Schizophrenia
(for non-clinicians)

2022 Computational Psychiatry Course

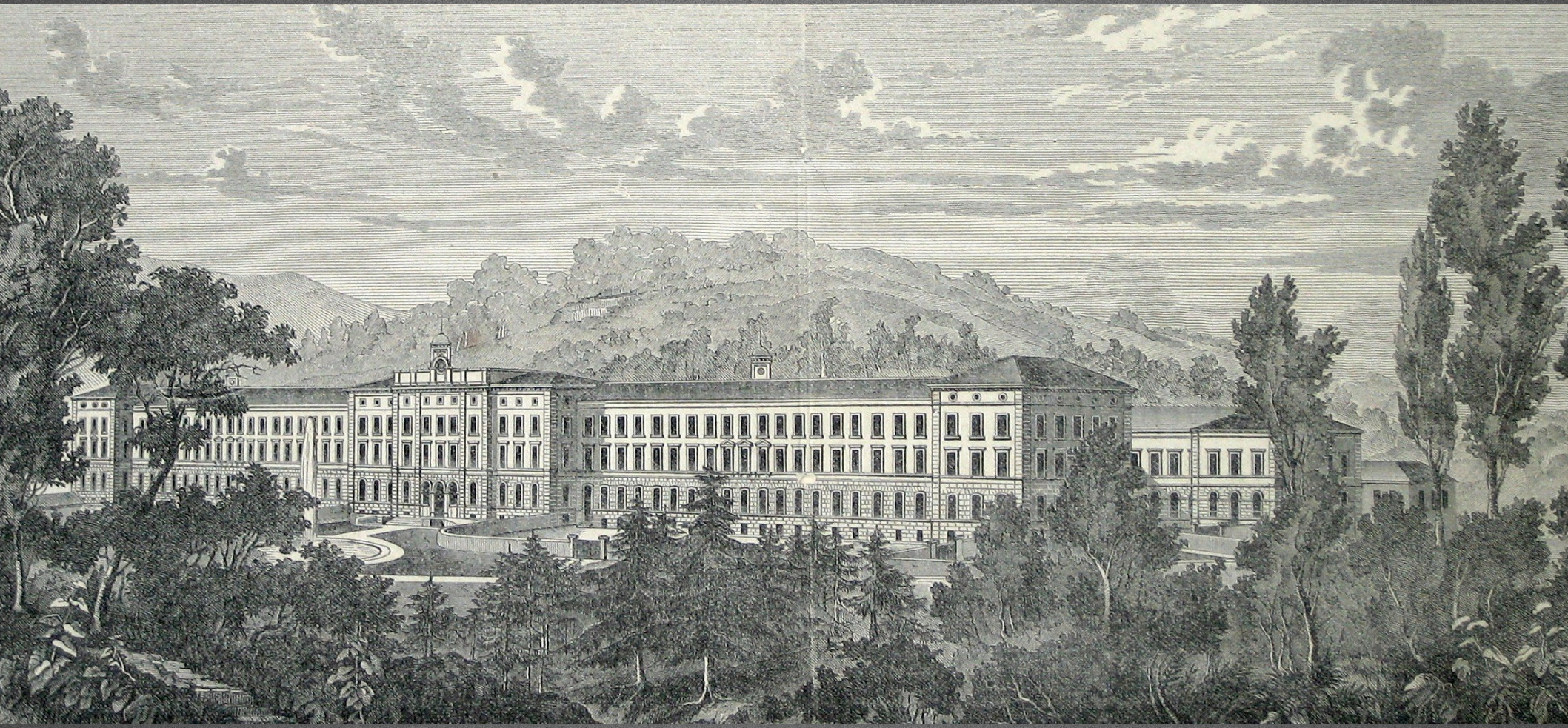
Translational Neuromodeling Unit

Universität Zürich[UZH]

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

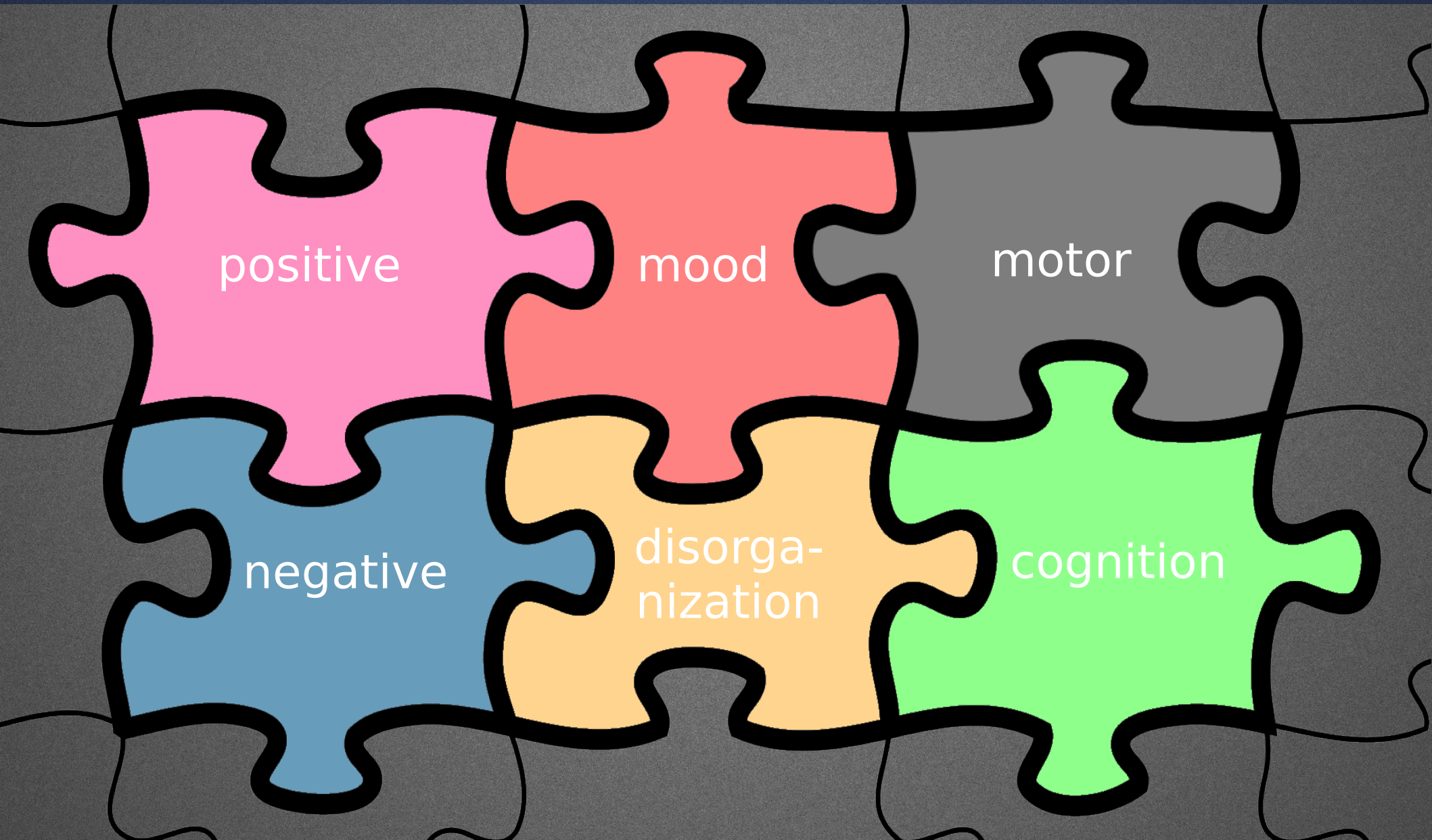
- 37yo librarian
- Messy apartment
- Has been talking “weirdly” for weeks, but now unable to talk
- Apathy
- Slowed down
- Lost her job months ago

Schizophrenia

- 19yo student of physics
- Neighbor:
  - Spying on him
  - 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?)

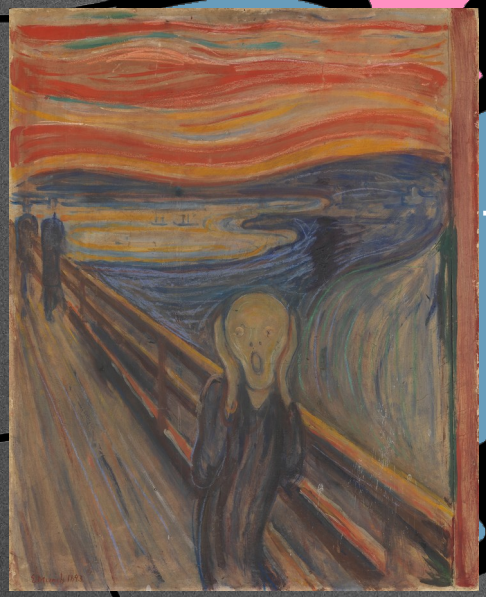
Main Symptom Categories



Main Symptom Categories

positive

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

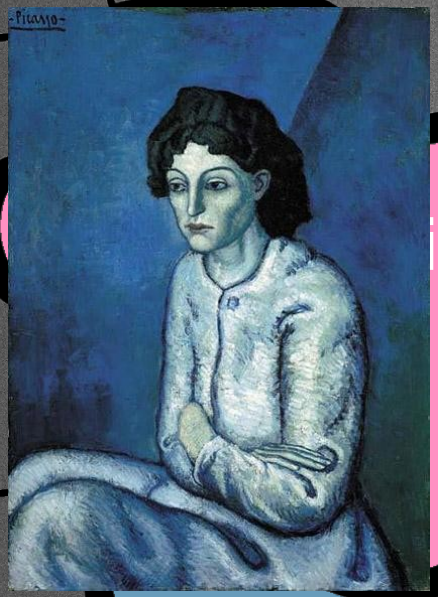


tive

disorga-
nization

cognition

Main Symptom Categories



ive

negative

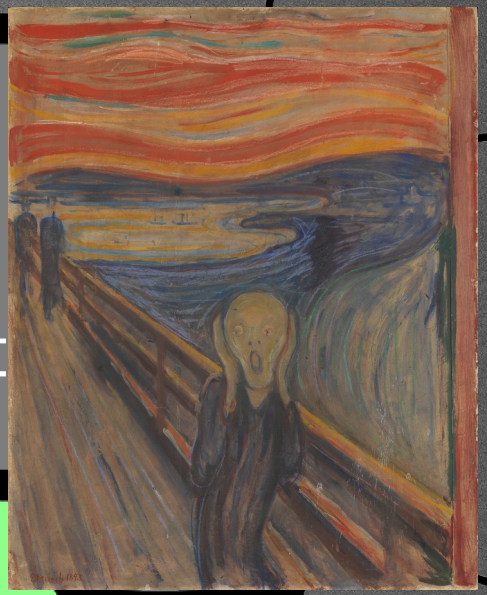
- loss of affective and driving functions
- impaired affective experience/expression
- loss of motivation & initiative
- reduced social drive
- slowed thinking

Main Symptom Categories

(Netherlands, Wikimedia, 2010)

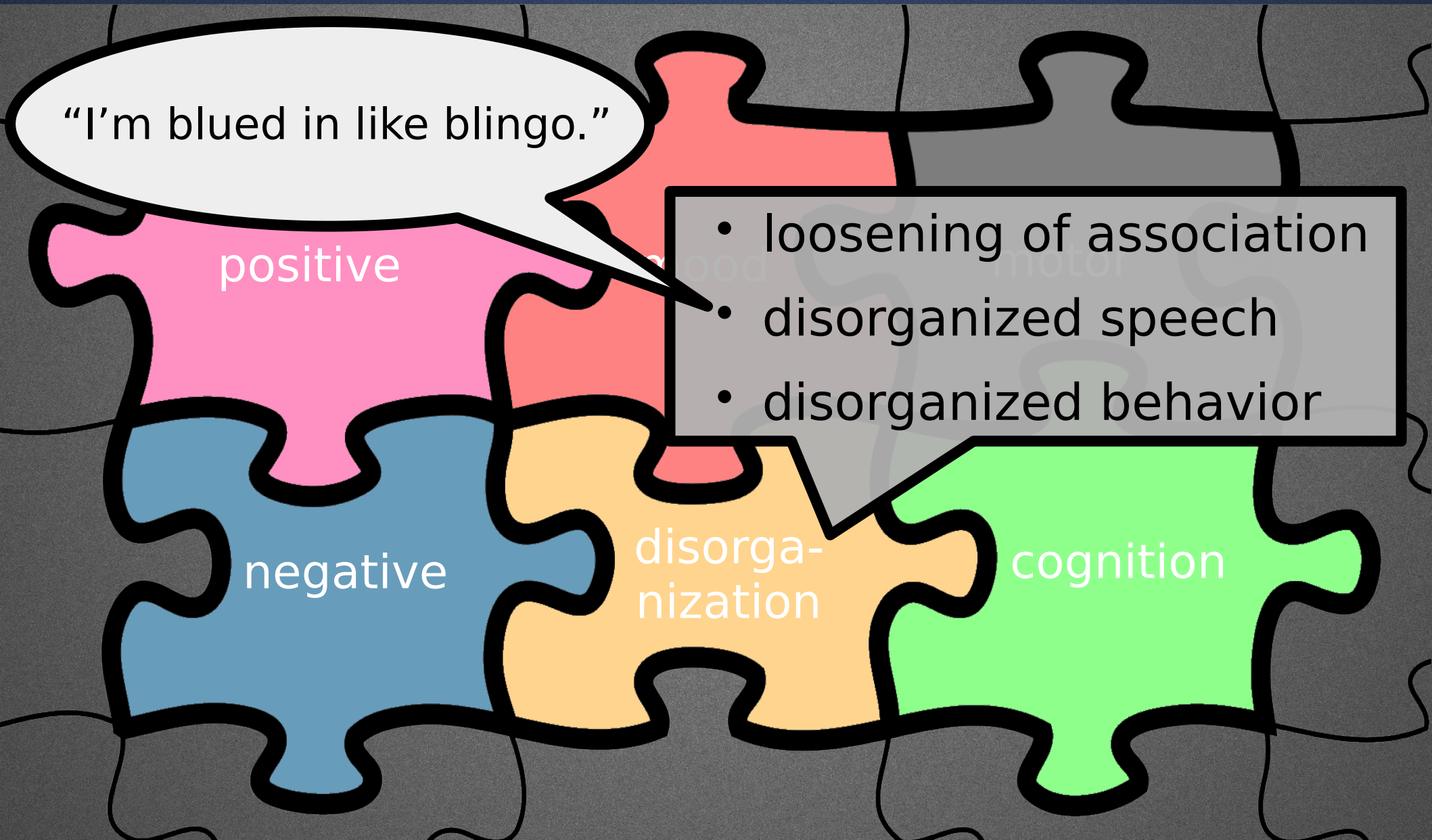
mood

mot



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

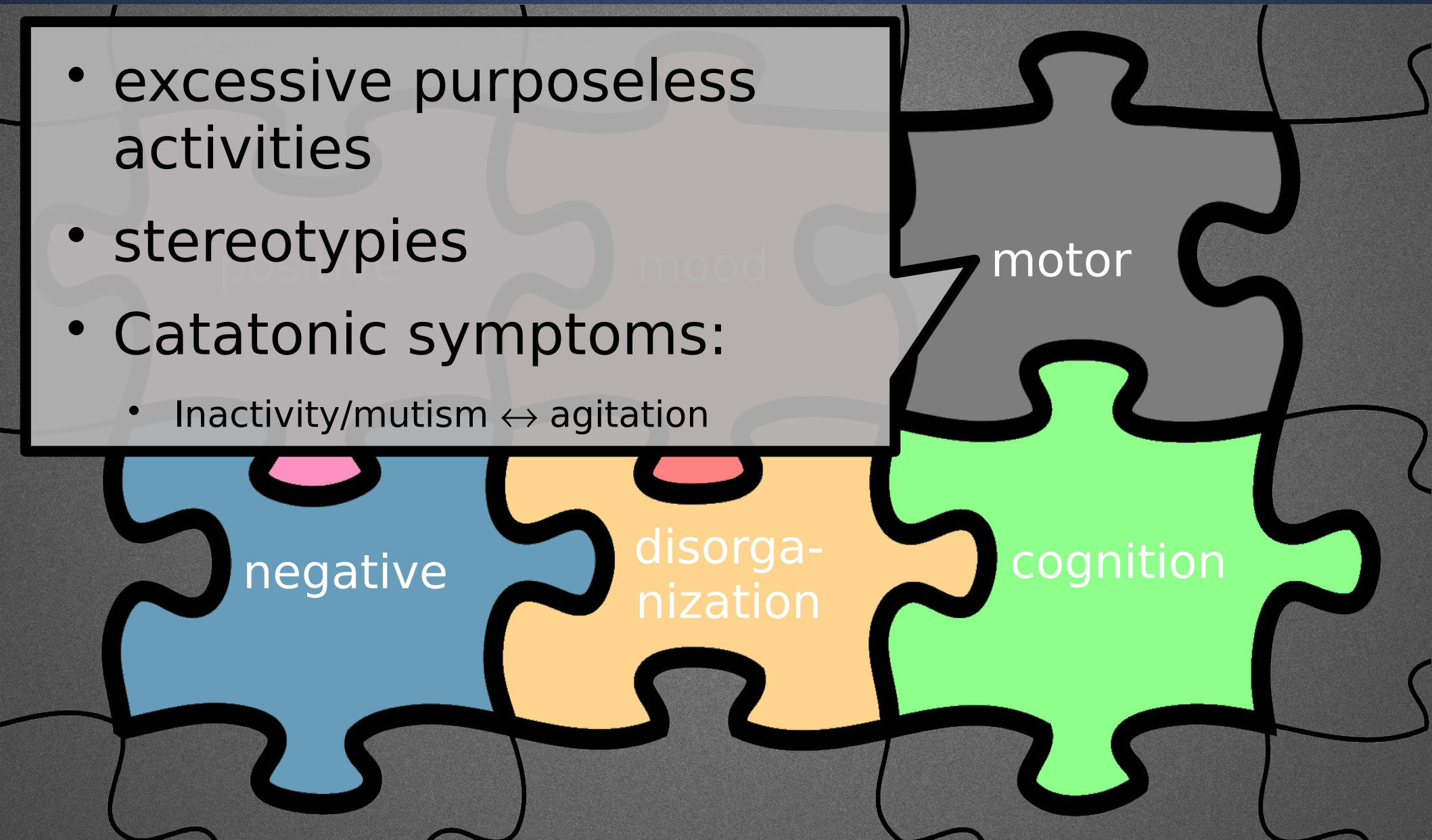
Main Symptom Categories



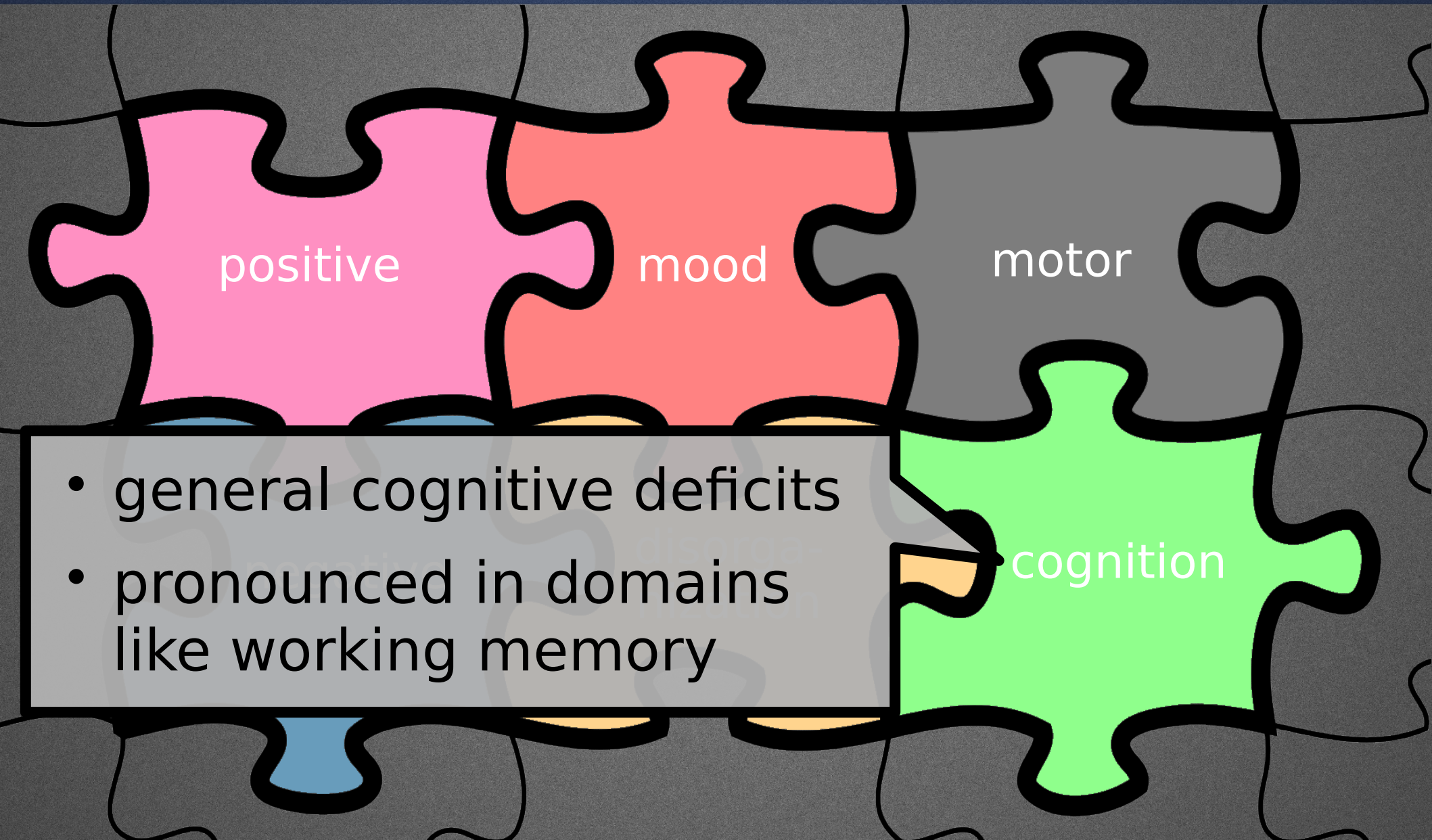
- loosening of association
- disorganized speech
- disorganized behavior

Main Symptom Categories

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

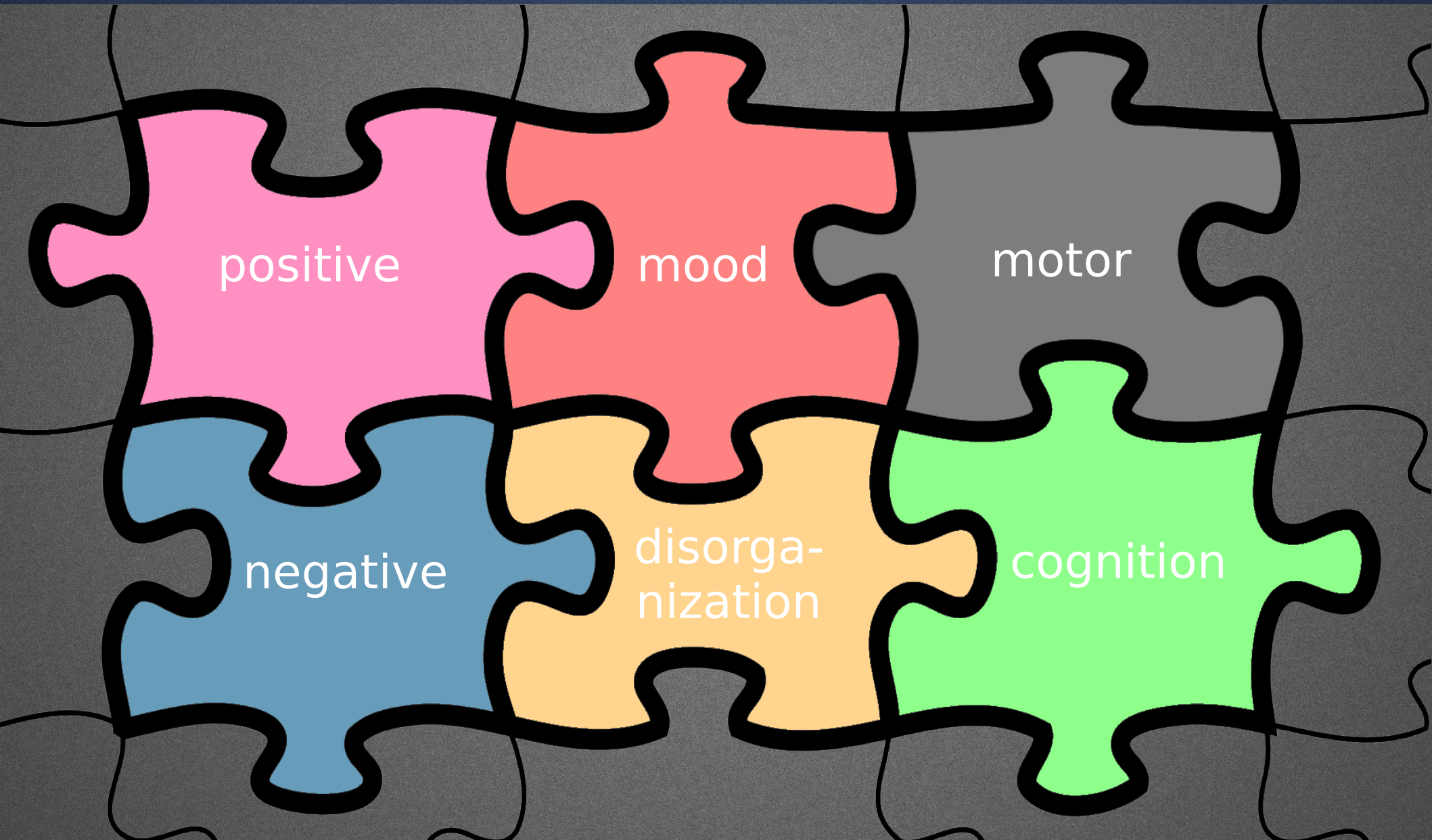


Main Symptom Categories



- general cognitive deficits
- pronounced in domains like working memory

Main Symptom Categories



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
- 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

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

- 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

- Exam, lab & MRI results ok

  → Schizophrenia

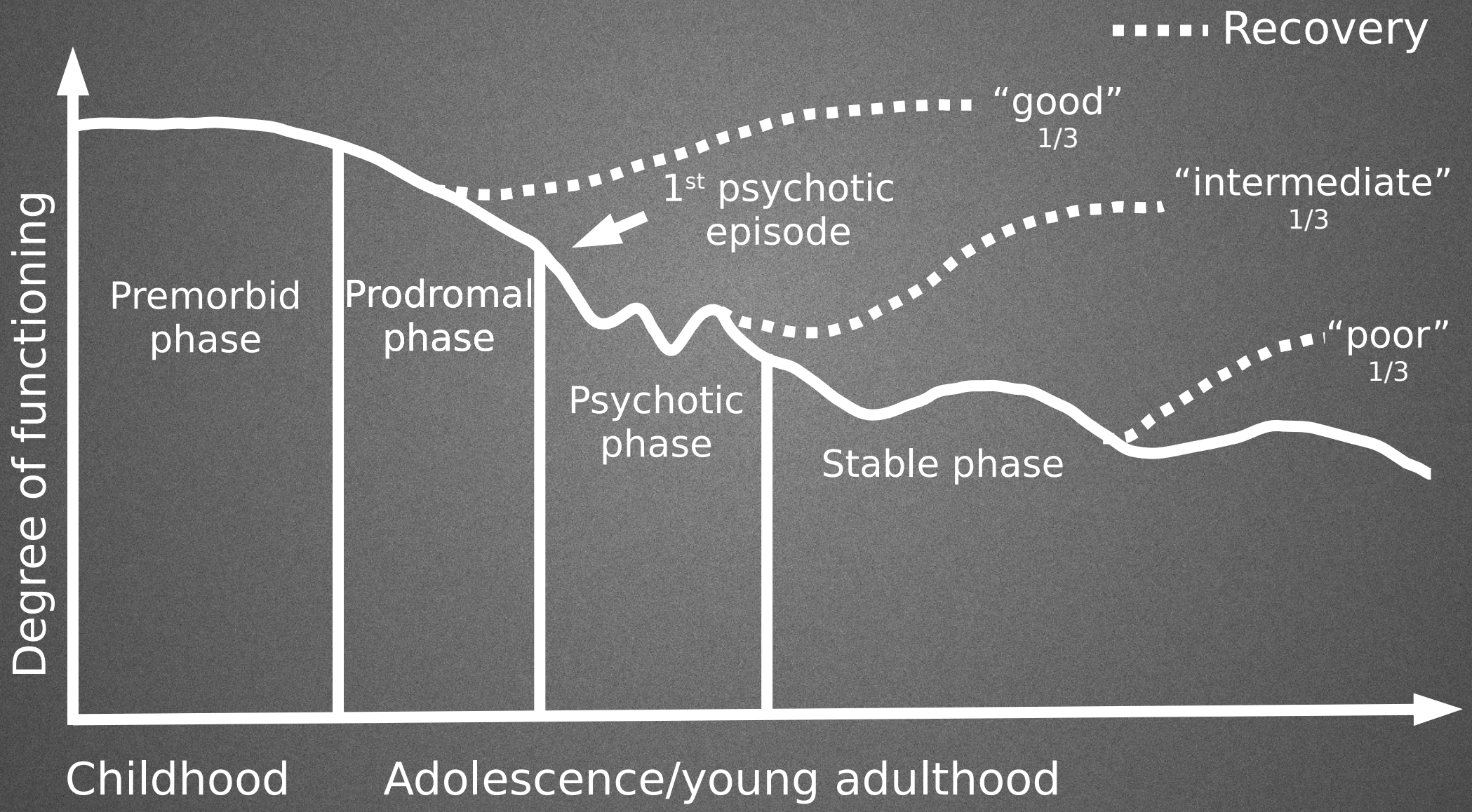
Diagnostic Criteria

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)

