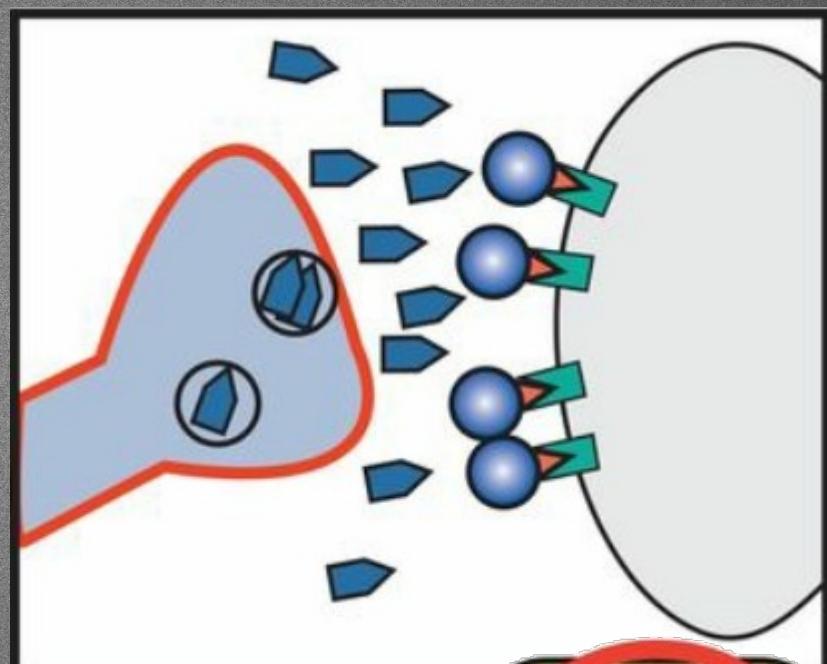
Antipsychotics

Mesolimbic Pathway
Untreated Schizophrenia



"hyperactive"
dopaminergic system

Mesolimbic Pathway
D2 Antagonist



"normalized"
dopaminergic system



Antipsychotics

Overall change in symptoms

SMD (95% CrI)

Clozapine -0.88 (-1.03 to -0.73)

Amisulpride -0.66 (-0.78 to -0.53)

Olanzapine -0.59 (-0.65 to -0.53)

Risperidone -0.56 (-0.63 to -0.50)

Paliperidone -0.50 (-0.60 to -0.39)

Zotepine -0.49 (-0.66 to -0.31)

Haloperidol -0.45 (-0.51 to -0.39)

Quetiapine -0.44 (-0.52 to -0.35)

Aripiprazole -0.43 (-0.52 to -0.34)

Sertindole -0.39 (-0.52 to -0.26)

Ziprasidone -0.39 (-0.49 to -0.30)

Chlorpromazine -0.38 (-0.54 to -0.23)

Asenapine -0.38 (-0.51 to -0.25)

Lurasidone -0.33 (-0.45 to -0.21)

Iloperidone -0.33 (-0.43 to -0.22)



Favours active drug

-0.5

0

(adapted from Leucht et al., 2013)

Antipsychotics

- 50% respond to 1st line treatment
- Response ≠ remission, recovery or cure
- No prediction which antipsychotic is effective → “*trial & error*”
- Discontinuation of treatment major problem
 - Side effects
 - Poor insight

Treatment strategies

- **Building trust, therapeutic relationship & working alliance**
- Early treatment with antipsychotics
- Management and prevention of side-effects

Treatment strategies

- Activation & social support
- Psychoeducation
- Low-threshold service
- Cognitive Behavioural Therapy

Clinical Care



National Schizophrenia & Psychosis Awareness Day
May 24th, 2018
www.earlypsychosisintervention.ca



