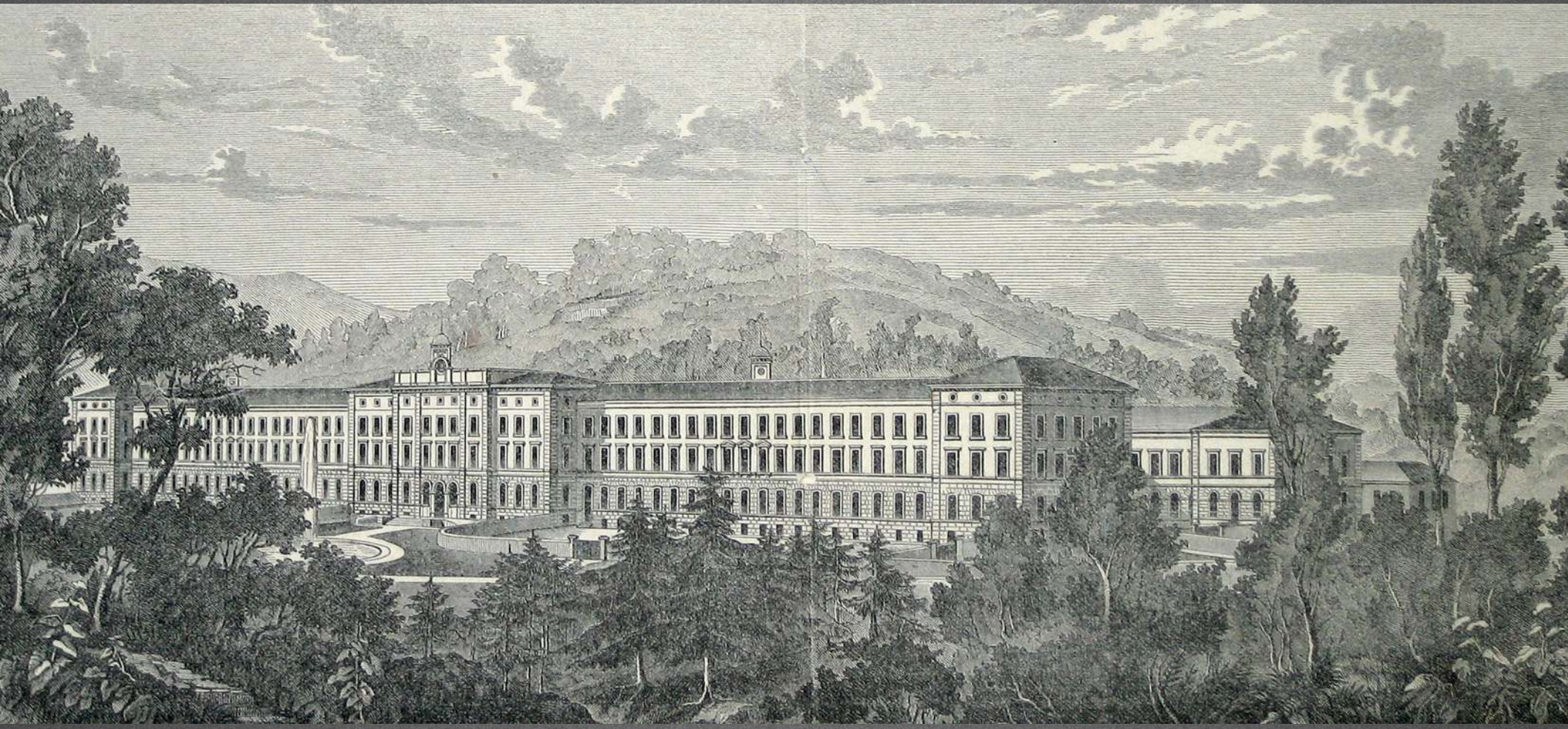
Schizophrenia
(for non-clinicians)

2021 Computational Psychiatry Course

Translational Neuromodeling Unit
Universität Zürich[UZH]
ETH Eidgenössische Technische Hochschule Zürich Swiss Federal Institute of Technology Zurich
universitäre altersmedizin felix platter

Jakob Siemerkus
University of Zurich & ETH Zurich // Universitäre Altersmedizin Felix Platter

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

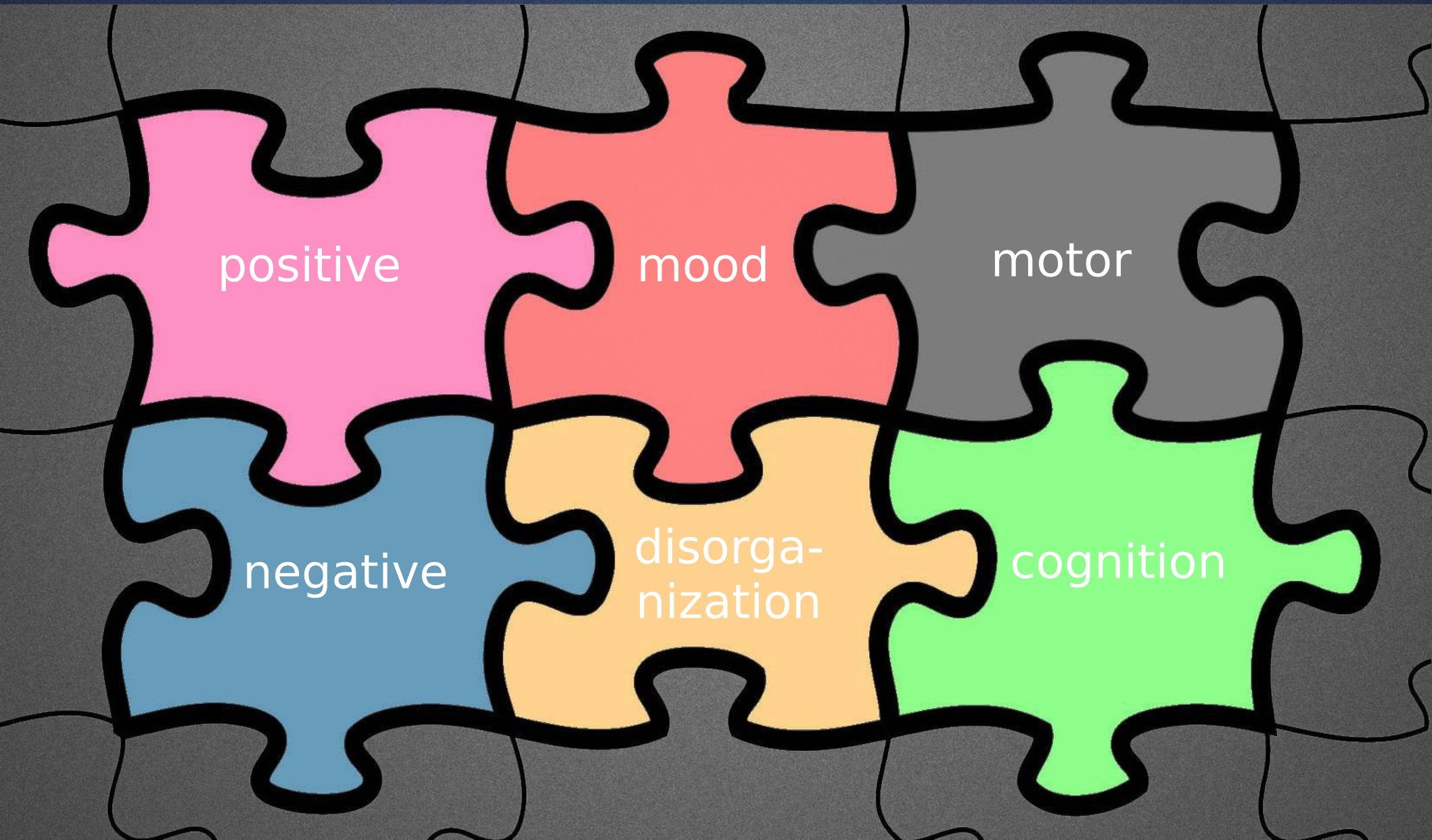
- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
- Apathy
- Slowed down
- Lost her job months ago

Schizophrenia

- 19yo student of physics
- Neighbor:
  - Spying on him
  - Plotting to murder him
  - CIA-affiliate
  - Hears N.’s voice
  - N. can read his mind
  - Started six weeks ago
- Did not attend classes for ½ year

Schizophrenia(s?)

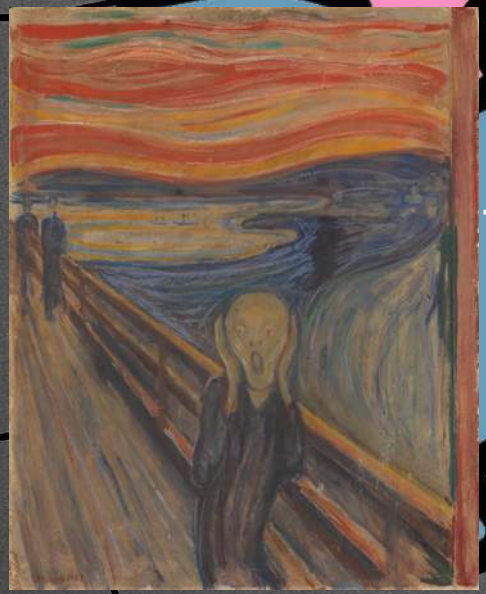
Main Symptom Categories



Main Symptom Categories

positive

- “failure in reality testing”
- delusion
- hallucination
- ego-boundary distortion



tive

disorga-
nization

cognition

Main Symptom Categories

ive

negative

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

Main Symptom Categories

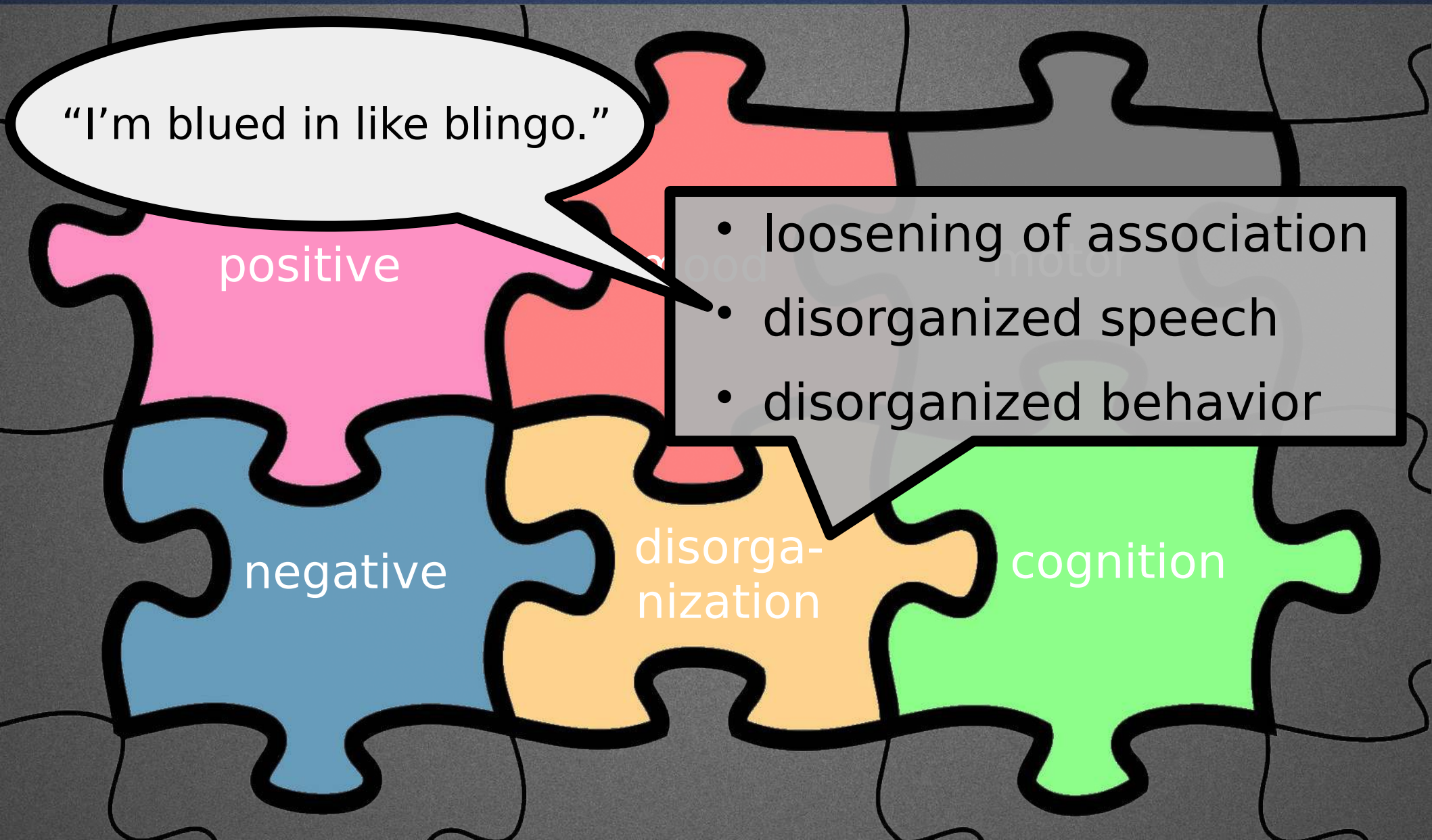
(Netherlands, Wikimedia, 2010)

