Psychotic Disorders

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Nasser is a 28 year-old single male

Emergency room by his family

gradual changes in his behavior 9 months

Eat only canned food but not cooked food made by his family

agitated

He talks to himself and stares occasionally on the roof of his room.

Afraid of being poisoned

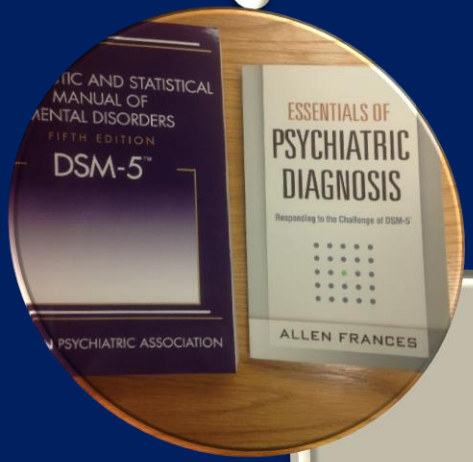
Had two brief psychiatric hospitalizations in last 3 years.

Precipitated by anger at his neighbor and voices commenting about his behavior

Healthy child

Bed wetter

Slower to develop than his sibling

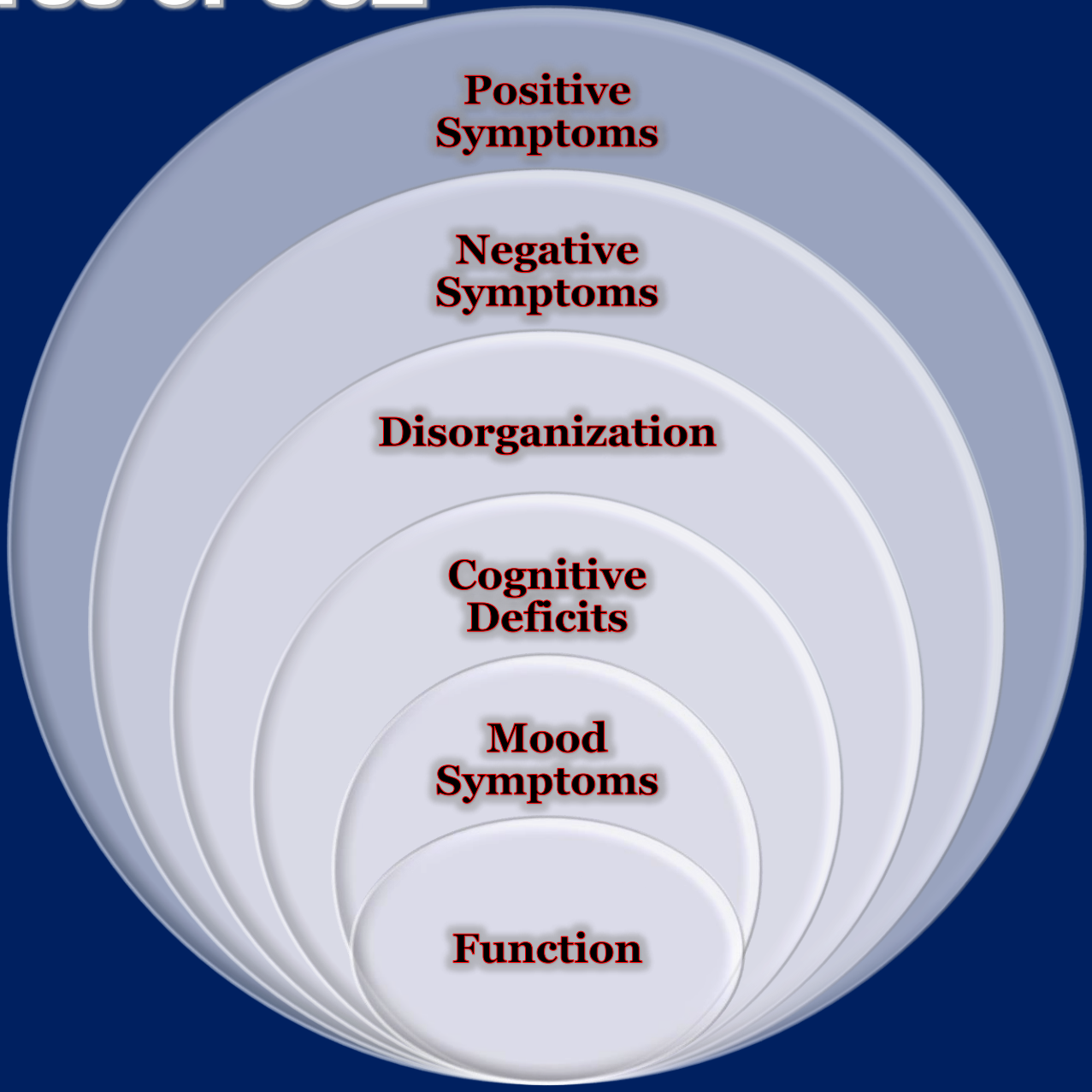


What are the possible etiological reasons ? DDX?

What are the main symptoms & signs?


Not single disease
10-25 ♂
Vs
25-35 ♀
Prevalence & incidence worldwide.
SCZ
Age of onset
Prevalence 0.6– 1.9 %
Annual incidence of 0.5 – 5.0 per 10,000

Features of SCZ



Unknown

- Symptoms → Vulnerability
- Biological, Psychosocial and Environmental

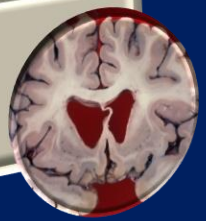
Stress-Diathesis Model:

- Areas of the brain
- Dopamine
- Other

Neurobiology

- structures or connections
- Limbic system
- Basal ganglia
- Cerebellum

Neuropathology



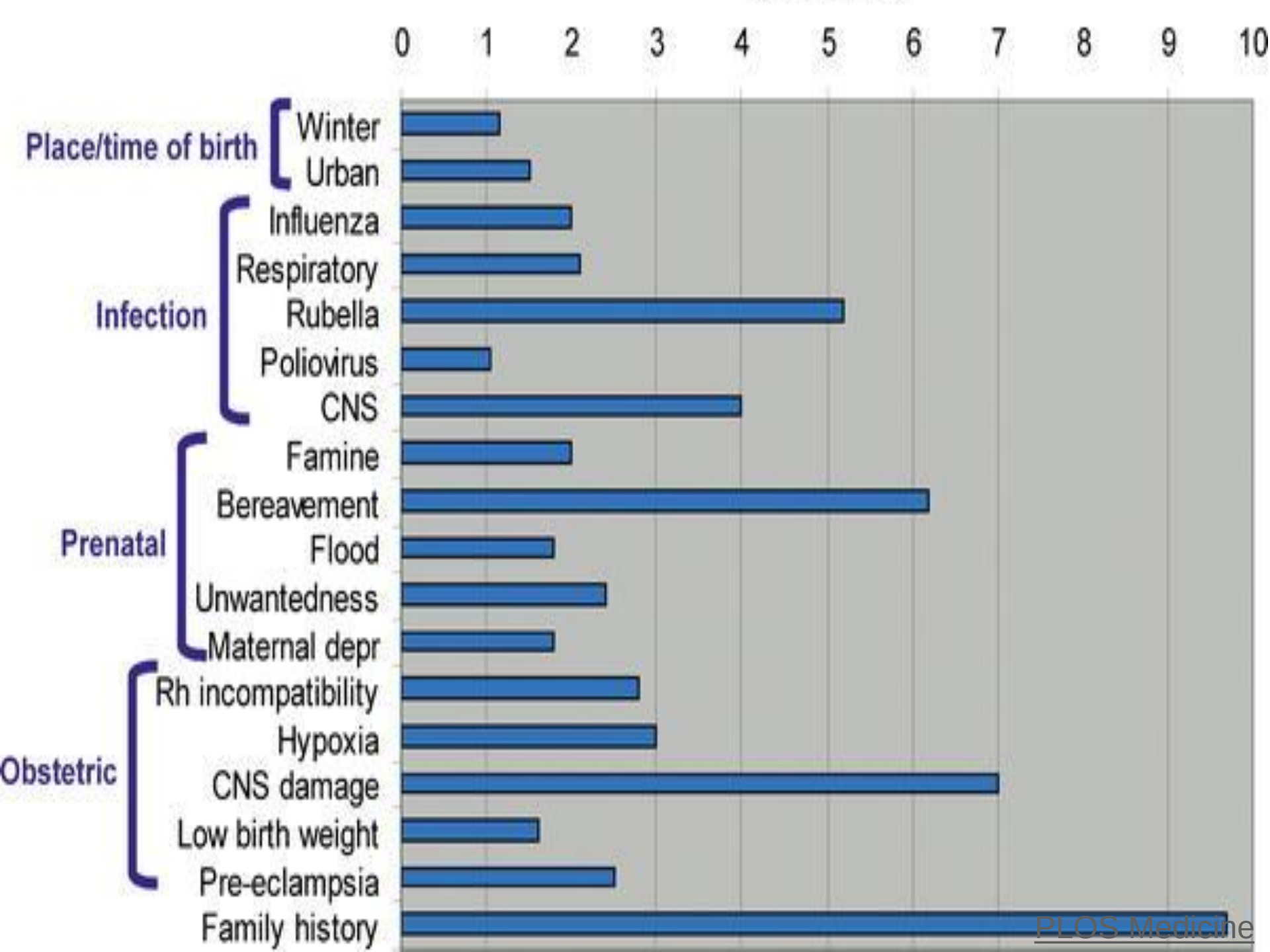
- Family studies
- Twin studies
- Chromosome.