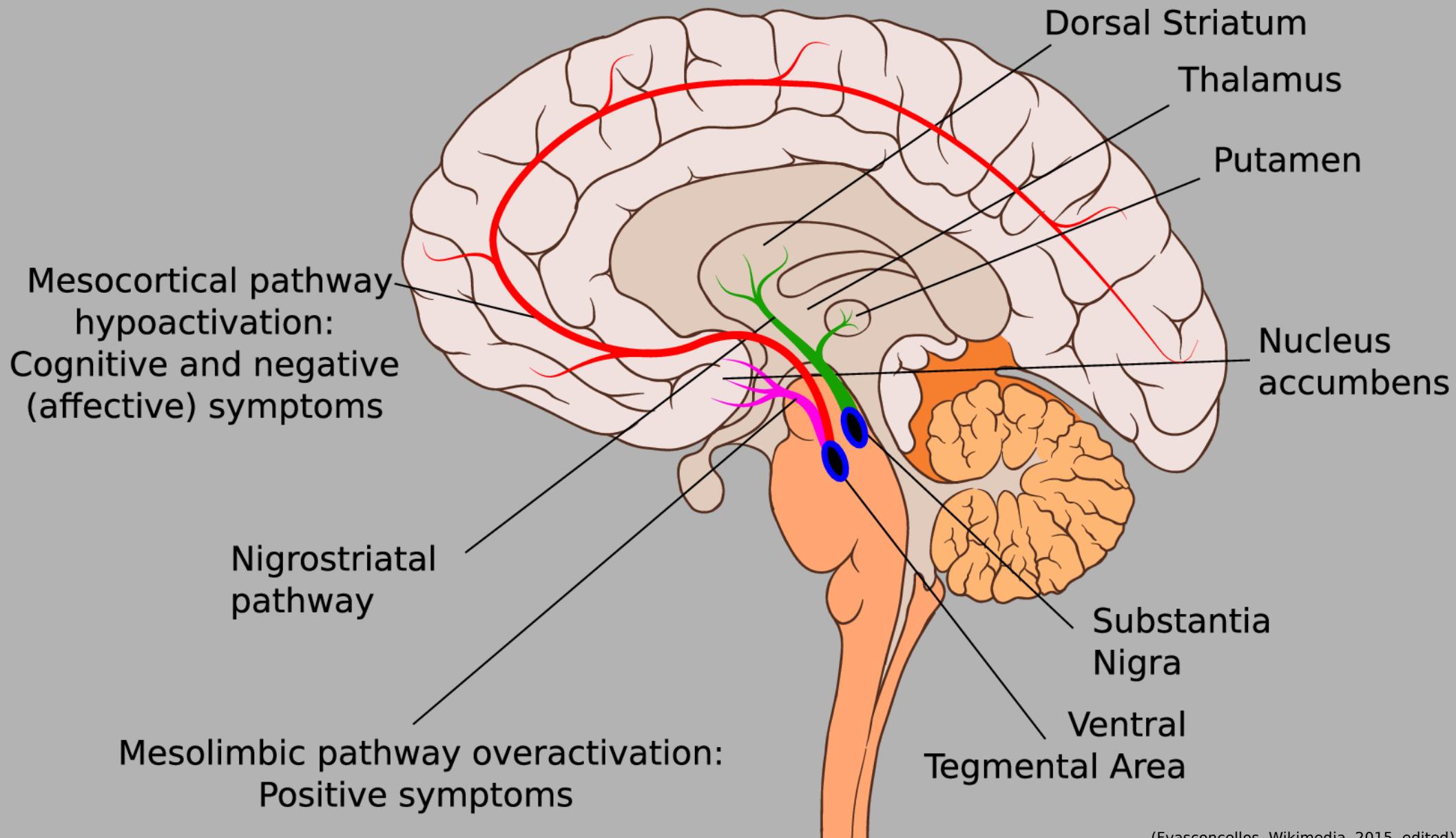
Pathophysiology



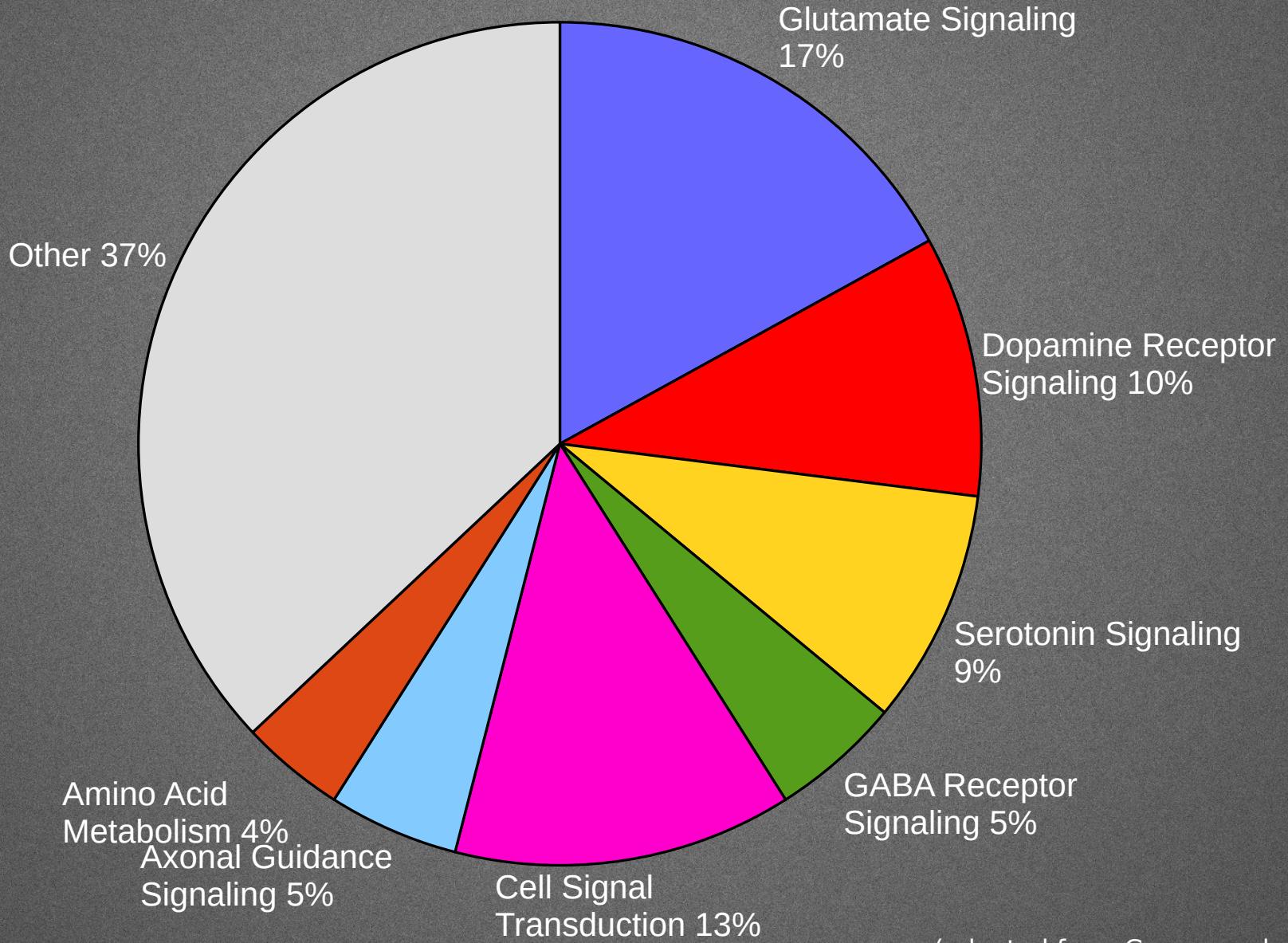
???

- Phentotypic expression
 - Continuum with affective disorders (Crow, 1986)
 - Failure of filter mechanisms (Hemsley and Zawada, 1976)
 - Internal monitoring deficiency (positive symptoms) & action initiation failure (negative symptoms) (Frith & Done, 1988)
 - Deficit vs. non-deficit SZ (Carpenter et al., 1988)
 - Aberrant salience syndrome (Kapur, 2003)
 - Dysconnection hypothesis (Stephan, 2009; Konrad & Winterer, 2008; dysmyelination: Segal et al., 2007)
 - Lateralization deficiency/language processing and distinction of thoughts and speech output (Crow, 2000)
- Pathophysiological
 - Abnormal transcallosal inter-hemispheric interaction → delusions of alien control (Nasralah, 1985)
 - Dysfunction of inhibitory circuits (reduced power in the gamma range bands) (Kwon, 1999)
 - Corollary discharge (Feinberg, 1978; Frith & Done, 1988)
 - Hyperdopaminergic models (Carlsson, 1977; Randrup & Munkvad, 1967, Snyder, 1976); prefrontal-limbic DA imbalance (Weinberger, 1987), phasic-tonic FA imbalance model (Grace, 1991); common pathway hypothesis (Seeman, 2010)
 - NMDAr-hypofunction (Olney & Farber, 1995)
 - Altered GABAergic transmission (altered neural synchrony/cognitive deficits; reductions in GABAergic neurons) (Benes & Berreta, 2001)
 - Cholinergic hypotheses (Tandon and Greden, 1989)
 - Inflammation – kynurenic acid as endogenous NMDAr antagonist (tryptophane metabolism)
- Pathogenesis
 - Early developmental models – disruptions intruterine/early postnatal (neuronal proliferation, migration, differentiation, elimination, neurogenesis) → impaired neuronal structure, abnormal brain maturation (Murray, 2002)
 - Late developmental models – deviations in later emerging processes such as synaptic/axonal pruning/neuronal apoptosis and/or myelination)
 - Neurodegeneration → atrophic processes
 - Acceleration of aging → cortico-limbic glutamatergic activity because of reduced inhibition by GABAergic interneurons → excitotoxicity
 - Disturbed excitatory/inhibitory balance as a
- Etiological
 - Polygenic/mutifactorial (Gottesman & Shields, 1967) → heritability, heterogeneity; copy number variations
 - Infectious diseases
 - Gene-environment interaction → two-hit-hypothesis (first genetic risk and early developmental alterations; then environmental factor) // epigenetic factors