mood

mot

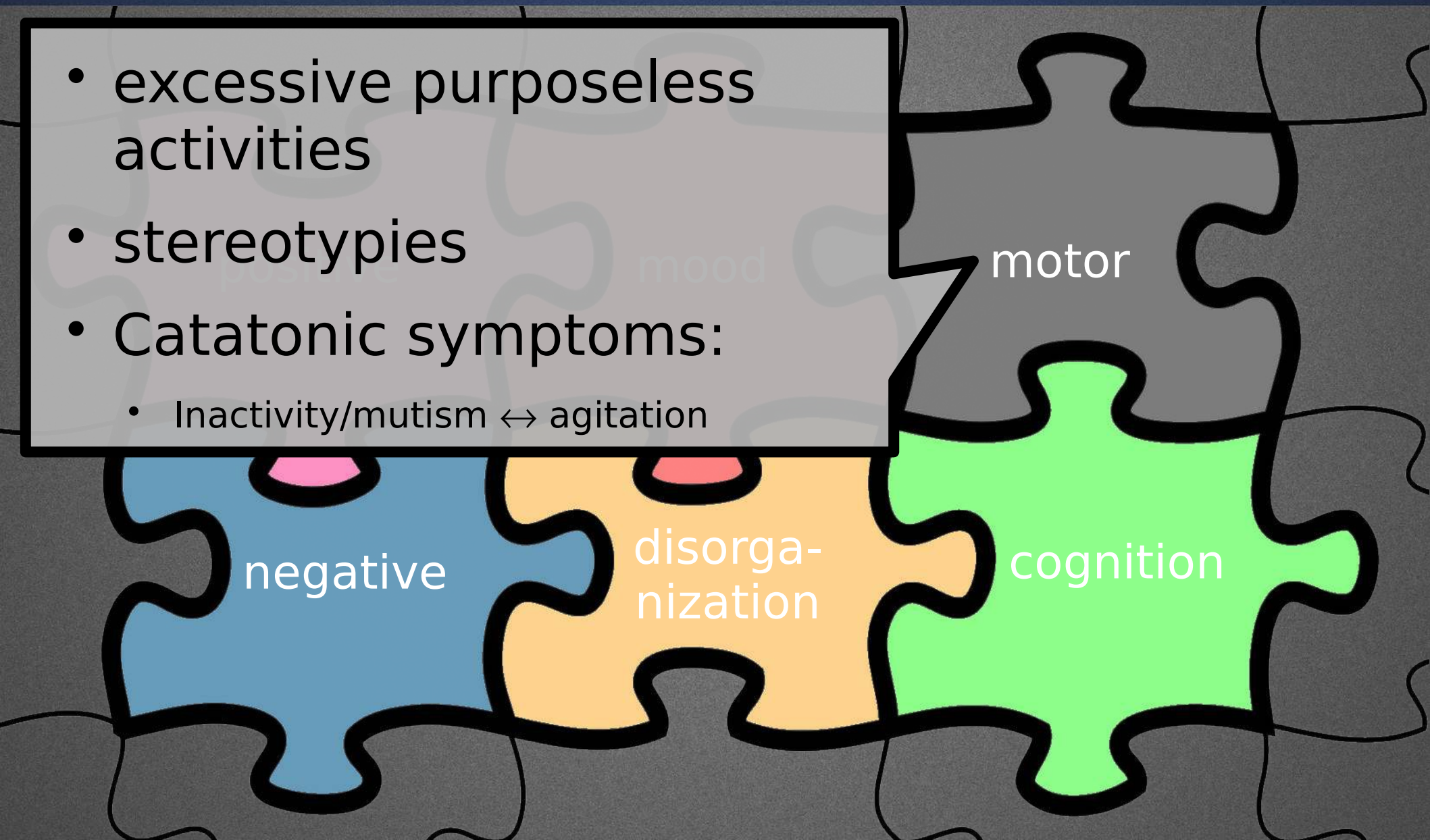
- overlap with negative symptoms
- anxiety, emotional arousal, and depression very frequent

Main Symptom Categories



Main Symptom Categories

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



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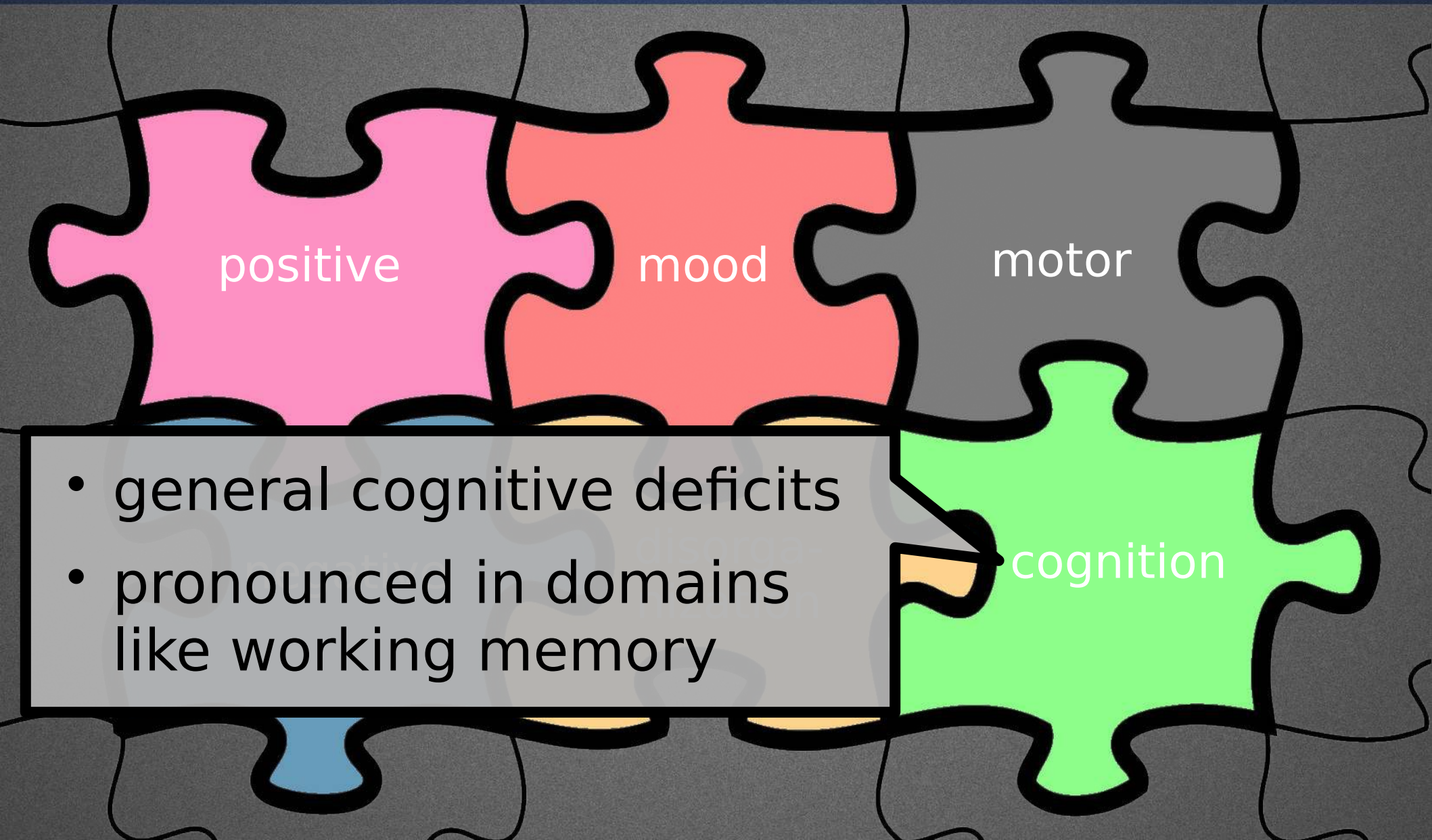

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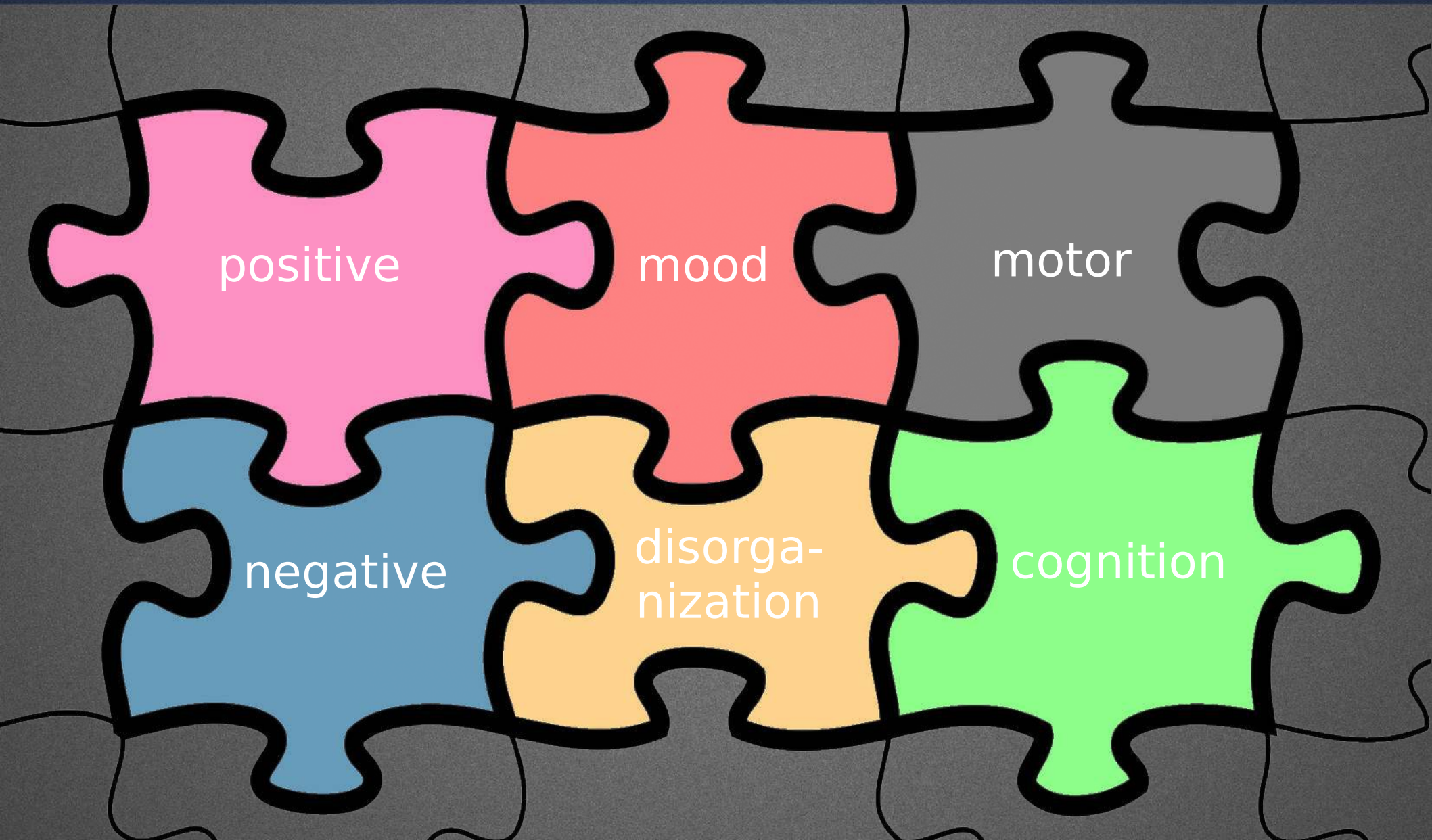

