

When you read schizophrenia it is referred to **schizophrenia spectrum disorders**

# Schizophrenia

## 2019 Computational Psychiatry Course

I added a number of slides here and some annotations – again if you have questions don't hesitate to get in touch!



Translational Neuromodeling Unit



Universität  
Zürich UZH



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Swiss Federal Institute of Technology Zurich

Jakob Siemerkus  
University of Zurich & ETH Zurich

# A Cross-Diagnostic Approach

This is intended to serve different groups of people – keep in mind that many of the slides are oversimplified for this reason!

The CPC Crowd  
Engineers  
Clinicians  
Neuroscientists





# Schizophrenia

II. *Bleuler-Burghölzli: Die Prognose der Dementia praecox (Schizophreniegruppe)*<sup>1</sup>.

Wenn im folgenden von Dementia praecox die Rede ist, so möchte ich immer das darunter verstehen, was der Schöpfer des Begriffes mit dem Worte hat bezeichnen wollen, und was Ihnen Herr Kollege *Jahrmärker* soeben im Detail umschrieben hat. Von anderen Anschauungen aus kann das uns gestellte Thema nicht fruchtbringend behandelt werden. Im Interesse der Diskussion möchte ich nochmals hervorheben, daß es sich bei der Kräpelinschen Dementia praecox weder um eine notwendige Dementia, noch um eine notwendige Praecocitas handelt. Aus diesem Grunde und weil man von dem Ausdruck Dementia praecox keine adjektivischen und substantivischen Weiterbildungen machen kann, erlaube ich mir, hier das Wort Schizophrenie zur Bezeichnung des *Kräpelinschen* Begriffes zu benützen. Ich glaube nämlich, daß die Zerreißung oder Spaltung der psychischen Funktionen ein hervorragendes Symptom der ganzen Gruppe sei, und werde dies an anderem Orte begründen.

I personally do not like the term schizophrenia because of the stigmatizing character (it wasn't originally intended to be stigmatizing) – until we have come up with something better there is still some use in terms of communication

If you are interested in a credible account of schizophrenia in a movie watch this  
<https://vimeo.com/23611157>  
It's by Bas Labruyère, a filmmaker, who suffered from schizophrenia.

Visit  
<https://www.youtube.com/watch?v=YJC-AJWNES8>  
for the video!

(Time to Change, 2010)

Time to Change. "Schizo: The Movie" trailer - YouTube. From <https://www.youtube.com/watch?v=YJC-AJWNES8>

# Schizophrenia

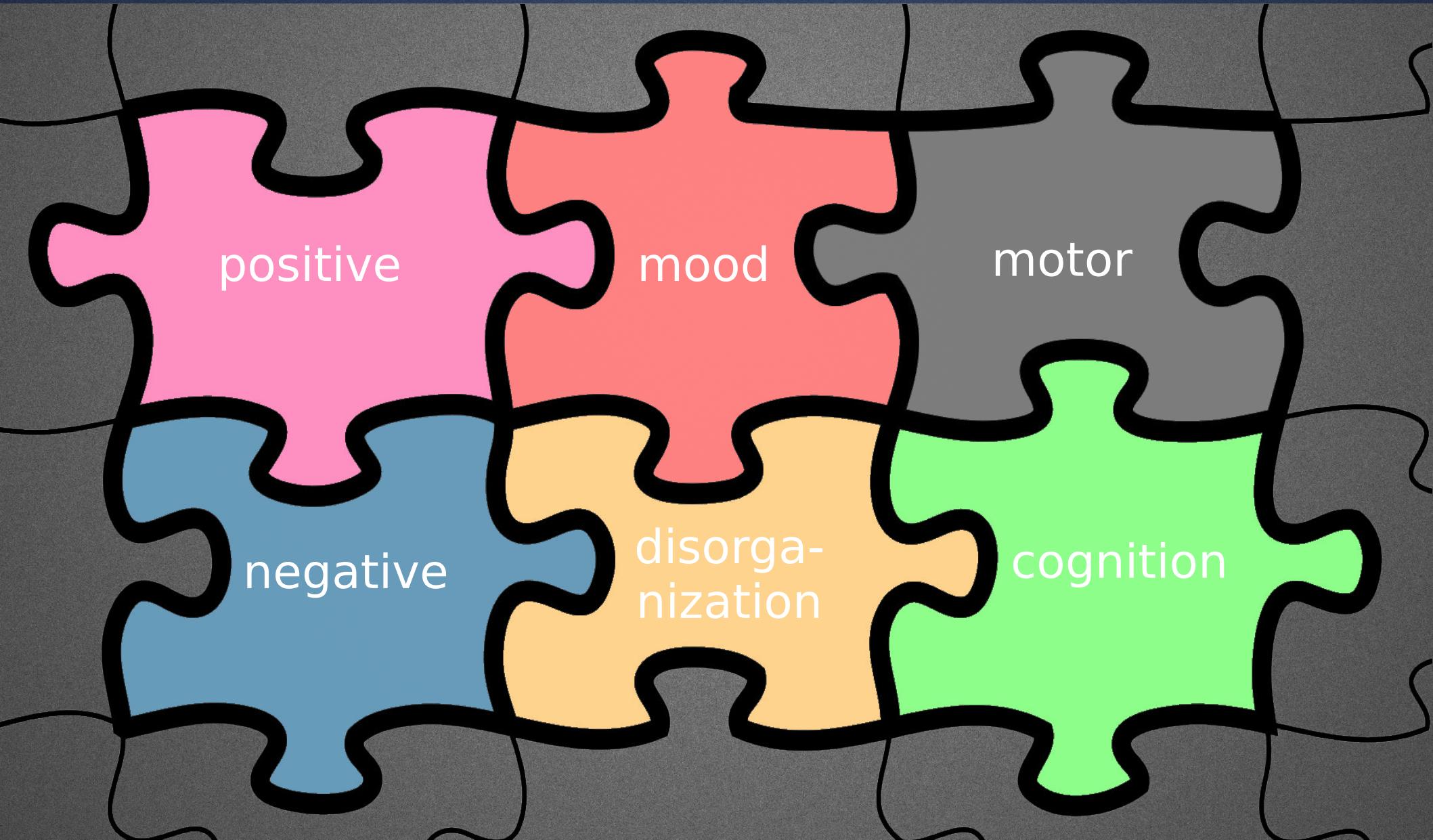
- It's bad.

- Severe mental illness
- Immense functional impairment
- 1% of world's population
- Among 10 most frequent causes for years lived with disability
- Peak during early adulthood: That affects
  - Career & education
  - Social life & family planning
  - Significant social and socioeconomic impact

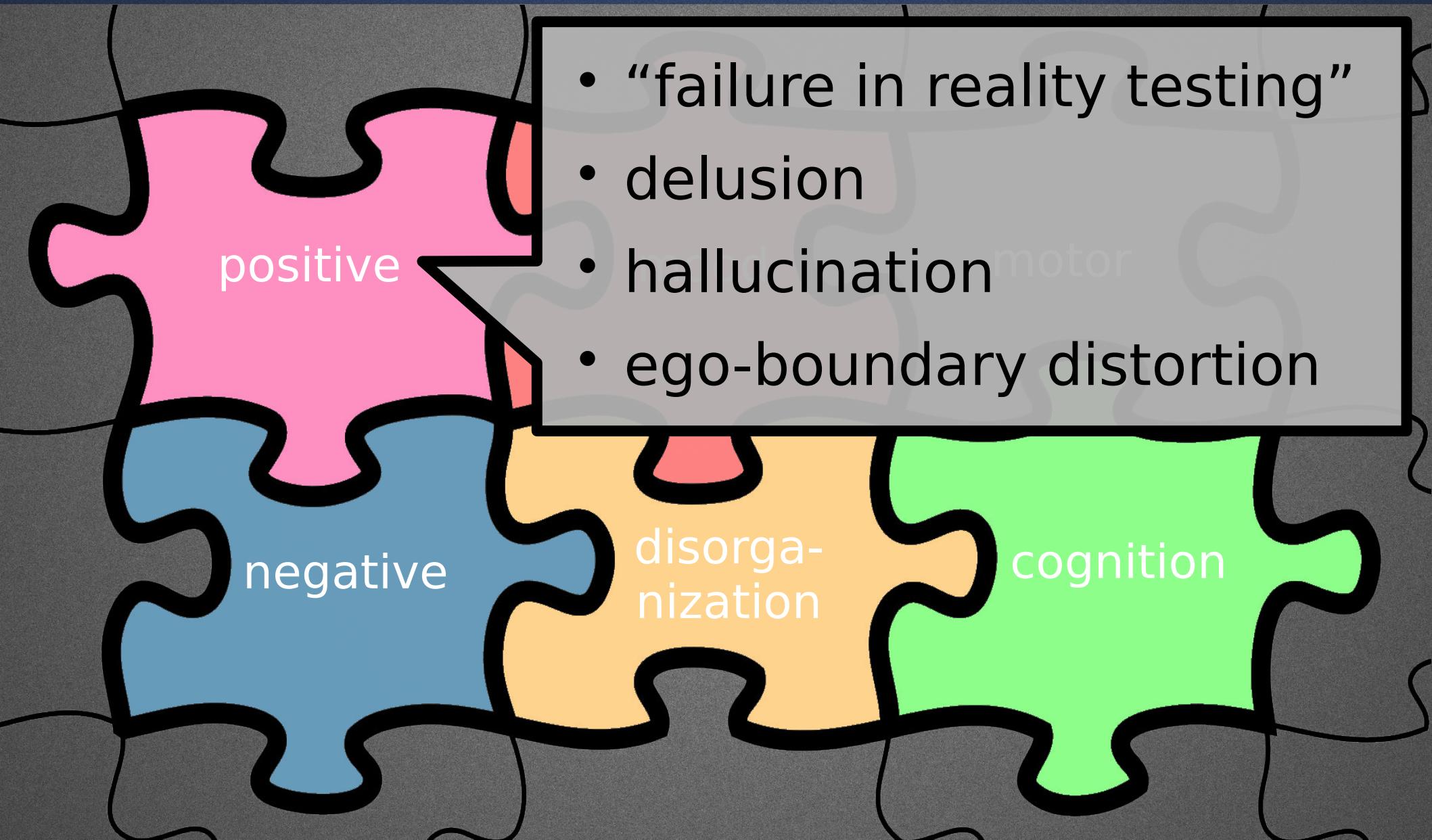
# Clinical Manifestation



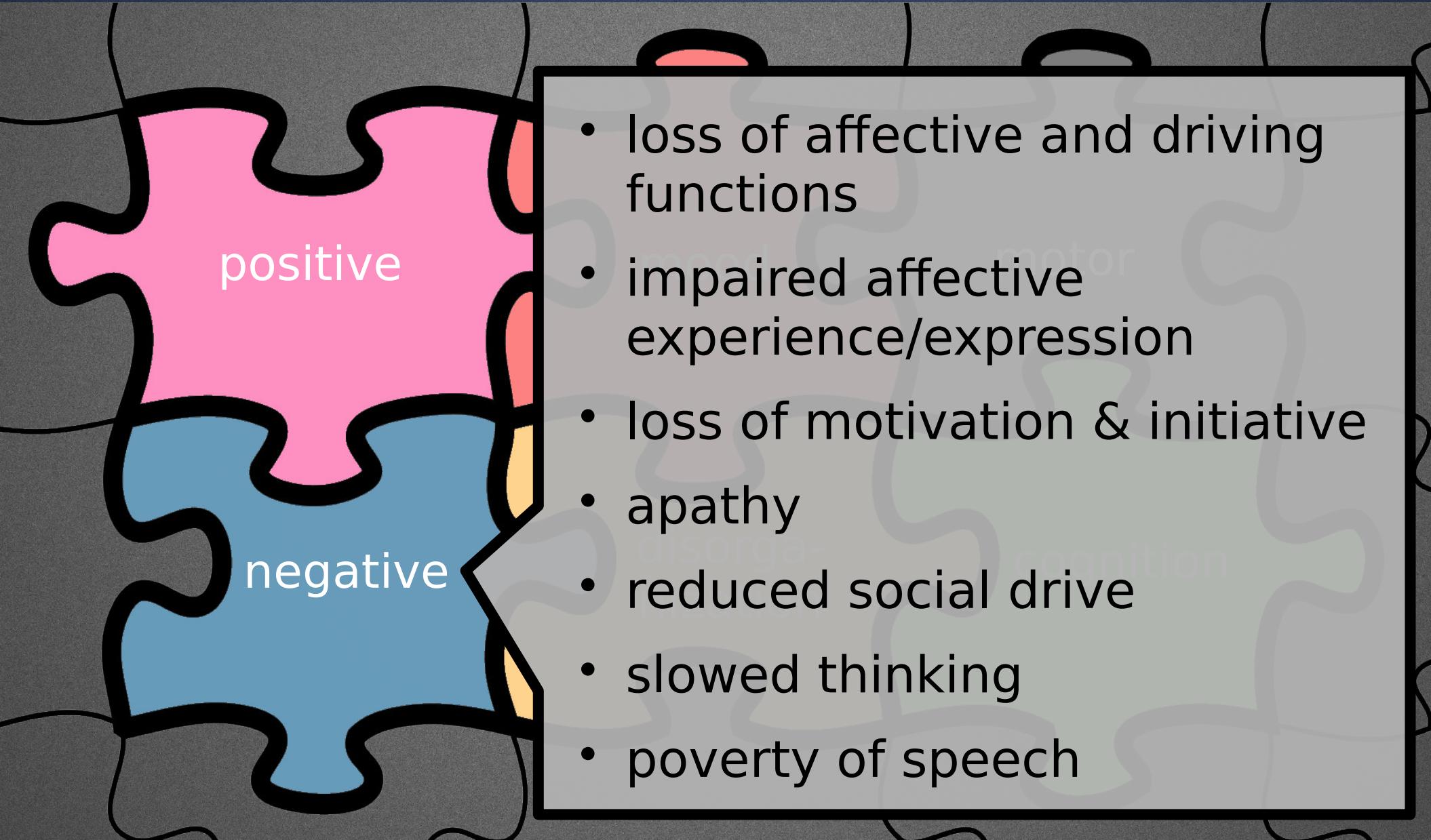
# Main Symptom Categories



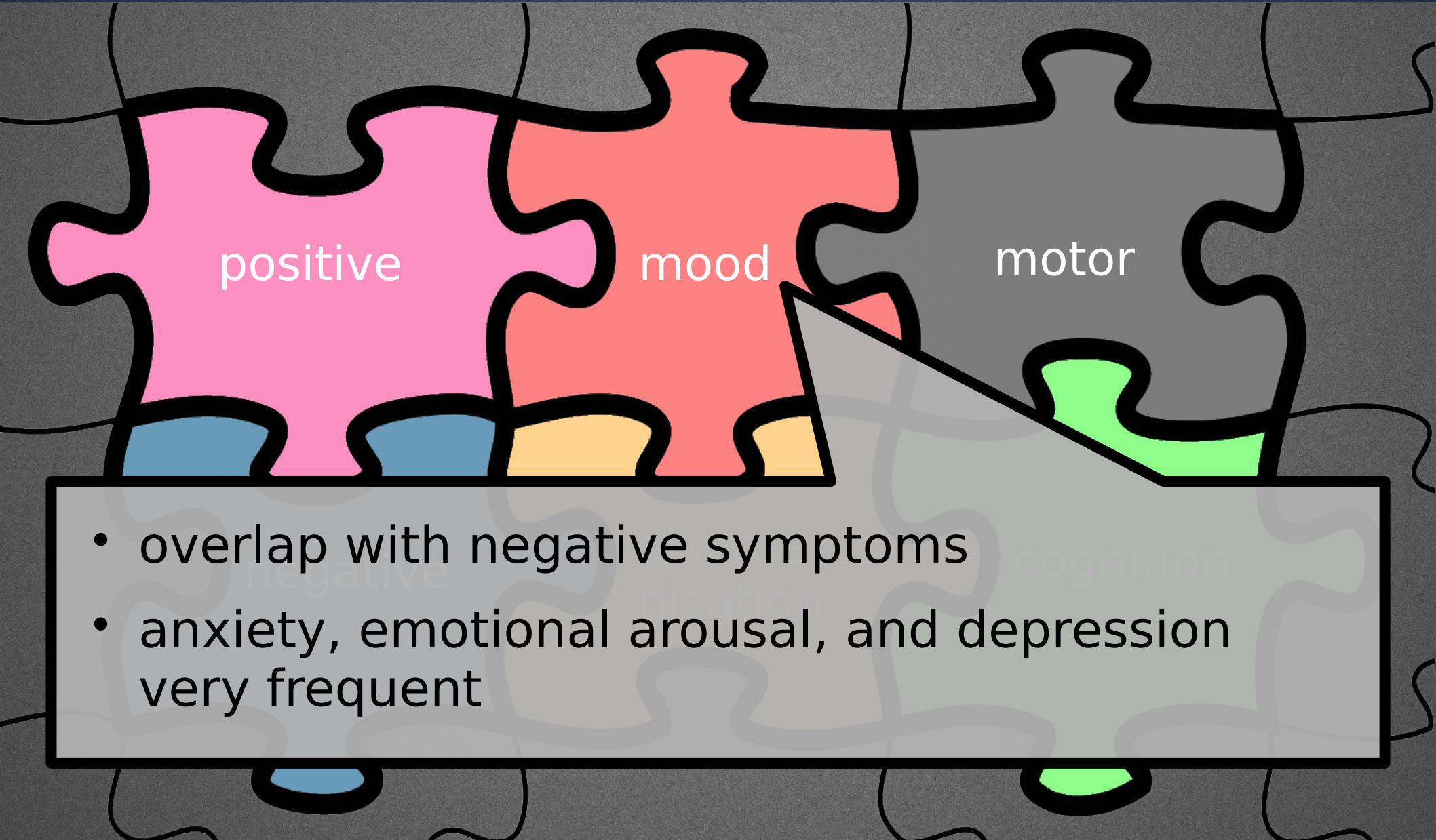
# Main Symptom Categories



# Main Symptom Categories



# Main Symptom Categories



# Main Symptom Categories

- positive formal thought disorder
- disorganized behaviour

positive

mood

"I could not brag the icy lettuce  
some upsides at this CPC."