Dopamine Hypothesis

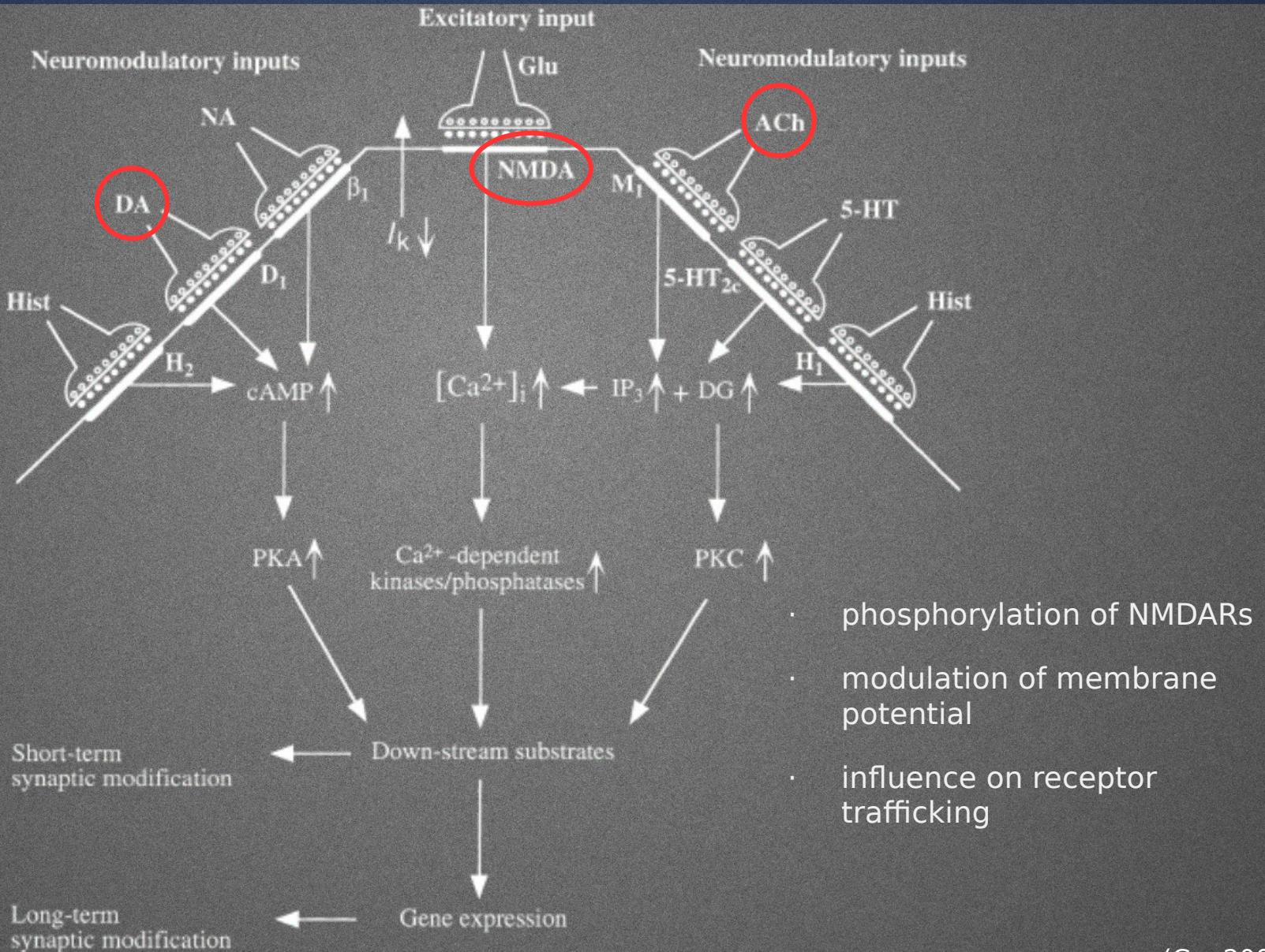


Candidate Genes



(adapted from Greenwood et al., 2012)