Diagnostic Criteria

DSM 5	
MAIN CRITERIA	• ≥ 2 symptom (categories) present • AND ≥ 1 core symptom • no other cause
TIME	• ≥ 1 month main criteria • ≥ 6 months symptoms/functional impairment
SYMPTOMS	• (core) delusions • (core) hallucinations • (core) disorganized speech • negative symptoms (especially avolition, diminished emotional expression) • disorganized or catatonic behaviour

(APA, 2013)

Schizophrenia

- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
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- 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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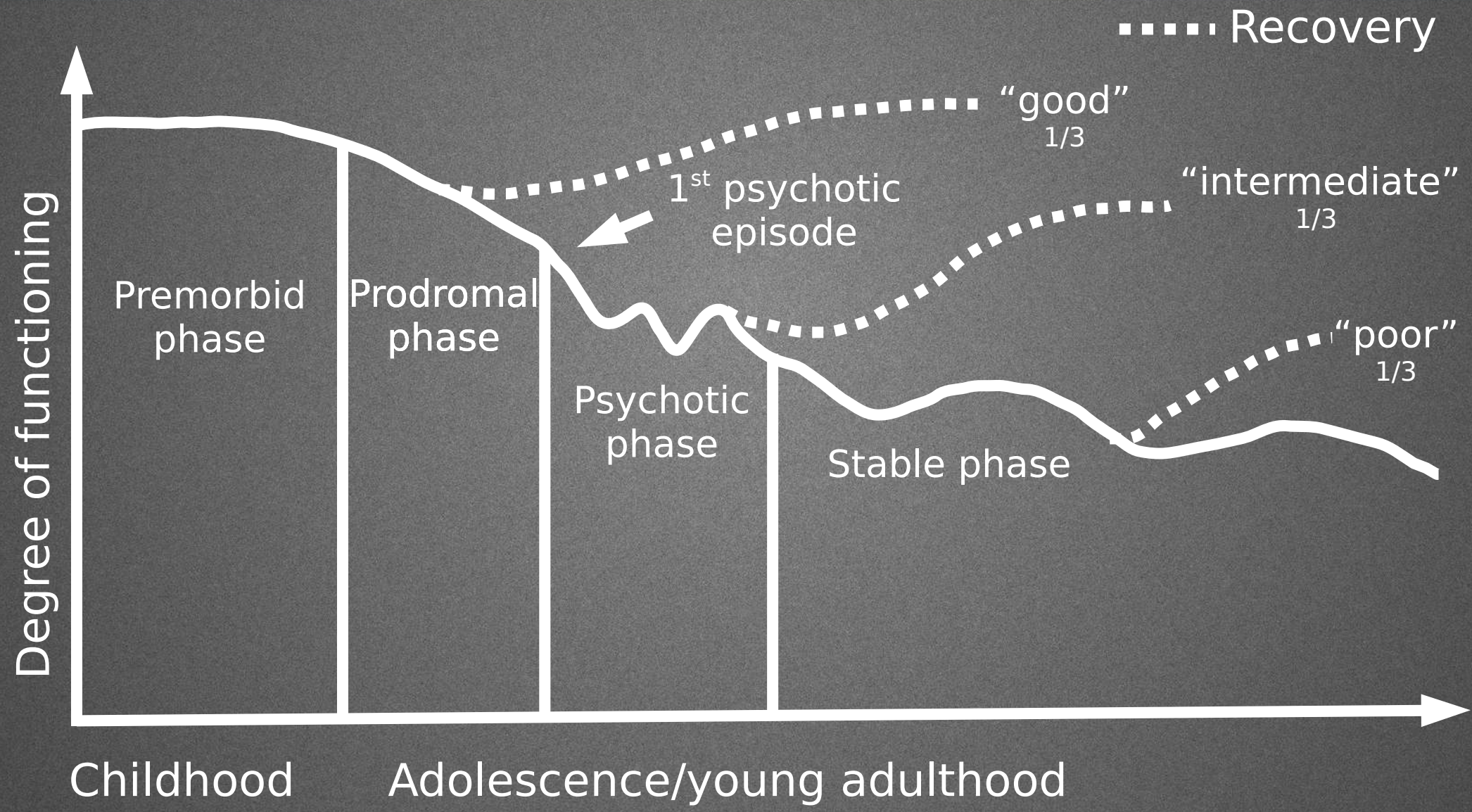
(APA, 2013)

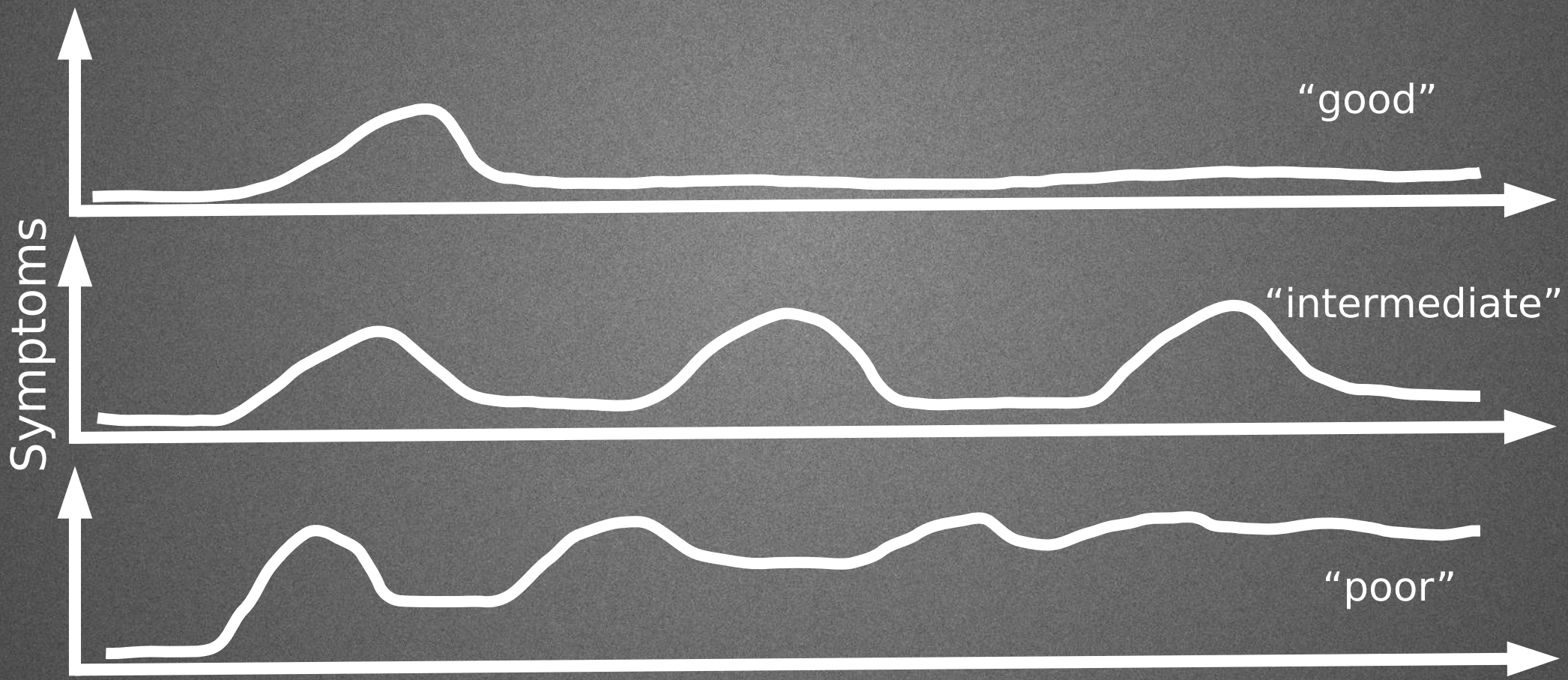
Trajectory
Risk factors
Outcome

Trajectory

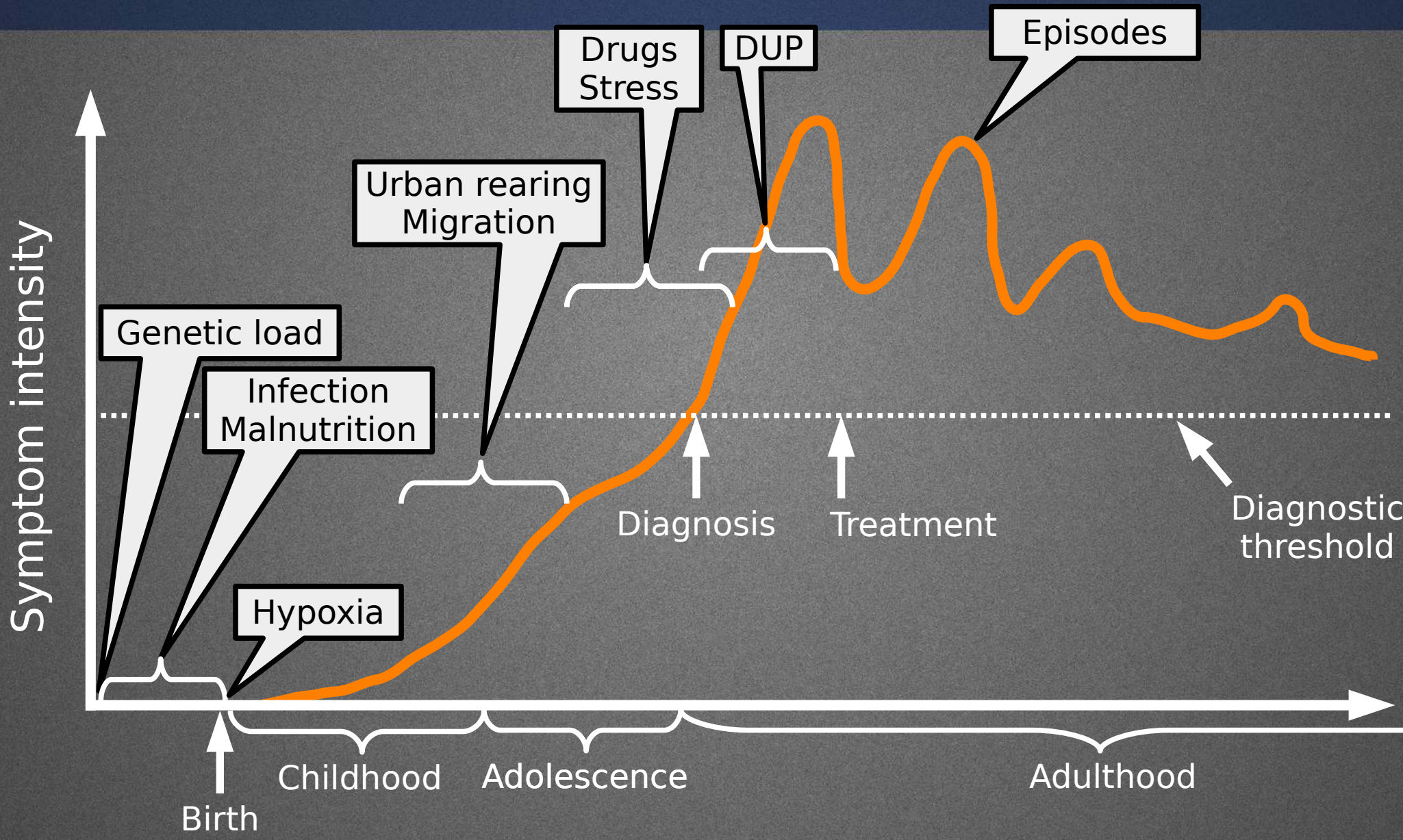


(modified from Tandon et al., 2009)

Trajectory



Risk Factors



(adapted from Millan et al., 2016)

Clinical Care

Schizophrenia

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

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

- Exam&lab results ok
- Starts talking, uses “blue” in many contexts like “I’m blued in like blingo.”