negative

disorga-  
nization

cognition

# Main Symptom Categories

- excessive purposeless activities
- stereotypies
- posturing & mannerism
- catatonic states

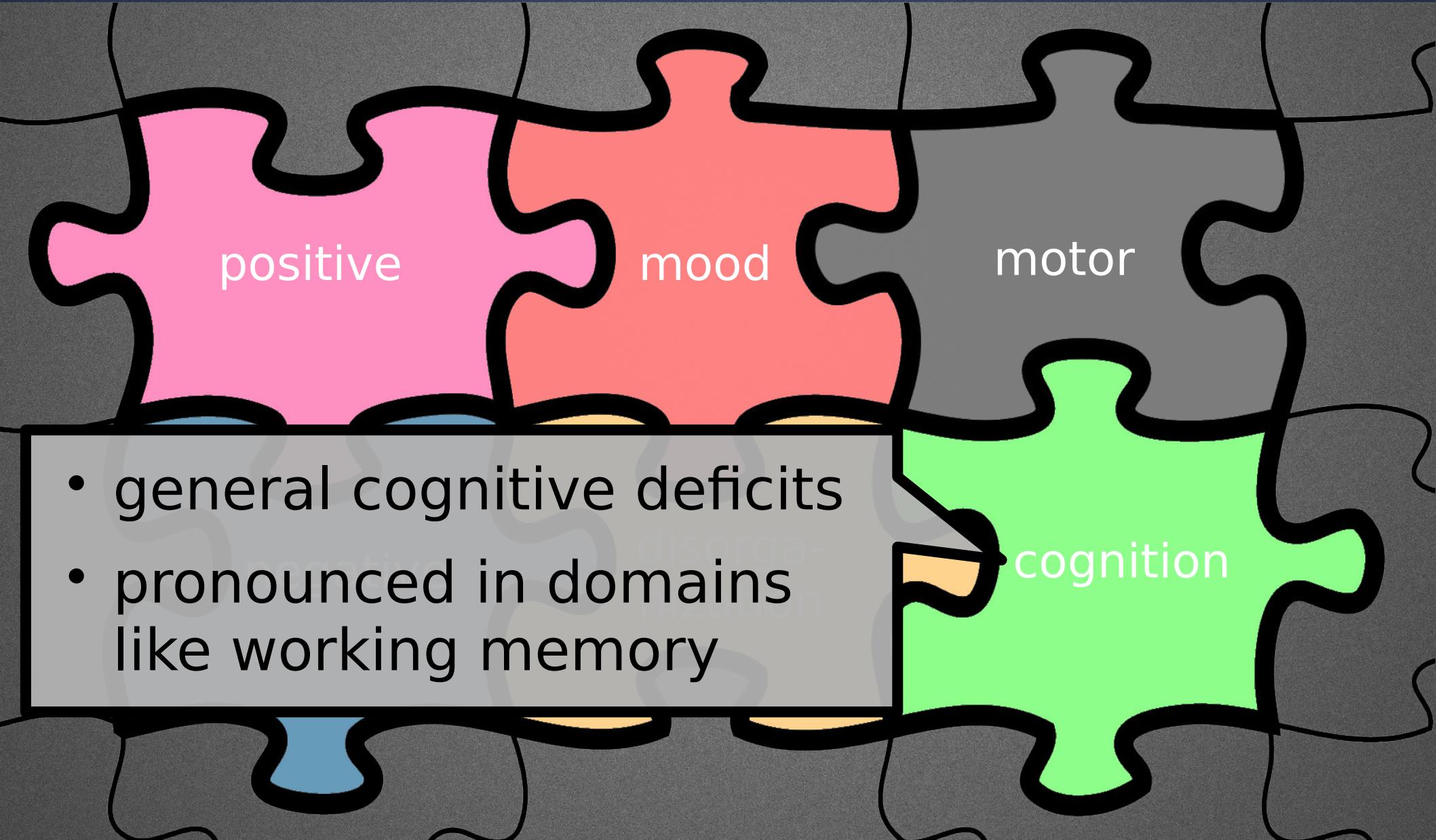
negative

disorga-  
nization

motor

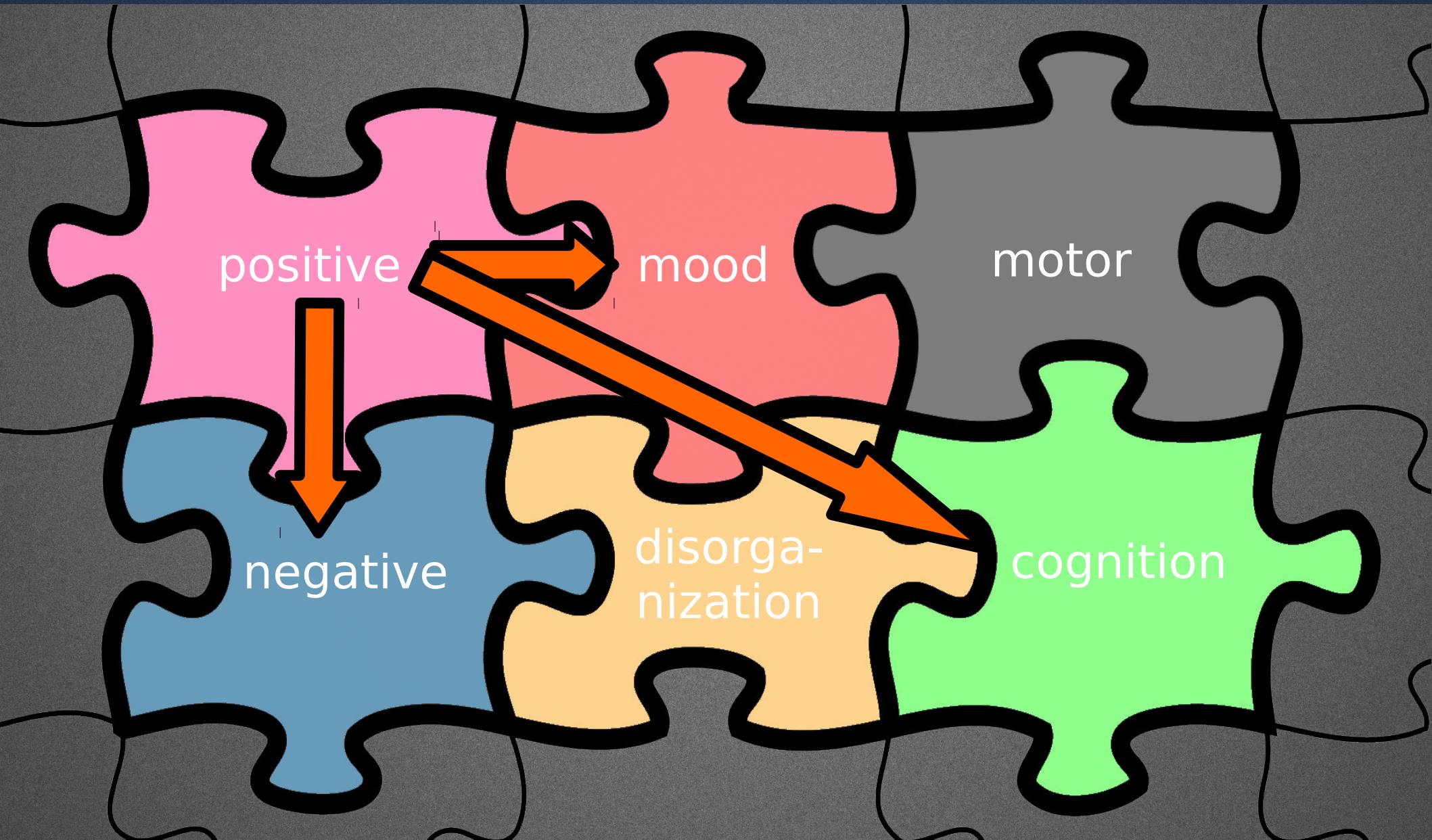
cognition

# Main Symptom Categories



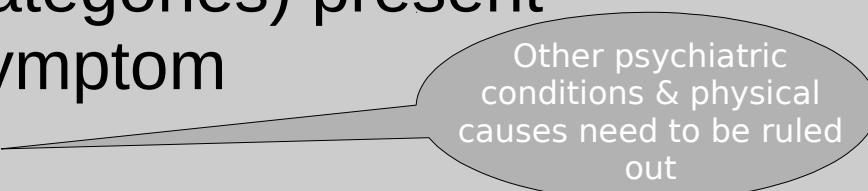
Symptom categories often overlap or cause or worsen each other and “mimic” another primary symptom, for example:

- paranoid delusion → anxiety
- paranoid delusion → “active” social withdrawal
- hallucinations → attentional problems



# Diagnostic Criteria

## DSM 5

MAIN CRITERIA	<ul style="list-style-type: none"><li>• ≥ 2 symptom (categories) present</li><li>• AND ≥ 1 core symptom</li><li>• no other cause</li></ul>  <p>Other psychiatric conditions &amp; physical causes need to be ruled out</p>
TIME	<ul style="list-style-type: none"><li>• ≥ 1 month main criteria</li><li>• ≥ 6 months symptoms/functional impairment</li></ul>
SYMPTOMS	<ul style="list-style-type: none"><li>• (core) delusions</li><li>• (core) hallucinations</li><li>• (core) disorganized speech</li><li>• negative symptoms (especially avolition, diminished emotional expression)</li><li>• disorganized or catatonic behaviour</li></ul>

# Other SZ-spectrum disorders

- Delusional Disorder
  - Delusion  $\geq$  1 month
- Brief Psychotic Disorder
  - SZ main criteria  $\leq$  1 month
- Schizophreniform Disorder
  - main criteria fulfilled, but  $\leq$  6 months any symptoms
- Schizoaffective Disorder
  - Major Depression/Manic Episode while main criteria for SZ fulfilled
  - Affective disorder most of the time during symptomatic SZ
  - $\geq$  2 weeks delusions/hallucinations without episode of affective disorder

This is just a summary!

# Clinician-Rated Dimensions of Psychosis Symptom Severity

Name: \_\_\_\_\_ Age: \_\_\_\_\_ Sex: [ ] Male [ ] Female Date: \_\_\_\_\_

**Instructions:** Based on all the information you have on the individual and using your clinical judgment, please rate (with checkmark) the presence and severity of the following symptoms as experienced by the individual in the past seven (7) days.

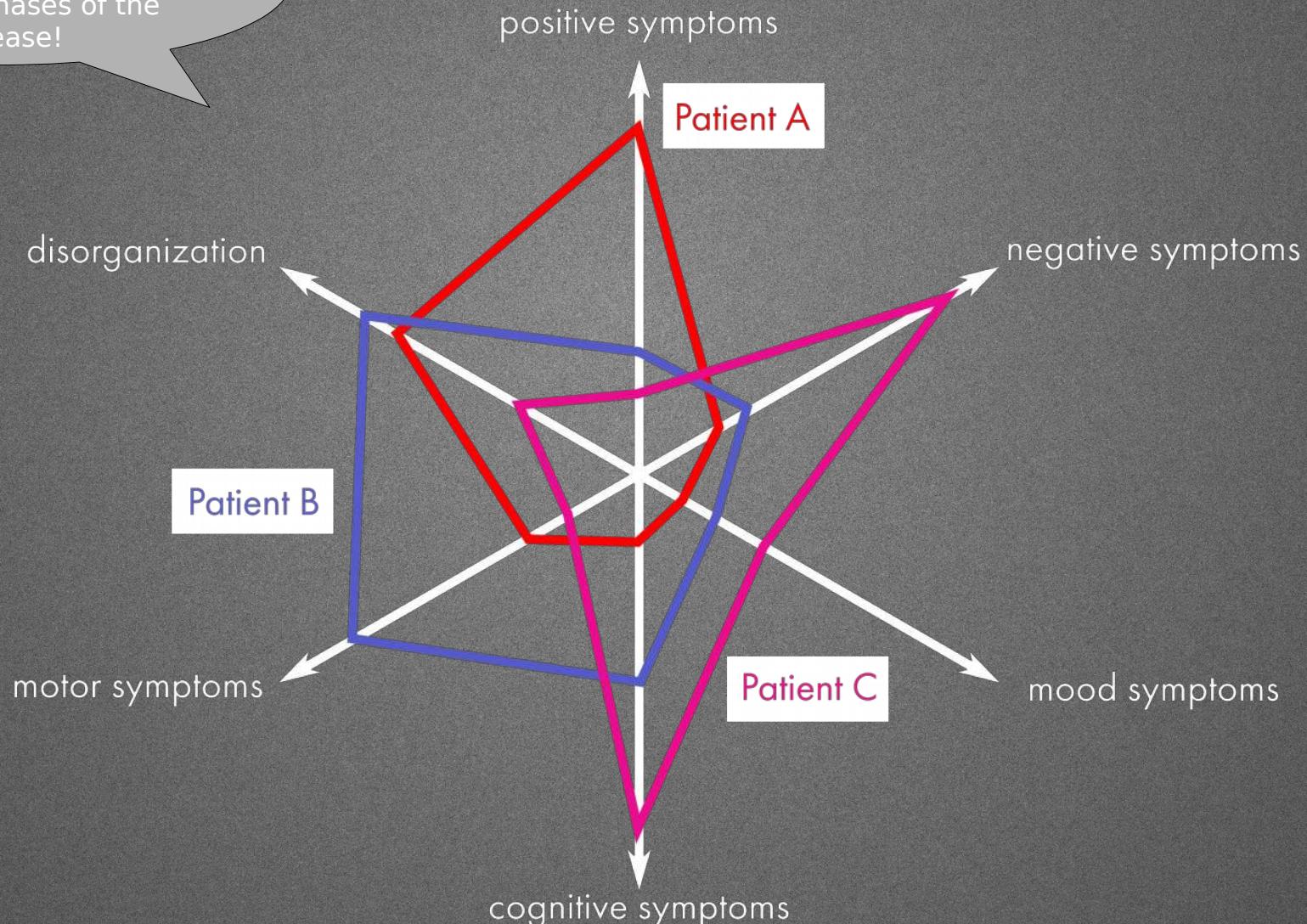
Domain	0	1	2	3	4	Score
I. Hallucinations	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (severity or duration not sufficient to be considered psychosis)	<input type="checkbox"/> Present, but mild (little pressure to act upon voices, not very bothered by voices)	<input type="checkbox"/> Present and moderate (some pressure to respond to voices, or is somewhat bothered by voices)	<input type="checkbox"/> Present and severe (severe pressure to respond to voices, or is very bothered by voices)	
II. Delusions	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (severity or duration not sufficient to be considered psychosis)	<input type="checkbox"/> Present, but mild (little pressure to act upon delusional beliefs, not very bothered by beliefs)	<input type="checkbox"/> Present and moderate (some pressure to act upon beliefs, or is somewhat bothered by beliefs)	<input type="checkbox"/> Present and severe (severe pressure to act upon beliefs, or is very bothered by beliefs)	
III. Disorganized speech	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (severity or duration not sufficient to be considered disorganization)	<input type="checkbox"/> Present, but mild (some difficulty following speech)	<input type="checkbox"/> Present and moderate (speech often difficult to follow)	<input type="checkbox"/> Present and severe (speech almost impossible to follow)	
IV. Abnormal psychomotor behavior	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (severity or duration not sufficient to be considered abnormal psychomotor behavior)	<input type="checkbox"/> Present, but mild (occasional abnormal or bizarre motor behavior or catatonia)	<input type="checkbox"/> Present and moderate (frequent abnormal or bizarre motor behavior or catatonia)	<input type="checkbox"/> Present and severe (abnormal or bizarre motor behavior or catatonia almost constant)	
V. Negative symptoms (restricted emotional expression or avolition)	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal decrease in facial expressivity, prosody, gestures, or self-initiated behavior	<input type="checkbox"/> Present, but mild decrease in facial expressivity, prosody, gestures, or self-initiated behavior	<input type="checkbox"/> Present and moderate decrease in facial expressivity, prosody, gestures, or self-initiated behavior	<input type="checkbox"/> Present and severe decrease in facial expressivity, prosody, gestures, or self-initiated behavior	
VI. Impaired cognition	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (cognitive function not clearly outside the range expected for age or SES; i.e., within 0.5 SD of mean)	<input type="checkbox"/> Present, but mild (some reduction in cognitive function; below expected for age and SES, 0.5–1 SD from mean)	<input type="checkbox"/> Present and moderate (clear reduction in cognitive function; below expected for age and SES, 1–2 SD from mean)	<input type="checkbox"/> Present and severe (severe reduction in cognitive function; below expected for age and SES, > 2 SD from mean)	
VII. Depression	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (occasionally feels sad, down, depressed, or hopeless; concerned about having failed someone or at something but not preoccupied)	<input type="checkbox"/> Present, but mild (frequent periods of feeling very sad, down, moderately depressed, or hopeless; concerned about having failed someone or at something, with some preoccupation)	<input type="checkbox"/> Present and moderate (frequent periods of deep depression or hopelessness; preoccupation with guilt, having done wrong)	<input type="checkbox"/> Present and severe (deeply depressed or hopeless daily; delusional guilt or unreasonable self-reproach grossly out of proportion to circumstances)	
VIII. Mania	<input type="checkbox"/> Not present	<input type="checkbox"/> Equivocal (occasional elevated, expansive, or irritable mood or some restlessness)	<input type="checkbox"/> Present, but mild (frequent periods of somewhat elevated, expansive, or irritable mood or restlessness)	<input type="checkbox"/> Present and moderate (frequent periods of extensively elevated, expansive, or irritable mood or restlessness)	<input type="checkbox"/> Present and severe (daily and extensively elevated, expansive, or irritable mood or restlessness)	

Note. SD = standard deviation; SES = socioeconomic status.