Genetic Factors

Symptoms → Vulnerability

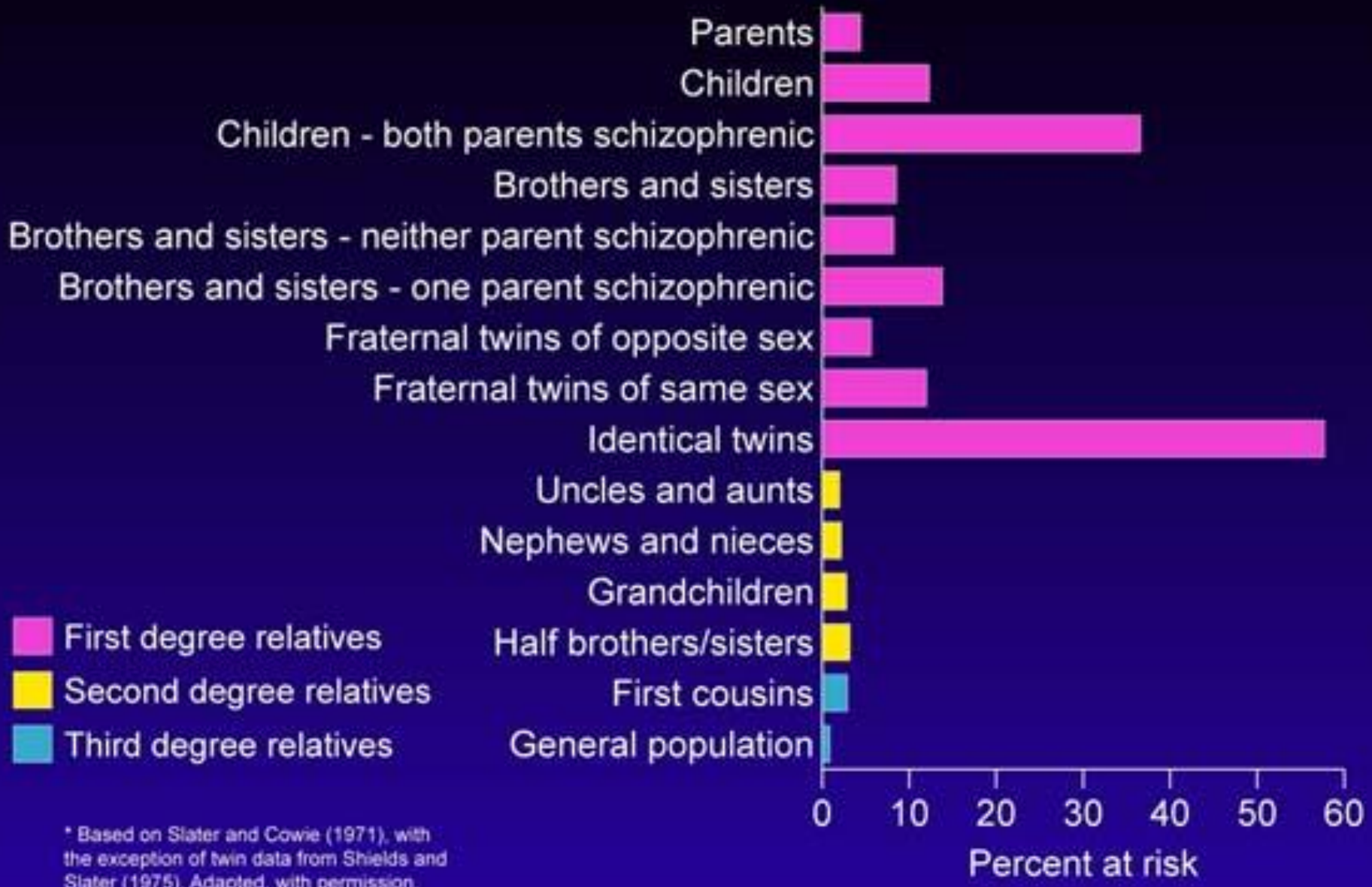
- Biological, Psychosocial and Environmental

Stress-Diathesis Model:




• Family studies
• Twin studies
• Chromosome.
Genetic Factors

Rates of Schizophrenia Among Relatives of Schizophrenic Patients*



* Based on Slater and Cowie (1971), with the exception of twin data from Shields and Slater (1975). Adapted, with permission, from Tsuang and Vandermey (1980).

Schizophrenia: genes plus stressors

TABLE.
Susceptibility Genes for Schizophrenia

Dysbindin	Erb-B4
Neuregulin	FEZ1
DISC-1	MUTED
DAOA	MRDS1
DAAO	BDNF
RGS4	Nur77
COMT	MAO-A
CHRNA7	Spinophylin
GAD1	Calcyon
GRM3	Tyrosine hydroxylase
PPP3CC	$Dopamine_2$ receptor
PRODH2	$Dopamine_3$ receptor
AKT1	

DISC-1=disrupted in schizophrenia-1; DAOA=D-amino acid oxidase activator (G72/G30); DAAO=D-amino acid oxidase; RGS4=regulator of G-protein signalling 4; COMT=catechol O methyl transferase; CHRNA7=α-7 nictonic cholinergic receptor; GAD1=glutamic acid decarboxylase 1; GRM3=glutamate receptor, metabotropic 3; BDNF=brain derived neurotrophic factor; MAO-A=monoamine oxidase A.

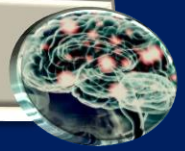
Stahl SM. *CNS Spectr*. Vol 12, No 8. 2007.

Schizophrenia is mostly caused by various possible combinations of many different genes (which are involved in neurodevelopment, neuronal connectivity and synaptogenesis) plus stressors from the environment conspiring to cause abnormal neurodevelopment. There is also abnormal neurotransmission at glutamate synapses, possibly involving hypofunctional NMDA receptors .

