

Common Presentations in Primary Care: Schizophrenia

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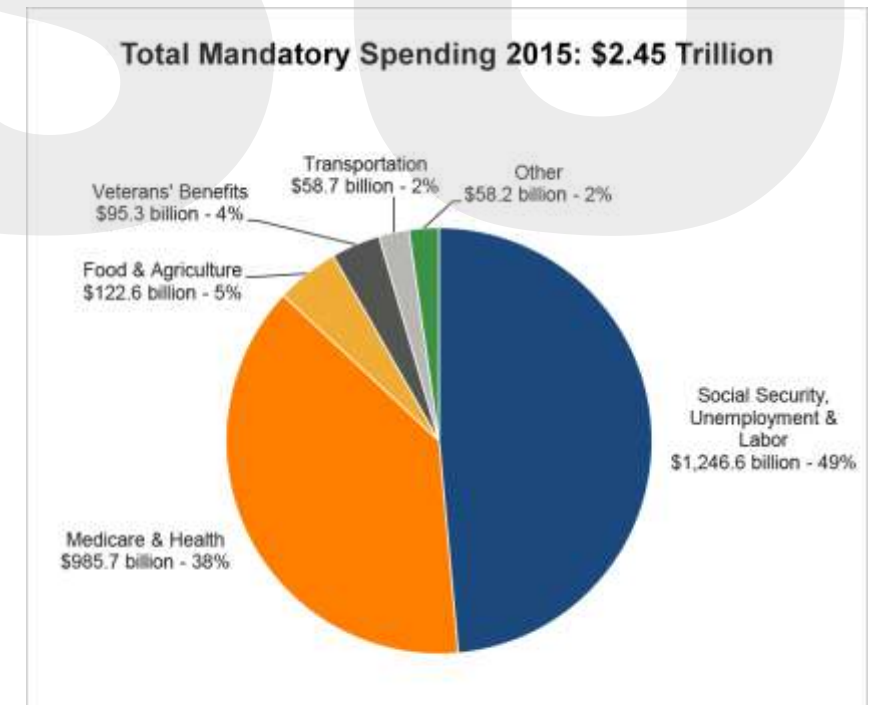
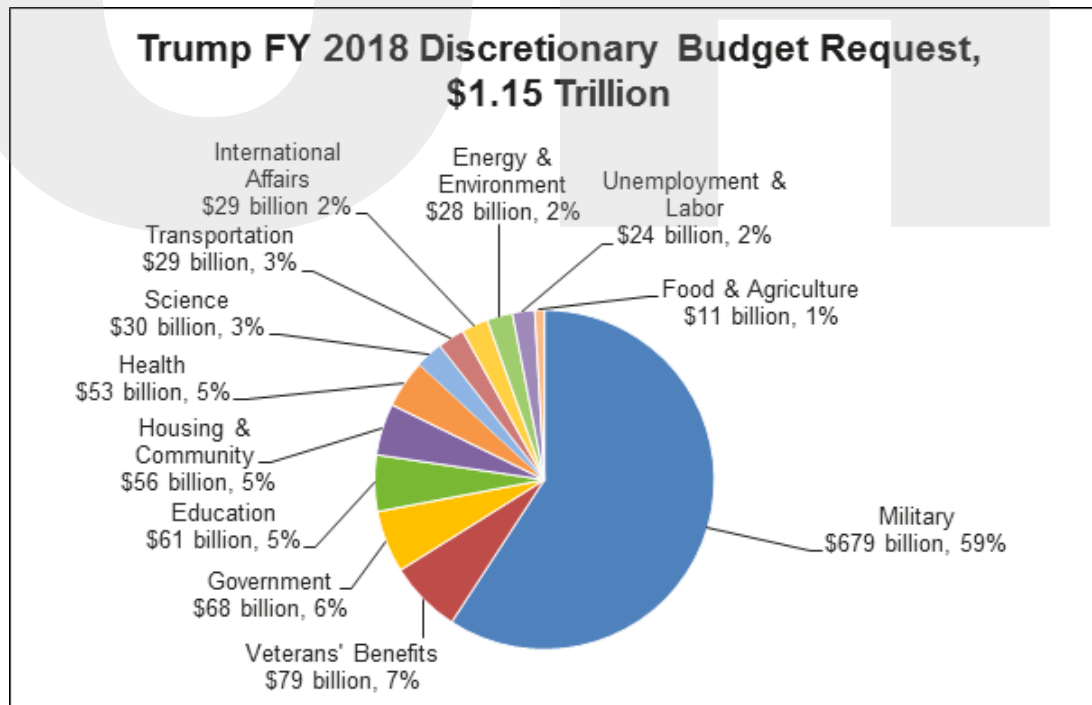
Staff Psychiatrist, Portland VA Medical Center

Outline

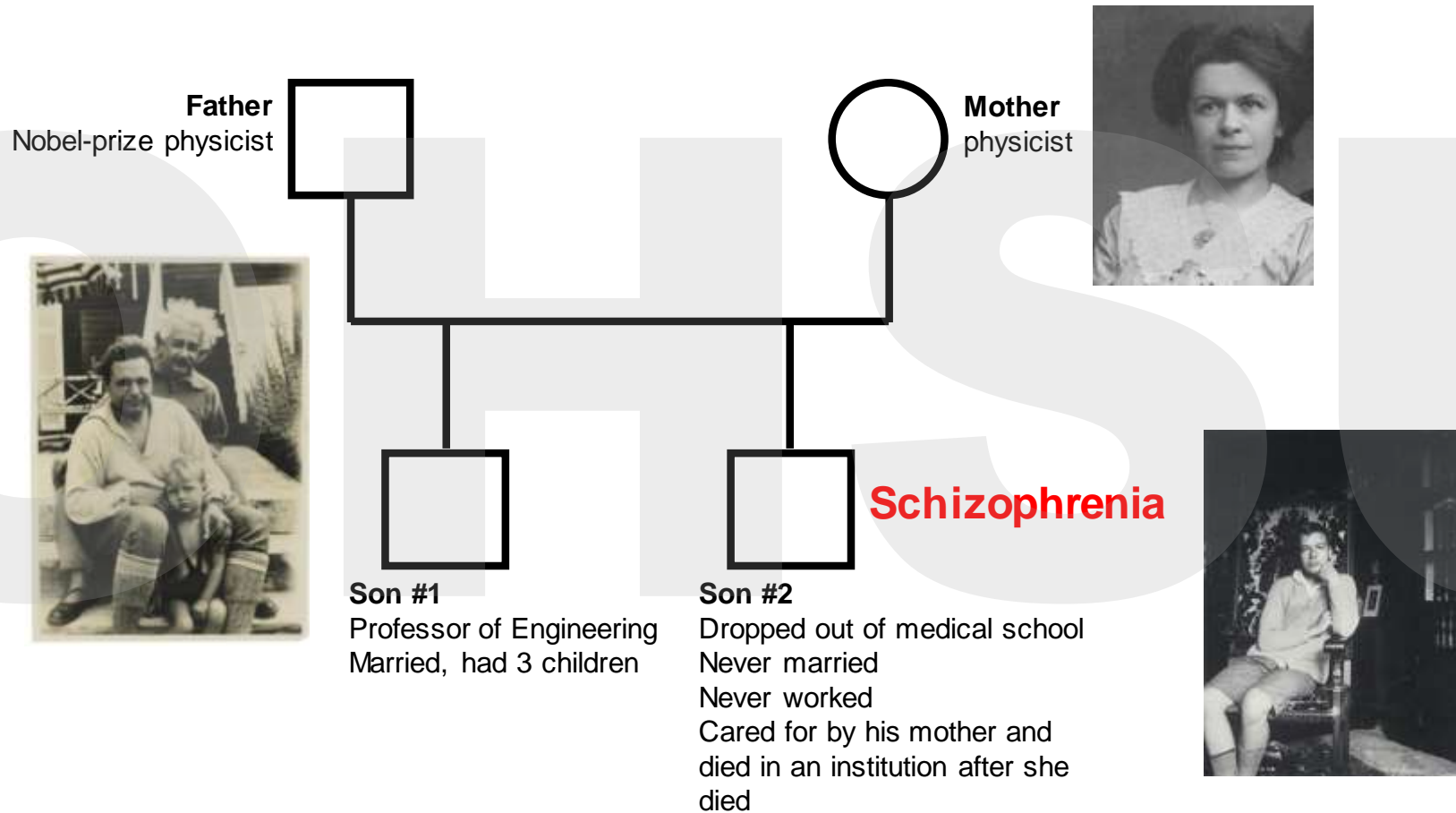
- **Epidemiology and impact of schizophrenia**
- **Schizophrenia symptoms**
- **Neurobiology of schizophrenia**
- **Antipsychotics – Important considerations for medical providers**
- **Common comorbidities in schizophrenia**
- **Take home points**

The Impact of Schizophrenia

- 50 to 500-fold increased risk of suicide (Hor et al, 2010)
- 10-20 year decrease in life expectancy (Olfson et al, 2015)
- Unemployment rate estimates range between 60-90% in Western countries (Evensen et al, 2016)
- Economic costs associated with schizophrenia: \$102 billion/year