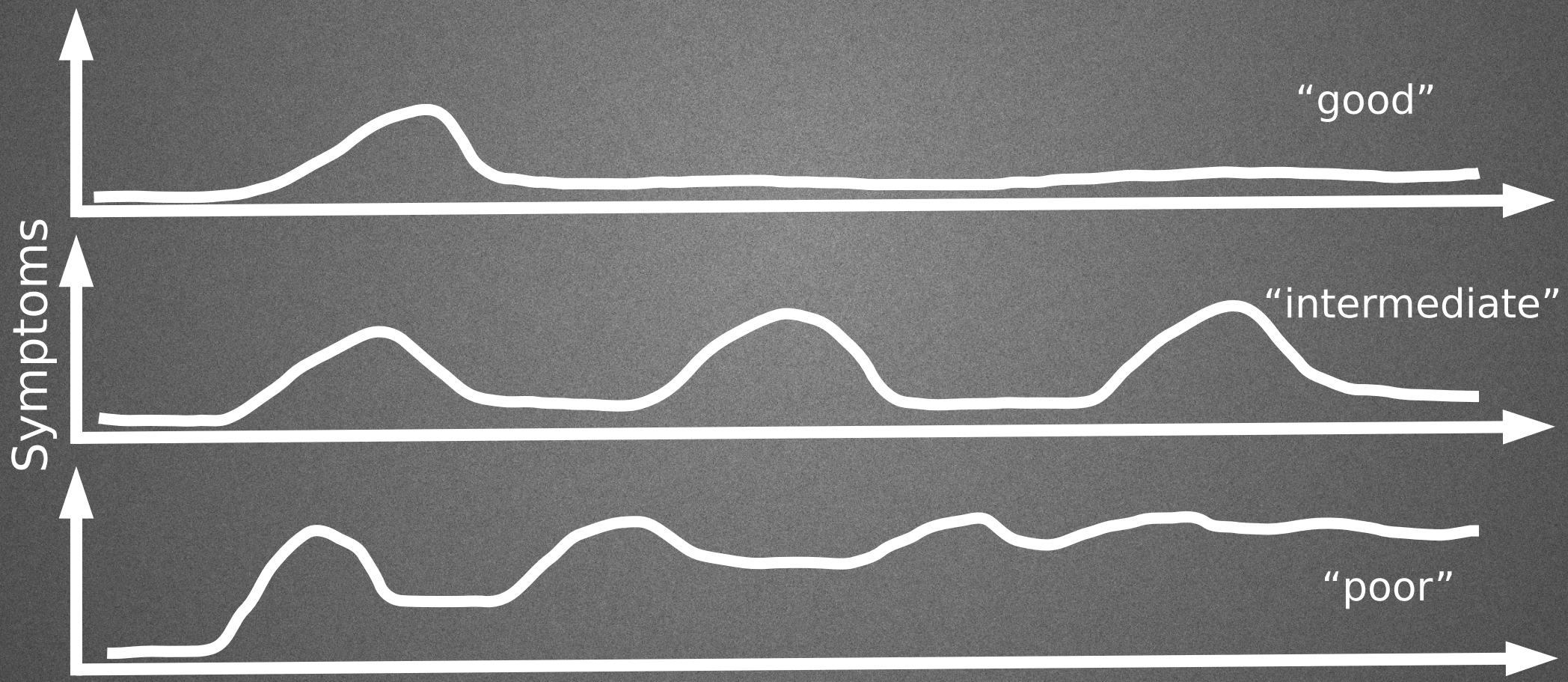
Trajectory
Risk factors
Outcome

Trajectory

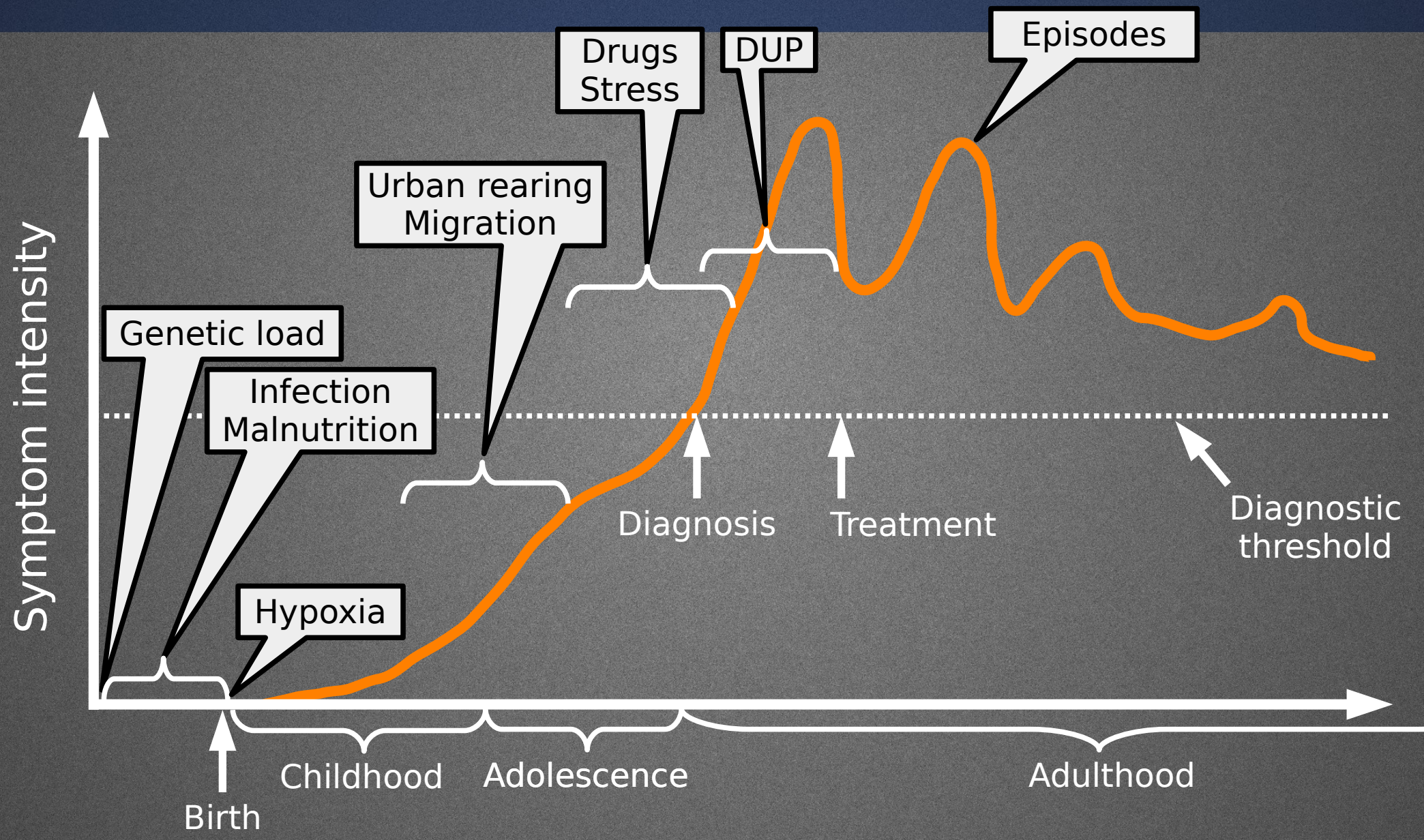


(modified from Tandon et al., 2009)

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

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

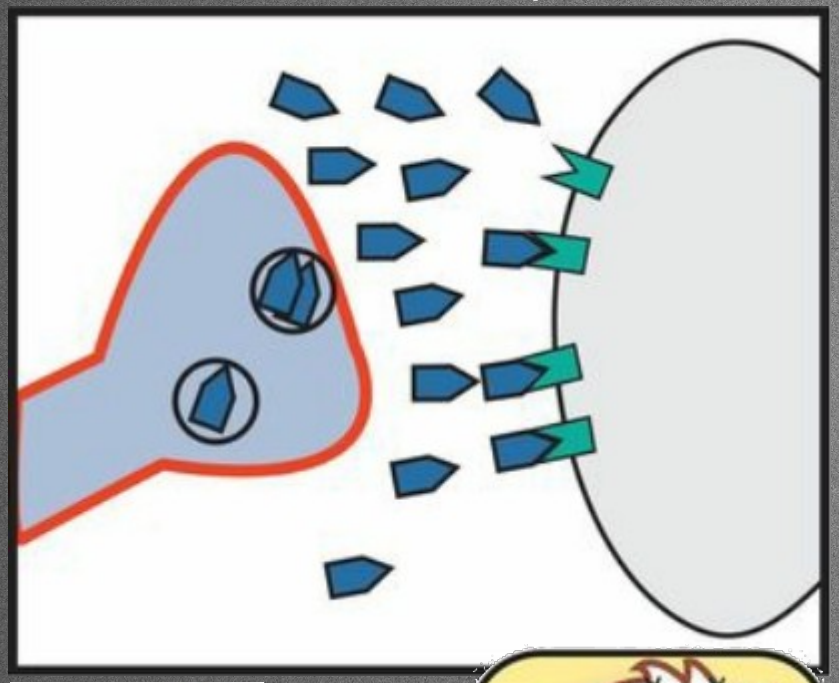
- Exam, lab & MRI results ok

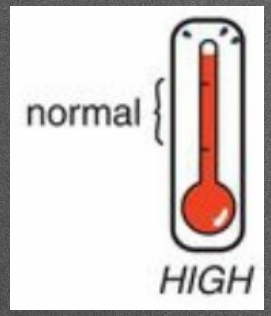
  → Schizophrenia

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

Antipsychotics

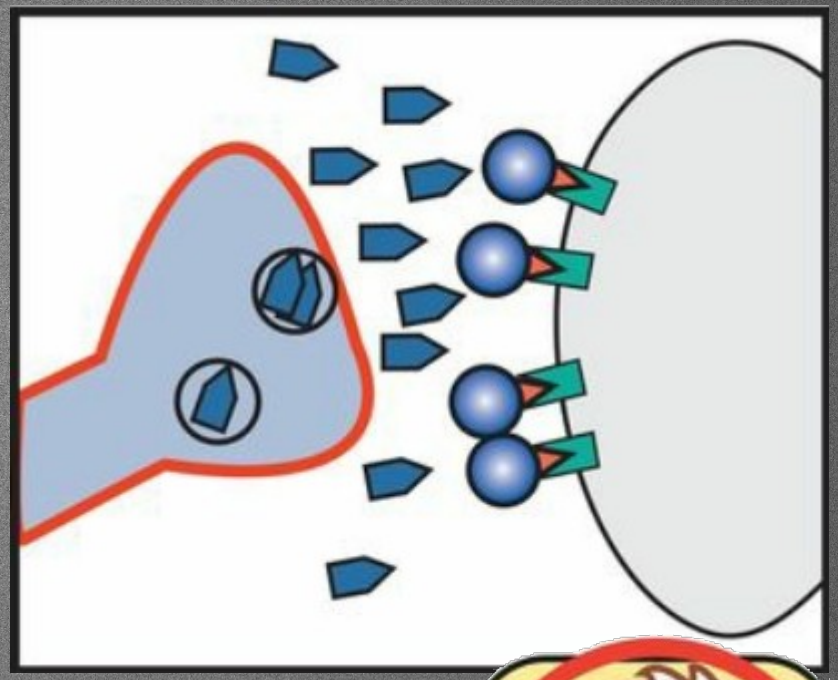
Mesolimbic Pathway
Untreated Schizophrenia

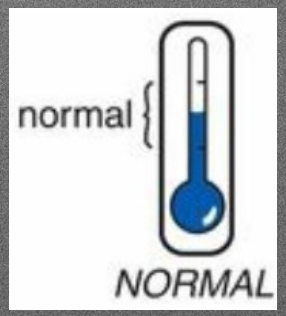




"hyperactive"
dopaminergic system

Mesolimbic Pathway
D2 Antagonist

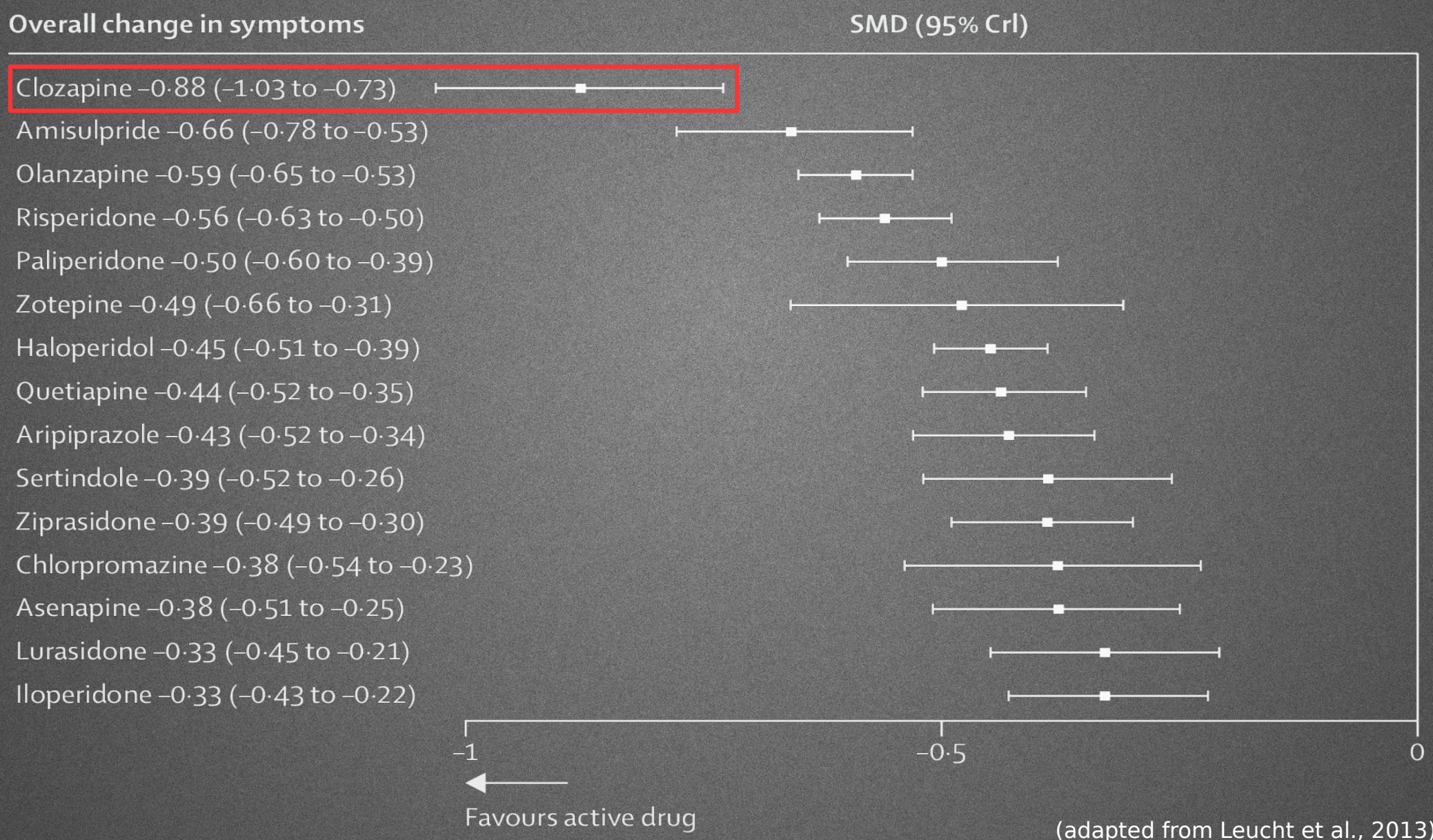




"normalized"
dopaminergic system

(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

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

Clinical Care

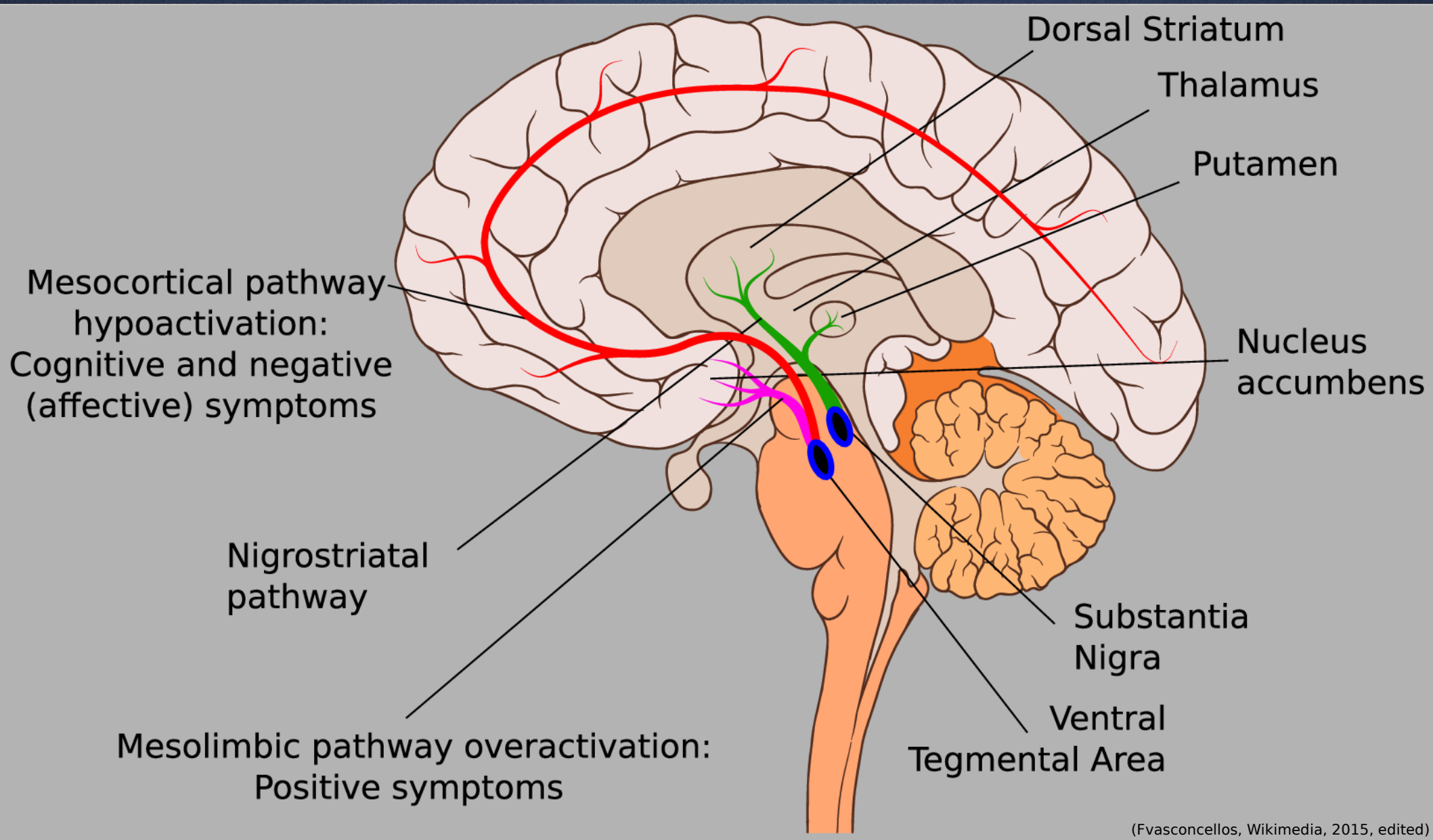
(Schizophrenia Canada, 2018)

Pathophysiology

???

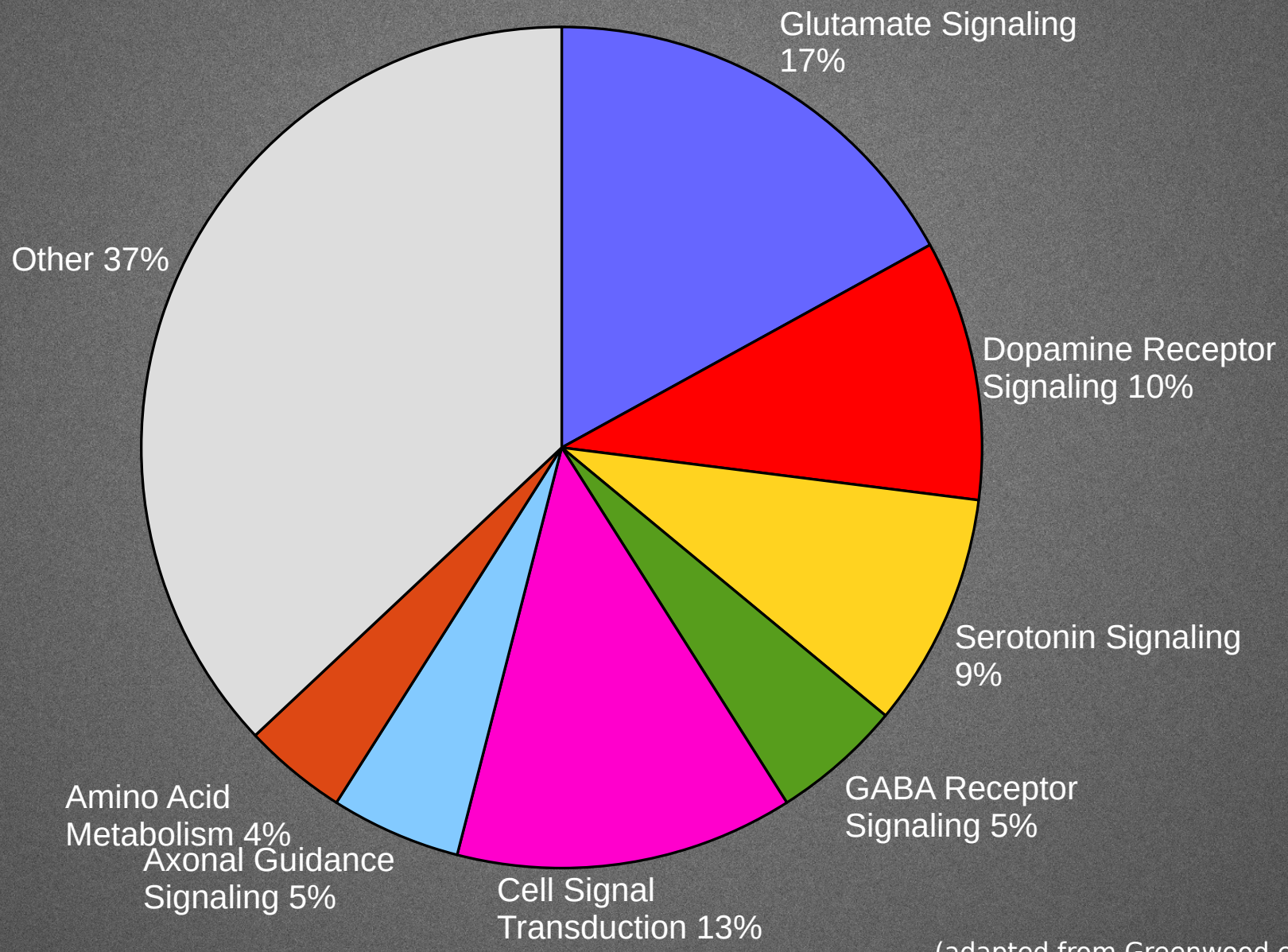
- Phentoypic expression
  - Continuum with affective disorders (Crow, 1986)
  - Failure of filter mechanisms (Hemsley and Zawada, 1976)
  - Internal monitoring deficiency (positive symptoms) & action initiation failure (negative symptoms) (Frith & Done, 1988)
  - Deficit vs. non-deficit SZ (Carpenter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



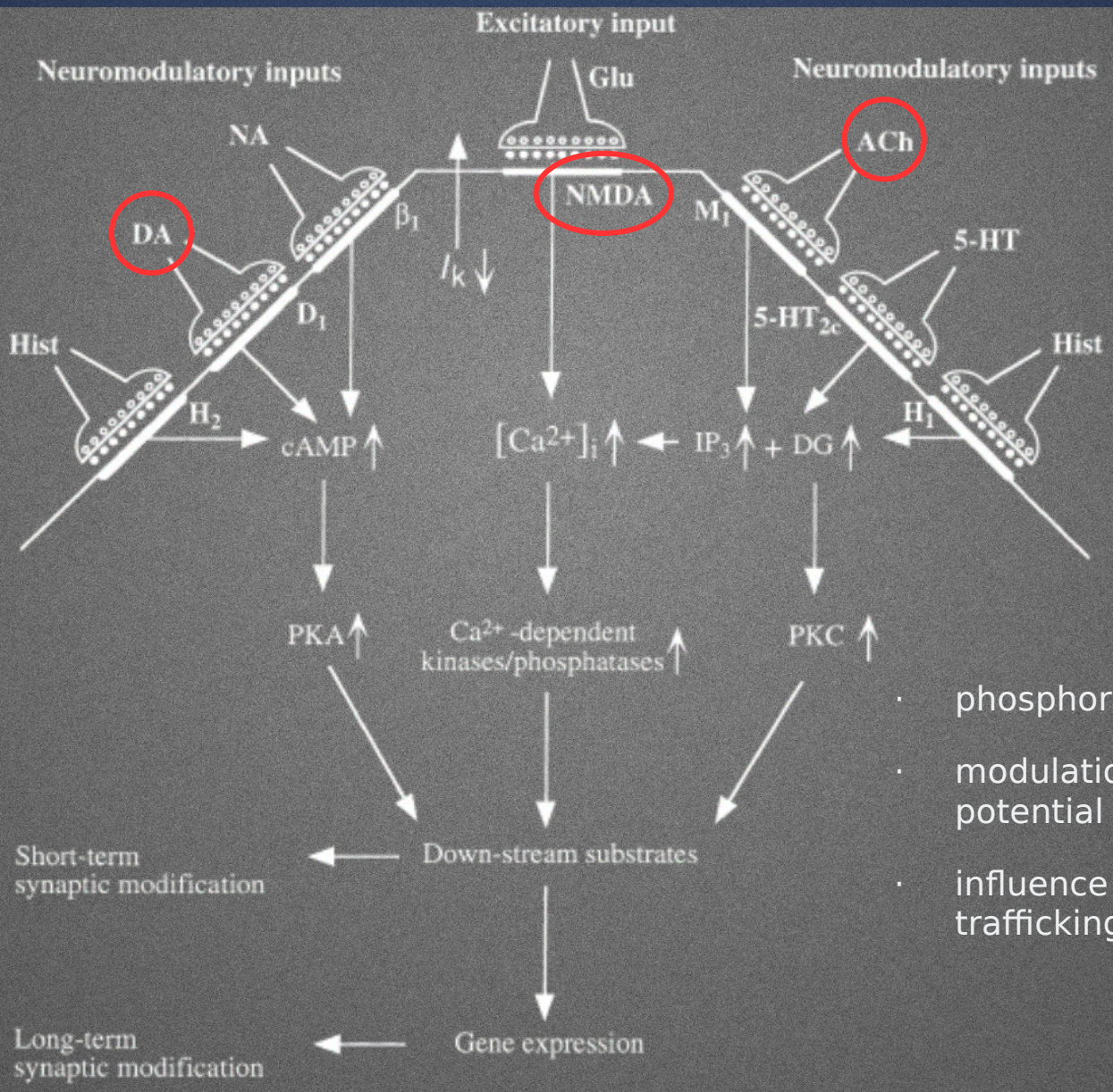
(Fvasconcellos, Wikimedia, 2015, edited)

