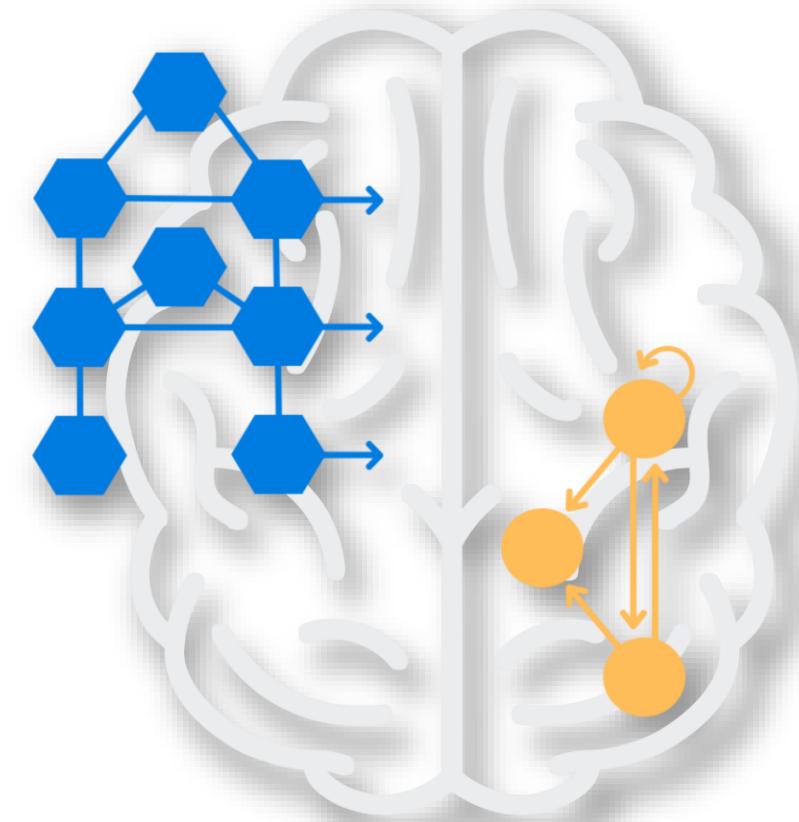


Schizophrenia (for non-clinicians)

01.09.2025, CPC Zurich

Dr. med. Jakob Siemerkus
Translational Neuromodeling Unit
University of Zurich & ETH Zurich

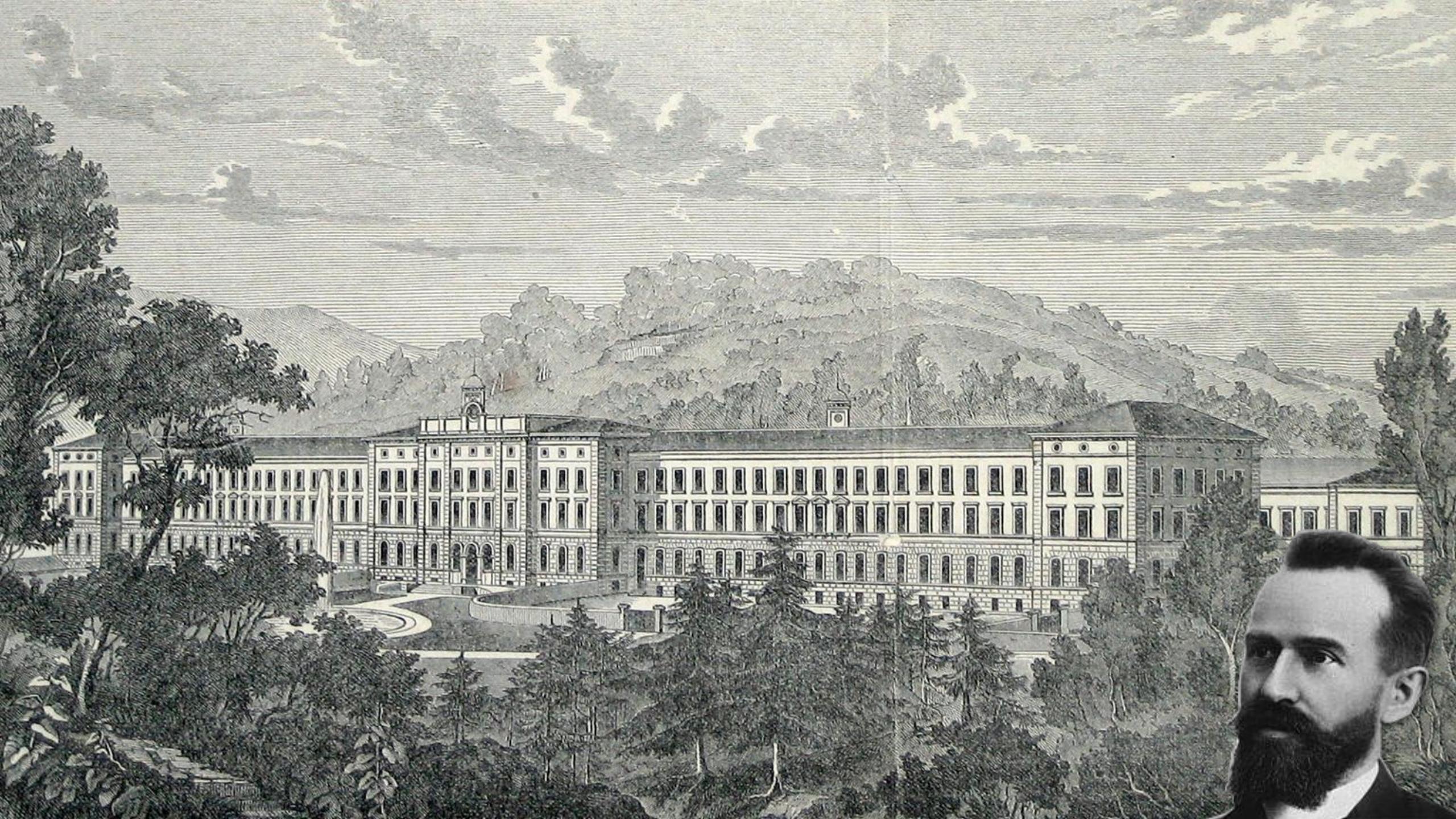
siemerkus@biomed.ee.ethz.ch





Why is it important to know about schizophrenia?

- One of the “major” psychiatric disorders
- 0.5% prevalence (Saha, 2005)
- Functional impairment (42 DALYs; GBD 2019 Mental Disorders Collaborators, 2022)
- Social dimension (Holm et al., 2021; Lin et al., 2022)
- 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“
(Yamaguchi, 2017; Angermeyer, 2004)



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Clinical Manifestation







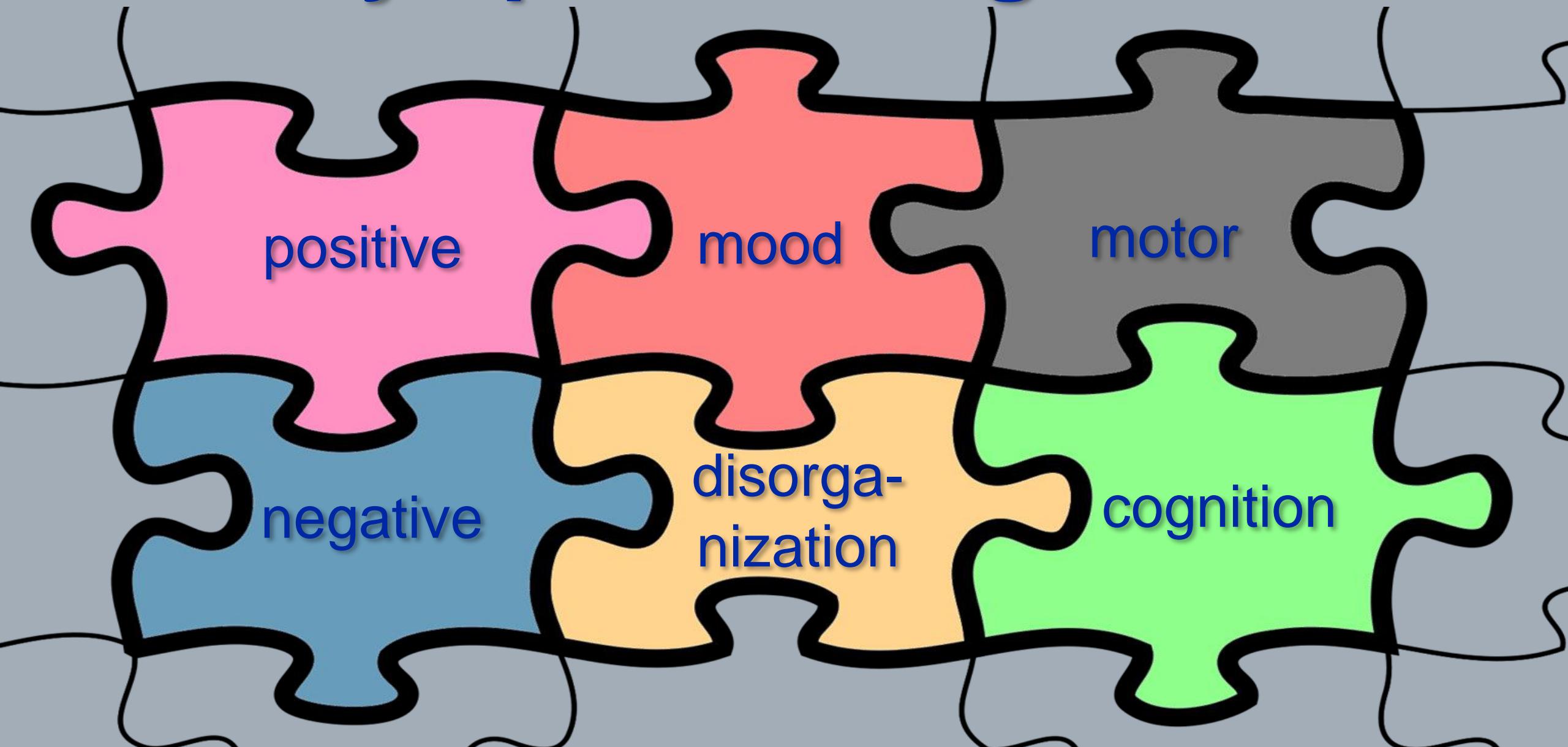
- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
- Apathy
- Slowed down
- Lost her job months ago

- 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 $\frac{1}{2}$ year





Symptom Categories



Symptom Categories



positive

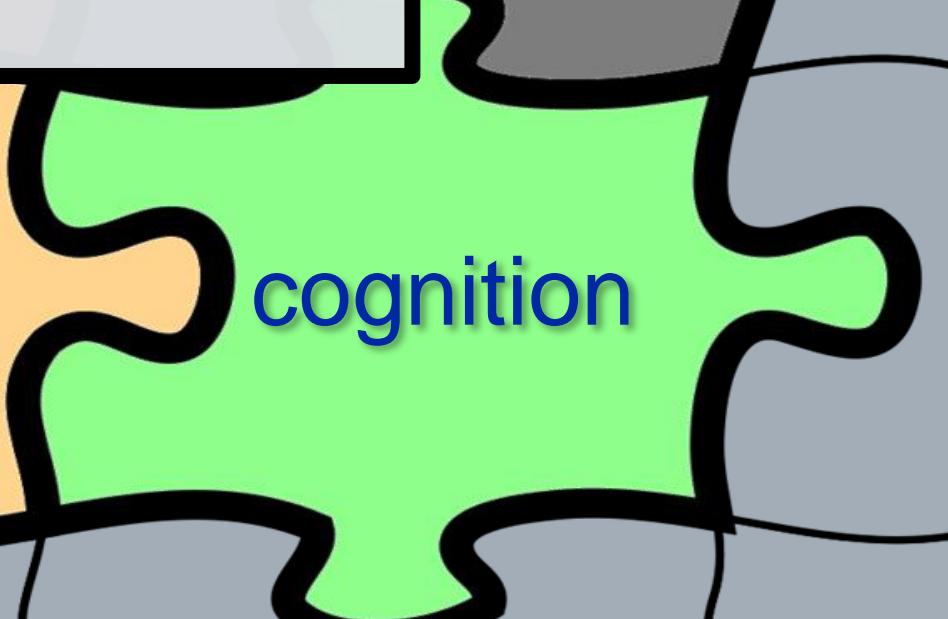
- “failure in reality testing”
- delusion
- hallucination
- ego-boundary distortion



