Schizophrenia (for non-clinicians)

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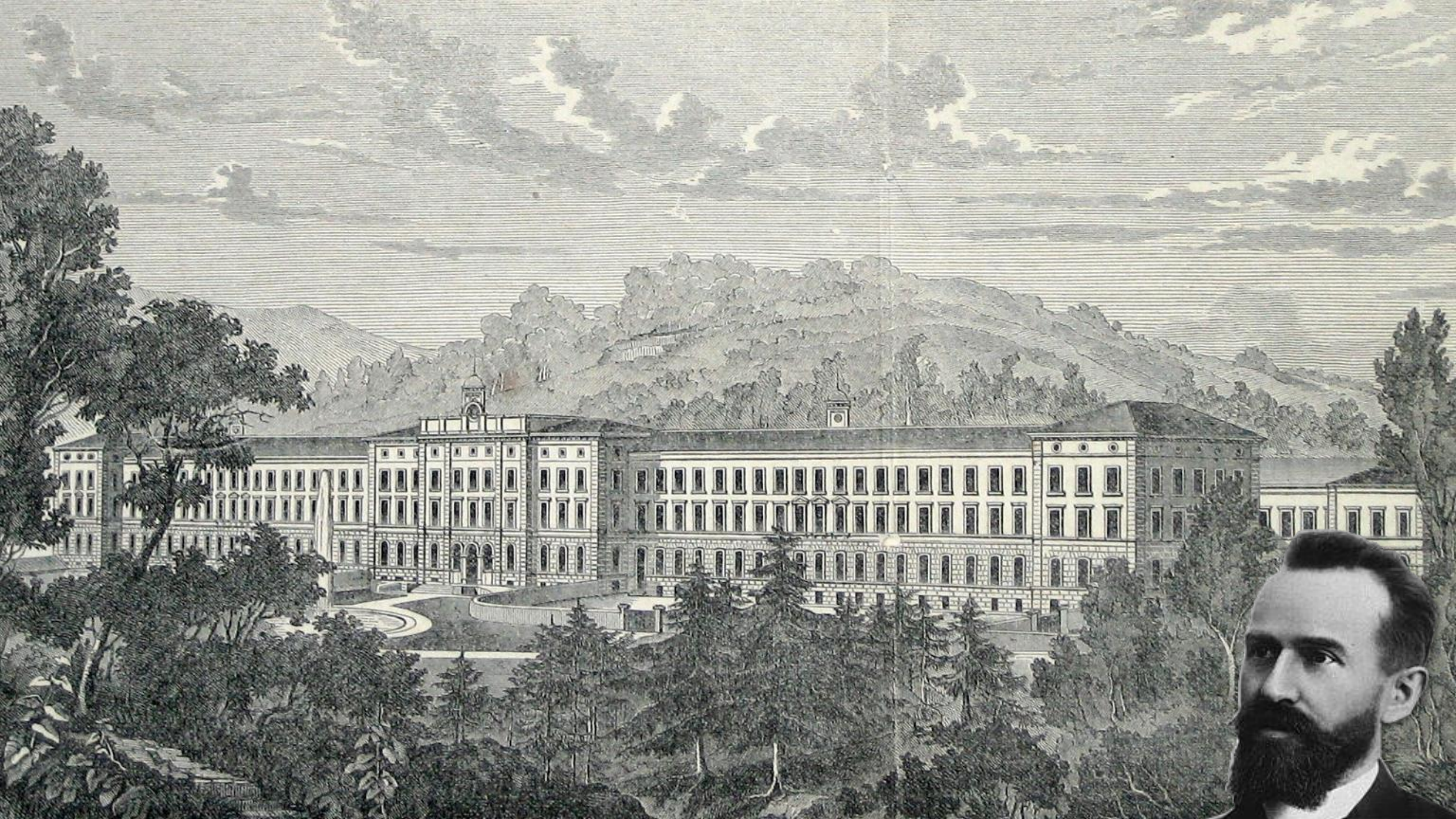
Why is it important to know about schizophrenia?

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



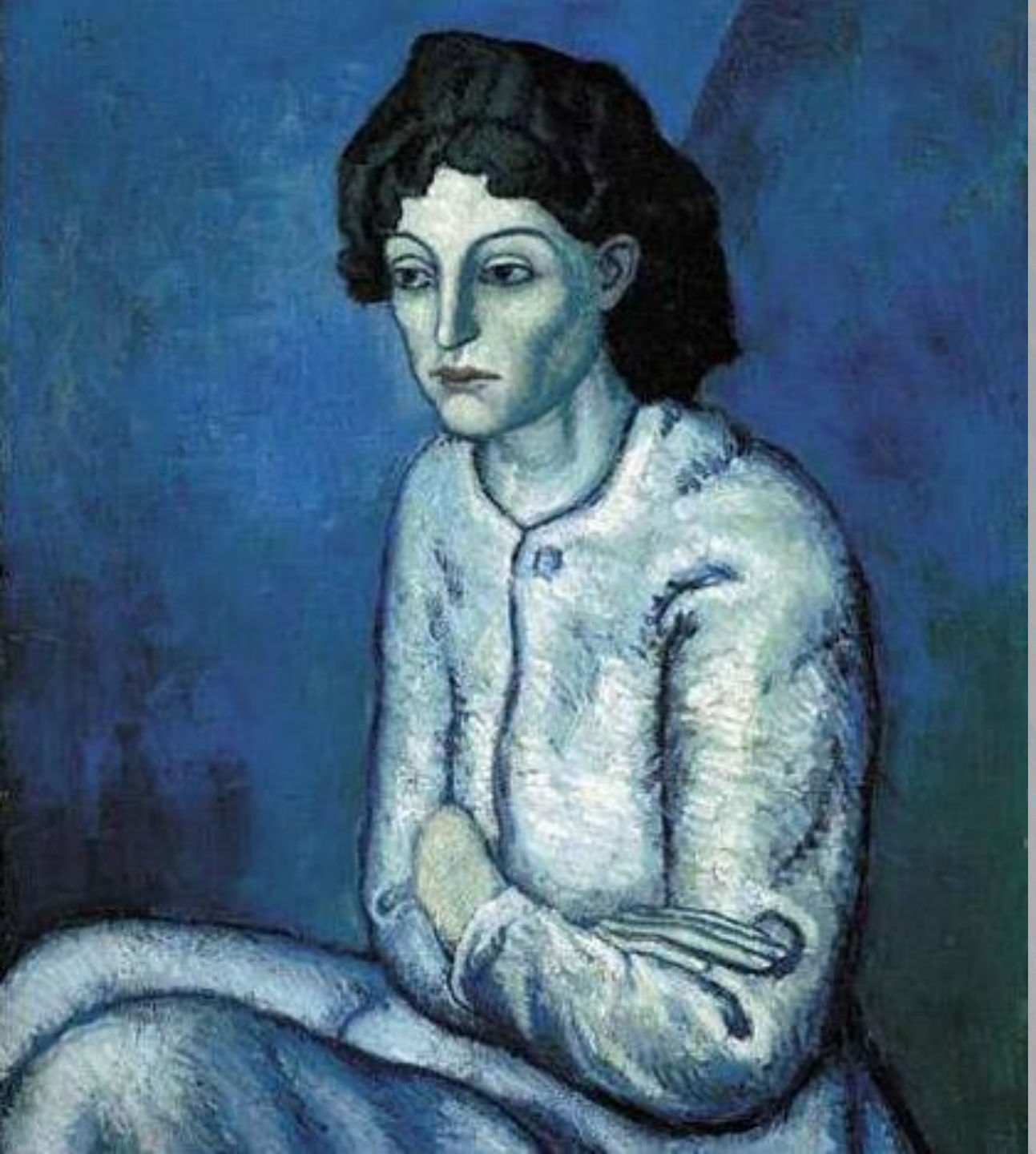
Terminology

- **Schizophrenia**: Diagnosis
- **Psychotic Disorder/Psychosis**: Collective term for conditions with psychotic symptoms, used when course and causal factor(s) are unknown
- **Psychotic**: Symptoms related to difficulties in reality testing (delusions, hallucination, disorganized behaviour, …); can occur in many psychiatric conditions
- Terms often used incorrectly and interchangeably

Important side-note

- Always use „person/patient with schizophrenia“, never use „~~schizophrenic~~“
- “Schizophrenia” perceived as stigmatizing, most prefer to use the term „psychosis“

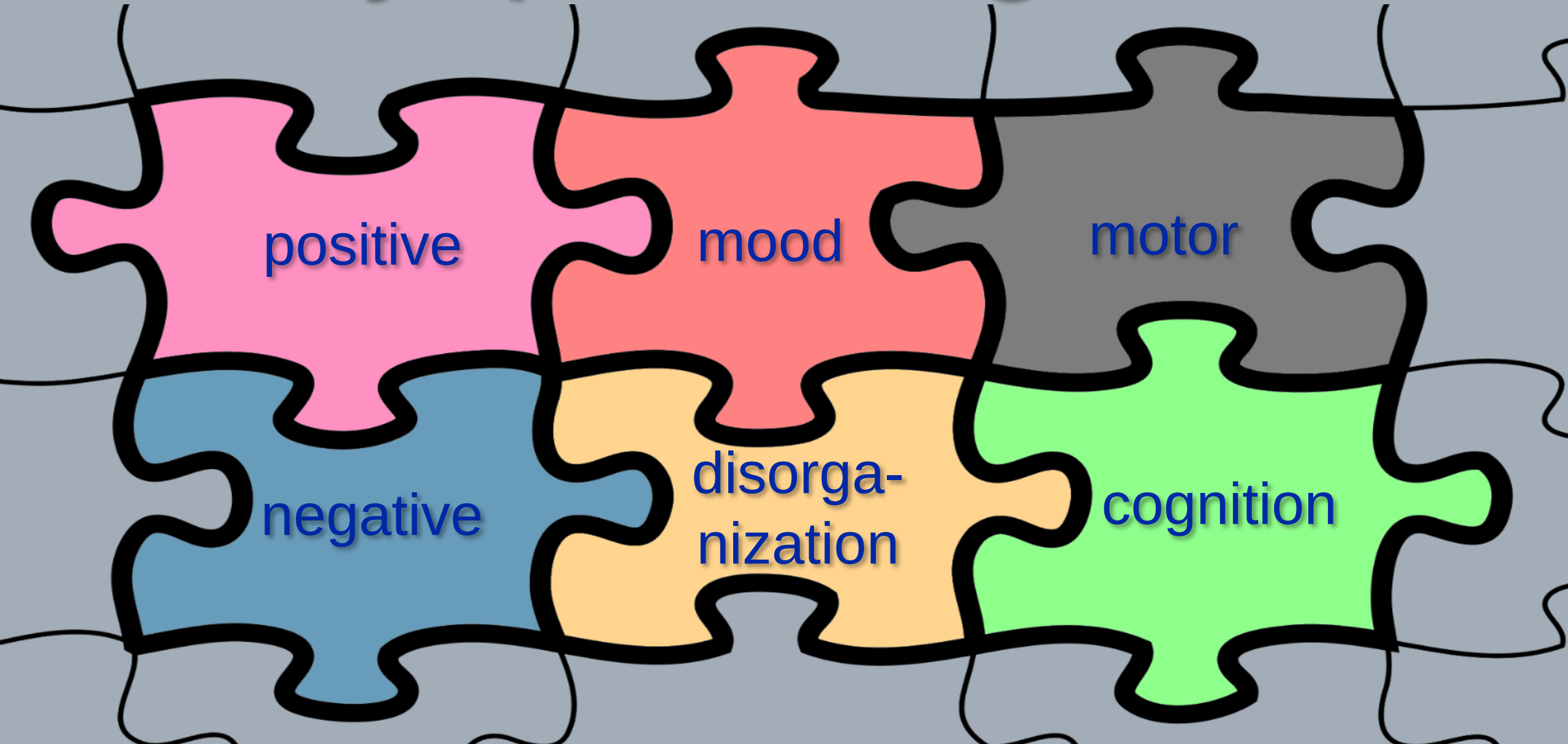
Clinical Manifestation



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

- 19yo student of physics
- Neighbour:
  - 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