The Impact of Schizophrenia



DSM-5 Criteria for Schizophrenia

Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

1. Decreased functioning

2. 6 months of symptoms with 1 month meeting criterion A

3. Not schizoaffective disorder and depressive or bipolar disorder with psychotic features

4. Not related to drugs or a medical problem

5. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

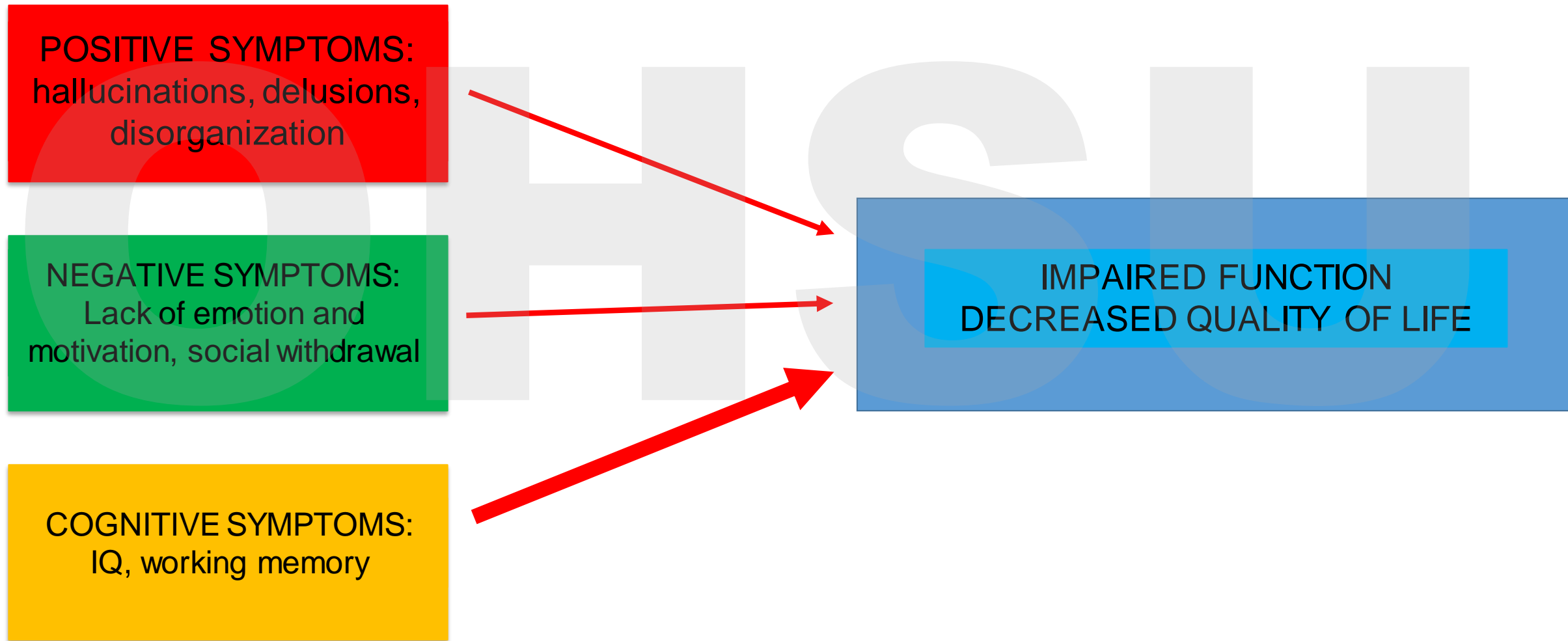
Symptom Domains in Schizophrenia

POSITIVE SYMPTOMS:
hallucinations, delusions,
disorganization

NEGATIVE SYMPTOMS:
Lack of emotion and
motivation, social withdrawal

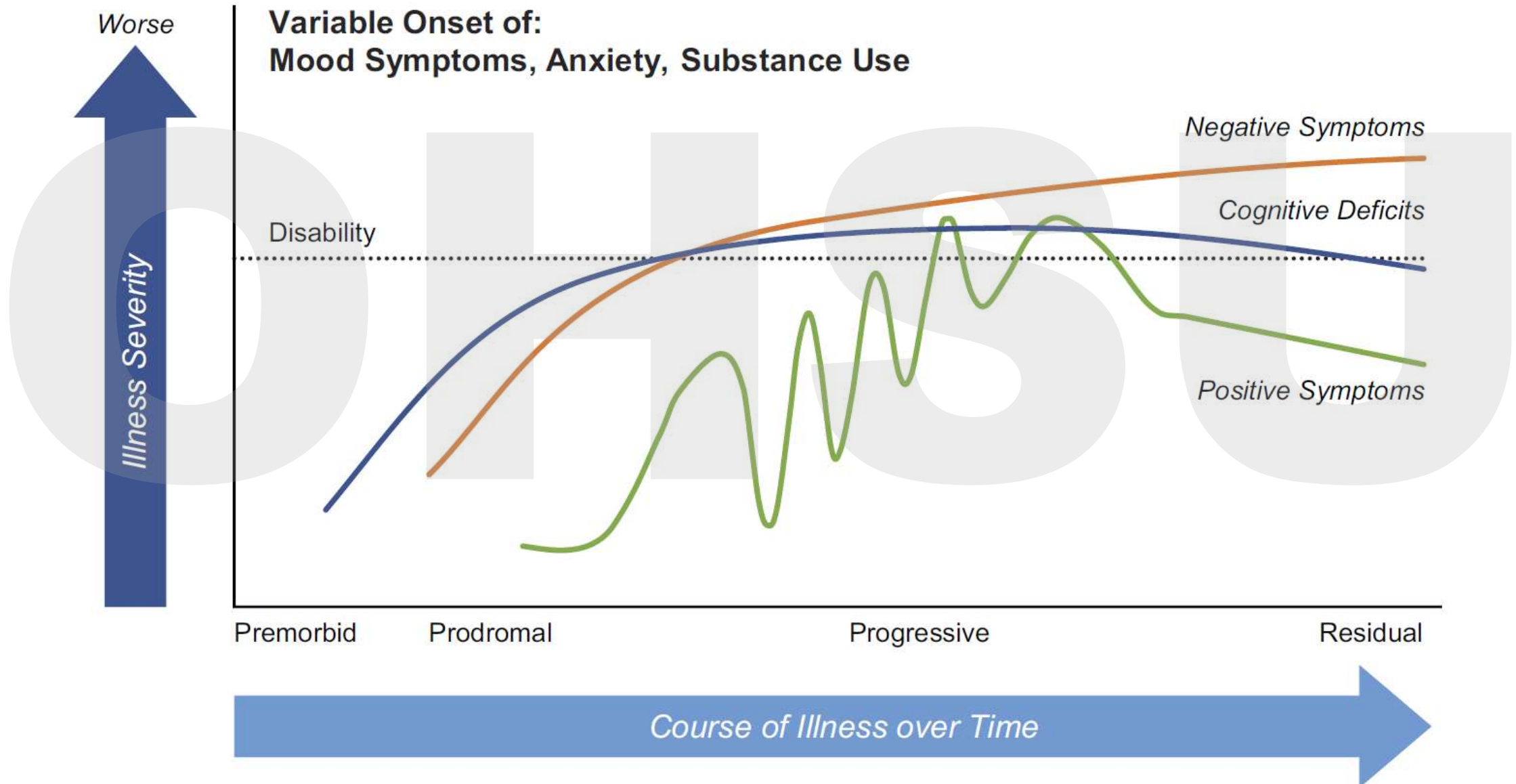
COGNITIVE SYMPTOMS:
IQ, working memory

Functional Impairment in Schizophrenia

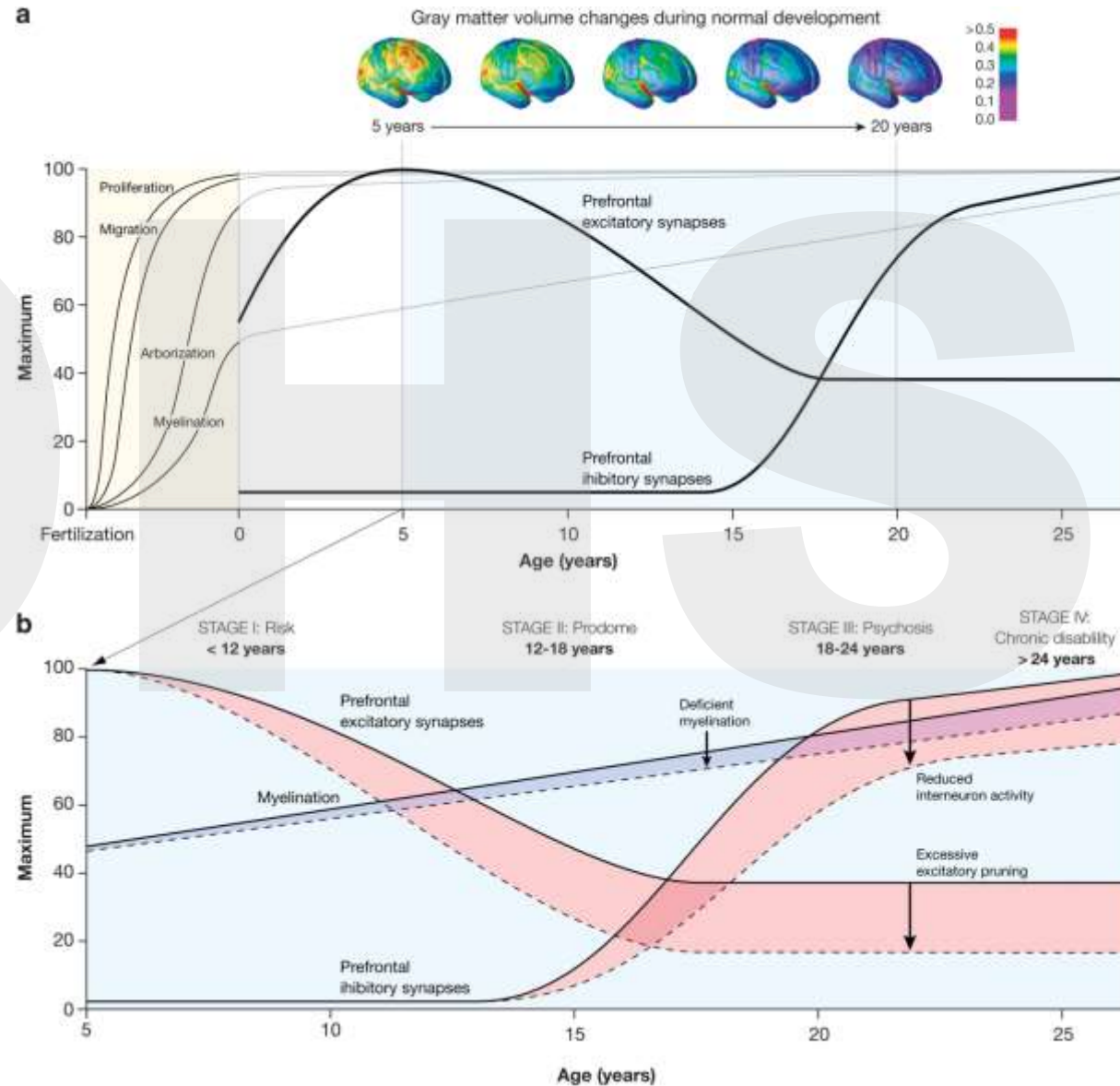


Keefe et al, *Schiz Bull*, 1999; Green et al, *Schiz Bull*, 2000; Brekke et al, *Schiz Bull*, 2007; Green et al, *J Clin Psych*; Torrent et al, *BJP*, 2006; Levy et al, *Dep Res and Tx*, 2012; Bonnín et al, *J Affective Dis*, 2008

Illness Course



Neurodevelopment in SCZ



Positive Symptoms

- Hallucinations: experienced by most patients; auditory (>70%) > visual (~20%) > tactile (~20%) > olfactory (~20%) > gustatory (~5%)
- Delusions: examples – paranoid, grandiose, ideas of reference
- Disorganized speech – (ranging from circumstantiality to tangentiality to word salad)
- Disorganized behavior – ranging from mildly unusual to bizarre

Negative Symptoms

Blunted
Affect

Difficulty expressing emotions

Alogia

Impoverished speech

Avolition

Decreased motivation

Asociality

Decreased desire to engage in social activities

Anhedonia

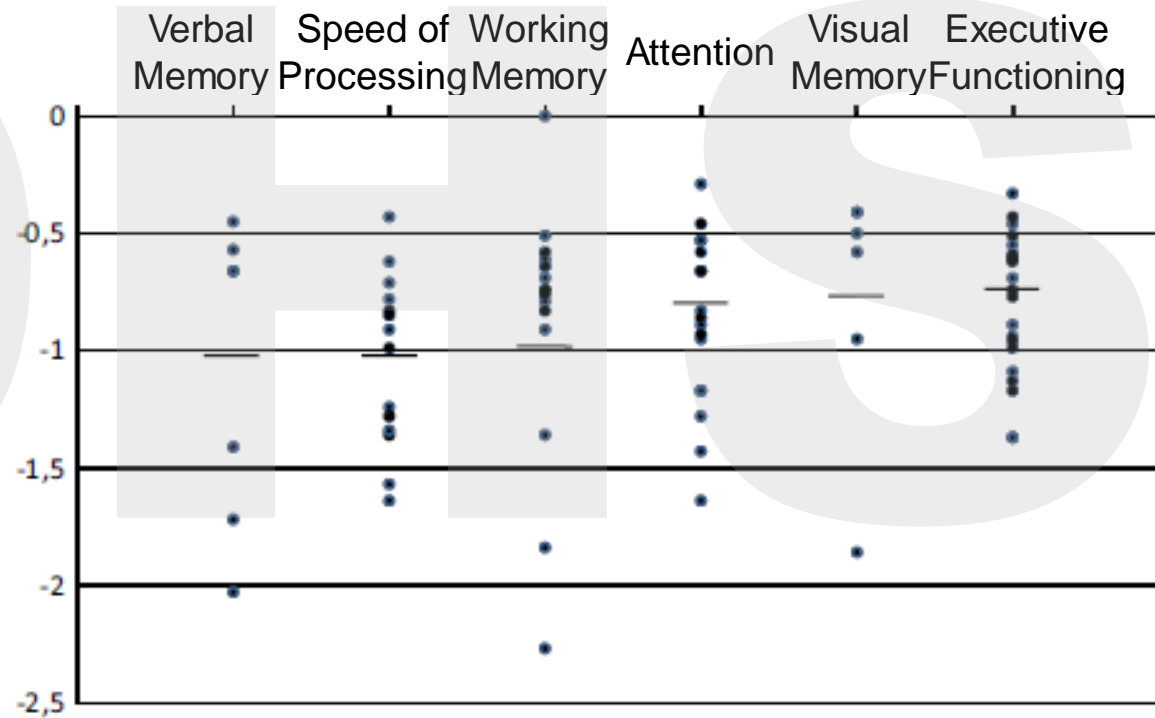
Decreased ability to experience pleasure

Cognitive Deficits

- Patients with schizophrenia are globally cognitively impaired (IQ is 1 SD lower than expected)
- Deficits are present at the onset of illness (or before) and are not due solely to motivational deficits or drug treatment.
- The deficits worsen with age, probably somewhat faster than in normal controls.
- There are marked deficits in executive function and working memory related to pre-frontal cortical dysfunction.

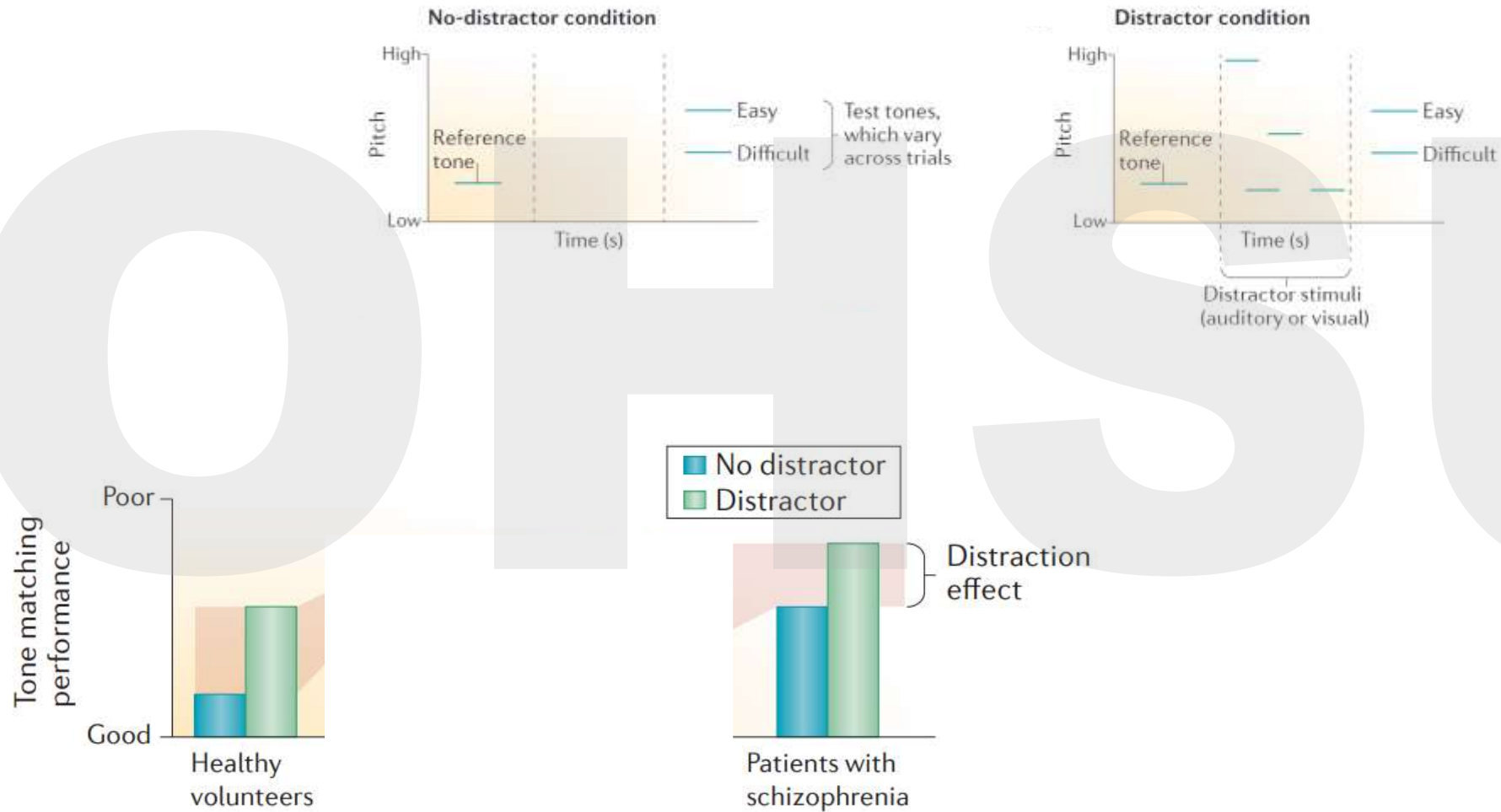
Cognitive Deficits

Cognitive Performance in drug-naïve Schizophrenic subjects

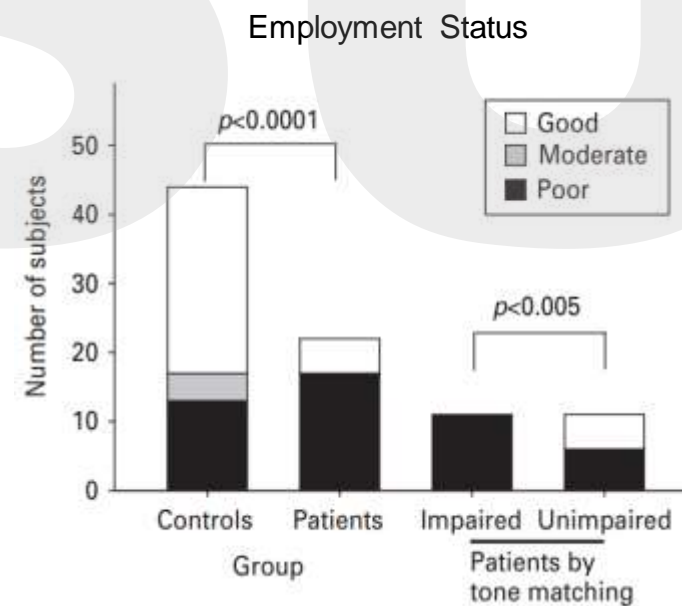
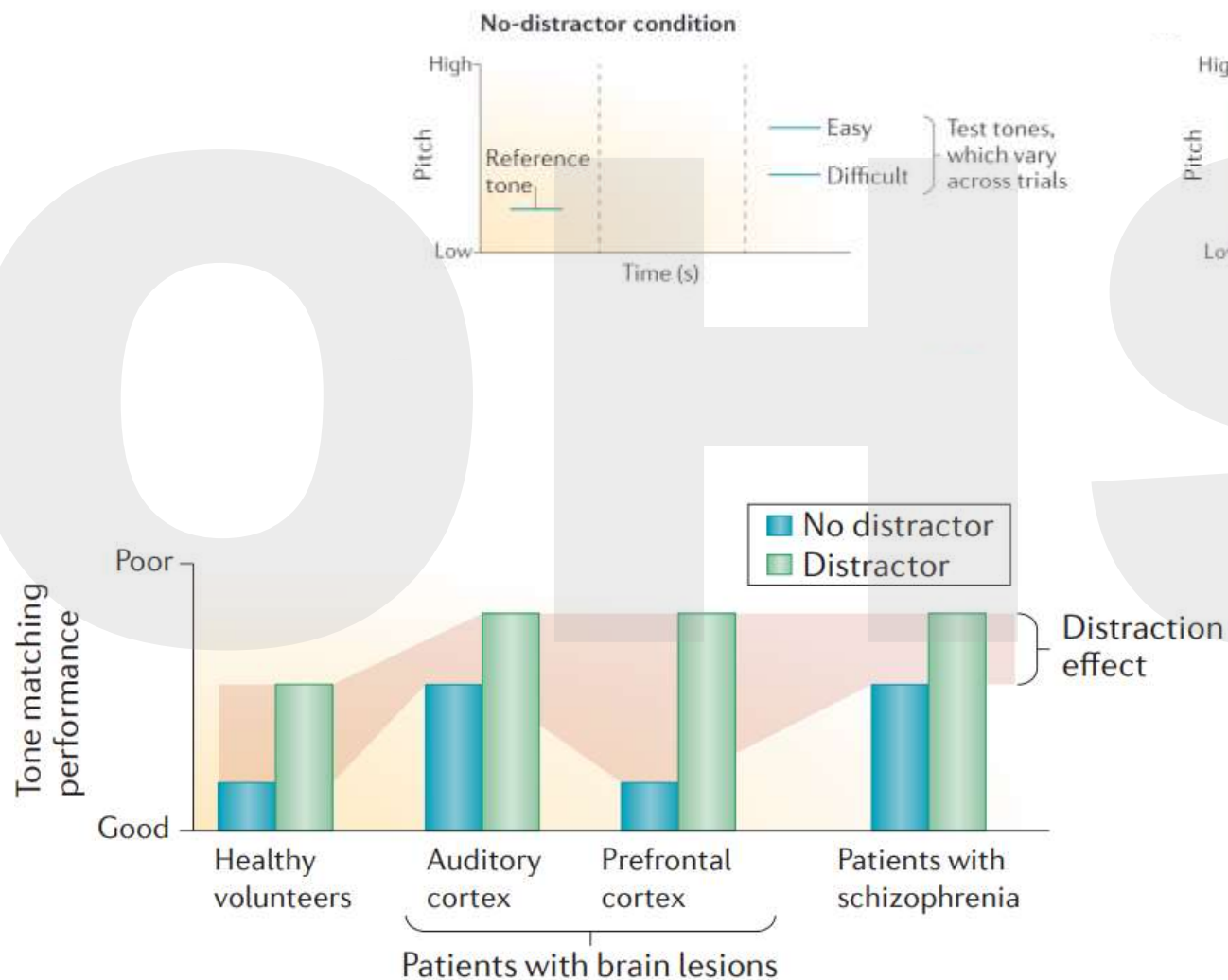