negative

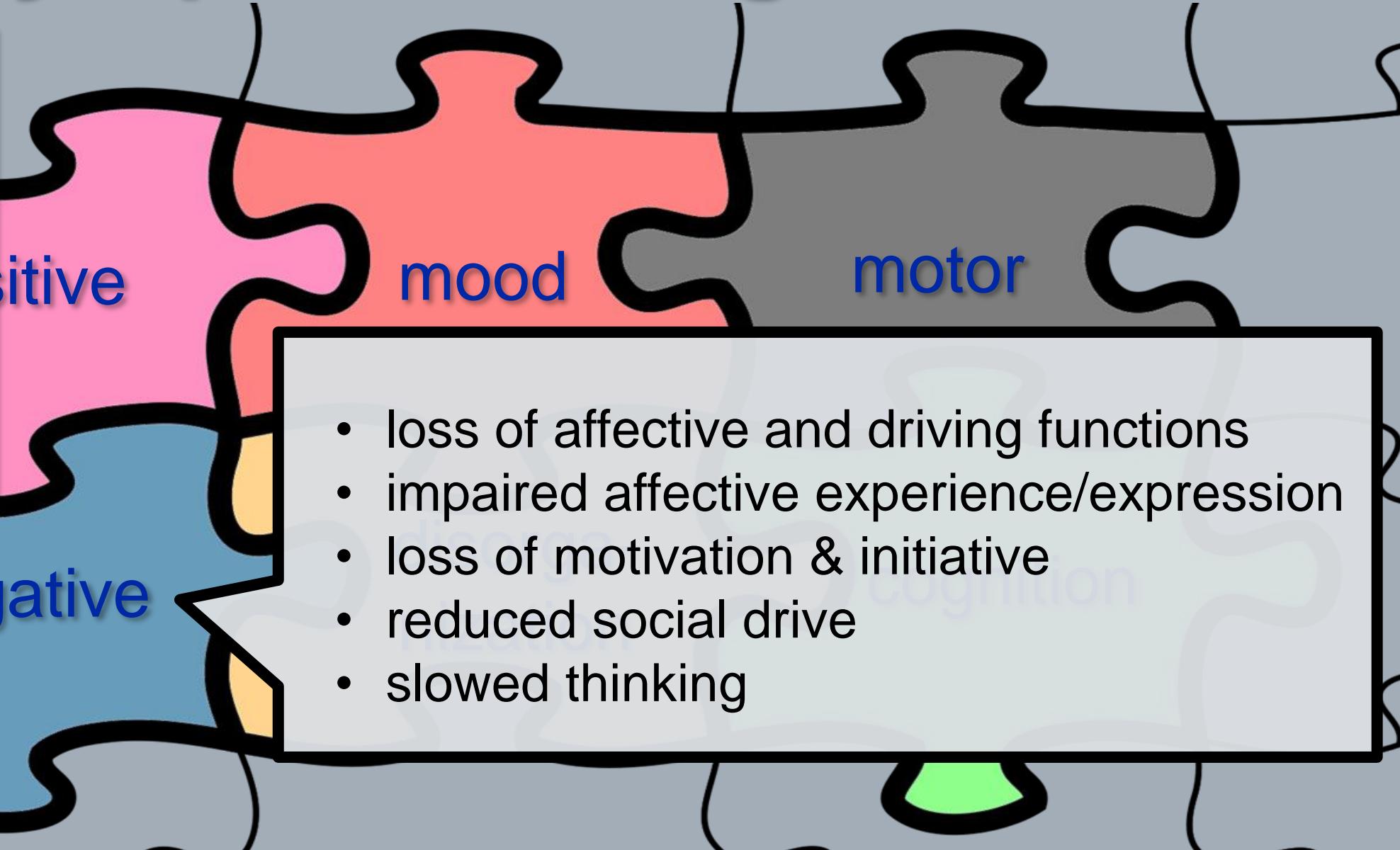


disorga-
nization

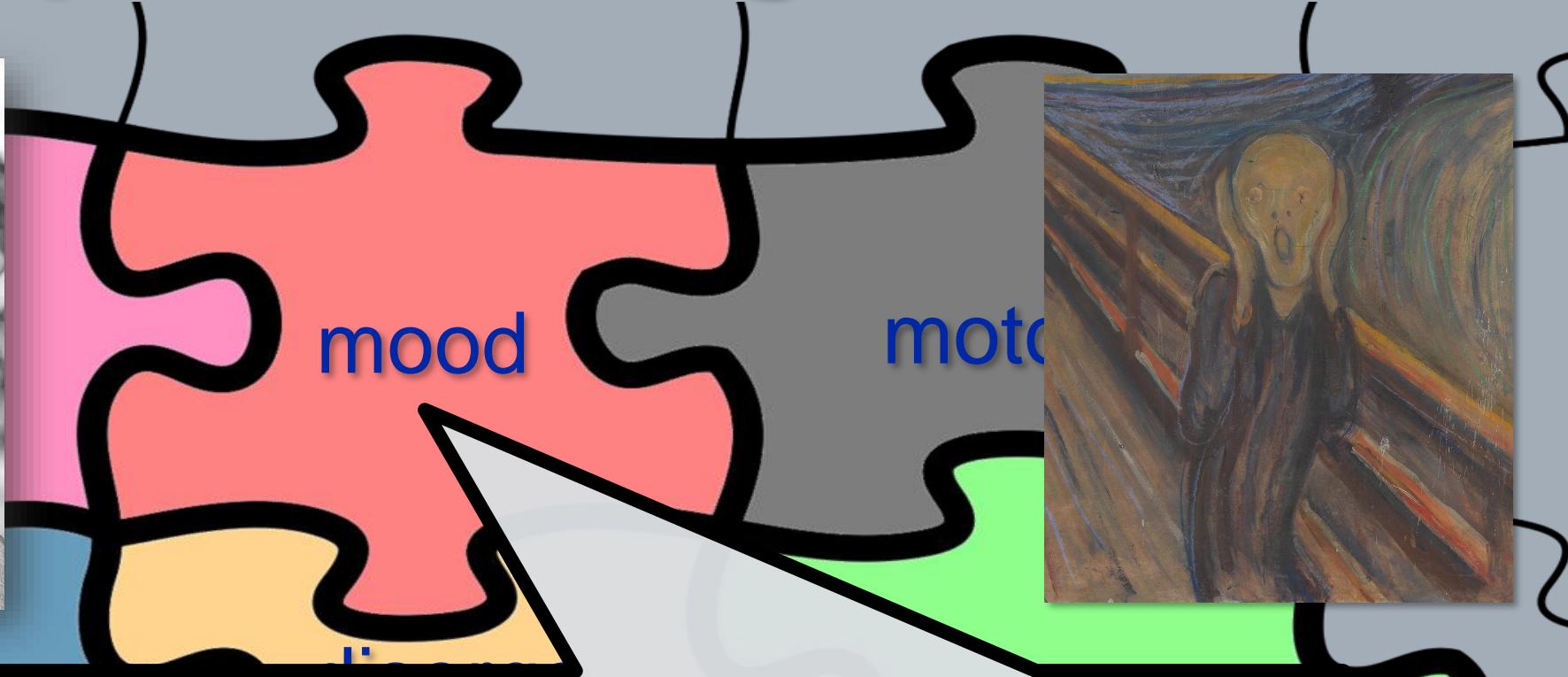


cognition

Symptom Categories

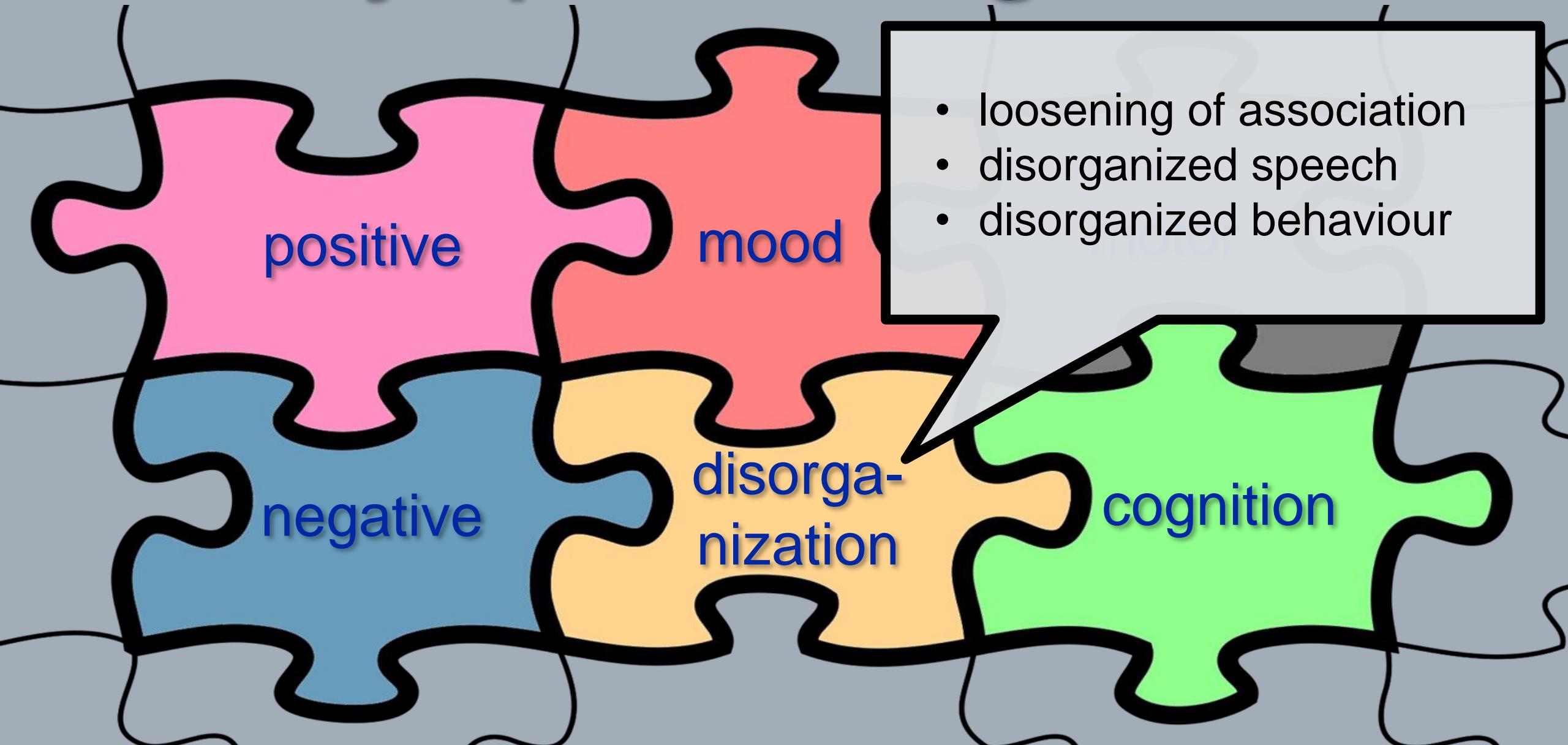


Symptom Categories

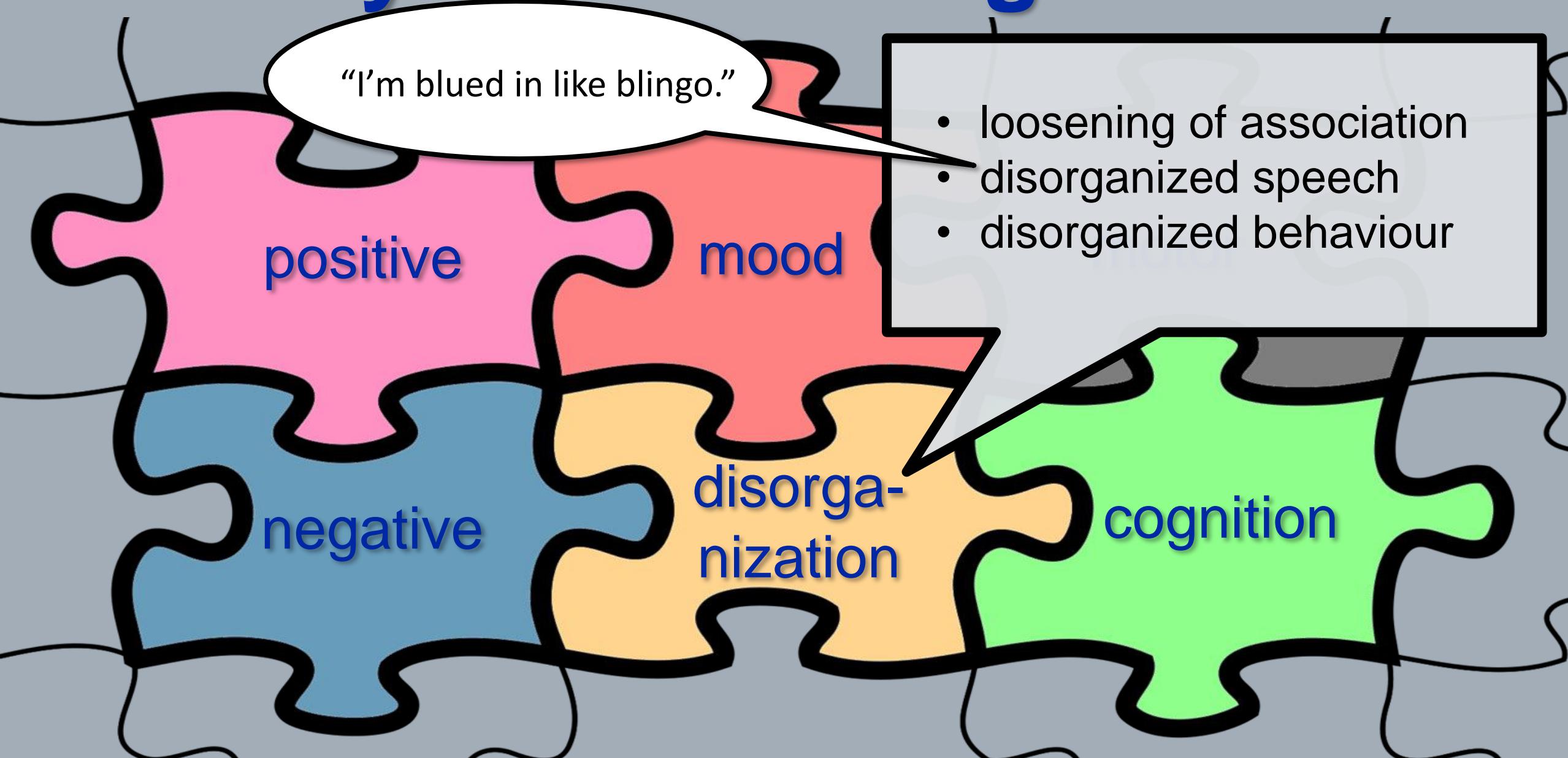


- overlap with negative symptoms
- anxiety, emotional arousal, and depression very frequent