The CRDPSS is an attempt to systematically assess different symptoms additionally to a categorical diagnosis

# Phenotypic Heterogeneity

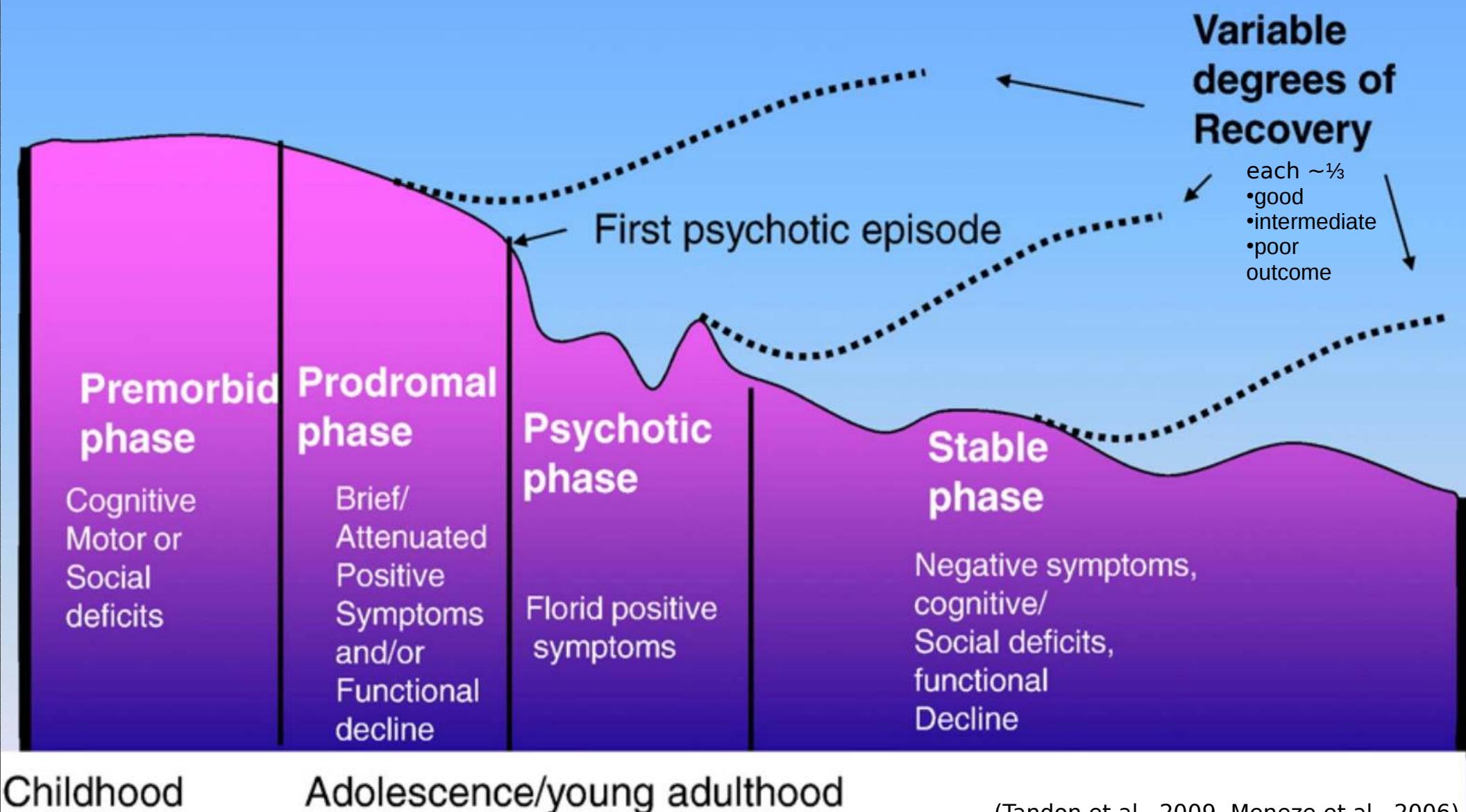
All profiles could also represent the same patient during different phases of the disease!



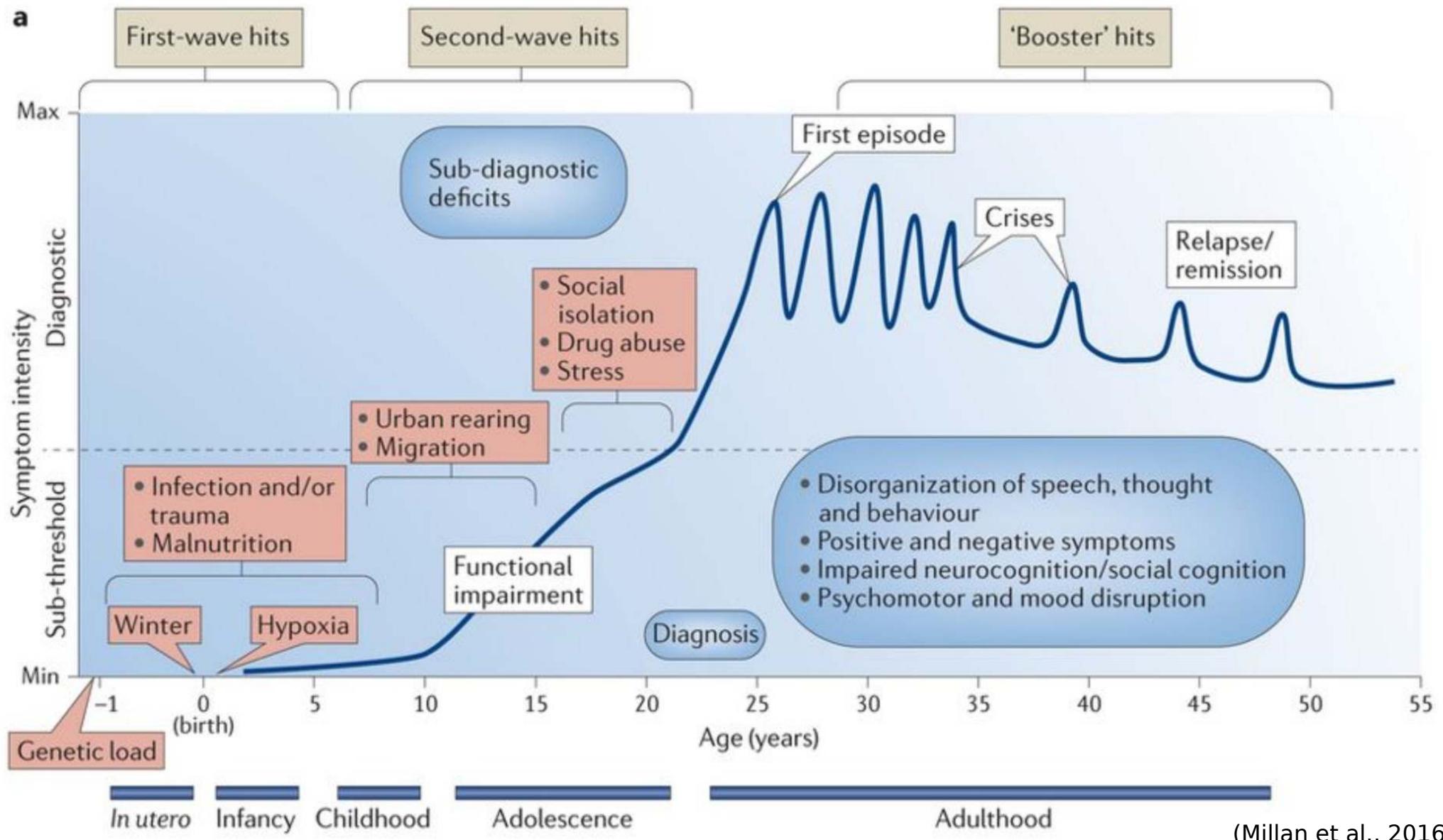


Trajectory  
Risk factors  
Outcome

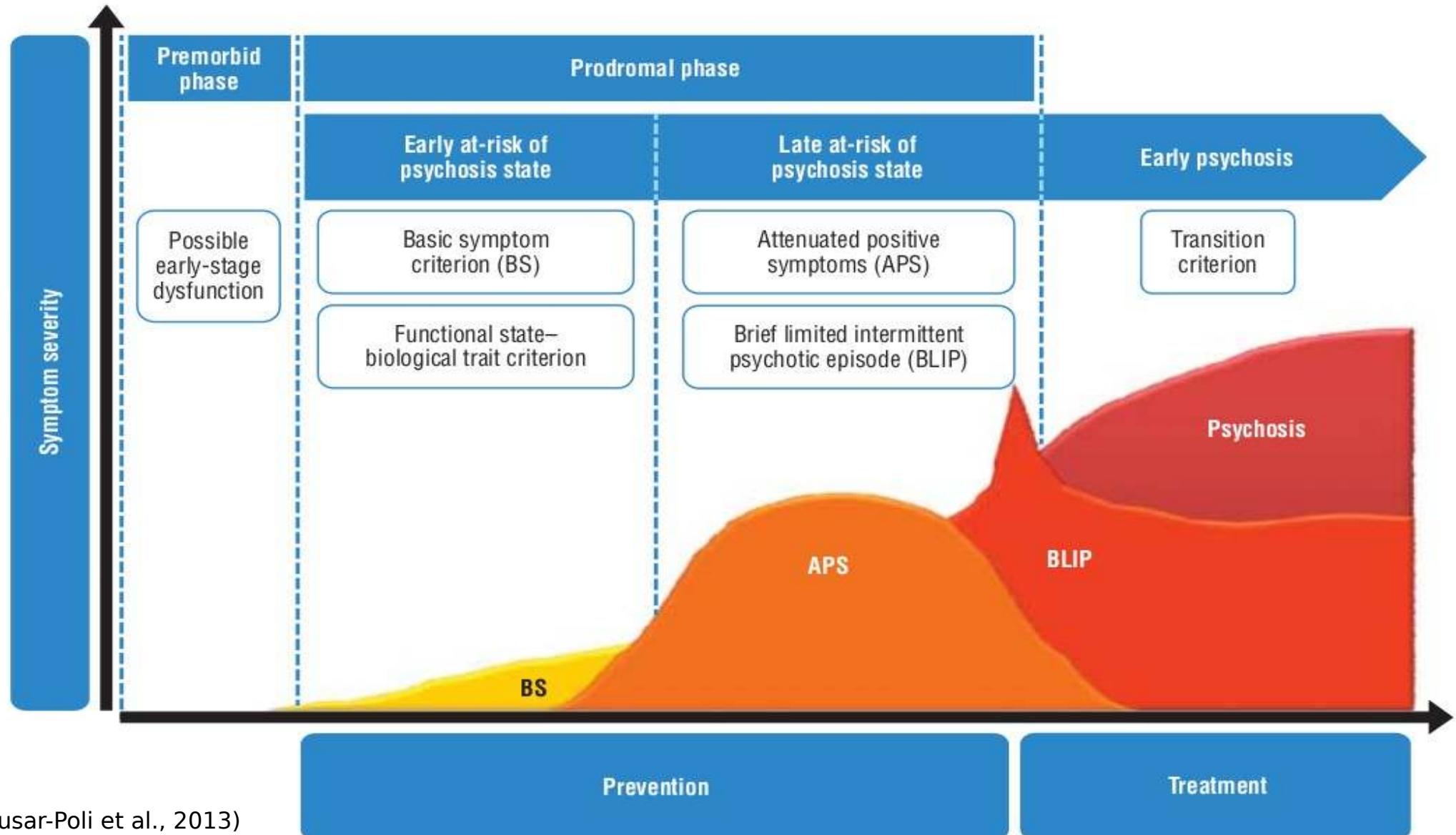
# Trajectory



# Risk Factors



# Trajectory



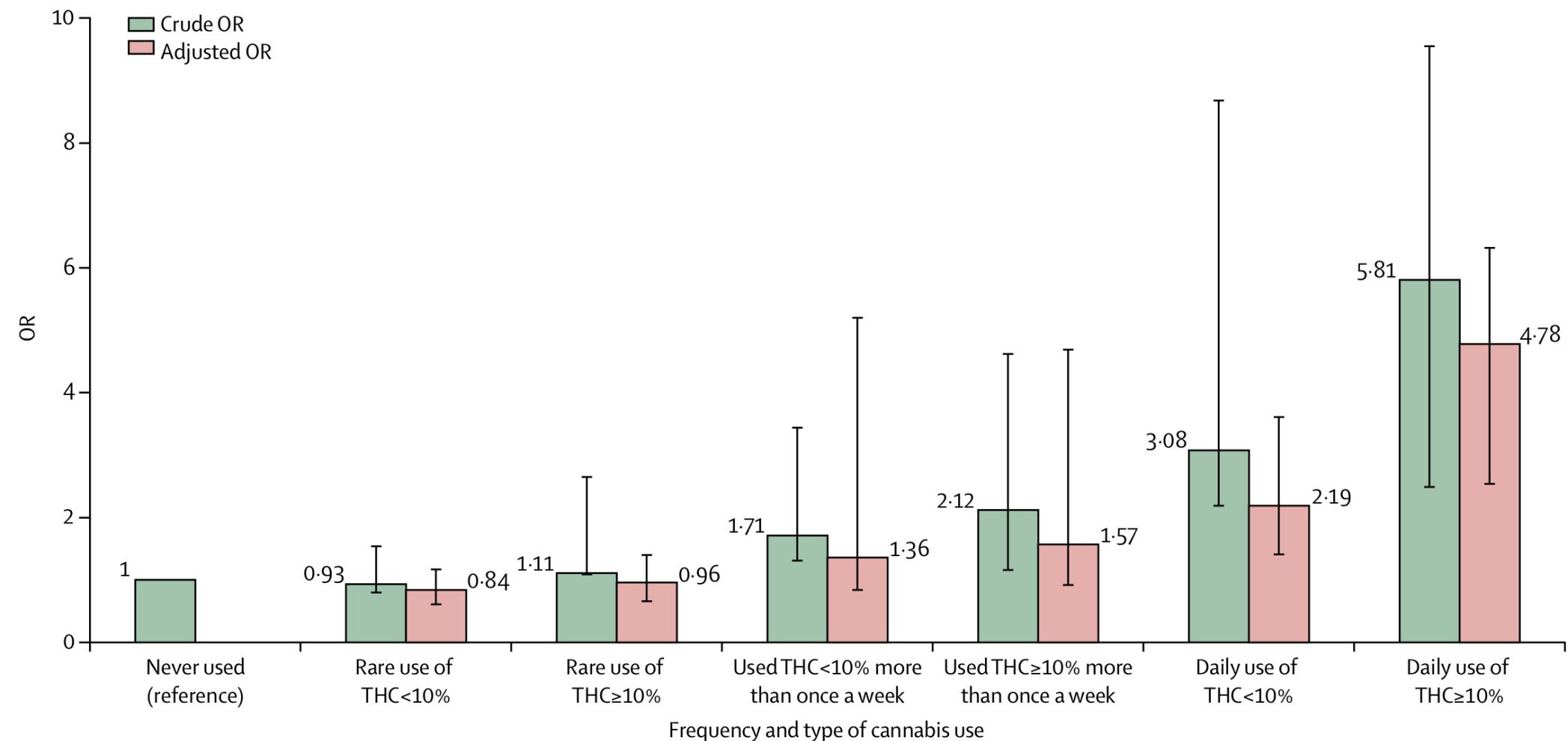
# Risk factors

Estimates of relative risk for schizophrenia due to various genetic and environmental risk factors

Risk factor	Average relative risk of schizophrenia if risk factor present (approximate)
Family history of schizophrenia	2–70
Monozygotic twin	50–70
Both parents affected	40–60
Dizygotic twin or 1st degree relative	9–18
2 <sup>nd</sup> degree relative (e.g., grandparent)	3–6
3 <sup>rd</sup> degree relative (e.g., 1st. cousin)	2–3
Any specific single gene variant	1.1–1.5
Urbanicity	2–3
Migration	2–3
1 <sup>st</sup> or 2 <sup>nd</sup> trimester maternal infection or malnutrition	2–3
Winter birth	1.1
Obstetric and perinatal complications	2–3
Cannabis or stimulant use	2–3
Paternal age >35 years	1.5–3
Male gender	1.4

(Tandon et al., 2006)

# Cannabis as Risk Factor



# Basic Symptoms

Different combinations of these symptoms often occur in individuals that later develop schizophrenia (Prodrome, “At-risk-mental-state”, High-risk individuals, etc.)