Fatouros-Bergman et al, *Schiz Res*, 2014

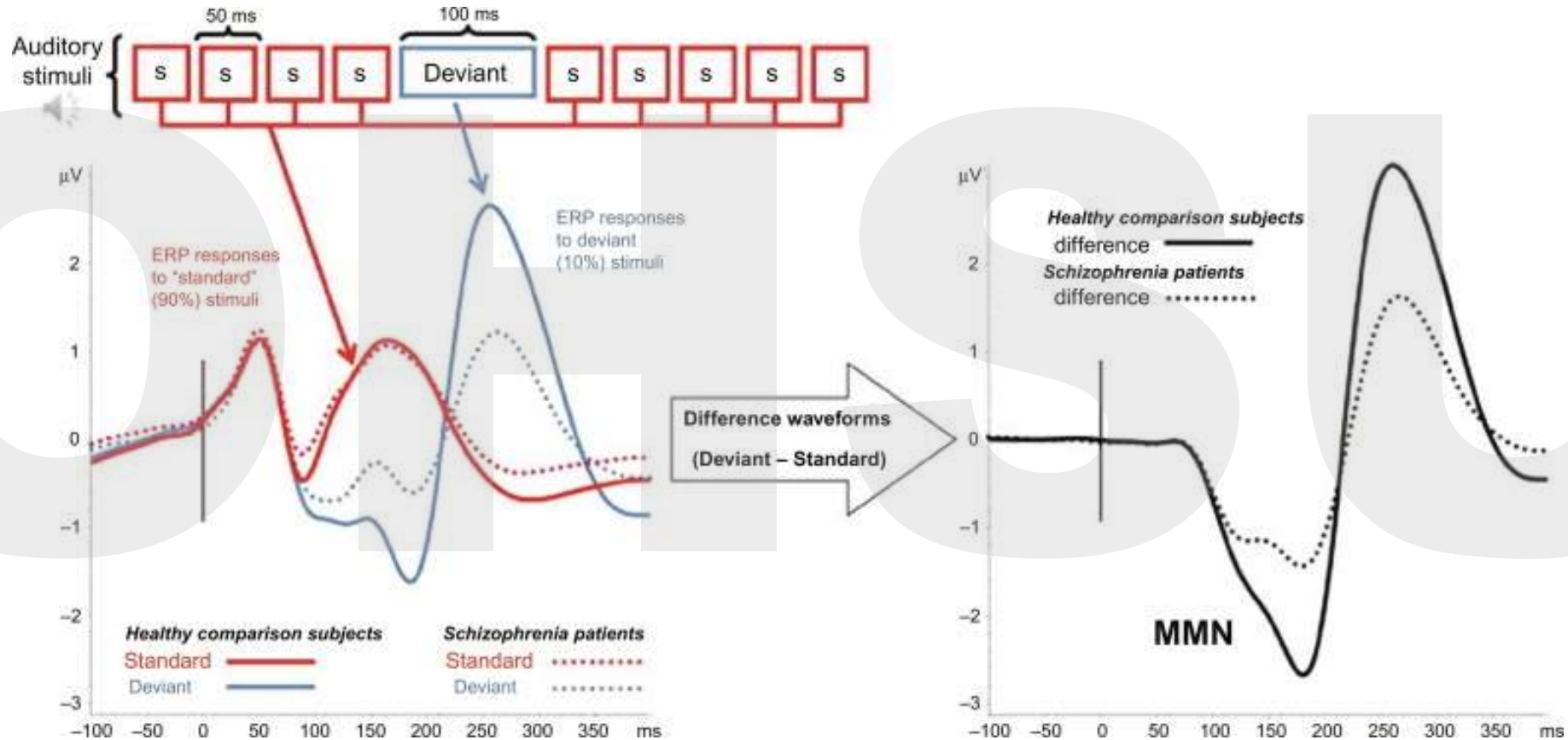
Sensory Dysfunction



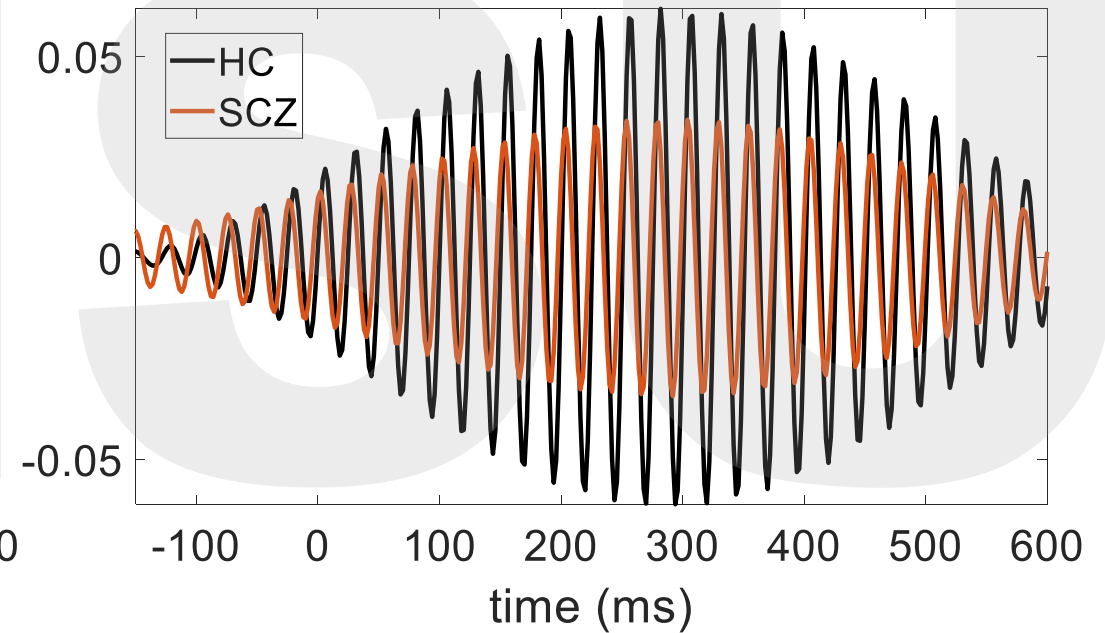
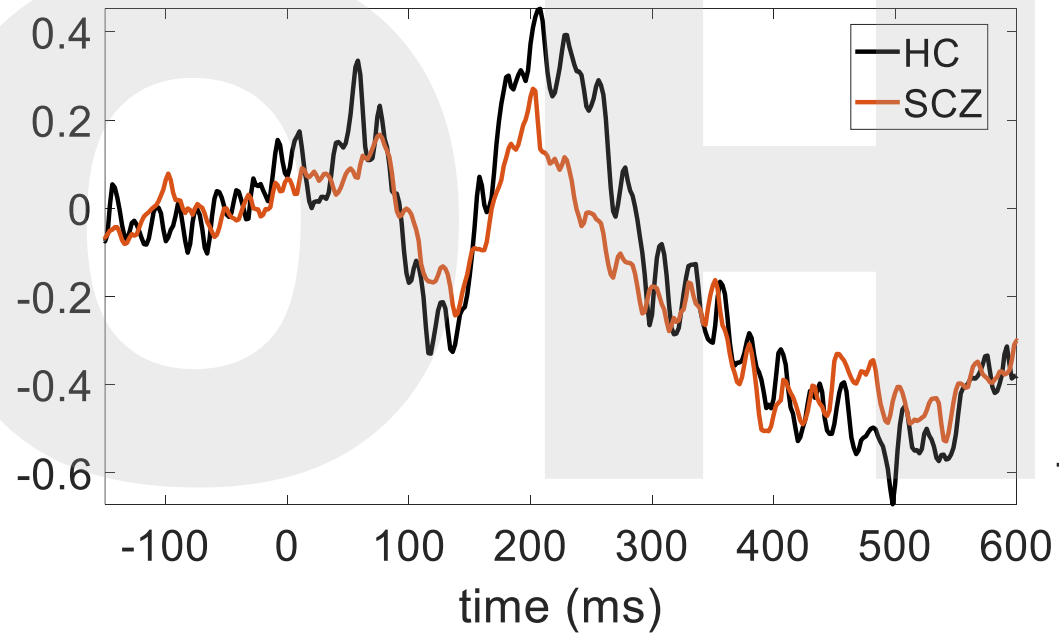
Sensory Dysfunction



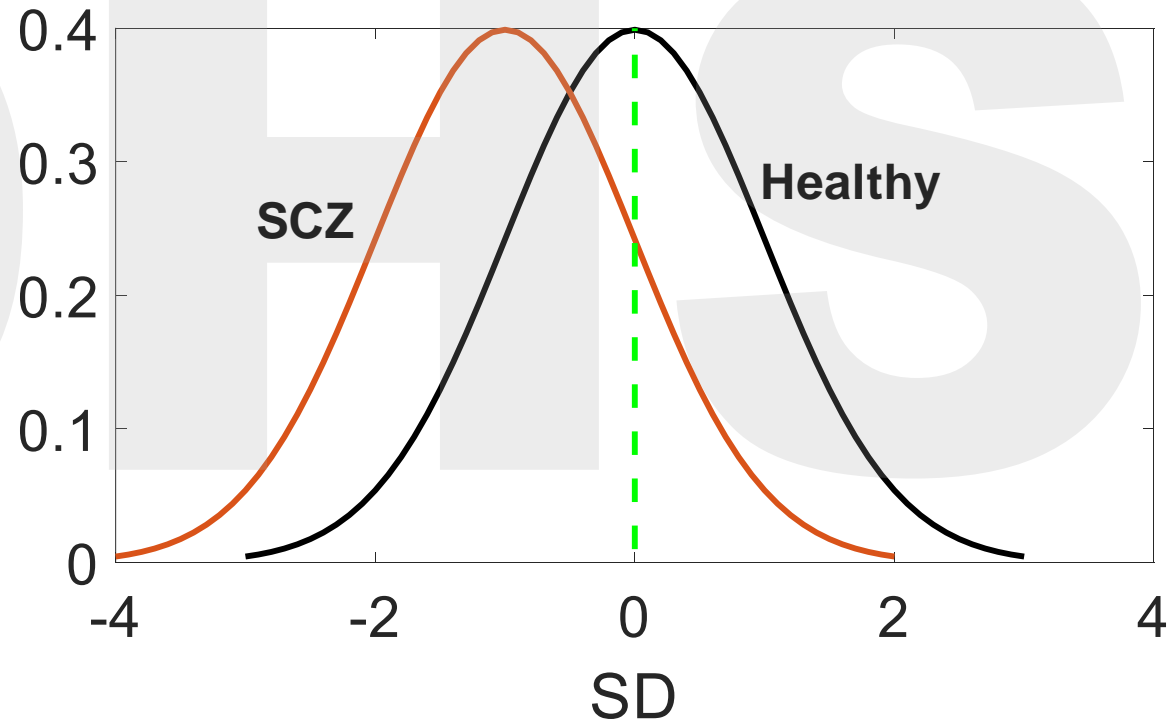
Sensory Dysfunction, Mismatch Negativity



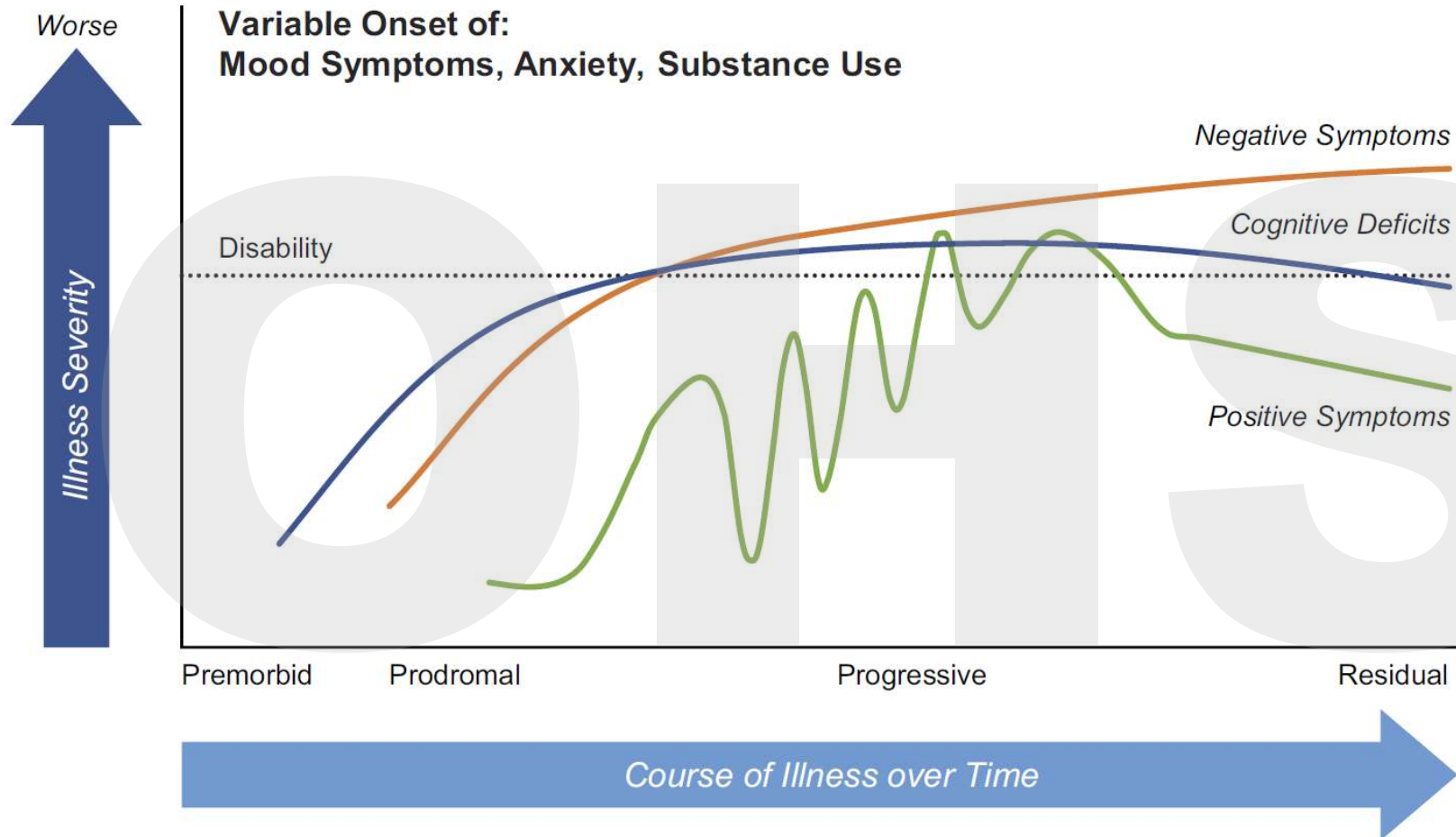
Sensory Dysfunction, Auditory Steady State Response, 40 Hz clicks