Symptom Categories

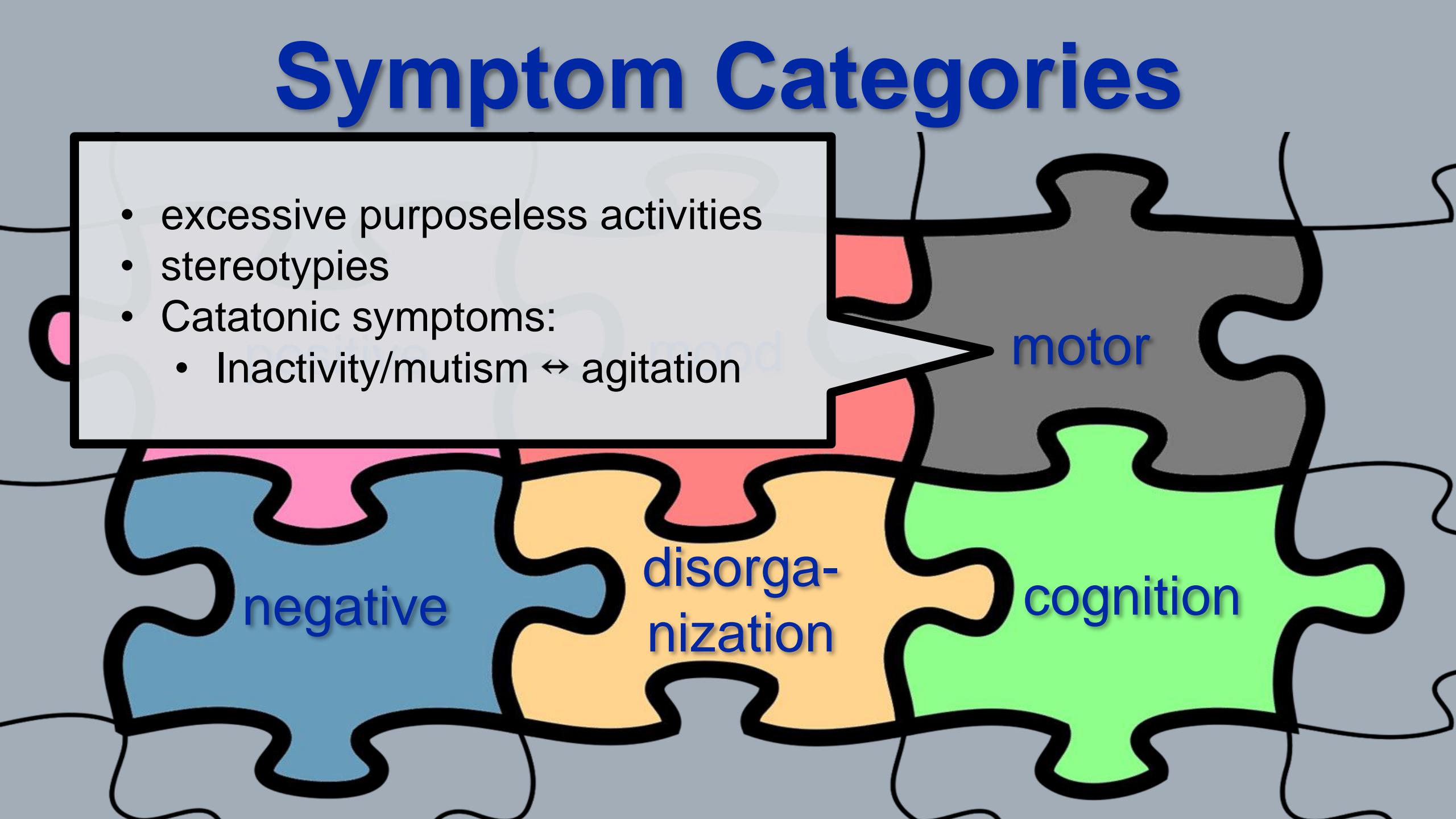


Symptom Categories



Symptom Categories

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



negative

disorga-
nization

motor

cognition

Symptom Categories

-
- general cognitive deficits
 - pronounced in domains like working memory

negative

organization

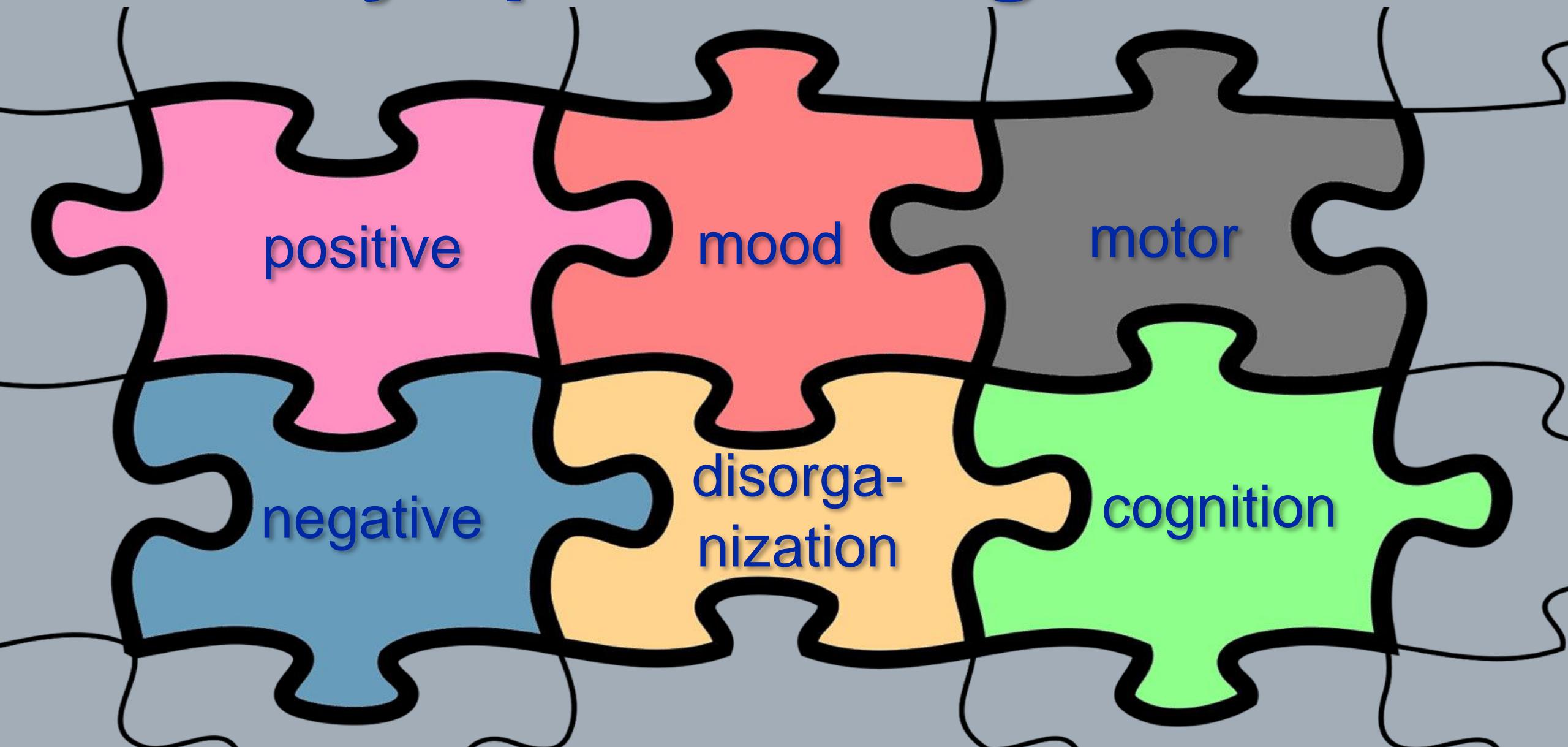
positive

mood

motor

cognition

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• disorganized or catatonic behaviour

(APA, 2013)



- 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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(APA, 2013)



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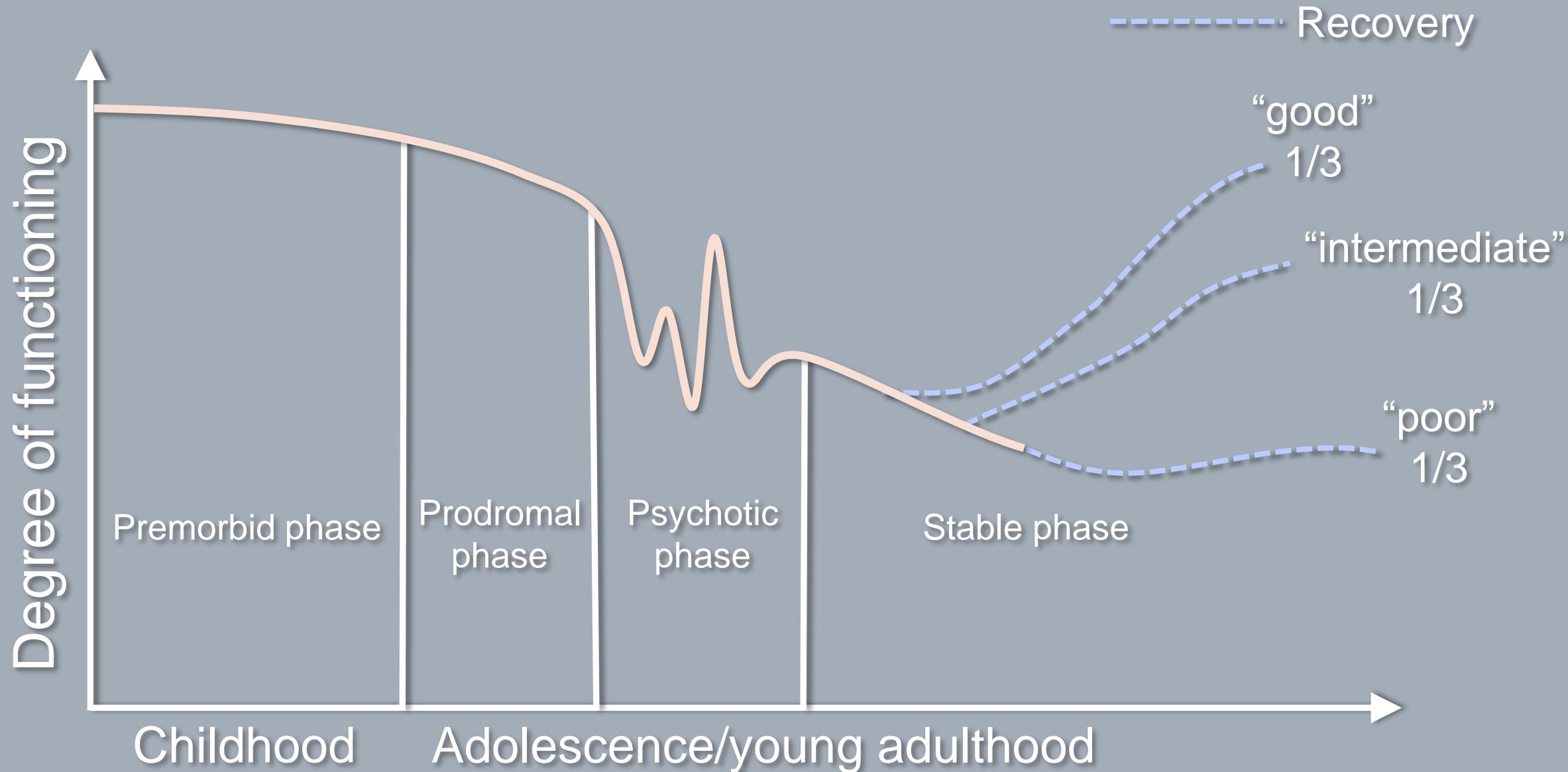