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*

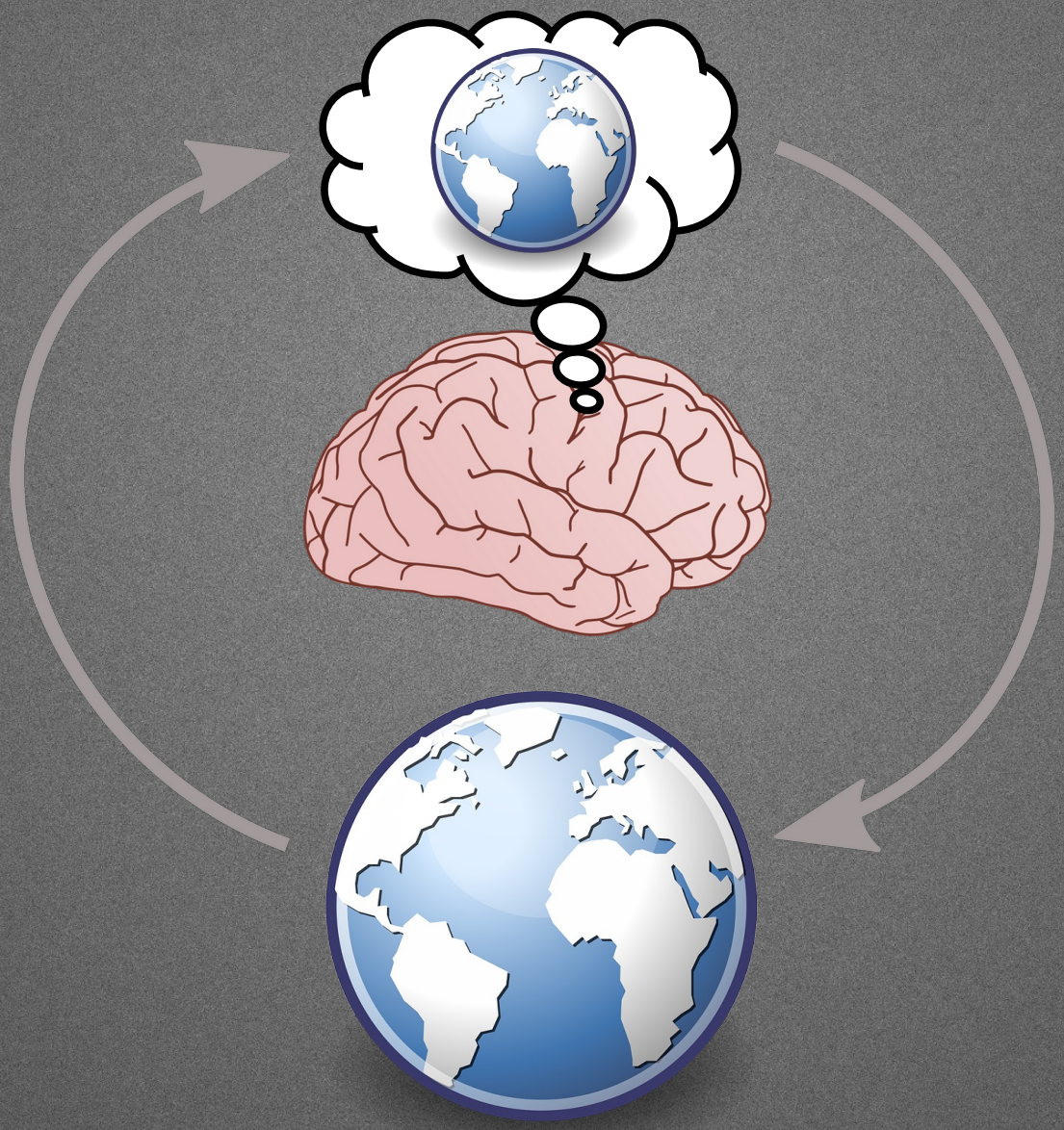
  → ...more of this later:

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

(Friston et al., 2016)

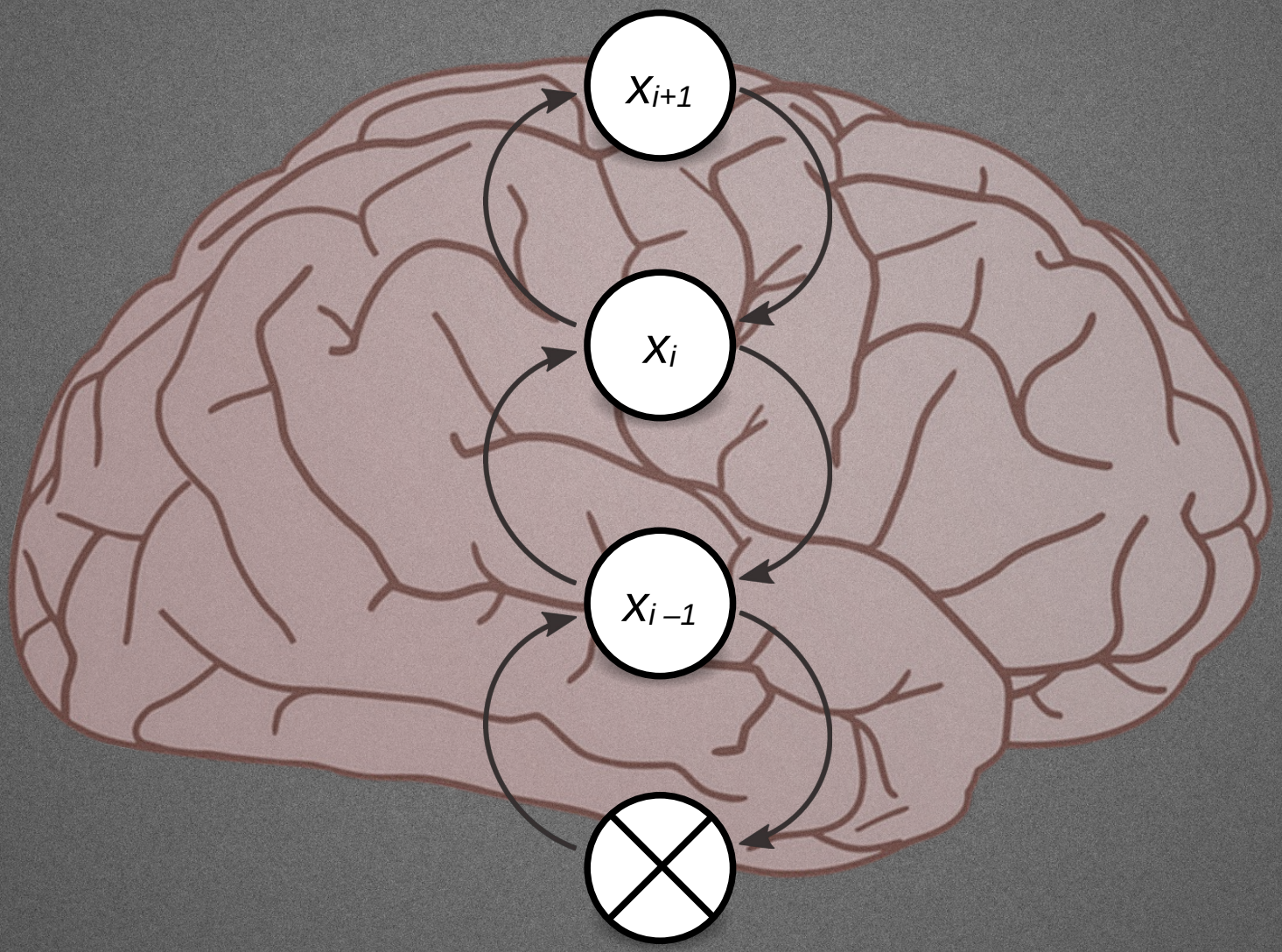
Bayesian Brain

- Sensory Evidence



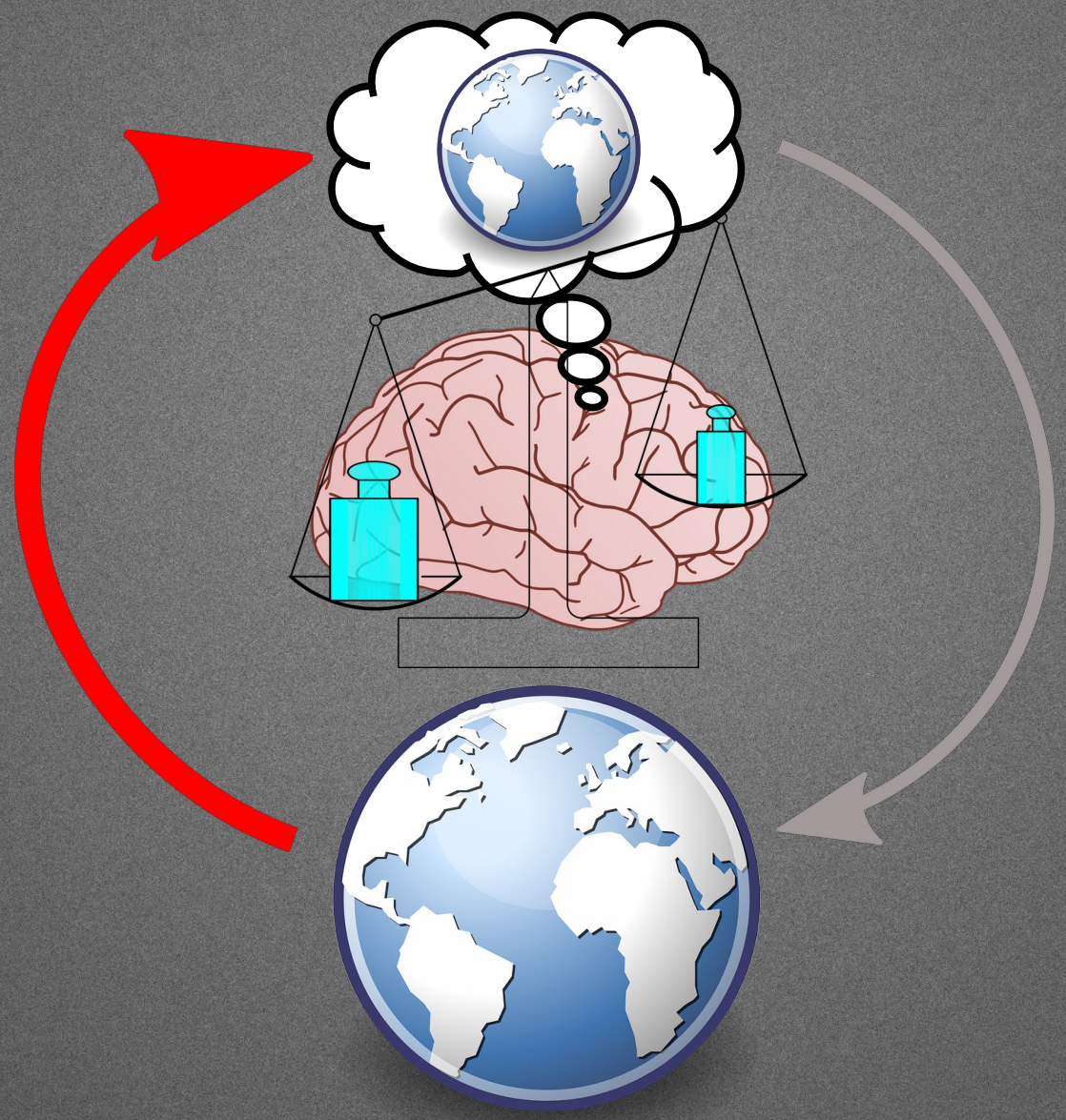
- Predictions

Predictive Coding



Bayesian Brain

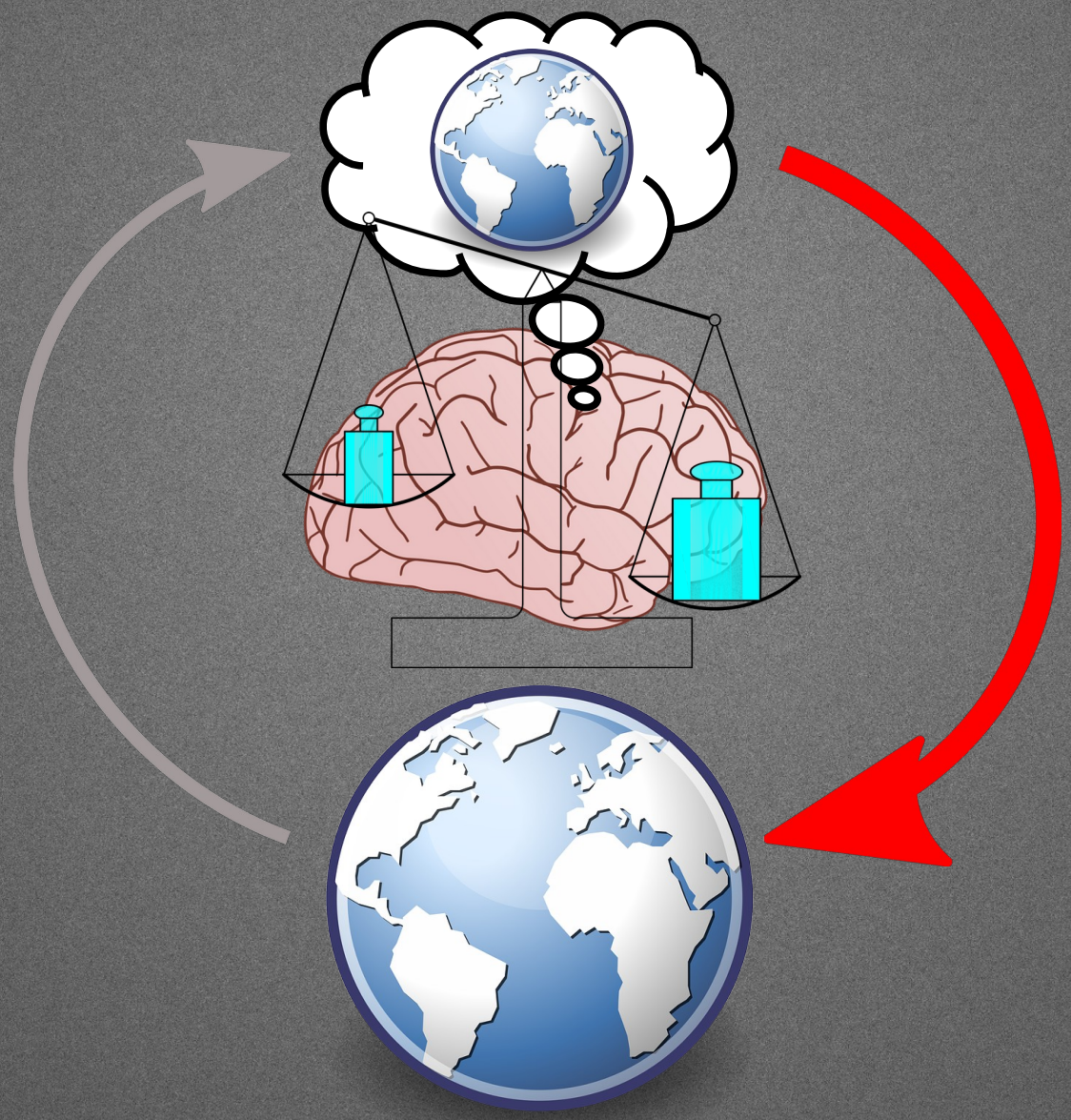
- Sensory Evidence



- Predictions

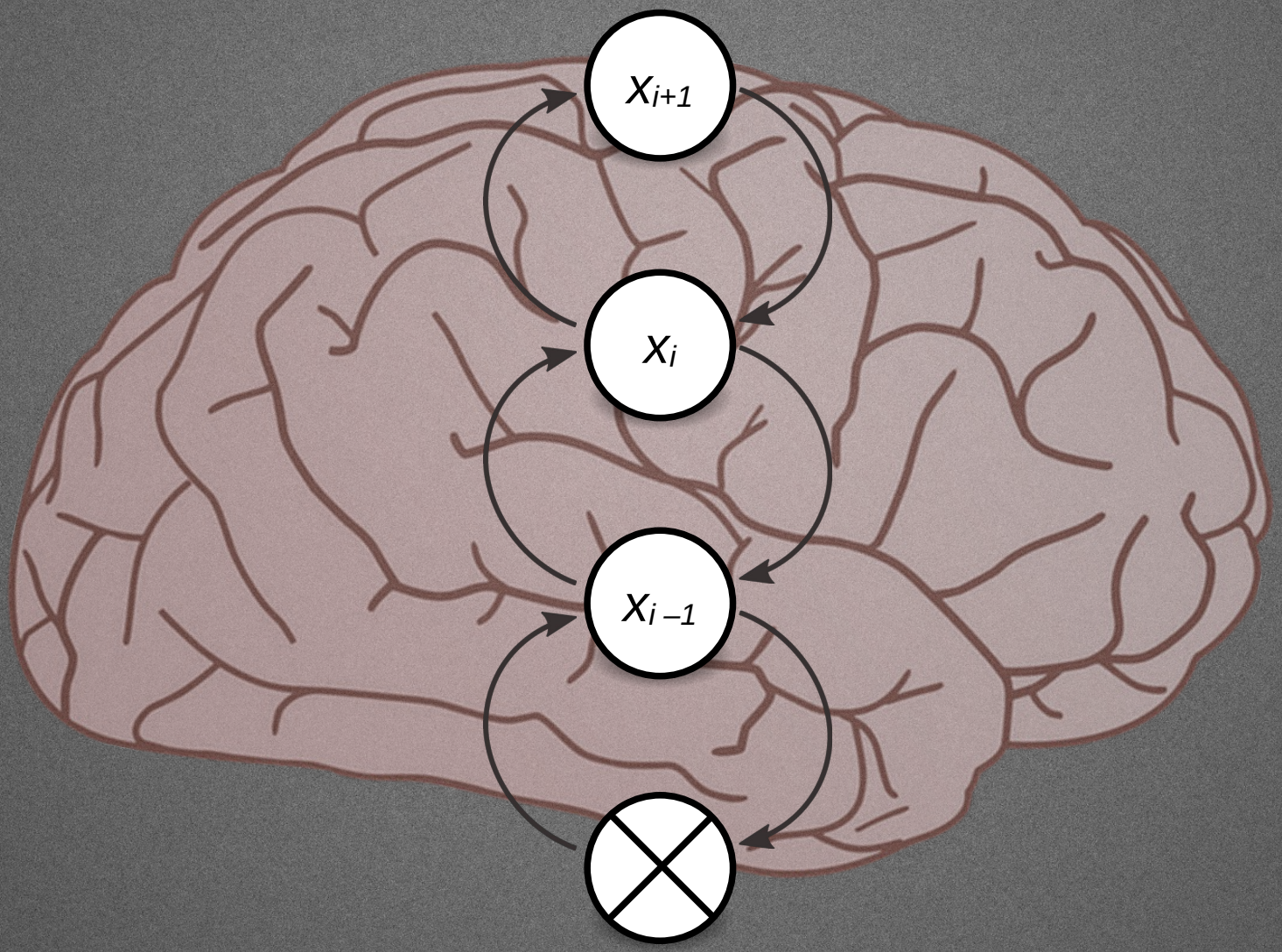
Bayesian Brain

- Sensory Evidence

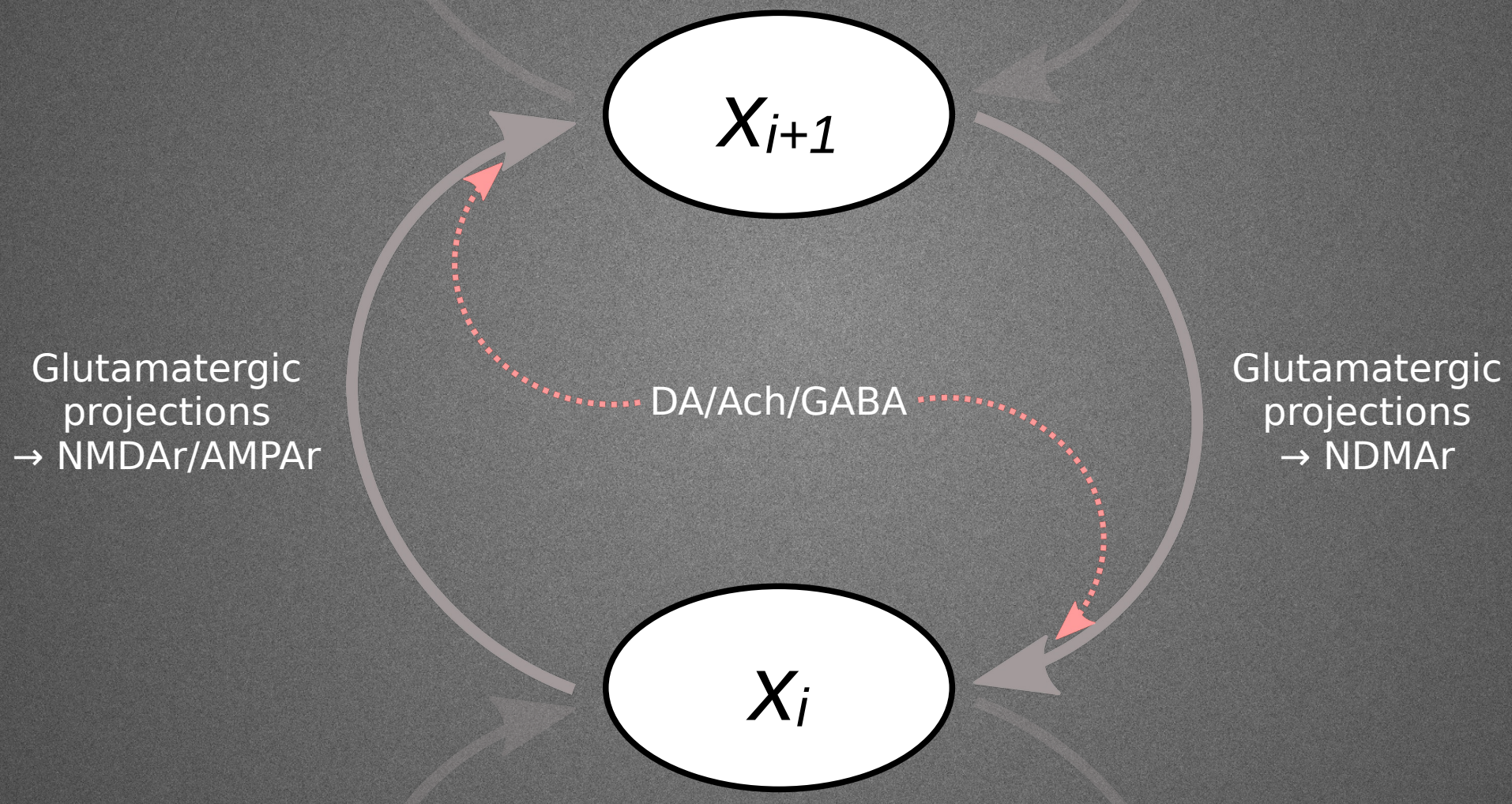


- Predictions

Predictive Coding



Dysconnectivity?

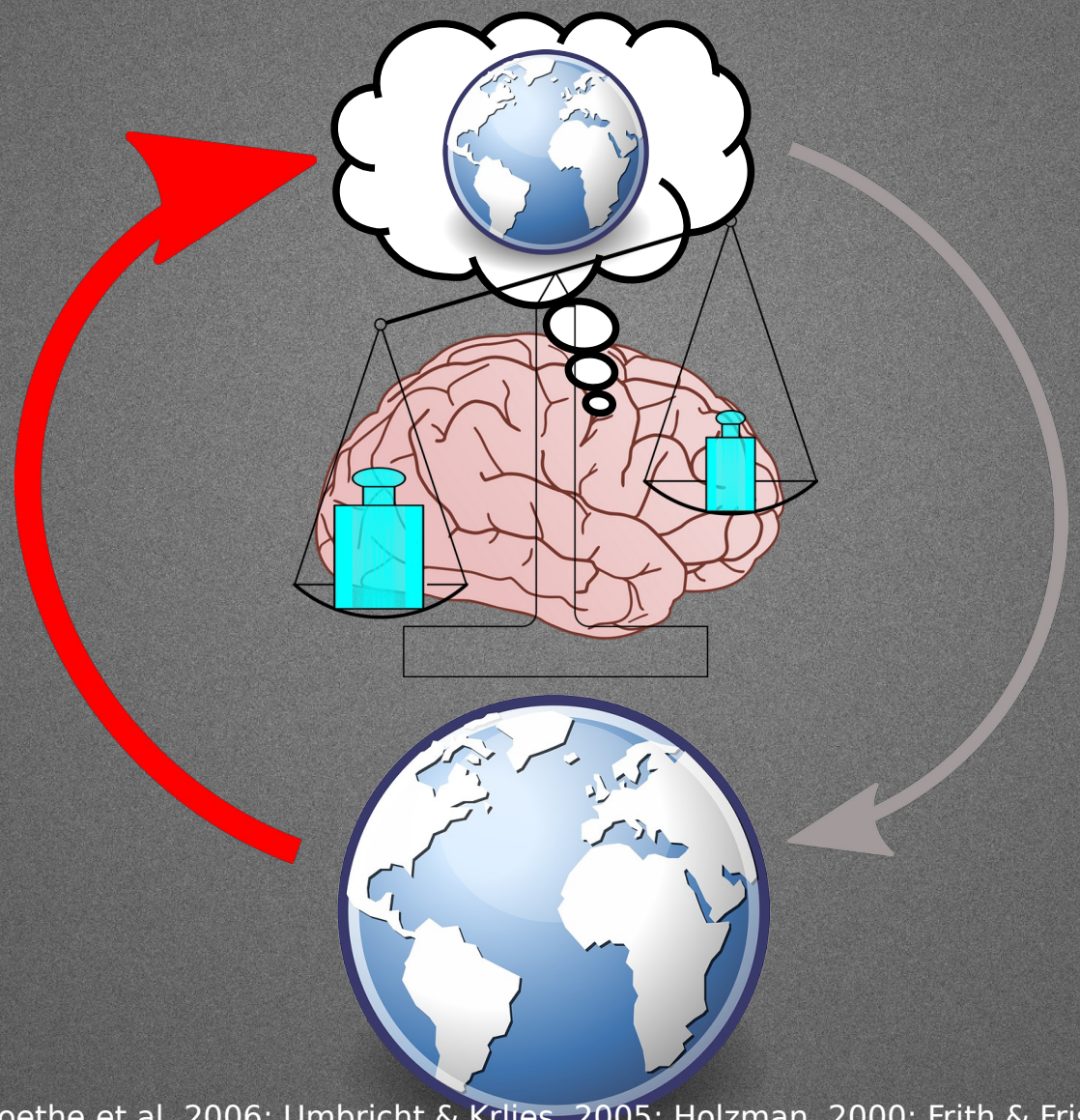


(Stephan et al., 2016)