Symptom Categories



Symptom Categories

positive

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

motor

egative

disorga-
nization

cognition

Symptom Categories

sitive

mood

motor

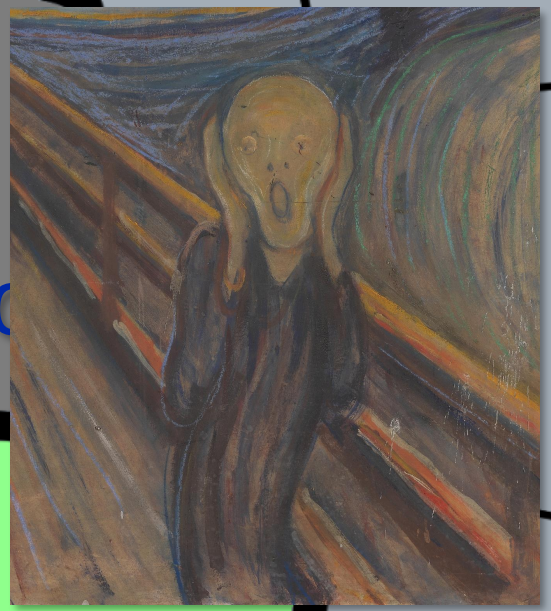
negative

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

Symptom Categories

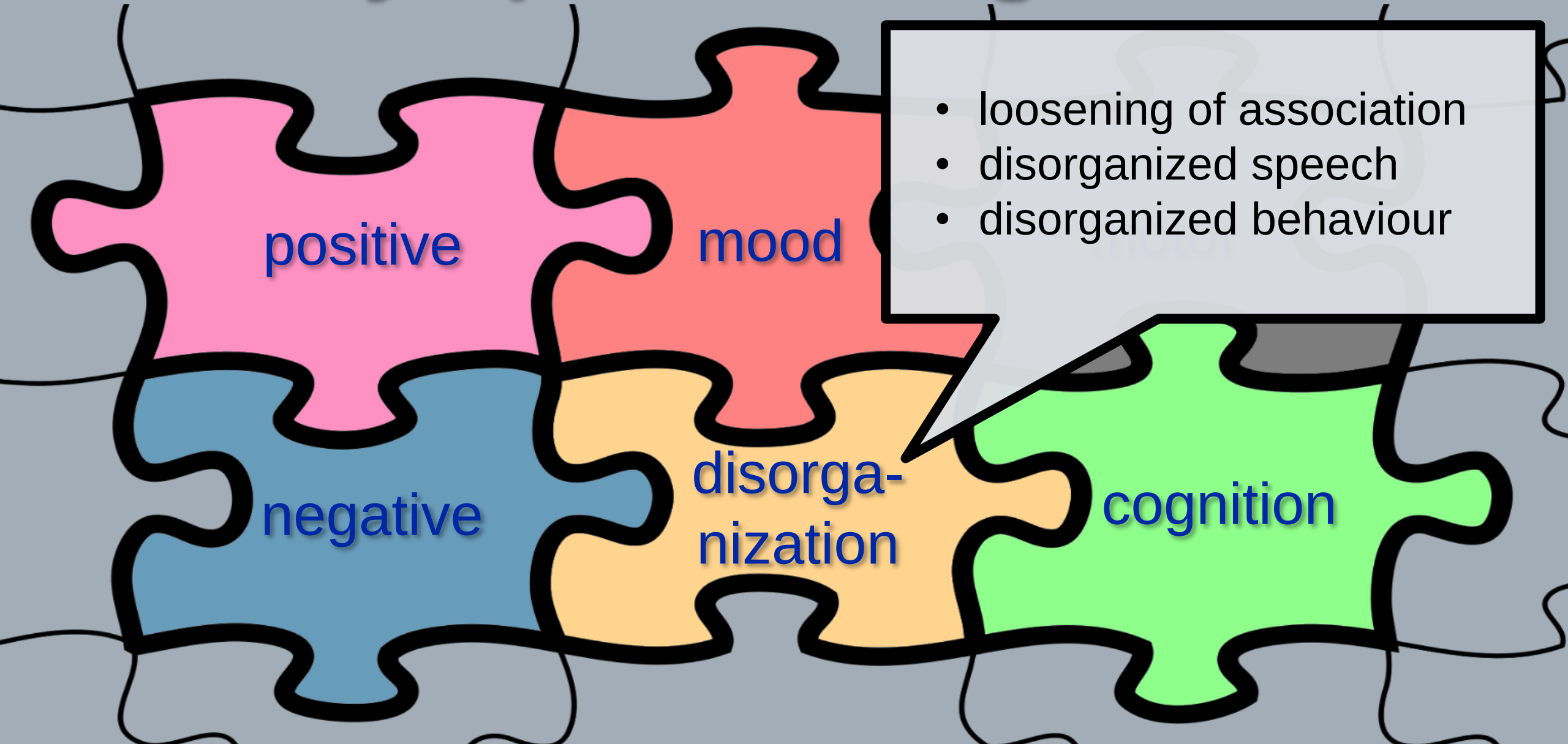
mood

moto



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

Symptom Categories



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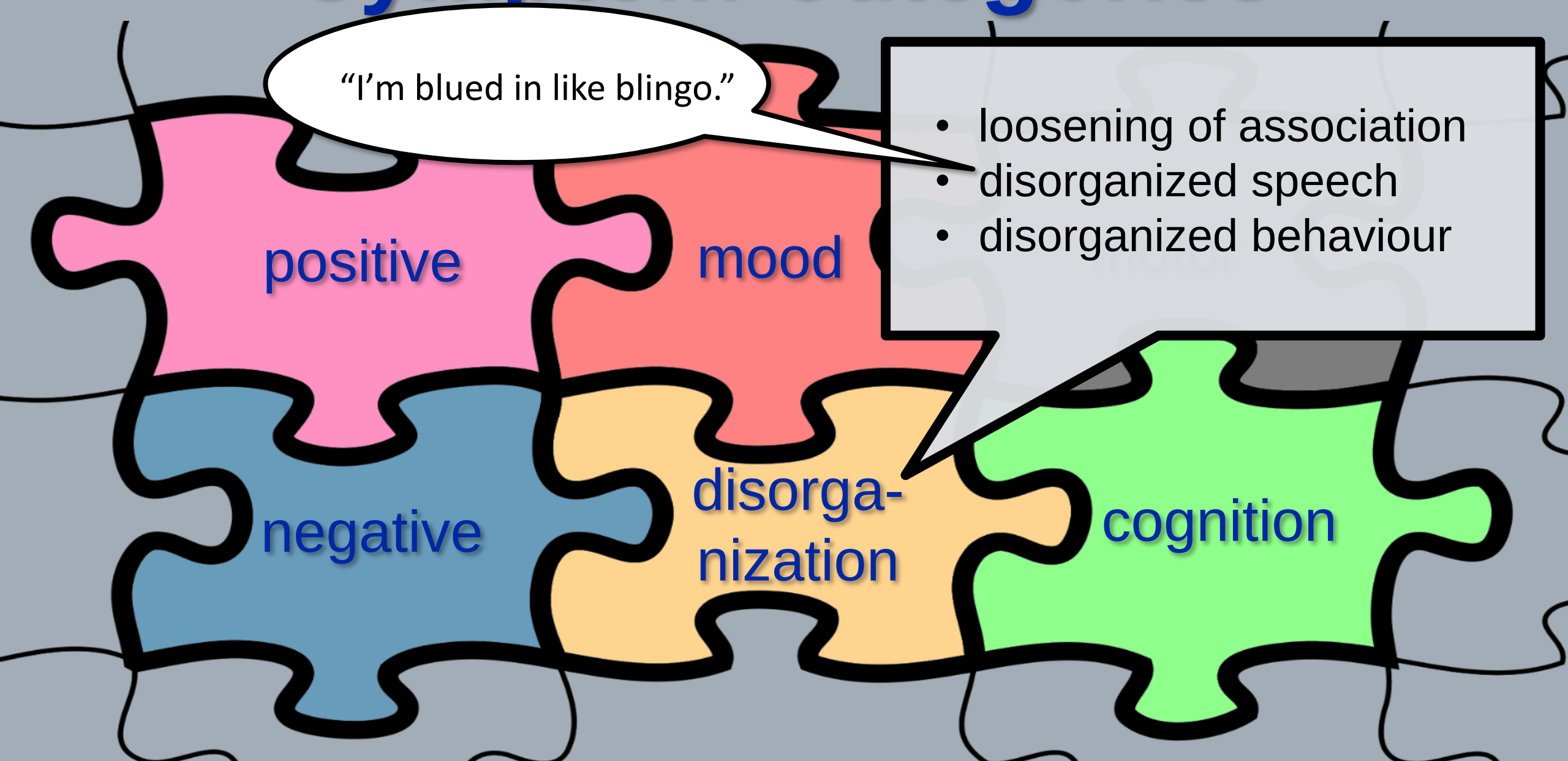
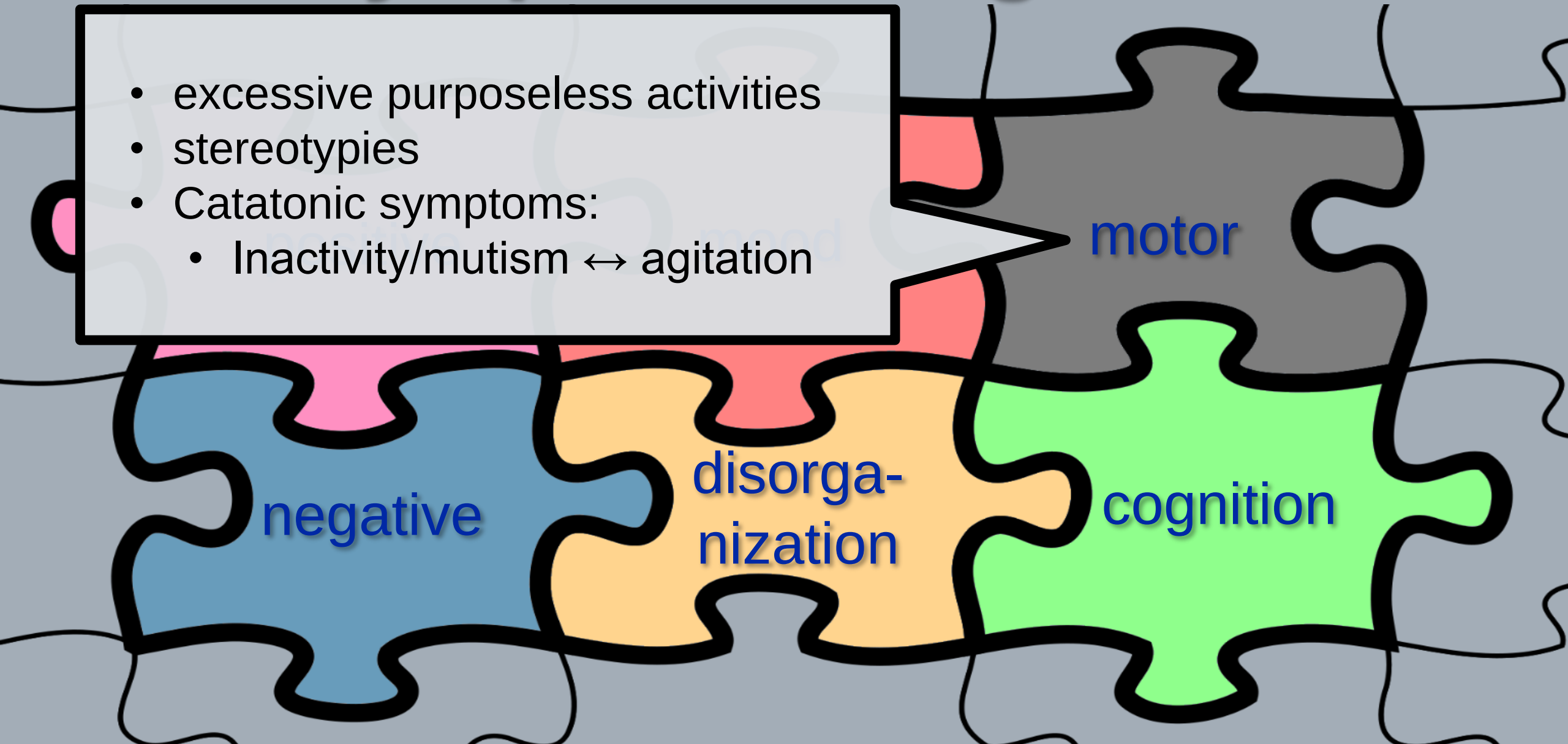