Symptom	Description
Thought interference	Unimportant, irrelevant thoughts hinder thinking
Thought blockages	Loss of train of thought
Thought pressure	Thoughts without common theme pop up
Thought perseveration	Repetitive thoughts
Disturbance of receptive language	Lack of immediate comprehension (speech or text)
Disturbance of expressive language	Difficulty speaking or writing
Disturbances of abstract thinking	Difficulty comprehending idioms and metaphors.
Inability to divide attention	Difficulty to focus on one sense
Captivation of attention by details of the visual field	Attention is “drawn” to unimportant details
Decreased ability to discriminate between perception and ideas, true memories and fantasies	Difficulty discriminating between what observations and imagination
Unstable ideas of reference with insight	Referential ideation (not yet stable and discussable)
Derealization	Feeling of disconnection/unreality in one's environment
Visual/acoustic perceptual disturbances with insight	Disturbances/distortion of the perception (brightness or loudness, color or sound quality, or distortions in one's perceptions that are still recognized as false)

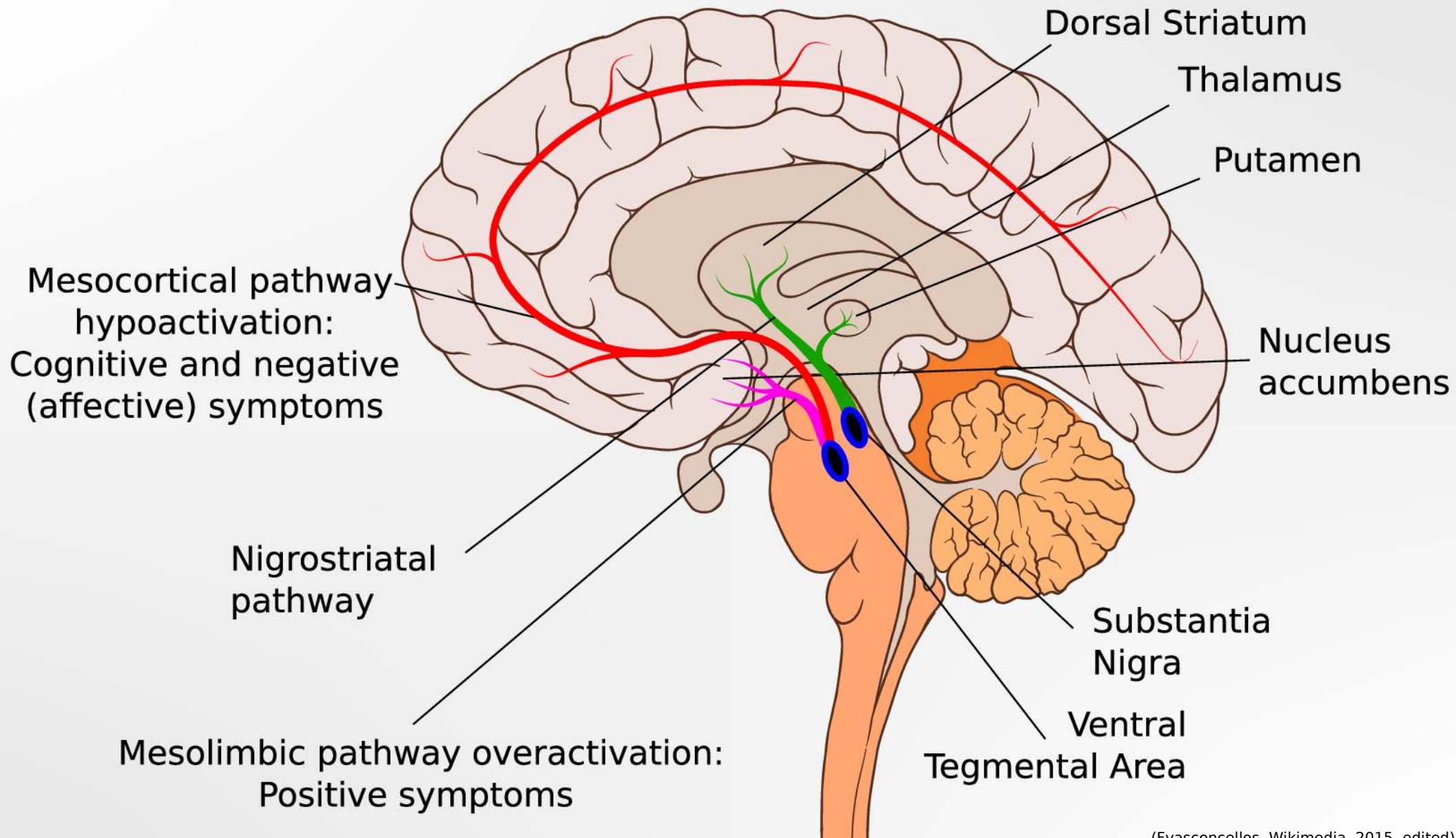
# Predictors for good Outcome

- Social support (?)
- Short Duration of untreated psychosis
- Insight that one suffers from a psychotic disorder

# Pathophysiology

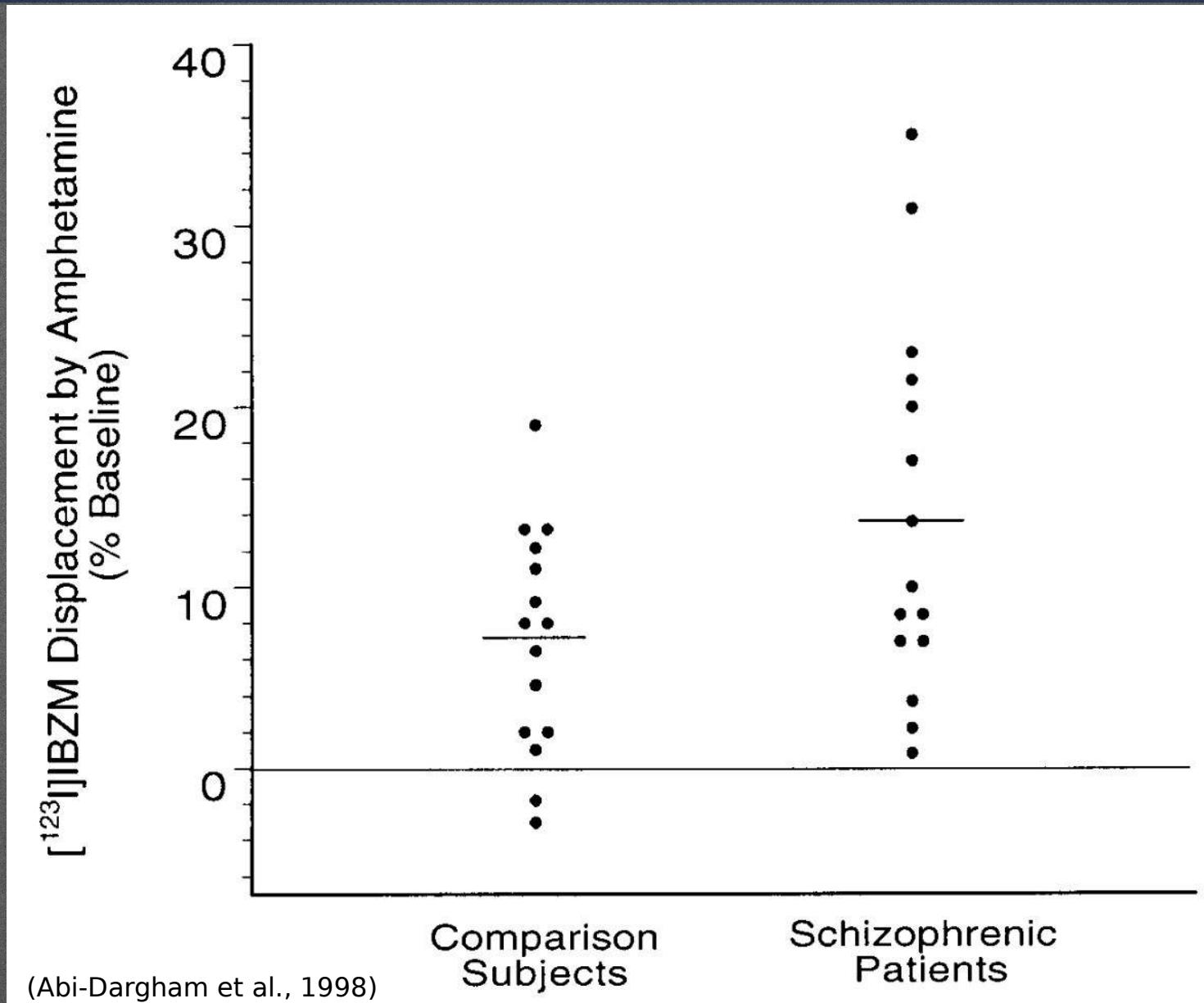


# Dopamine Hypothesis



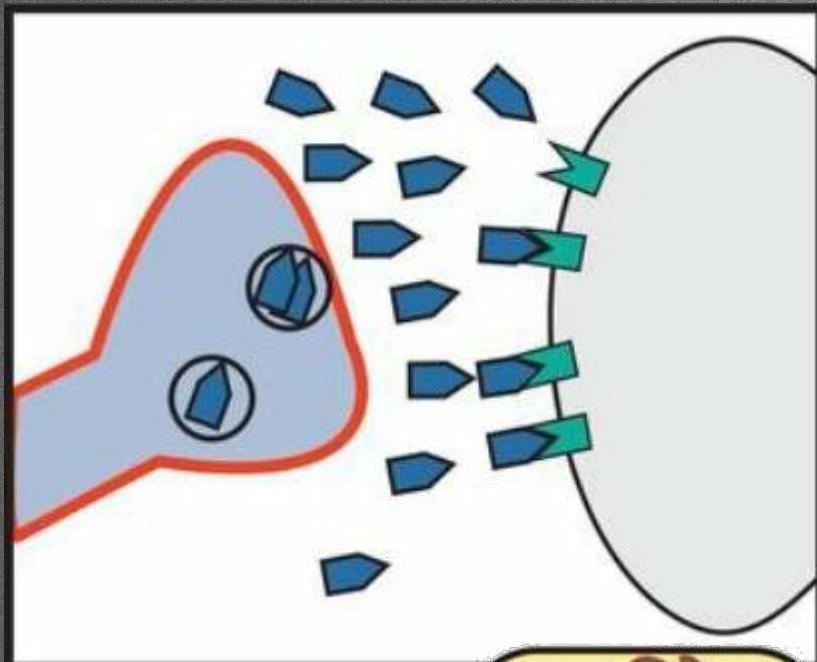
# Neurobiology: Dopamine

Evidence for disrupted regulation  
of dopamine in the striatum



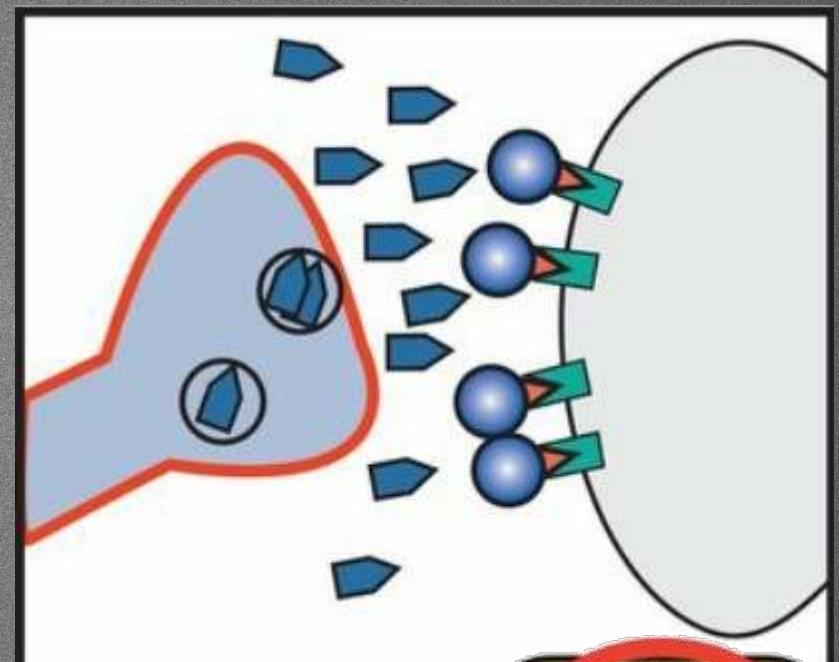
# Antipsychotics

Mesolimbic Pathway  
Untreated Schizophrenia



"hyperactive"  
dopaminergic system

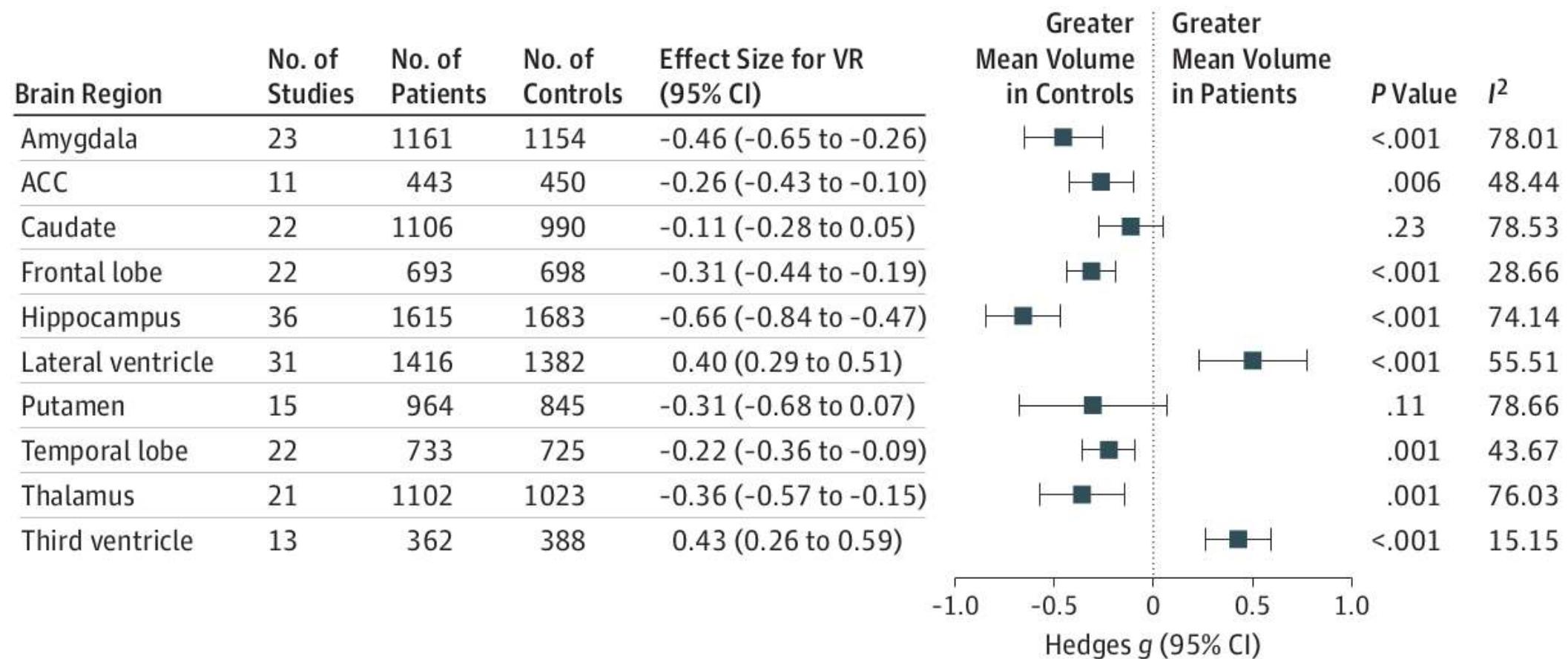
Mesolimbic Pathway  
D2 Antagonist



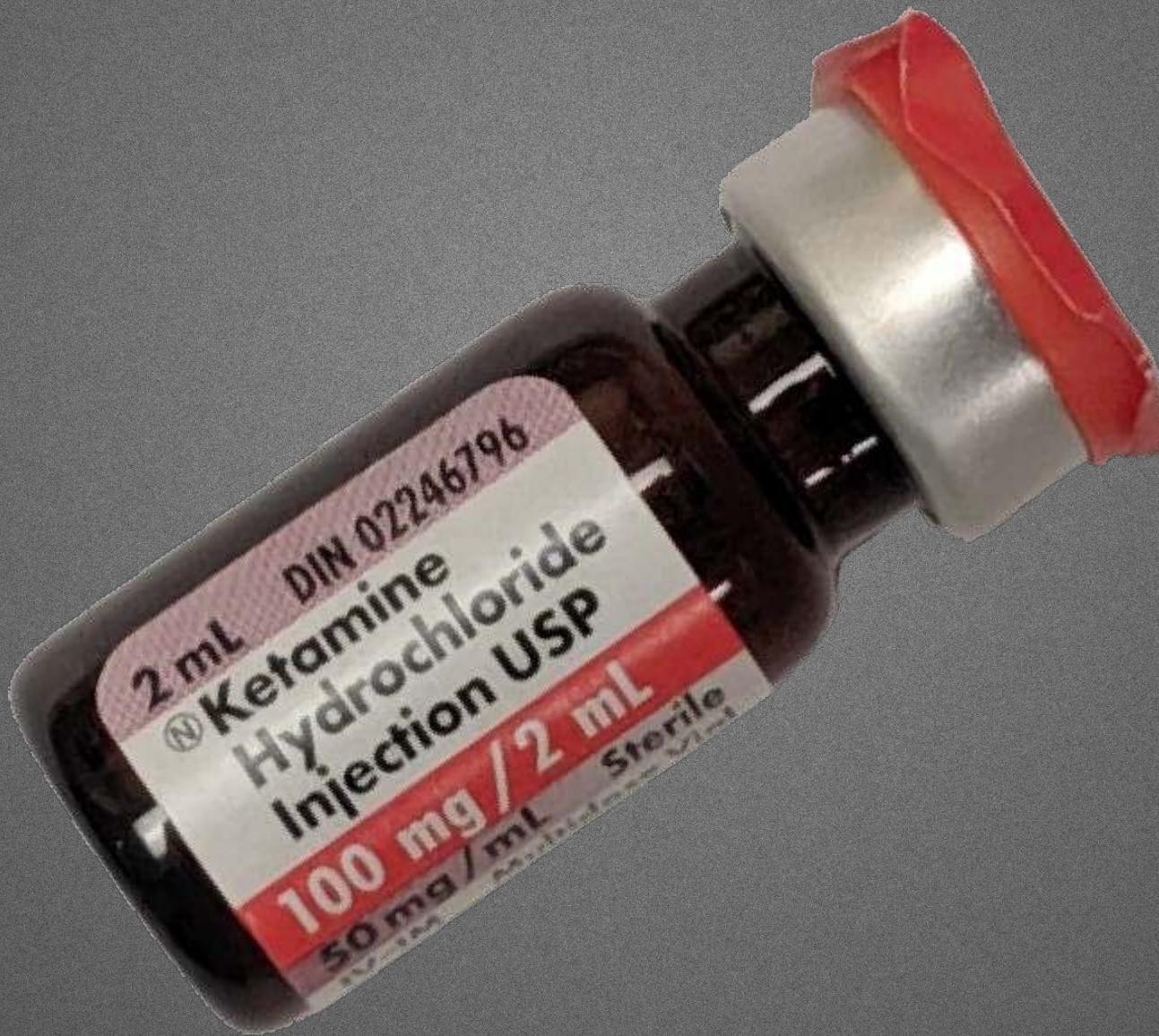
"normalized"  
dopaminergic system

# Volume

Volume reductions in different areas are frequently reported – still this does not help too much in identifying a mechanism behind schizophrenia