Bayesian Brain - Dysconnectivity

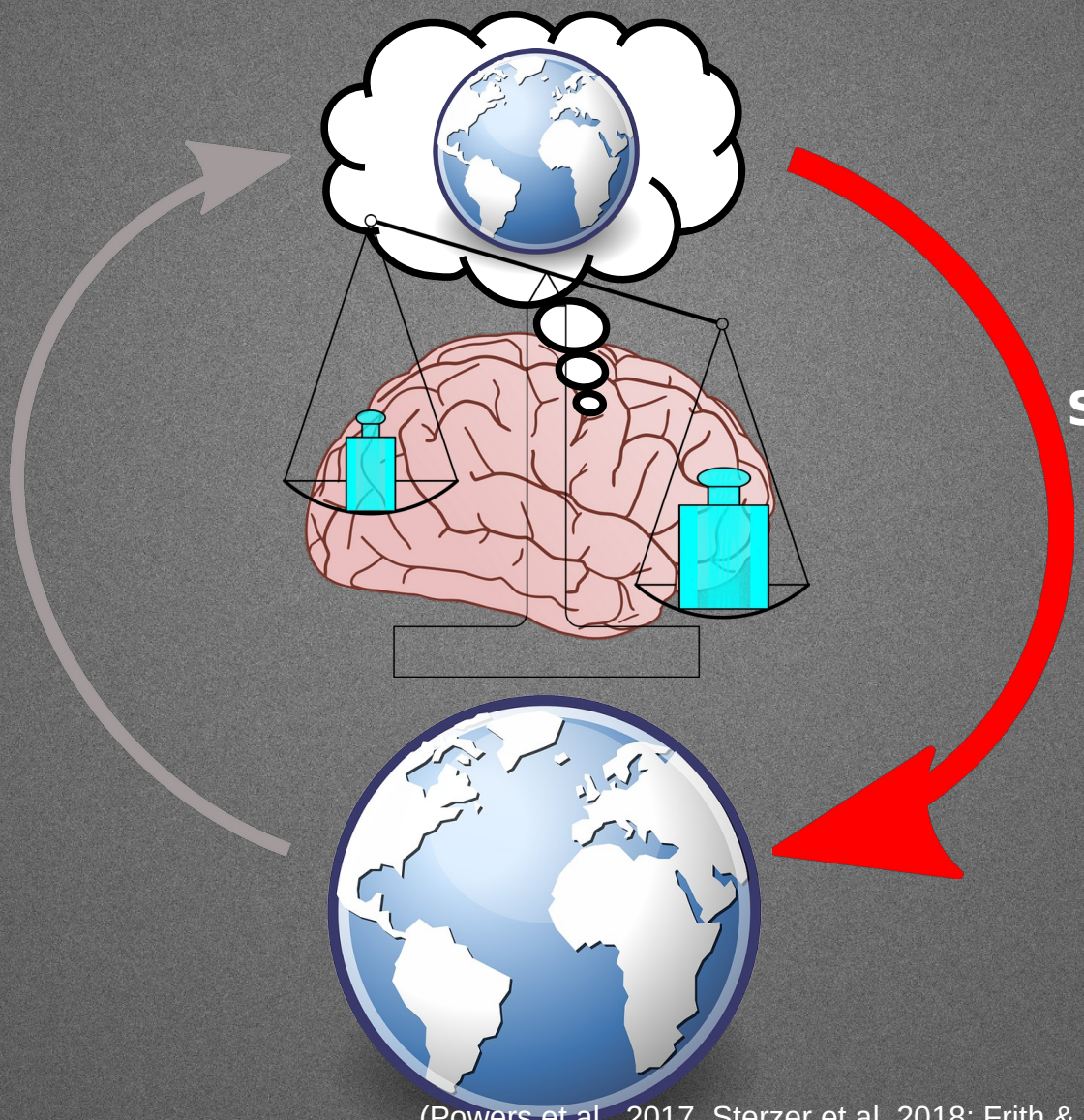
Trait phenomena

- ↓ susceptibility to illusions
- “Delusional mood”



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

Bayesian Brain - Dysconnectivity

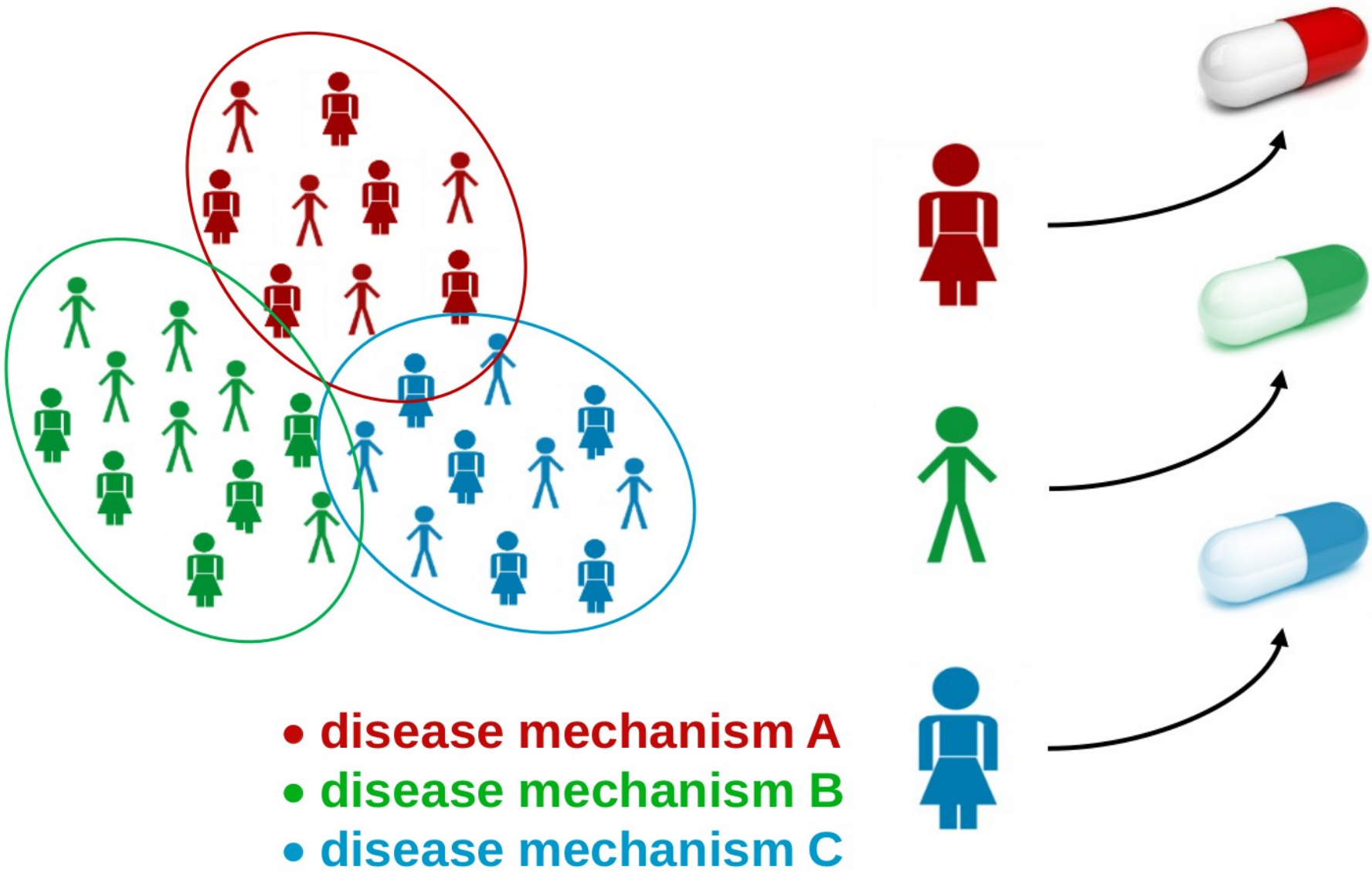


State phenomena

- Delusion
- Acoustic hallucinations

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

The goal of CP?

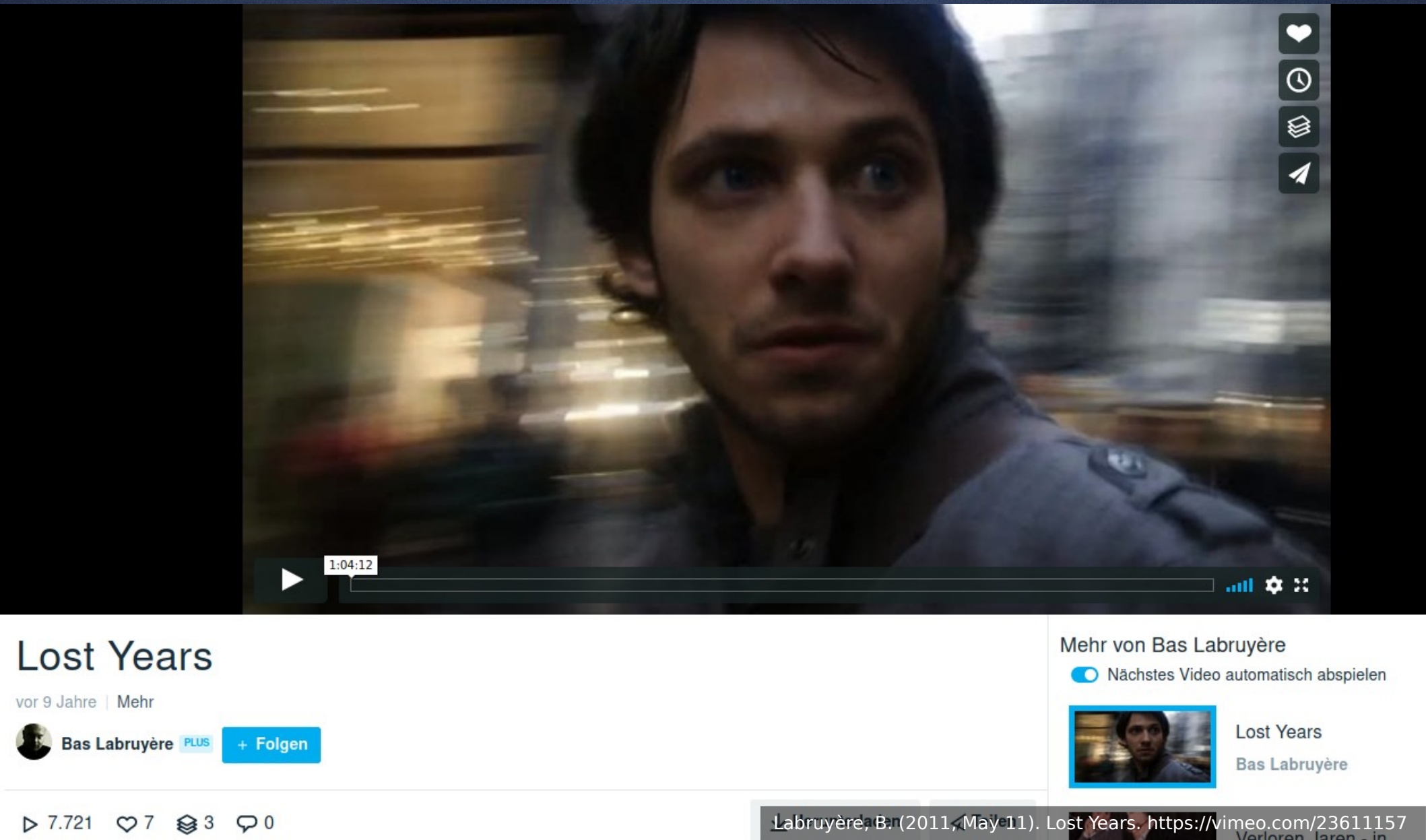


(Stephan et al., 2015)

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



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

Questions?

Translational Neuromodeling Unit

Universität Zürich[UZH]

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

CONTACT:
siemerkus@biomed.ee.ethz.ch
translationalneuromodeling.org

References

Adams, R. A., Stephan, K. E., Brown, H. R., Frith, C. D., & Friston, K. J. (2013). The computational anatomy of psychosis. Frontiers in Psychiatry, 4, 47. https://doi.org/10.3389/fpsyt.2013.00047

American Psychiatric Association. (2006). American Psychiatric Association Practice Guidelines for the treatment of psychiatric disorders: compendium 2006.

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5 (5 edition). Washington, D.C: American Psychiatric Publishing.

Benkert, O., Hippius, H., & Anghelescu, I.-G. (2014). Kompendium der Psychiatrischen Pharmakotherapie (10., vollst. überarb. und aktualisierte Aufl). Springer.

Bleuler, E. (1908). Die Prognose der Dementia praecox (Schizophreniegruppe). Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin, 65, 436–464.

Corlett, P. R., Frith, C. D. & Fletcher, P. C. From drugs to deprivation: a Bayesian framework for understanding models of psychosis. Psychopharmacology (Berl) 206, 515–530 (2009).

DGPPN, & Falkai, P. (Eds.). (2012). S3-Leitlinie Psychosoziale Therapien bei schweren psychischen Erkrankungen: S3-Praxisleitlinien in Psychiatrie und Psychotherapie. Springer-Verlag.

Drake, R. J., Dunn, G., Tarrier, N., Bentall, R. P., Haddock, G., & Lewis, S. W. (2007). Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. The Journal of Clinical Psychiatry, 68(1), 81–86.

Feldman, R. S., Jerrold S. Meyer, & Linda F. Quenzer. (1997). Principles of neuropsychopharmacology. Sunderland, Mass: Sinauer.

Frith, C. D., & Friston, K. J. (2013). False Perceptions & False Beliefs: Understanding Schizophrenia. In A. Battro, S. Dehaene, & W. Singer (Eds.), Neurosciences and the Human Person: New Perspectives on Human Activities. Retrieved from http://www.casinapioiv.va/content/dam/accademia/pdf/sv121/sv121-frithc.pdf

Friston, K., Brown, H. R., Siemerkus, J., & Stephan, K. E. (2016). The dysconnection hypothesis (2016). Schizophrenia Research, 176(2–3), 83–94. https://doi.org/10.1016/j.schres.2016.07.014

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., … Yung, A. (2013). The Psychosis High-Risk State: A Comprehensive State-of-the-Art Review. JAMA Psychiatry, 70(1), 107–120. https://doi.org/10.1001/jamapsychiatry.2013.269

Greenwood, T. A., Light, G. A., Swerdlow, N. R., Radant, A. D., & Braff, D. L. (2012). Association Analysis of 94 Candidate Genes and Schizophrenia-Related Endophenotypes. PLOS ONE, 7(1), e29630. https://doi.org/10.1371/journal.pone.0029630

Goldman, D., & Ducci, F. (2007). Deconstruction of Vulnerability to Complex Diseases: Enhanced Effect Sizes and Power of Intermediate Phenotypes [Research article]. https://doi.org/10.1100/tsw.2007.210

Holzman, P. S. (2000). Eye movements and the search for the essence of schizophrenia. Brain Research Reviews, 31(2), 350–356. https://doi.org/10.1016/S0165-0173(99)00051-X

Jaspers, K. (1973). Allgemeine Psychopathologie (9., unveränderte Auflage). Berlin, Heidelberg, New York: Springer.

Jones, C., Hacker, D., Meaden, A., Cormac, I., Irving, C. B., Xia, J., … Chen, J. (2018). Cognitive behavioural therapy plus standard care versus standard care plus other psychosocial treatments for people with schizophrenia. Cochrane Database of Systematic Reviews, (11). https://doi.org/10.1002/14651858.CD008712.pub3

Kaiser, S., Berger, G., Conus, P., Kawohl, W., Müller, T. J., Schimmelmann, B. G., … Seifritz, E. (2016). SGPP Behandlungsempfehlungen Schizophrenie - Version Februar 2016.

Koethe, D., Gerth, C. W., Neatby, M. A., Haensel, A., Thies, M., Schneider, U., … Leweke, F. M. (2006). Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. Schizophrenia Research, 88(1–3), 142–150.

Leucht, S., Busch, R., Kissling, W., & Kane, J. M. (2007). Early prediction of antipsychotic nonresponse among patients with schizophrenia. The Journal of Clinical Psychiatry, 68(3), 352–360.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., … Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet, 382(9896), 951–962. https://doi.org/10.1016/S0140-6736(13)60733-3

Keshavan, M. S., Nasrallah, H. A., & Tandon, R. (2011). Schizophrenia, “Just the Facts” 6. Moving ahead with the schizophrenia concept: From the elephant to the mouse. Schizophrenia Research, 127(1), 3–13. https://doi.org/10.1016/j.schres.2011.01.011

Keshavan, M. S., Tandon, R., Boutros, N. N., & Nasrallah, H. A. (2008). Schizophrenia, “just the facts”: What we know in 2008: Part 3: Neurobiology. Schizophrenia Research, 106(2), 89–107. https://doi.org/10.1016/j.schres.2008.07.020

Menezes, N. M., Arenovich, T., & Zipursky, R. B. (2006). A systematic review of longitudinal outcome studies of first-episode psychosis. Psychological Medicine, 36(10), 1349–1362. https://doi.org/10.1017/S0033291706007951

References

Millan, M. J., Andrieux, A., Bartzokis, G., Cadenhead, K., Dazzan, P., Fusar-Poli, P., … Weinberger, D. (2016). Altering the course of schizophrenia: progress and perspectives. Nature Reviews Drug Discovery, 15(7), 485–515. https://doi.org/10.1038/nrd.2016.28

National Collaborating Centre for Mental Health (UK). (2014). Psychosis and Schizophrenia in Adults: Treatment and Management. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK248060/

Perkins, D. O., Gu, H., Boteva, K., & Lieberman, J. A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. The American Journal of Psychiatry, 162(10), 1785–1804. https://doi.org/10.1176/appi.ajp.162.10.1785

Powers, A. R., Mathys, C., & Corlett, P. R. (2017). Pavlovian conditioning–induced hallucinations result from overweighting of perceptual priors. Science, 357(6351), 596–600. https://doi.org/10.1126/science.aan3458

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A Systematic Review of the Prevalence of Schizophrenia. PLOS Medicine, 2(5), e141. https://doi.org/10.1371/journal.pmed.0020141

Saklad, S. R. (2018). Graphic representation of pharmacology: Development of an alternative model. The Mental Health Clinician, 7(5), 201–206. https://doi.org/10.9740/mhc.2017.09.201

Schwartz, T. L., Sachdeva, S., & Stahl, S. M. (2012). Glutamate Neurocircuitry: Theoretical Underpinnings in Schizophrenia. Frontiers in Pharmacology, 3. https://doi.org/10.3389/fphar.2012.00195

Siafis, S., Tzachanis, D., Samara, M., & Papazisis, G. (2018). Antipsychotic Drugs: From Receptor-binding Profiles to Metabolic Side Effects. Current Neuropharmacology, 16(8), 1210–1223. https://doi.org/10.2174/1570159X15666170630163616

Stephan, K. E., Diaconescu, A. O., & Iglesias, S. (2016). Bayesian inference, dysconnectivity and neuromodulation in schizophrenia. Brain, 139(7), 1874–1876. https://doi.org/10.1093/brain/aww120

Stephan, K. E., Iglesias, S., Heinzle, J., & Diaconescu, A. O. (2015). Translational Perspectives for Computational Neuroimaging. Neuron, 87(4), 716–732. https://doi.org/10.1016/j.neuron.2015.07.008

Stephen M. Stahl. (2013). Stahl’s essential psychopharmacology: neuroscientific basis and practical application (4th ed.). Cambridge: Cambridge University Press.

Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., … Corlett, P. R. (2018). The predictive coding account of psychosis. Biological Psychiatry. https://doi.org/10.1016/j.biopsych.2018.05.015

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008a). Schizophrenia, “Just the Facts”: What we know in 2008: Part 1: Overview. Schizophrenia Research, 100(1), 4–19. https://doi.org/10.1016/j.schres.2008.01.022

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008b). Schizophrenia, “Just the Facts” What we know in 2008. 2. Epidemiology and etiology. Schizophrenia Research, 102(1), 1–18. https://doi.org/10.1016/j.schres.2008.04.011

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia, “just the facts” 4. Clinical features and conceptualization. Schizophrenia Research, 110(1), 1–23. https://doi.org/10.1016/j.schres.2009.03.005

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2010). Schizophrenia, “Just the Facts” 5. Treatment and prevention Past, present, and future. Schizophrenia Research, 122(1), 1–23. https://doi.org/10.1016/j.schres.2010.05.025

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia: a meta-analysis. Schizophrenia Research, 76(1), 1–23. https://doi.org/10.1016/j.schres.2004.12.002

van Os, J. (2009). A salience dysregulation syndrome. The British Journal of Psychiatry, 194(2), 101–103. https://doi.org/10.1192/bjp.bp.108.054254

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008). Schizophrenia, “Just the Facts” What we know in 2008. 2. Epidemiology and etiology. Schizophrenia Research, 102(1), 1–18. https://doi.org/10.1016/j.schres.2008.04.011

References - Media

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

Canada, S. (2018T06:29). Today is #NSPAD18! #Recovery is possible, and expected, with the right treatments. Effective treatment can include counselling, medication, meaningful activity, & support from loved ones --> https://www.earlypsychosisintervention.ca/psychosis #SupportSZ #CMHA100 #Schizophrenia #EndStigmapic.twitter.com/cTseJJT9Yd [Tweet]. Retrieved August 23, 2019, from @schizophreniaca website: https://twitter.com/schizophreniaca/status/999643428605526016

Covid-19 may cause brain complications in some, say doctors. (2020, June 26). The Guardian. http://www.theguardian.com/science/2020/jun/25/doctors-find-brain-issues-linked-to-covid-19-patients-study

James, D. (2019). English: Two doses of intravenous ketamine, 50mg/ml and 10mg/ml. Retrieved from https://commons.wikimedia.org/wiki/File:Two_doses_of_iv_ketamine.jpg, edited

JanBaby. (n.d.). Free Image on Pixabay - Signpost, Road Signs, Sign, Post. Retrieved August 23, 2019, from https://pixabay.com/illustrations/signpost-road-signs-sign-post-2030780/

kaboldy. (2008). English: Kinematic sketches of mechanical scales. Retrieved from https://commons.wikimedia.org/wiki/File:Mechanical_scales2.svg; edited

mcmurryjulie | Pixabay. (n.d.). Retrieved August 30, 2019, from https://pixabay.com/users/mcmurryjulie-2375405/

Netherlands, S. van der W. from. (2010). In order to reach the highest mountains, you shouldn't be afraid of the deepest valleys. Retrieved from https://commons.wikimedia.org/wiki/File:Depressed_(4649749639).jpg

Munch, E. (1893). English: The Scream [Oil, tempera & pastel on cardboard]. National Gallery of Norway. https://commons.wikimedia.org/wiki/File:Edvard_Munch,_1893,_The_Scream,_oil,_tempera_and_pastel_on_cardboard,_91_x_73_cm,_National_Gallery_of_Norway.jpg

Open-Clipart-Vectors. (n.d.). Free Image on Pixabay - Biology, Brain, Cortex, Holiday. Retrieved September 1, 2019, from https://pixabay.com/vectors/biology-brain-cortex-holiday-1295897/

OpenIcons. (n.d.). Free Image on Pixabay - World, Globe, Global, Earth. Retrieved September 1, 2019, from https://pixabay.com/vectors/world-globe-global-earth-97864/

Pablo Picasso, 1901-02, Femme aux Bras Croisés, Woman with Folded Arms (Madchenbildnis), oil on canvas, 81 × 58 cm (32 × 23 in).jpg. (2020). In Wikipedia. https://en.wikipedia.org/w/index.php?title=File:Pablo_Picasso,_1901-02,_Femme_aux_Bras_Crois%C3%A9s,_Woman_with_Folded_Arms_(Madchenbildnis),_oil_on_canvas,_81_%C3%97_58_cm_(32_%C3%97_23_in).jpg&oldid=974424175

Unknown. (1962). English: Advert from ca. 1962 for Thorazine (trade-name of chlorpromazine in the U.S.). An antipsychotic (neuroleptic, major tranquilizer, antischizophrenic, actaractic). In Europe it is known as Largactil. Retrieved from https://commons.wikimedia.org/wiki/File:Thorazine_advert.jpg

User:Fvasconcellos, U. P. J. L. (2015). English: The main dopaminergic pathways of the human brain: the mesocortical pathway, connecting the ventral tegmental area (VTA) with the frontal cortex; the mesolimbic pathway, connecting the VTA with the nucleus accumbens; the nigrostriatal pathway, connecting the substantia nigra with the dorsal striatum; and the tuberoinfundibular pathway, connecting the hypothalamus with the pituitary. Retrieved from https://commons.wikimedia.org/wiki/File:Dopaminergic_pathways.svg; edited

Questions?

Translational Neuromodeling Unit

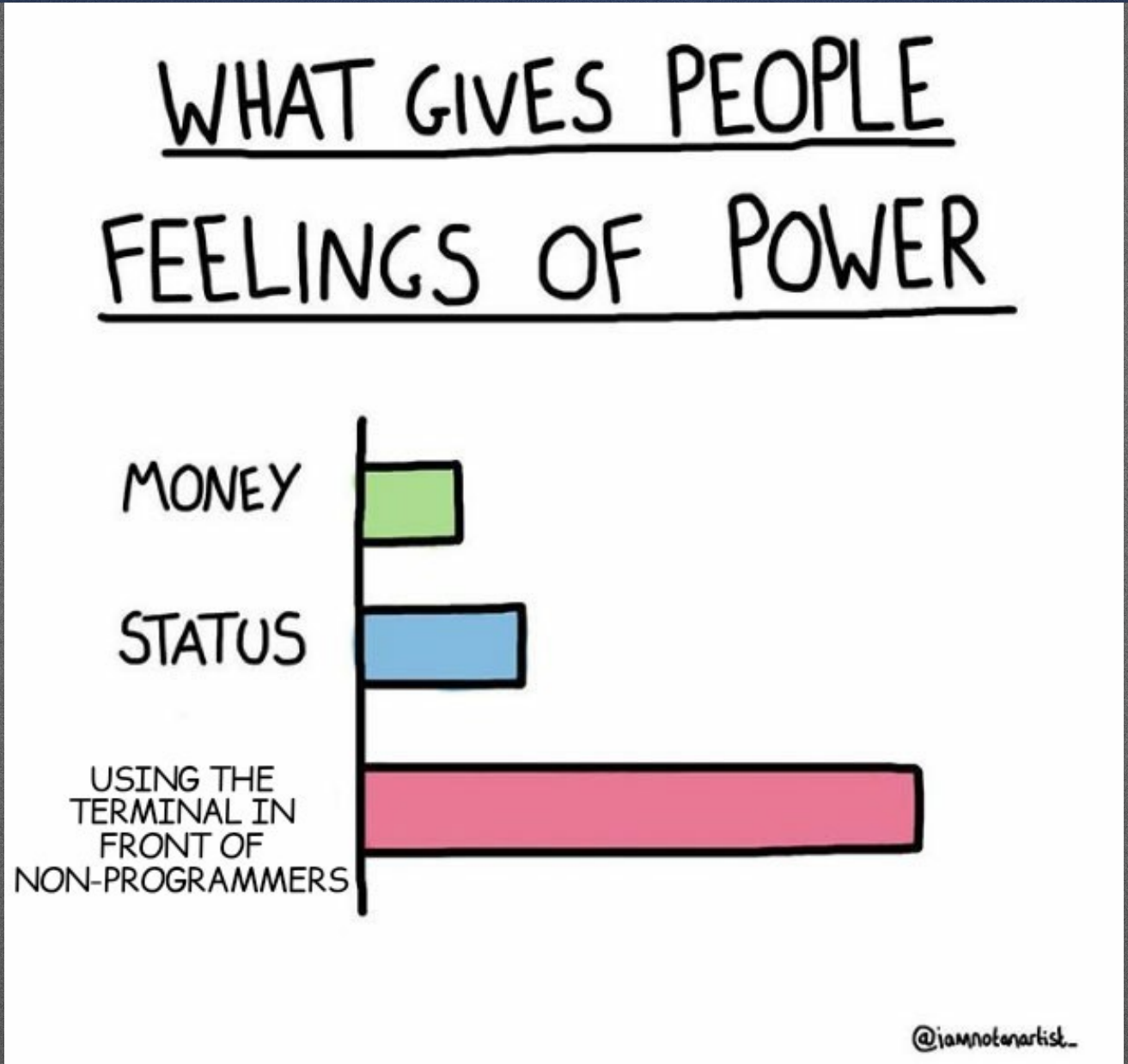
Universität Zürich[UZH]