Symptom Categories

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



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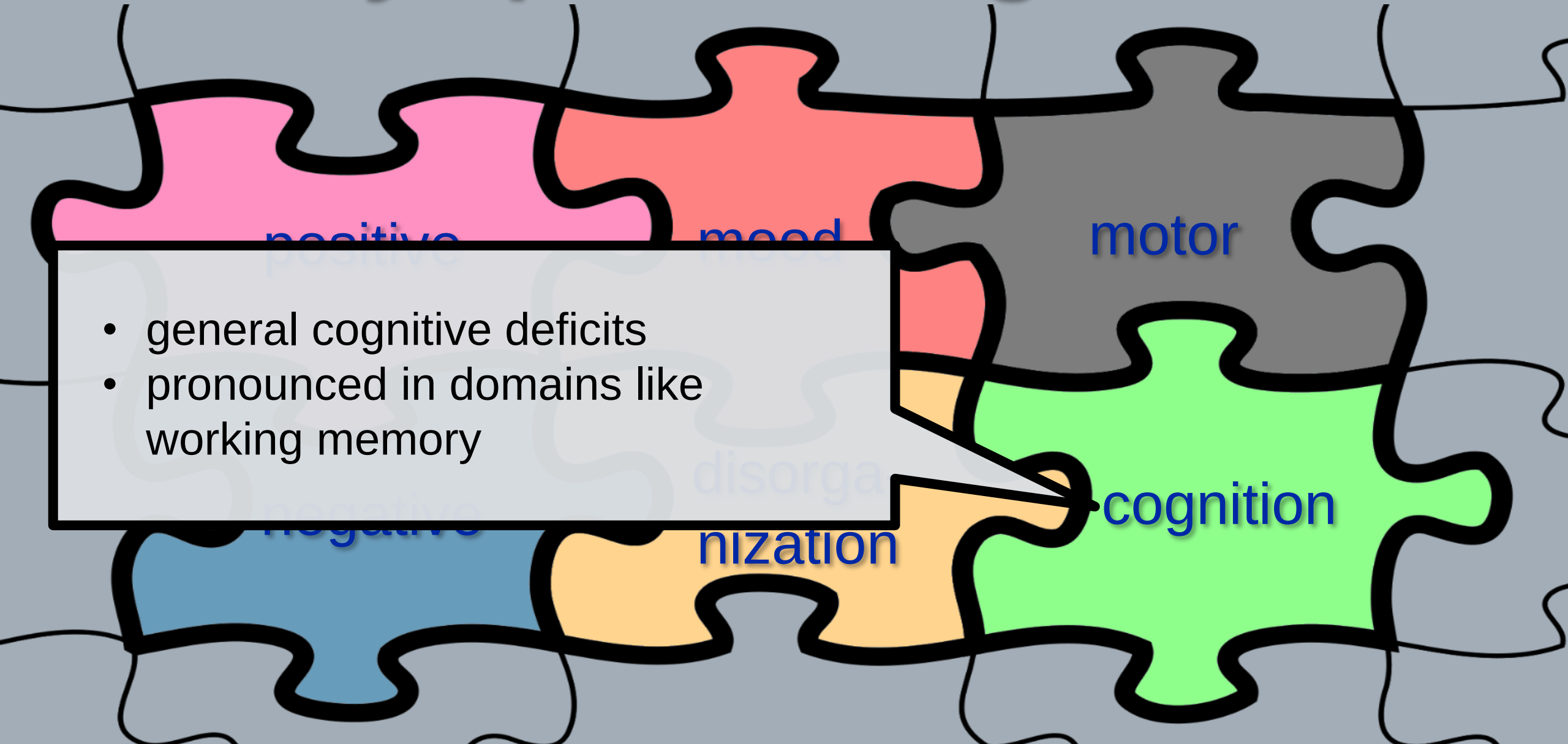
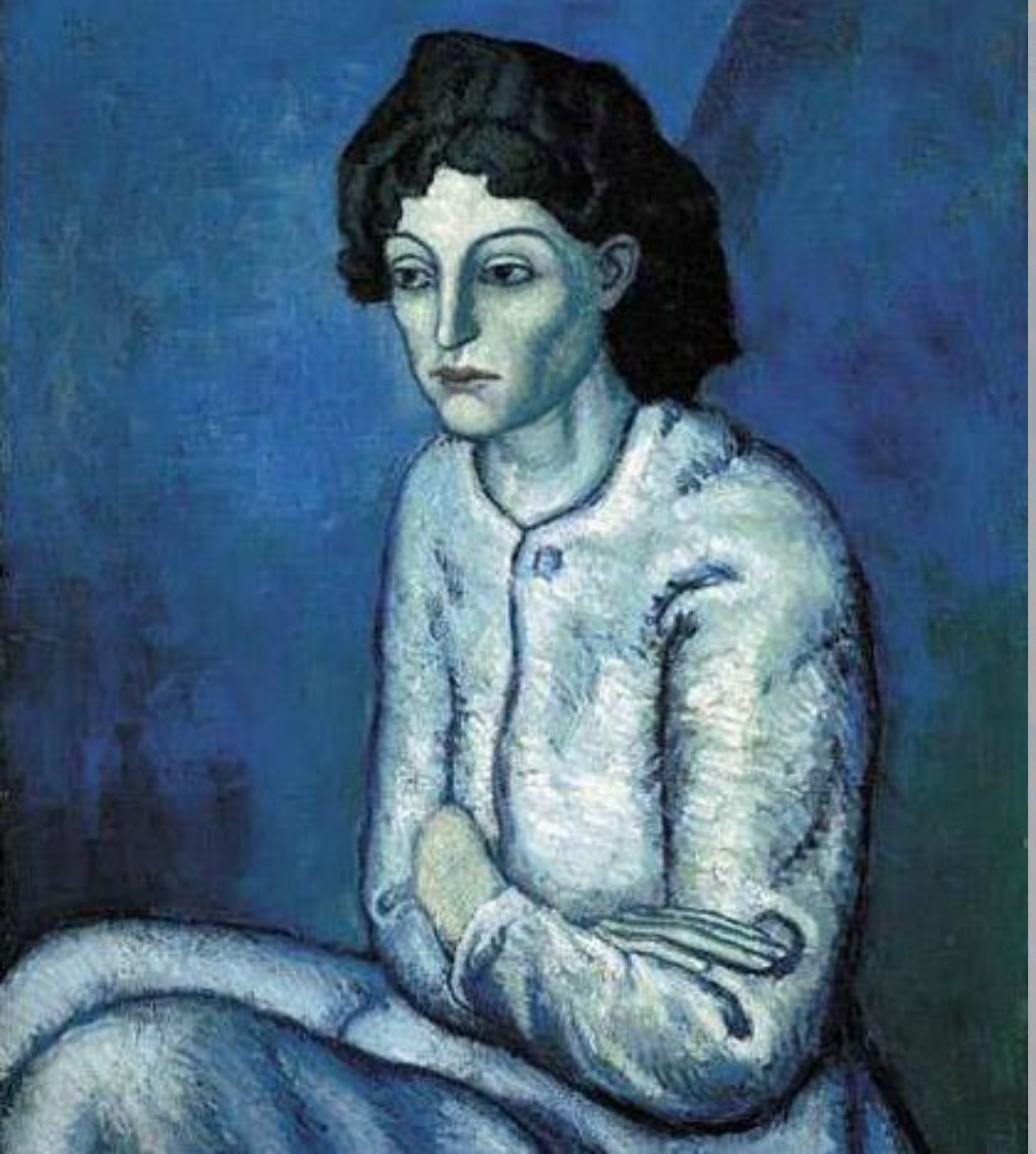


- general cognitive deficits
- pronounced in domains like working memory

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 • disorganized or catatonic behaviour

(APA, 2013)