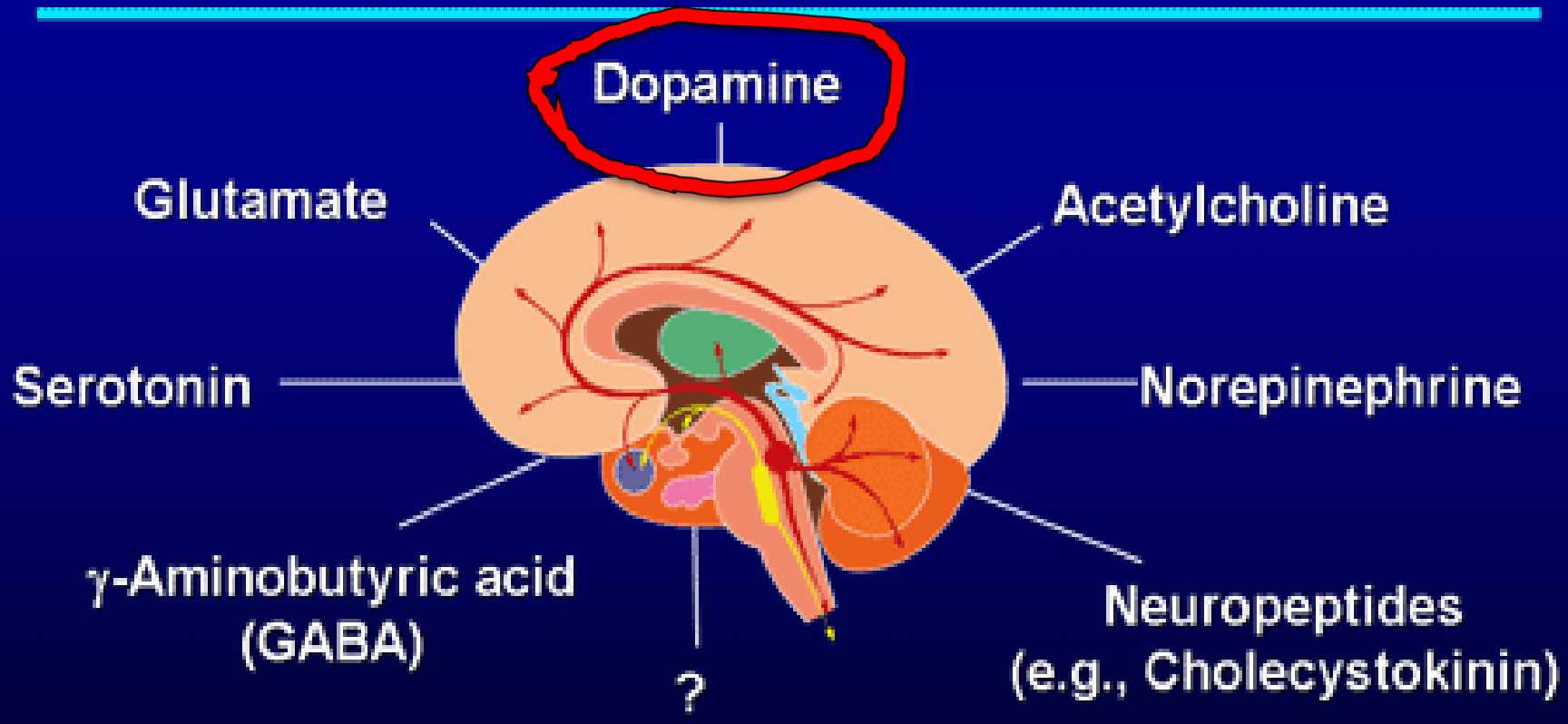
Stephen M The Genetics Of Schizophrenia Converge,Upon,The NMDA Glutamate Receptor, *CNS Spectr*. 2007

- Areas of the brain
- Dopamine
- Other

Neurobiology



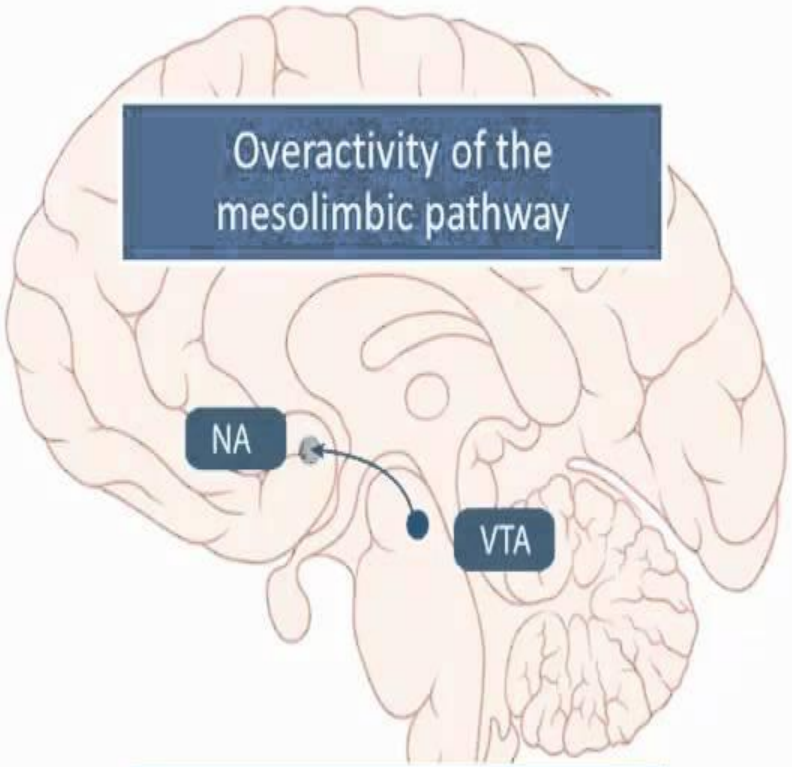
Neurotransmitter Systems Implicated in Schizophrenia



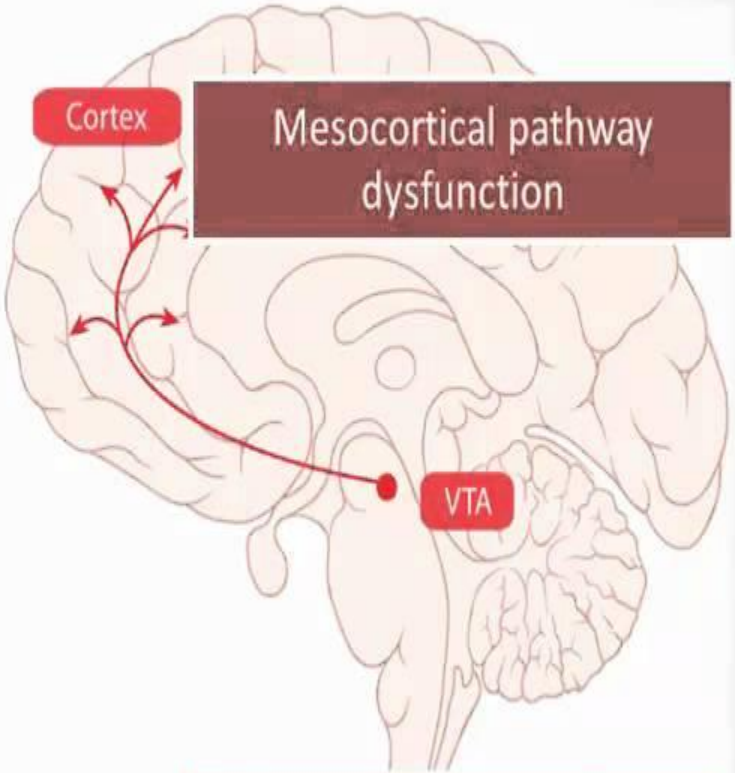
Schizophrenia Probably Involves Multiple Neurotransmitter System Abnormalities[1, 2]

[1]Goff et al. (2001), Med Clin North Am 85:663-689; [2]Casey, Zorn (2001), J Clin Psychiatry 62(suppl 7):4-10

Dopamine Pathways Relevant to Schizophrenia Symptoms



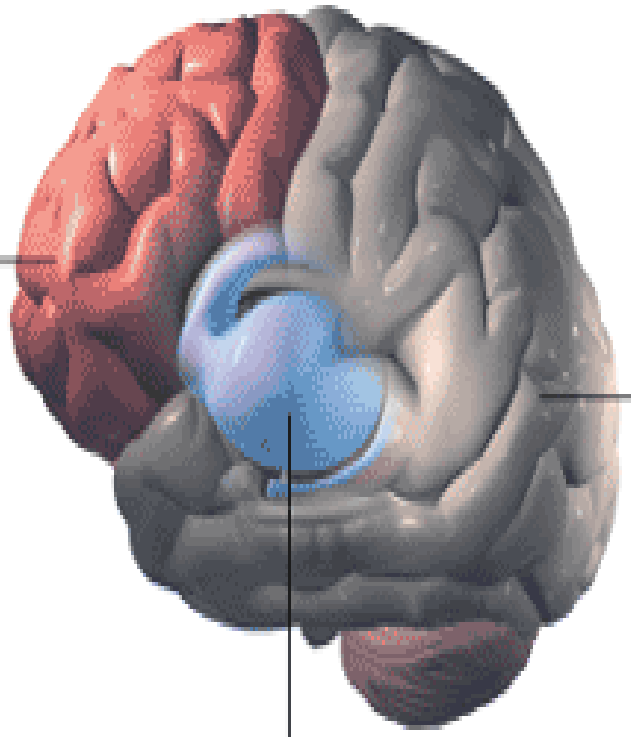
Positive symptoms



Negative and cognitive symptoms

DIFFERENT NEUROTRANSMITTERS, SAME RESULTS

SOME SCIENTISTS have proposed that too much dopamine leads to symptoms emanating from the basal ganglia and that too little dopamine leads to symptoms associated with the frontal cortex. Insufficient glutamate signaling could produce those same symptoms, however.