Schizophrenia Associated Impairments



Schizophrenia



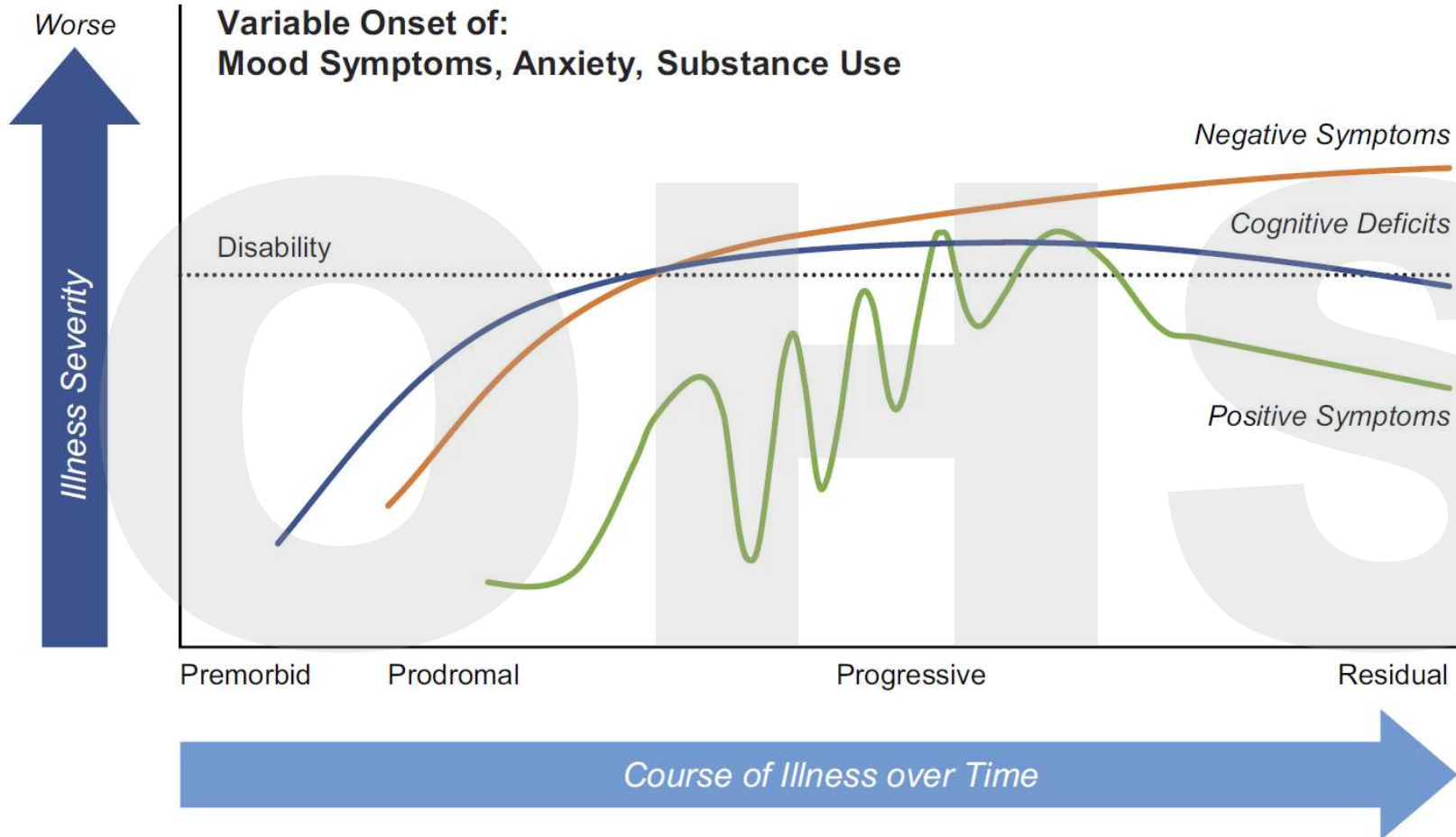
Schizophrenia is neurodegenerative disorder associated with dysfunction of sensory, cognitive, and motivational/reward processing

Dementia Praecox

- Emil Kraepelin, Professor of Psychiatry and Director of the Psychiatric Clinic at Heidelberg University
- In the 6th edition of his textbook of psychiatry published in 1899, he distinguished between two main classes of psychiatric disorders
 - “dementia praecox” – psychiatric disorder with chronic course and progressive cognitive deterioration
 - “manic depressive insanity” – psychiatric disorder with periodic course and no cognitive deterioration



Schizophrenia



What is the pathophysiology that explain these phenomena?

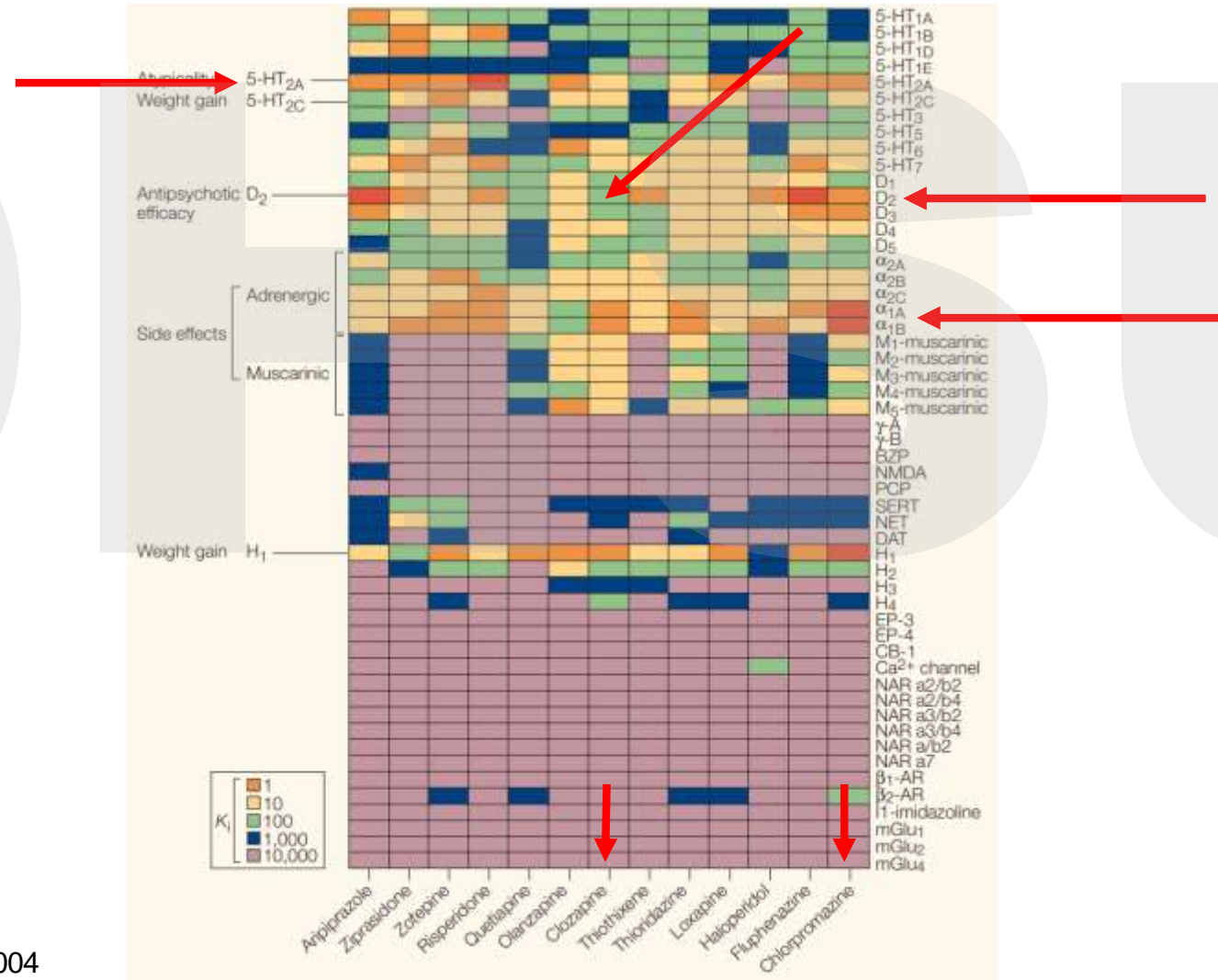
Early Treatments for Schizophrenia

- The first drug (antipsychotic) for schizophrenia:
 - **Chlorpromazine**, initially synthesized in 1950 for use as a component of an anesthesia cocktail to block signs of surgical stress (including lowering blood pressure)
 - A French surgeon experimenting with chlorpromazine noticed that it had a calming effect on patients during the pre-operative period
 - First given to psychiatric patients in 1952 and case reports quickly accumulated attesting to its effectiveness
- Many early antipsychotics were chemical variants of chlorpromazine which were tested by giving high doses to rodents and looking for a characteristic motor immobility that results if the drug has antipsychotic properties

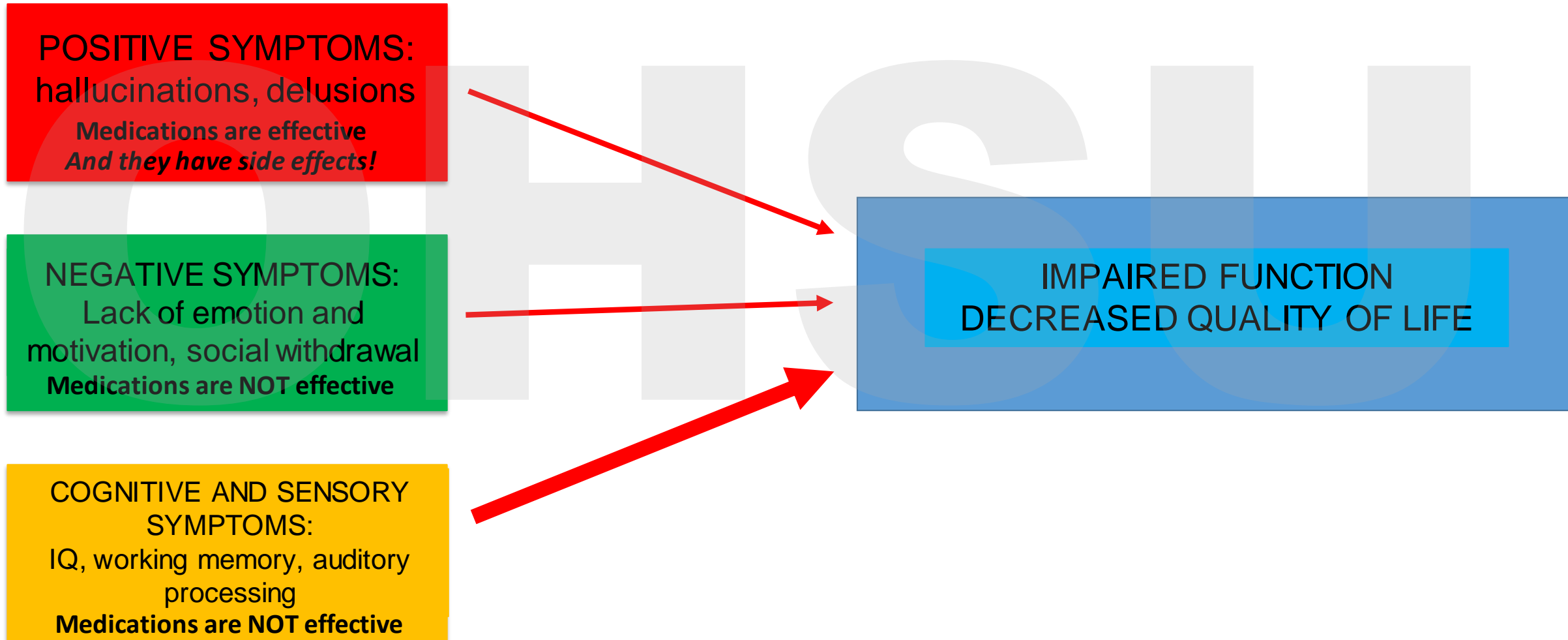
The Dopamine Hypothesis

- It was theorized in 1966 that antipsychotics exert their clinical efficacy by blockade of dopamine receptors
 - “Dopamine Hypothesis”
- In the 1970’s, it was shown that antipsychotics block a specific type of dopamine receptors - D₂ dopamine receptors
- Further drug development was based on beginning by screening promising chemicals for activity at D₂ receptors

A “Receptor-and-Drug-centric” Approach to Schizophrenia and its Treatment

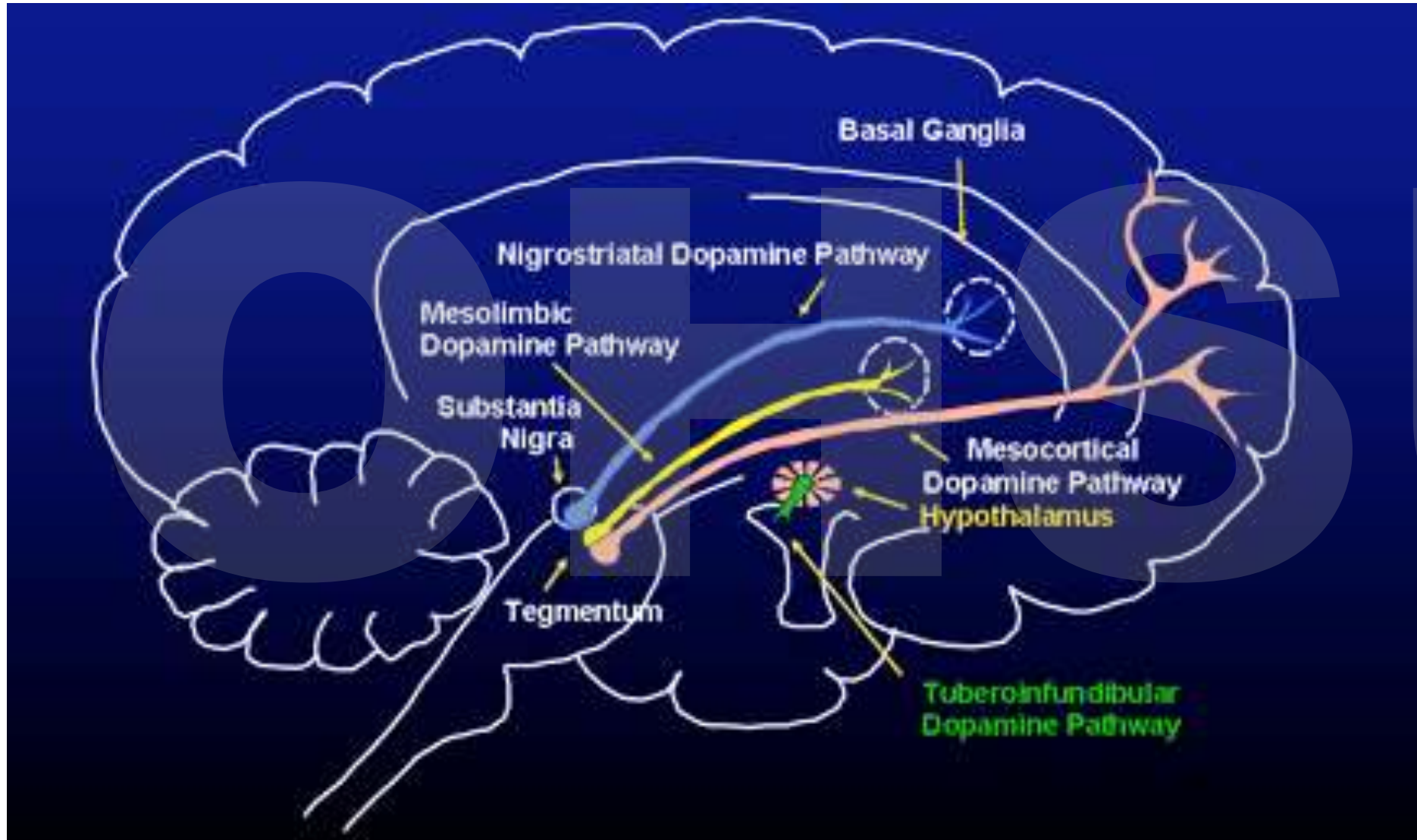


Medication Effectiveness



Keefe et al, *Schiz Bull*, 1999; Green et al, *Schiz Bull*, 2000; Brekke et al, *Schiz Bull*, 2007; Green et al, *J Clin Psych*; Torrent et al, *BJP*, 2006; Levy et al, *Dep Res and Tx*, 2012; Bonnin et al, *J Affective Dis*, 2008