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

→ Schizophrenia

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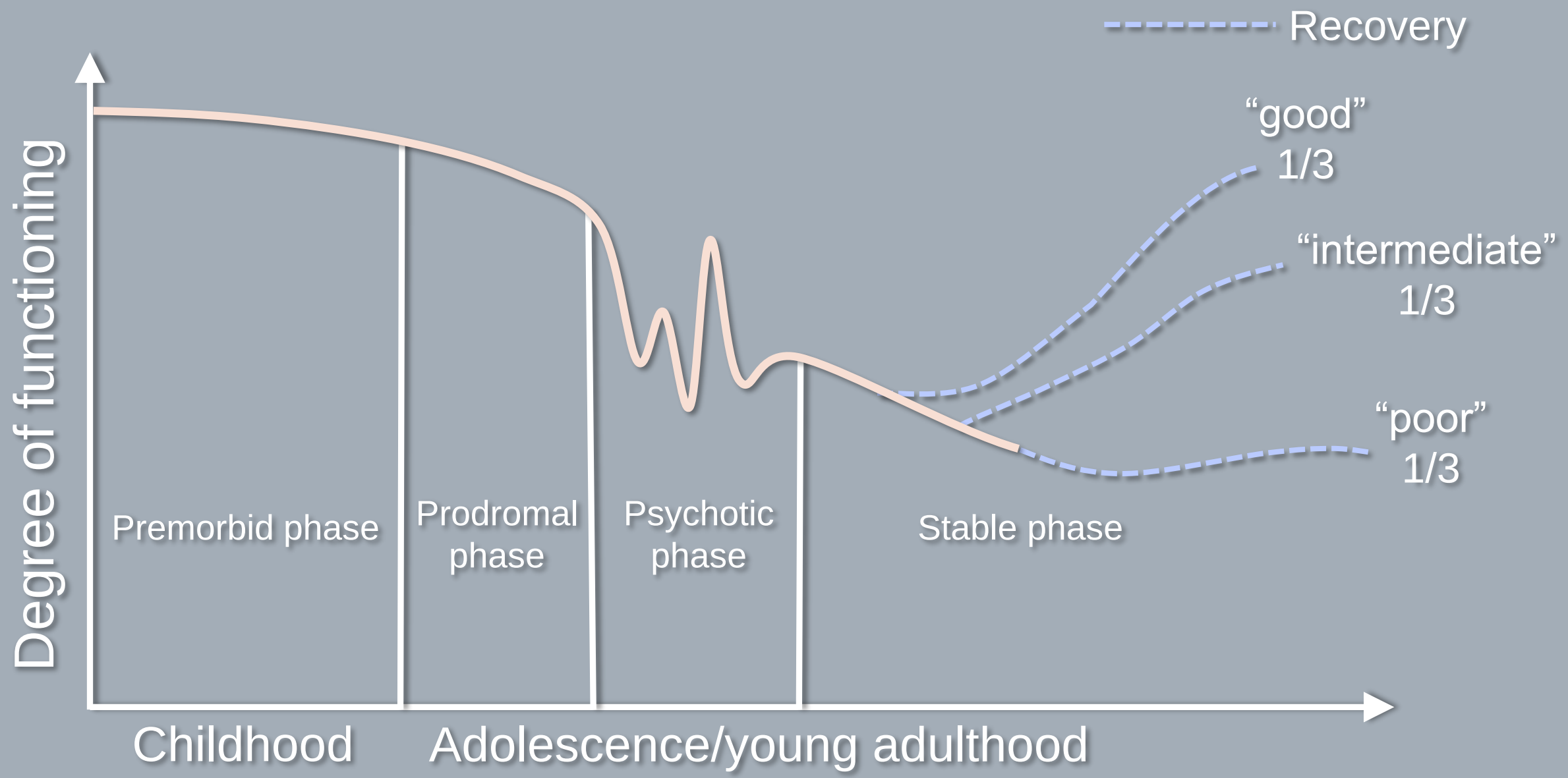
→ Schizophrenia

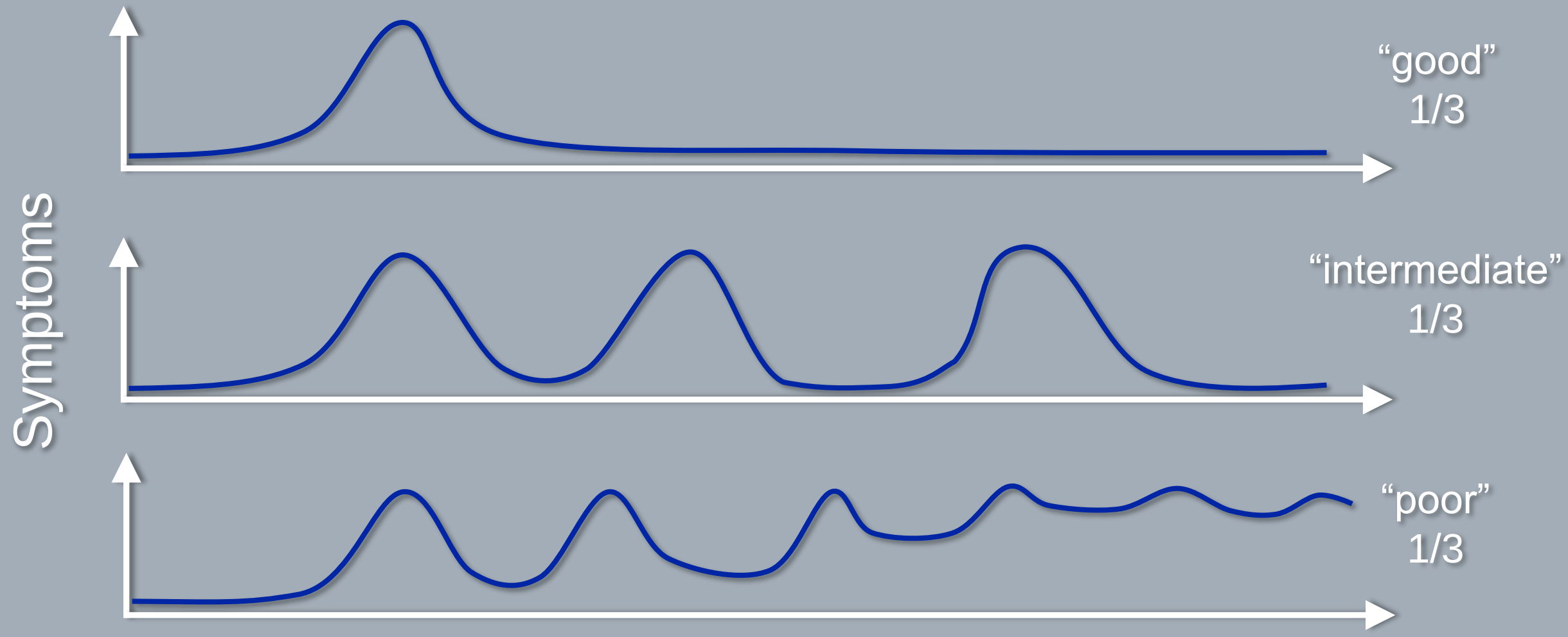
Course, Risk Factors, Outcome

Course of Schizophrenia



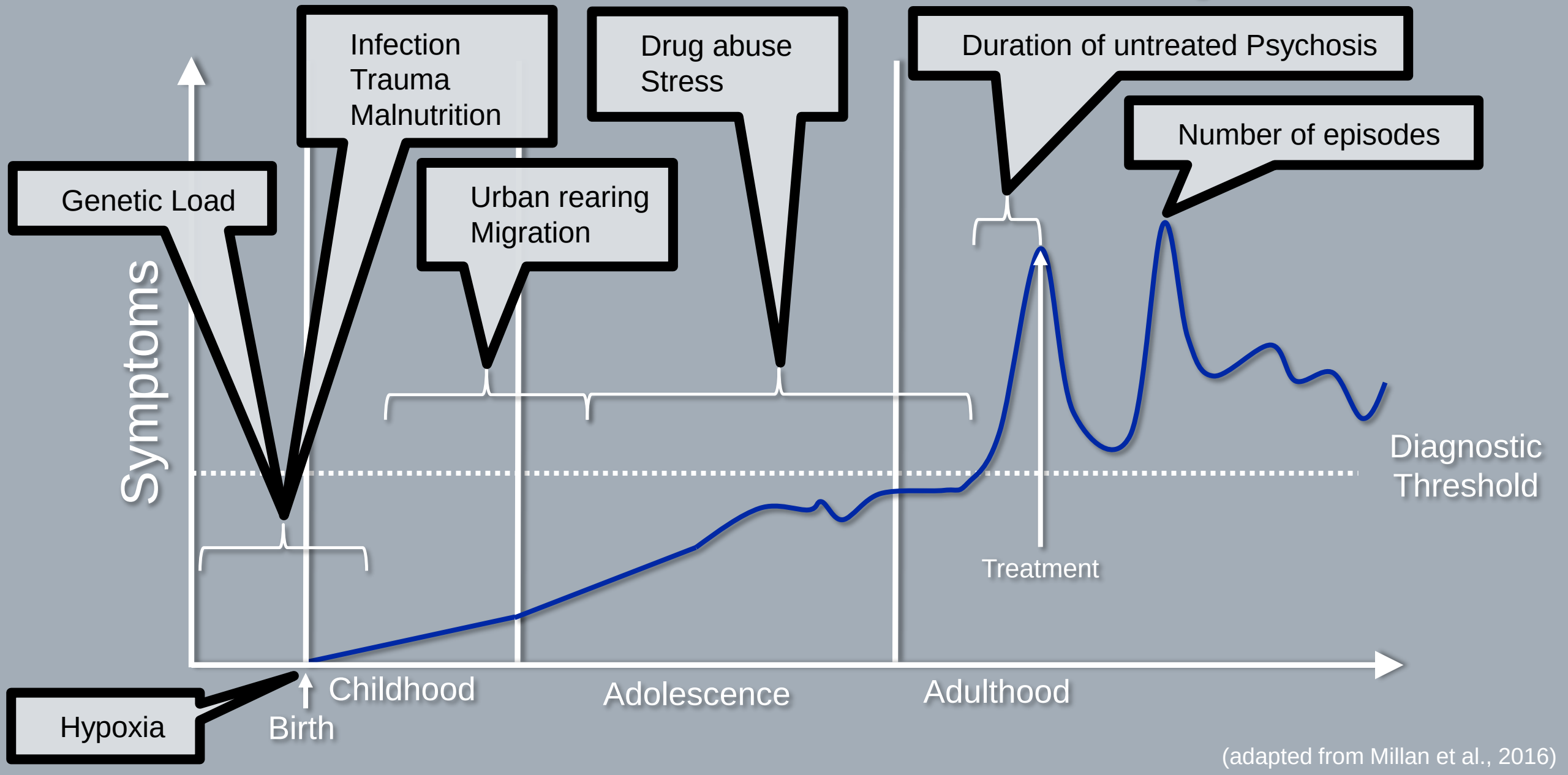
(modified from Tandon et al., 2009)

Course: Episodes & Outcome



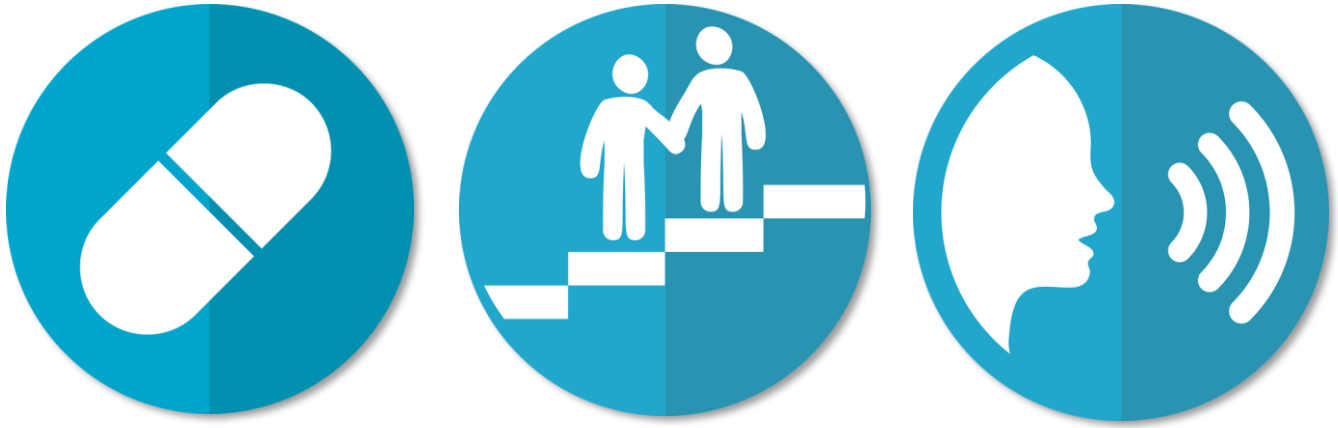
(modified from Tandon et al., 2009)

Risk Factors across Lifespan



(adapted from Millan et al., 2016)