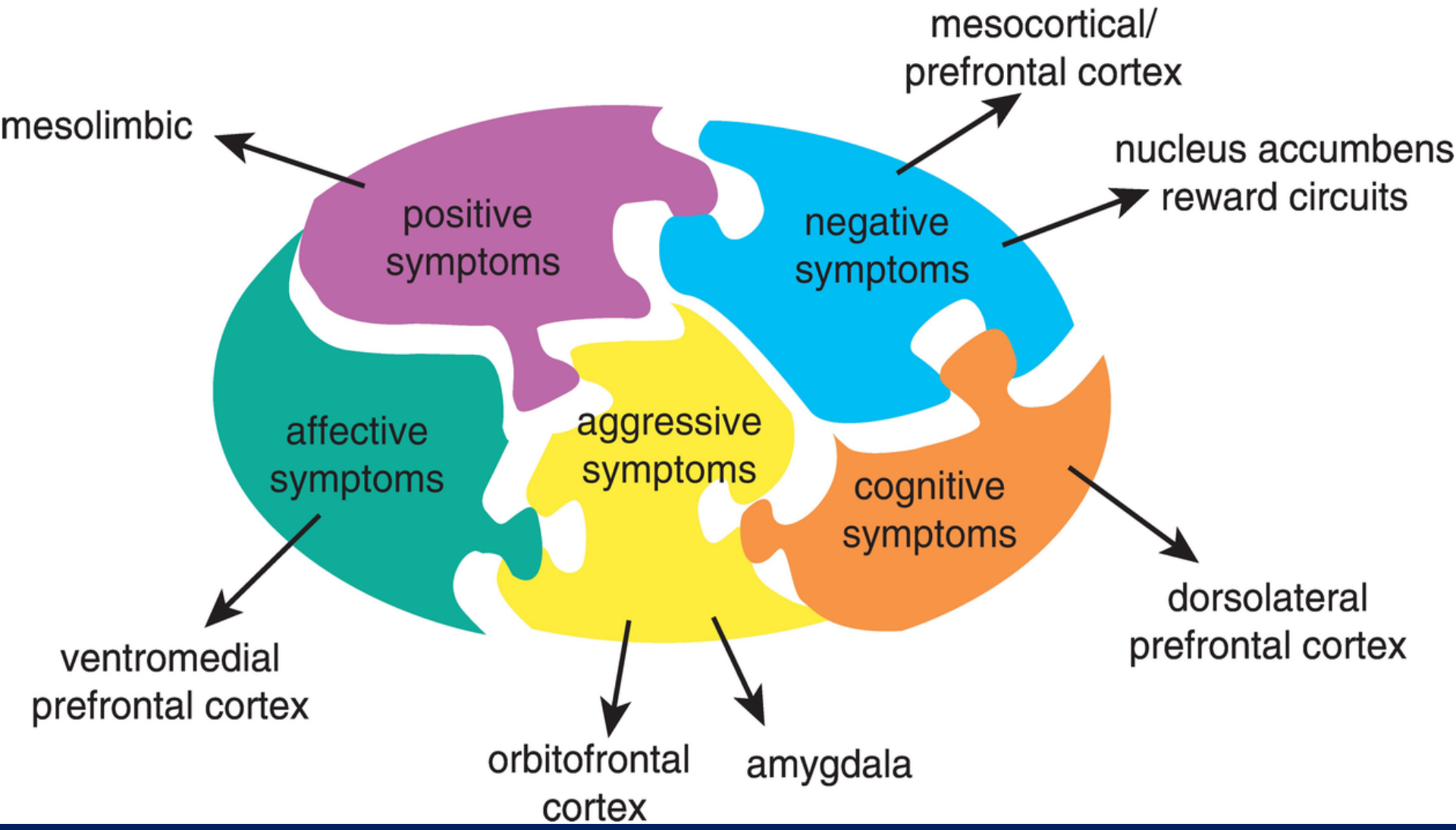
IN THE REST OF THE CORTEX, glutamate is prevalent, but dopamine is largely absent.

IN THE FRONTAL CORTEX, where dopamine promotes cell firing (by acting on D1 receptors), glutamate's stimulatory signals amplify those of dopamine; hence, a shortage of glutamate would decrease neural activity, just as if too little dopamine were present.

IN THE BASAL GANGLIA, where dopamine normally inhibits cell firing (by acting on D2 receptors on nerve cells), glutamate's stimulatory signals oppose those of dopamine; hence, a shortage of glutamate would increase inhibition, just as if too much dopamine were present.

ALFRED T. KAMAJIAN

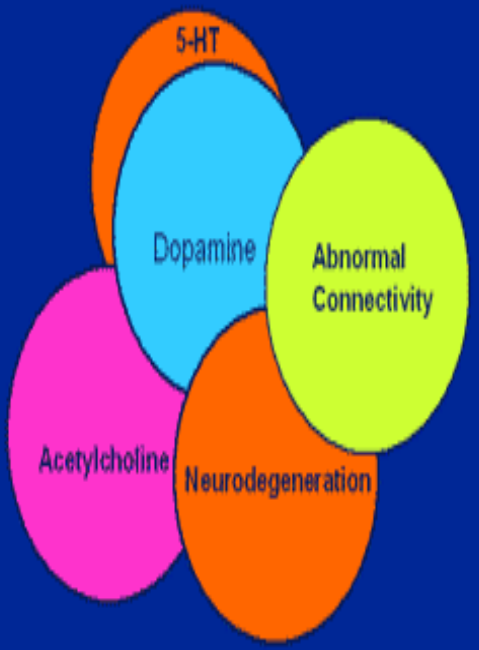
Match Each Symptom to Hypothetically Malfunctioning Brain Circuits



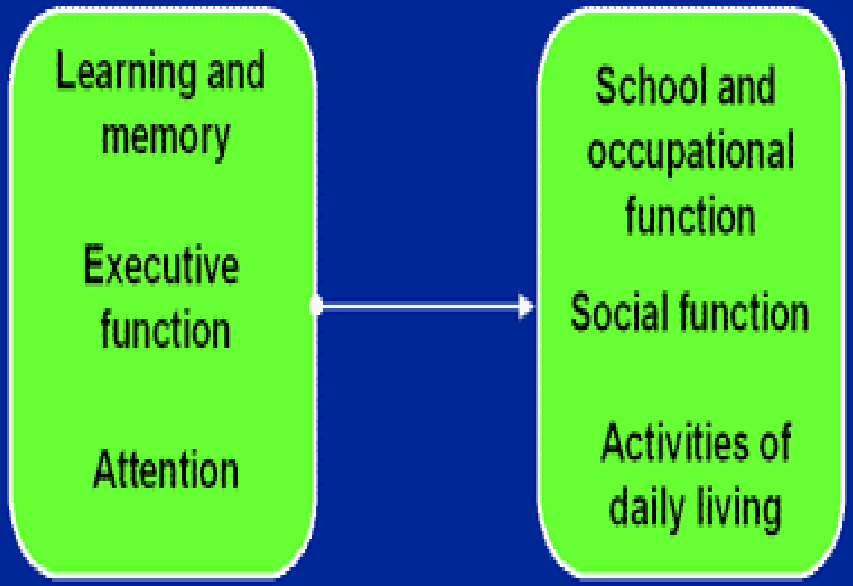
http://stahlonline.cambridge.org/essential_4th_chapter.jsf?page=chapter4_summary.htm&name=Chapter%204&title=Summary