Dopamine Circuits



Antipsychotics

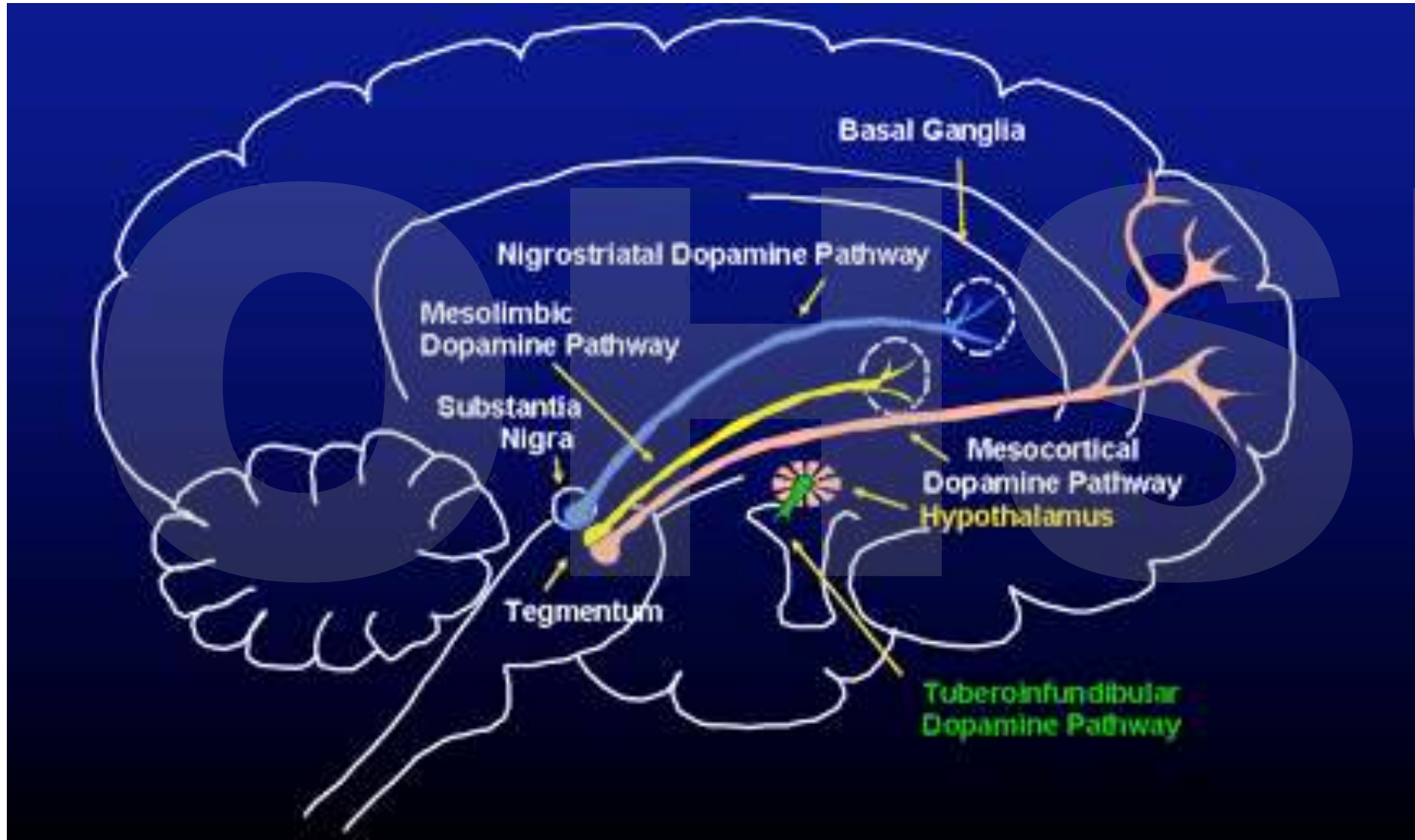
✓ Positive Sx

✗ Negative Sx

✗ Cognitive Sx

+++ Side effects

Dopamine Circuits



Trace amine-associated receptor 1 (TAAR1)

-Discovered at OHSU by David Grandy

-data published last year in NEJM showed that a drug that activates TAAR1 is an effective antipsychotic

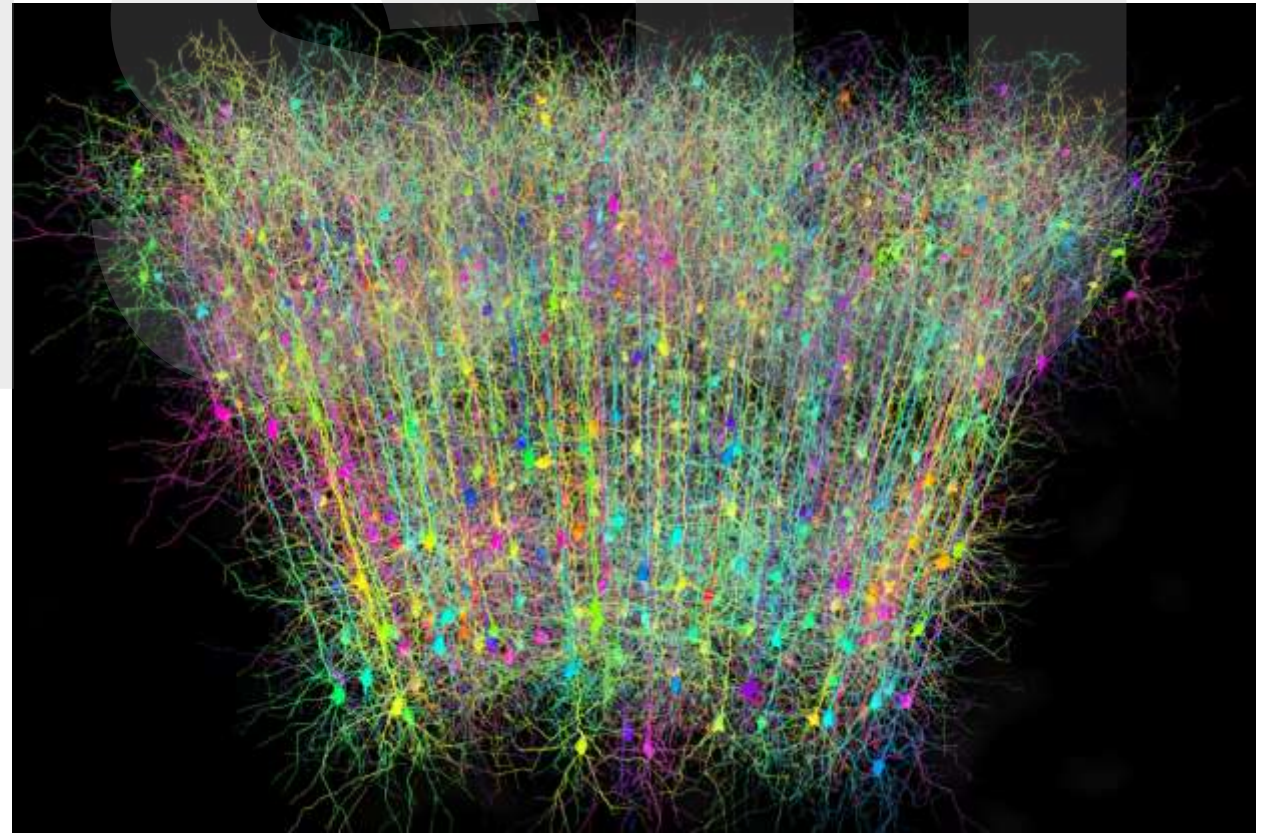
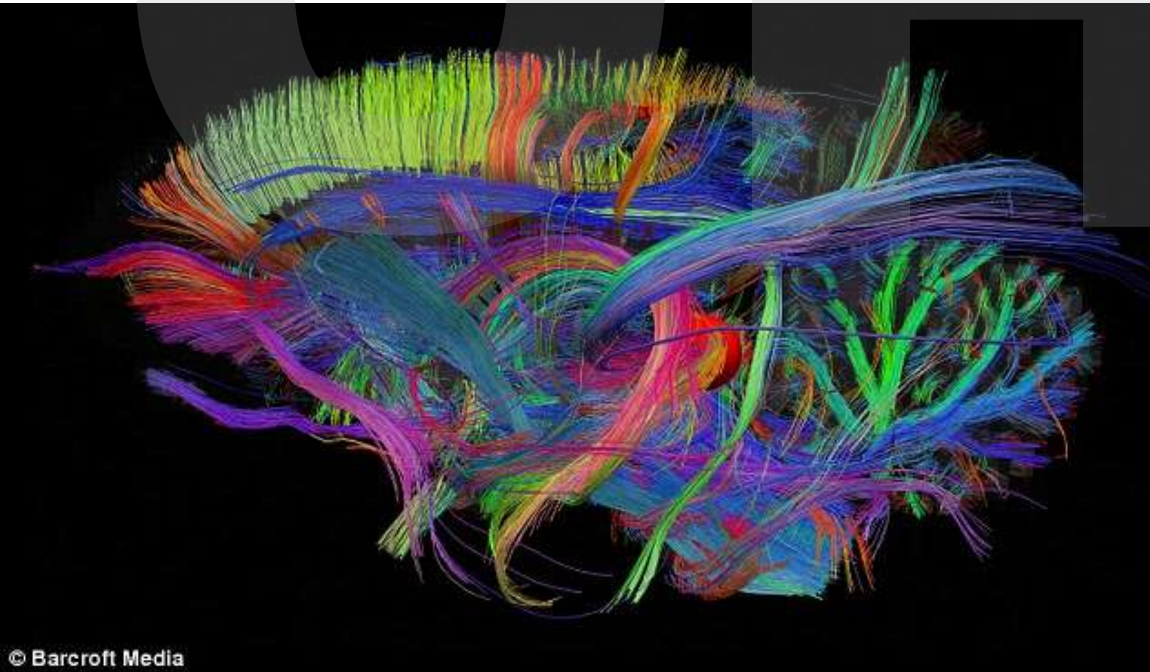
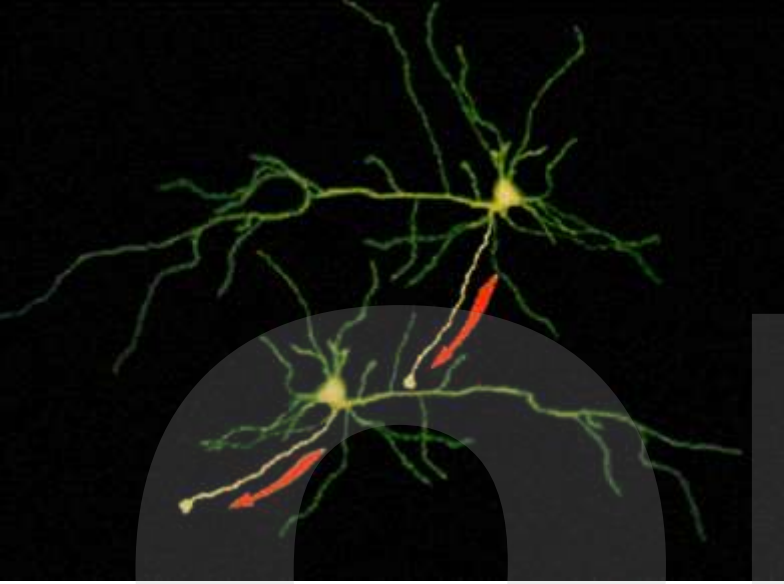
-activating it decreases VTA firing

- ✓ Positive Sx
- ✗ Negative Sx
- ✗ Cognitive Sx
- + Side effects

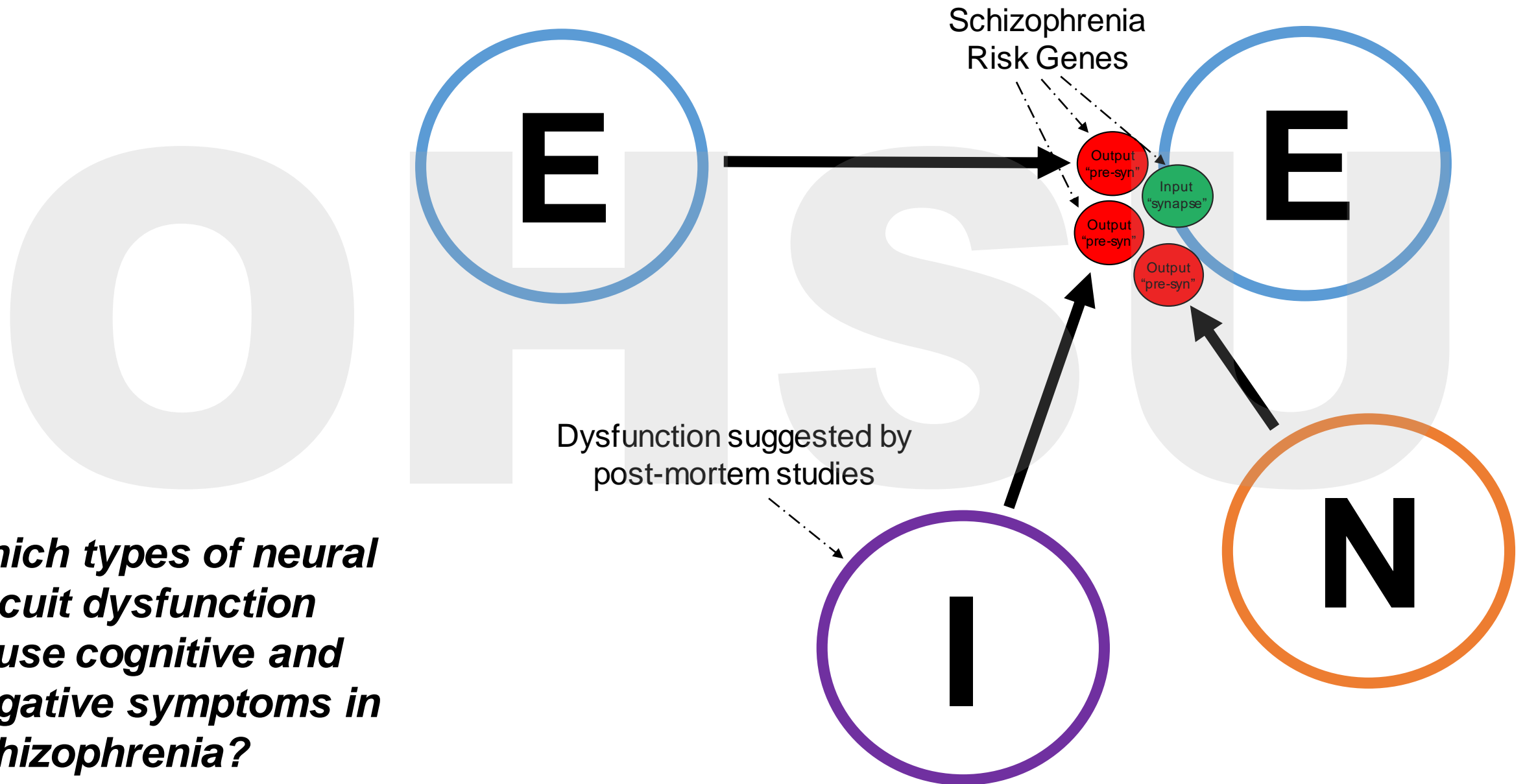
~100,000 dopamine neurons (Nair-Roberts et al, 2008)