Clinical Care



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

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

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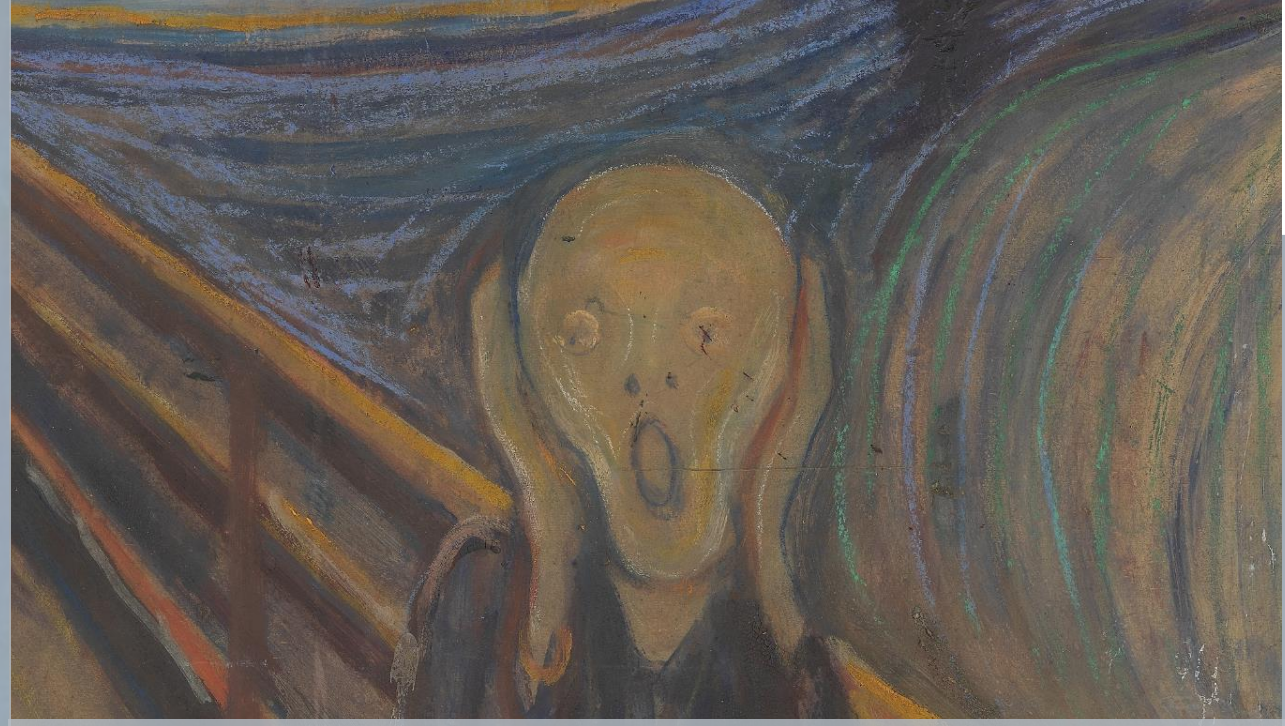
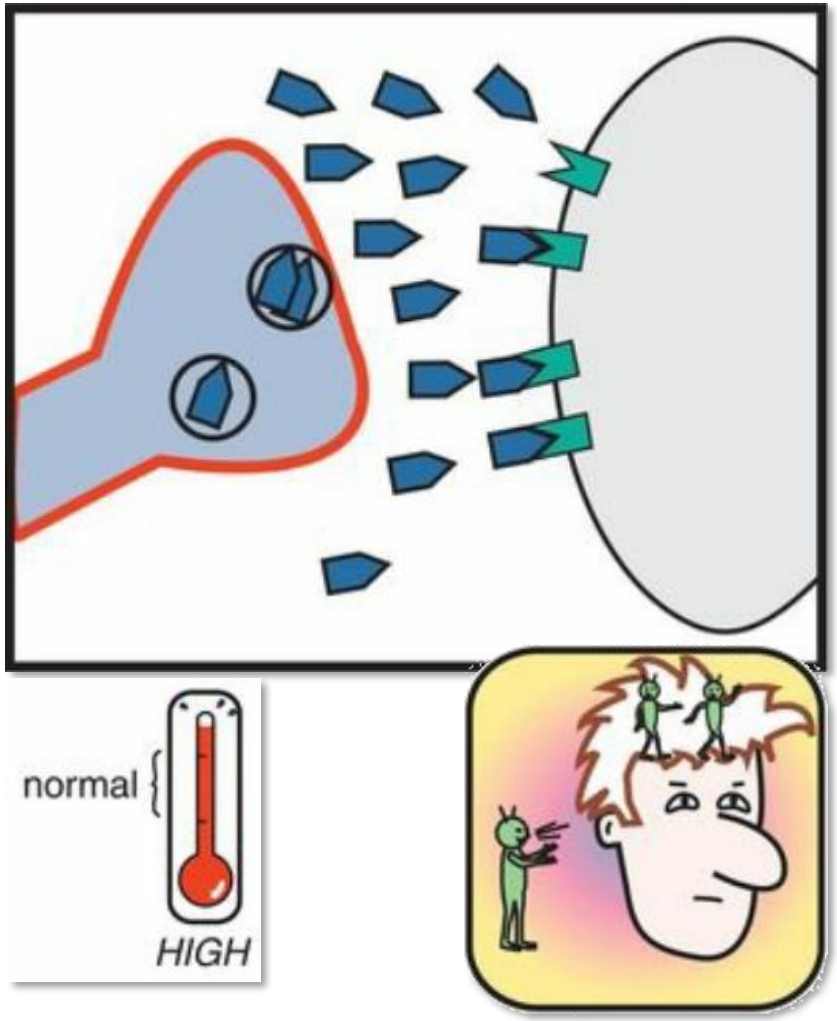


- Risperidone → remission after 20d
- Day care clinic for 6wks
- Returns to uni after 9wks

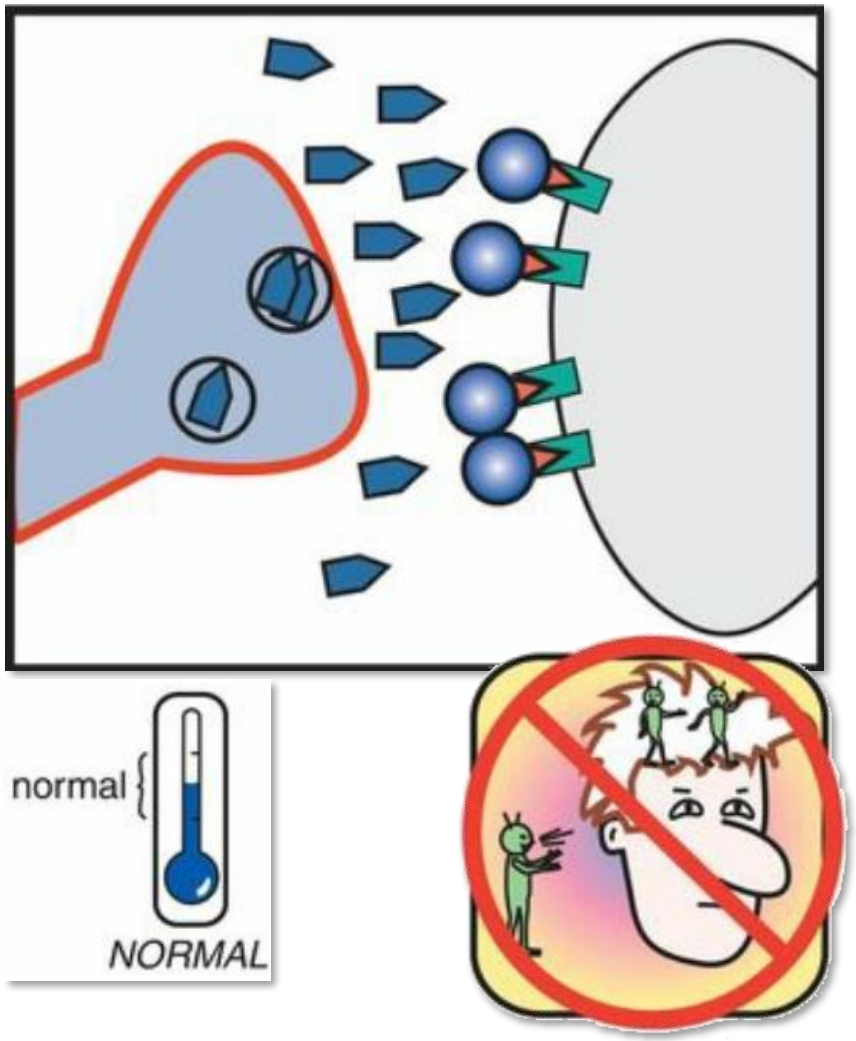
Antipsychotics

Mesolimbic Pathway
Untreated Schizophrenia



“hyperactive” dopaminergic system

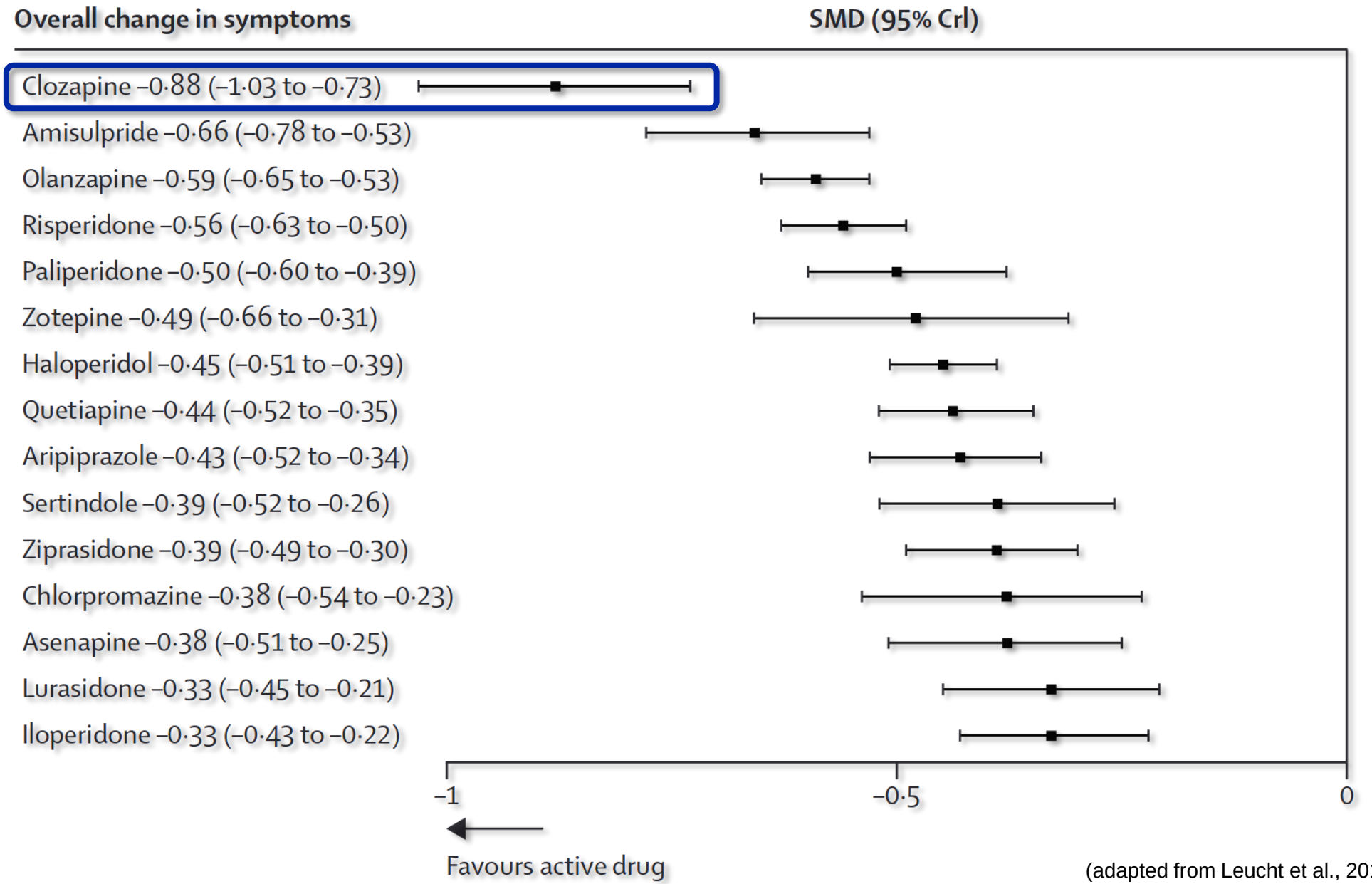
Mesolimbic Pathway
D2 Antagonist



“normalized” dopaminergic system

(Stahl, 2013)