NMDAR × neuromodulator interactions



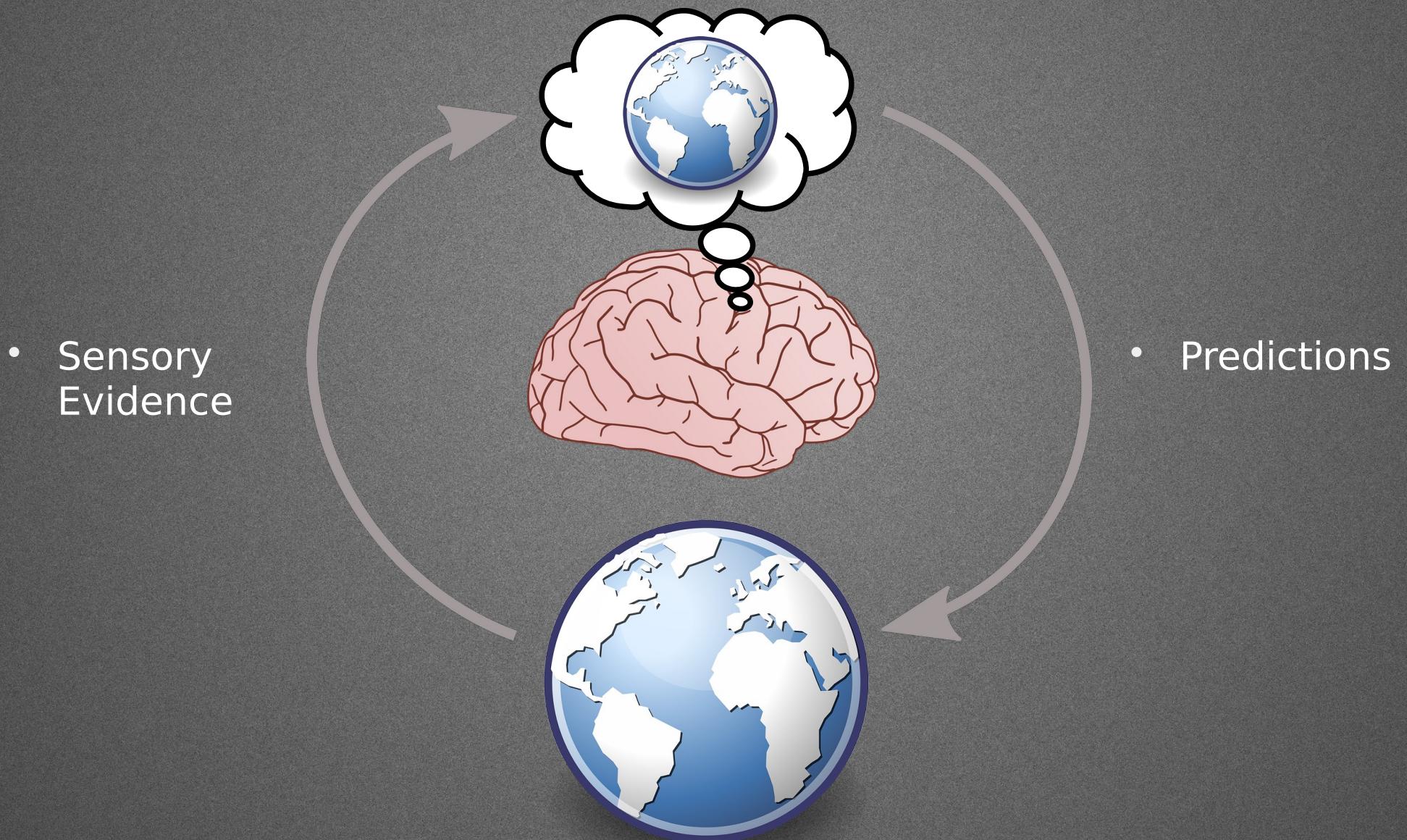
Dysconnection Hypothesis

- Integrates findings into computational framework
- Disturbed modulation of synaptic gain:
“Dysbalance” in the integration of *sensory evidence* and *predictions*

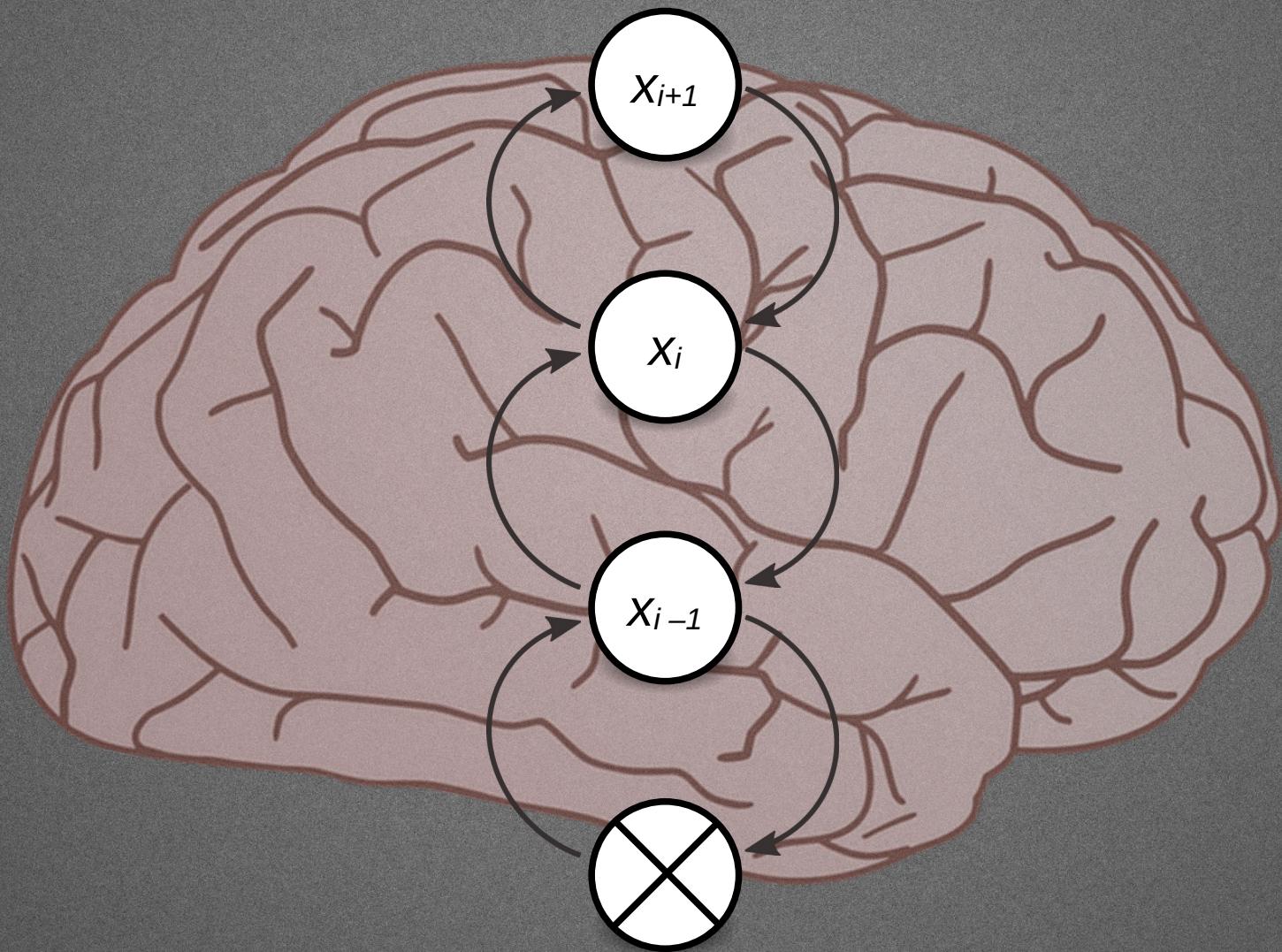
→ ...more of this later:

- Alex Hess, Chris Mathys, Albert Powers...