Cognitive deficits in schizophrenia

Multiple Mechanisms for Cognitive Dysfunction in Schizophrenia

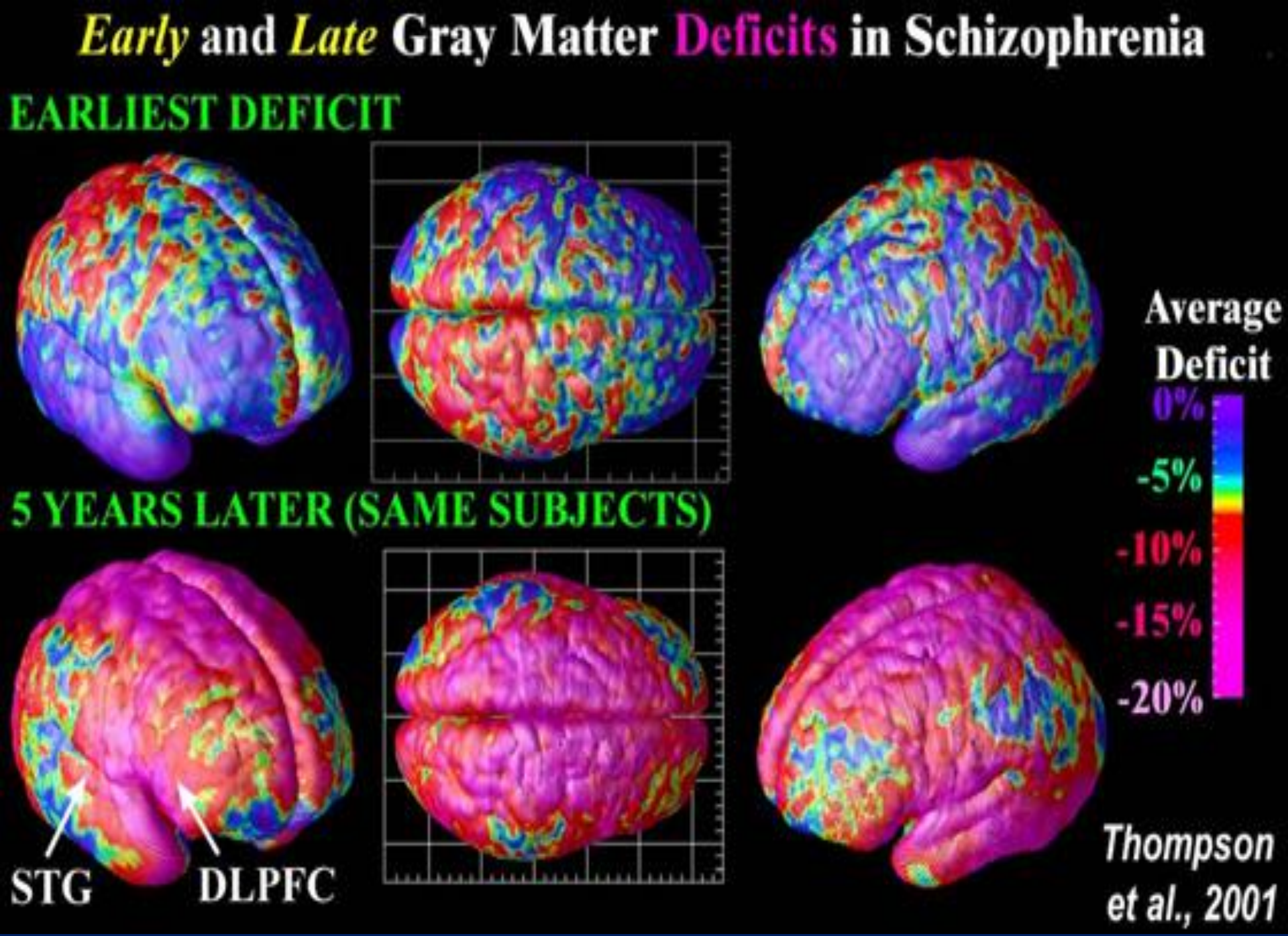


Cognitive Deficits Predict Functional Outcomes



Green 1996; Velligan et al 1997

Early and *Late* Gray Matter Deficits in Schizophrenia



Psychoneuro immunology

Psychoneuro endocrinolog y

Psychosocial Factors

- Evidence
- High Expressed Emotion family (EE)

Diagnosis

 # DSM-5 Diagnostic Criteria for Schizophrenia:

A- ≥ two characteristic symptoms for one month, at least one of them is (1),(2) or (3)

1- Delusions

2- Hallucinations

3- Disorganized speech (frequent derailment or incoherence)

4- Grossly disorganized or catatonic behavior

5- Negative symptoms (diminished emotional expression or lack of drive (avolition))

B- Social, Occupation or self-care *dysfunction*

C- Duration of at least *6 months* of disturbance (include at least one month of active symptoms that meet Criterion A; in addition of periods of prodromal and residual symptoms).

D- Schizoaffective & mood disorder *exclusion*

E- The disturbance is not due to Substance or another medical condition.

F- If there is history of autism spectrum disorder or a communication disorder of childhood onset, schizophrenia diagnosis is made only if delusion or hallucinations plus other criteria are present.

Clinical Features

- No single clinical sign or symptom is **pathognomonic** for schizophrenia
- Patient's history & mental status examination are essential for diagnosis.
- Premorbid history includes schizoid or schizotypal personalities, few friends & exclusion of social activities.
- **Prodromal features** include obsessive compulsive behaviors , attenuated positive psychotic features.