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

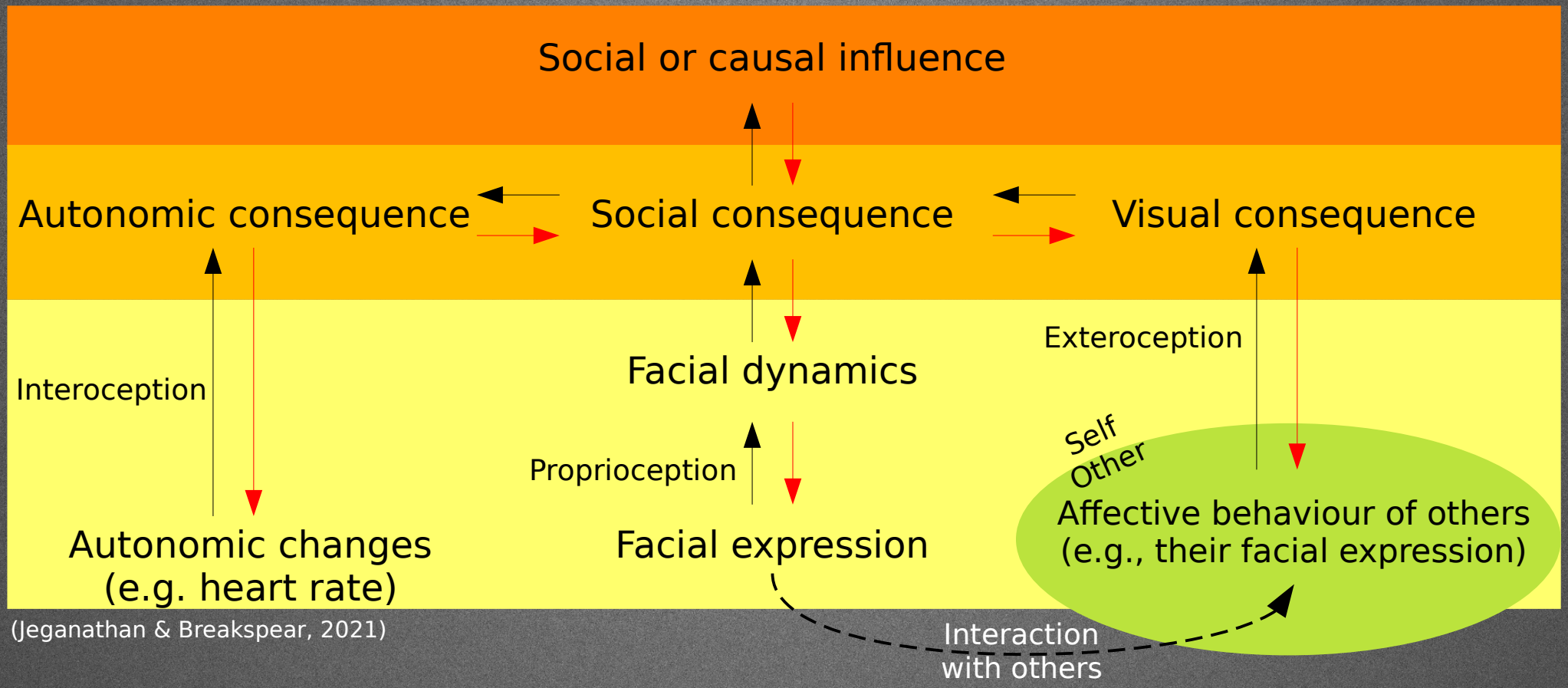
CONTACT:
siemerkus@biomed.ee.ethz.ch
translationalneuromodeling.org

Additional Slides

A message to the clinicians



Active Social Inference/Negative Symptoms



(Jeganathan & Breakspear, 2021)

Diagnostic Criteria

ICD-11	DSM 5
≥ 2 symptom (categories) present for “most of the time” AND ≥ 1 core symptom	≥ 2 symptom (categories) present AND ≥ 1 core symptom
≥ 1 month	≥ 1 month, ≥ 6 months symptoms/functional impairment
• (core) persistent delusion of any kind • (core) persistent hallucinations • (core) thought disorder • (core) distortions of self-experience • negative symptoms • disorganized behaviour • psychomotor disorders	• (core) delusions • (core) hallucinations • negative symptoms (especially avolition, diminished emotional expression) • (core) disorganized speech • disorganized or catatonic behaviour
• allows to add information about symptomatic manifestations (positive, negative, depressive, manic, psychomotor, cognitive symptoms)	• Clinician-Rated Dimensions of Psychosis Symptom Severity (C-RDPSS)
• no subtypes • different delusions or particular kinds of verbal hallucinations are equally weighted • Catatonia as separate diagnosis	• no subtypes • special case bizarre delusions dropped • Catatonia as separate diagnosis

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

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

APA, 2013

Other SZ-spectrum disorders

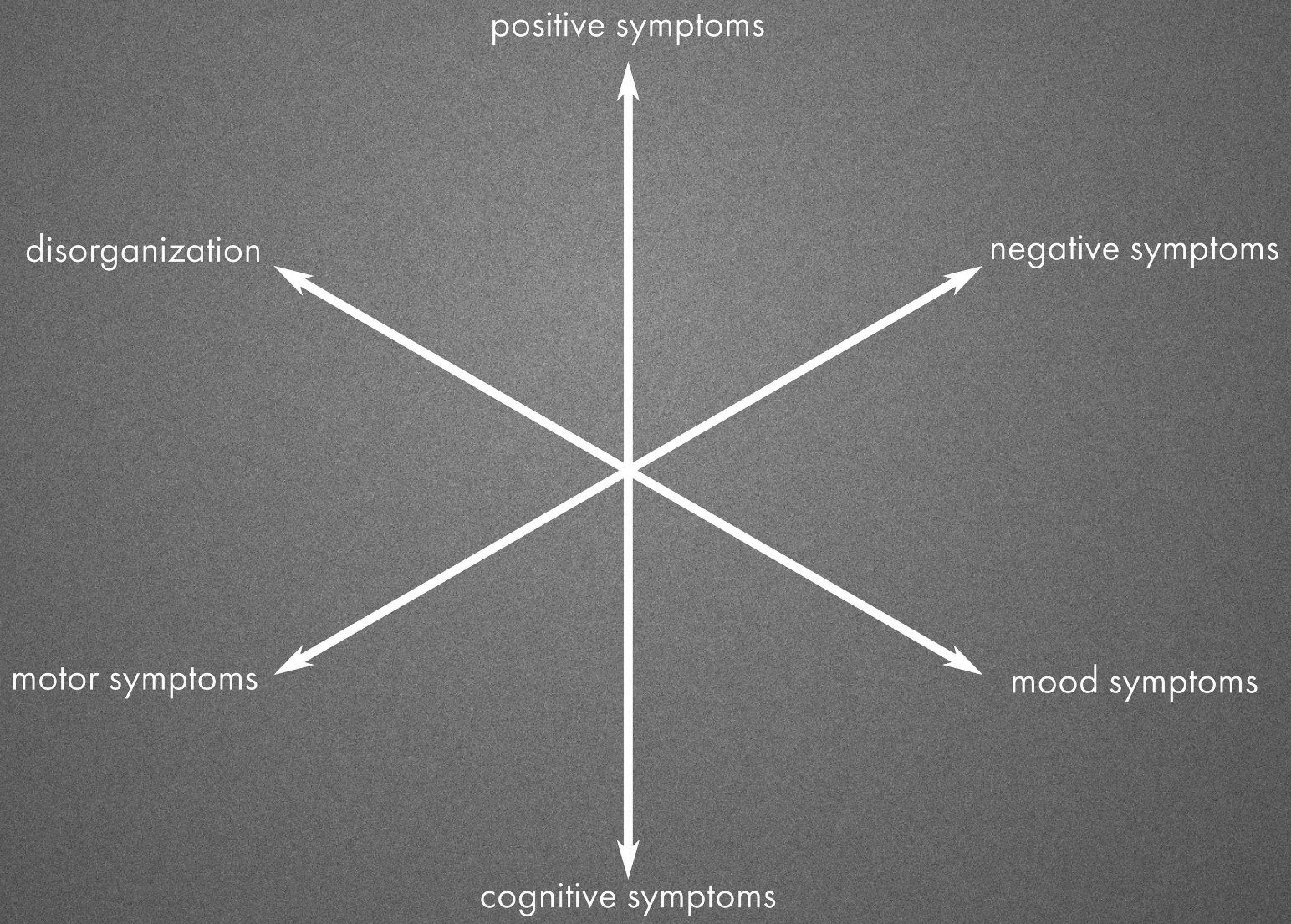
- Delusional Disorder
  - Delusion ≥ 1 month
- Brief Psychotic Disorder
  - SZ main criteria ≤ 1 month
- Schizophreniform Disorder
  - main criteria fulfilled, but ≤ 6 months any symptoms
- Schizoaffective Disorder
  - Major Depression/Manic Episode while main criteria for SZ fulfilled
  - Affective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

(APA, 2013)

Basic Symptoms

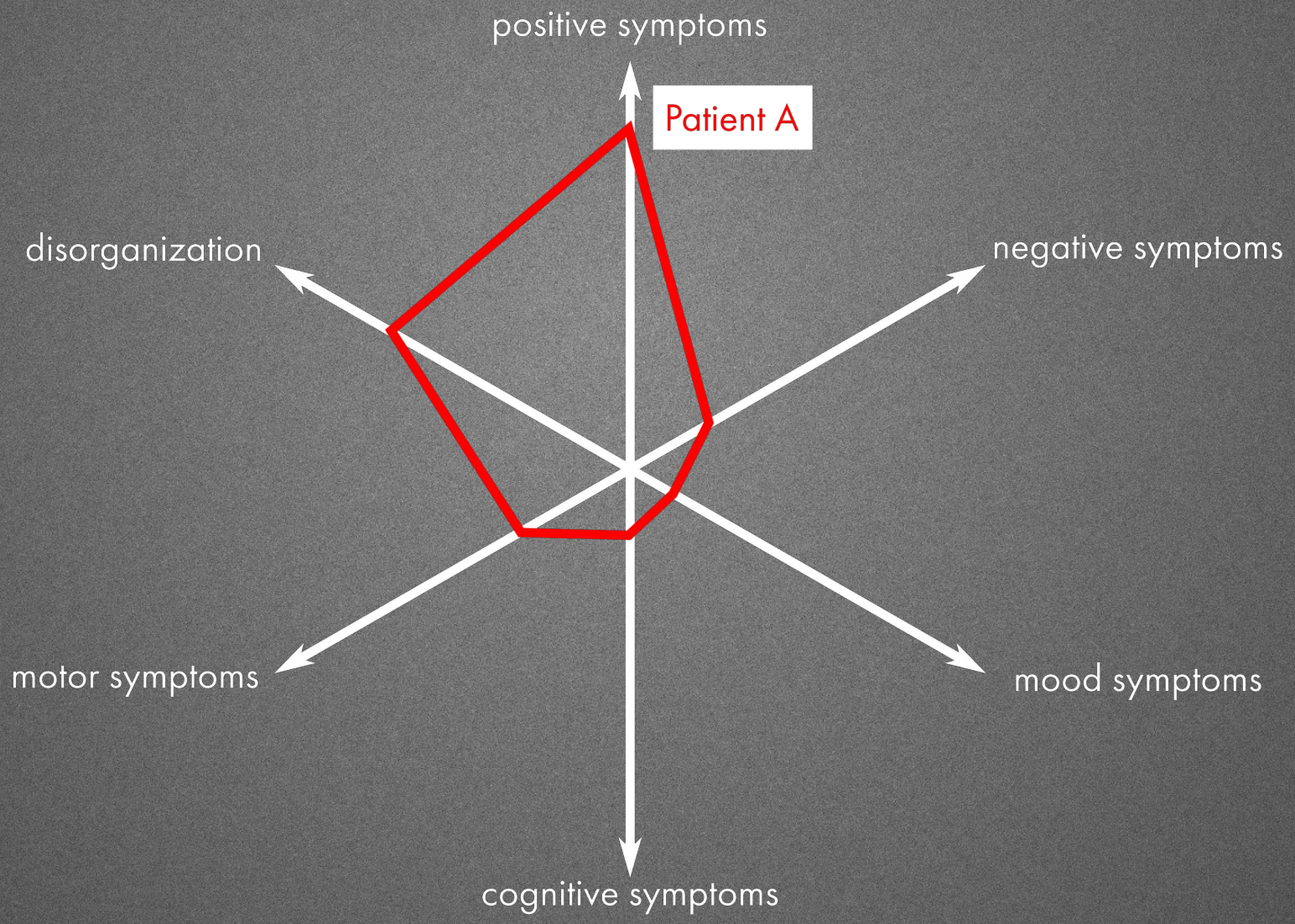
Symptom	Description
Thought interference	Interference of unimportant, irrelevant thoughts that hinders thinking and concentration.
Thought perseveration	Repetition of thoughts that have little or no salience.
Thought pressure	Many thoughts with no common theme pop up uncontrollably.
Thought blockages	Sudden loss of train of thought that may be accompanied by the intrusion of a new thought.
Disturbance of receptive language	Lack of immediate comprehension of speech or text in one's native language.
Disturbance of expressive language	Difficulty producing speech or text that is appropriate to one's message in one's native language.
Disturbances of abstract thinking	Difficulty comprehending idioms and metaphors.
Inability to divide attention	Difficulty doing something with one sense (such as vision) while simultaneously using another sense for something else (such as hearing).
Captivation of attention by details of the visual field	Attention is drawn to unimportant details as if one were "spellbound".
Decreased ability to discriminate between perception and ideas, true memories and fantasies	Difficulty discriminating between what one has observed and what one has imagined.
Unstable ideas of reference with insight	Sub-psychotic referential ideation that is thereafter immediately corrected by the person.
Derealization	Sense of disconnect or unreality in one's environment.
Visual or acoustic perceptual disturbances with insight	Disturbances of the perception of brightness or loudness, color or sound quality, or distortions in one's perceptions that are recognized by the person as false.

Phenotypic Heterogeneity



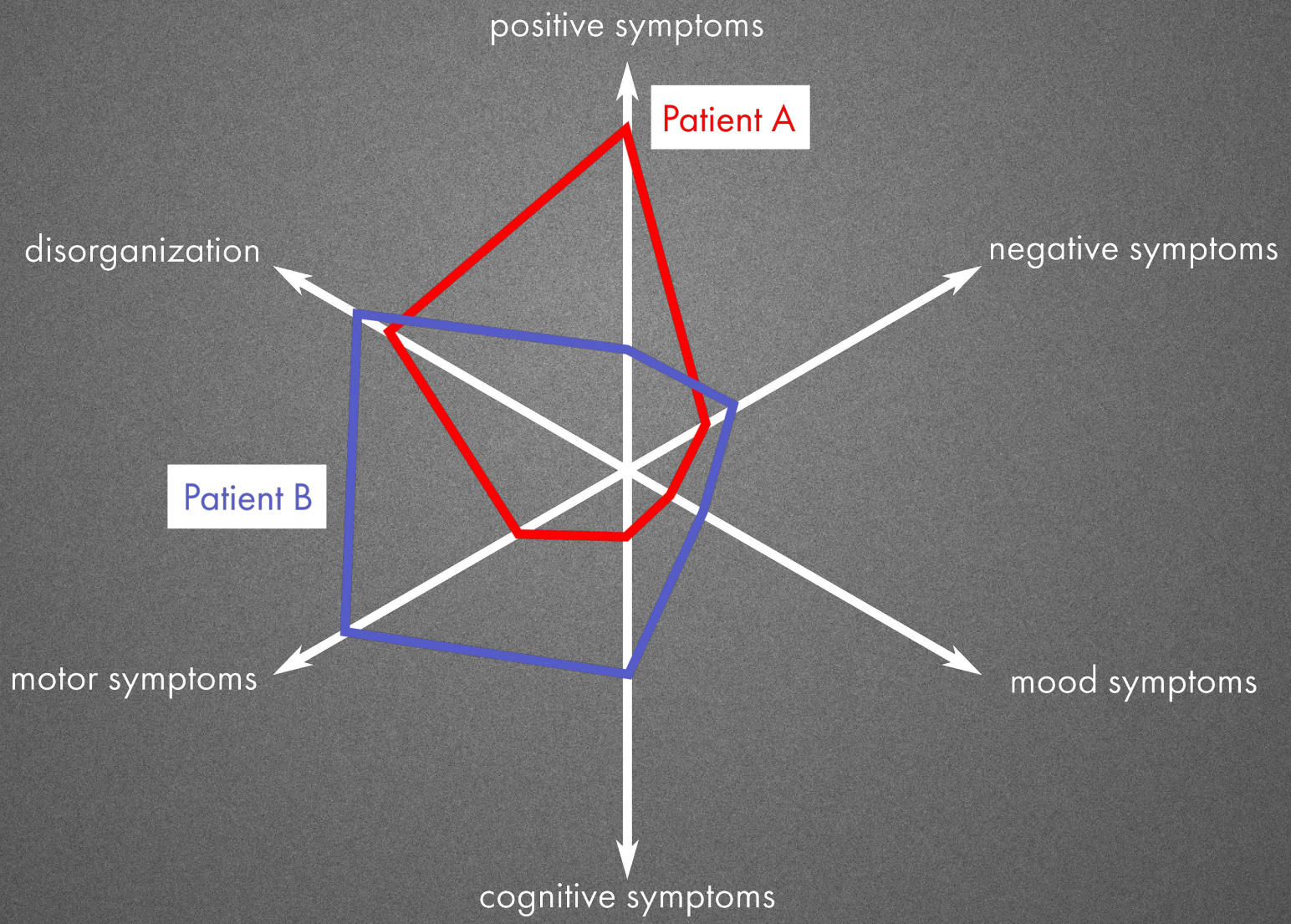
(adapted from van Os, 2009)

Phenotypic Heterogeneity



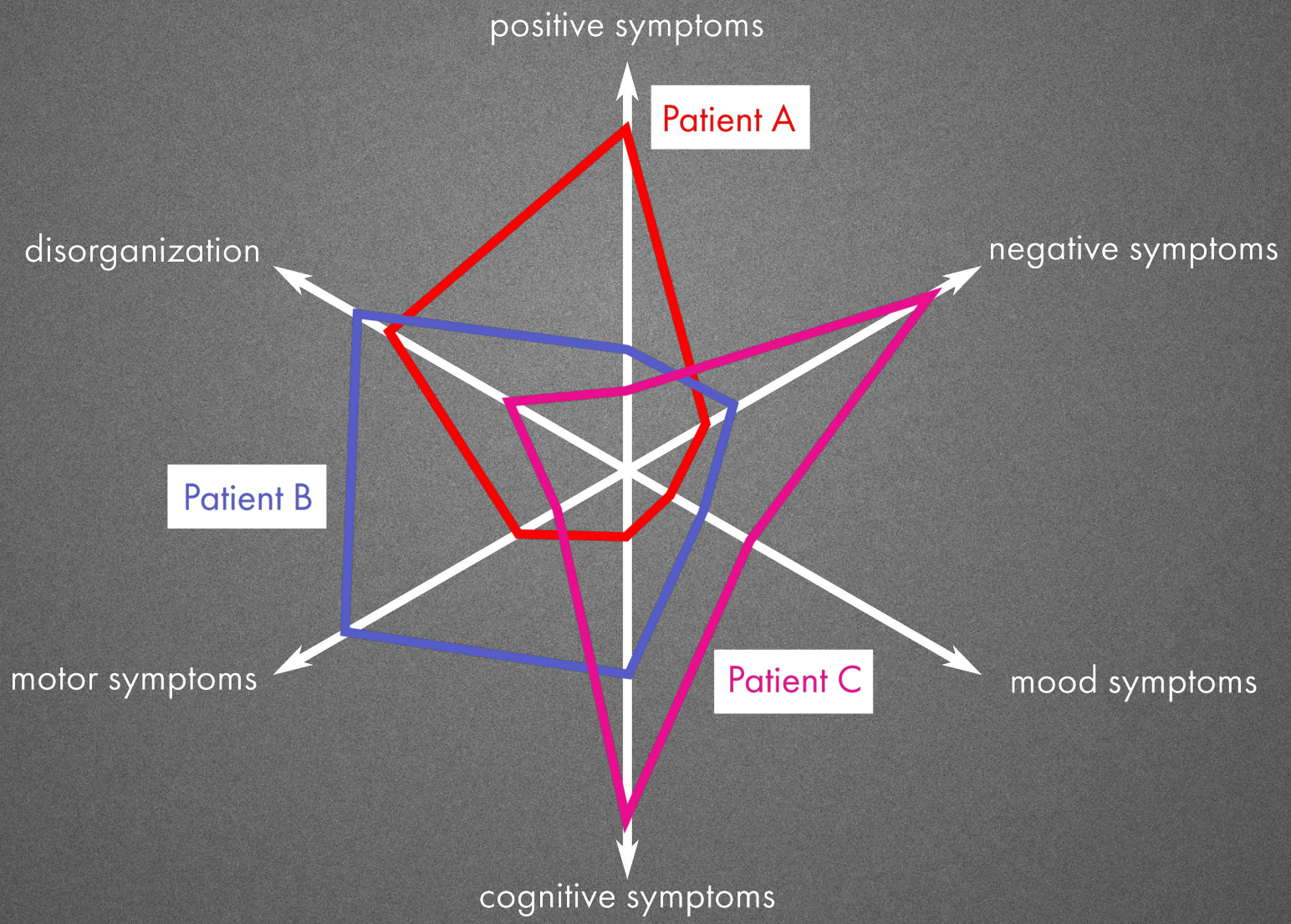
(adapted from van Os, 2009)

Phenotypic Heterogeneity



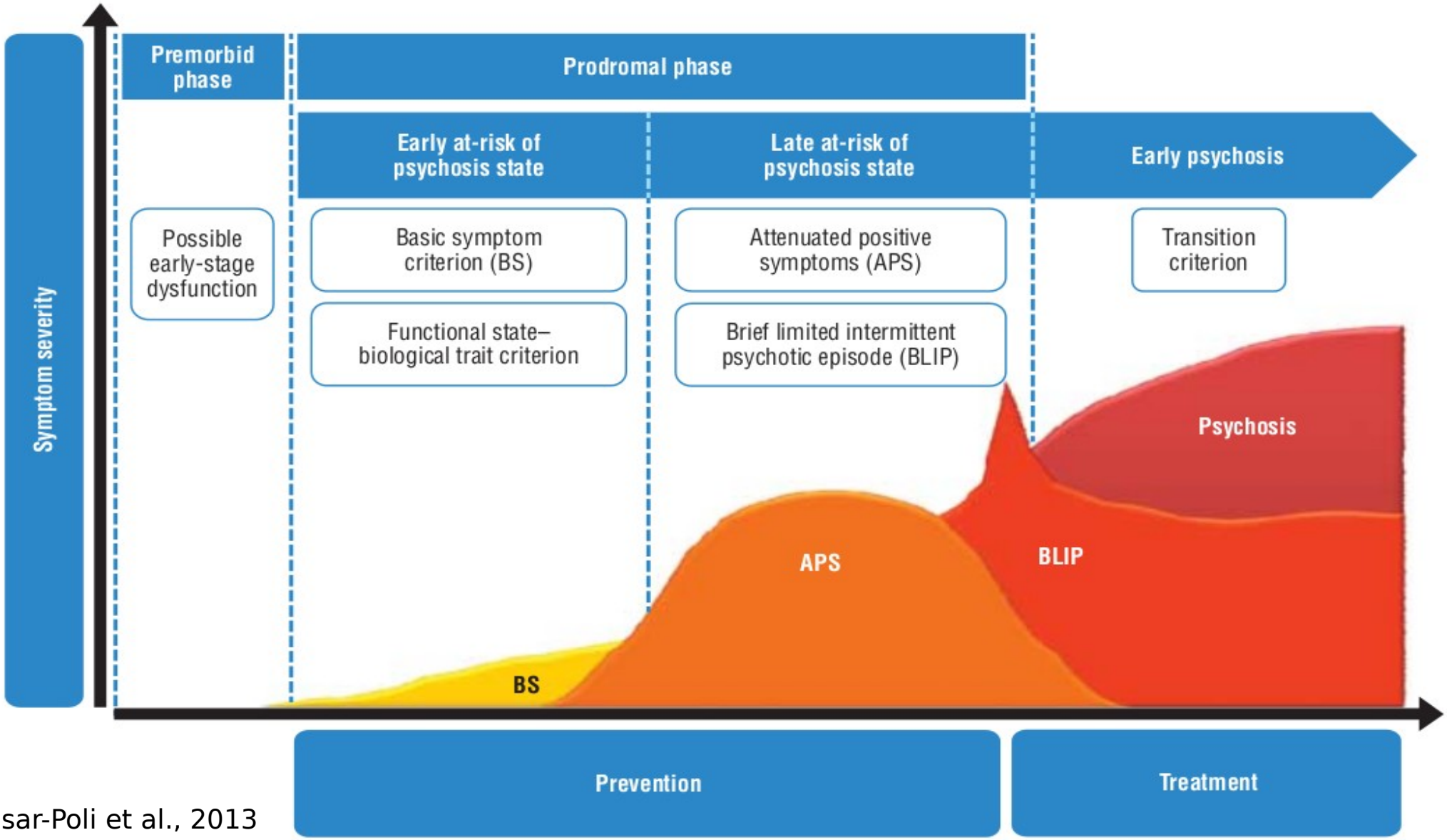
(adapted from van Os, 2009)

Phenotypic Heterogeneity



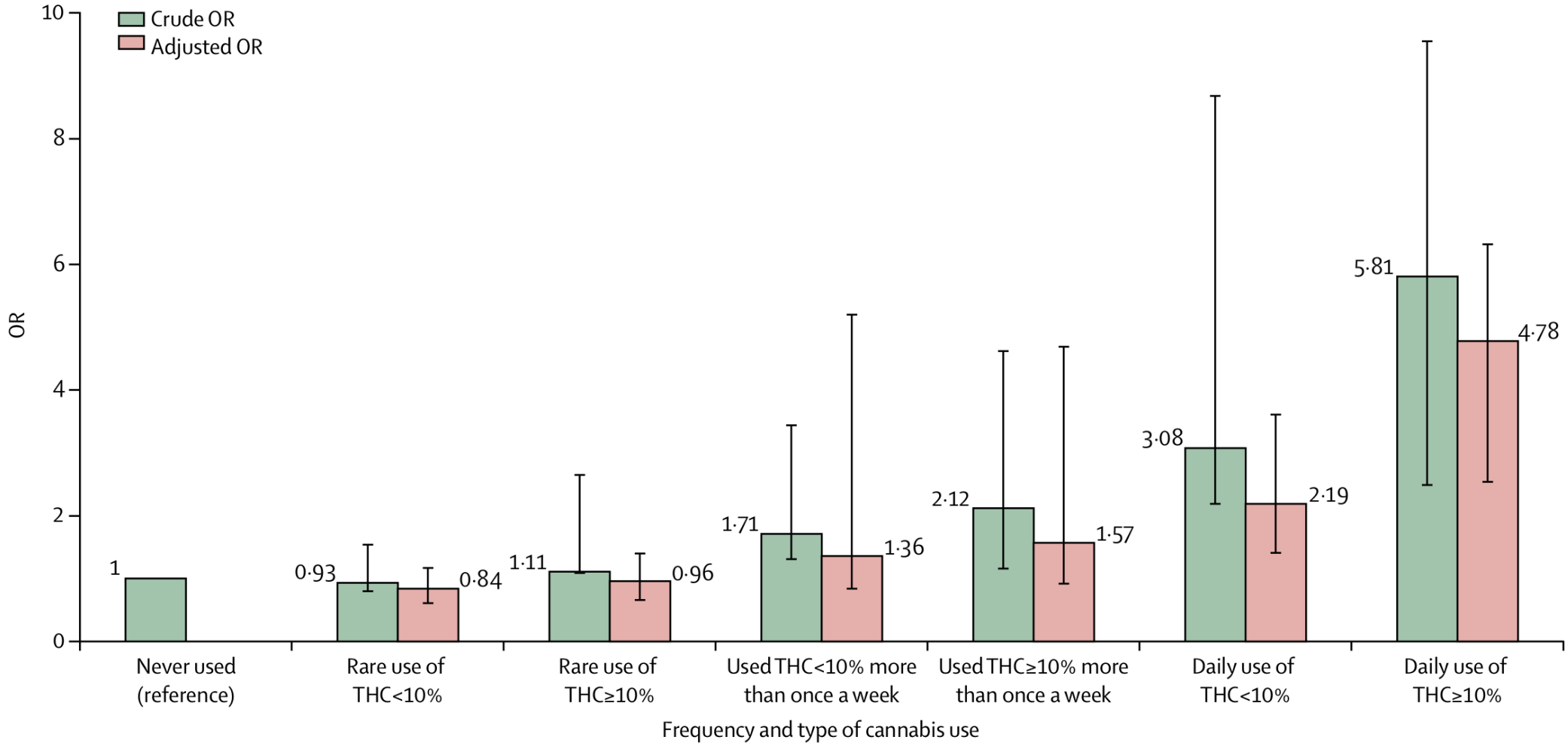
(adapted from van Os, 2009)