Antipsychotics



(adapted from Leucht et al., 2013; Huhn et al., 2019)

Antipsychotics

- 50% respond to 1st line treatment
  Response ≠ remission, recovery or cure
- No prediction which antipsychotic is effective → *"trial & error"*
  in CH: 24 licensed, ~14 relevant for the treatment of Schizophrenia
- Major problem: discontinuation of treatment
  - Side effects
  - Poor insight

Treatment Strategies

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

Treatment Strategies

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

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

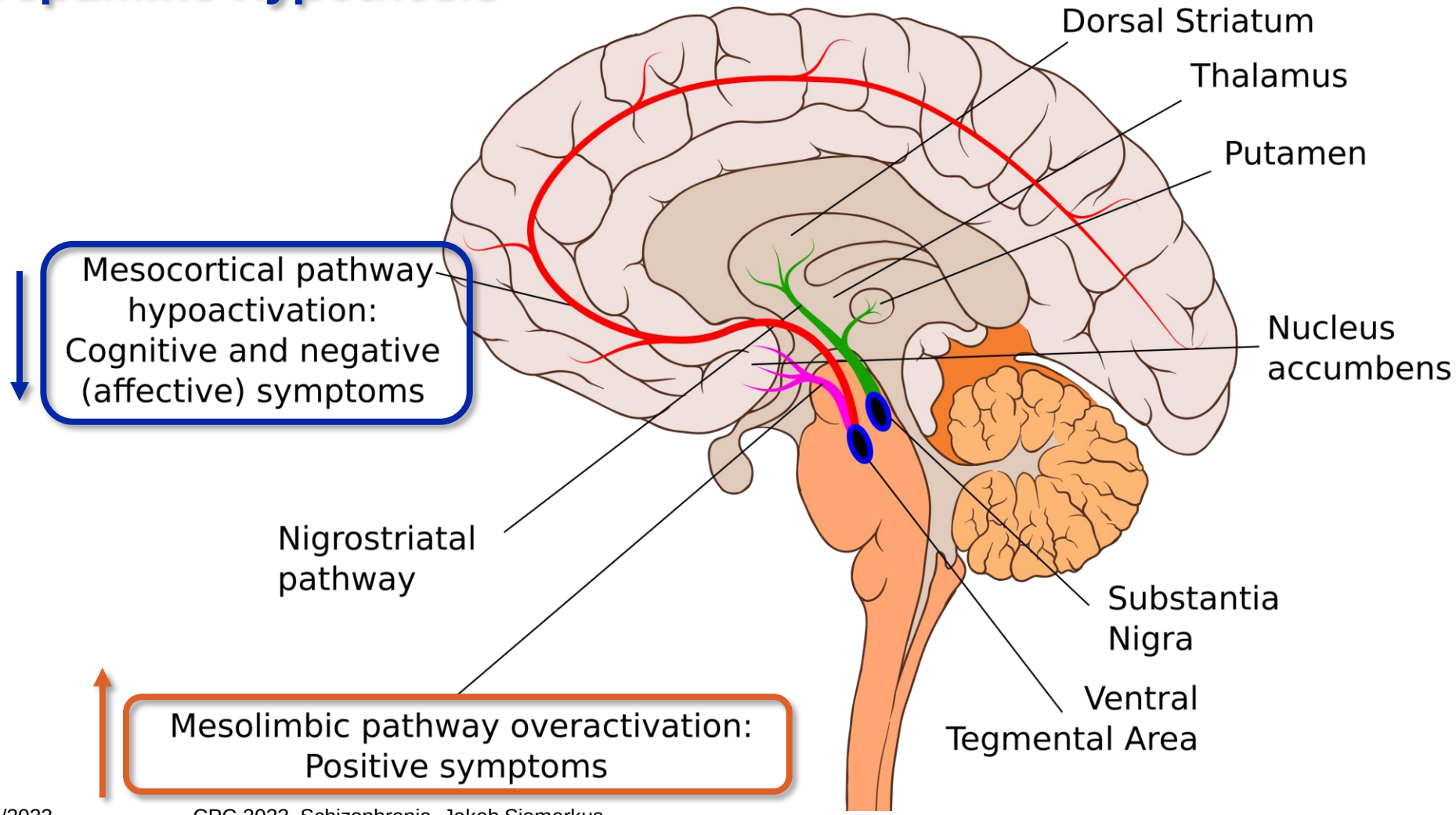
Treatment Strategies

(Schizophrenia Canada, 2018)

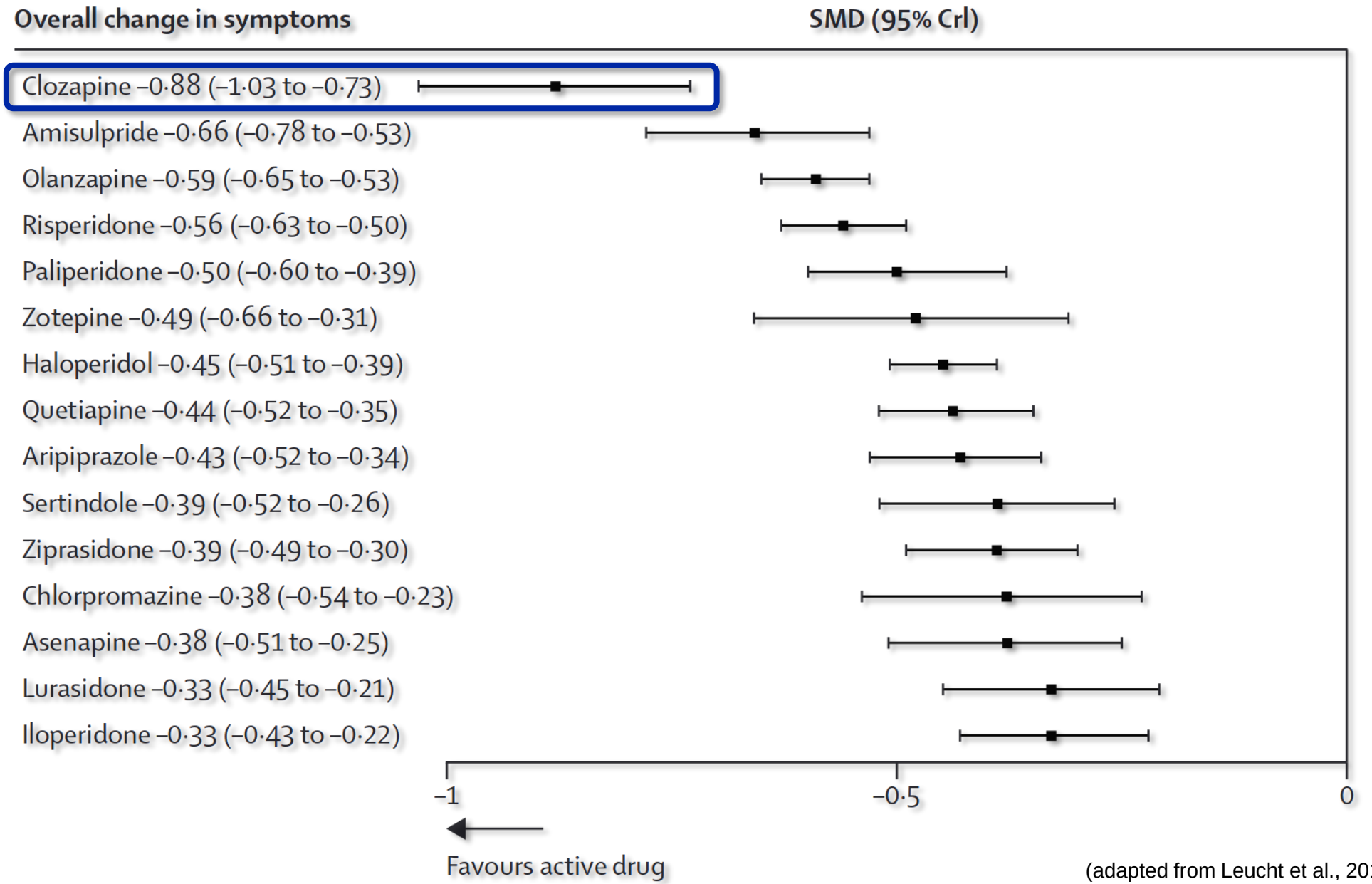
Pathophysiology

- **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
- **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
  - „By-product" of evolution of language (Crow, 2000)