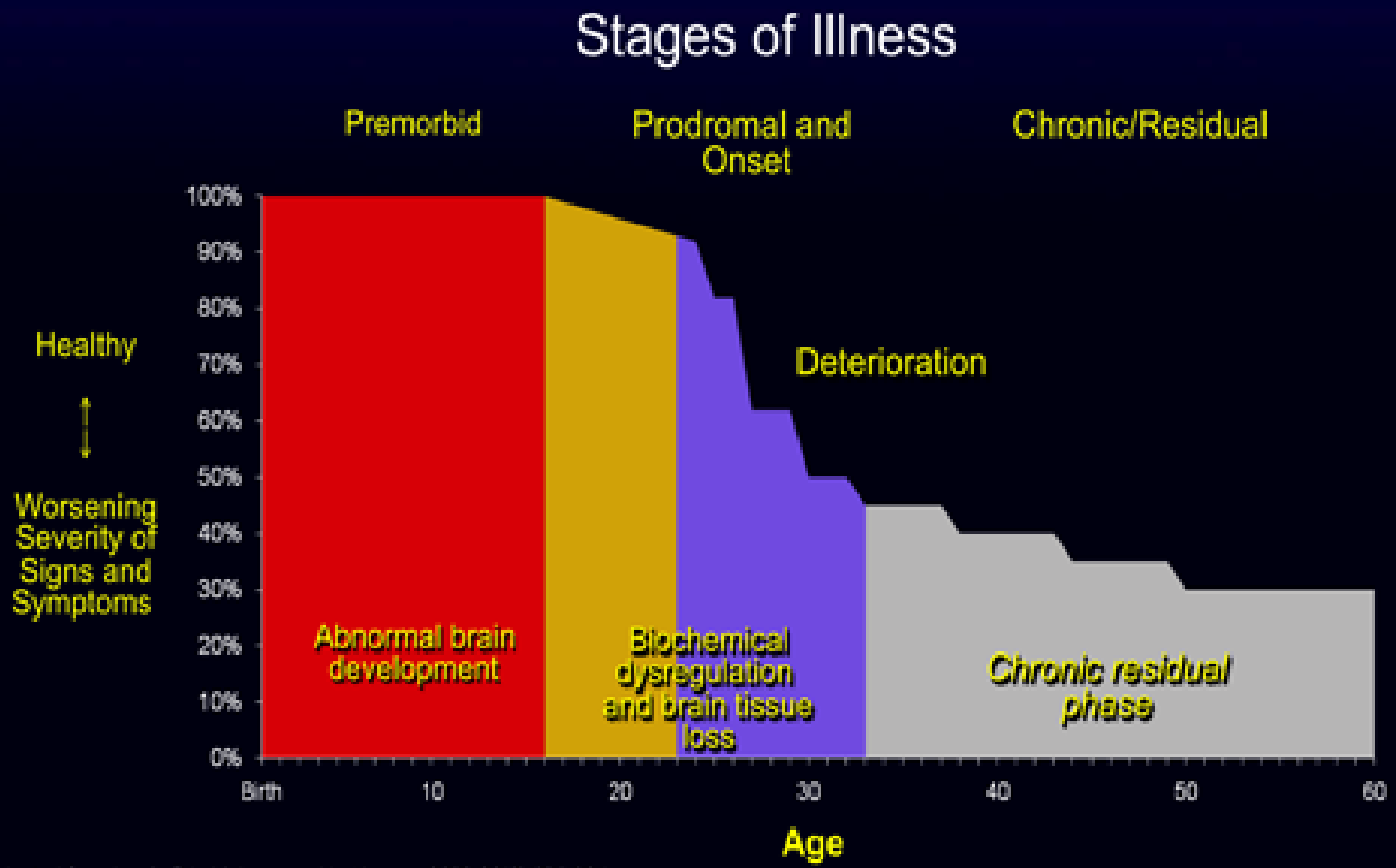
Mental Status Examination

- Appearance & behavior
- Mood, feelings & affect
- Perceptual disturbances
- Thought: Thought content
  Form of thought
  Thought process (thought blocking, poverty of thought content, poor abstraction, perseveration)
- Impulsiveness, violence, suicide & homicide
- Cognitive functioning
- Poor insight and judgment

Course

- Acute exacerbation with increased residual impairment
- Full recovery: very rare
- Longitudinal course: downhill

Natural History of Schizophrenia



Adapted from Lewis DA, Lieberman JA. *Neuron*. 2000;28(2):325–334.

Prognosis

Good P.F	Poor P.F
1. Late age of onset 2. Acute onset 3. Obvious precipitating factors 4. Presence of mood component 5. Good response to Tx 6. Good supportive system	1. Young age of onset 2. Insidious onset 3. Lack of P.F. 4. Multiple relapses 5. Low IQ 6. Poor premorbid personality 7. Negative symptom 8. Positive family history

Differential Diagnosis

Secondary psychiatric disorders:

-Substance-induced disorders

-Psychotic disorders due to another medical disorder :

Epilepsy (complex partial)

CNS diseases

Trauma

Others

Primary Psychiatric disorders:

Schizophreniform disorder

Brief psychotic disorder

Delusional disorder

Schizoaffective disorder

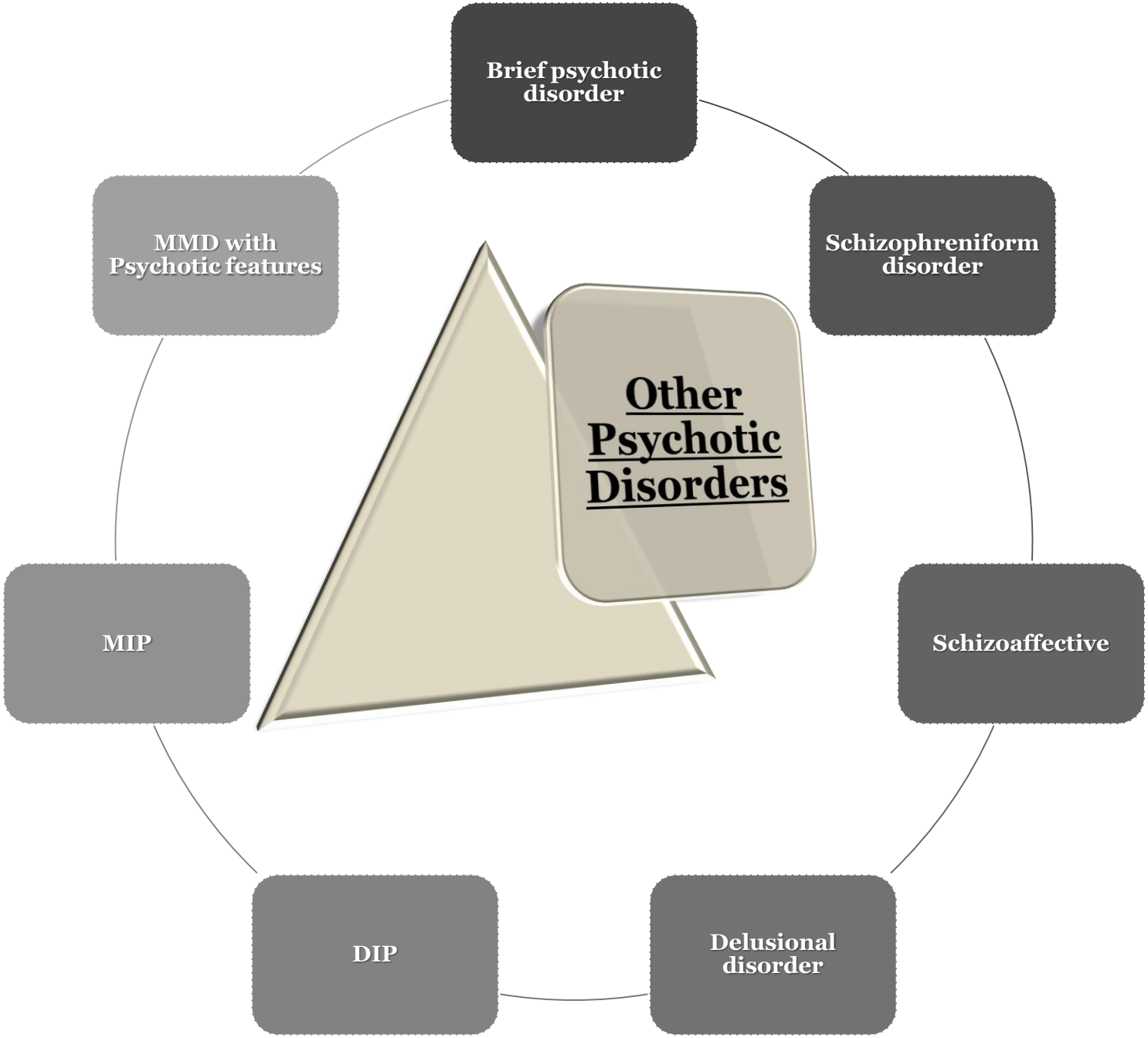
Mood disorders

Personality disorders

(schizoid, schizotypal & borderline personality)

Factitious disorder

Malingering


Brief psychotic disorder
Schizophreniform disorder
Schizoaffective
Delusional disorder
DIP
MIP
MMD with Psychotic features
Other Psychotic Disorders

Antipsychotic Medications

Conventional Antipsychotics	Atypical Antipsychotics
Chlorpromazine	Aripiprazole
Fluphenazine	Clozapine
Haloperidol	Olanzapine
Loxapine	Paliperidone
Molindone	Quetiapine
Perphenazine	Risperidone
Pimozide	Ziprasidone
Prochlorperazine	
Thiothixene	
Thioridazine	
Trifluoperazine	

DSM-5 Diagnostic Criteria for Schizoaffective disorder

- An uninterrupted period of illness that includes either a major depressive disorder or a manic episode along with at least two active symptoms of schizophrenia (hallucinations, delusions, disorganized speech, severely disorganized or catatonic behaviors, negative symptoms like decreased emotional expression or movement)
- Delusions or hallucinations occur at least two weeks without major depressive or manic symptoms at some time during the illness.
- The major mood symptoms occur for most of the duration of the illness.
- The illness is not the result of a medical condition or the effects of alcohol, other drugs of abuse, or a medication.

Substance-Induced psychiatric Disorder

- Potentially severe, usually temporary.
- Context of substances of abuse, medications, or toxins of any of the 10 classes of substances.
- Clinically significant presentation of a secondary psychiatric disorder.
- Evidence in history, PE, MSE and labs of:
  - Develop during or within 1 month of use
  - Capable of producing mental disorder seen
- Not an independent mental disorder
  - Preceded onset of use
  - Persists for substantial time after use (more that a month after off of substance use)

Treatment

What are the indications for hospitalization?