Bayesian Brain

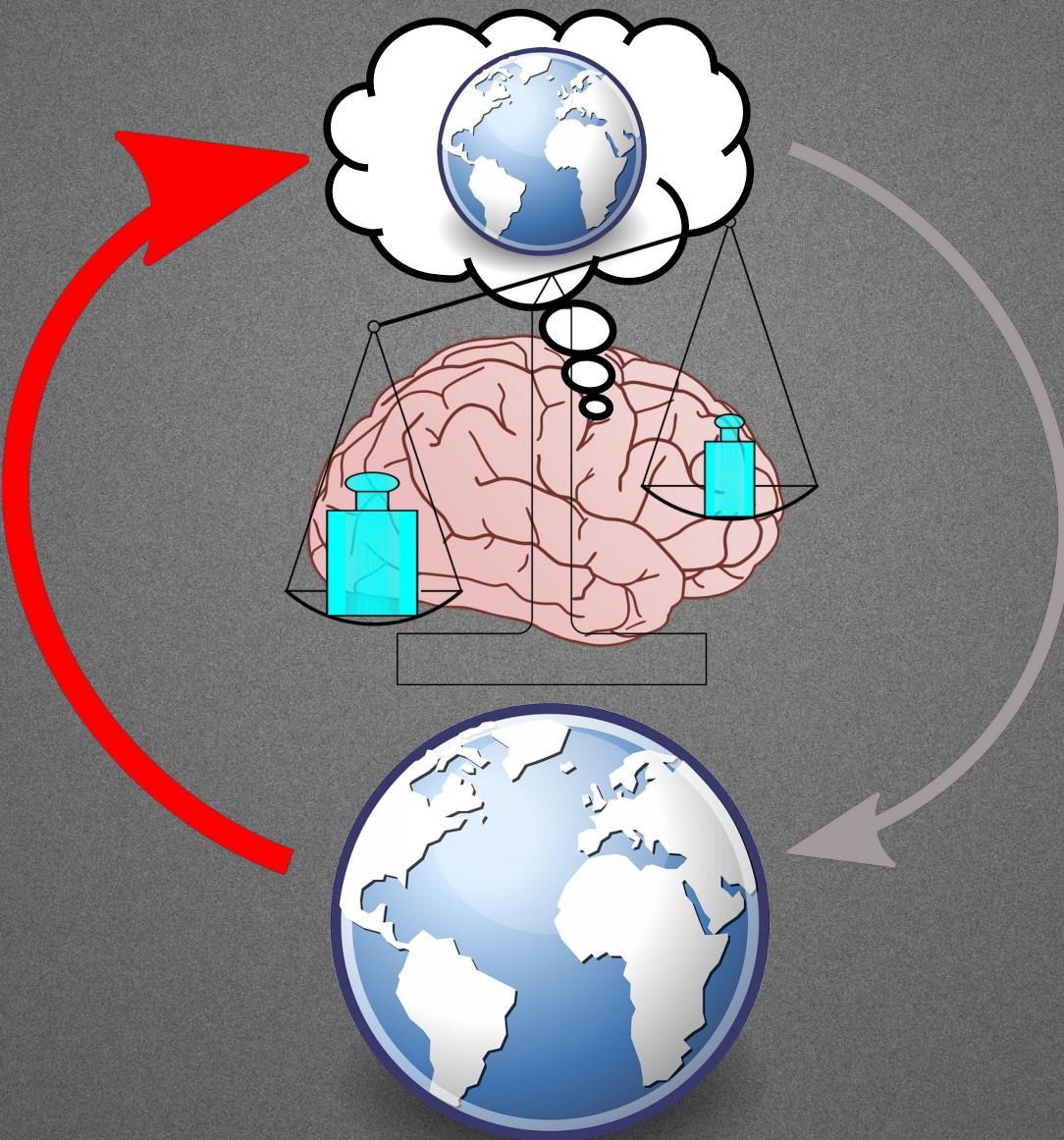


Predictive Coding



Bayesian Brain

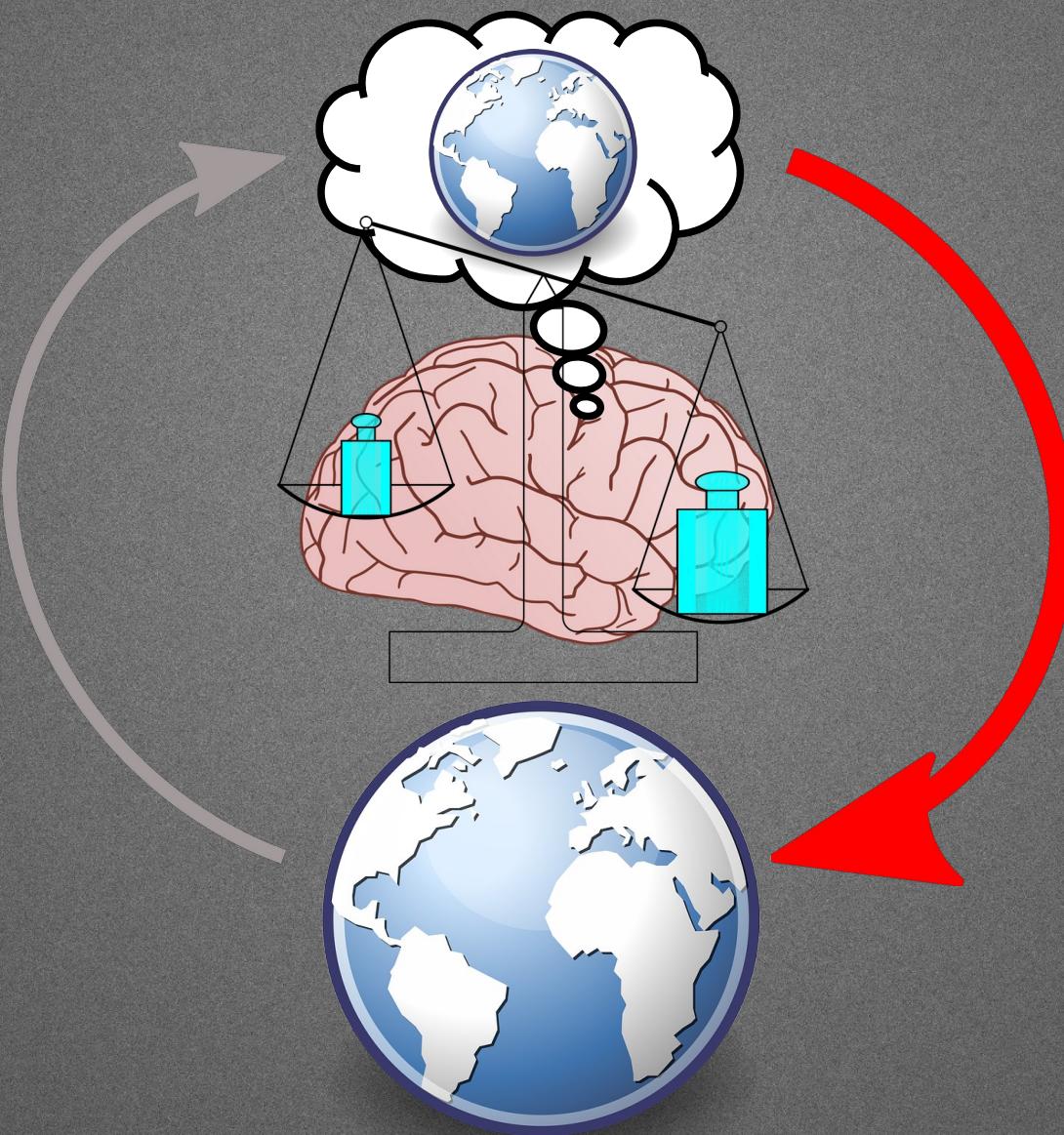
- Sensory Evidence