→Schizophrenia

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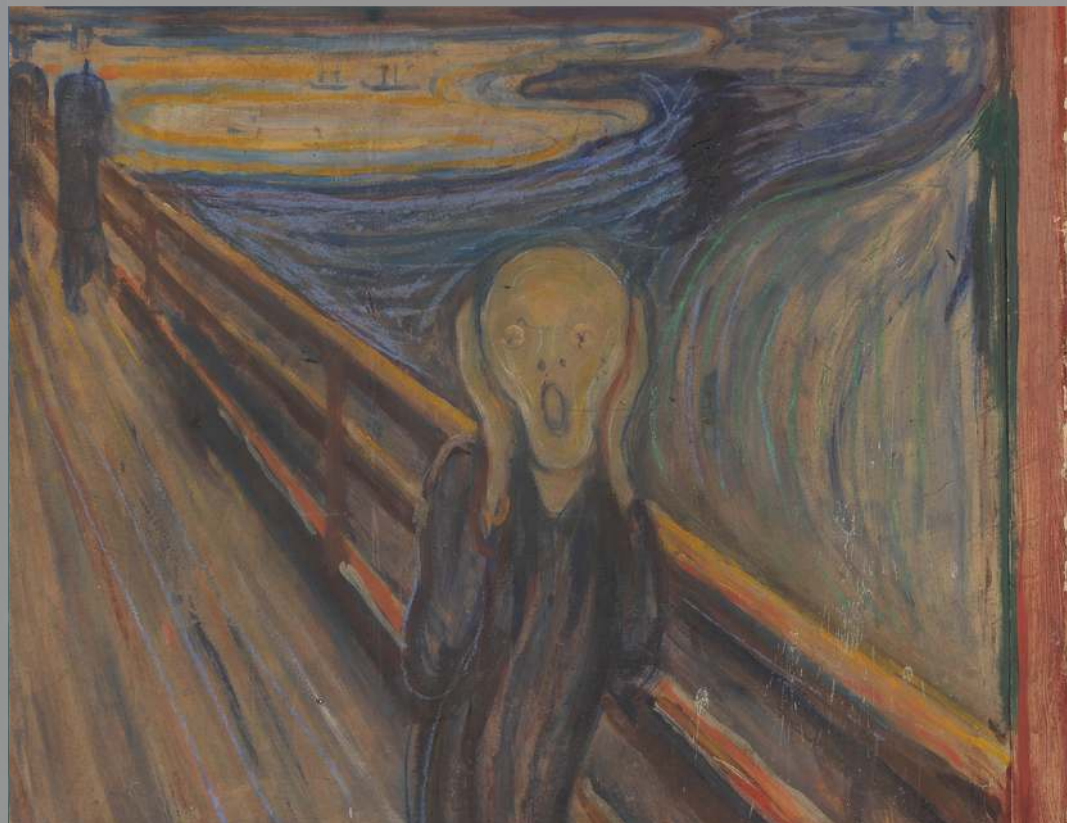
- Exam, lab & MRI results ok

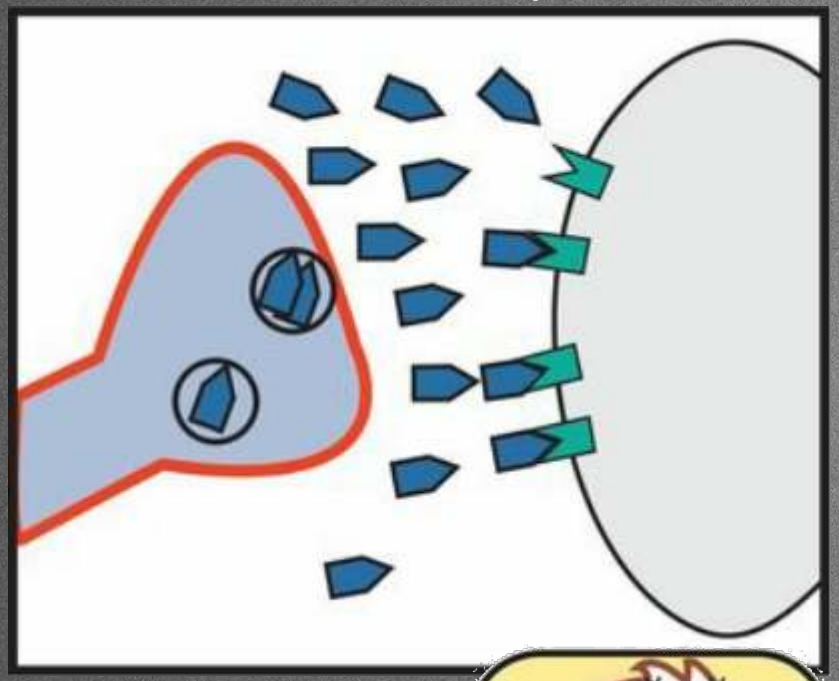
  → Schizophrenia

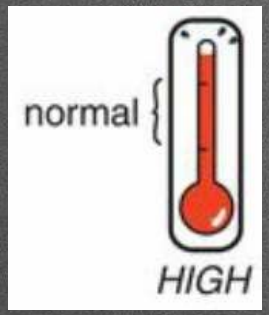
- Risperidone → remission after 20d
- Day care clinic for 6wks
- Returns to uni after 9wks

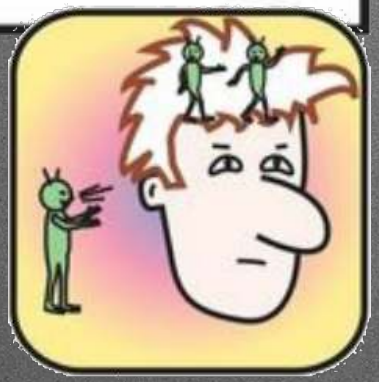


Antipsychotics

Mesolimbic Pathway
Untreated Schizophrenia

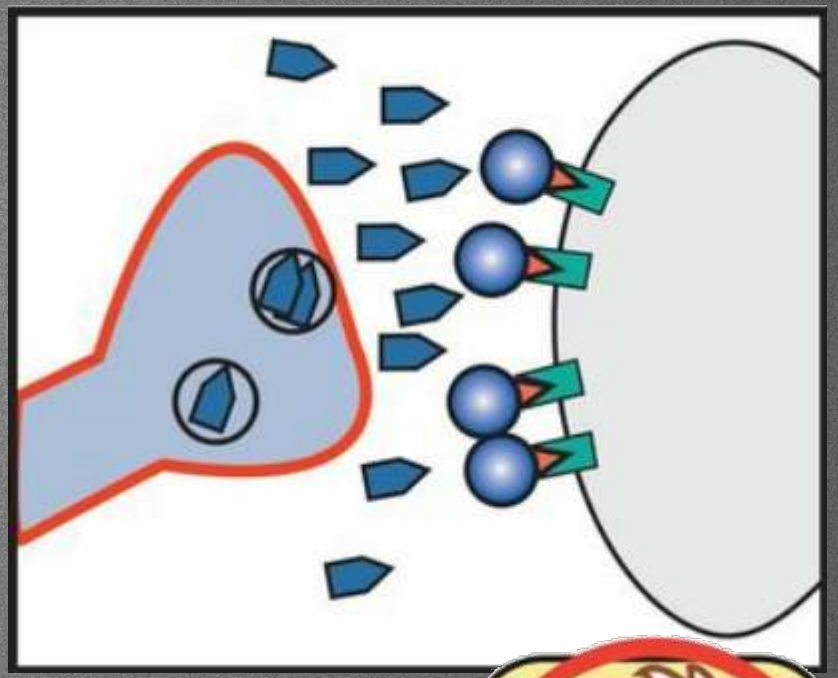


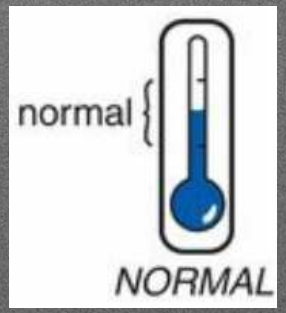




"hyperactive"
dopaminergic system

Mesolimbic Pathway
D2 Antagonist

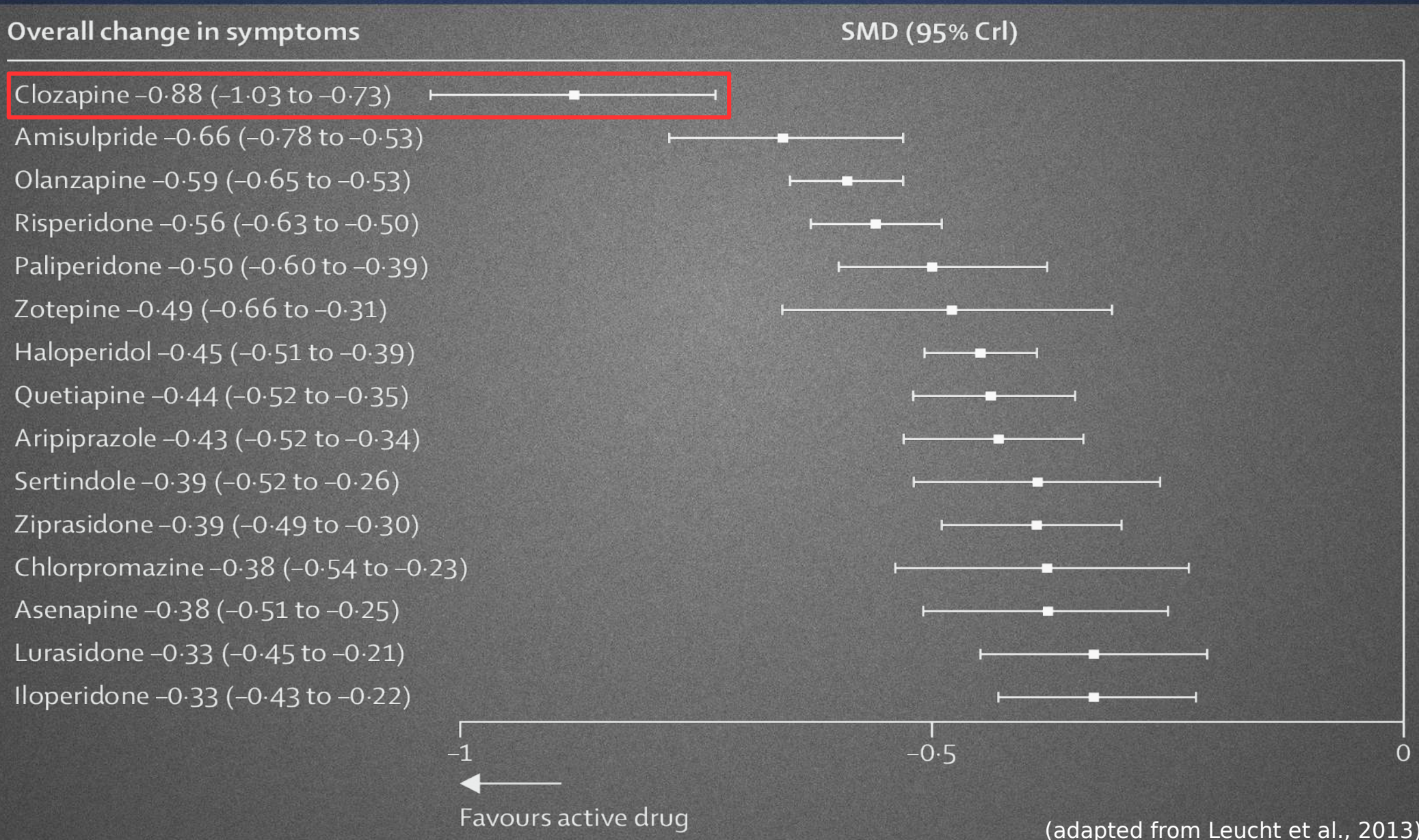




"normalized"
dopaminergic system

(Stahl, 2013)