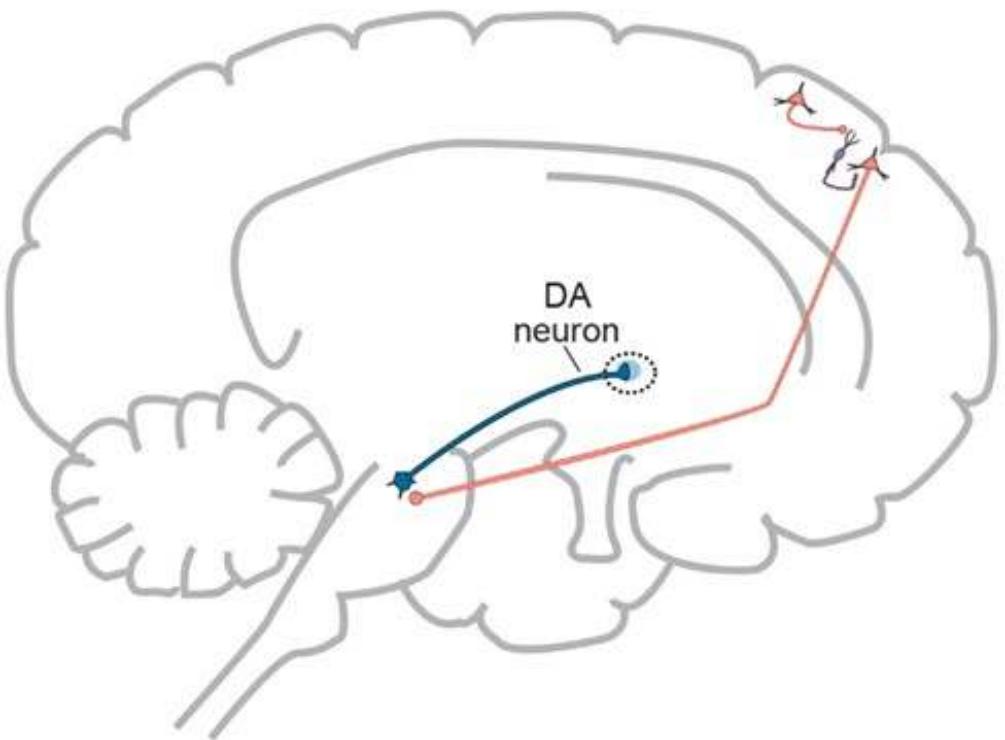
# Glutamate Hypothesis



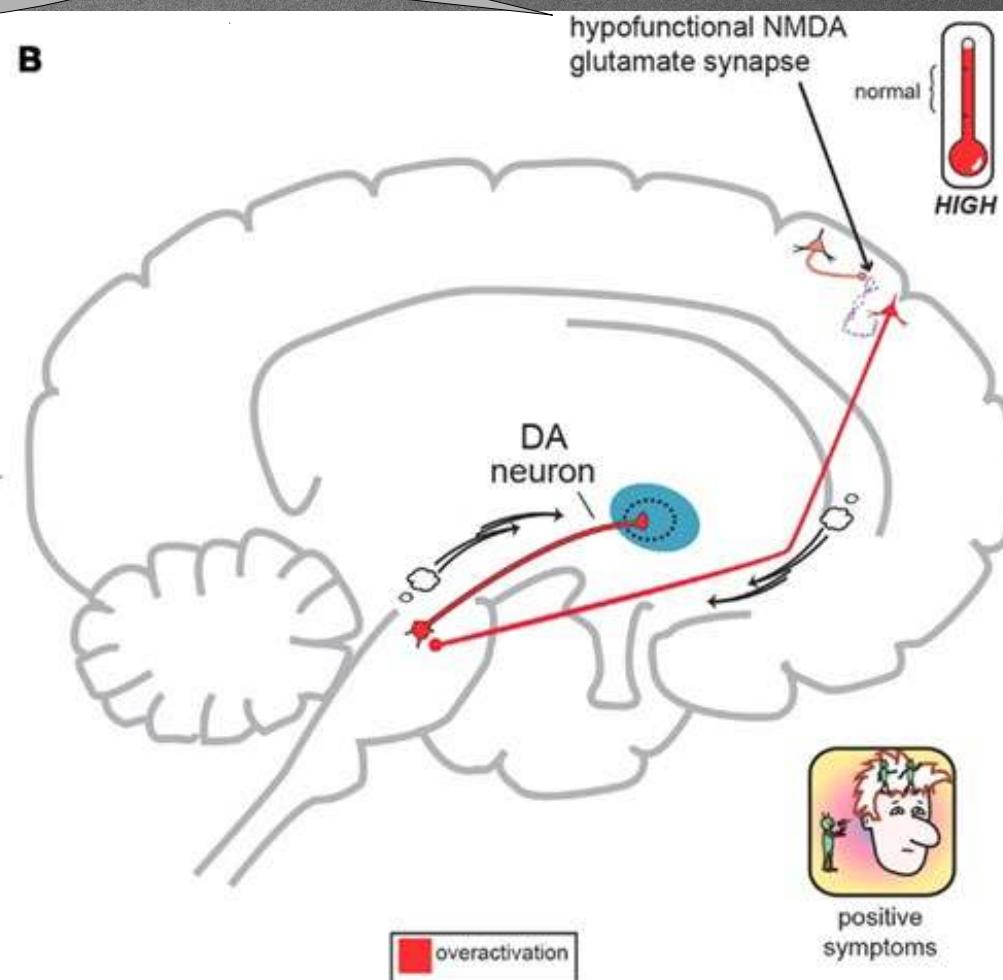
# Glutamate Hypothesis

Hypofunctional glutamatergic synapses could lead to hypoactivation of GABAergic interneurons → positive and negative symptoms

A



B



overactivation

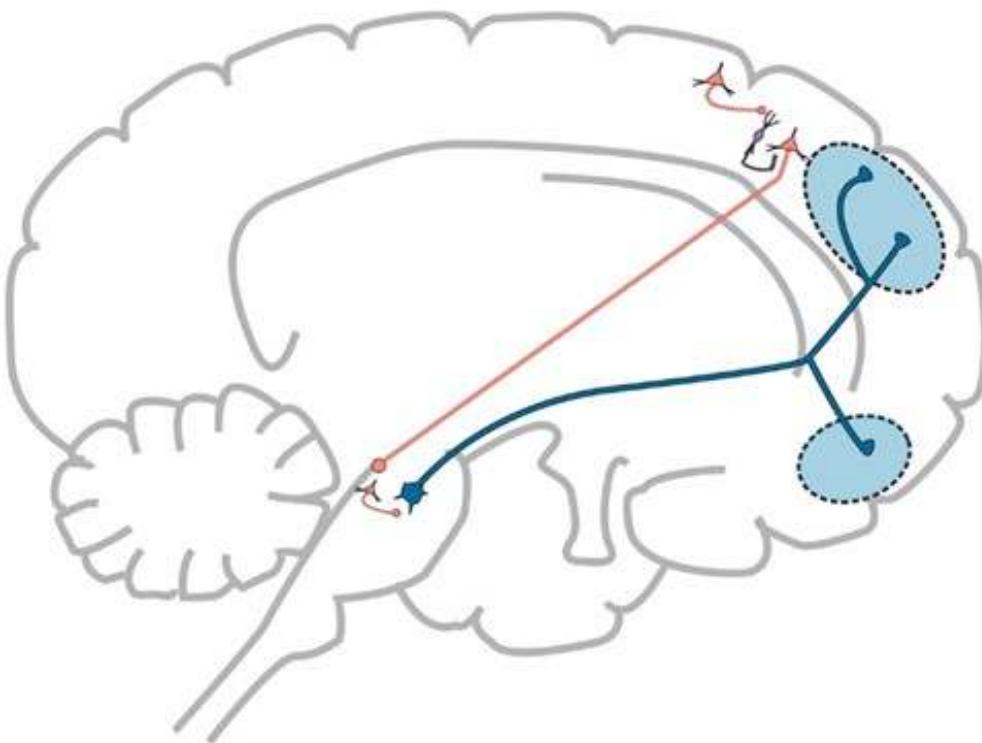


positive symptoms

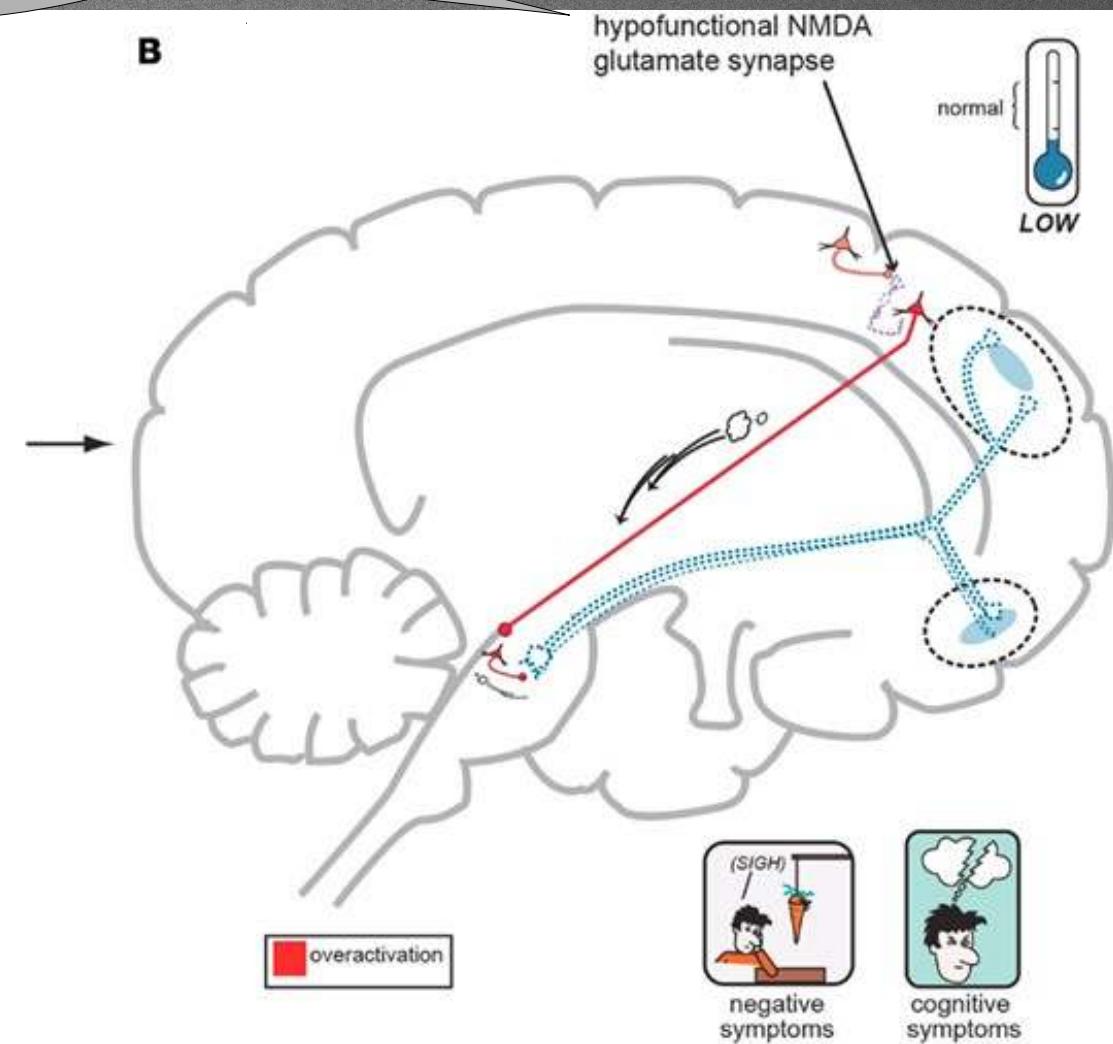
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A



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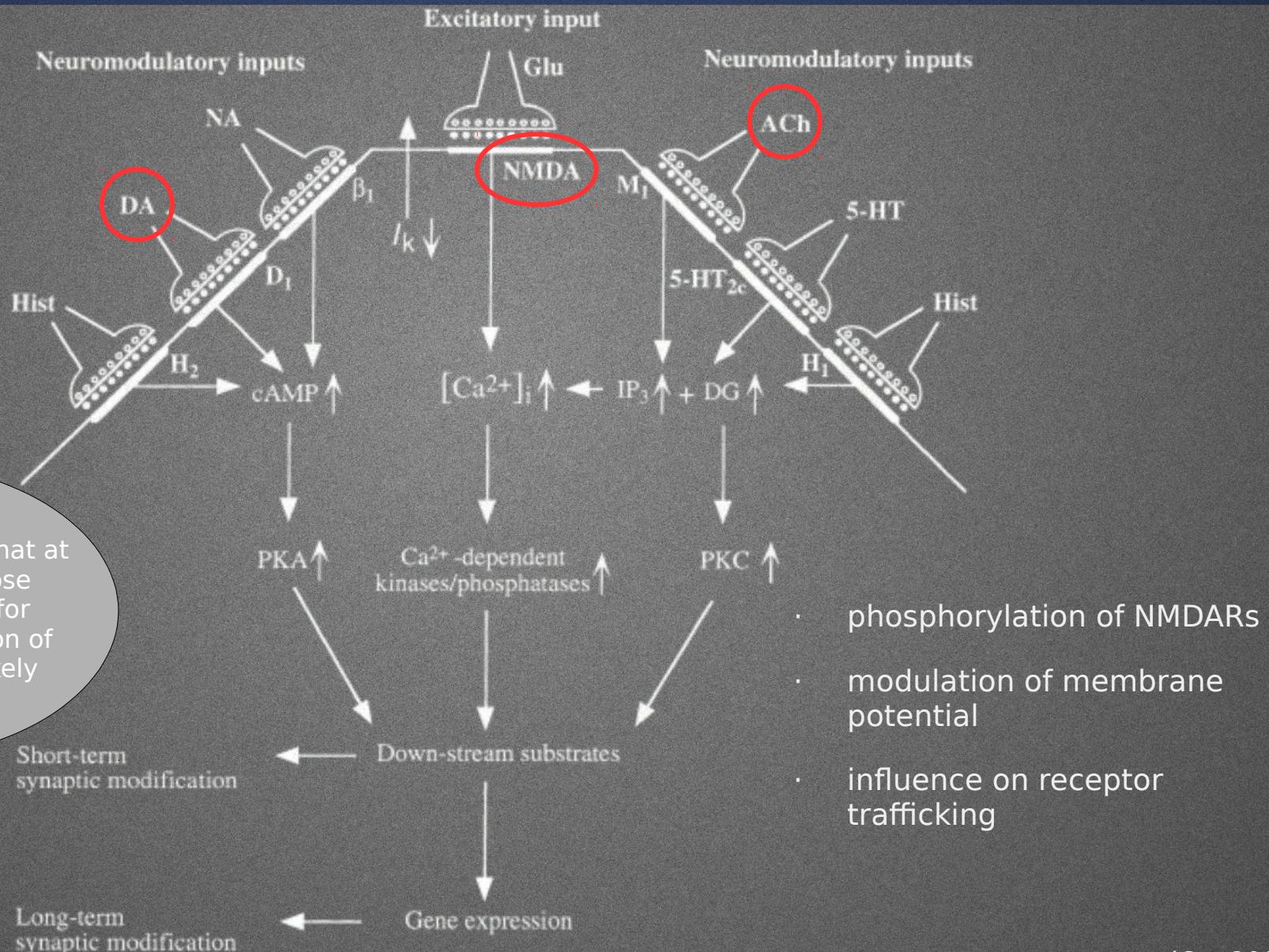
overactivation