Koblan et al, *NEJM*, 2020

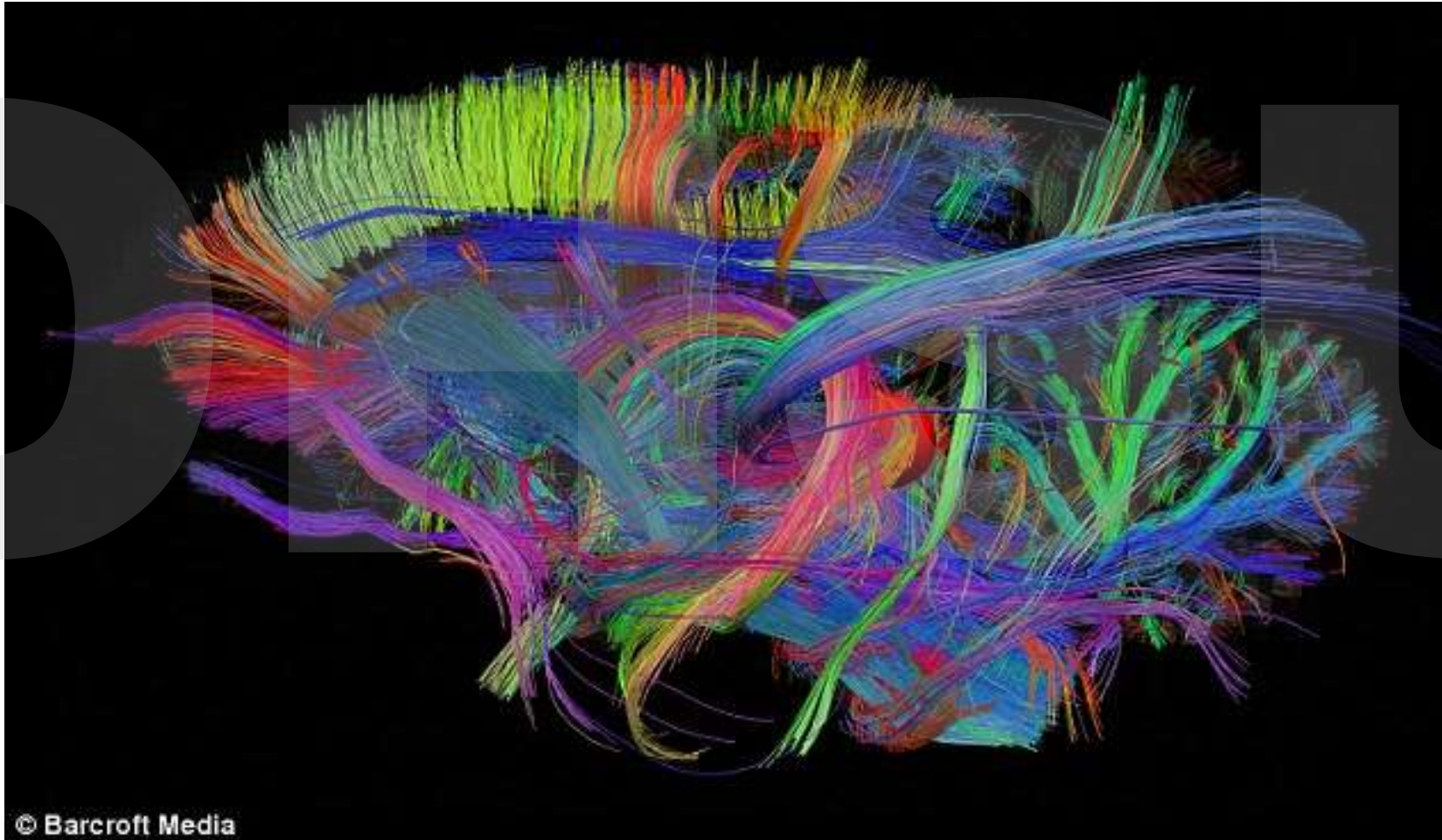
A “Neural Circuits” Approach



Excitatory and Other Circuits

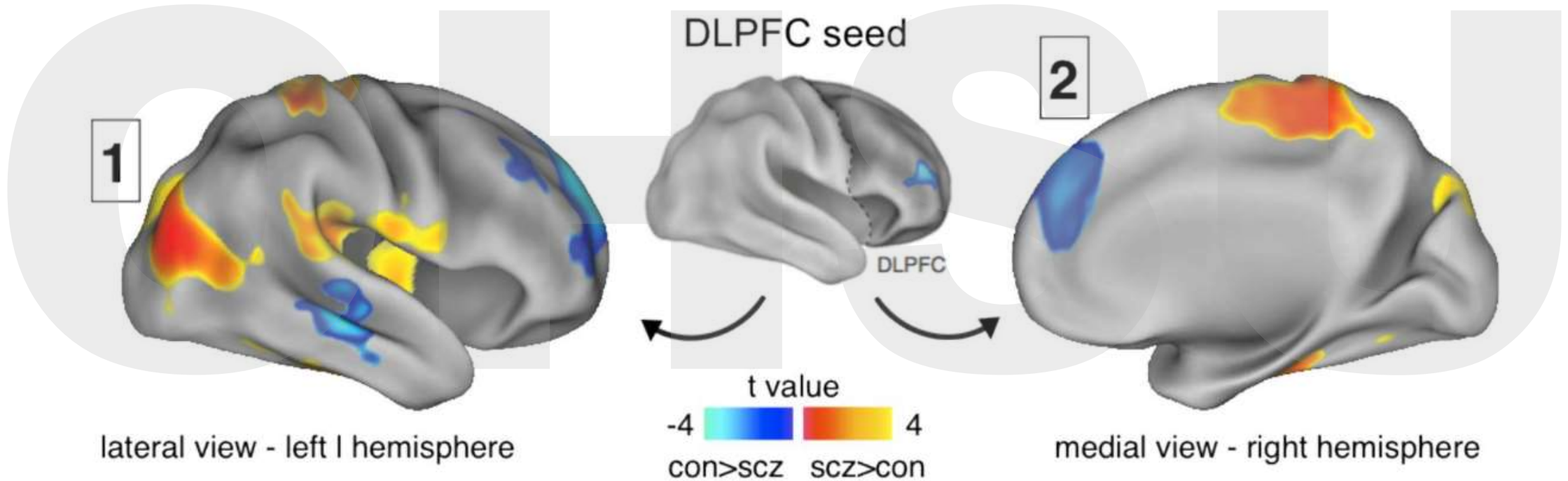


Synaptic Dysfunction Leads to Dysconnectivity



Dysconnectivity in Schizophrenia

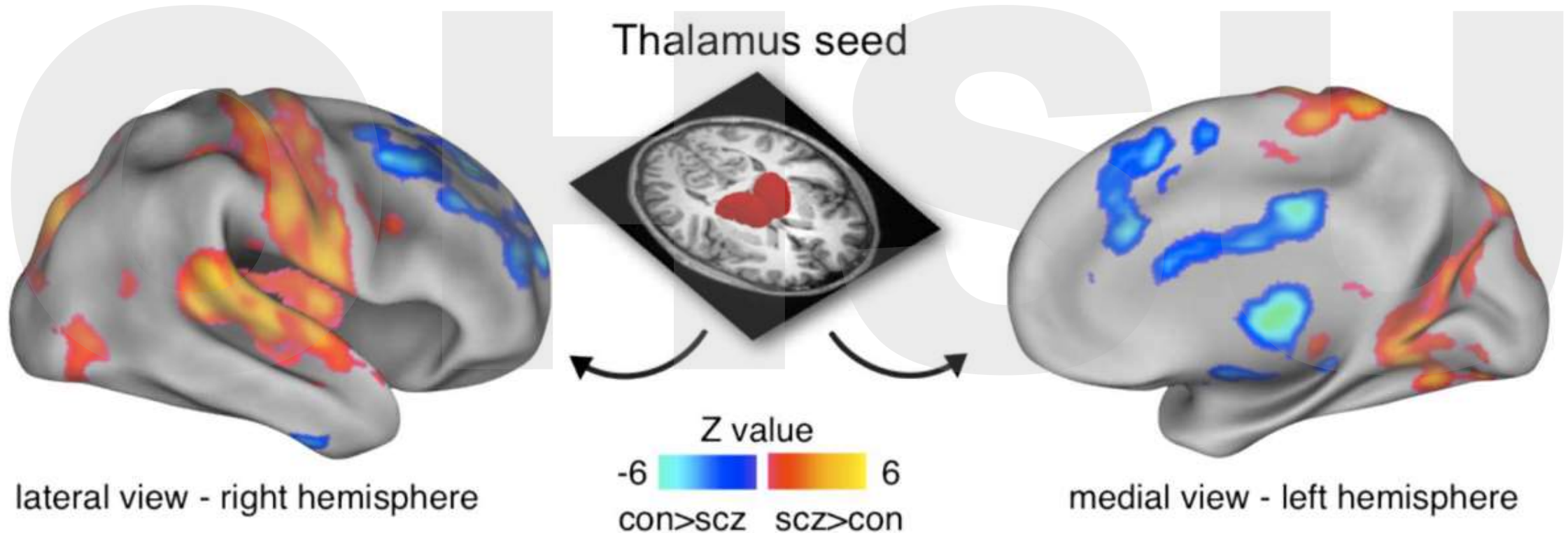
DLPFC Dysconnectivity



Cole et al, *Biol Psychiatry*, 2011

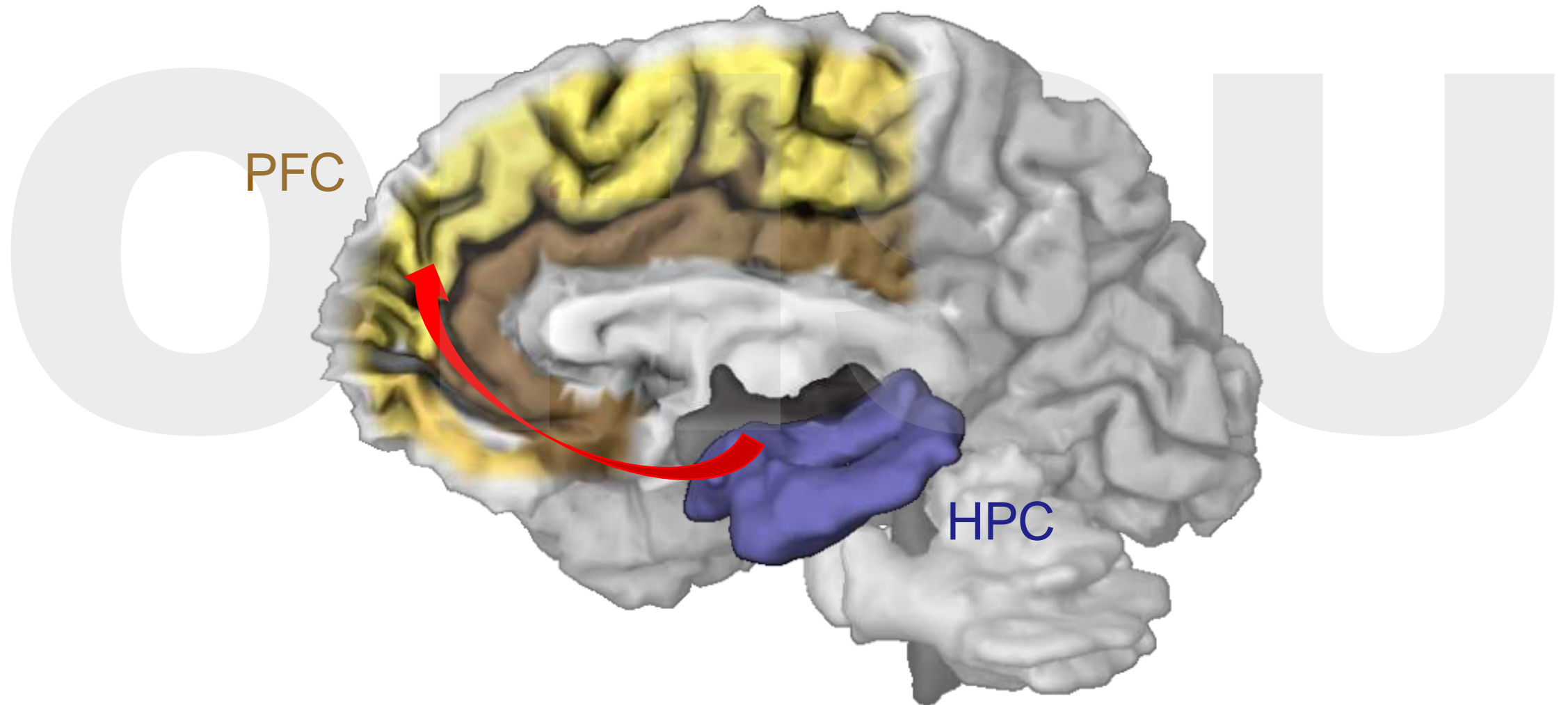
Dysconnectivity in Schizophrenia

Thalamo-cortical Dysconnectivity

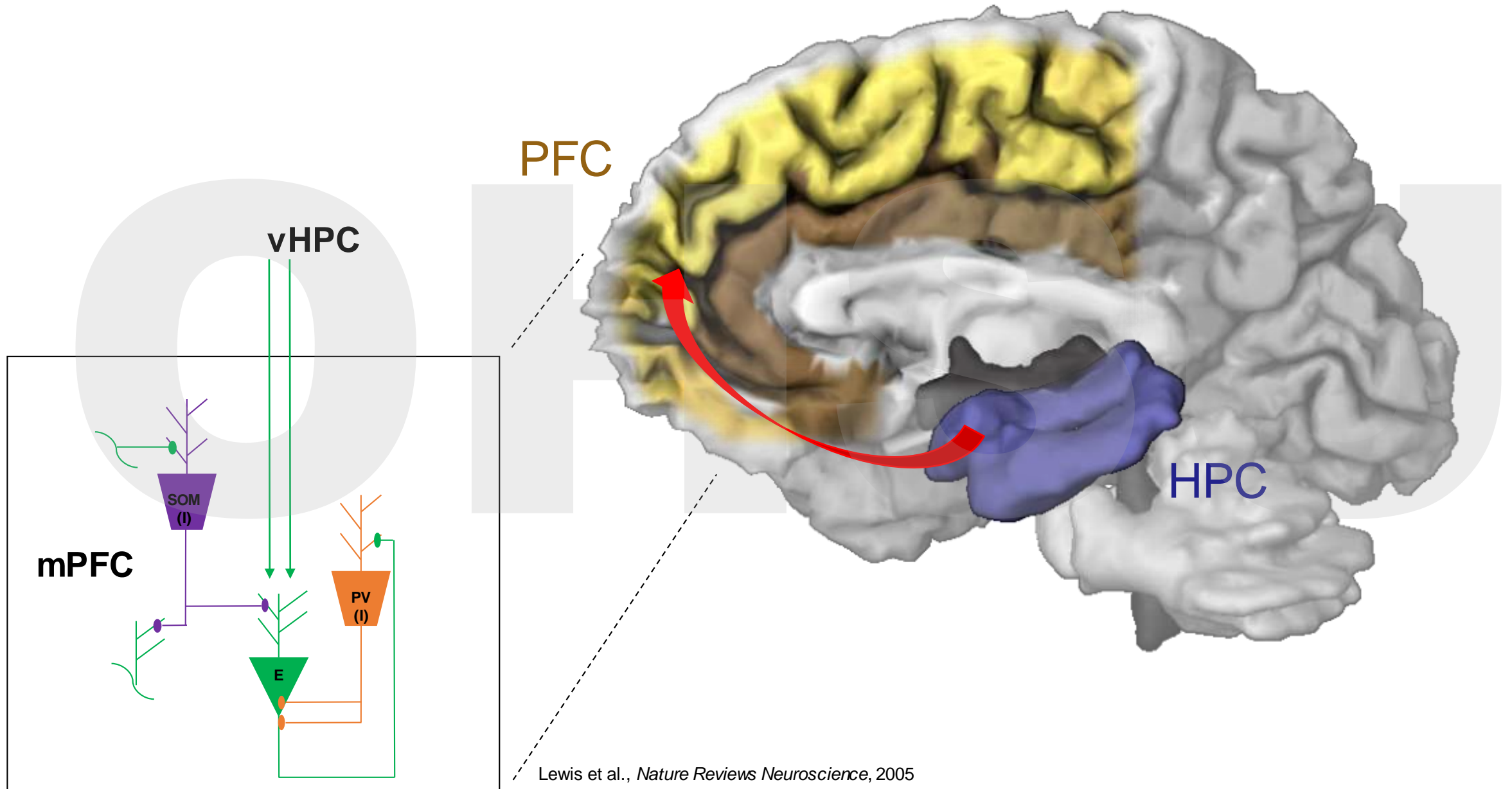


Anticevic et al, *Cereb Cortex*, 2013

Studying Working Memory Circuitry to Understand the Consequence of Dysconnectivity

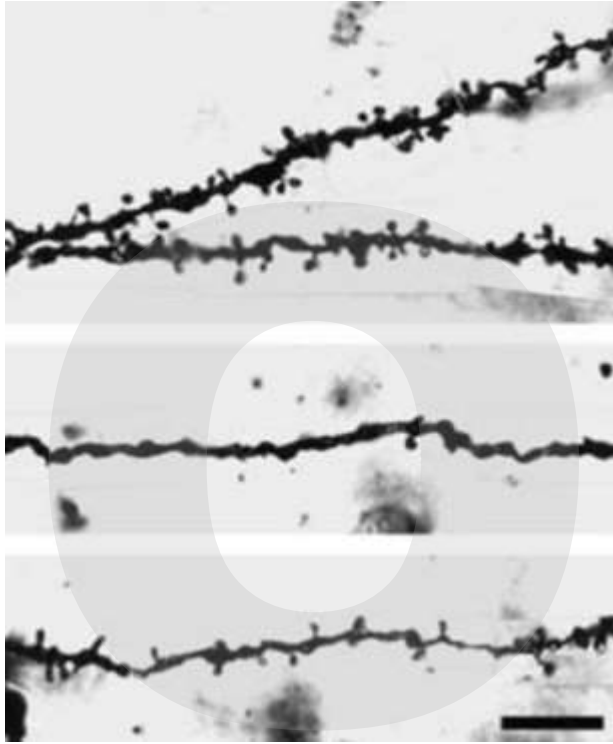


Working Memory Circuitry



Lewis et al., *Nature Reviews Neuroscience*, 2005
Hashimoto et al., *Mol Psych*, 2008