- Predictions

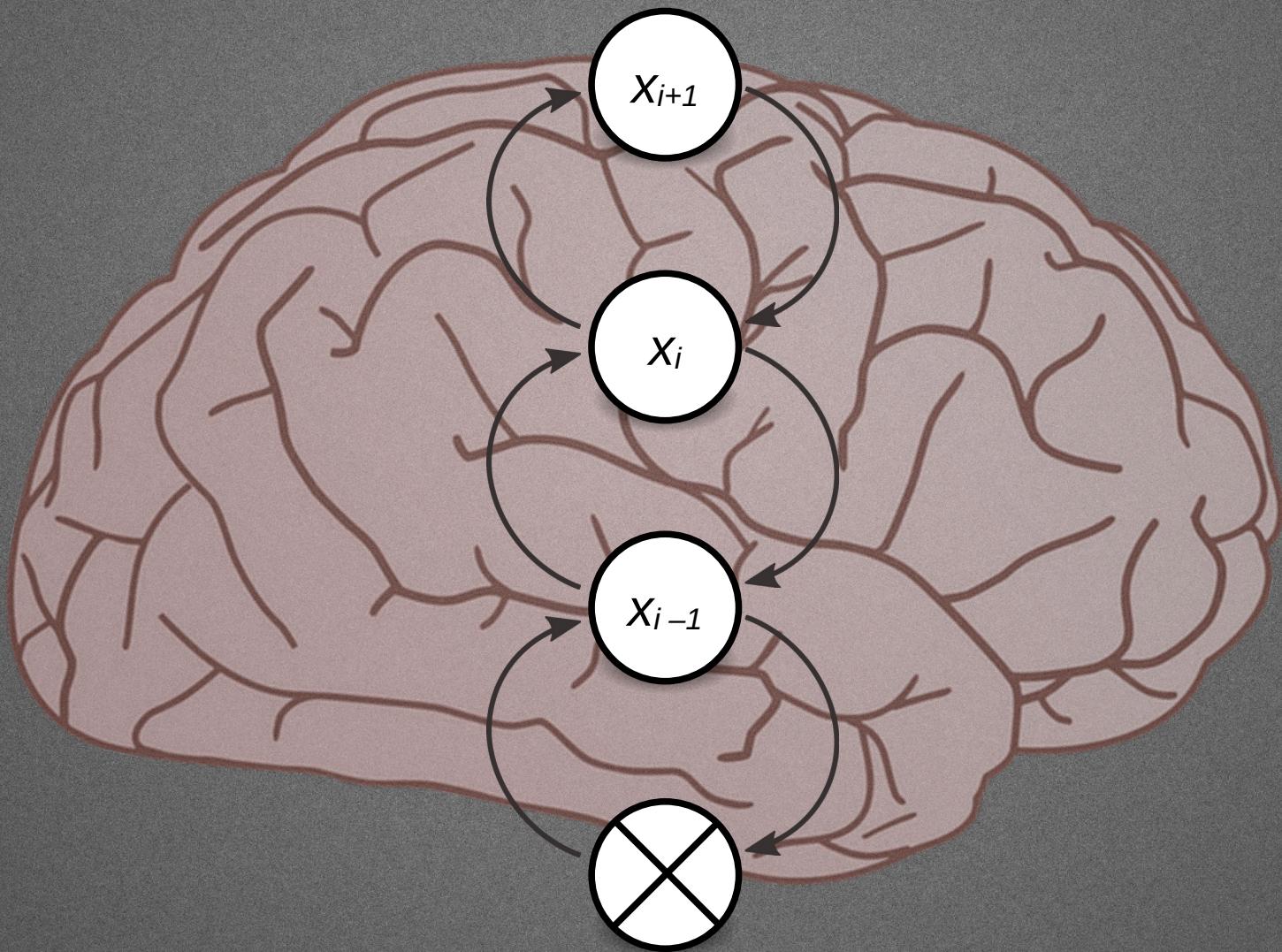
Bayesian Brain

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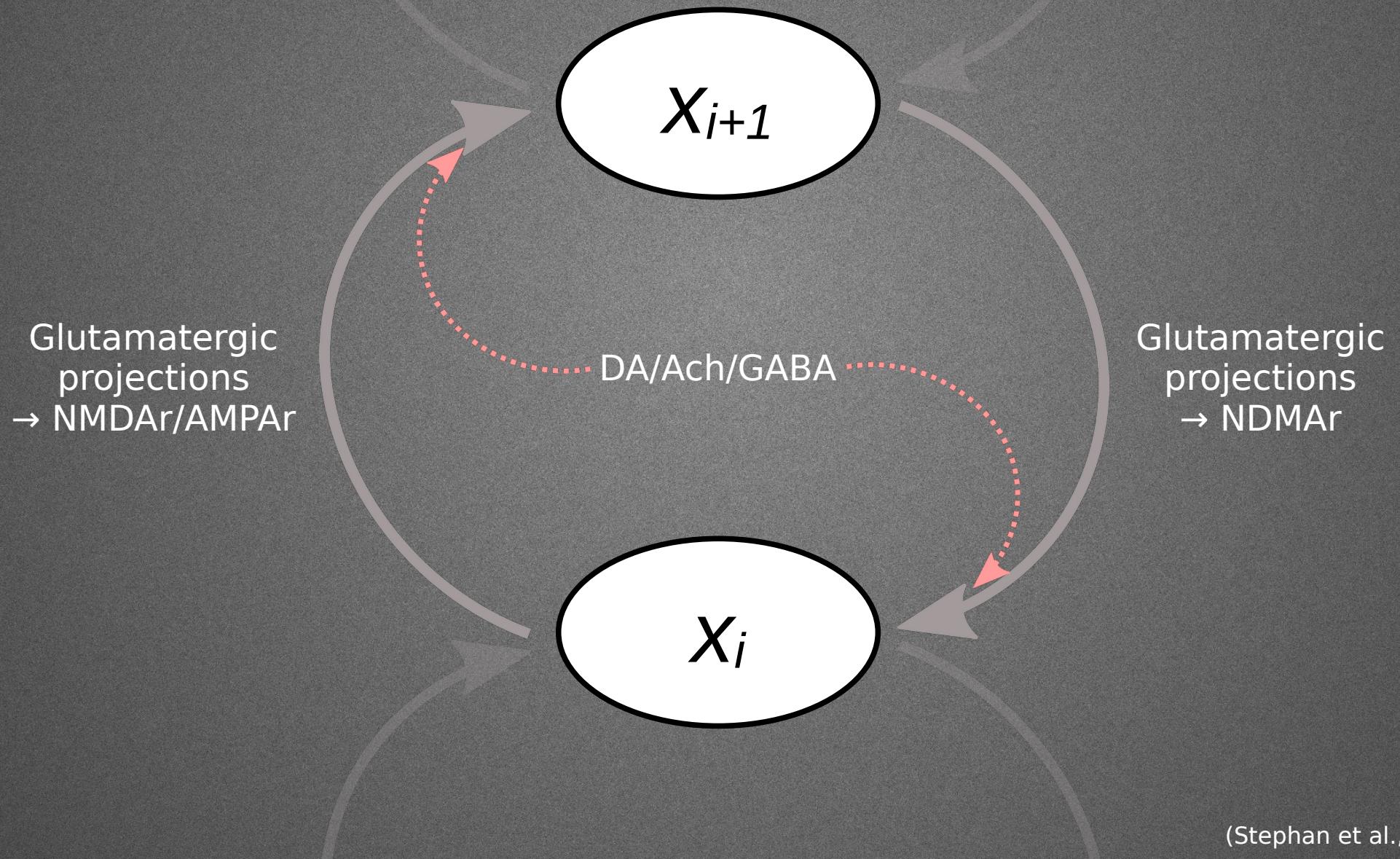