positive  
symptoms

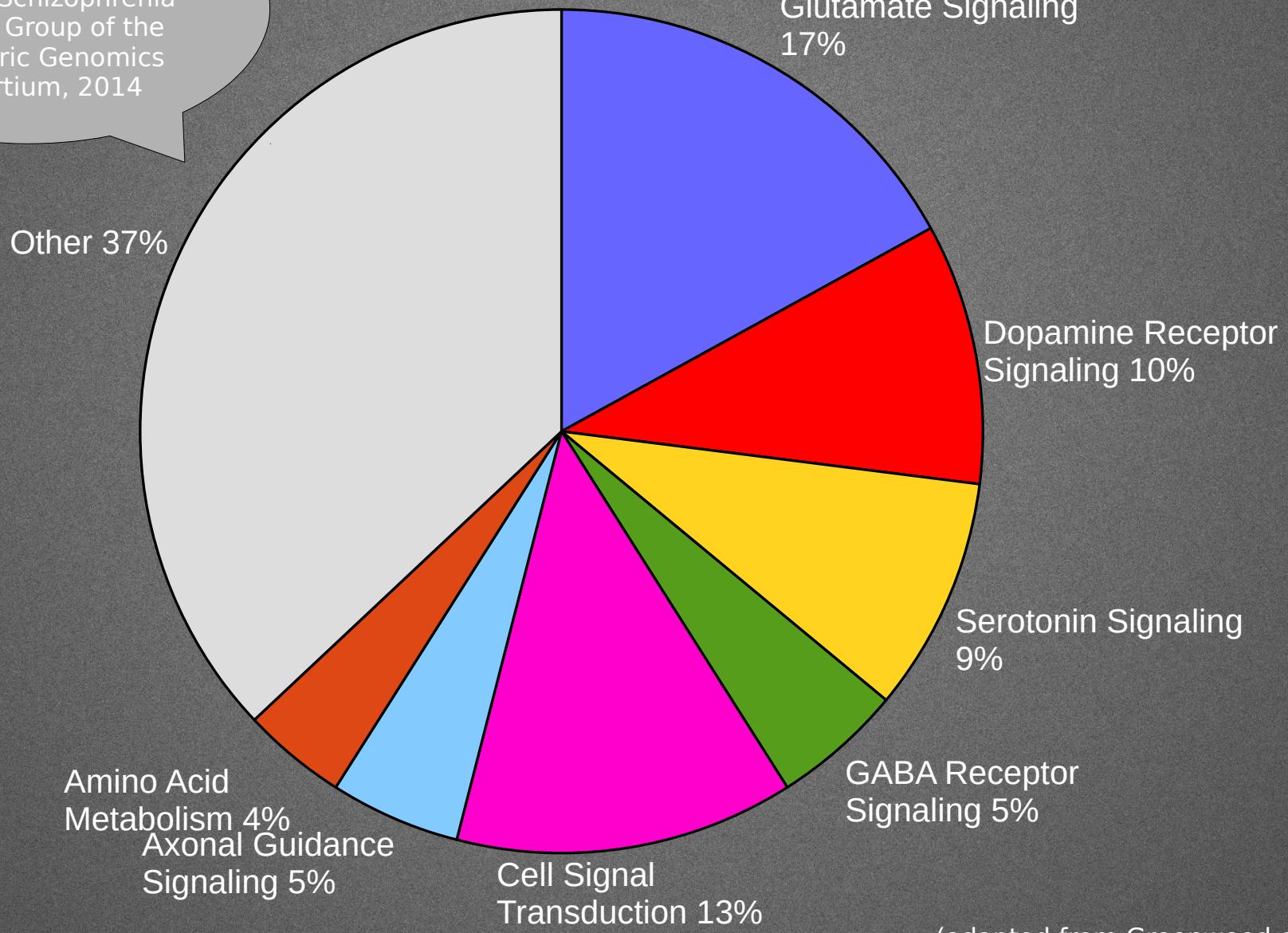


# NMDAR × neuromodulator interactions



# Candidate Genes

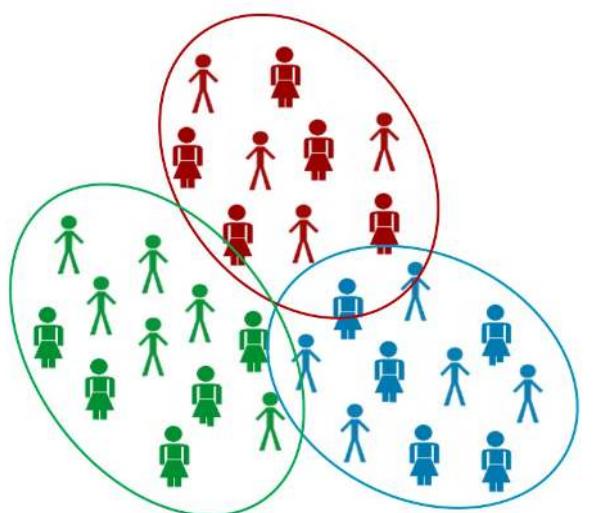
This is also represented in genetic findings!  
See also Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014



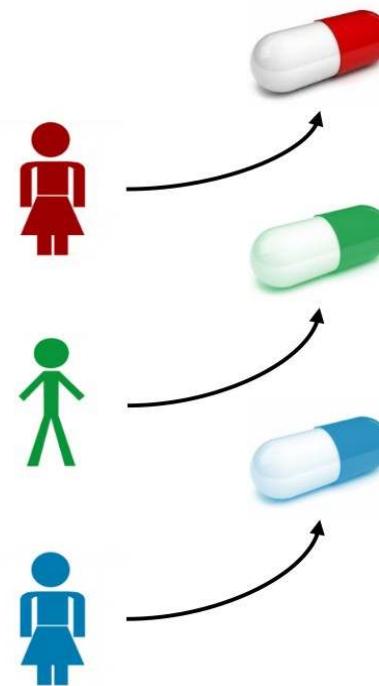
(adapted from Greenwood et al., 2012)

# Pathophysiology

- Probably different mechanisms and many “Schizophrenias”
- Identifying “groups” of mechanisms could lead to differential treatment



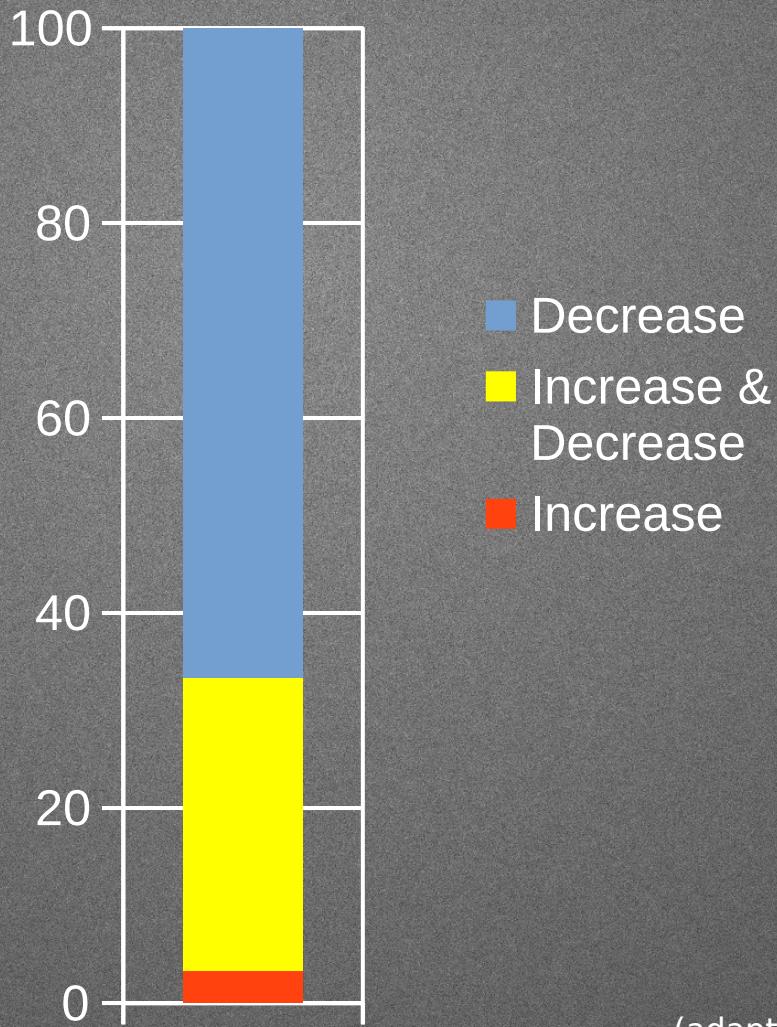
- disease mechanism A
- disease mechanism B
- disease mechanism C



# Dysconnectivity

## Functional connectivity in chronic SZ % of studies with main finding

trend towards connectivity reductions in individuals with schizophrenia - aberrant synaptic transmission as a possible cause or the other way around?



(adapted from Pettersson et al., 2011)

# Dysconnection Hypothesis

- Integrative computational perspective
- Aberrant synaptic transmission
  - disturbed modulation of synaptic gain
- Disrupted integration of *sensory evidence and predictions*

→ ...more of this later:

- Models of perception (F. Petzschner)
- Predictive Coding (L. Weber)
- Active Inference (P. Schwartenbeck)
- Dissecting Psychosis through Computational Psychiatry (P. Corlett)
- ...

# Clinical Care



# Antipsychotics

Thorazine or Chlorpromazine was the first antipsychotic that was used in clinical practice – it was originally not developed as antipsychotic

Advertisements like this actually added to the marginalization of individuals with mental disorders

When the patient lashes out against "them"—

**THORAZINE®**  
brand of chlorpromazine

quickly puts an end to his violent outburst

"Thorazine" is especially effective when the psychotic episode is triggered by delusions or hallucinations.

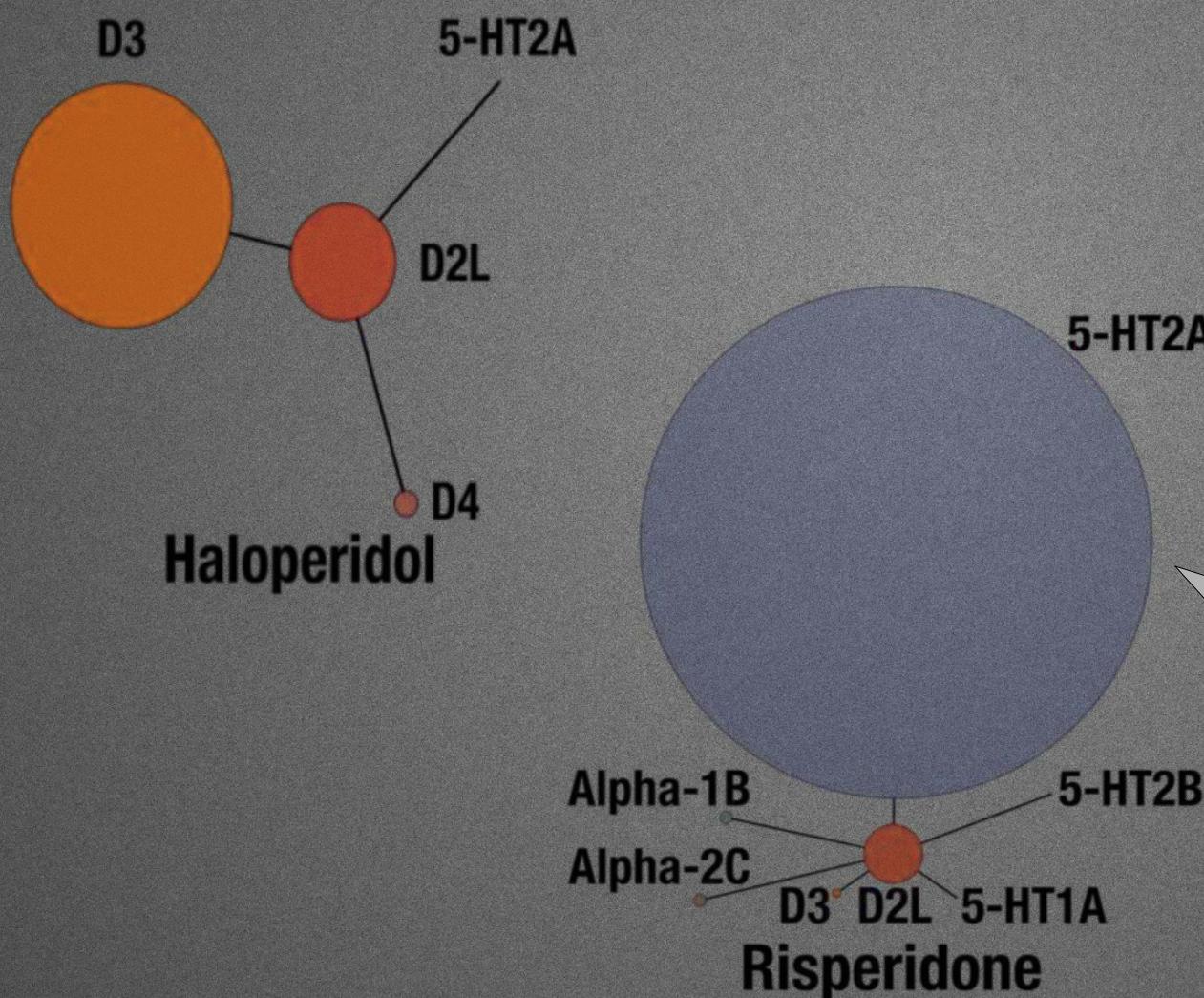
At the outset of treatment, Thorazine's combination of antipsychotic and sedative effects provides both emotional and physical calming. Assaulitive or destructive behavior is rapidly controlled.

As therapy continues, the initial sedative effect gradually disappears. But the antipsychotic effect continues, helping to dispel or modify delusions, hallucinations and confusion, while keeping the patient calm and approachable.

**SK** SMITH KLINE & FRENCH LABORATORIES  
Leaders in psychopharmaceutical research

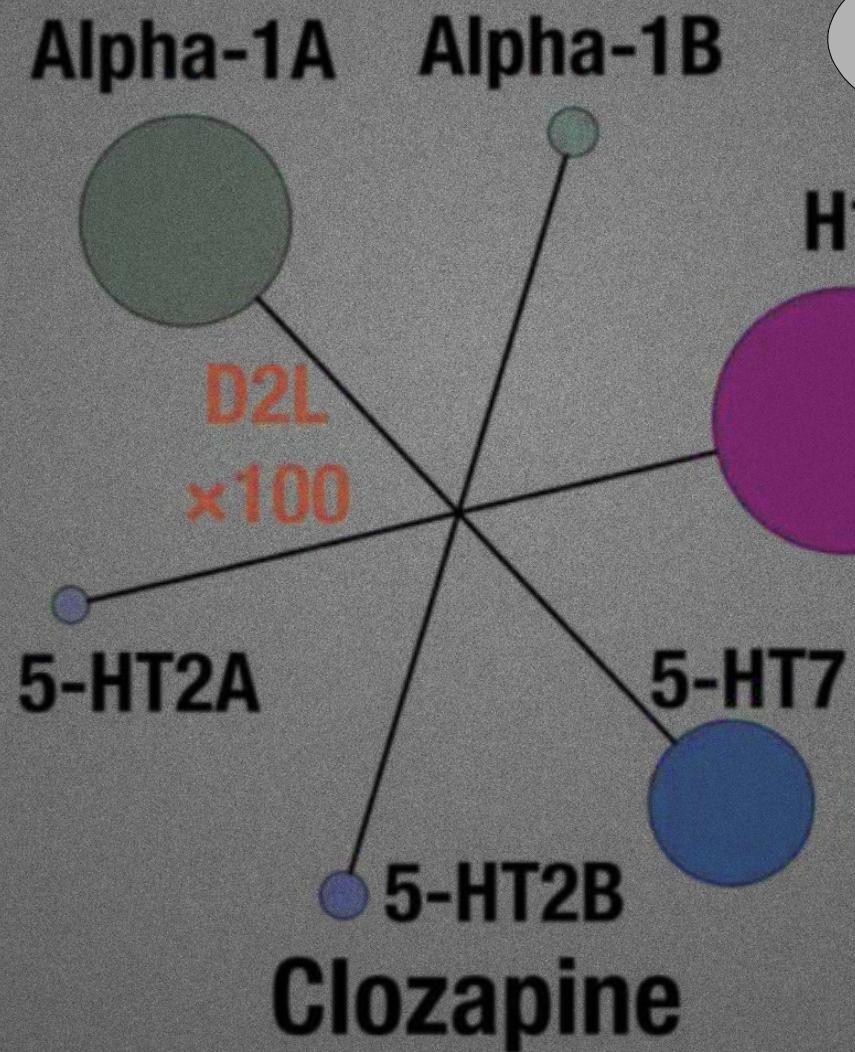
A reminder advertisement—For prescribing information, please see [PDR](#) or available literature.  
(Unknown, Wikimedia, ca. 1962)

# Antipsychotics



The size of the circles indicate the affinity towards different receptors  
– this is an important factor in estimating the antagonism at the given receptor – though many receptors are “blocked”, most antipsychotics show a robust affinity towards D2 receptors.

# Curious Case of Clozapine



Clozapine shows a weak affinity (at least in classical testing) towards D2 receptors

# Antipsychotics

Even though clozapine shows weak affinity towards D2 receptors it is very effective in the treatment of schizophrenia

## Overall change in symptoms

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)

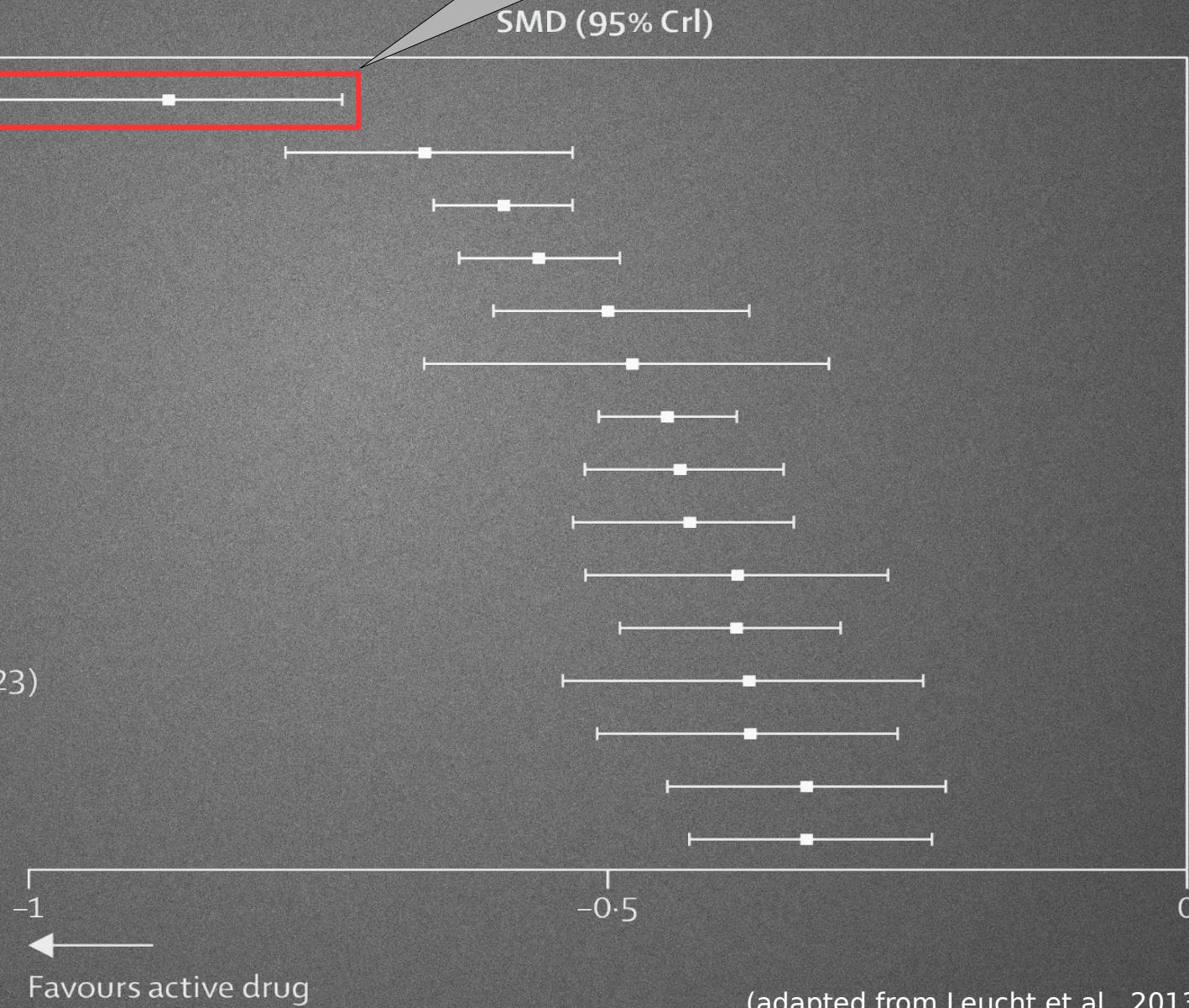
Ziprasidone -0.39 (-0.49 to -0.30)