Antipsychotics



(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

(SGPP, 2016; DGPPN, 2012; NICE, 2014; APA, 2006)

Treatment strategies

- Activation & social support
- Psychoeducation
- Low-threshold service
- Cognitive Behavioural Therapy
- Treatment resistance → Clozapine
- Antidepressant as co-medication

(SGPP, 2016; DGPPN, 2012; NICE, 2014; APA, 2006)

Clinical Care

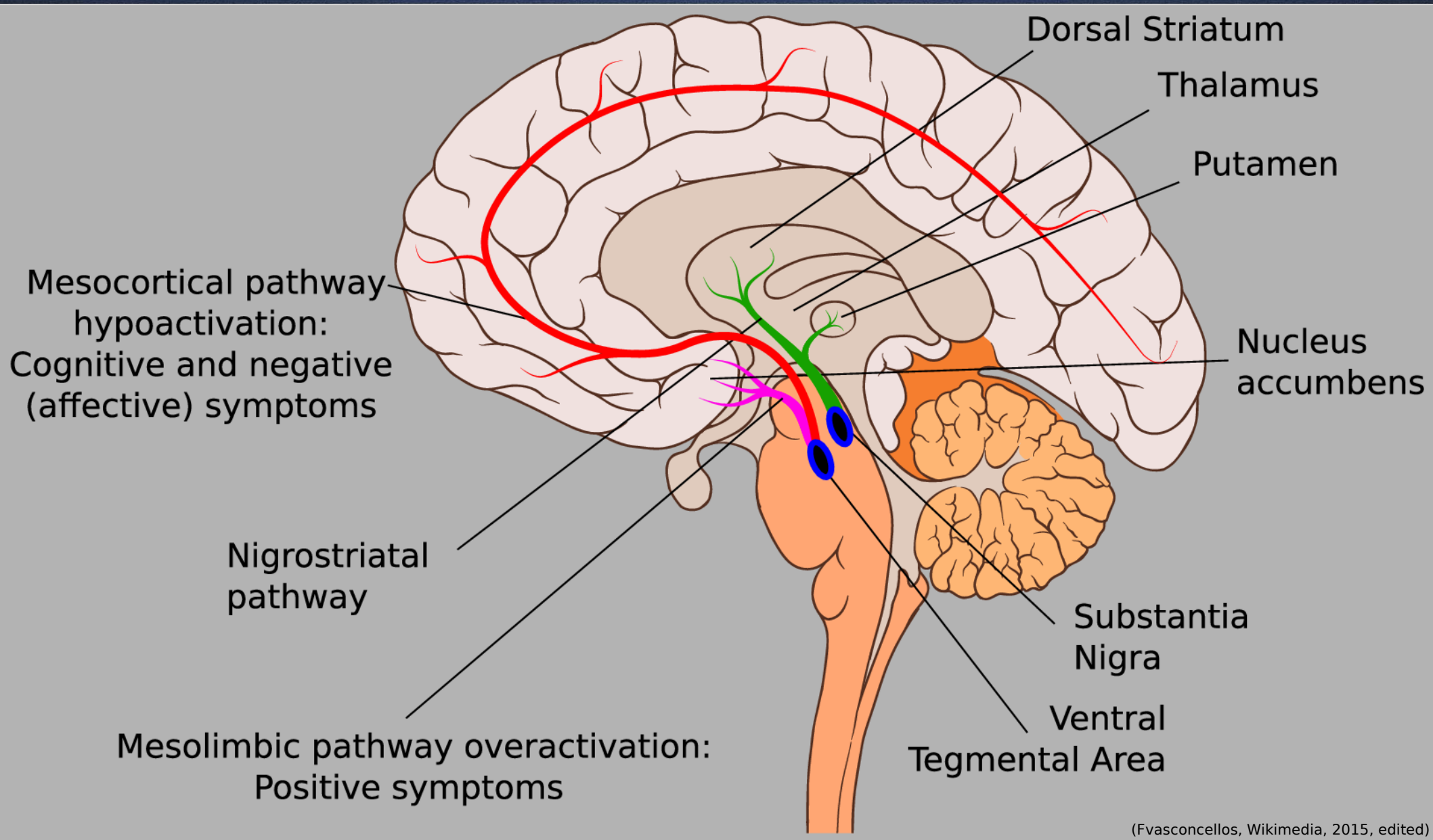
(Schizophrenia Canada, 2018)

Pathophysiology

???

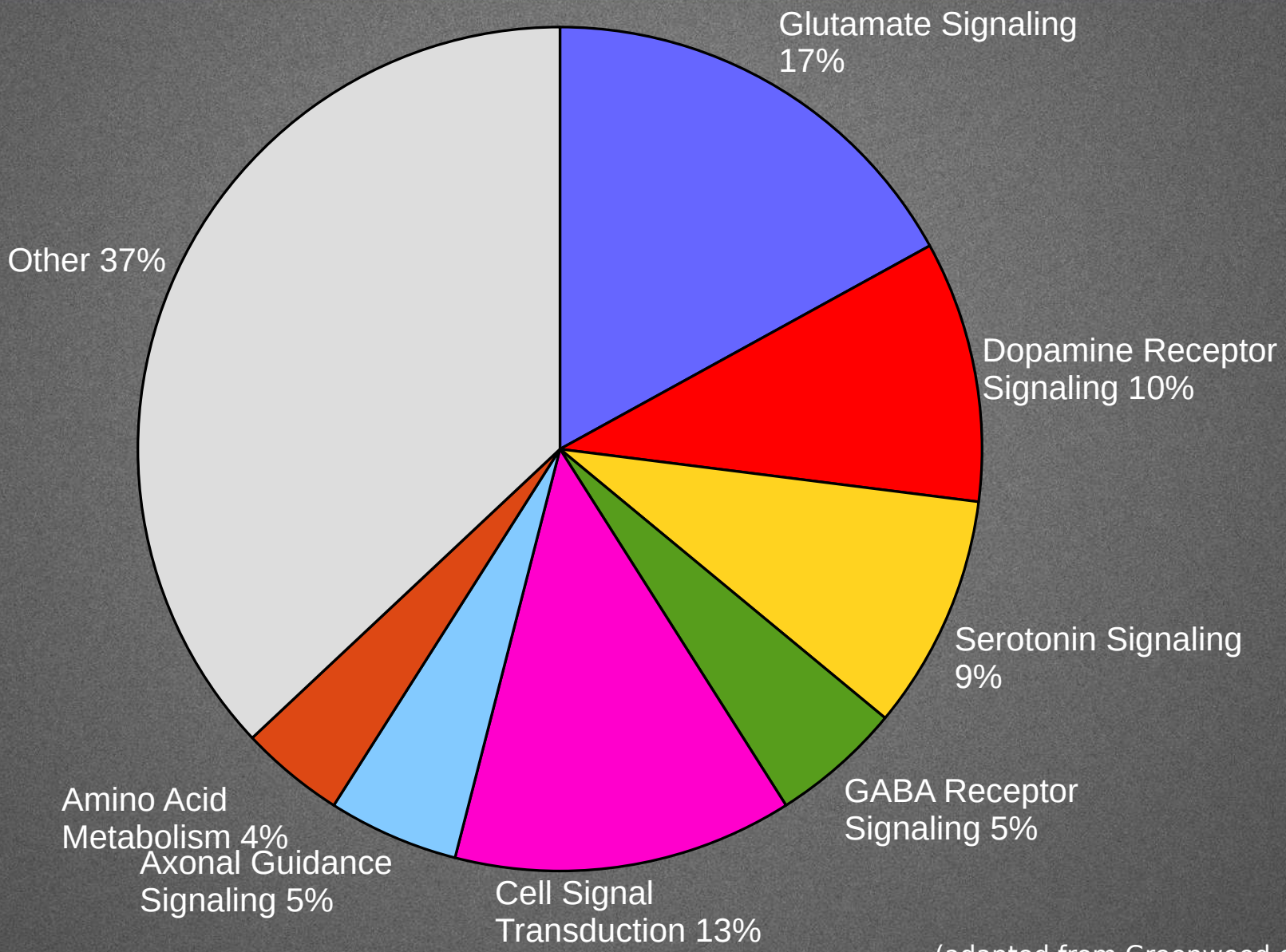
- Phentoypic expression
  - Continuum with affective disorders (Crow, 1986)
  - Failure of filter mechanisms (Hemsley and Zawada, 1976)
  - Internal monitoring deficiency (positive symptoms) & action initiation failure (negative symptoms) (Frith & Done, 1988)
  - Deficit vs. non-deficit SZ (Carpenter 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 andogenic 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/inhibotory balance as a
- Etiological
  - Polygenic/mutifactorial (Gootesman & 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



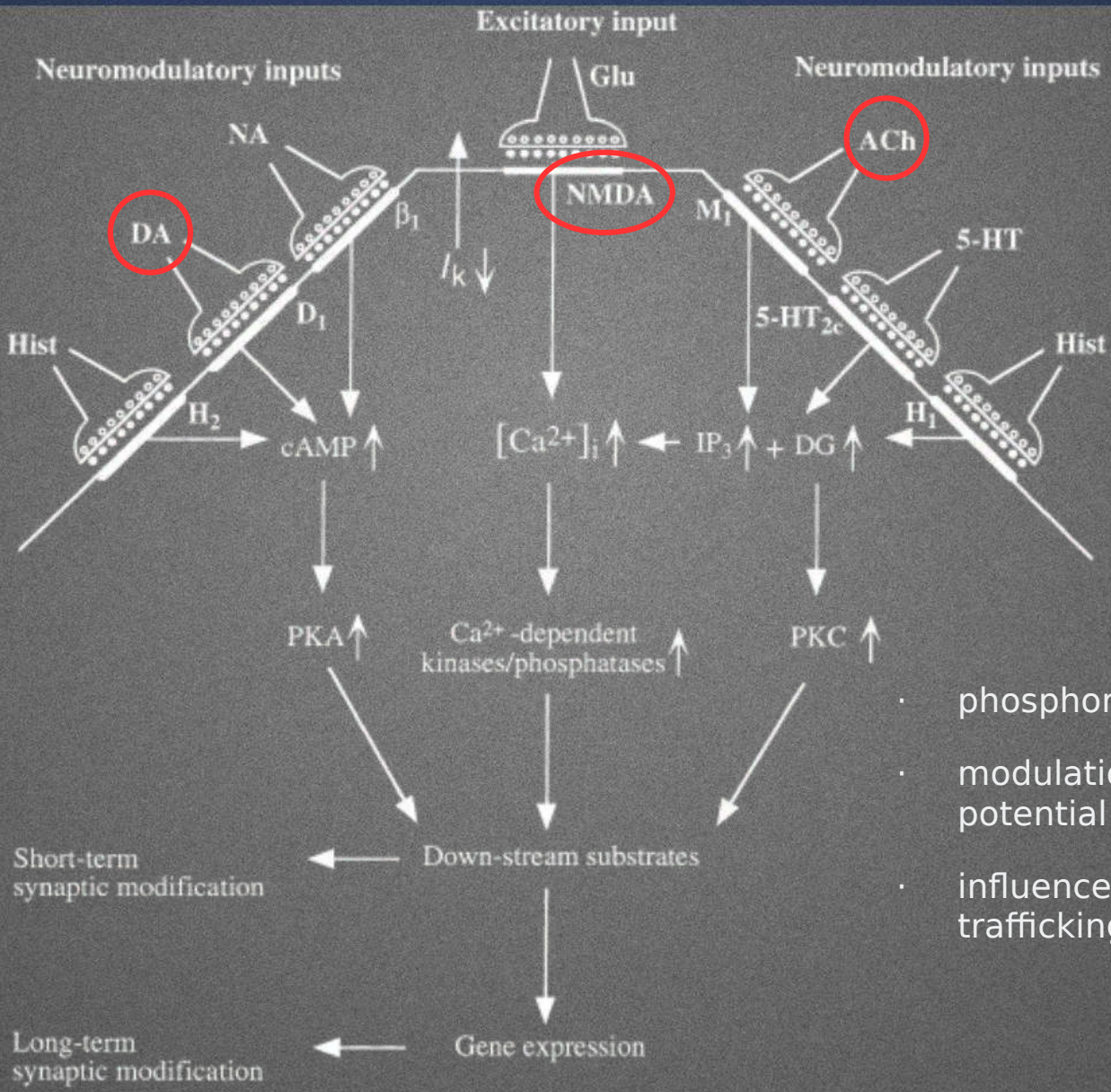
(Fvasconcellos, Wikimedia, 2015, edited)