Diagnostic purpose

Patient & other's safety

Initiating or stabilizing medications

Establishing an effective association between patient & community supportive systems

Biological therapies

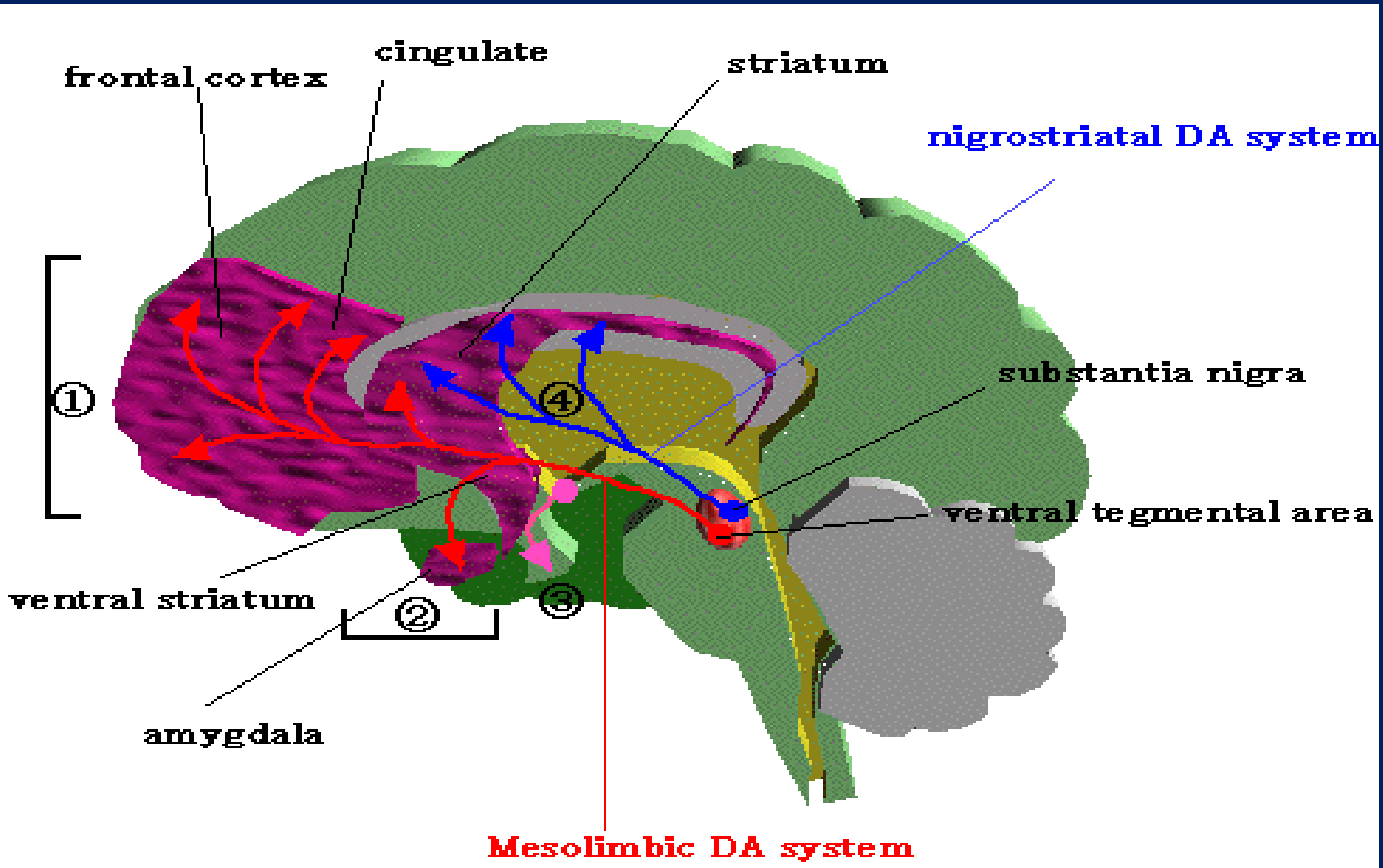
- Antipsychotic medications are the mainstay of the treatment of schizophrenia.
- Generally, they are remarkably safe.
- Two major classes:

-Dopamine receptor antagonists (haloperidol, chlorpromazine)

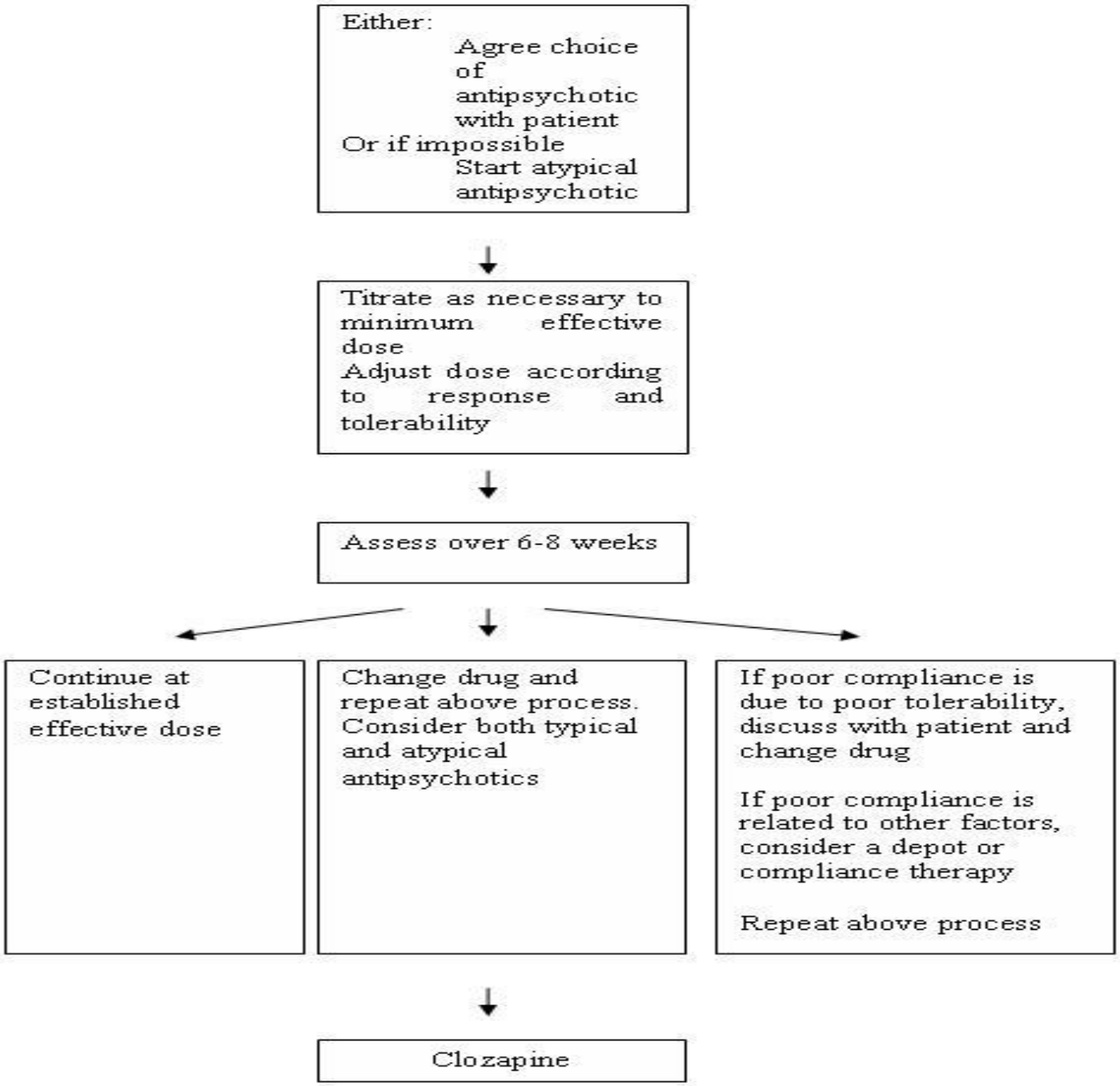
-Serotonin-dopamine receptor antagonists (Risperidone, clozapine, olanzapine).