- Predictions

Predictive Coding



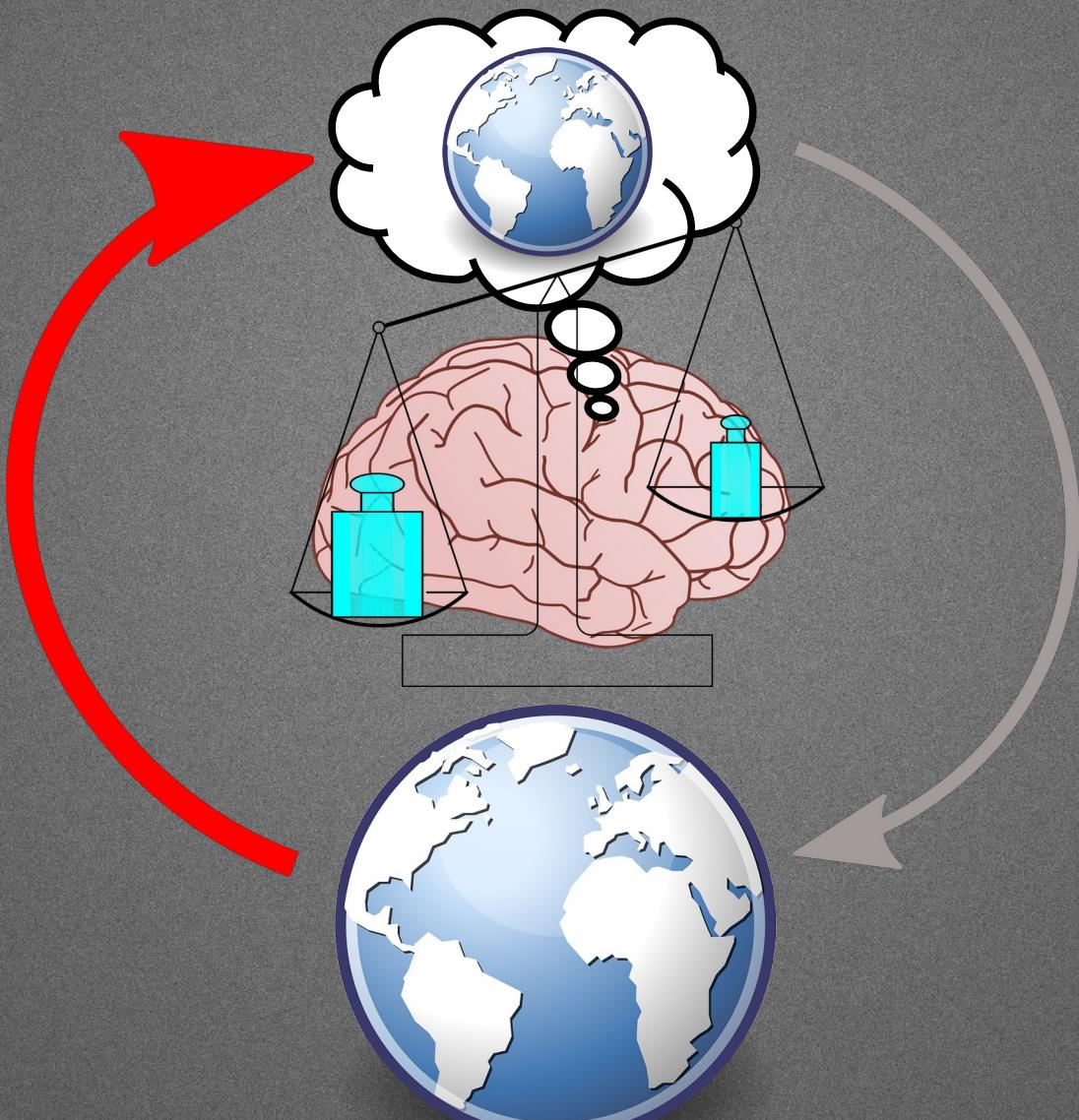
Dysconnectivity?