Candidate Genes



(adapted from Greenwood et al., 2012)

NMDAR × neuromodulator interactions



- phosphorylation of NMDARs
- modulation of membrane potential
- influence on receptor trafficking

(Gu, 2002)

Dysconnection Hypothesis

- Integrates findings into computational franework

- Disturbed modulation of synaptic gain:

  “Dysbalance” in the integration of *sensory evidence* and *predictions*

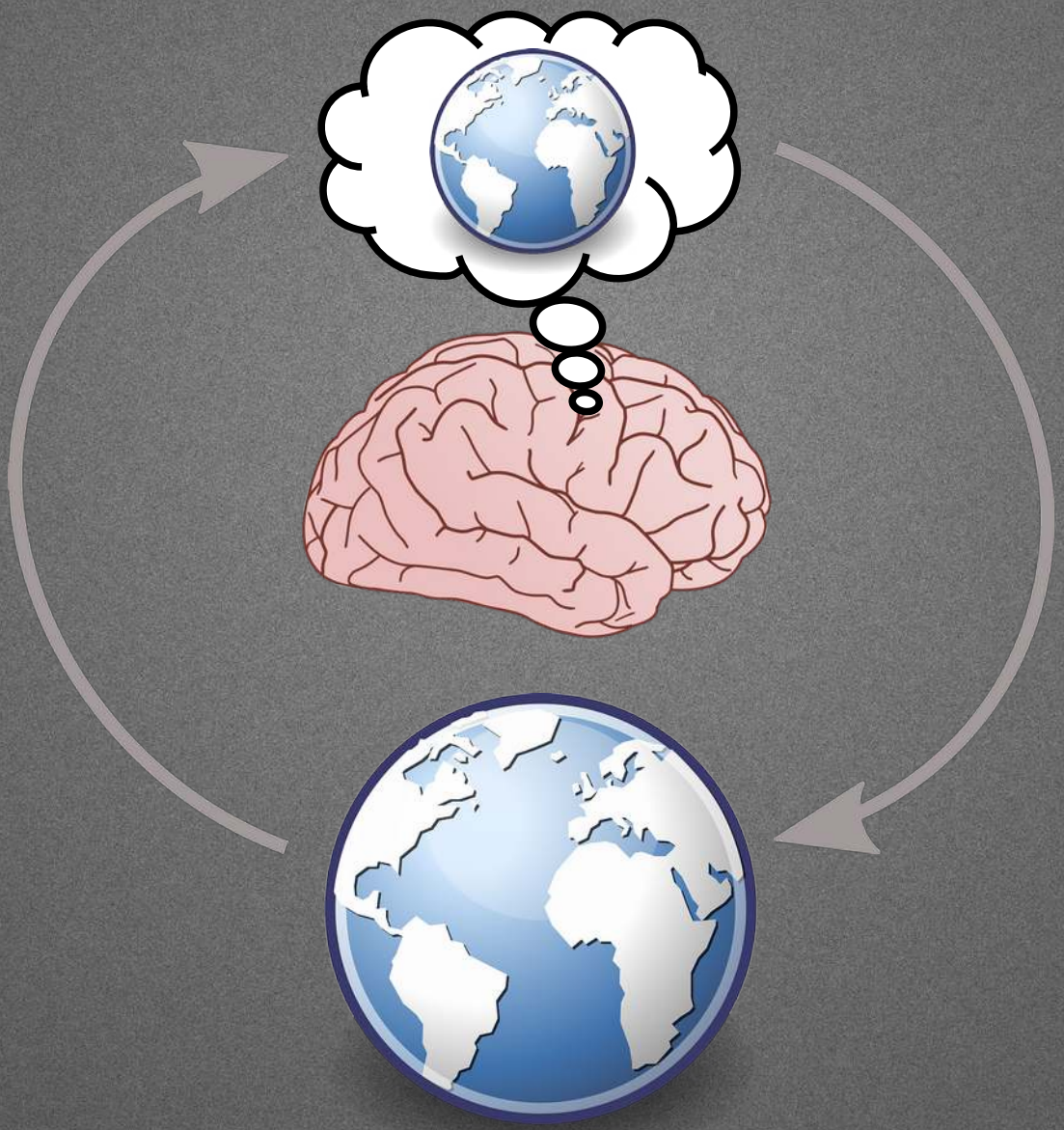
  → ...more of this later:

  - Bayesian Models of Perception (F. Petzschner)
  - Predictive Coding (L. Weber)
  - Active Inference (R. Smith)
  - ...

(Friston et al., 2016)

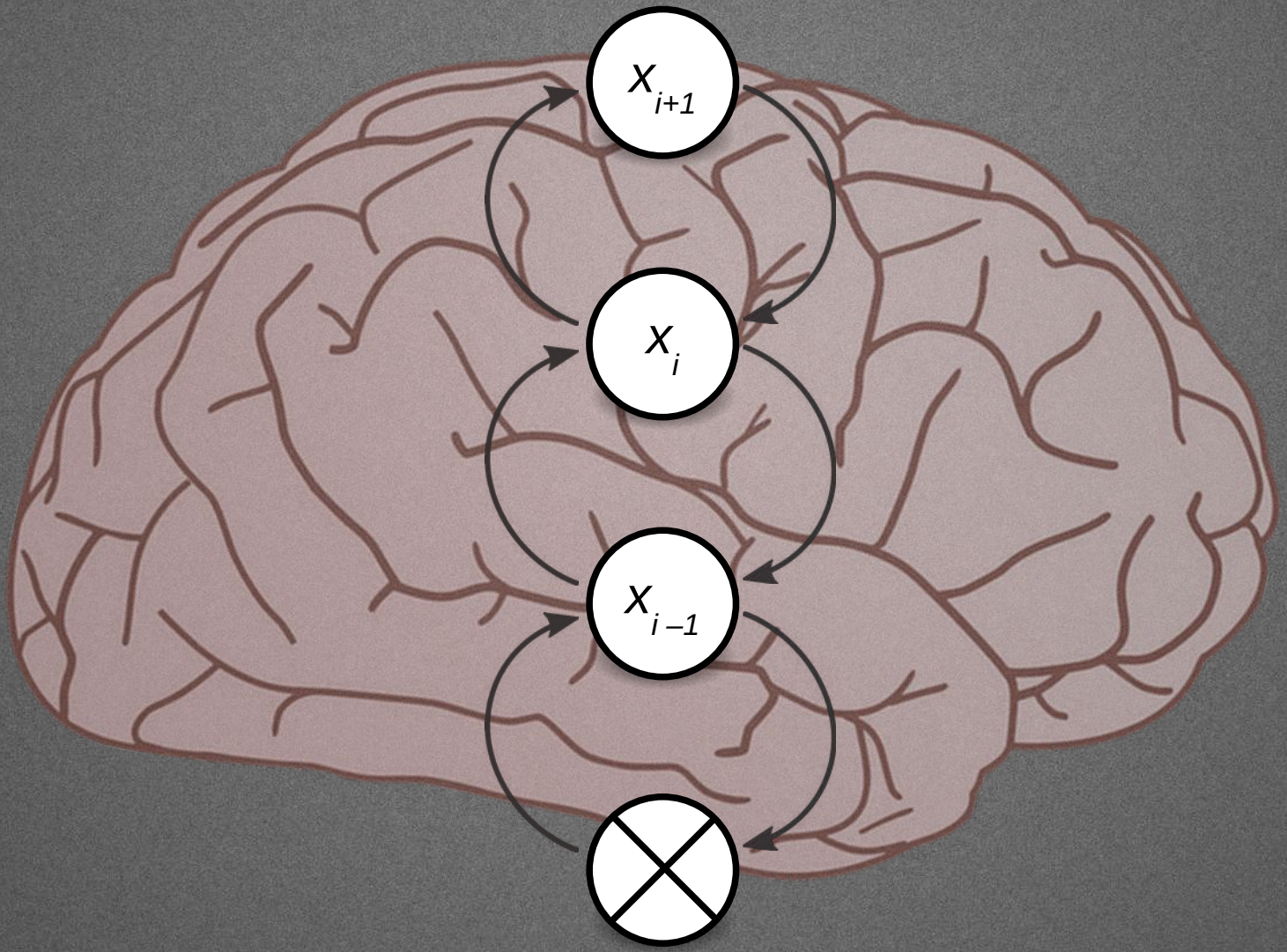
Bayesian Brain

- Sensory Evidence



- Predictions

Predictive Coding



Bayesian Brain

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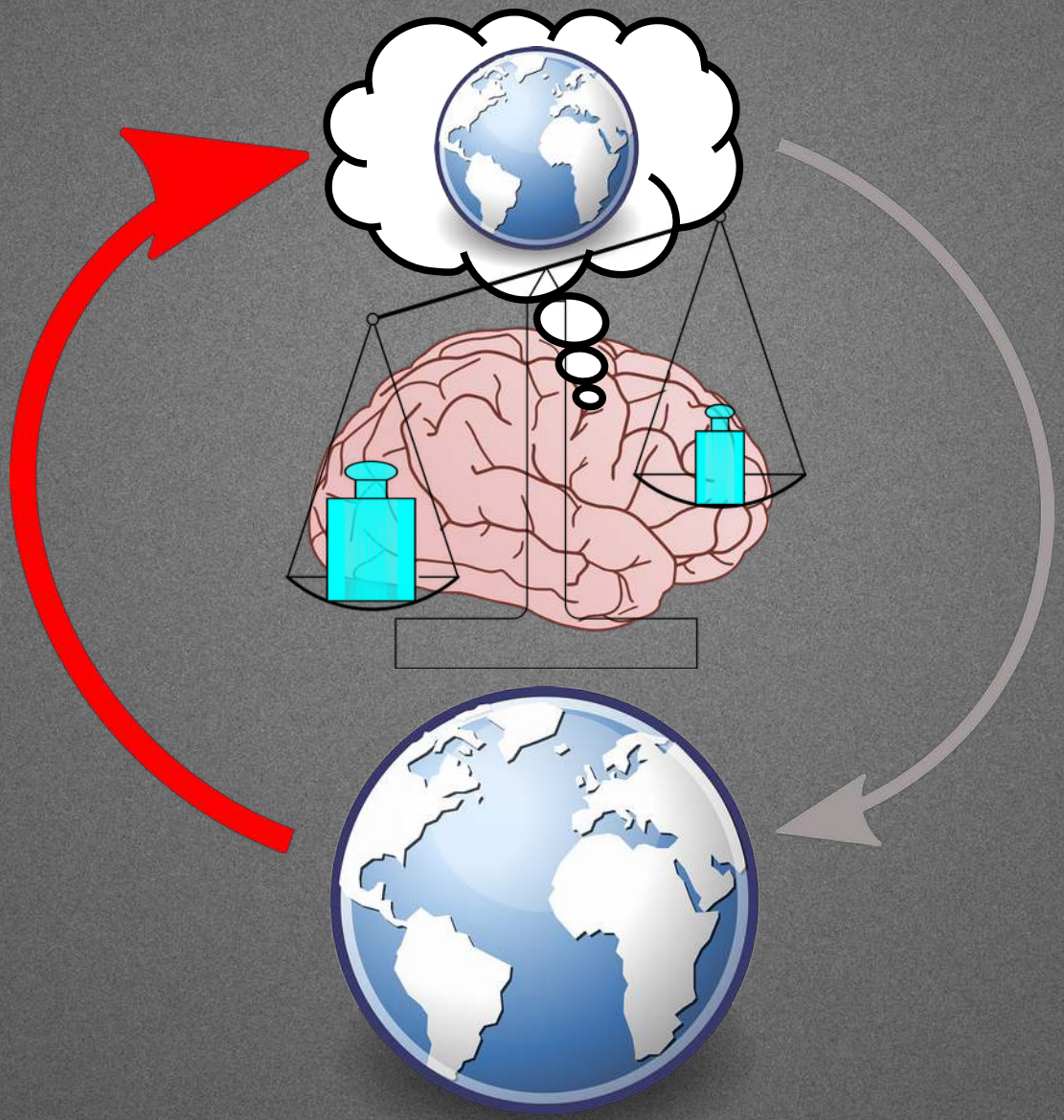