Trajectory



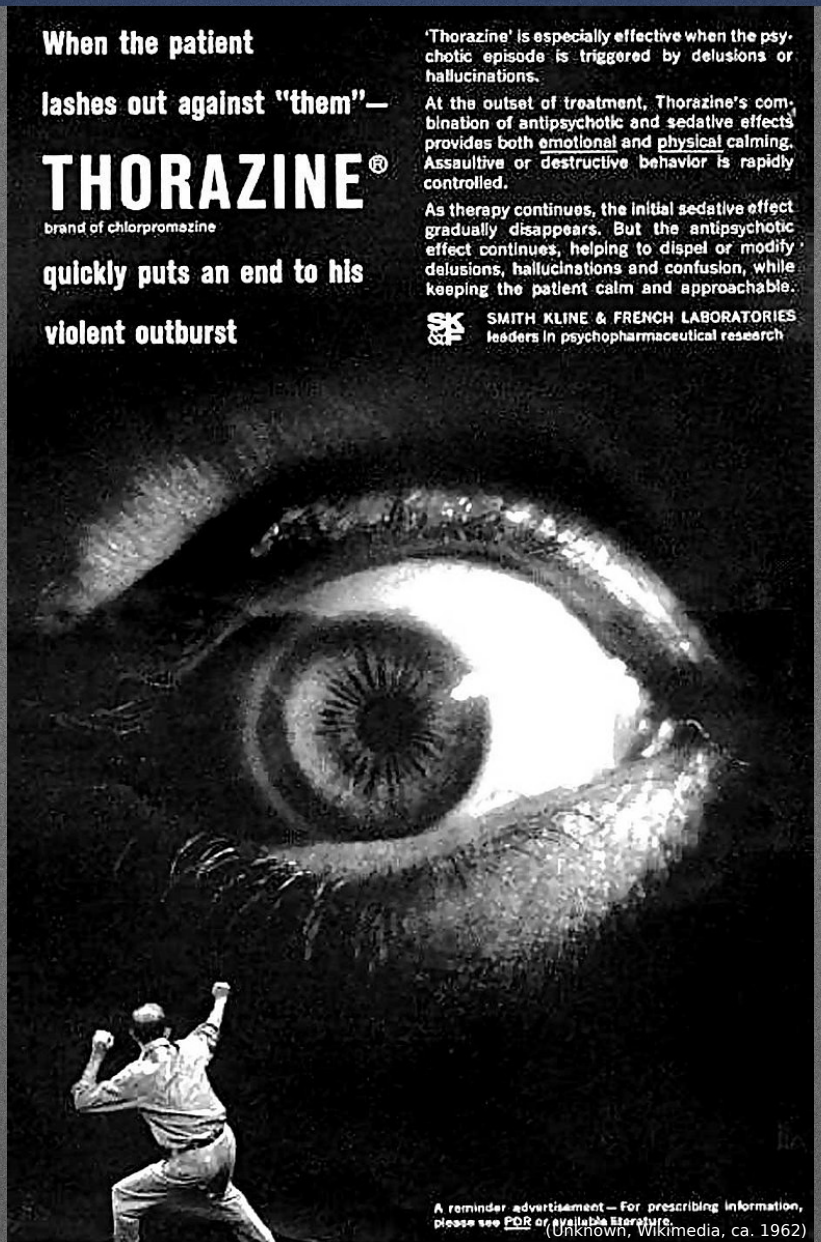
Fusar-Poli et al., 2013

Cannabis as Risk Factor



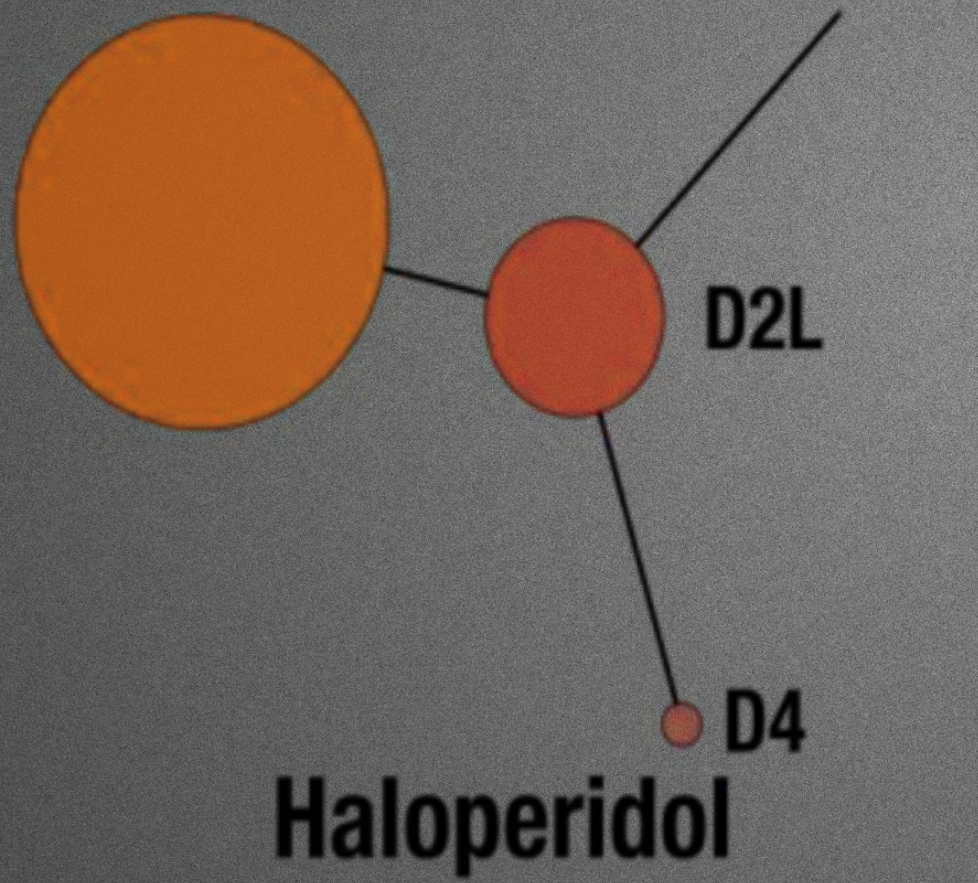
(Forti et al., 2019)

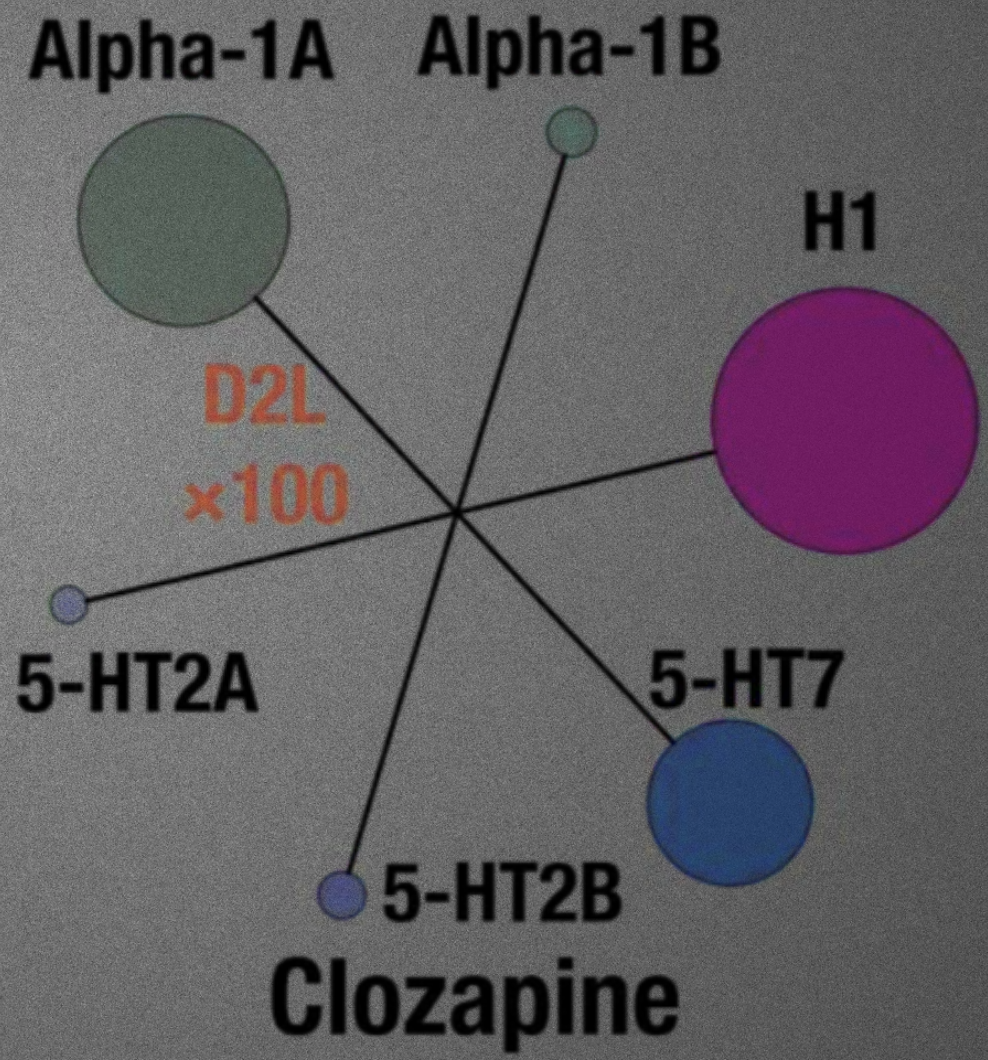
Antipsychotics



(Unknown, Wikimedia, ca. 1962)

Antipsychotics





(adapted from Saklad, 2018)

Antipsychotics

Name	Receptor Binding			
	D2	5-HT2	M1	H1
Amisulpride	+++	0	0	0
Aripiprazole	+++	++	0	+
Asenapine	+	++	0	+
Brexpiprazole	+++	+++	?	++
Cariprazine	+++	++	?	++
Chlorpromazine	+++	+++	++	+
Clozapine	+	+++	+++	+++
Haloperidol	+++	+	0	0
Lurasidone	+++	+++	0	0
Olanzapine	+++	+++	++	+++
Paliperidone	+++	+++	0	+
Quetiapine	+	+	0	++
Risperidone	+++	+++	0	+

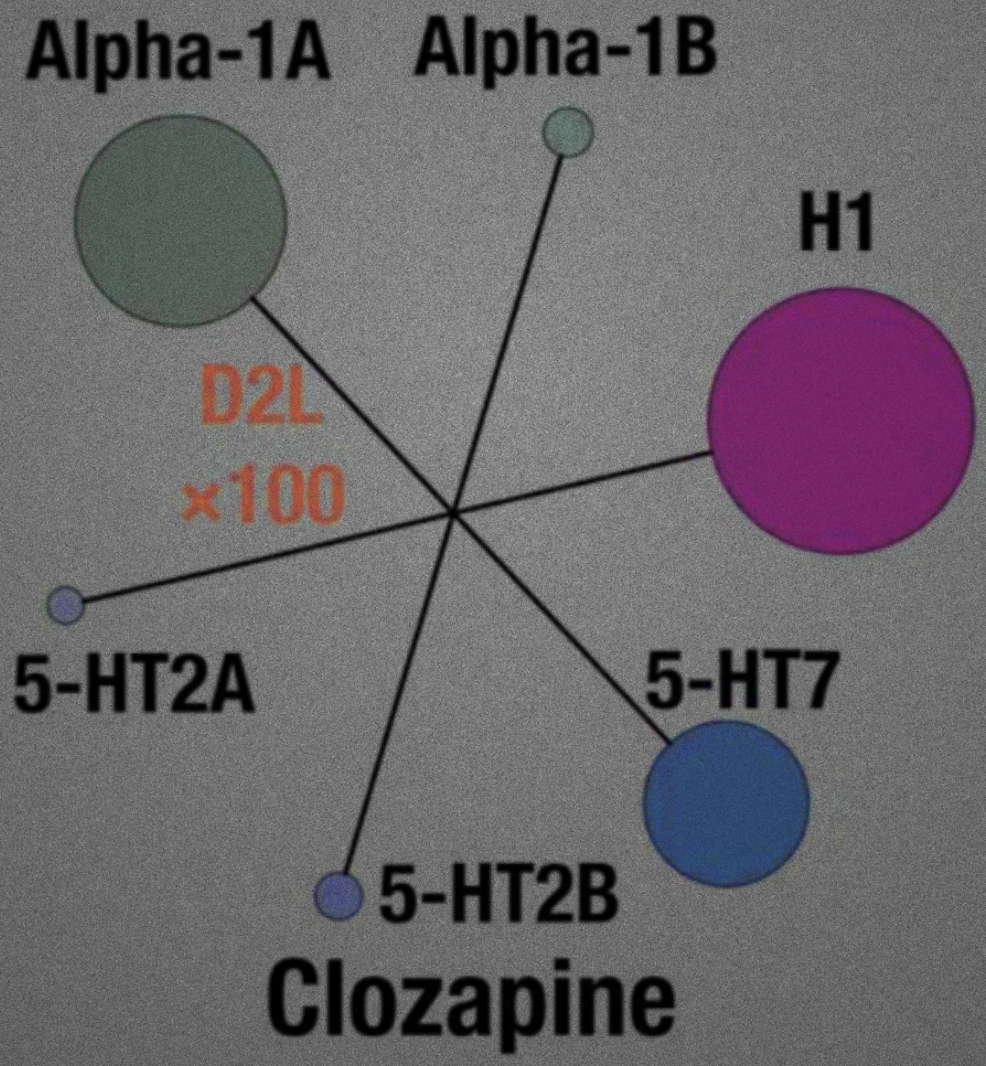
(adapted from Benkert et al., 2014 and Siafis et al., 2018)

Predictors for Outcome

- Social support (?)
- Short Duration of untreated psychosis
- Insight

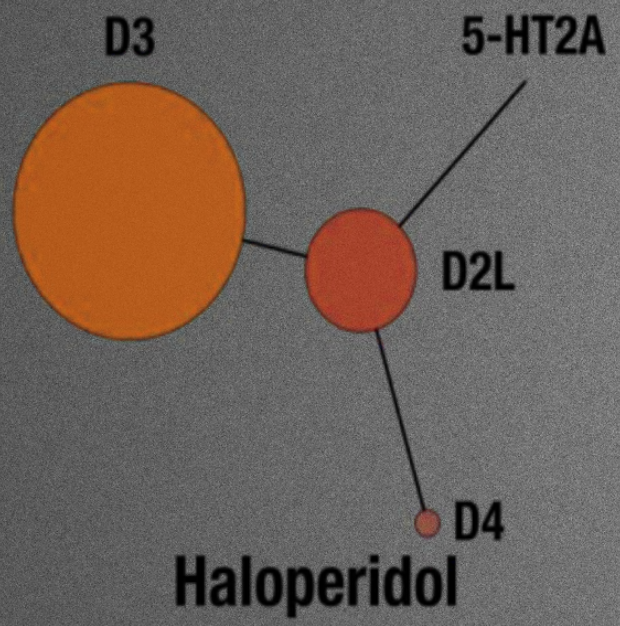
(Perkins et al., 2005; Drake et al., 2007; Leucht et al., 2007)

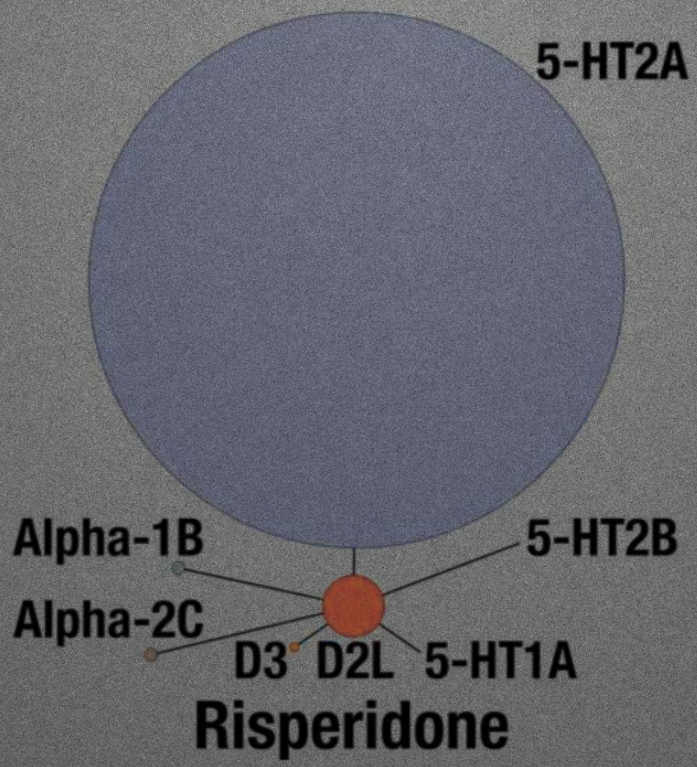
Curious Case of Clozapine

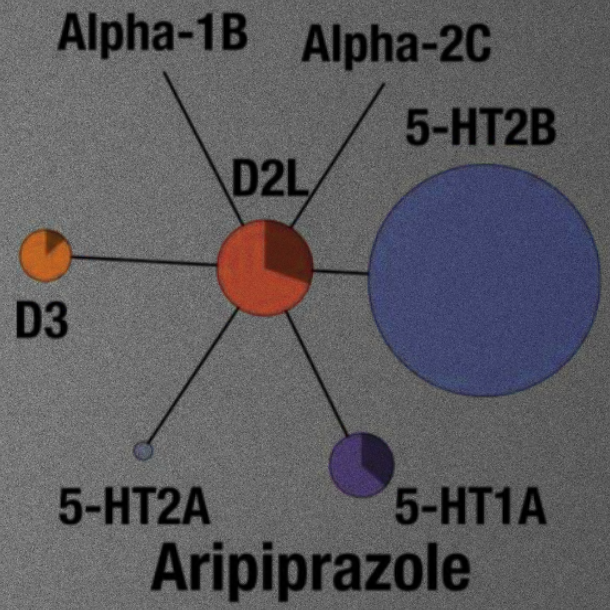


(adapted from Saklad, 2018)

Antipsychotics

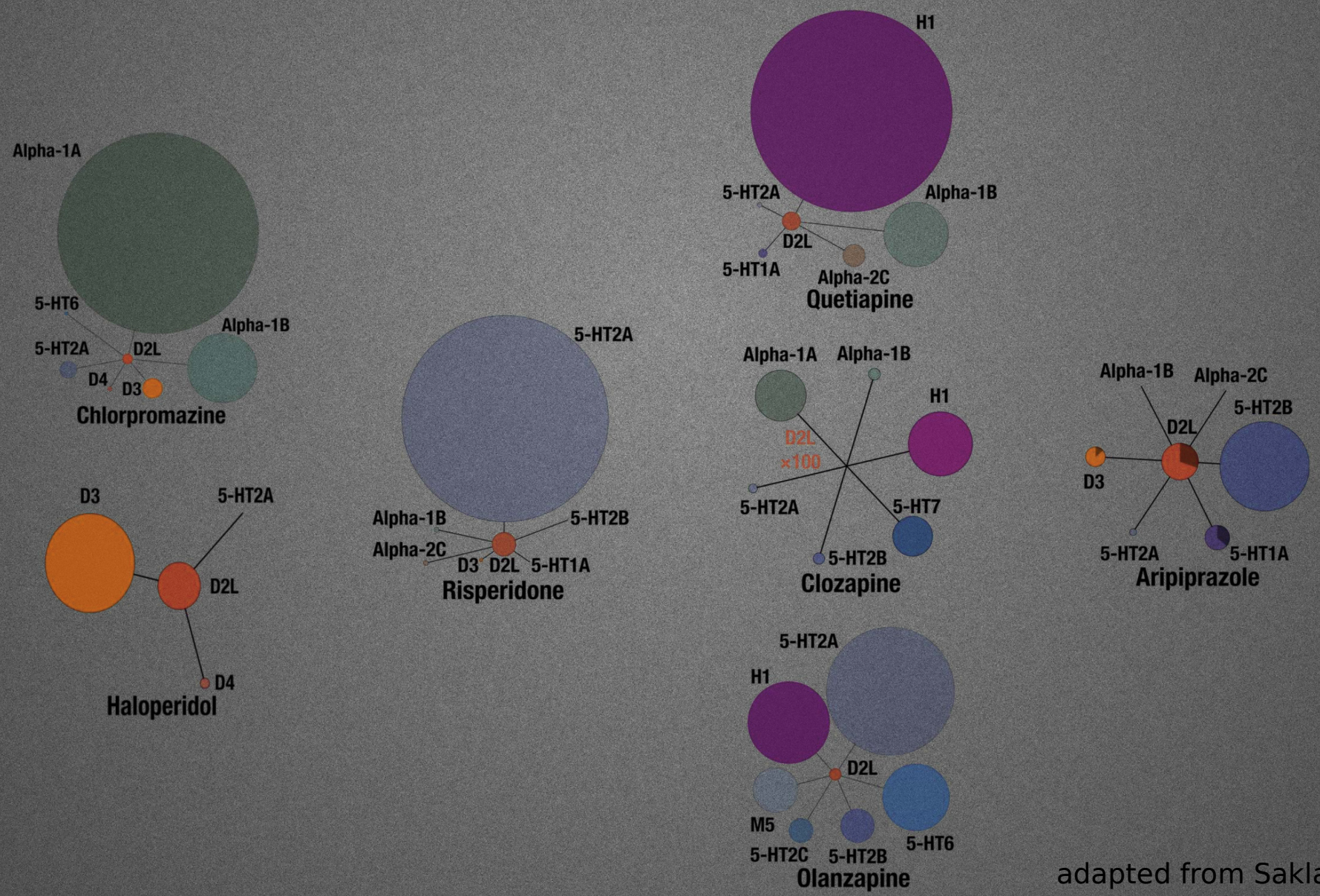






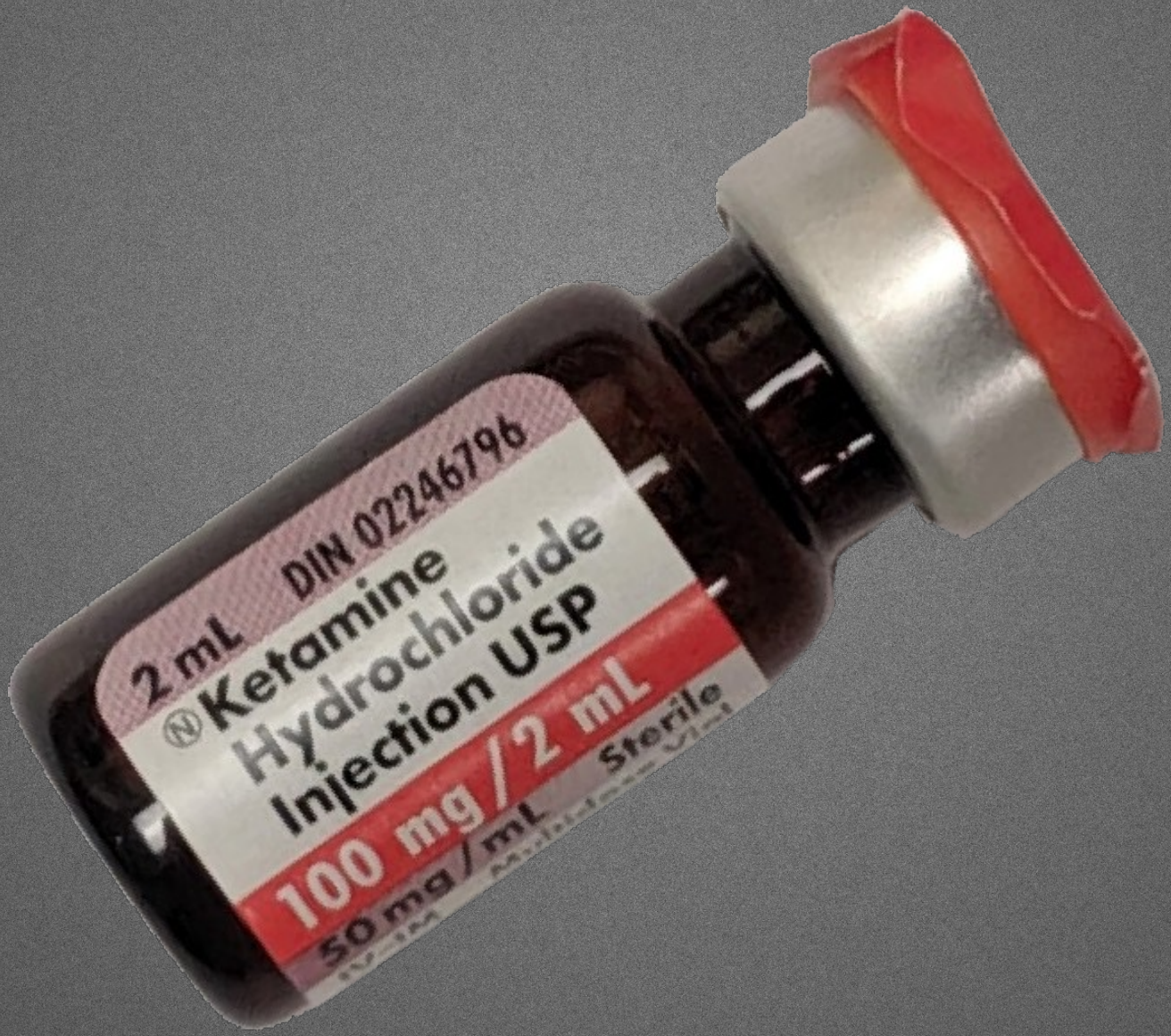
(adapted from Saklad, 2018)

Clinical Care: Antipsychotics



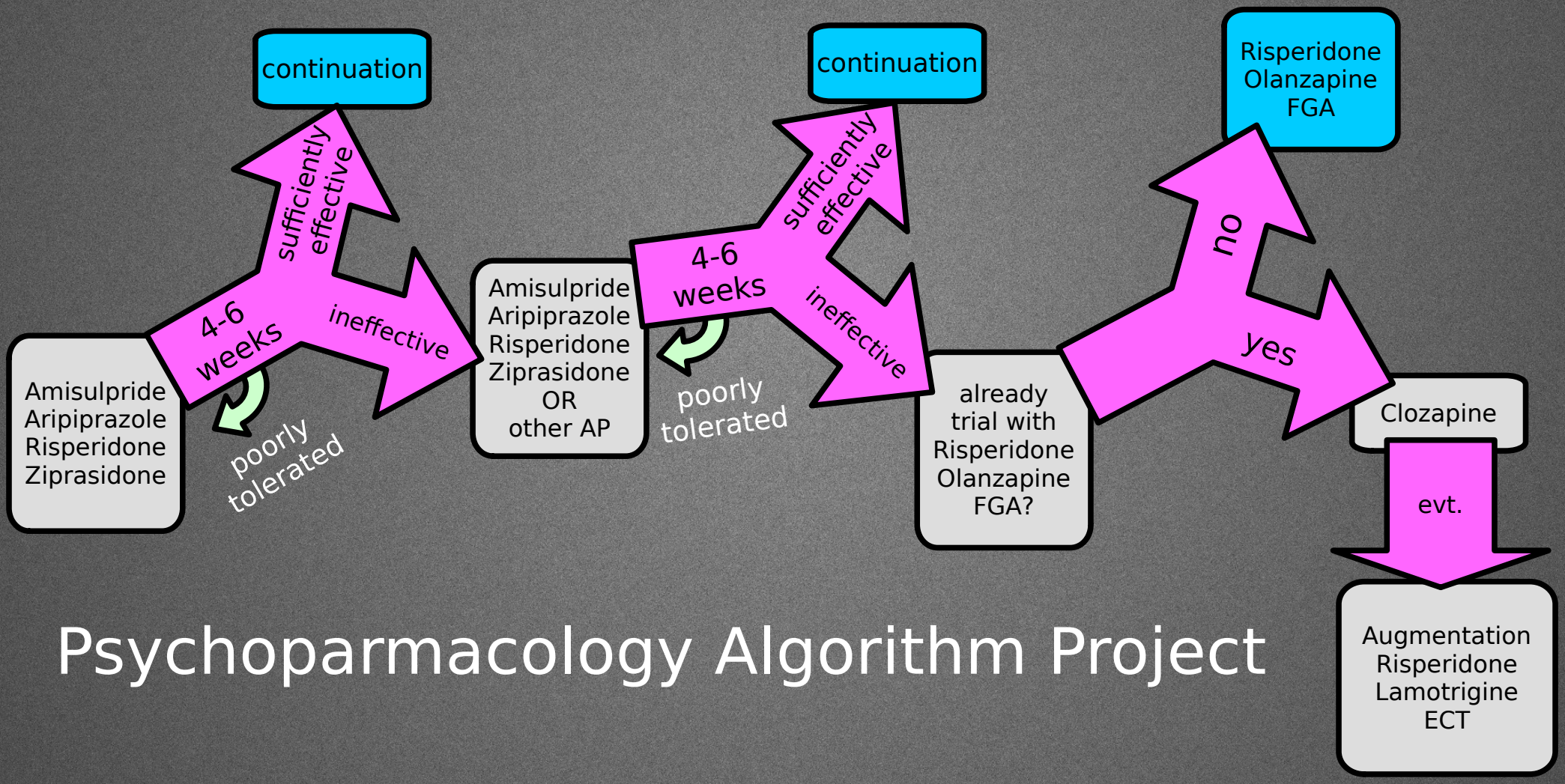
adapted from Saklad, 2018

Glutamate Hypothesis



(James, Wikimedia, 2019, edited)