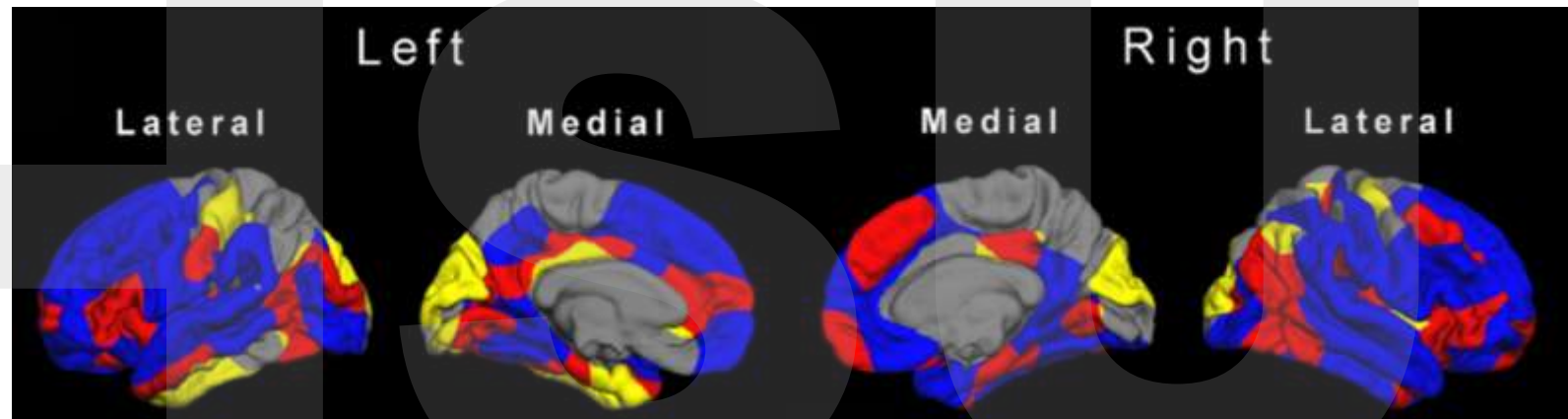
Other Pathology in Schizophrenia



HC

SCZ

SCZ



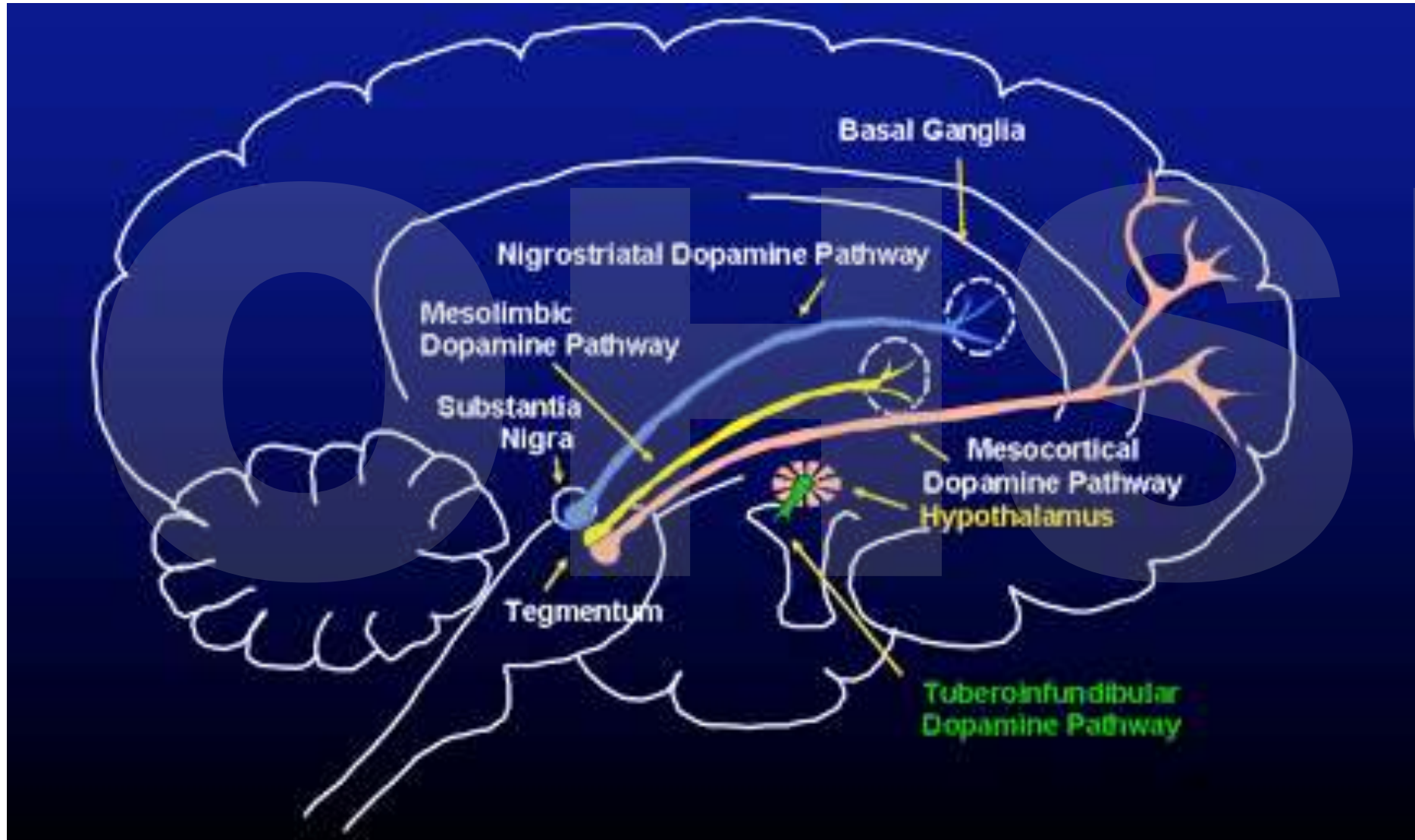
Decreased cortical thickness and/or area (blue = thinning; yellow = decreased area; red = both)

Rimol et al., *Biol Psych*, 2012

Fewer dendritic spines
in DLPFC of
individuals with
schizophrenia

Lewis et al., *Neuropsychopharm*, 2008

Treatment in Schizophrenia – Antipsychotics

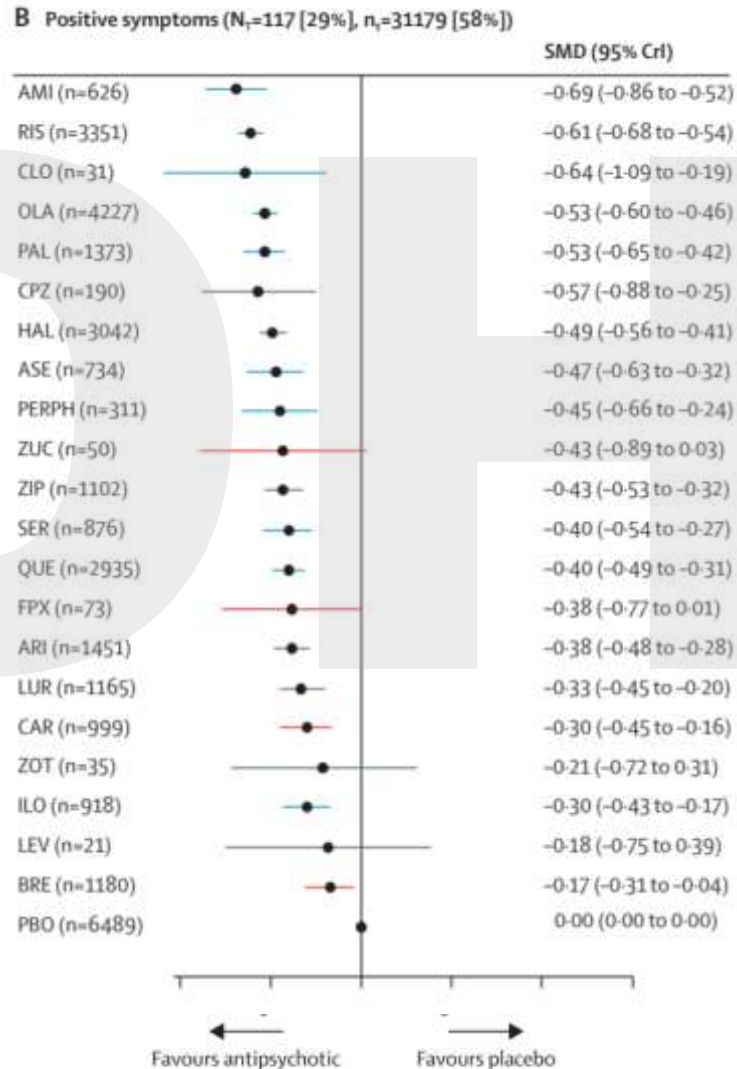


Antipsychotics remain the mainstay of treatment and have improved the course of illness for many affected individuals

A Few Antipsychotic Pearls

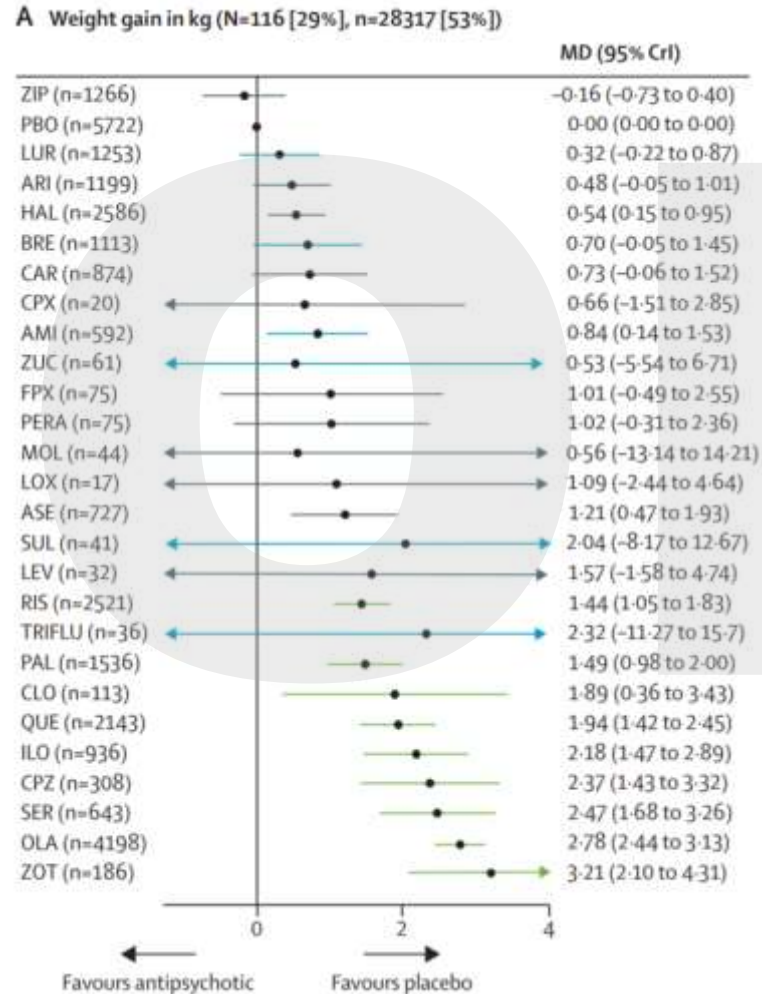
- Smoking cessation – smoking induces CYP1A2
 - When an individual on olanzapine or clozapine stops smoking, medication blood level can increase substantially
 - When smoking resumes (for example, after a psychiatric hospitalization), medication blood level can drop and symptoms may rapidly recur
- Most antipsychotics are highly protein-bound
- Typically hepatic metabolism via CYP1A2, CYP3A4, and/or CYP2D6

Antipsychotic Effectiveness and Side Effects



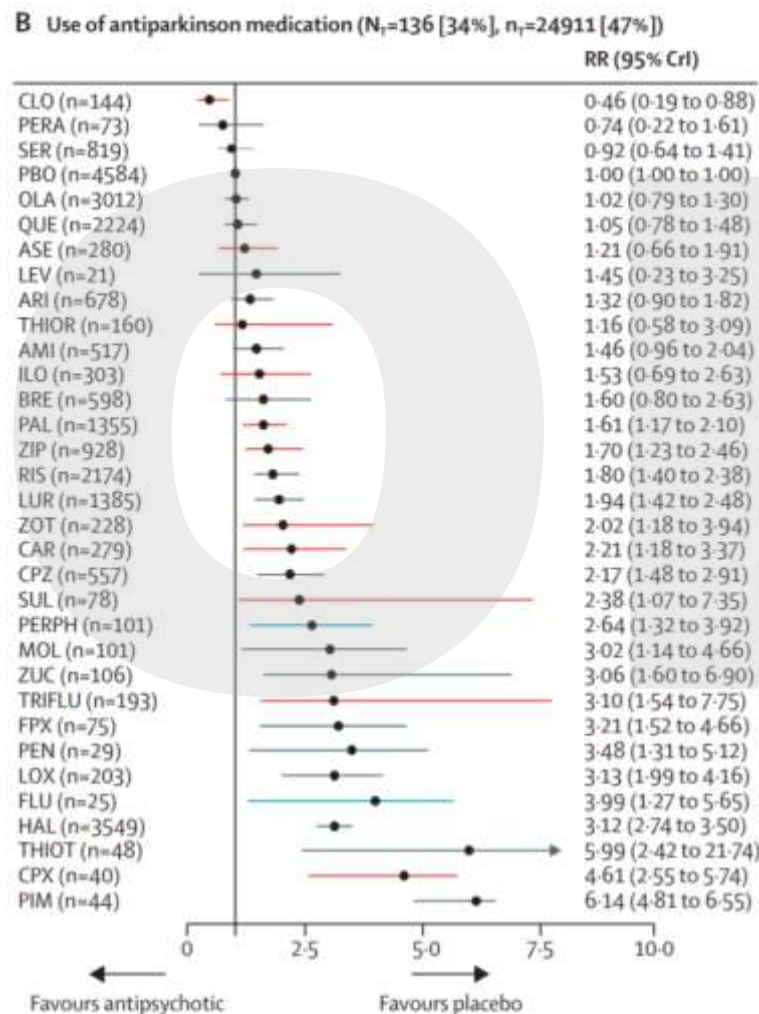
Most antipsychotics show similar effectiveness, but there may be some differences

Antipsychotic Effectiveness and Side Effects



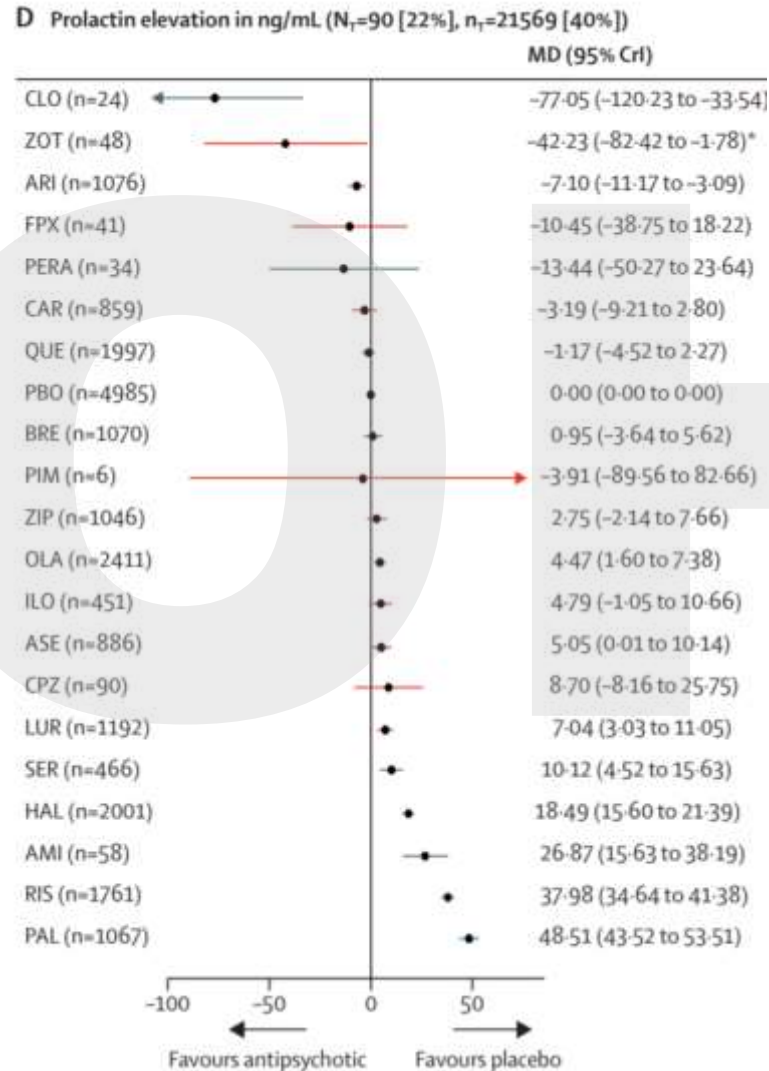
Antipsychotics have unique side effect profiles