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Bayesian Brain

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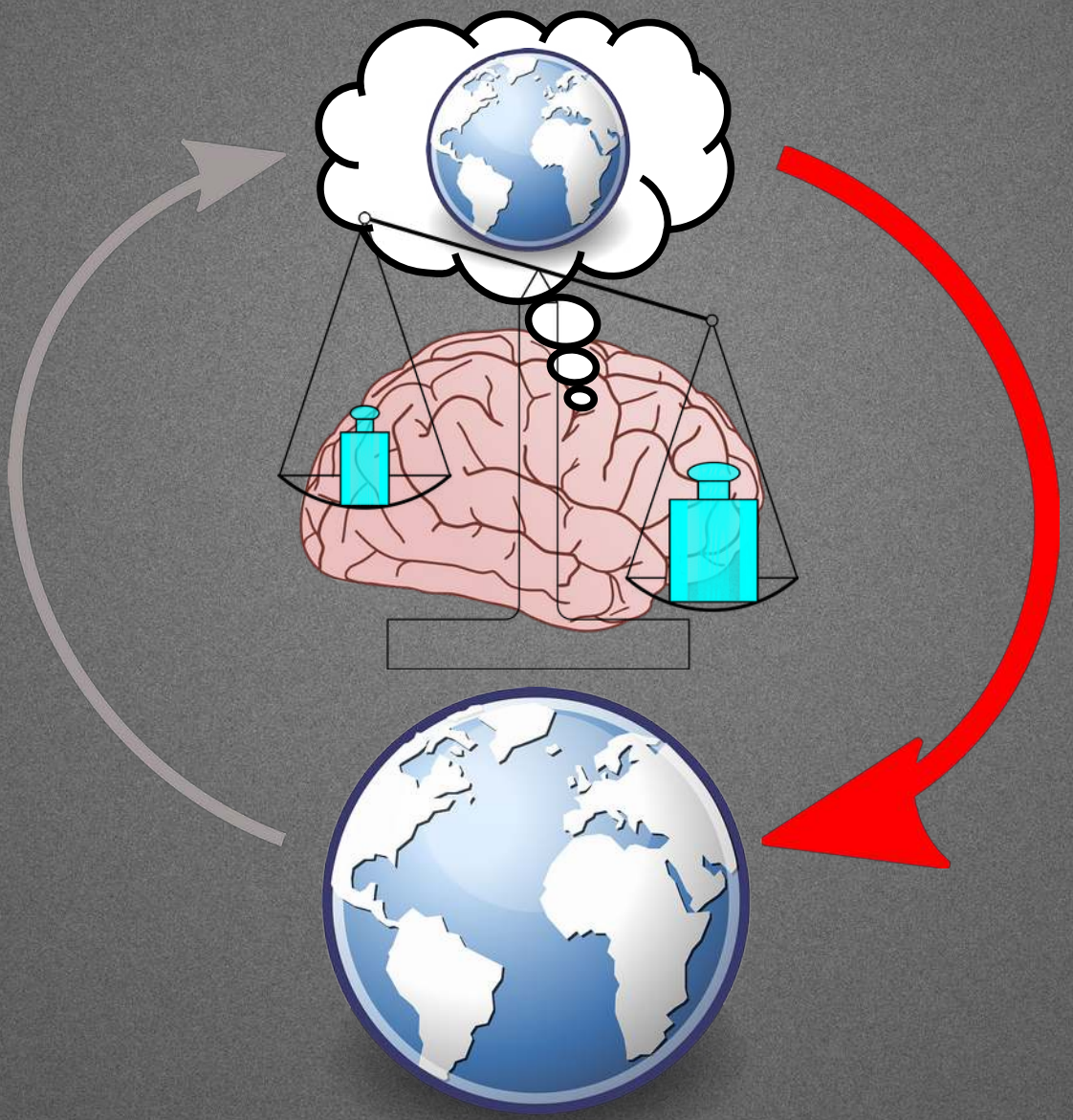

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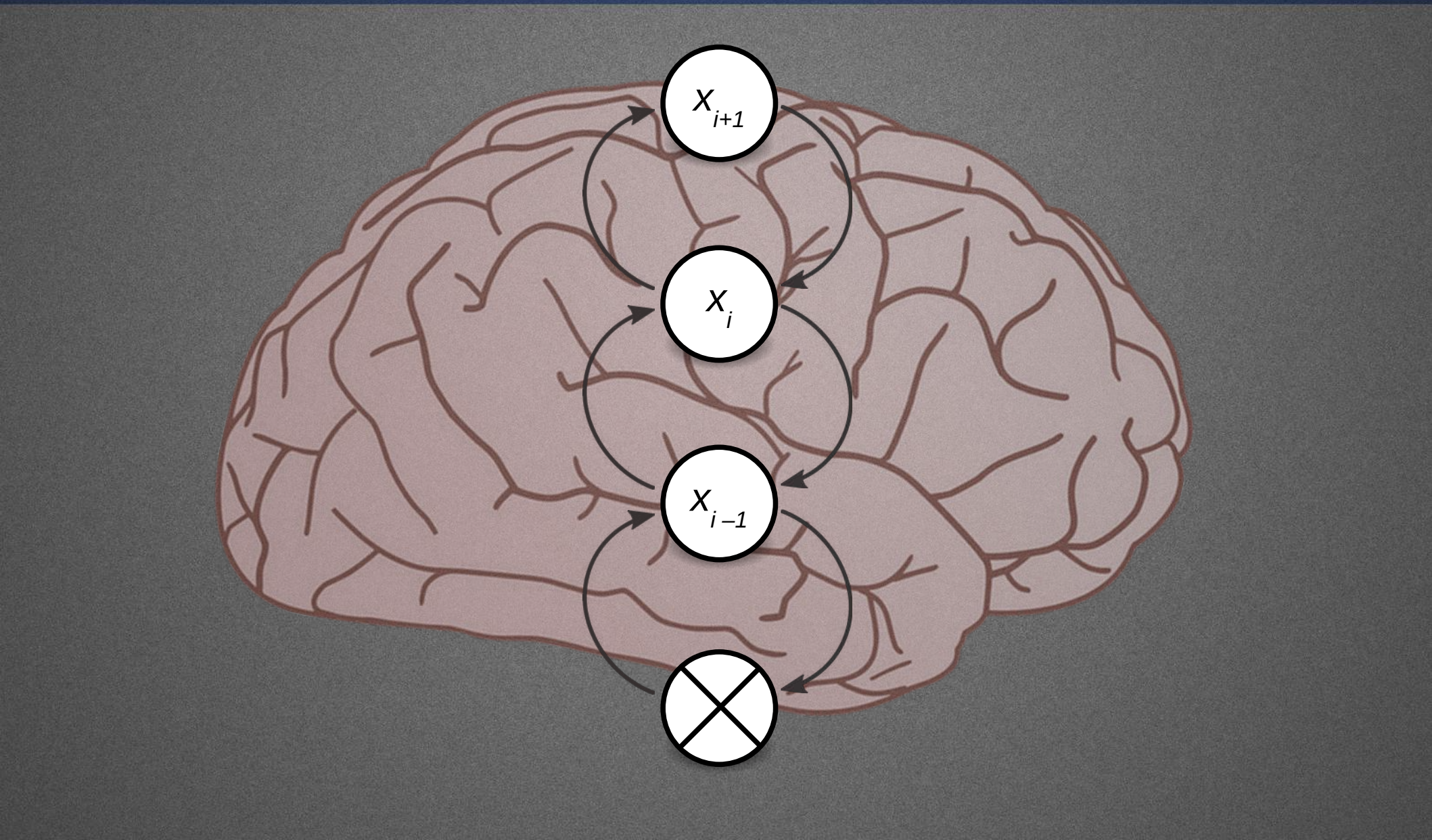
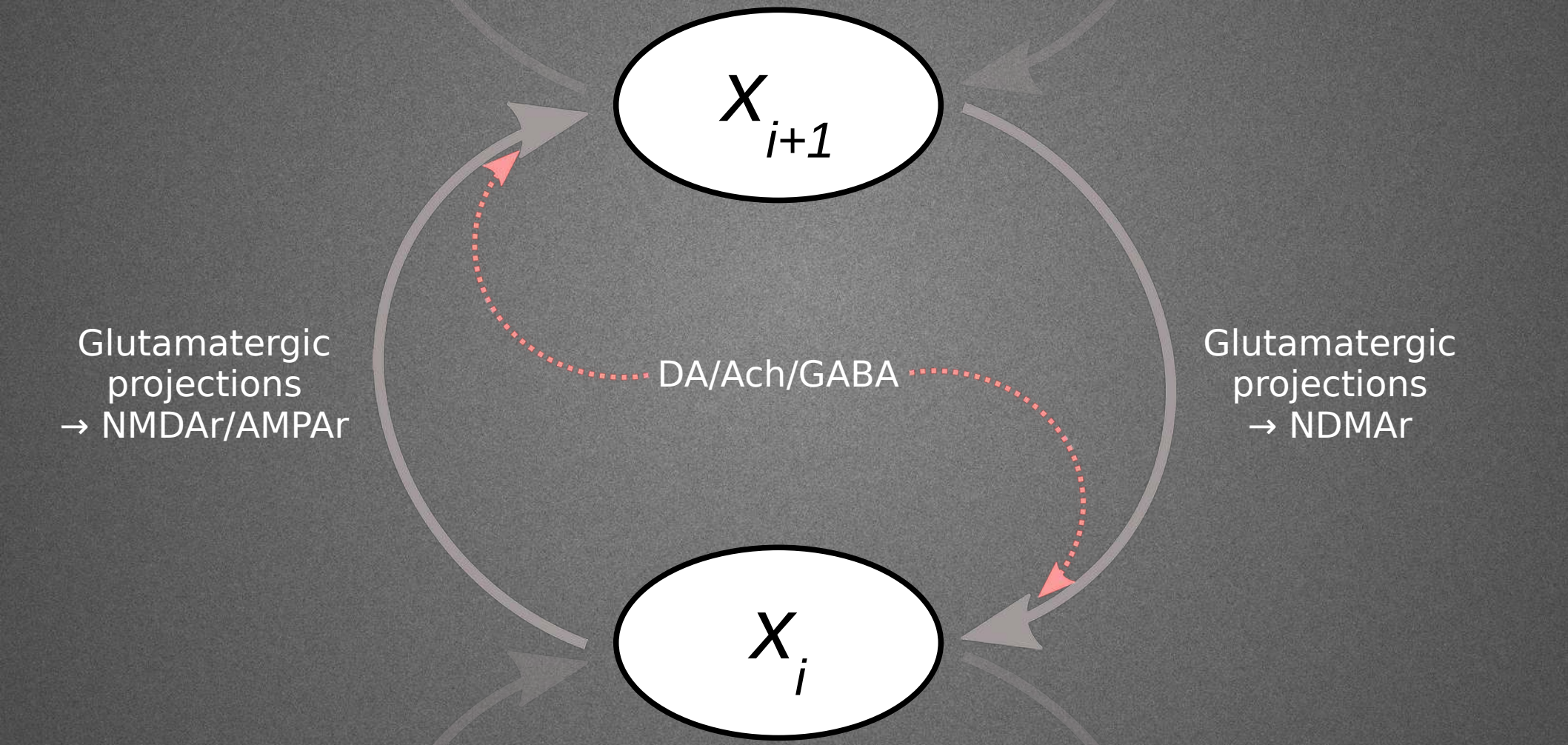


Dysconnectivity?