Translational Neuromodeling Unit

Course, Risk Factors, Outcome

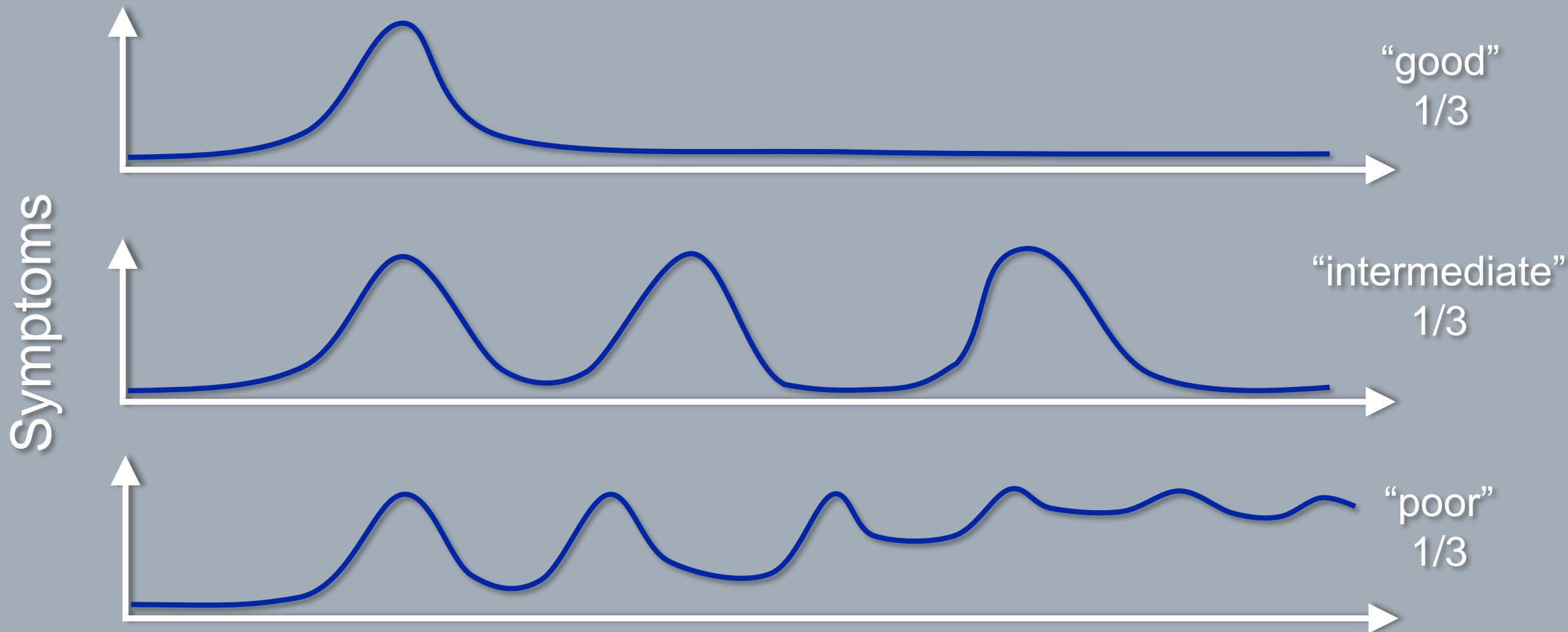


Course of Schizophrenia



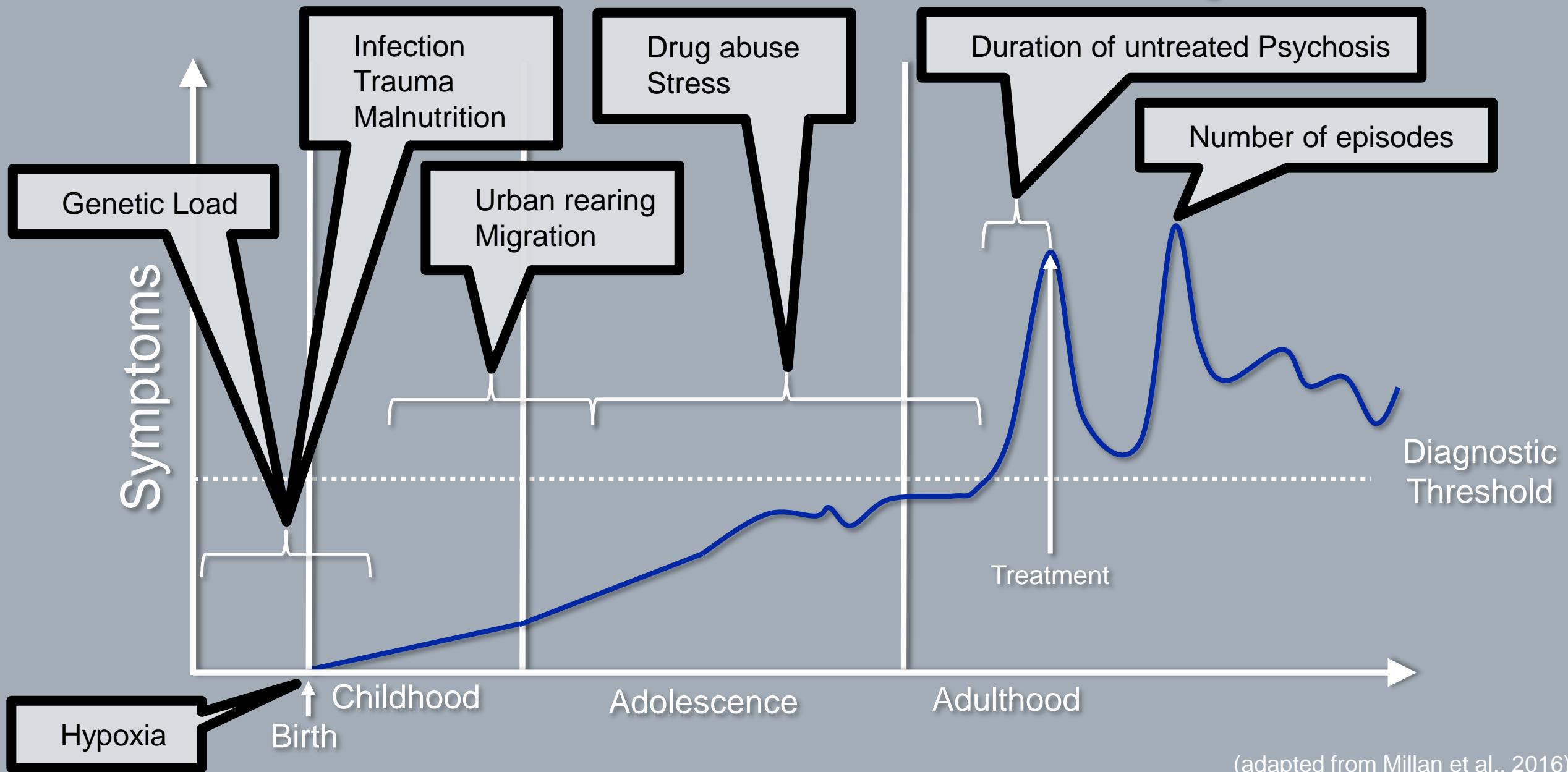
(modified from Tandon et al., 2009)

Course: Episodes & Outcome



(modified from Tandon et al., 2009)

Risk Factors across Lifespan





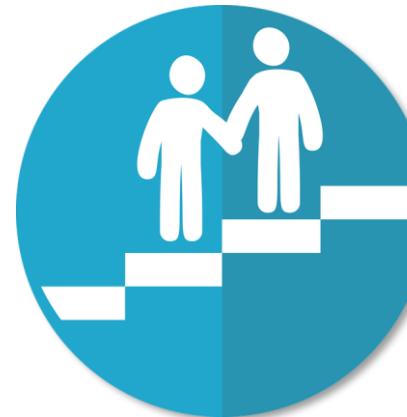
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Translational Neuromodeling Unit

Clinical Care





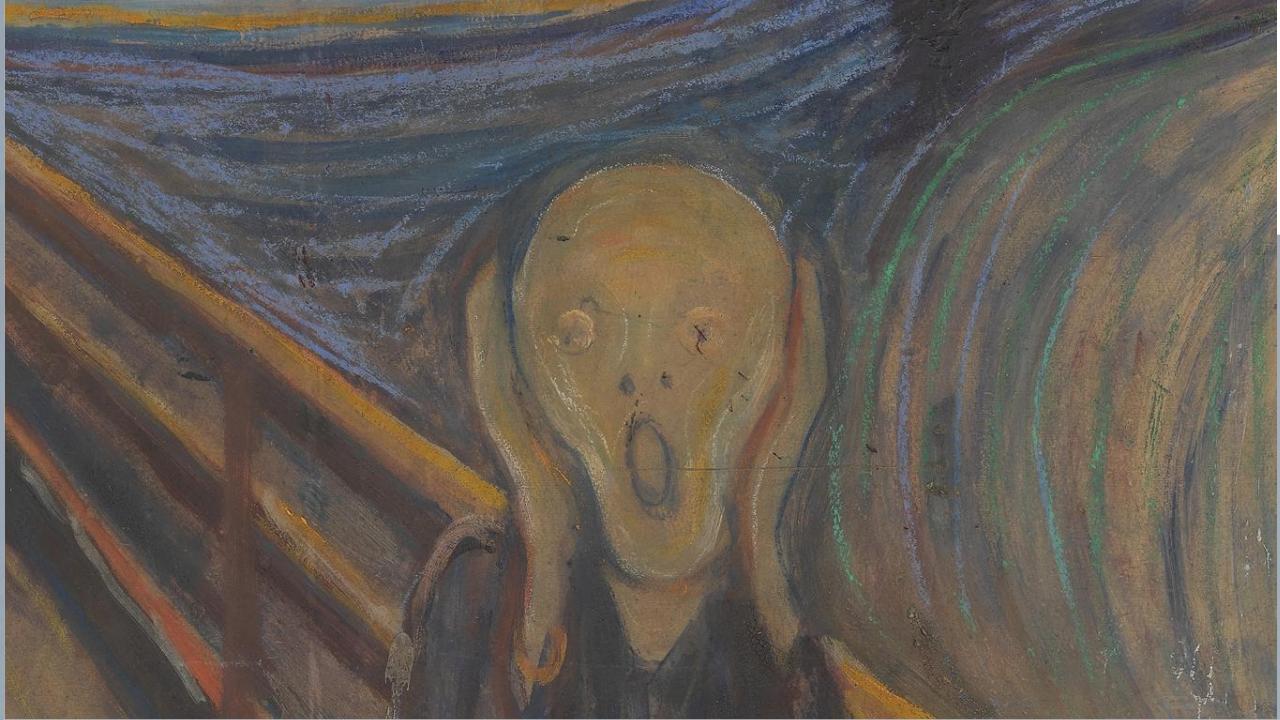
- Aripiprazole → no improvement
- Risperidone → improvement, but motor side-effects
- Clozapine → function improves much
- Discharge to live with parents after 3 months

- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
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- Exam & lab results ok
- Starts talking, uses “blue” in many contexts like “I’m blued in like blingo.”

→ Schizophrenia

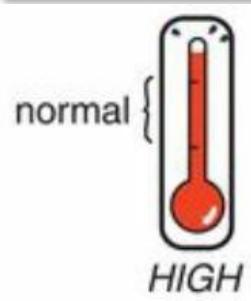
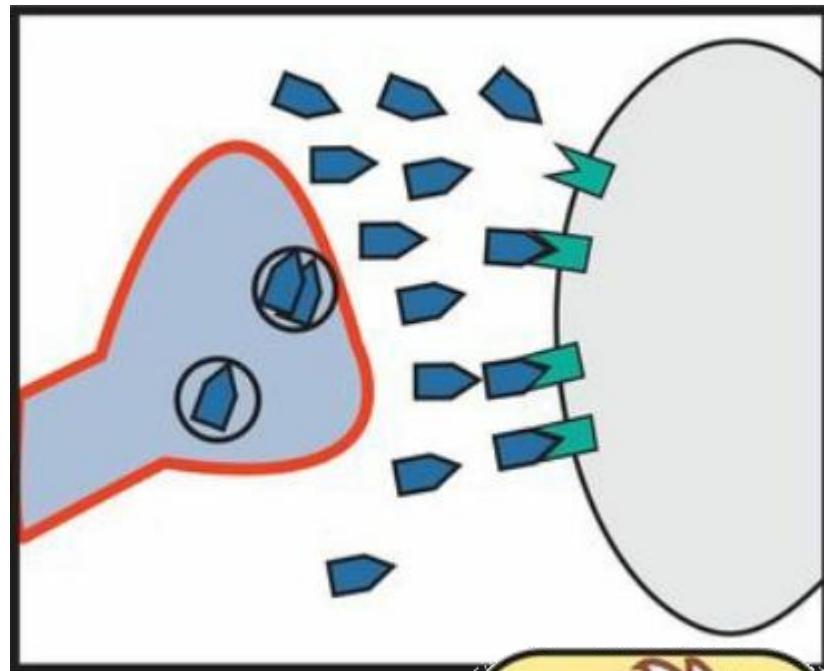
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 - Started six weeks ago
 - Did not attend classes for $\frac{1}{2}$ year
- Exam, lab & MRI results ok
- Schizophrenia