Dopamine Hypothesis

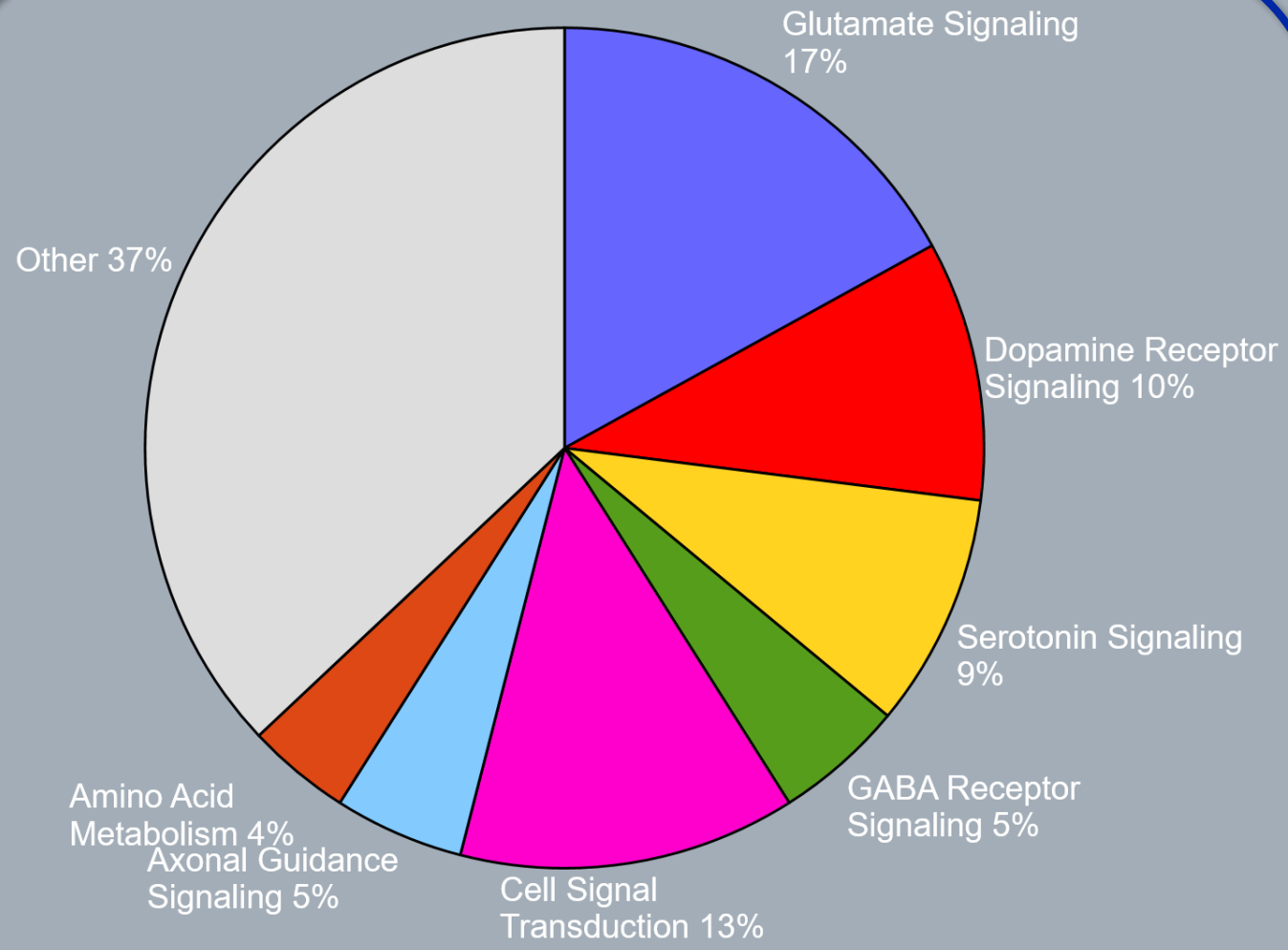


Antipsychotics



(adapted from Leucht et al., 2013; Huhn et al., 2019)

Genetic Evidence



(adapted from Greenwood et al., 2012)

Genome-wide association study of >35,000 cases:

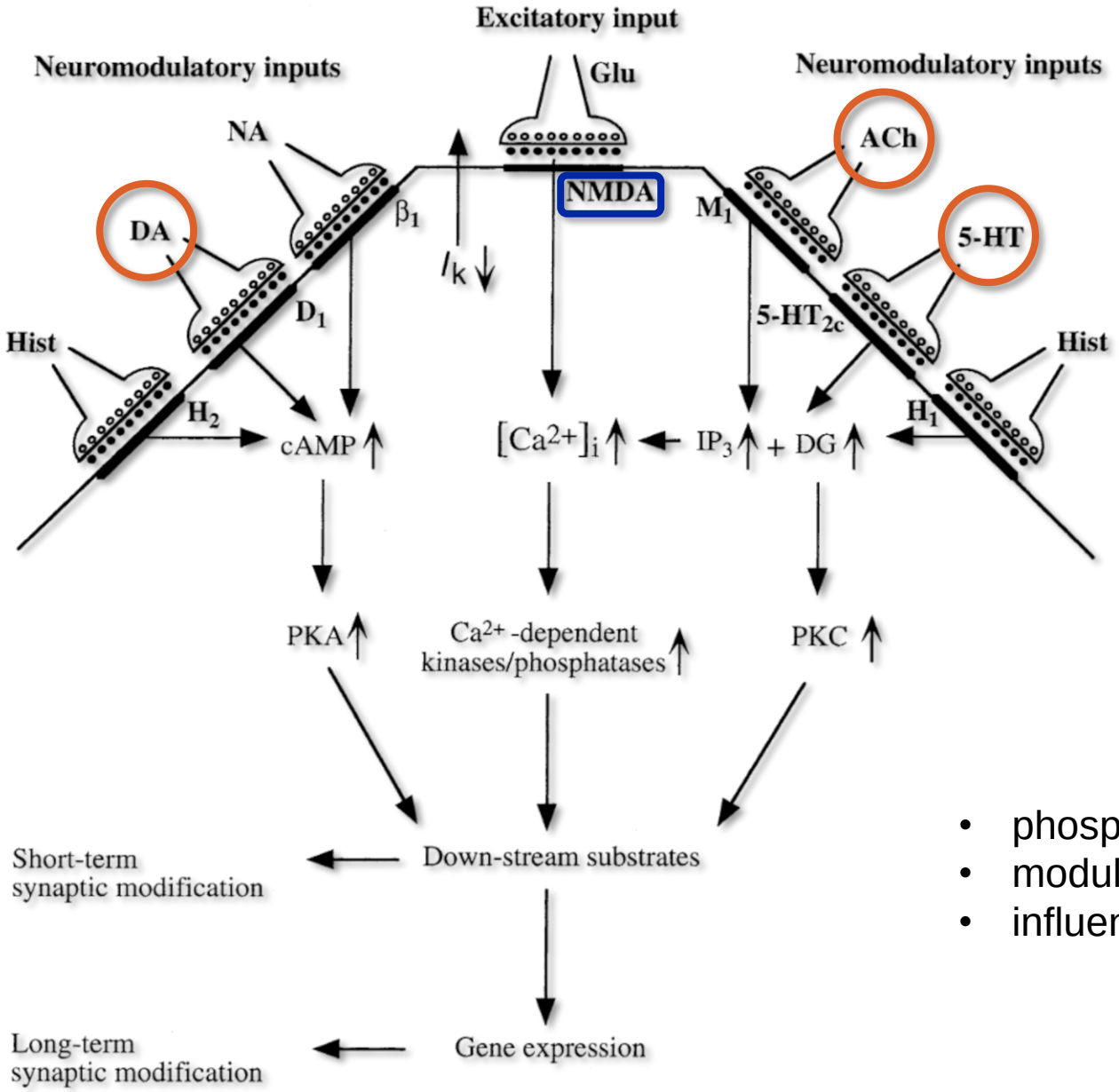
Dopamine
- DRD2

Glutamate/NMDAr
- GRM3
- GRIN2A
- GRIA1
- SRR

Acetylcholine
- CHRNA3
- CHRNA5
- CHRNB4

(SWGPGC, 2014)

NMDAR × neuromodulator interactions

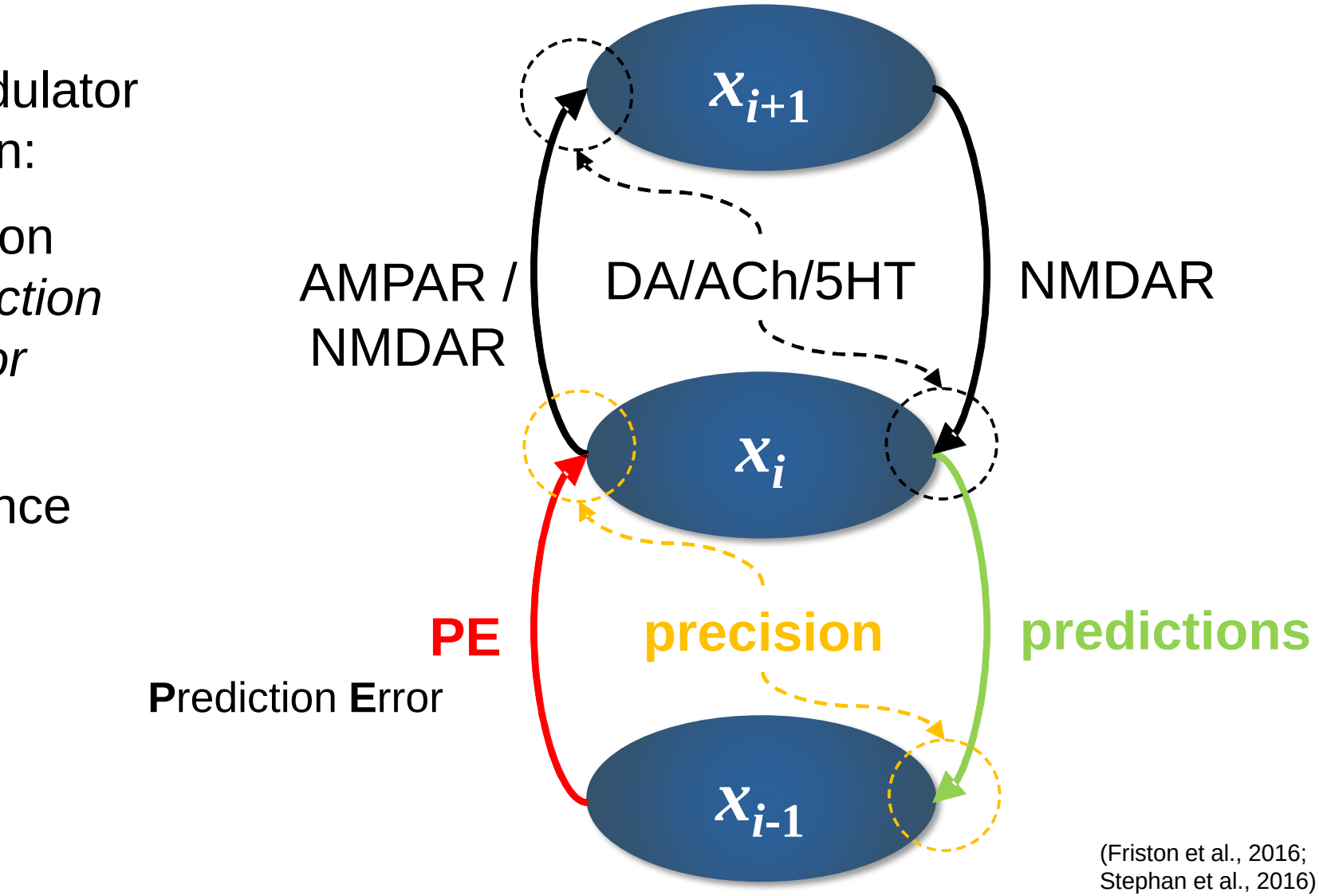


- phosphorylation of NMDARs
- modulation of membrane potential
- influence on receptor trafficking

(Gu, 2002)

Dysconnection Hypothesis

- NMDAR × neuromodulator interaction dysfunction:
  - Disturbed modulation (*precision*) of *prediction* and *Prediction Error* signals
  - Non-optimal inference



(Friston et al., 2016; Stephan et al., 2016)