Antipsychotics



Psychoparmacology Algorithm Project

(Osser et al., 2013)

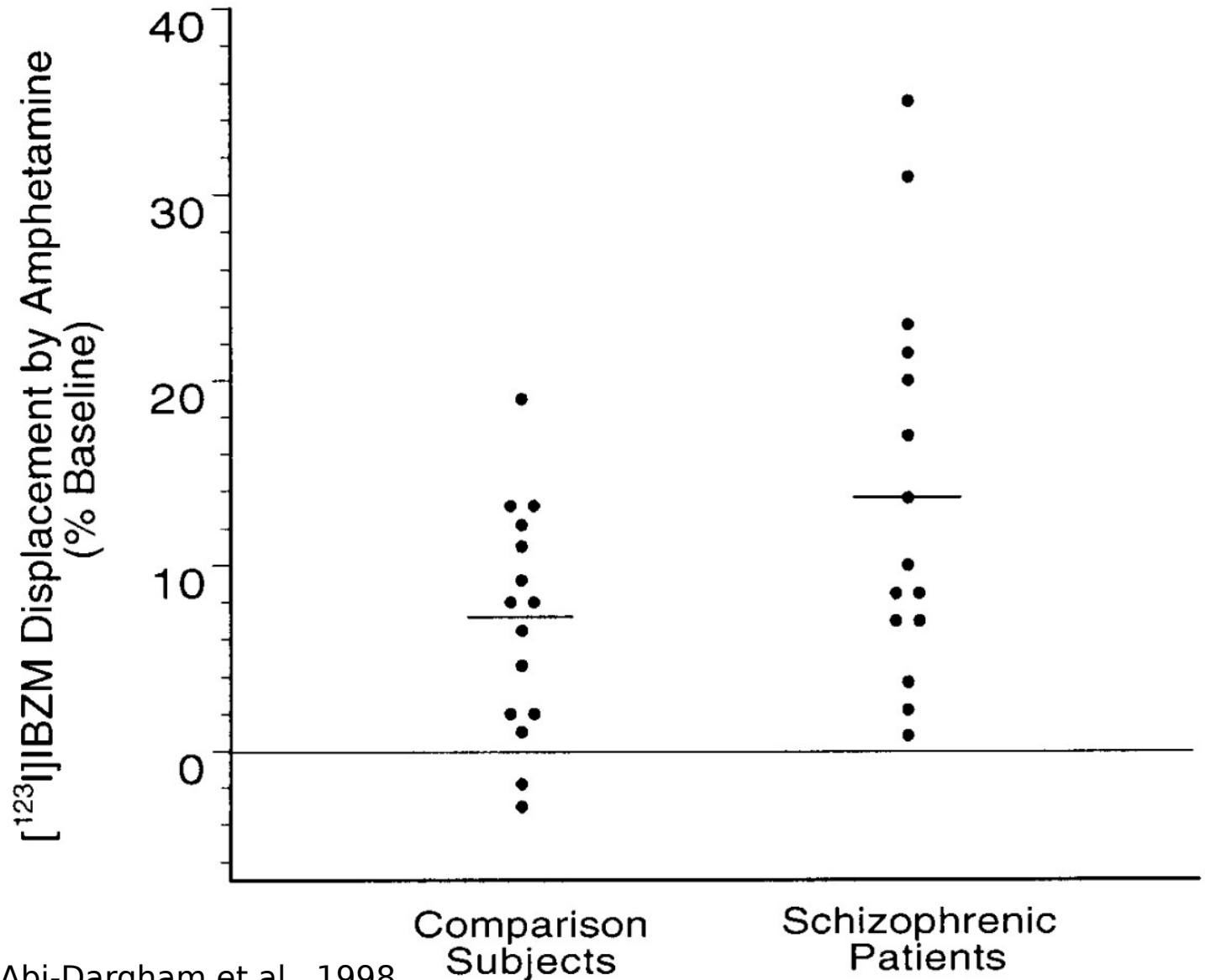
Risk factors

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
2nd degree relative (e.g., grandparent)	3–6
3rd degree relative (e.g., 1st. cousin)	2–3
Any specific single gene variant	1.1–1.5
Urbanicity	2–3
Migration	2–3
1st or 2nd 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

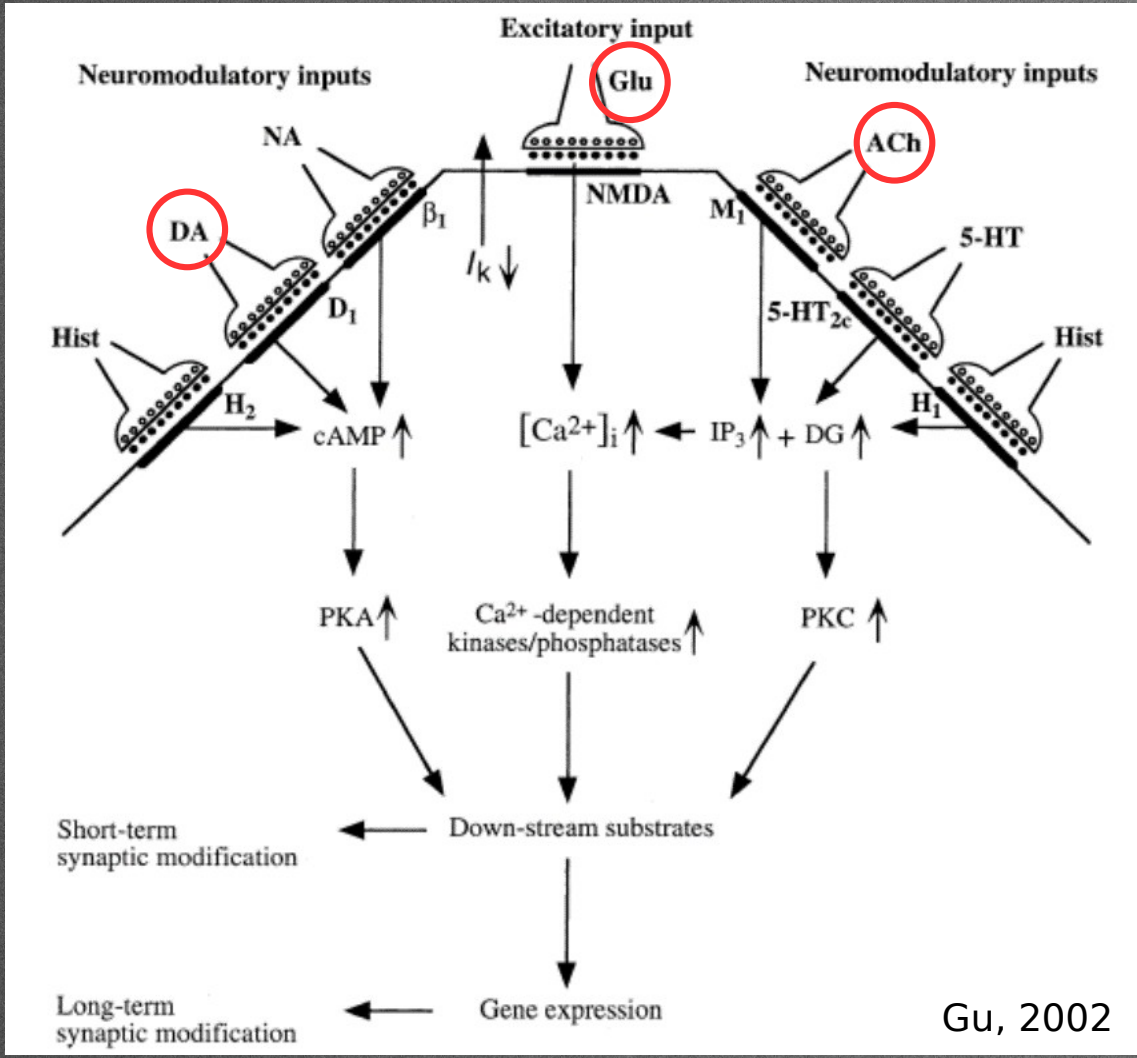
(Tandon et al., 2006)

Neurobiology: Dopamine

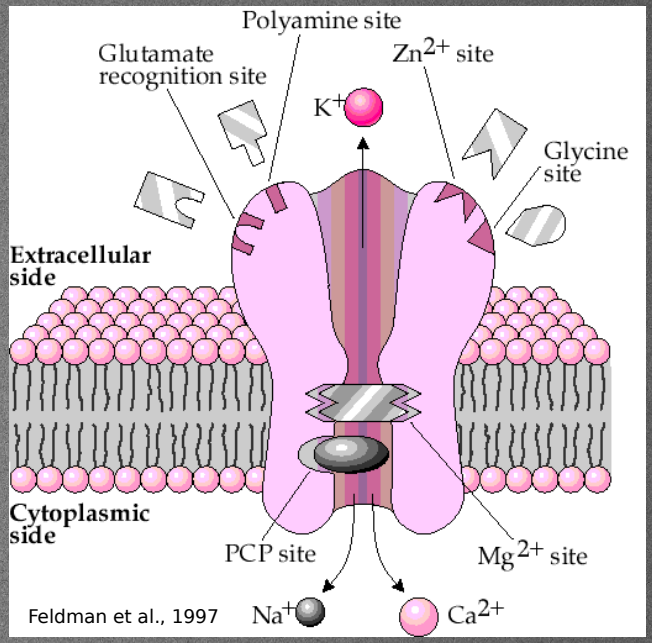


Abi-Dargham et al., 1998

NMDAR × neuromodulator interactions



Gu, 2002



Feldman et al., 1997

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

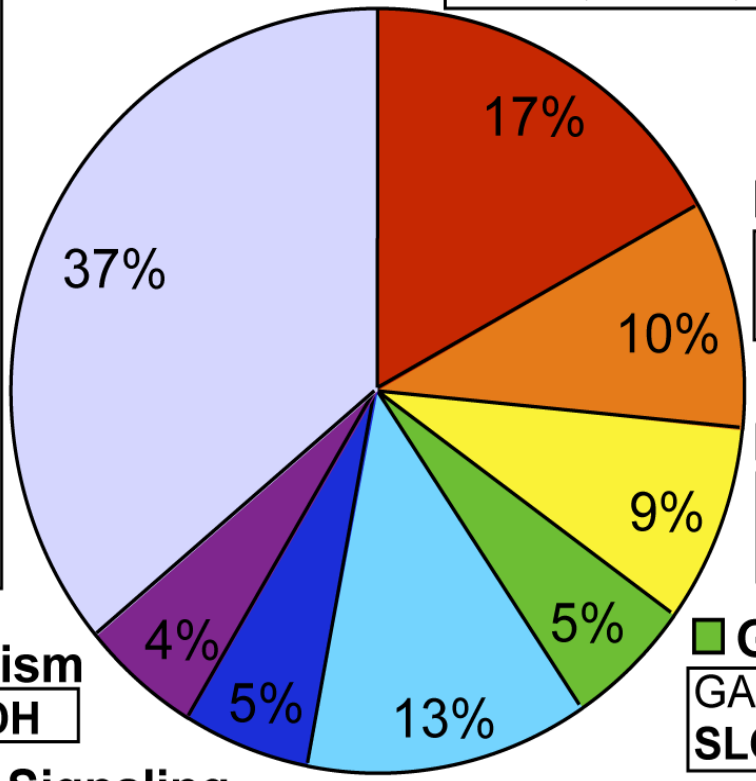
Neurobiology: Genetics

Other

ADRBK2, APOE, ASPM, BLOC1S1, BLOC1S2, CRHR1, **CRHR2**, **CTNNA2***, DAOA, **DBH**, DGCR2, **DISC1**, DTNBP1, EBF2, **EEA1**, **ERBB4***, **ESR1**, FEZ1, KCNH2, **MOG**, MUTED, **NCAM1**, NDE1, NDEL1, **NEUROG1**, **NOS1AP***, **NOTCH4***, **NRG1***, **PAFAH1B1**, **RELN***, SLC6A9,SNAPAP, SP4, YWHAE, ZDHHC8

Glutamate Signaling

DLG4, **GRID1**, **GRID2***, **GRIK3***, **GRIK4***, GRIN1, **GRIN2A***, **GRIN2B***, GRIN3A, **GRM1**, GRM2, GRM3, GRM4, GRM5, **SLC1A2**, SLC1A7



Dopamine Receptor Signaling

COMT, DRD1, DRD2, **DRD3**, DRD4, PPP1R1B, SLC18A1, **SLC6A3***, TH

Serotonin Receptor Signaling

HTR1A, HTR1B, **HTR2A**, HTR2C, **HTR4**, HTR6, HTR7, SLC6A4

GABA Receptor Signaling

GABRA3, GABRB1, **GABRB2**, **SLC32A1**, **SLC6A1**

Amino Acid Metabolism

DAO, GAD1, GAD2, **PRODH**

Axonal Guidance Signaling

AKT1, BDNF, **GSK3B**, MAG, PPP3CC

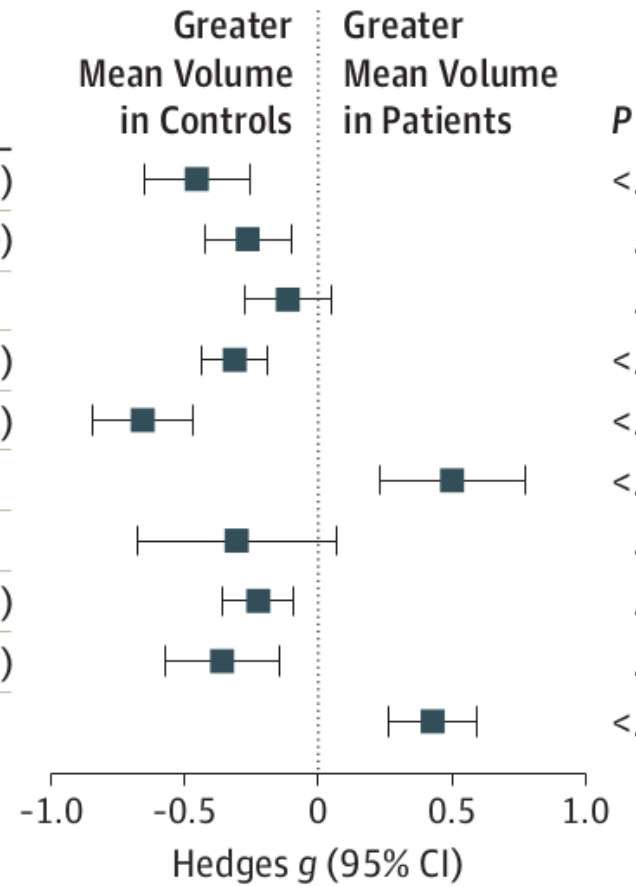
Cell Signal Transduction

ADORA2A, ADRA2A, **CACNG2***, CAMK2A, **CHRM1**, CHRNA4, **CHRNA7***, CHRNB2, **CHRNB3**, GPR88, RGS4, TAAR6

Greenwood et al., 2012

Neurobiology: Volume

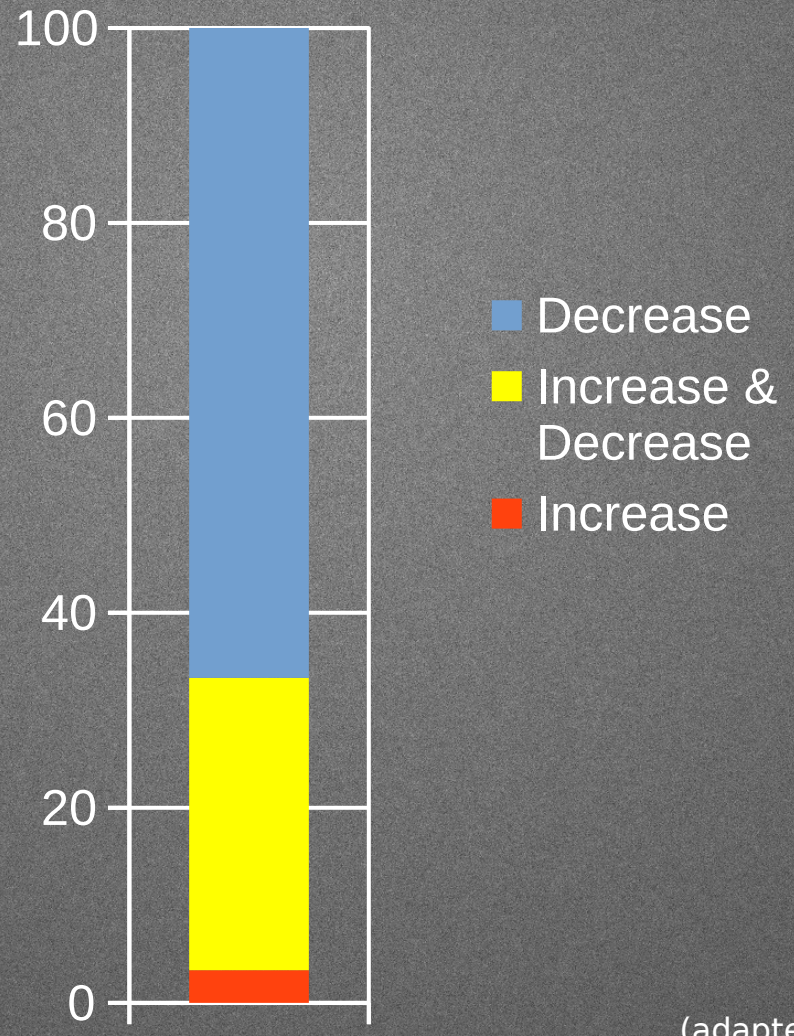
Brain Region	No. of Studies	No. of Patients	No. of Controls	Effect Size for VR (95% CI)	P Value	I^2
Amygdala	23	1161	1154	-0.46 (-0.65 to -0.26)	<.001	78.01
ACC	11	443	450	-0.26 (-0.43 to -0.10)	.006	48.44
Caudate	22	1106	990	-0.11 (-0.28 to 0.05)	.23	78.53
Frontal lobe	22	693	698	-0.31 (-0.44 to -0.19)	<.001	28.66
Hippocampus	36	1615	1683	-0.66 (-0.84 to -0.47)	<.001	74.14
Lateral ventricle	31	1416	1382	0.40 (0.29 to 0.51)	<.001	55.51
Putamen	15	964	845	-0.31 (-0.68 to 0.07)	.11	78.66
Temporal lobe	22	733	725	-0.22 (-0.36 to -0.09)	.001	43.67
Thalamus	21	1102	1023	-0.36 (-0.57 to -0.15)	.001	76.03
Third ventricle	13	362	388	0.43 (0.26 to 0.59)	<.001	15.15



Brugger & Howes, 2017

Dysconnectivity

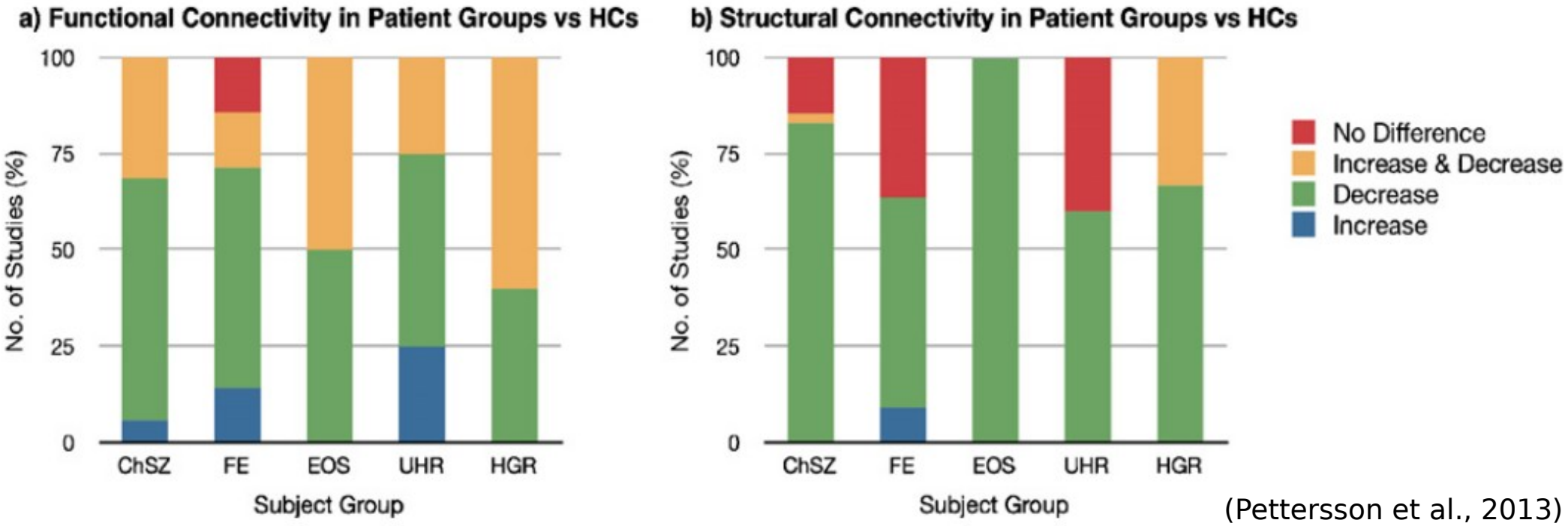
Functional connectivity in chronic SZ
% of studies with main finding



(adapted from Pettersson et al., 2011)

Neurobiology: Connectivity

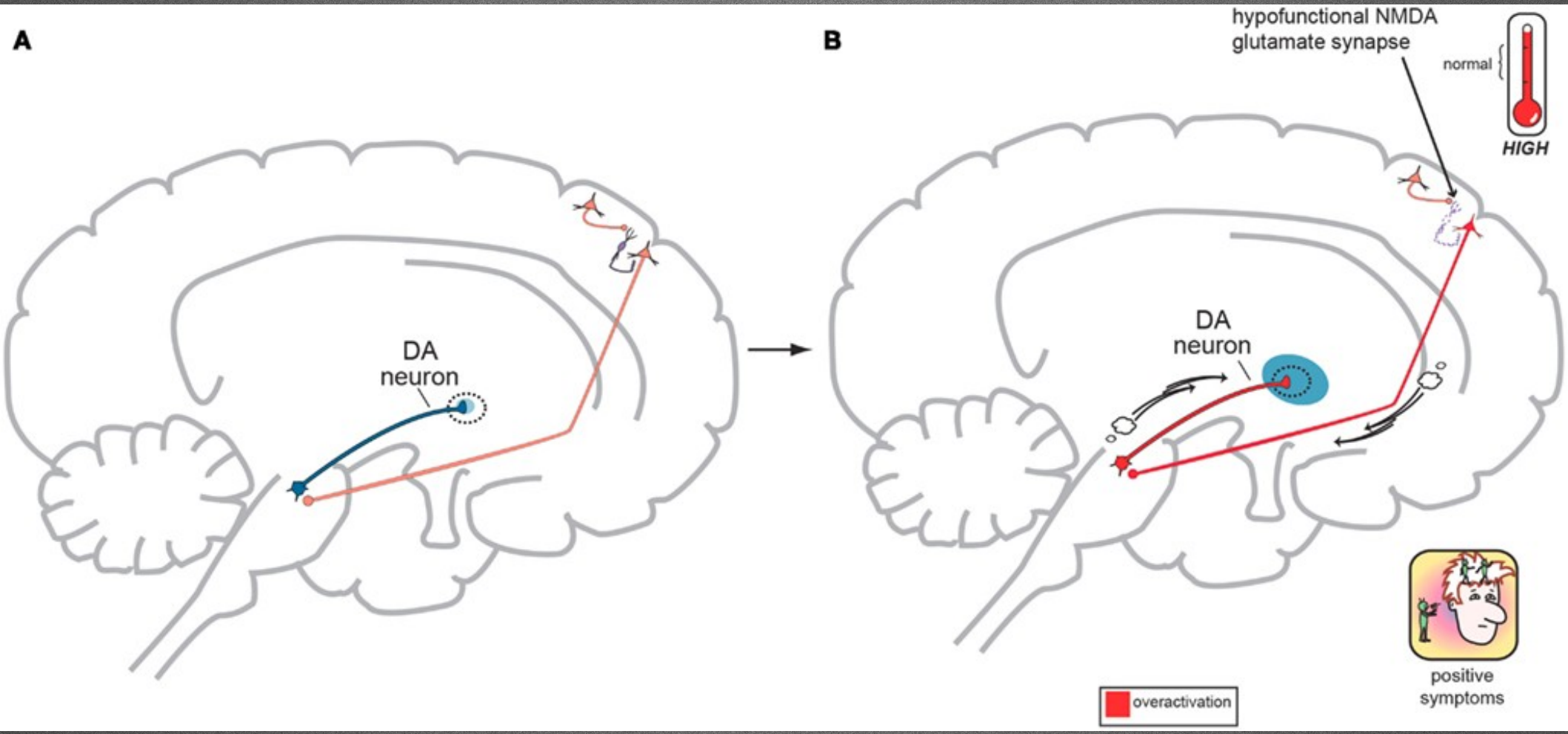
- Trend towards reduced connectivity
- Frequently Prefrontal Cortex involved



(Pettersson et al., 2013)

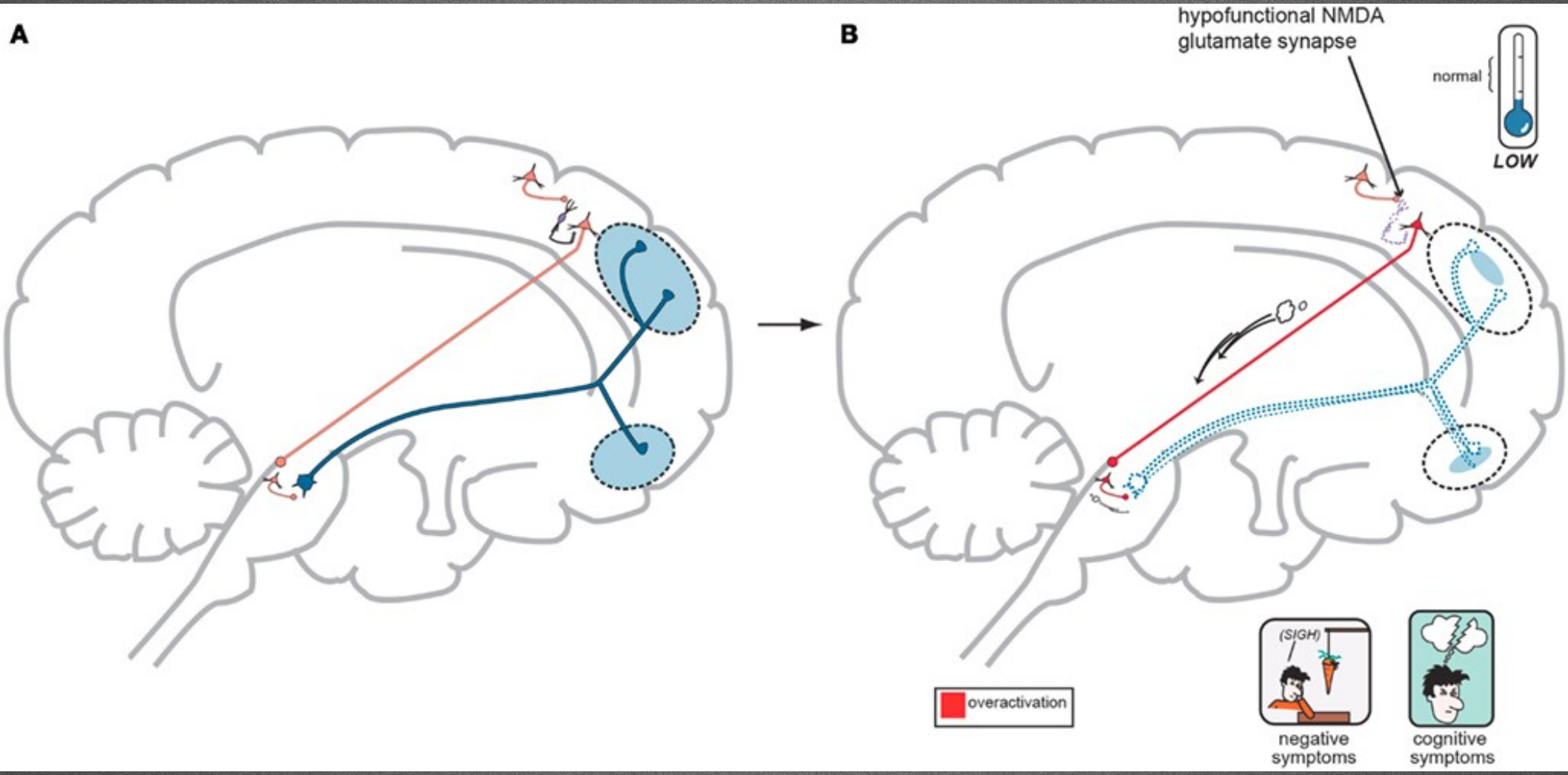
ChSZ – chronic schizophrenia; FE – first episode; EOS – early onset schizophrenia; UHR – ultra high risk for developing psychosis; HGR – high genetic risk