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

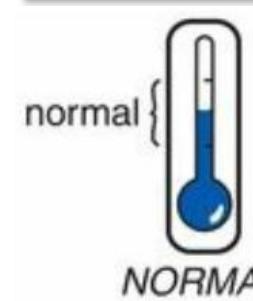
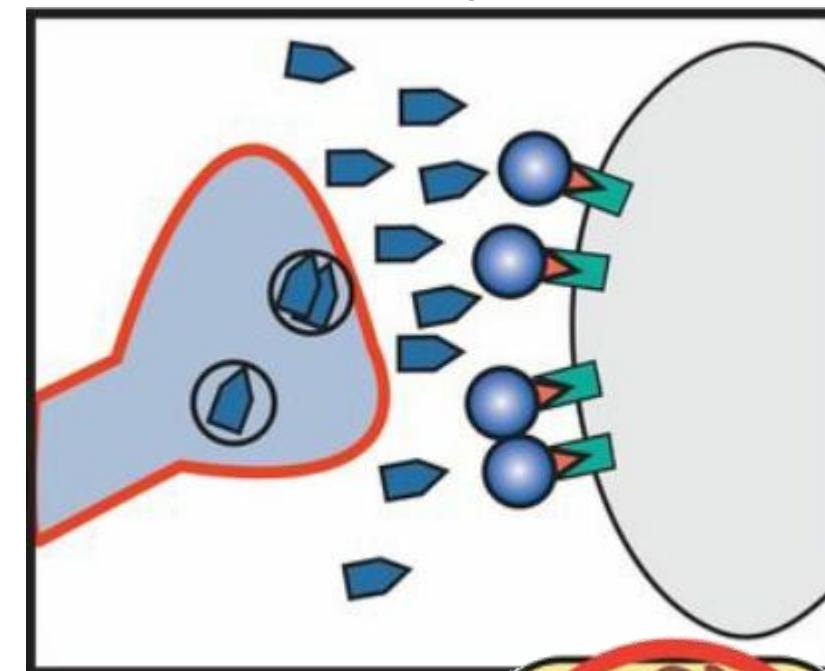
Antipsychotics

Mesolimbic Pathway
Untreated Schizophrenia



"hyperactive" dopaminergic system

Mesolimbic Pathway
D2 Antagonist

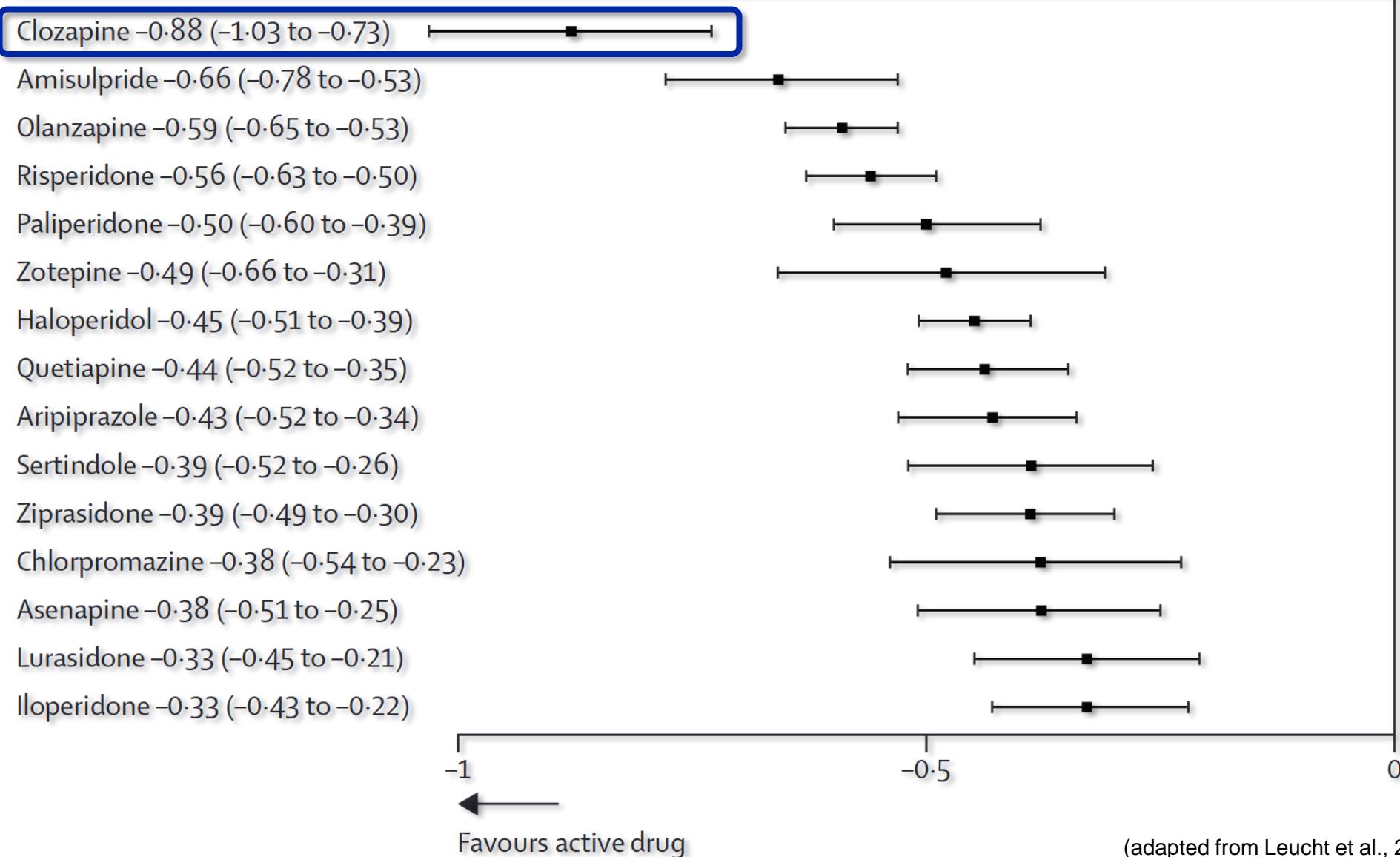


"normalized" dopaminergic system

Antipsychotics

Overall change in symptoms

SMD (95% CrI)



(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

- Lack of insight, hostility:
 - Building trust, therapeutic relationship & working alliance
- Side-effects:
 - Management and prevention of side-effects
- Duration of untreated psychosis:
 - Early treatment with antipsychotics

Treatment Strategies

- Functional impairment, negative symptoms:
 - Activation & social support, social skills training, cognitive remediation
 - Low-threshold medical service
- Insight, problems with coping, further episodes:
 - Psychoeducation

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



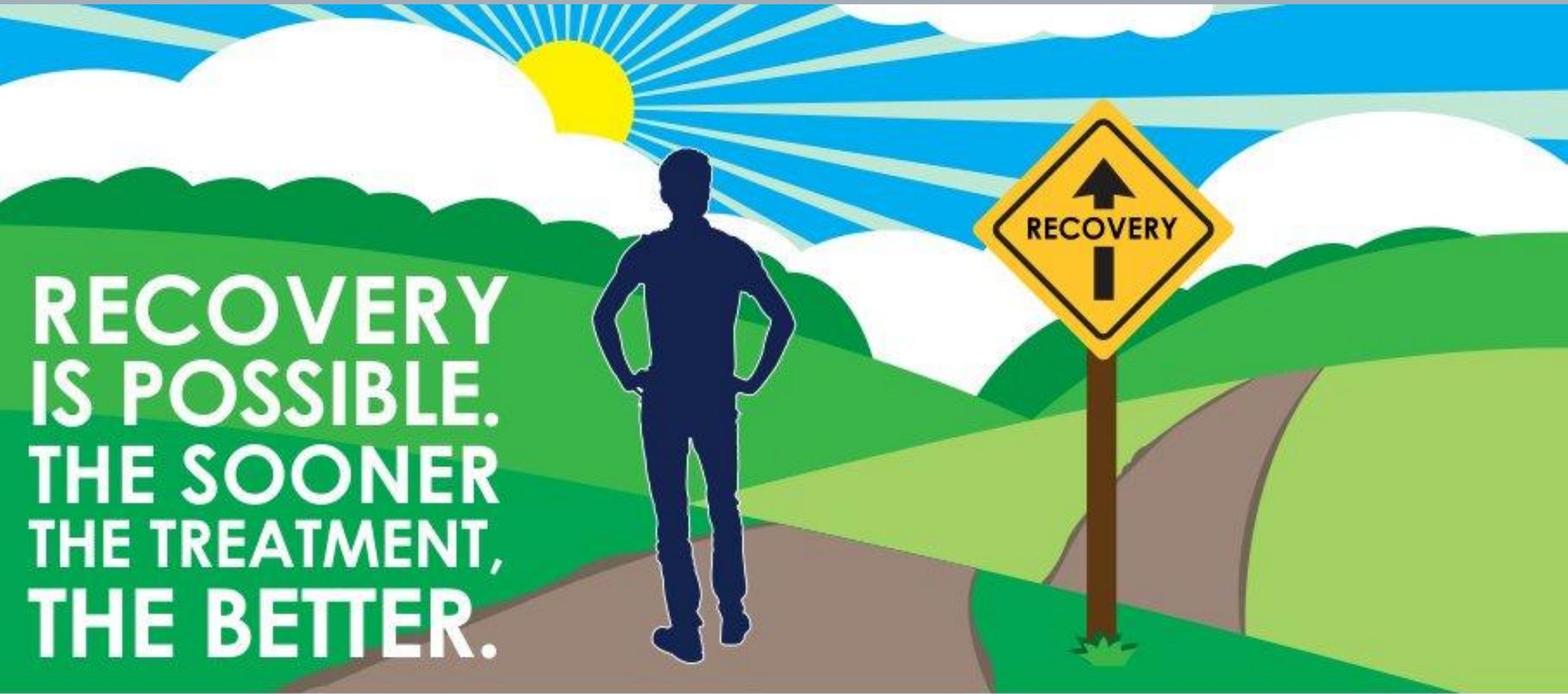
Treatment Strategies

- Stress reduction:
 - Involve families & caregivers
 - Symptoms resistant to antipsychotic treatment, stressful experience of symptoms:
 - Cognitive Behavioural Therapy / Motivational Interviewing

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

Treatment Strategies

(Schizophrenia Canada, 2018)



**RECOVERY
IS POSSIBLE.
THE SOONER
THE TREATMENT,
THE BETTER.**

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





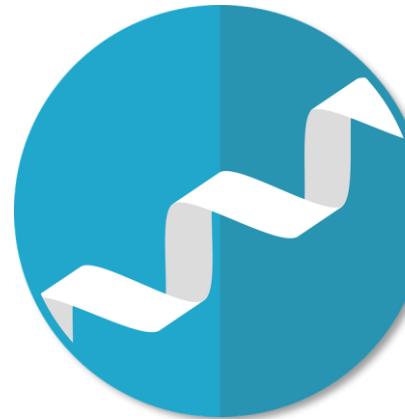
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Translational Neuromodeling Unit

Pathophysiology





- **Phenotypic 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
 - **Etiological**
 - Polygenic/multifactorial (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
 - „By-product“ of evolution of language (Crow, 2000)
- ???



ELSEVIER

medical
hypotheses

<http://intl.elsevierhealth.com/journals/mehy>

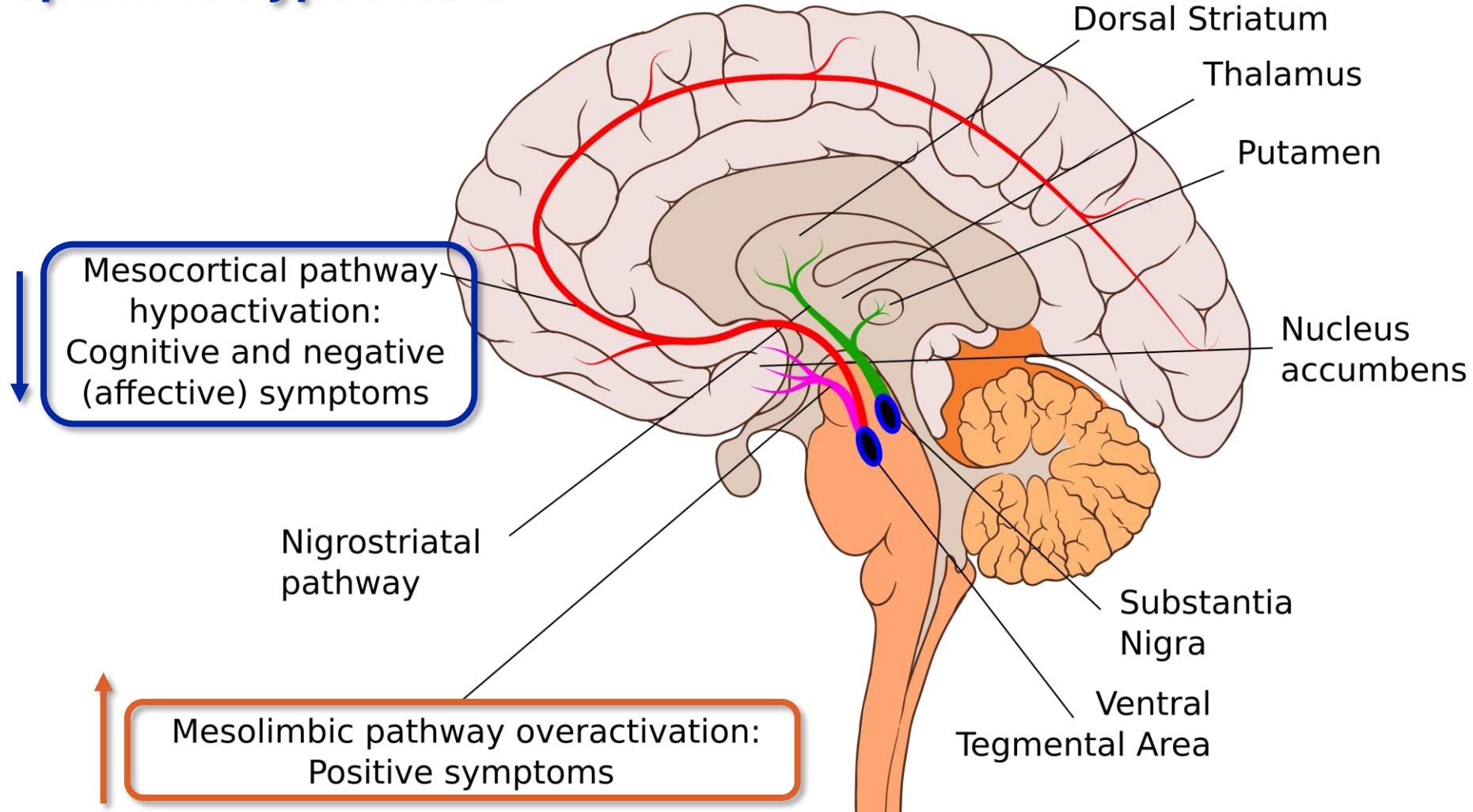
Is there an association between the use of heeled footwear and schizophrenia?