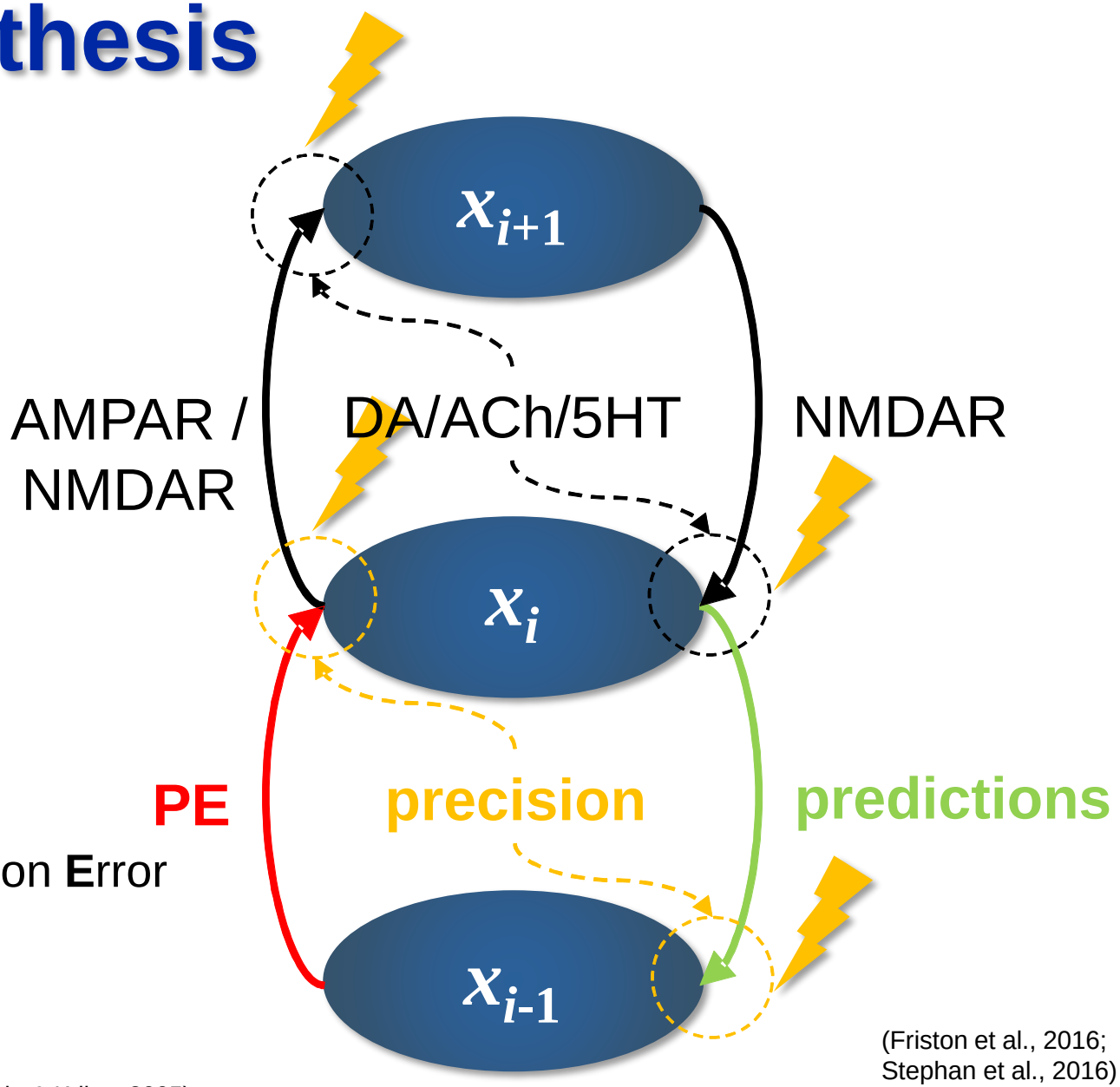
Dysconnection Hypothesis

„Overweight“ of Prediction Errors:
Trait phenomena?

- ↓ Susceptibility to illusions
- Aberrant Salience, Delusional Mood
- …

„Overweight“ of predictions:
State phenomena?

- Delusions
- Acoustic hallucinations
- …



(Friston et al., 2016; Stephan et al., 2016)

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

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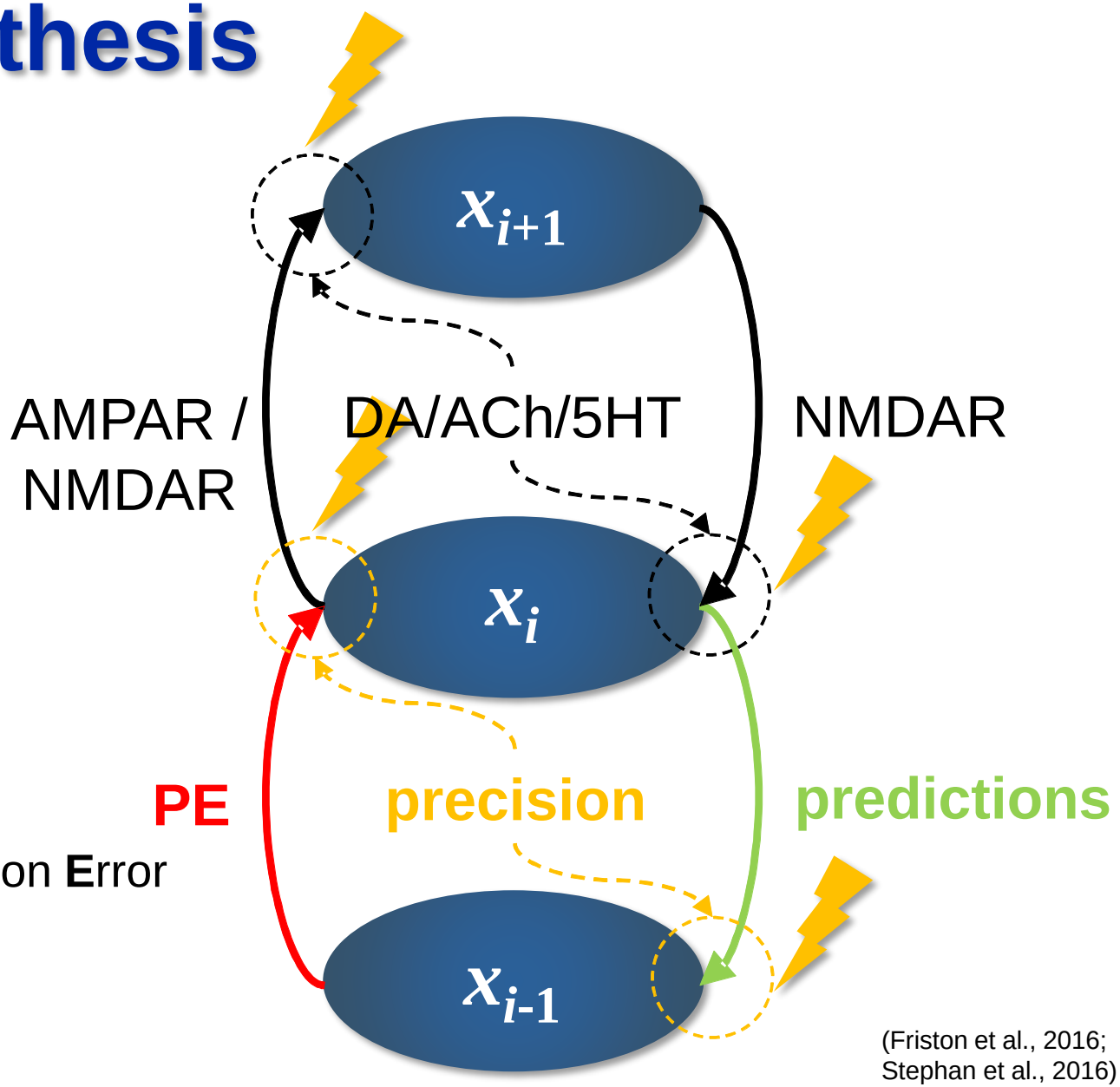


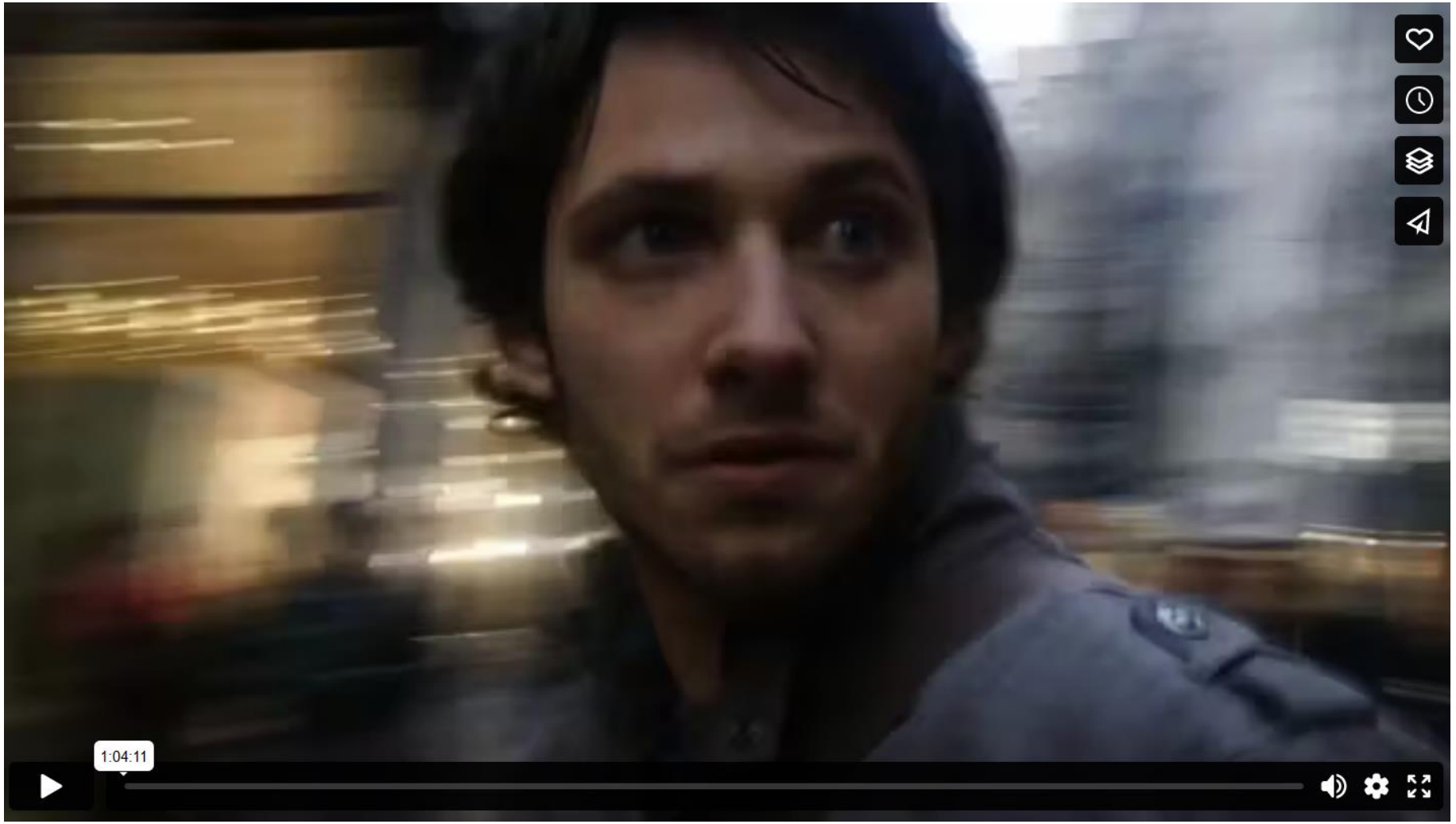
(Friston et al., 2016; Stephan et al., 2016)

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

To summarize…

- Severe mental disorder
- Functional impairment
- Heterogeneous
  - Risk factors – pathophysiology – symptoms – course - treatment response
- Antipsychotics are effective, but
  - focus on recovery!
- Computational Psychiatry → new approaches to treatment?

“Lost Years” by Bas Labruyère



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

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