Dysconnectivity



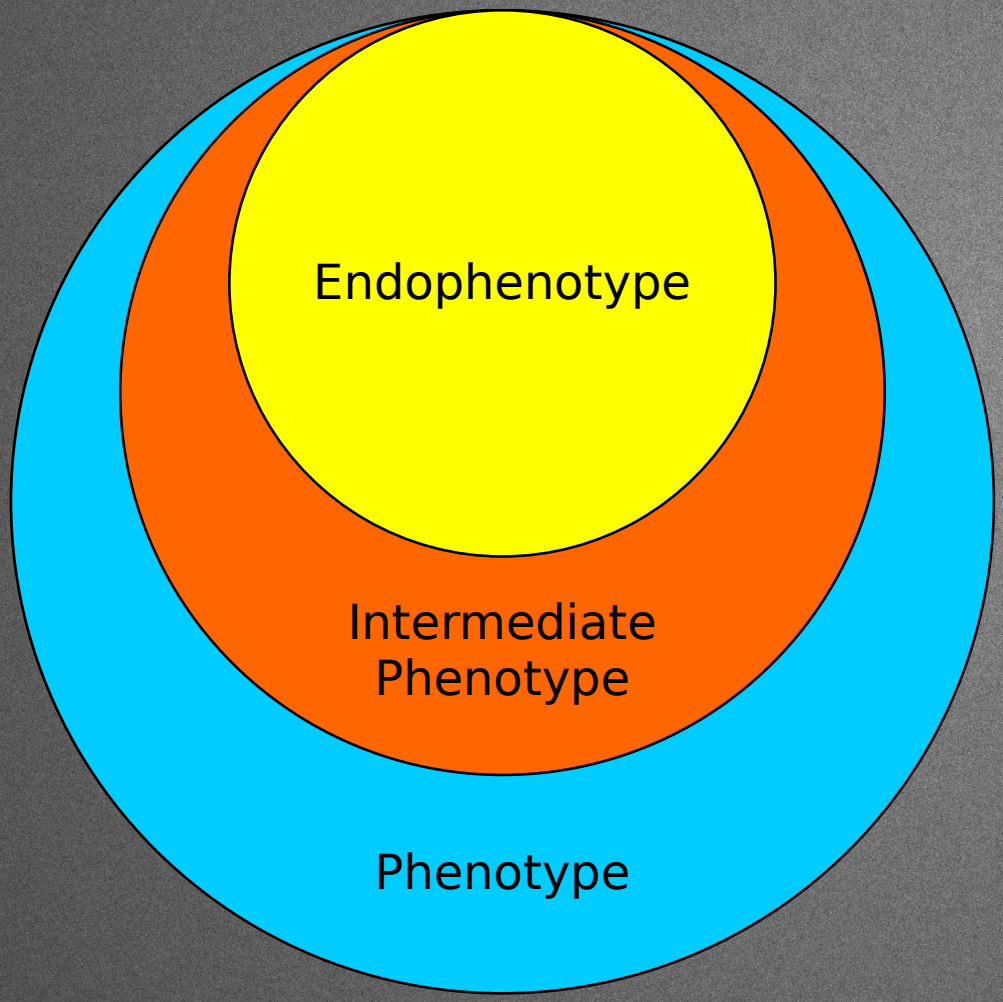
(Schwartz et al., 2012)

Dysconnectivity



(Schwartz et al., 2012)

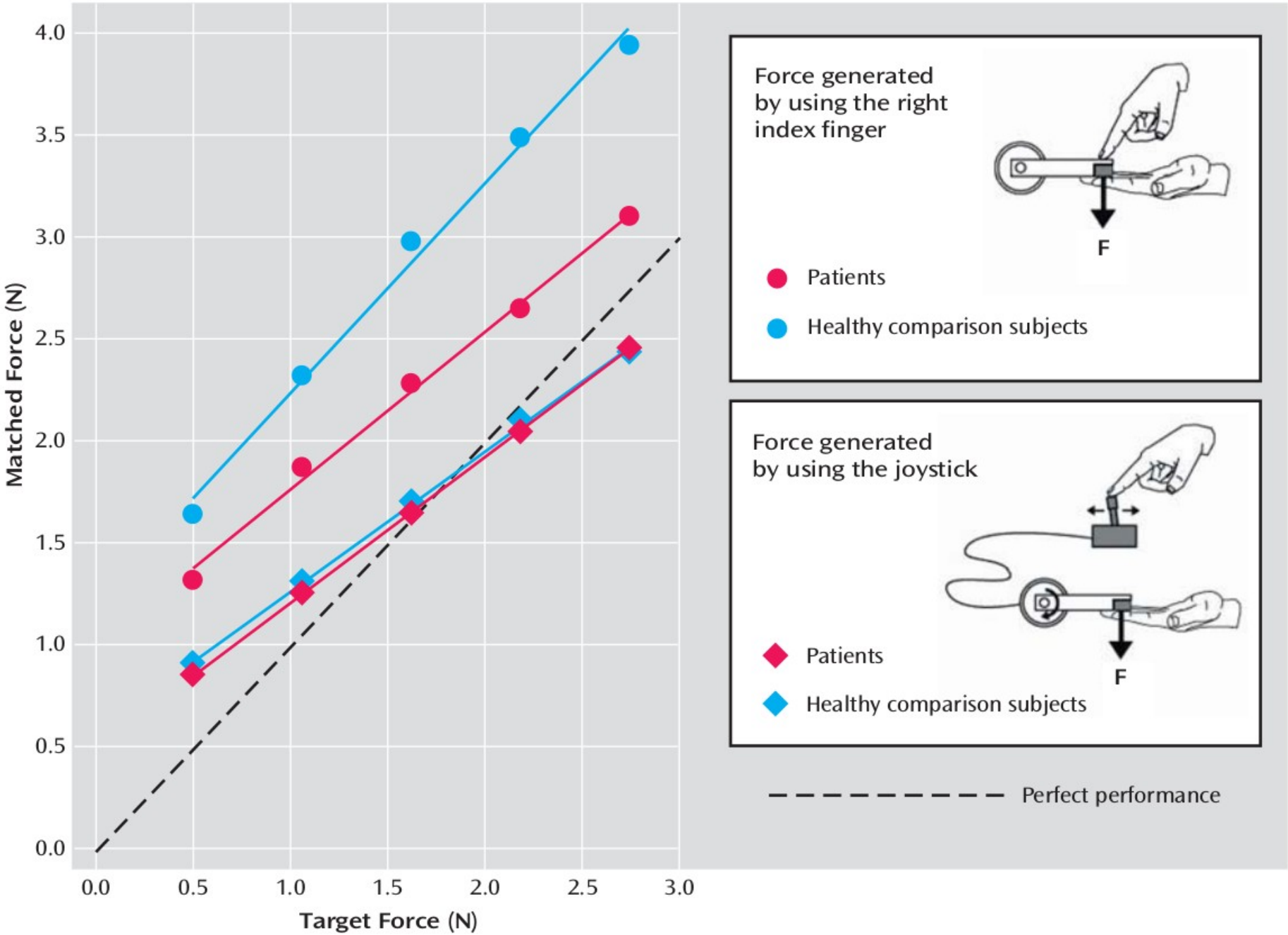
Intermediate Phenotypes



heritable intermediate phenotype associated with a disease
mechanism related manifestation of a complex phenotype
Any assessable characteristic

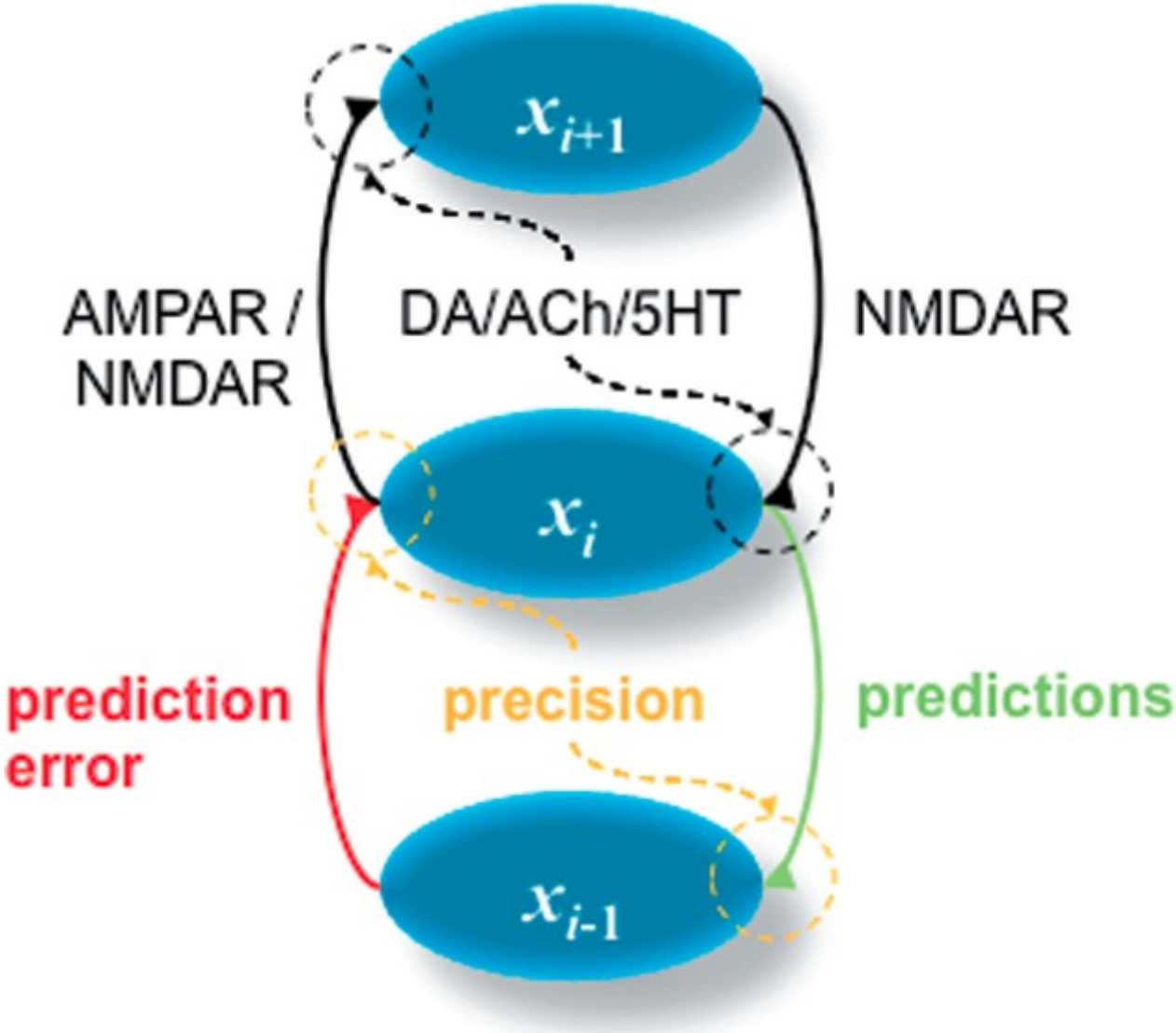
(Goldman & Ducci, 2007)

FIGURE 1. Matching Force Generated by 19 Patients With Schizophrenia and 19 Healthy Volunteers Using the Right Index Finger or Joystick as a Function of the Externally Generated Target Force[a]

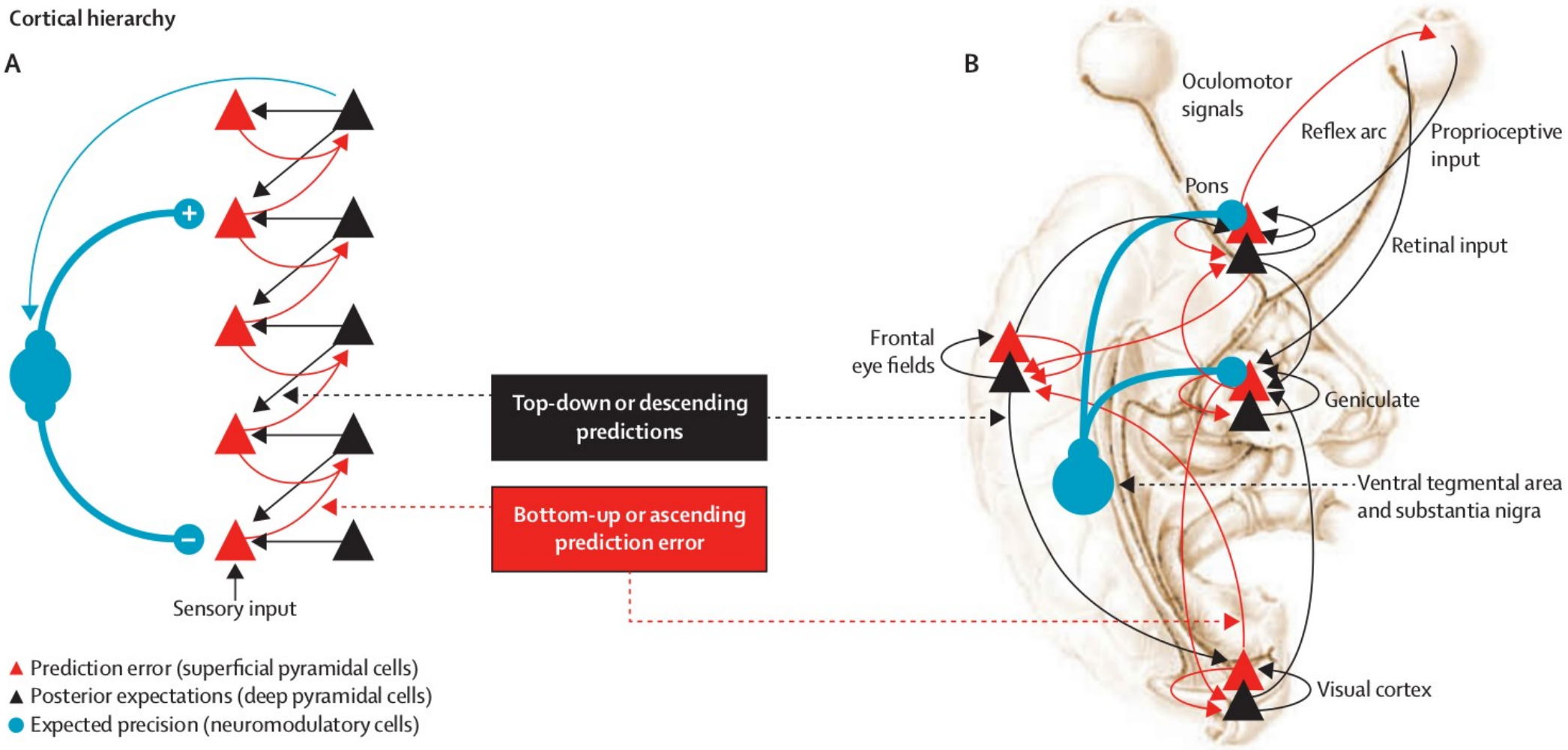


Shergill, S. S., Samson, G., Bays, P. M., Frith, C. D., & Wolpert, D. M. (2005). Evidence for Sensory Prediction Deficits in Schizophrenia. American Journal of Psychiatry, 162(12), 2384–2386.

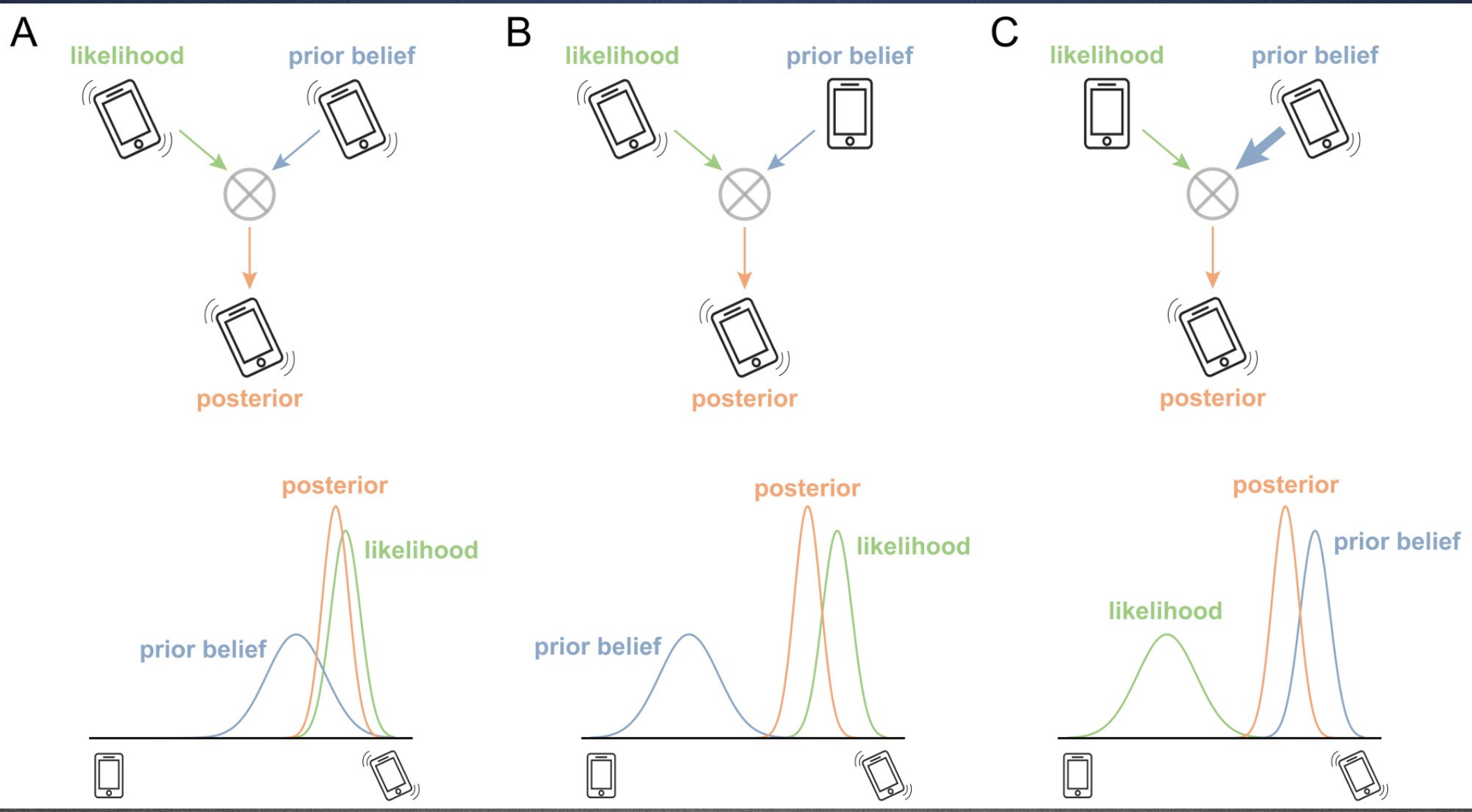
Bayesian Brain



(Stephan et al., 2016)

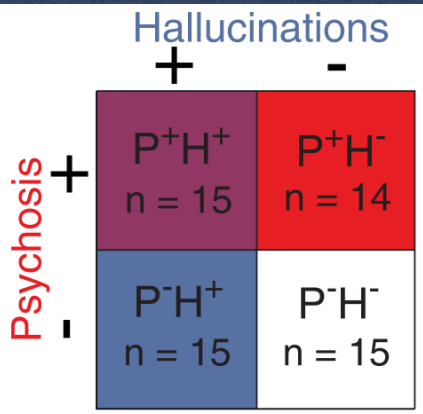

Cortical hierarchy
A
B
Top-down or descending predictions
Bottom-up or ascending prediction error
Sensory input
Prediction error (superficial pyramidal cells)
Posterior expectations (deep pyramidal cells)
Expected precision (neuromodulatory cells)
Oculomotor signals
Reflex arc
Proprioceptive input
Pons
Retinal input
Frontal eye fields
Geniculate
Ventral tegmental area and substantia nigra
Visual cortex

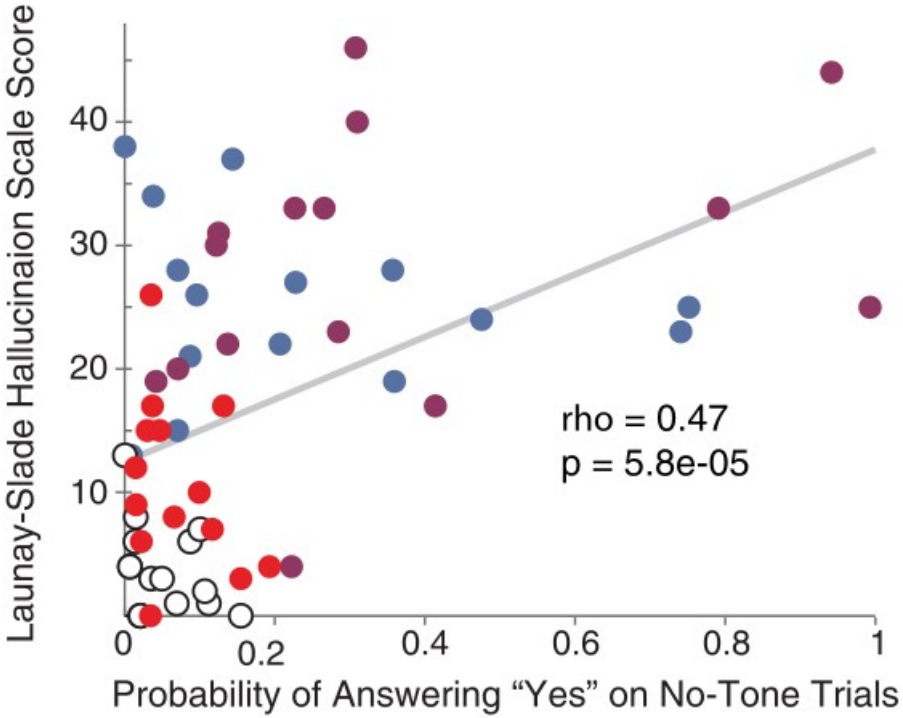
Bayesian Brain & Schizophrenia

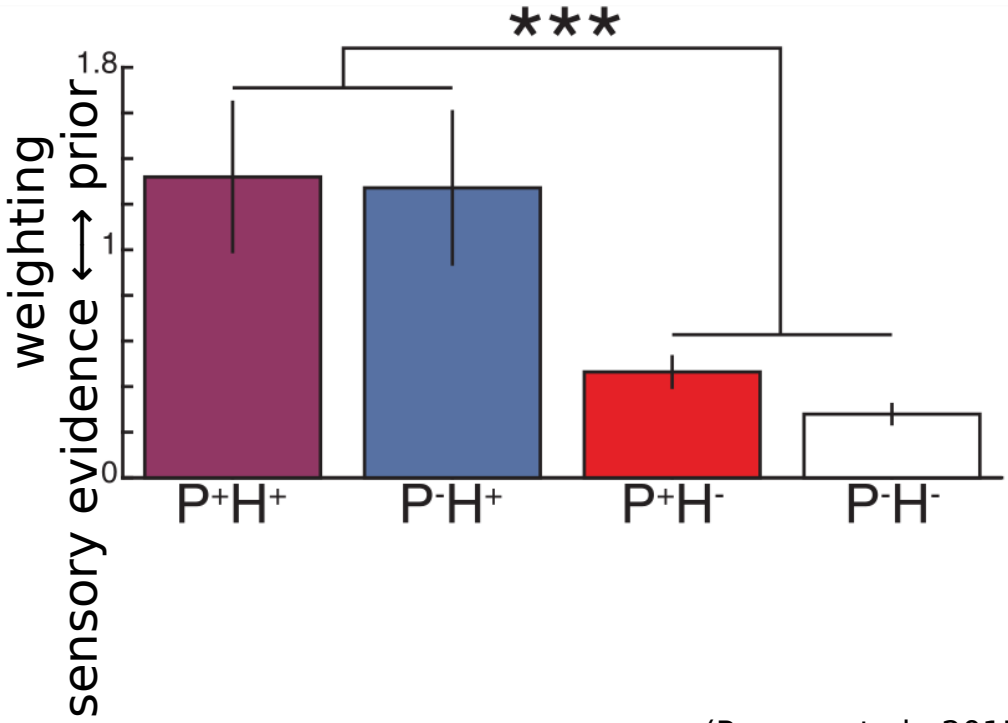


(Siemerkus et al., 2019)

Bayesian Brain & Schizophrenia

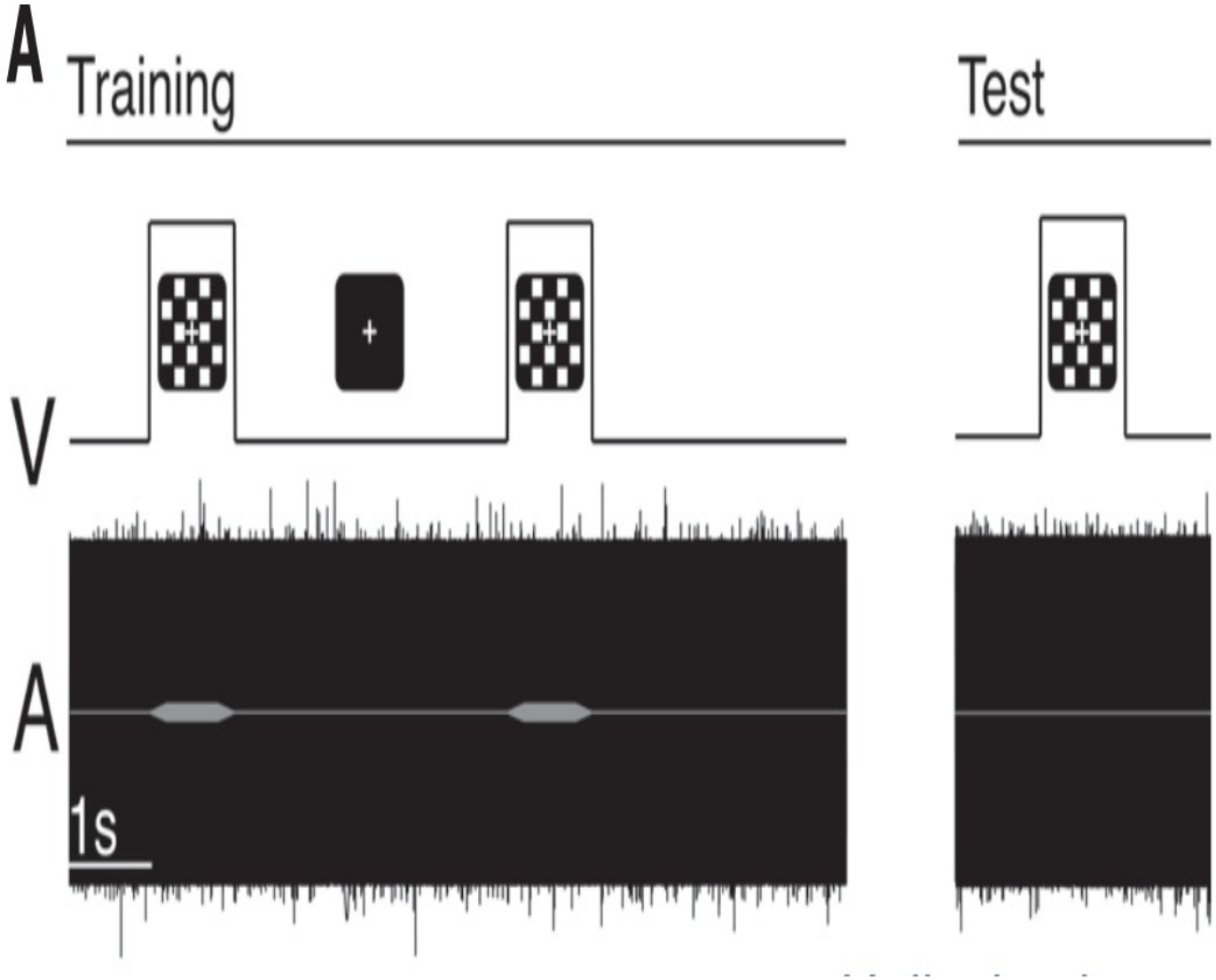






(Powers et al., 2017)

Bayesian Brain & Schizophrenia



(Powers et al., 2017)