Chlorpromazine -0.38 (-0.54 to -0.23)

Asenapine -0.38 (-0.51 to -0.25)

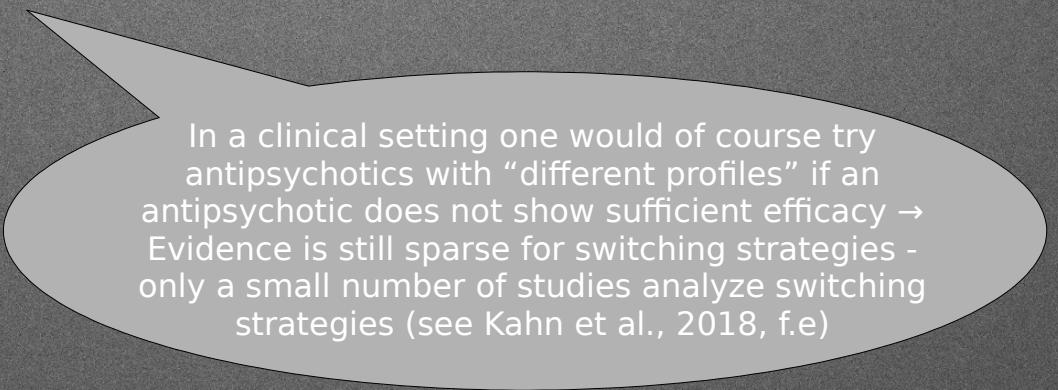
Lurasidone -0.33 (-0.45 to -0.21)

Iloperidone -0.33 (-0.43 to -0.22)



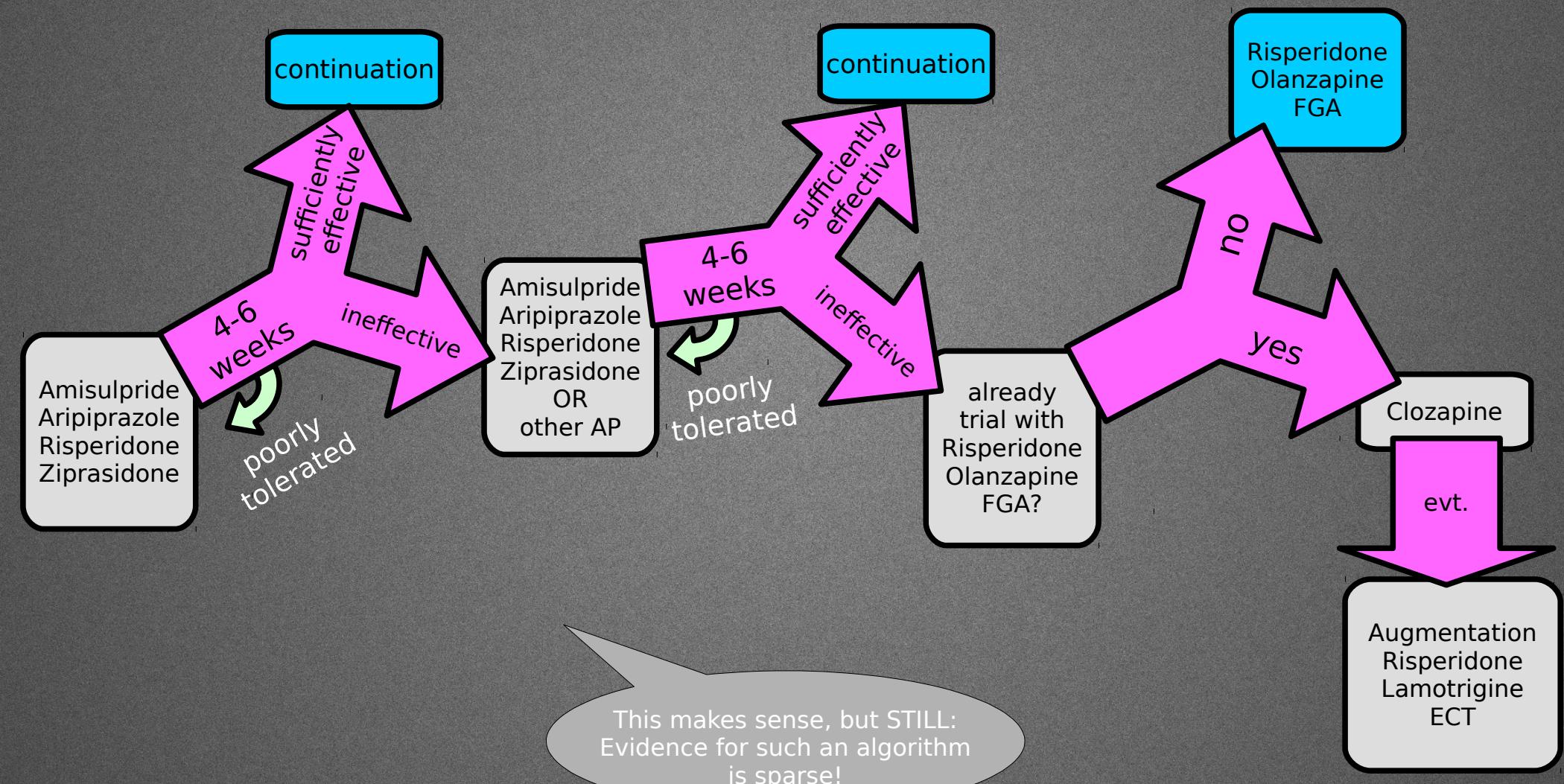
# Antipsychotics

- 50% respond to 1<sup>st</sup> line treatment
- Response ≠ remission, recovery or cure
- Adherence
- *Identifying the most effective medication by trial and error (?)*



In a clinical setting one would of course try antipsychotics with “different profiles” if an antipsychotic does not show sufficient efficacy → Evidence is still sparse for switching strategies - only a small number of studies analyze switching strategies (see Kahn et al., 2018, f.e)

# Antipsychotics



(adapted from Osser et al., 2013)

# Clinical Care

Recovery is guiding principle of modern therapy and means that restoring the function as opposed to symptom reduction is focus of treatment



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

National Schizophrenia & Psychosis Awareness Day  
May 24<sup>th</sup>, 2018  
[www.earlypsychosisintervention.ca](http://www.earlypsychosisintervention.ca)



Canadian Mental  
Health Association  
*Mental health for all*



# Treatment strategies

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

# Treatment strategies

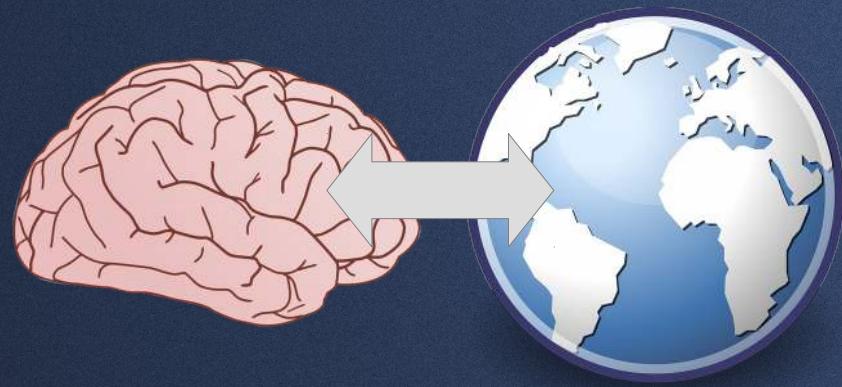
- Psychoeducation
- Low-threshold service
- Cognitive Behavioural Therapy
- Treatment resistance → Clozapine
- Antidepressant as co-medication

Providing information about the condition and strategies how to handle it

...but cf. Jones et al., 2018

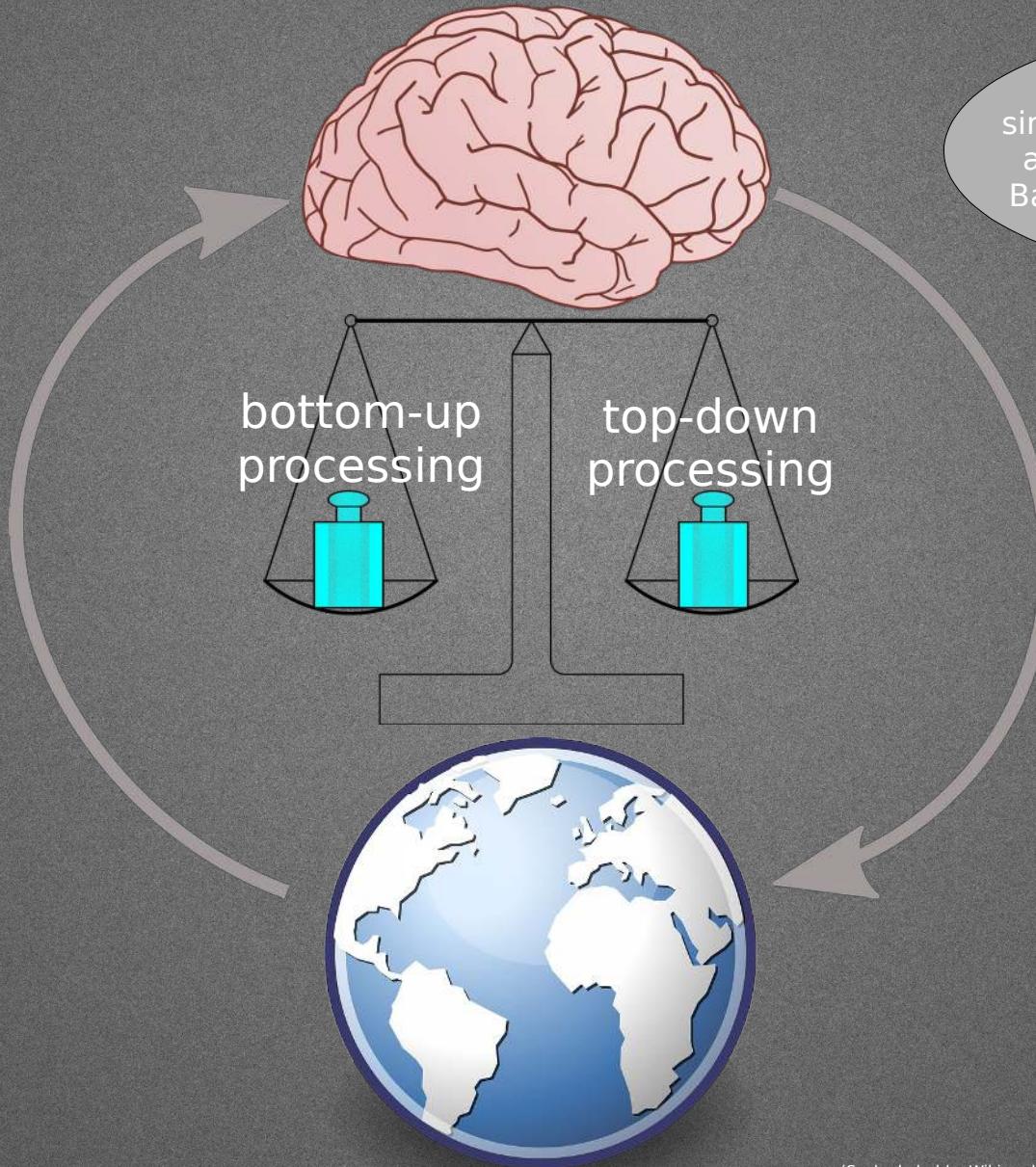
In case of depressive symptoms

# Bayesian Brain & Schizophrenia



# Bayesian Brain & Schizophrenia

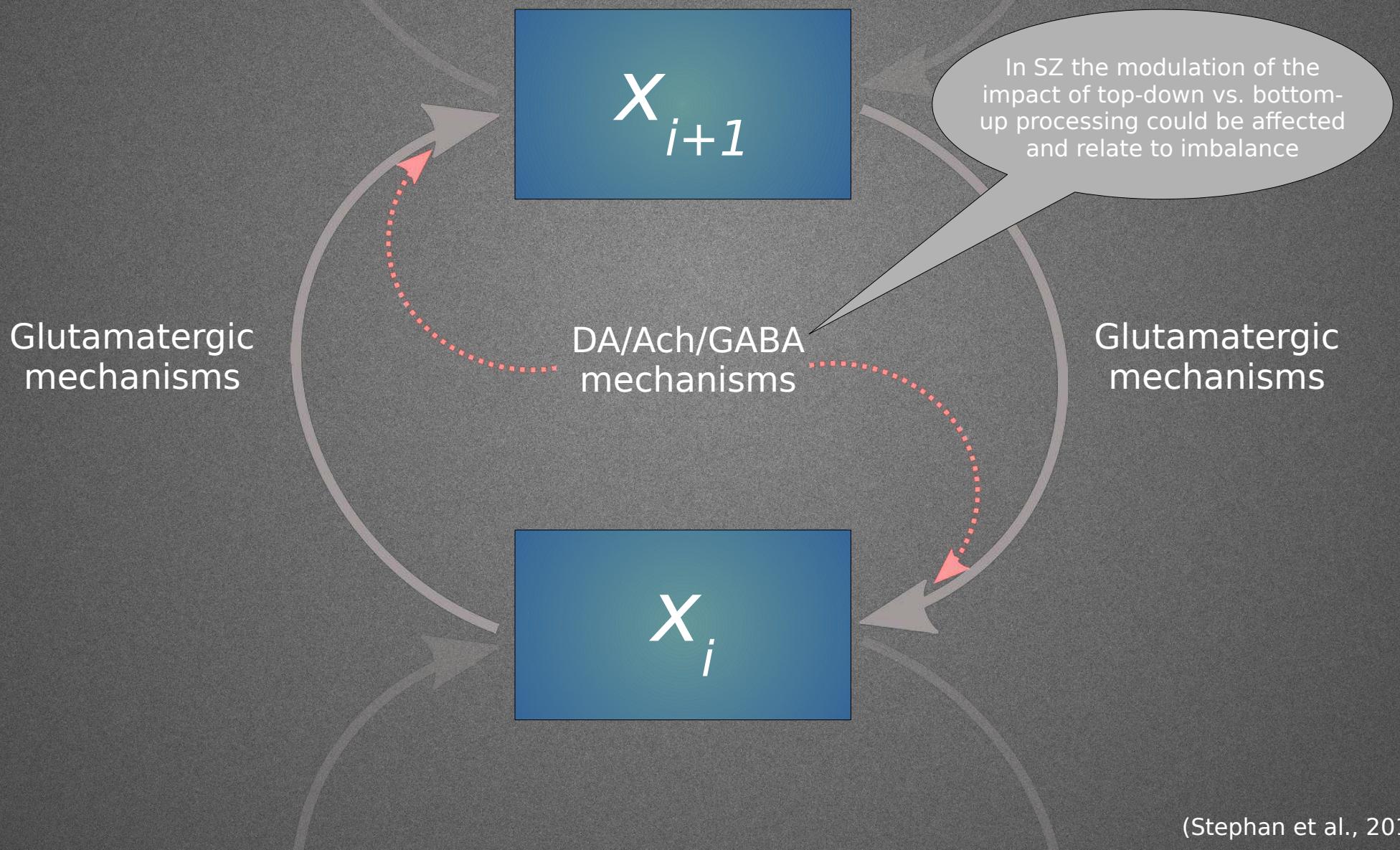
- Sensory Evidence
- (Prediction errors)



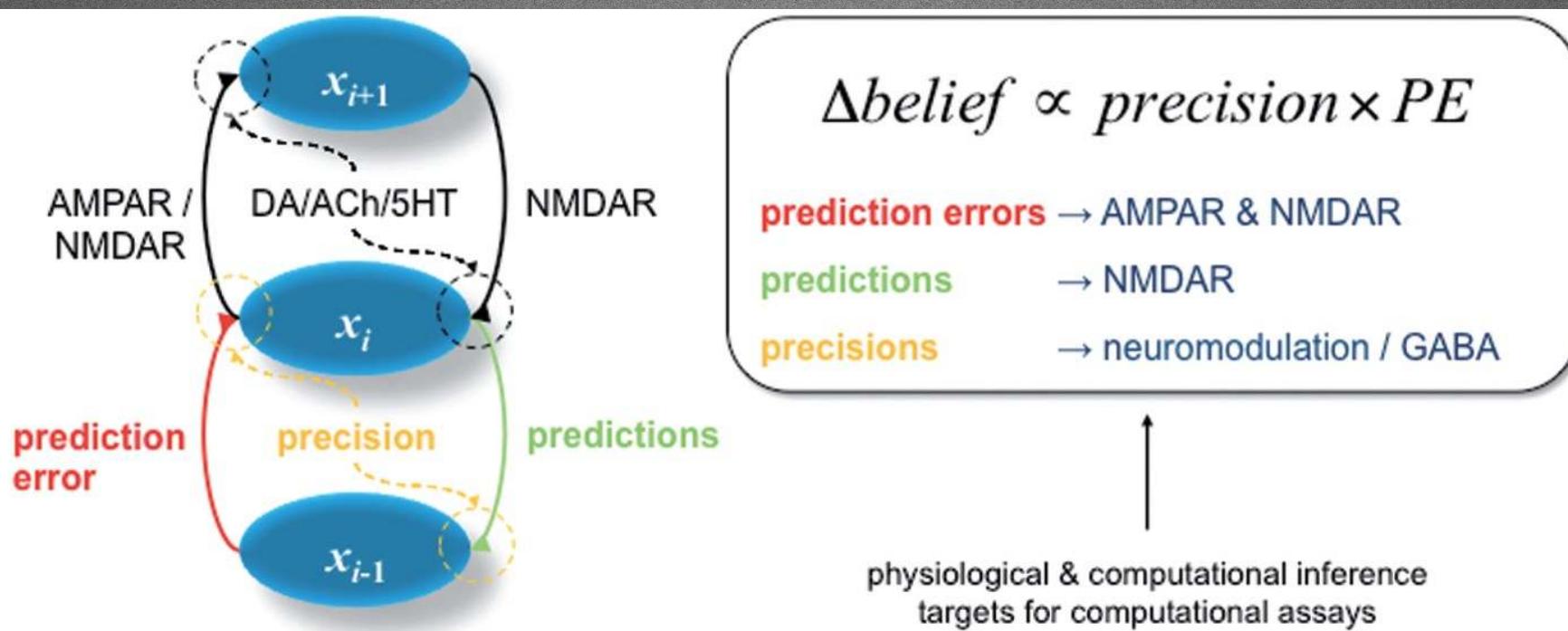
This is of course very much simplified, but it should give you an idea how we could think of Bayesian Brain abnormalities in schizophrenia.