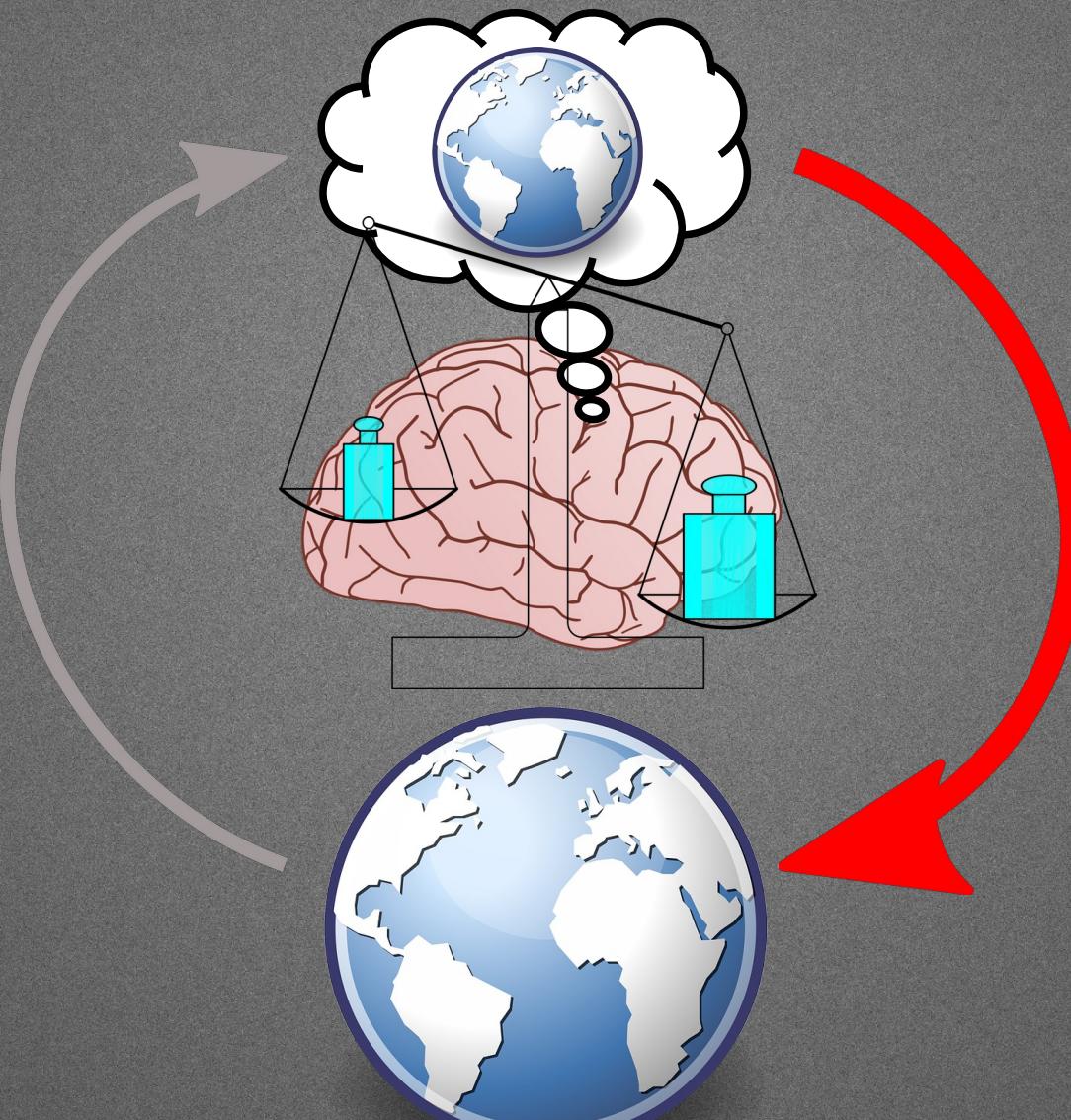
Bayesian Brain - Dysconnectivity

Trait phenomena

- ↓ susceptibility to illusions
- “Delusional mood”



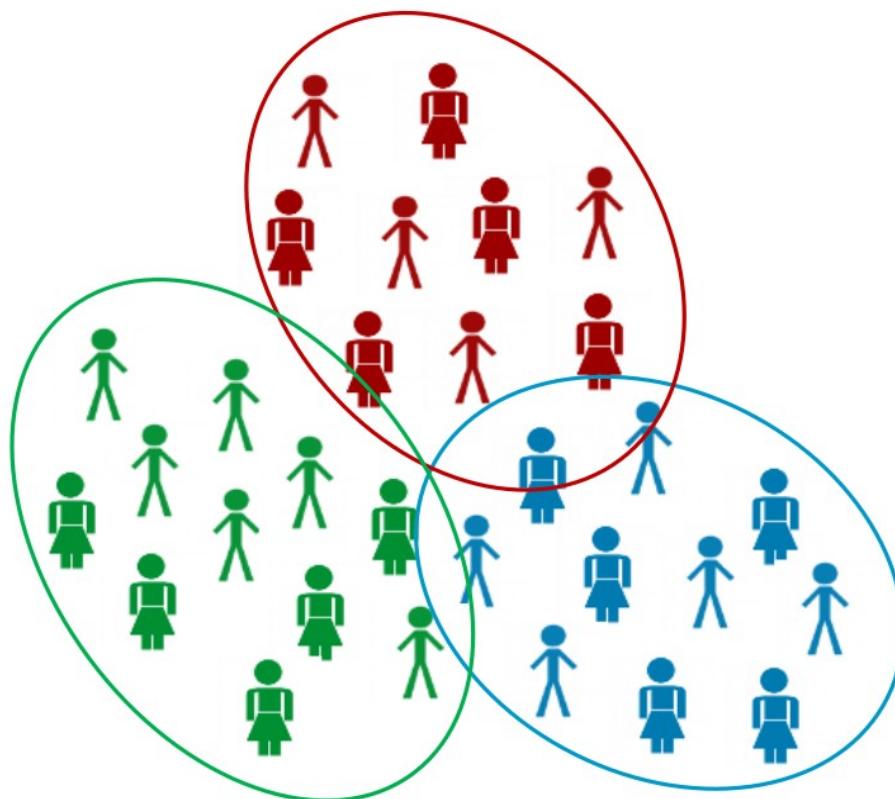
Bayesian Brain - Dysconnectivity



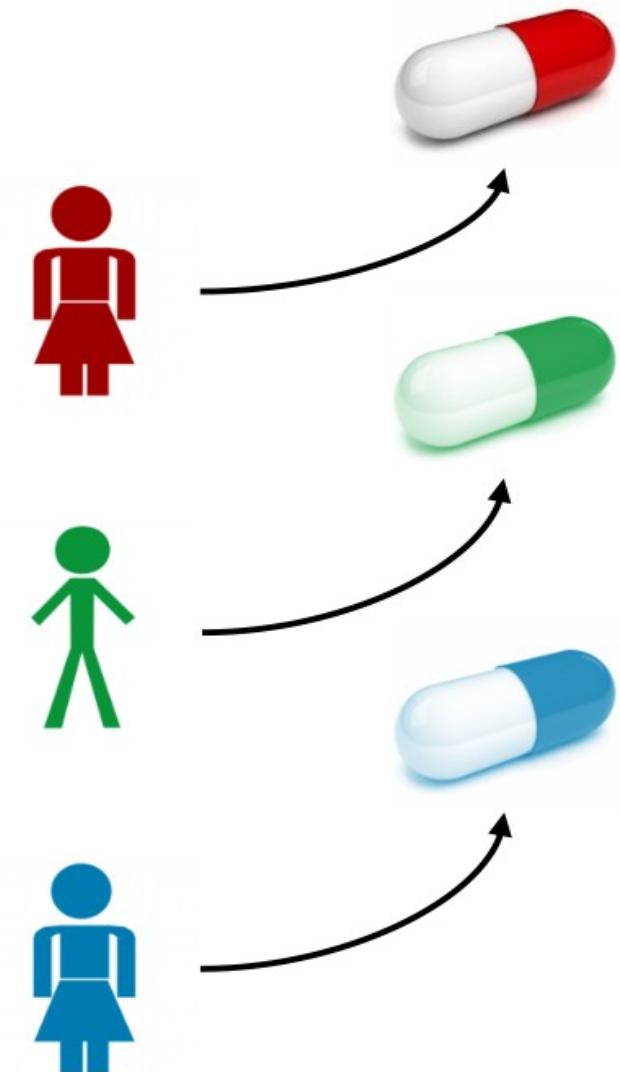
State phenomena

- Delusion
- Acoustic hallucinations

The goal of CP?



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



To summarize...

- SZ is a severe mental disorder
- Heterogeneous
- Functional impairment
- Antipsychotics are effective, but
 - focus on recovery!
- Pathophysiology?

“Lost Years” by Bas Labruyère:

<https://vimeo.com/23611157>



Lost Years

vor 9 Jahre | Mehr



Bas Labruyère

PLUS + Folgen

▷ 7.721 ❤ 7 💼 3 💬 0

Mehr von Bas Labruyère

Nächstes Video automatisch abspielen



Lost Years

Bas Labruyère

Labruyère, B. (2011, May 11). Lost Years. <https://vimeo.com/23611157>

Questions?



Translational Neuromodeling Unit



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Eidgenössische Technische Hochschule Zürich
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