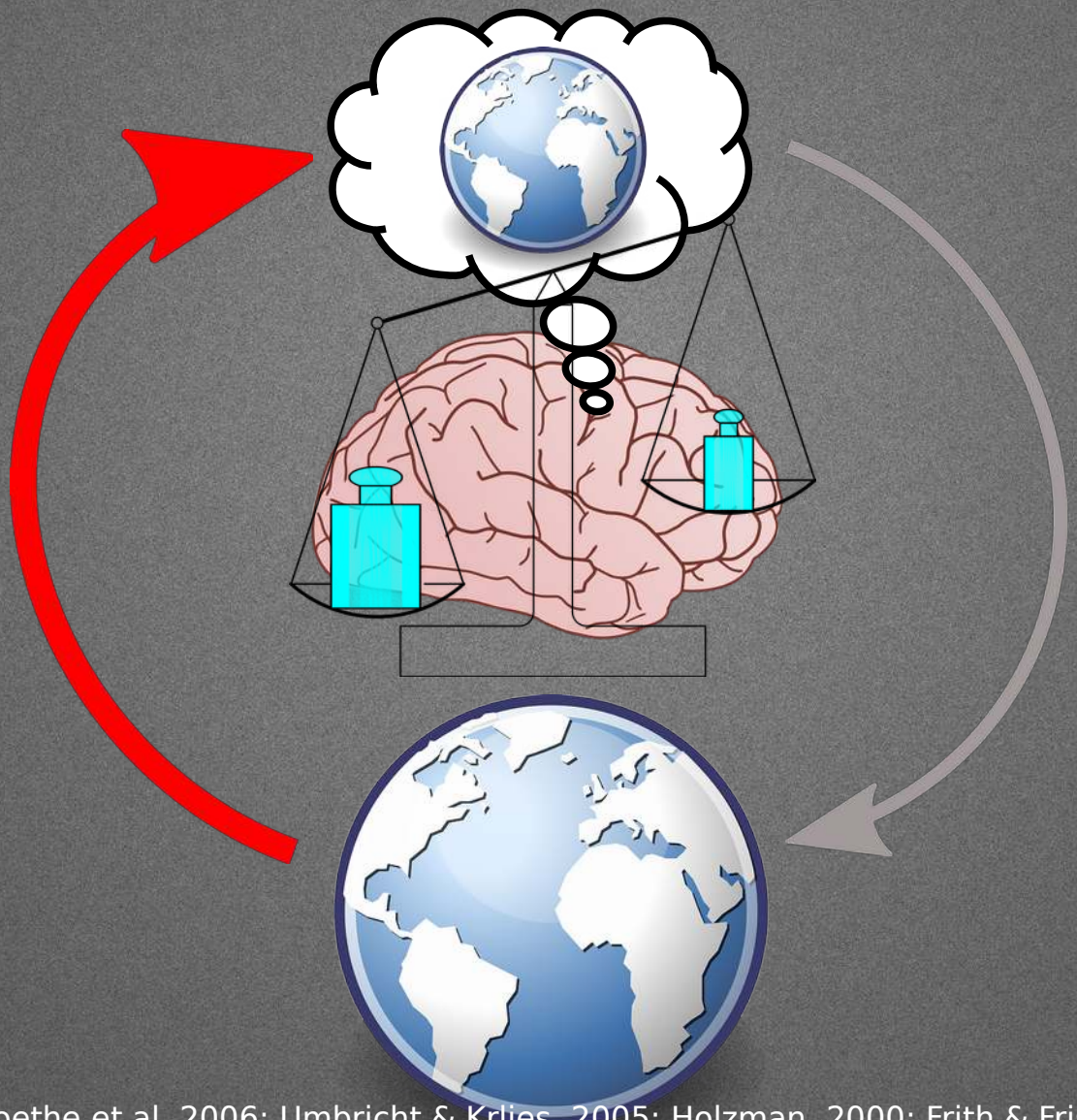


(Stephan et al., 2016)

Bayesian Brain - Dysconnectivity

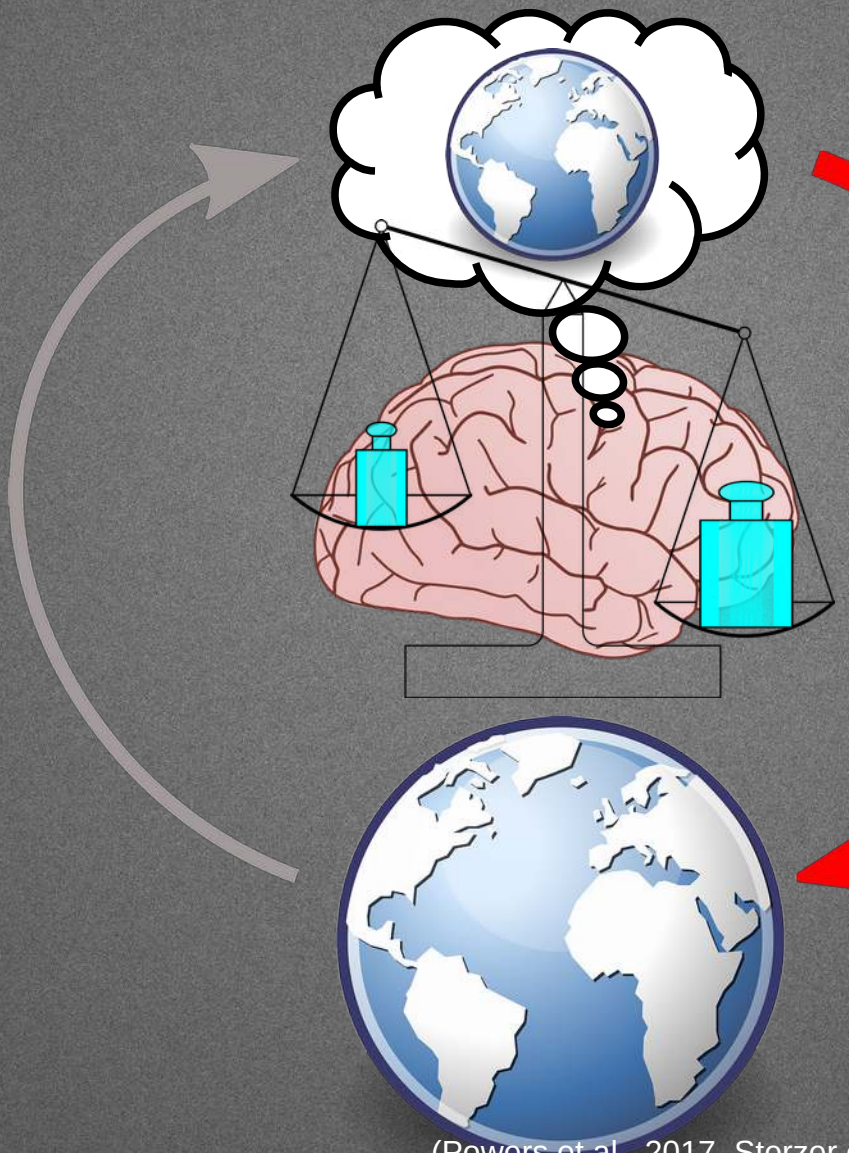
Trait phenomena

- ↓ susceptibility to illusions
- “Delusional mood”



(Koethe et al, 2006; Umbricht & Krljes, 2005; Holzman, 2000; Frith & Friston, 2013; Adams et al., 2013)

Bayesian Brain - Dysconnectivity

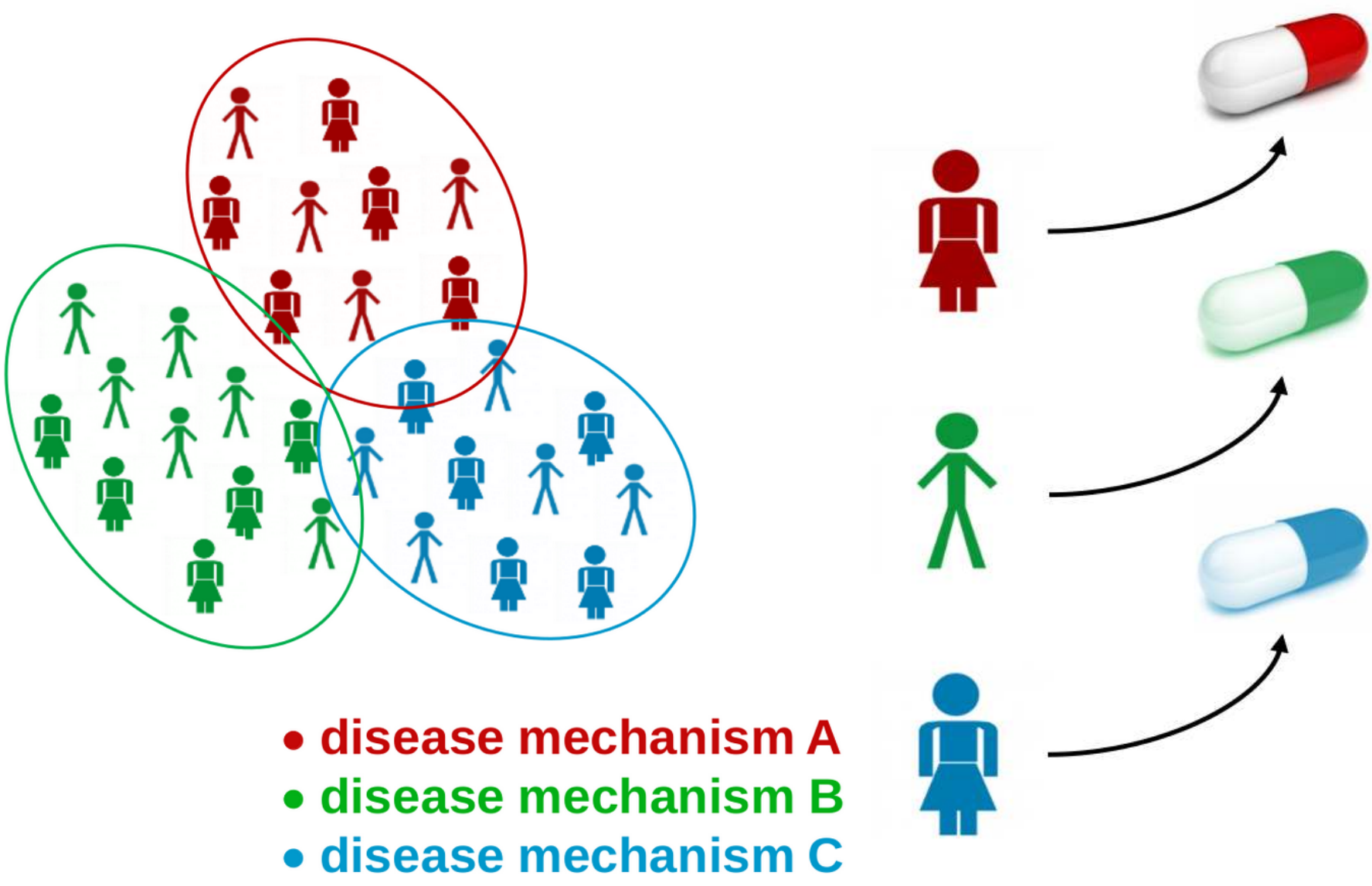


State phenomena

- Delusion
- Acoustic hallucinations

(Powers et al., 2017, Sterzer et al, 2018; Frith & Friston, 2013; Adams et al., 2013)

The goal of CP?



(Stephan et al., 2015)

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

Questions?

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