Jarl Flensmark*

Kristianstadsgatan 23 C, S-214 23 Malmö, Sweden

Received 15 April 2004; accepted 4 May 2004

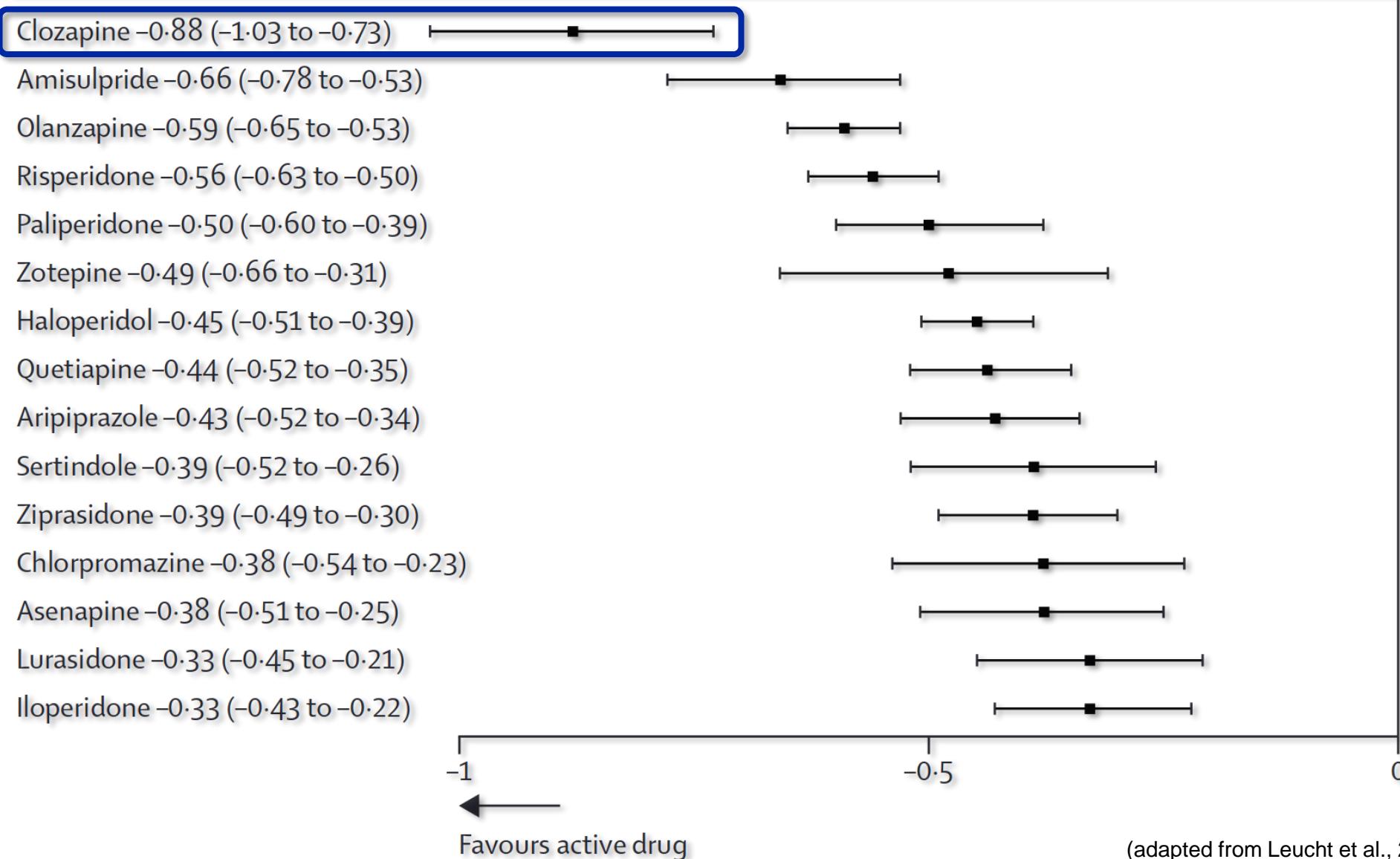
Dopamine Hypothesis



Antipsychotics

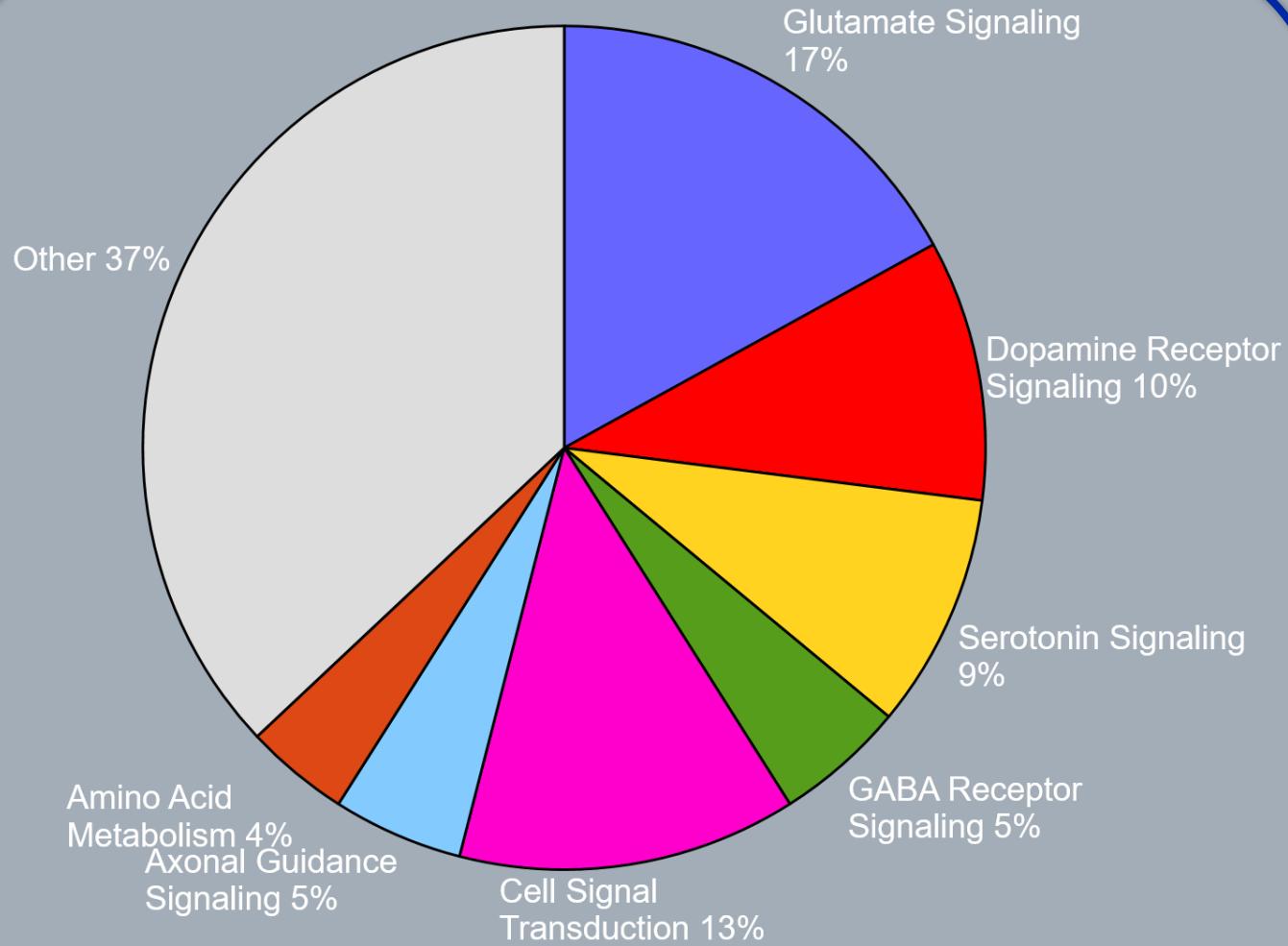
Overall change in symptoms

SMD (95% CrI)