Antipsychotic Effectiveness and Side Effects



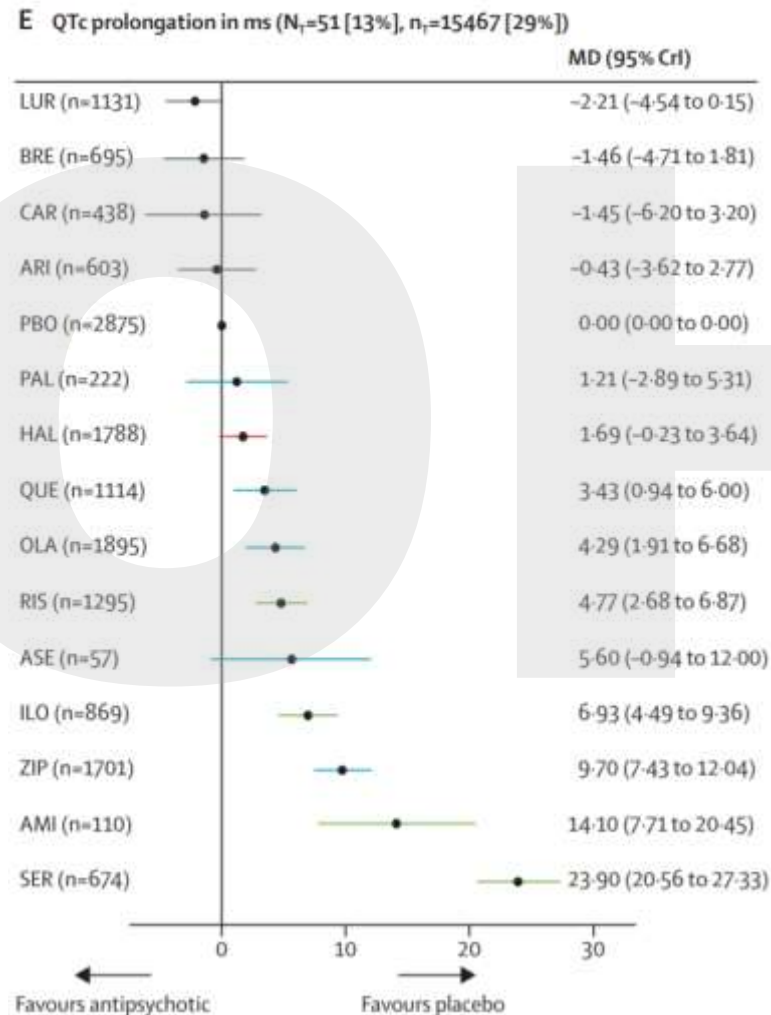
Antipsychotics have unique side effect profiles

Antipsychotic Effectiveness and Side Effects



Antipsychotics have unique side effect profiles

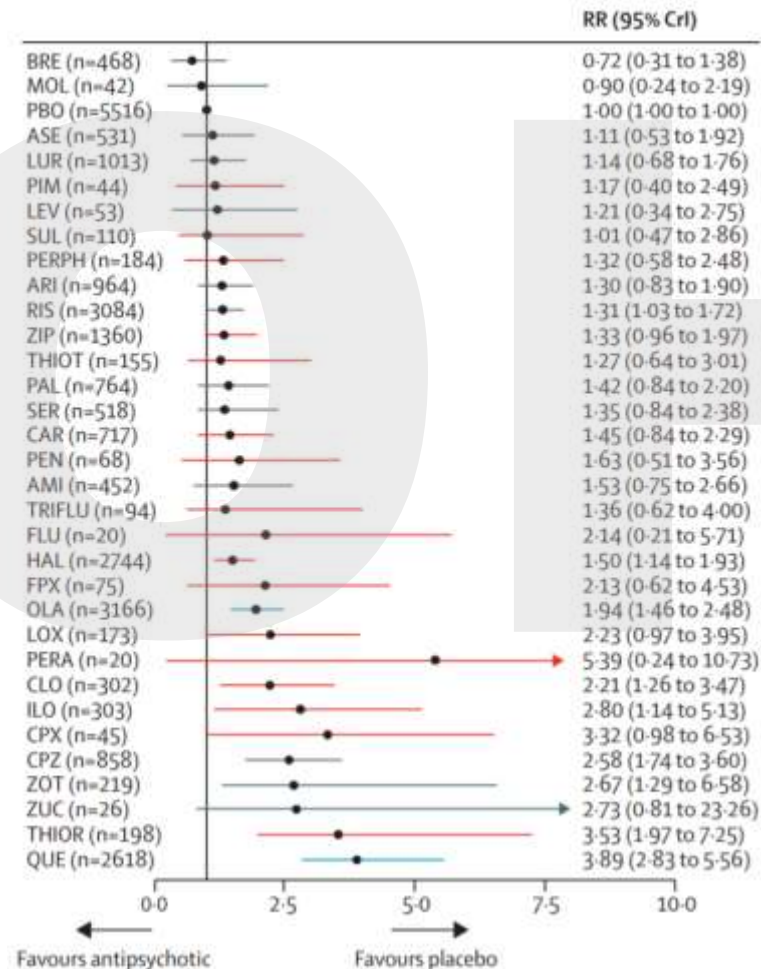
Antipsychotic Effectiveness and Side Effects



Antipsychotics have
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Antipsychotic Effectiveness and Side Effects

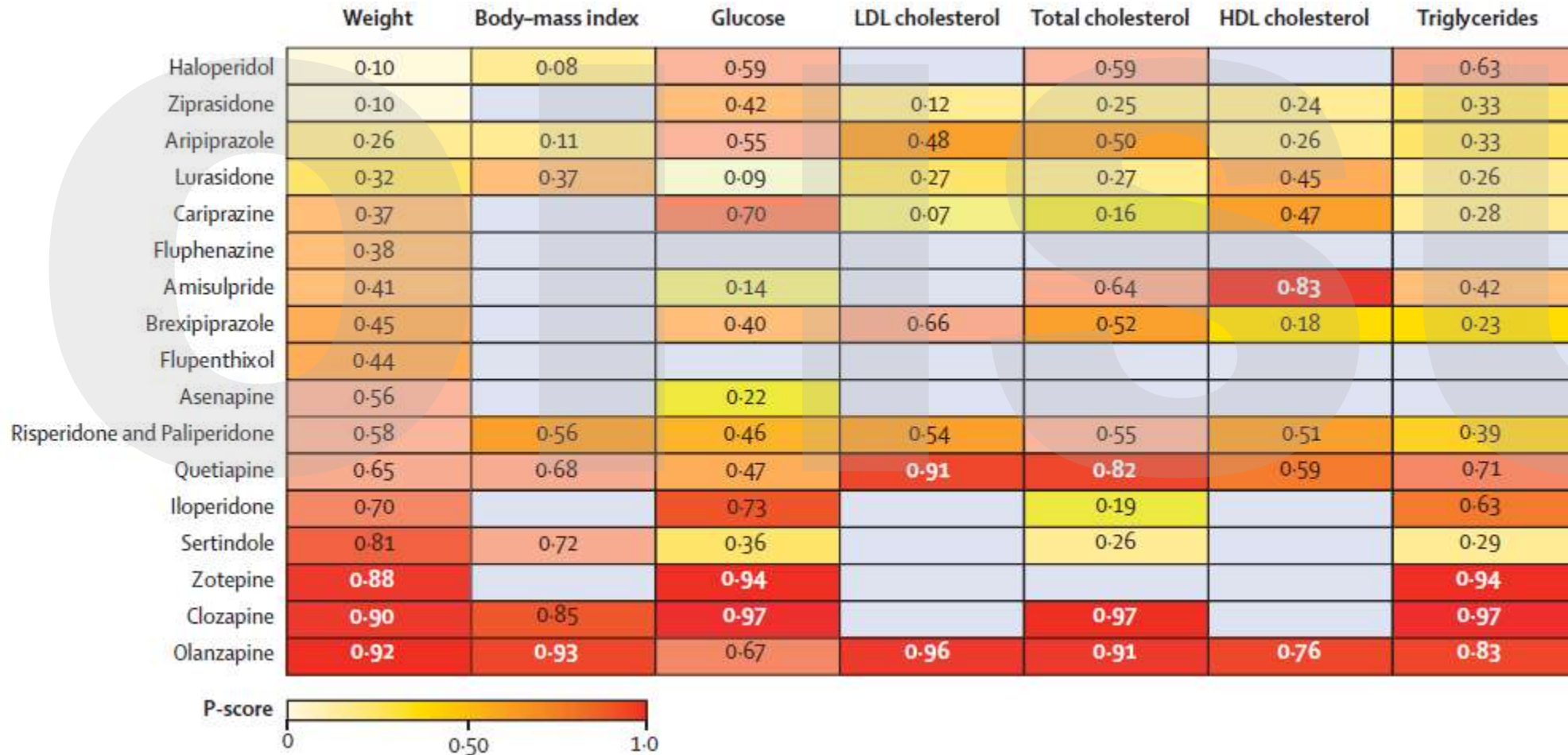
G At least one anticholinergic side-effect (N_t=134 [33%], n_r=26904 [50%])



Antipsychotics have unique side effect profiles

A Few Antipsychotic Pearls

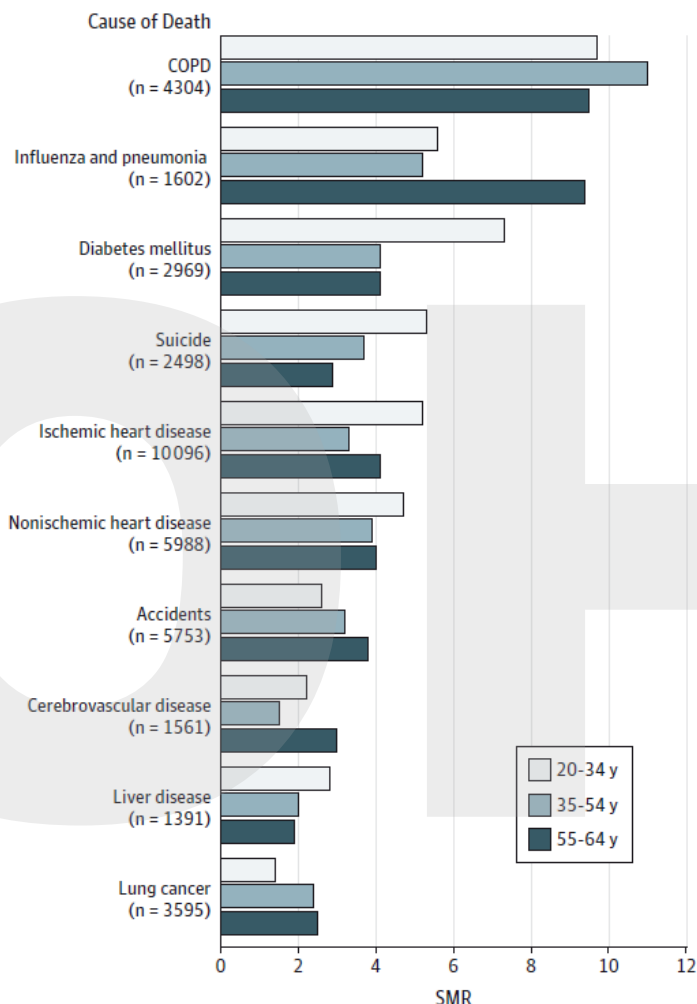
- Antipsychotics increase the risk of metabolic syndrome



Clozapine

- Superior to other antipsychotics for treatment-resistant schizophrenia
- Can cause fatal agranulocytosis so requires regular CBC/DIFF monitoring for ANC (see algorithm) and that data must be entered into an online database (clozapine REMS program)
- Other side effects: acute myocarditis, weight gain/metabolic syndrome, anticholinergic side effects
- Can be titrated to symptom control using blood level as a guide

Co-morbidity Burden



Unnatural deaths

Suicide

Homicide
assault

Accidents

Poisoning

Nonpoisoning

Undetermined
intent and other

3.9 (3.8-4.0)

3.9 (3.7-4.1)

2.3 (2.0-2.7)

3.8 (3.7-3.9)

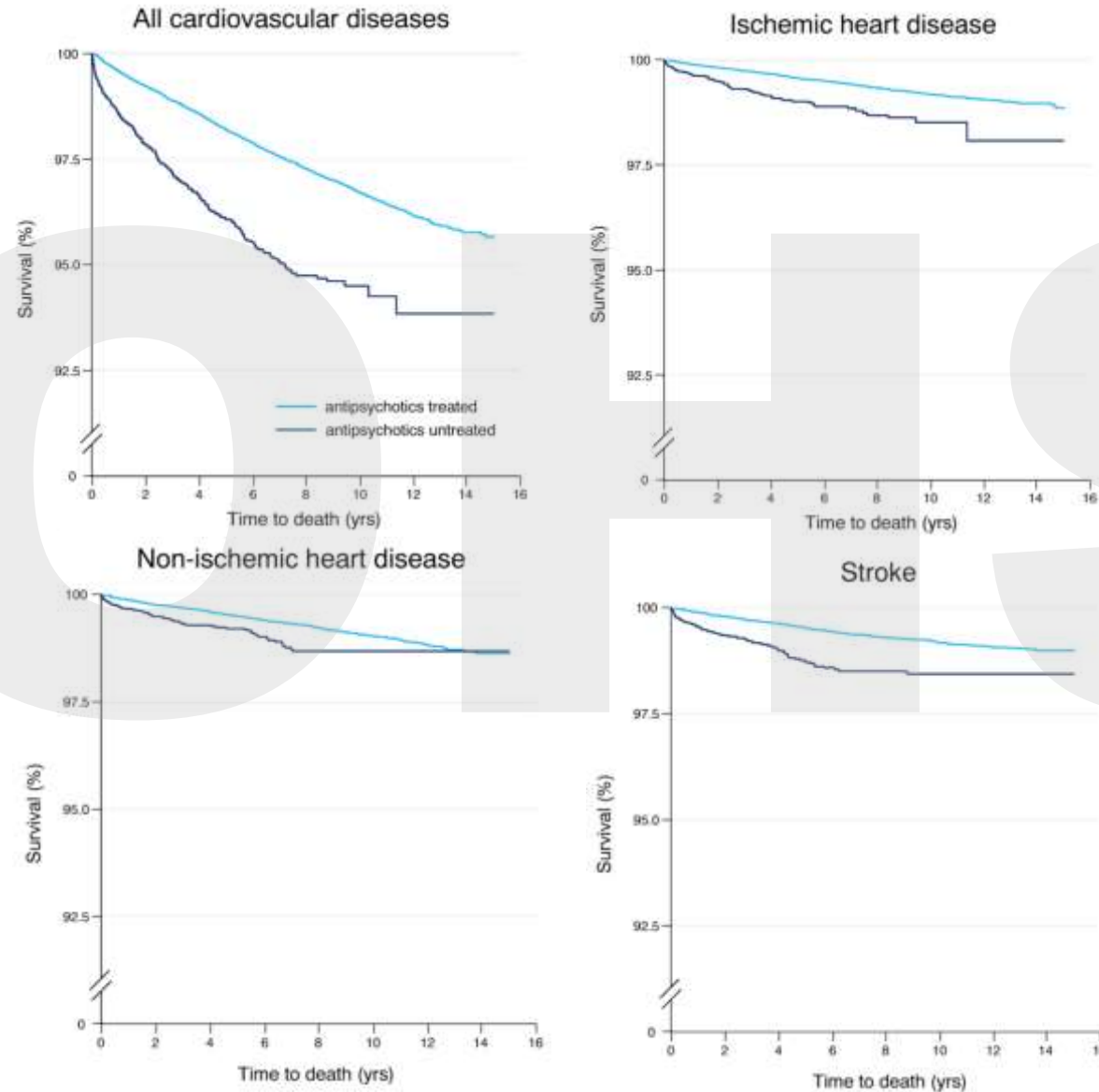
5.8 (5.5-6.0)

2.8 (2.6-2.9)

7.7 (7.1-8.3)

Cause of Death	20-34 y		35-54 y		55-64 y	
	Mortality Rate	SMR (95% CI)	Mortality Rate	SMR (95% CI)	Mortality Rate	SMR (95% CI)
Sepsis	2.8	3.2 (2.0-4.4)	16.1	3.5 (3.2-3.8)	83.7	5.8 (5.4-6.2)

Effect of Antipsychotics on Co-morbidity Burden



Despite their substantial side effect burden, the evidence to date shows that antipsychotics improve mortality in schizophrenia

Telehealth and schizophrenia

- Studies show telephone, internet, and video treatment is feasible for patients with schizophrenia
- Studies describe high acceptance by schizophrenia individuals
- Preliminary evidence suggests that telehealth may improve patient outcomes

Take Home Points

- Psychosis is only one of the prominent manifestations of schizophrenia and not the most disabling
- Schizophrenia is associated with a characteristic course of illness that includes deterioration in mental and psychosocial functioning
- Antipsychotics are only partially effective because they target one aspect of neural circuit dysfunction but not others
- Antipsychotics differ in their propensities for “on-target” and “off-target” side effects
- Schizophrenia is associated with substantial medical co-morbidity

OHHSU

Thank You!