- Predictions
- Beliefs
- Priors

# Bayesian Brain & Schizophrenia



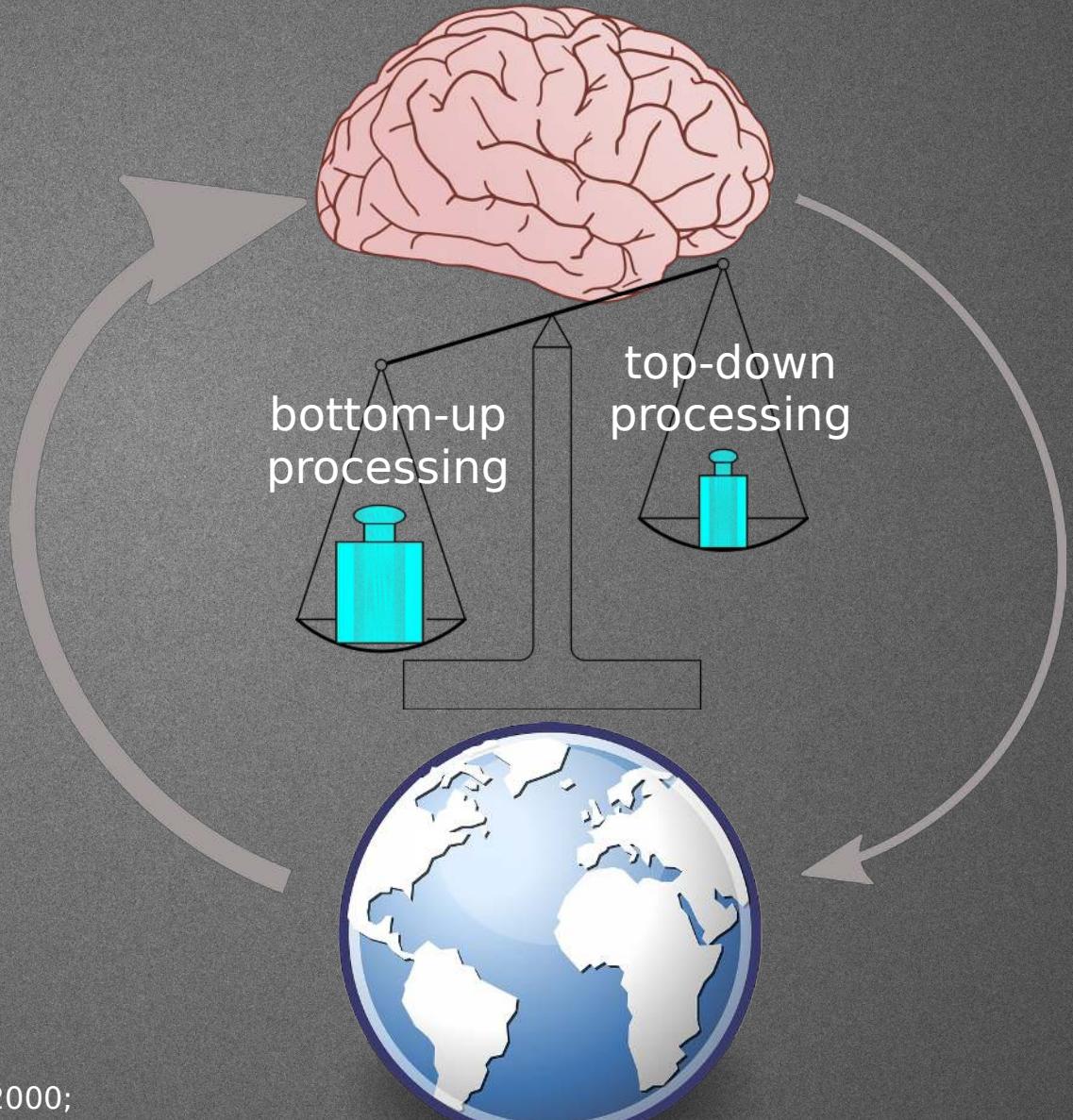
# Bayesian Brain



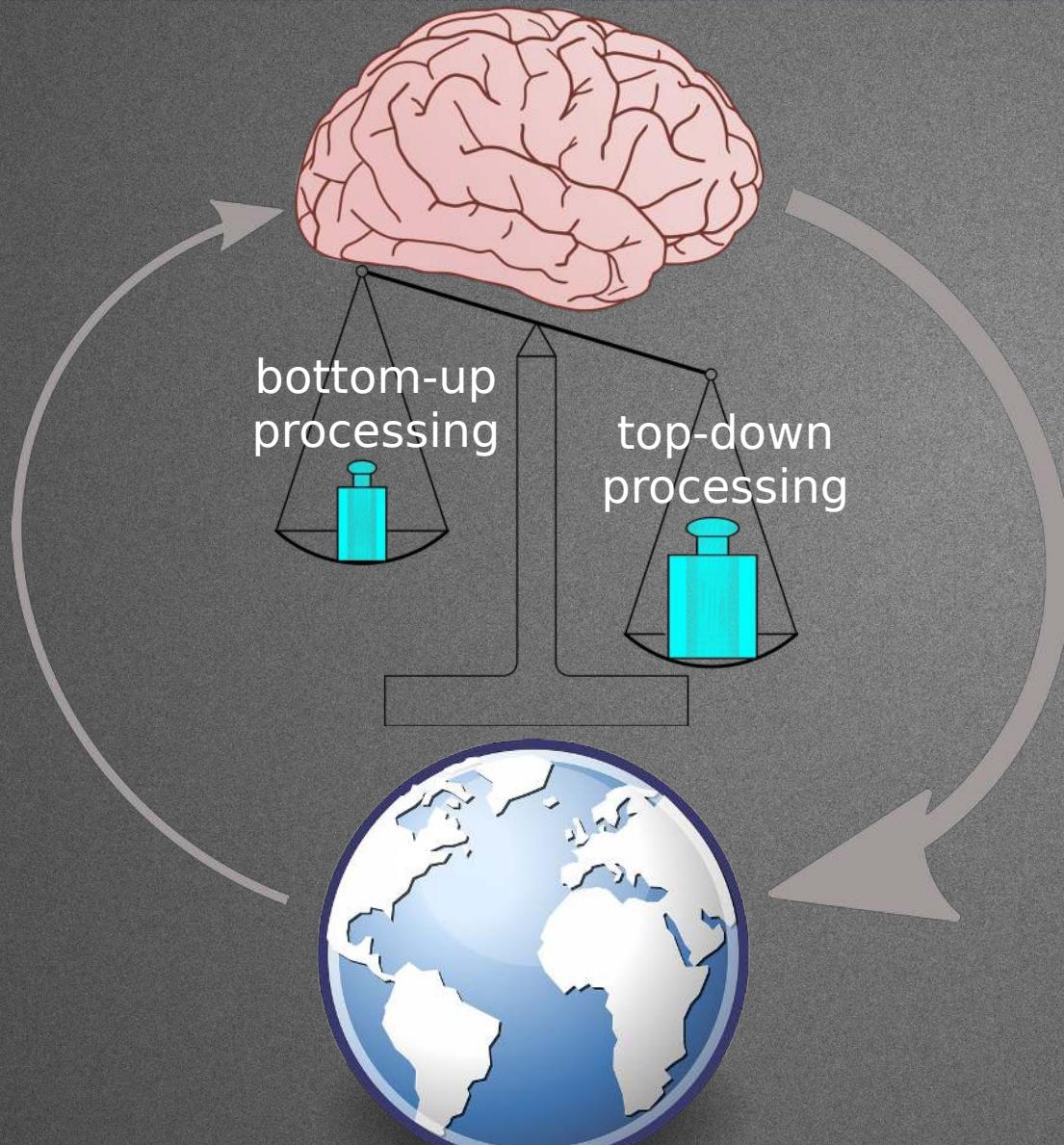
# Bayesian Brain & Schizophrenia

## Trait phenomena in SZ

- ↓ susceptibility to illusions
- Neurophysiology (↓MMN)
- Abnormal eye movement
- “Delusional mood”
- Negative symptoms



# Bayesian Brain & Schizophrenia

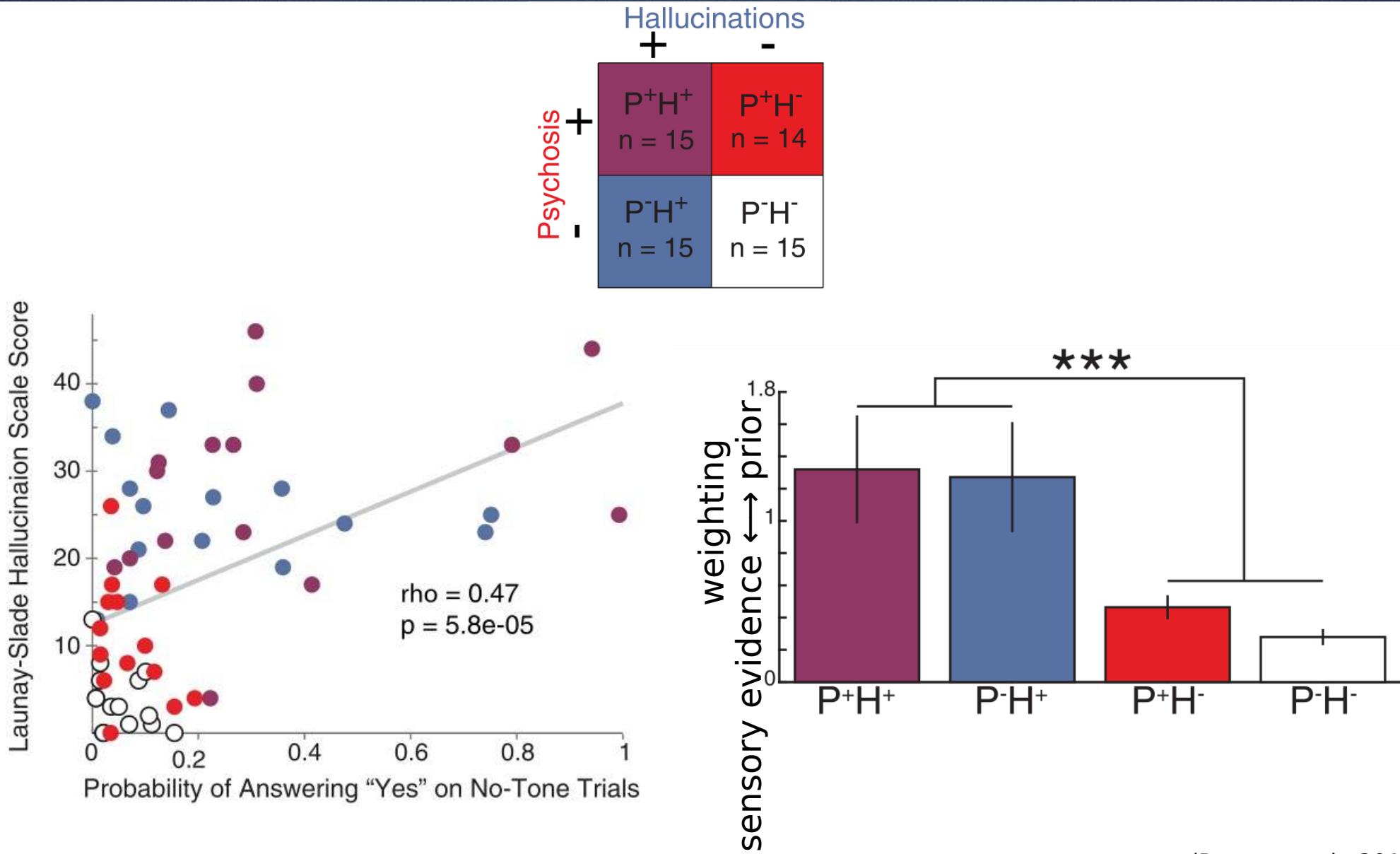


## State phenomena in SZ

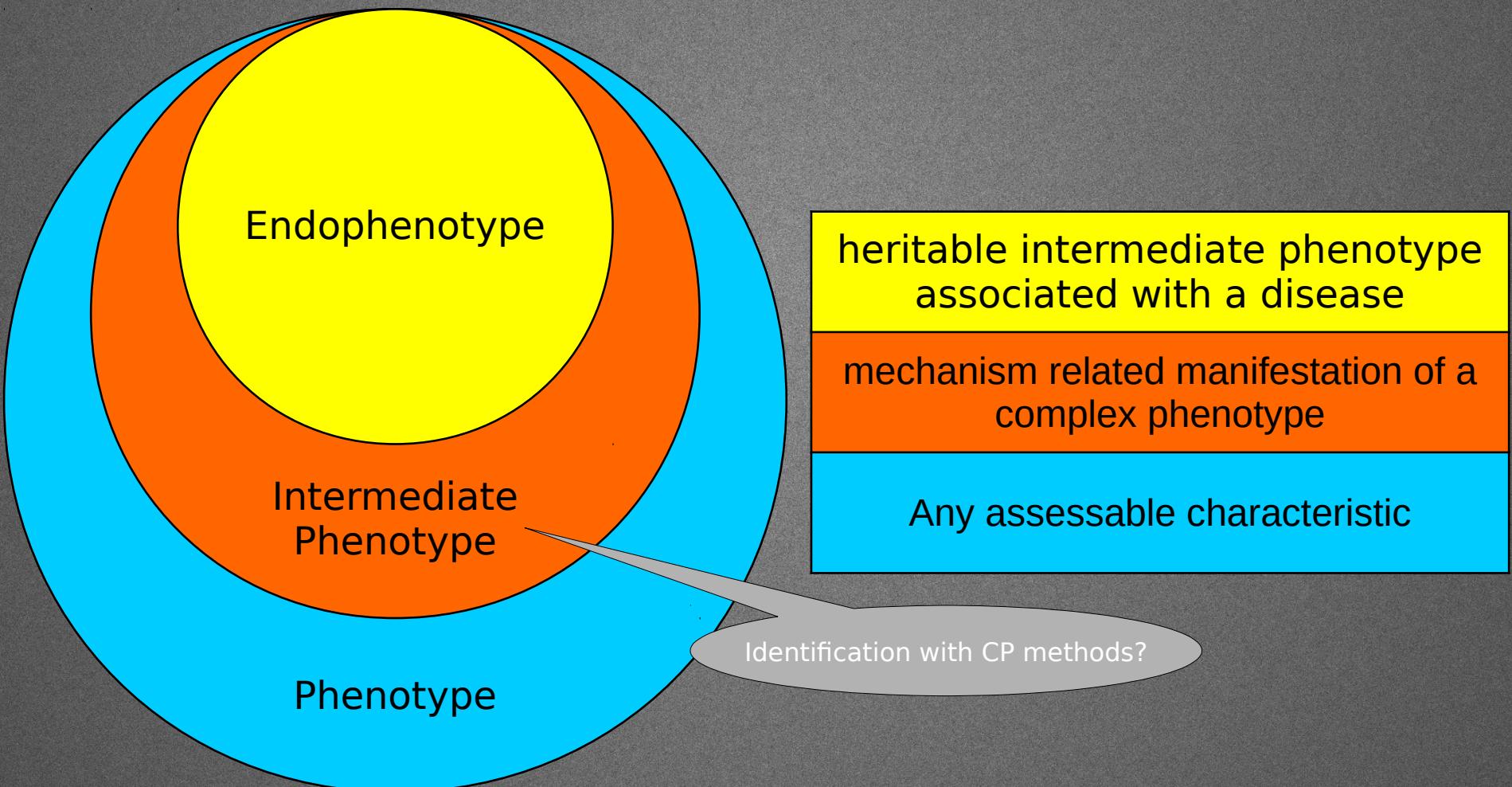
- Strong prediction/belief  
→ delusion
- Acoustic hallucinations

→ Evidence still sparse!

# Bayesian Brain & Schizophrenia



# Intermediate Phenotypes



# What clinicians demand from CP

## Mechanistic understanding

- **Useful** for clinical practice
- Clinically **feasible** tools
  - Early diagnosis
  - Different mechanisms  
→ specific medication/treatment
  - “Normalize” and de-stigmatize Schizophrenia

# Questions?



THANK YOU!



Translational Neuromodeling Unit



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