(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

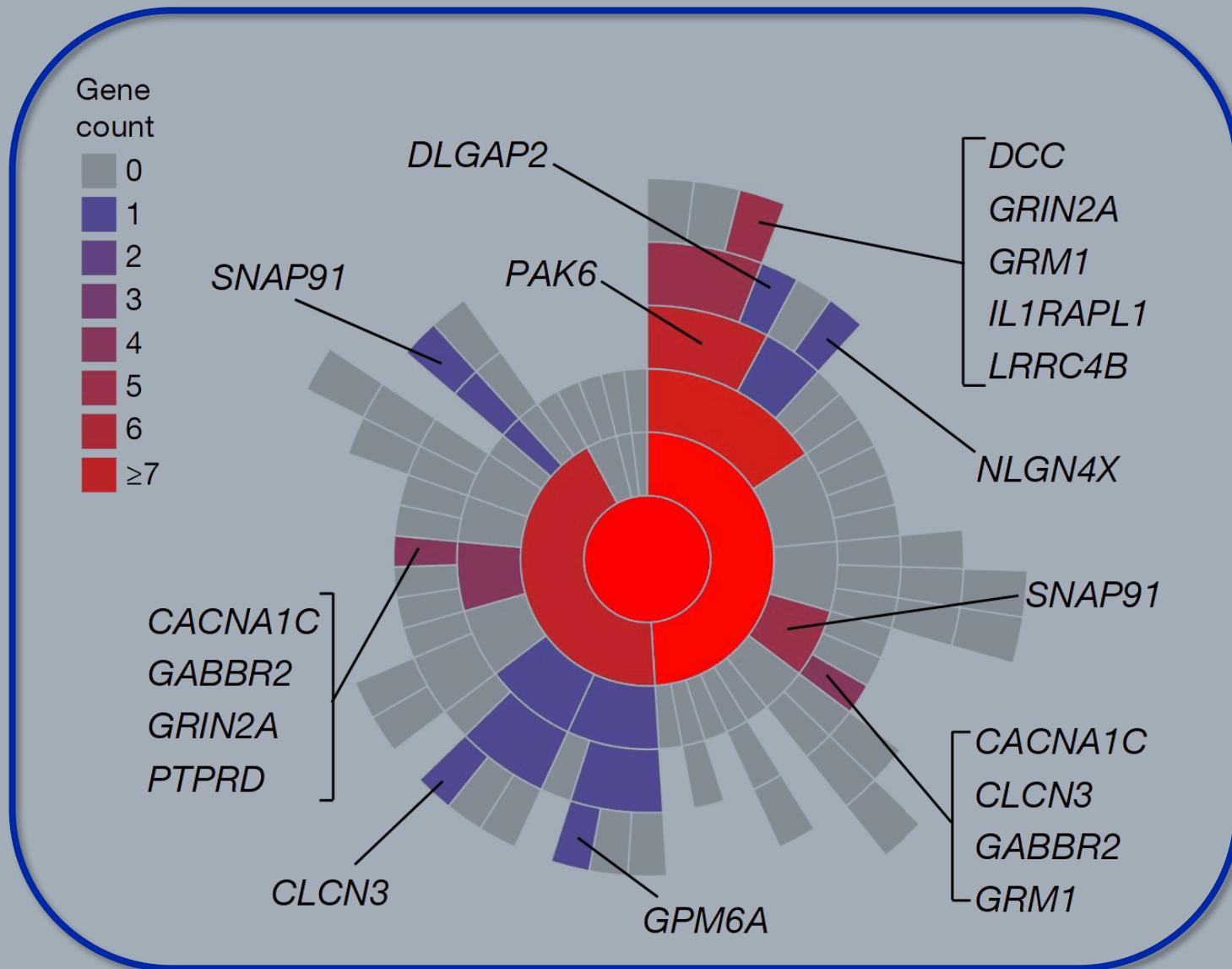
- GRM3
- GRIN2A
- GRIA1
- SRR

Acetylcholine

- CHRNA3
- CHRNA5
- CHRNB4

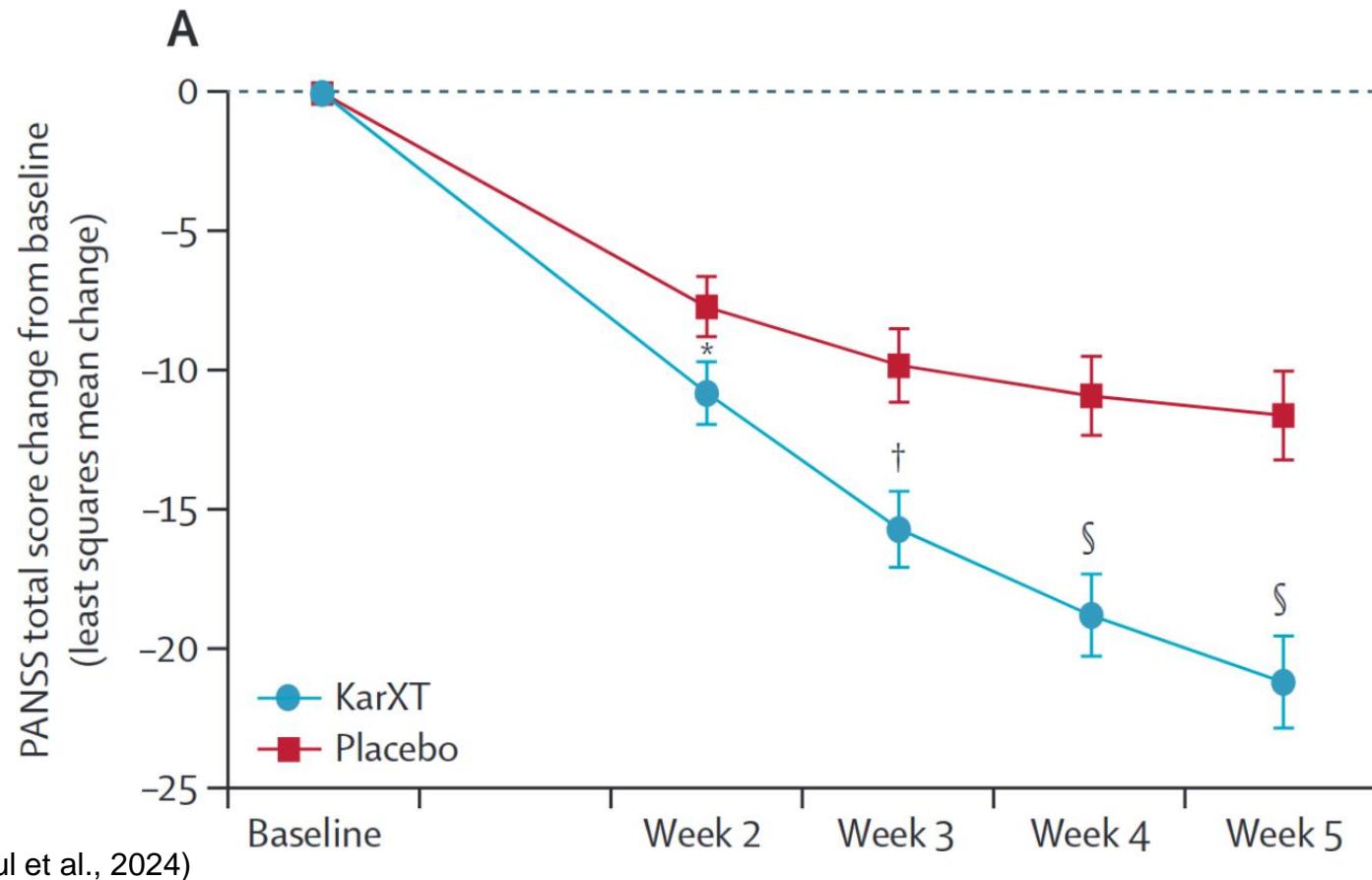
(SWGPGC, 2014)

Genetic Evidence

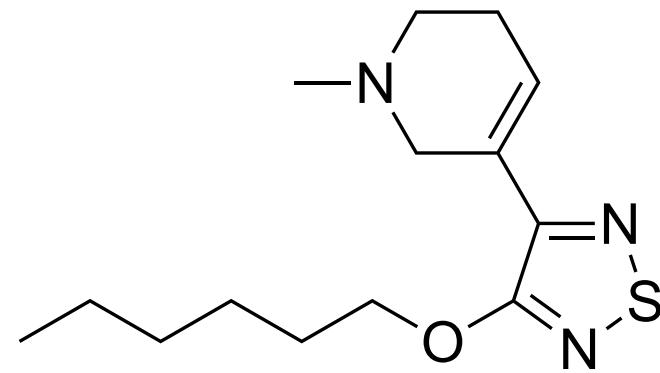


HEALTH • DRUGS

A New Drug Compound Shows Promise for Schizophrenia

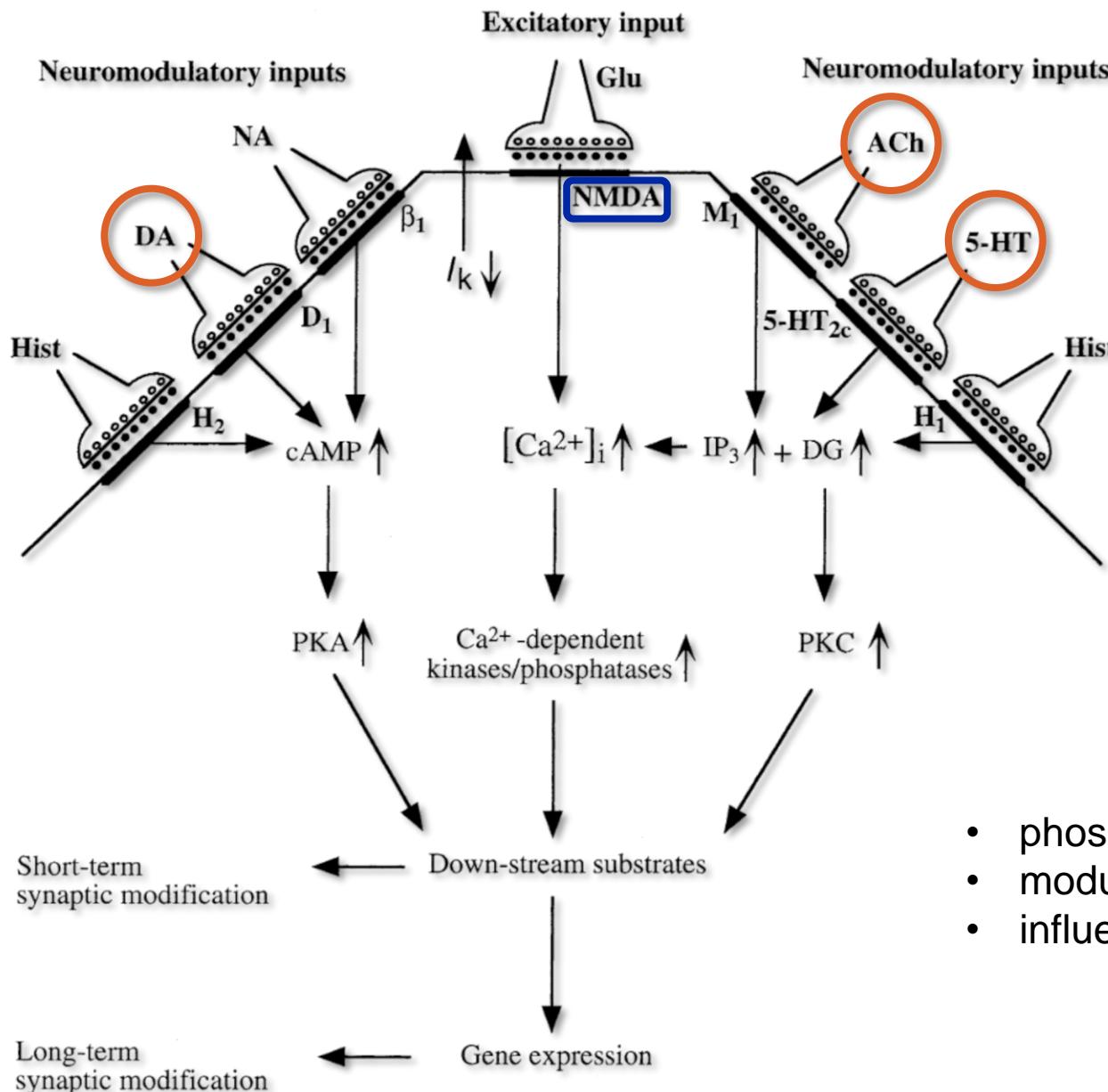


Xanomeline



- M1/M4 muscarinic receptor agonist
- Combined with trospium:
 - peripheral muscarinic antagonist
- **FDA approval 09/2024!**

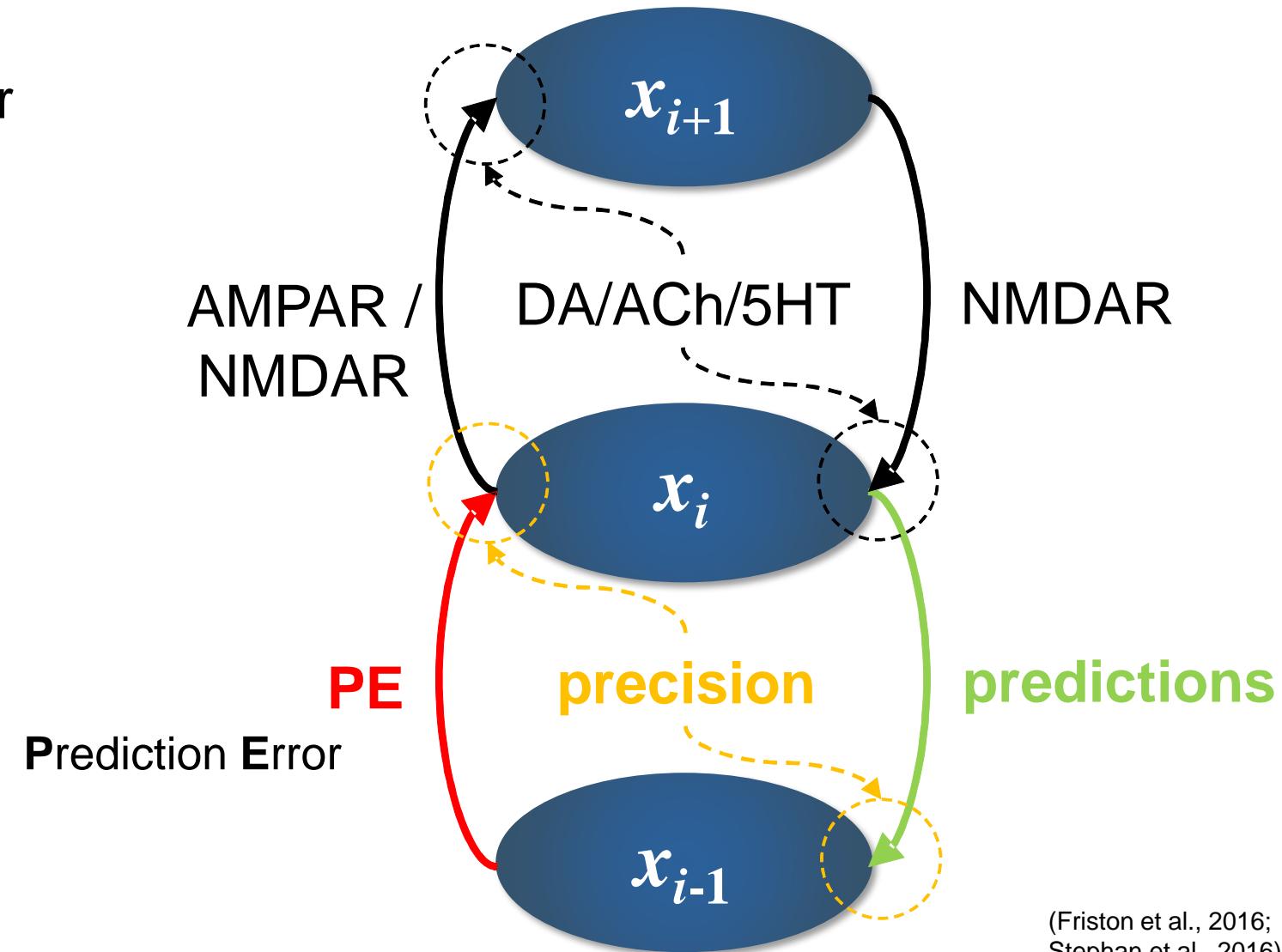
NMDAR × neuromodulator interactions



(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)

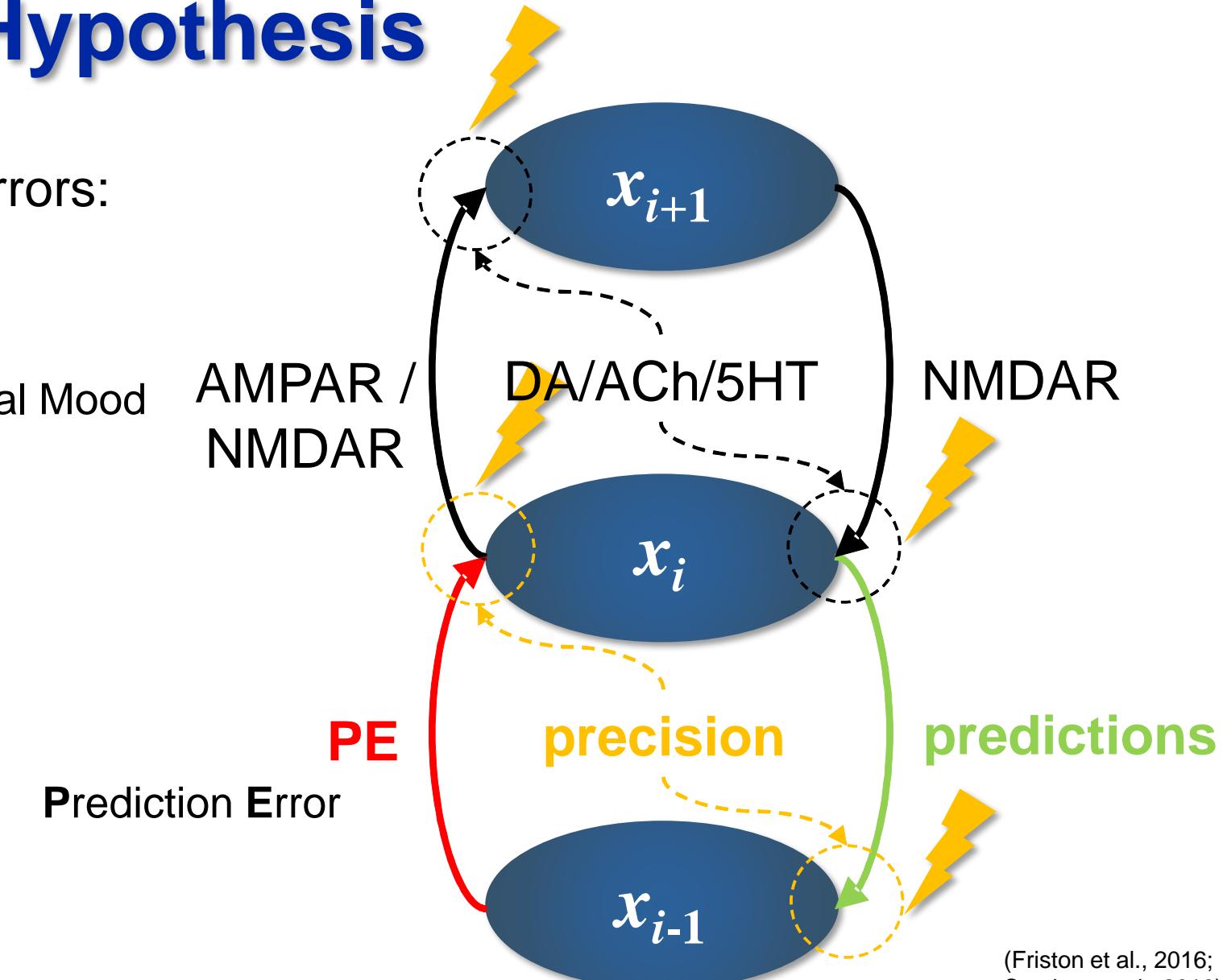
Dysconnection Hypothesis

„Overweight“ of Prediction Errors:
Trait phenomena?

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

„Overweight“ of predictions:
State phenomena?

- Delusions
- Acoustic hallucinations
- ...



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

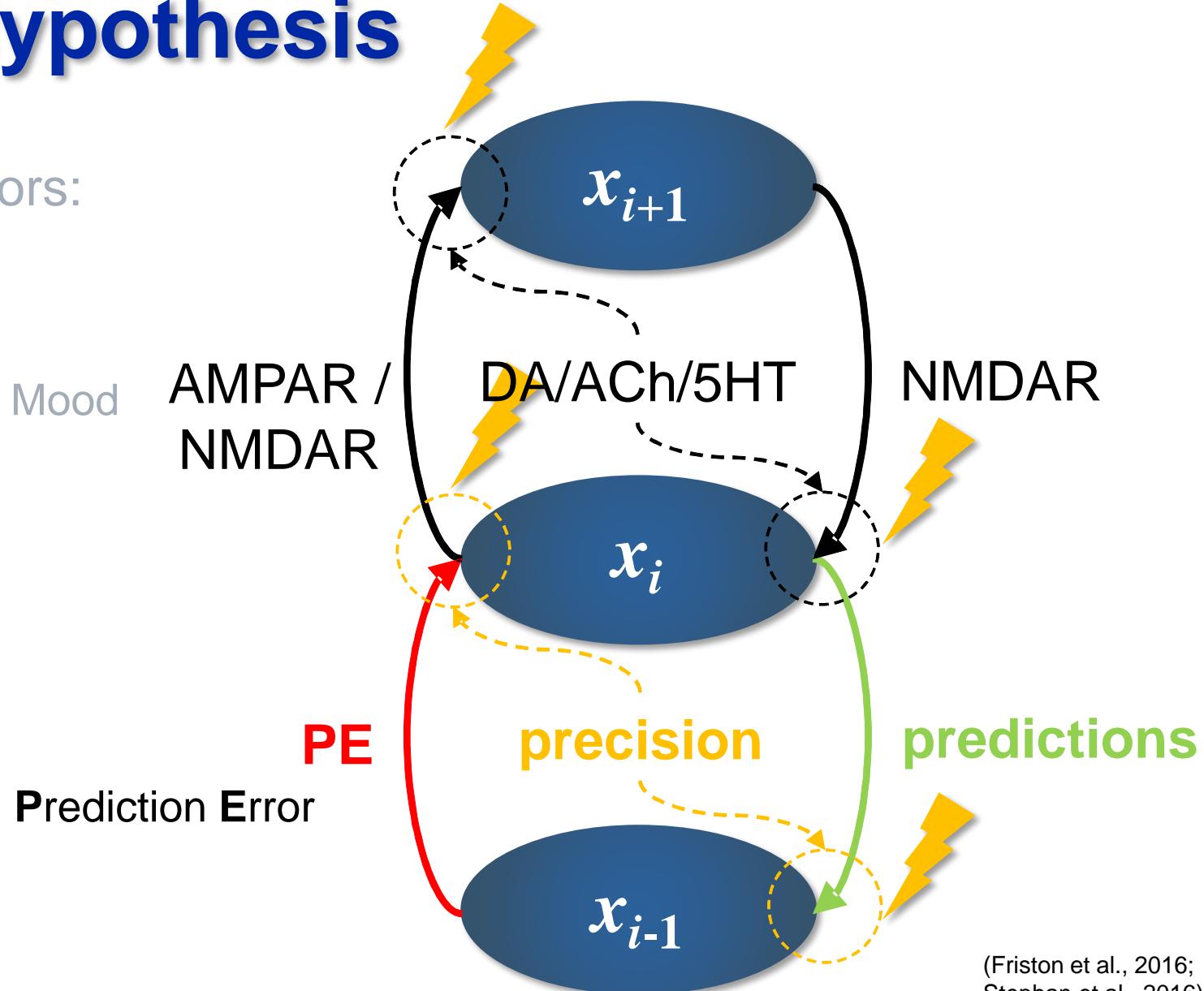
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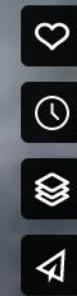
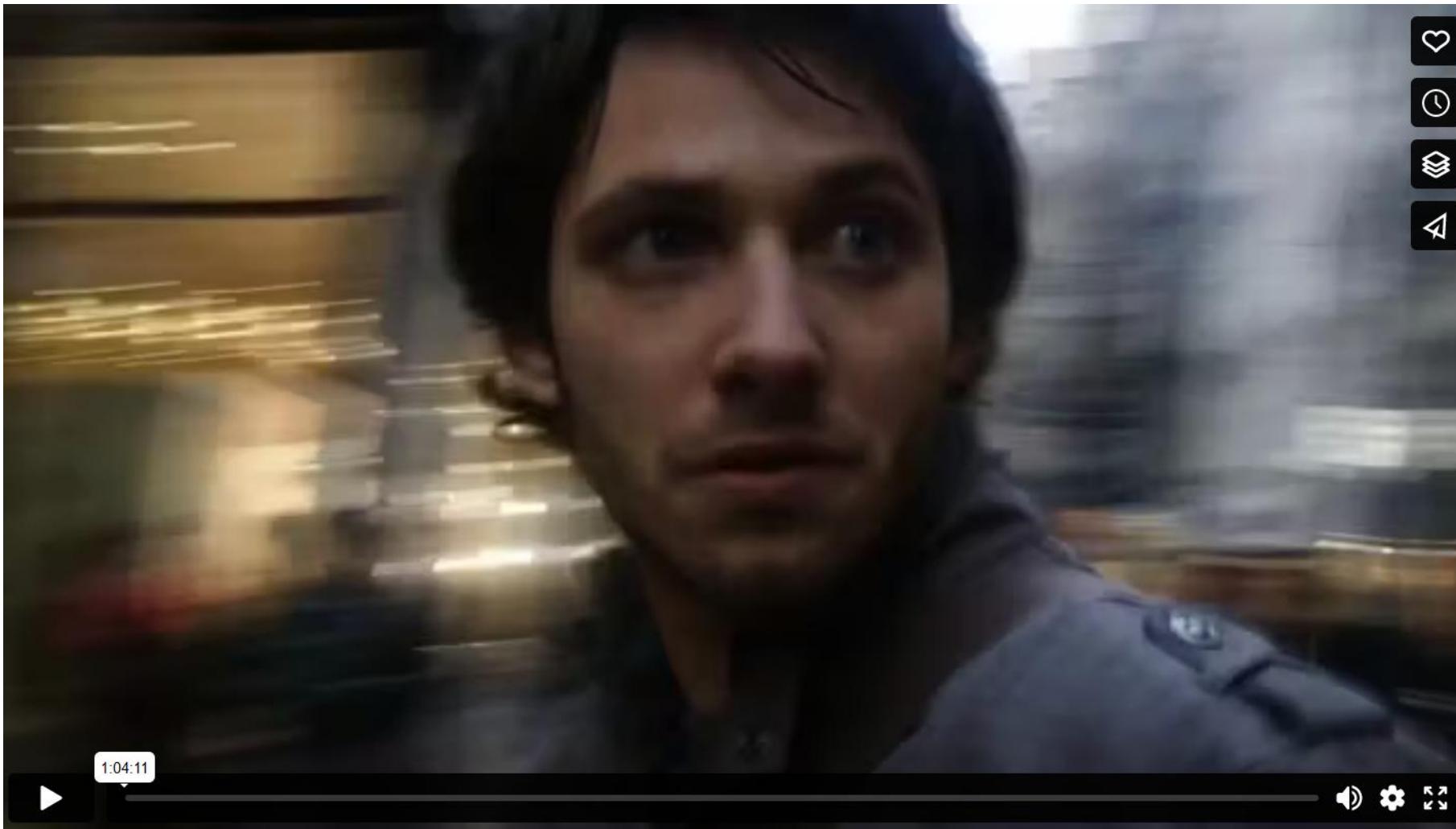
(Adams et al., 2013; Frith & Friston, 2013; Powers et al., 2017; Sterzer et al., 2018)



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/230260603>



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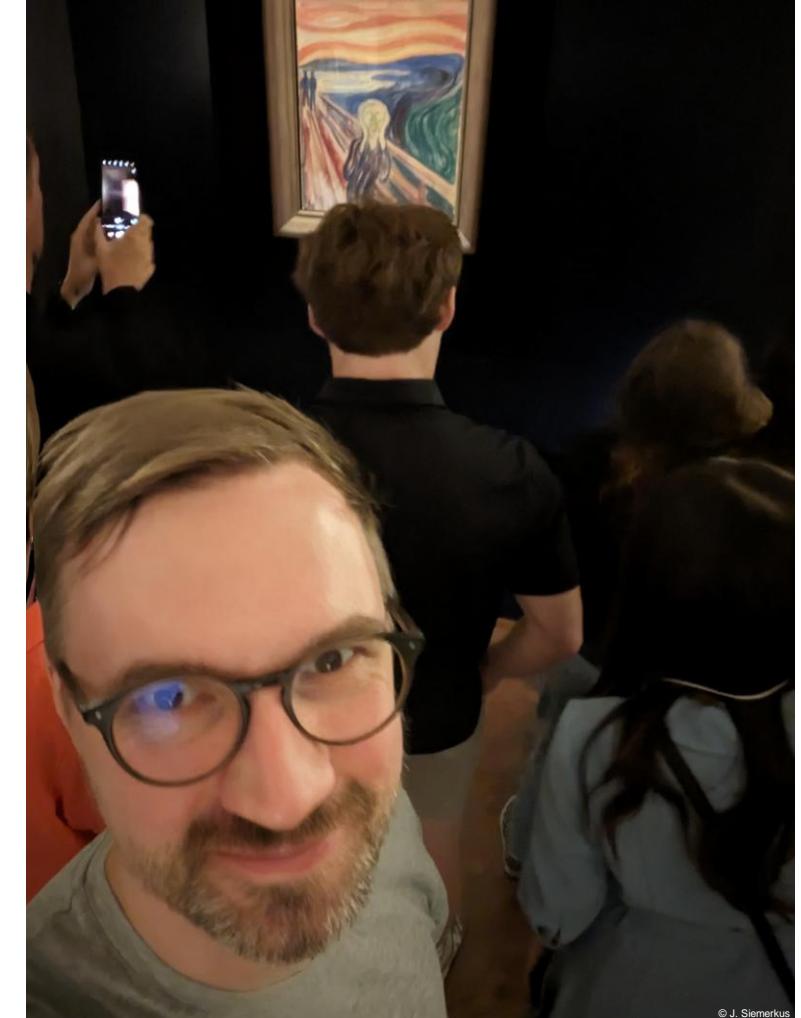
Translational Neuromodeling Unit

Thank you!

01.09.2025, CPC Zurich

Dr. med. Jakob Siemerkus
Translational Neuromodeling Unit
University of Zurich & ETH Zurich

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© J. Siemerkus



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