- Depot forms of antipsychotics eg. Risperidone Consta is indicated for poorly compliant patients.
- - Electroconvulsive therapy (ECT) for catatonic or poorly responding patients to medications

Antipsychotics and dopamine system



- **Pharmacological Treatment Algorithm Adapted from the Maudsley prescribing Guidelines (Taylor et al, 2005)**


Either:
Agree choice of antipsychotic with patient
Or if impossible
Start atypical antipsychotic
Titrate as necessary to minimum effective dose
Adjust dose according to response and tolerability
Assess over 6-8 weeks
Continue at established effective dose
Change drug and repeat above process. Consider both typical and atypical antipsychotics
If poor compliance is due to poor tolerability, discuss with patient and change drug
If poor compliance is related to other factors, consider a depot or compliance therapy
Repeat above process
Clozapine

First generation antipsychotics	*Second generation antipsychotics*	*Clozapine*
Extrapyramidal effects Dystonia Pseudoparkinsonism Akathisia Tardive dyskinesia	Olanzapine Weight gain Sedation Glucose intolerance and frank diabetes mellitus Hypotension	Sedation
Sedation		Hypersalivation
Hyperprolactinaemia	Risperidone Hyperprolactinaemia Hypotension EPS at higher doses Sexual dysfunction	Constipation
Reduced seizure threshold		Reduced seizure threshold
Postural hypotension	Amisulpiride Hyperprolactinaemia Insomnia Extrapyramidal effects	Hypo & hypertension
Anticholinergic effects Blurred vision Dry Mouth Urinary Retention	Quetiapine Hypotension Dyspepsia Drowsiness	Tachycardia
Neuroleptic malignant syndrome		Pyrexia
Weight gain		Weight gain
Sexual dysfunction		Glucose intolerance and diabetes mellitus
Cardio-toxicity (including prolonged QTc)		Nocturnal enuresis
		Rare serious side effects Neutropaenia 3% Agranulocytosis 0.8% Thromboembolism Cardiomyopathy Myocarditis Aspiration pneumonia

TABLE

RECEPTOR BLOCKADE AND ANTIPSYCHOTIC SIDE EFFECTS[2]

Receptor Type	*Side Effects*
D_2	EPS, prolactin elevation
M_1	Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision
H_1	Sedation, weight gain, dizziness
α_1	Hypotension
$5\text{-}HT_{2A}$	Anti-EPS (?)
$5\text{-}HT_{2C}$	Satiety blockade

D=dopamine; EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

Robinson DS. *Primary Psychiatry*. Vol 14, No 10. 2007.

TABLE 2

ANTIPSYCHOTICS: SAFETY AND TOLERABILITY[1]

Item	Typical Neuroleptic	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
EPS	+ to +++	±	± to +++*	± to +*	±	± to +*	± to +
TD	+++	±	± to ++	± (?)	± (?)	± (?)	± (?)
Somnolence	± to +++	+++	±	++	++	±	±
Prolactin	+++	±	+++	±	±	±	±
Weight	± to ++	+++	+	+++	++	±	±
Dyslipidemia	± to +	+++	+	+++	++	±	±
DM	± to +	+++	+	+++	++	±	±
QTc	+	++	+	+	+	++	±
Orthostatic BP↓	± to +++	+++	++	+	++	±	±

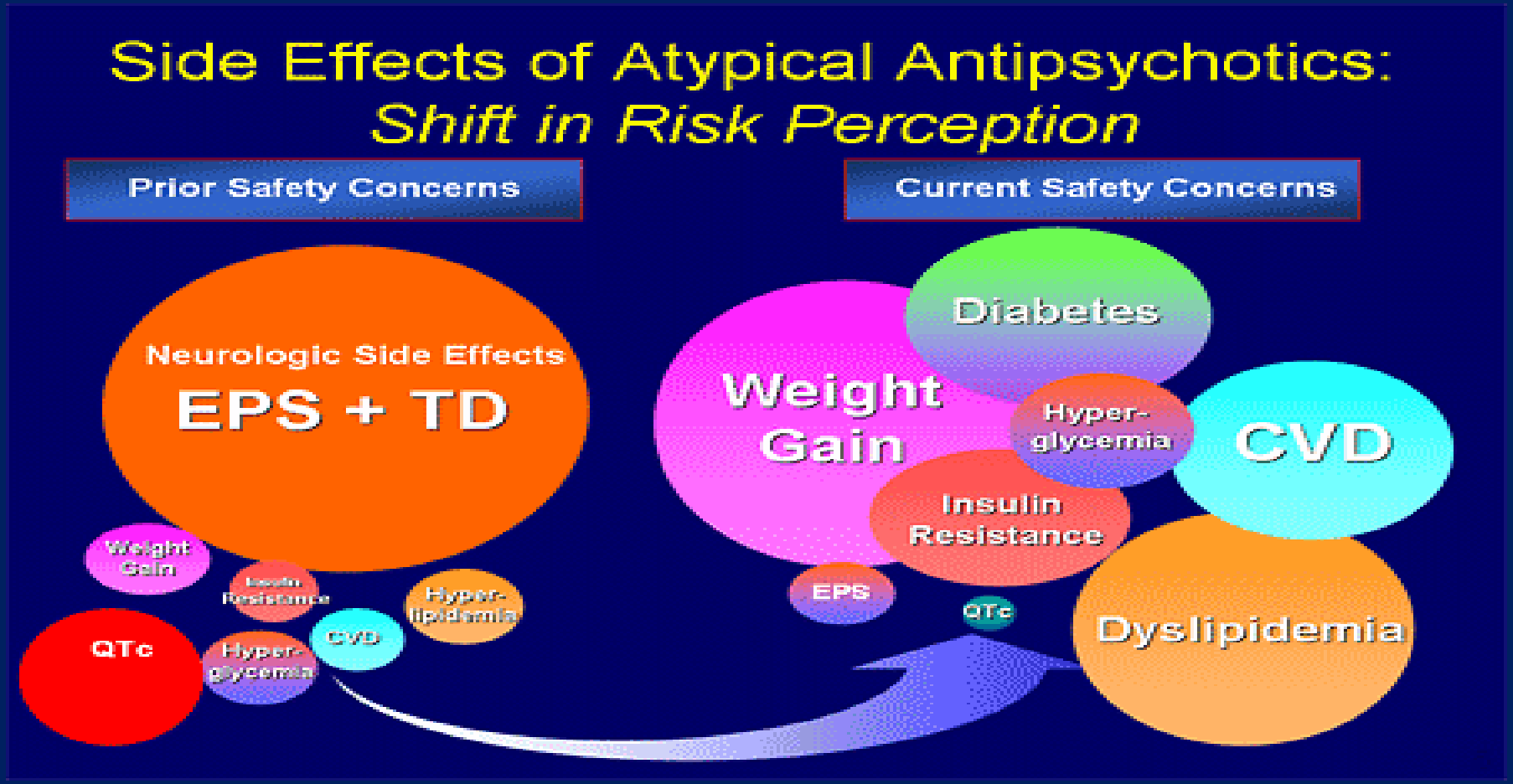
*Dose-related.

Key: ±=none-to-minimal; +=mild; ++=moderate; +++=marked; ?=no data, compared to placebo rates.

EPS=extrapyramidal symptoms; TD=tardive dyskinesia; DM=diabetes mellitus; QTc=corrected Q-T interval; BP=blood pressure.

Glick ID, He X, Davis JM. *Primary Psychiatry.* Vol 13, No 12. 2006.

Side effects of atypical antipsychotics



ADA Consensus on Antipsychotic Drugs: Metabolic Abnormalities of Second-Generation Antipsychotics

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	–	–
Ziprasidone*	+/-	–	–

+ = increased effect; - = no effect; D = discrepant results.
*Newer drugs with limited long-term data.

American Diabetes Association et al. 2004.

Box 4.6 Neuroleptic Malignant Syndrome (NMS) (2, 47, 48)

- Uncommon but potentially fatal complication of antipsychotic therapy
- Typically occurs soon after an antipsychotic is started or dose is increased but may occur late
- Risk factors include depot antipsychotics, intramuscular administration, rapid increase in dose of antipsychotics, high doses of antipsychotics, dehydration, malnutrition, iron deficiency, underlying brain abnormalities, and agitation.
- Diagnostic triad – fever ≥38° C (100.4° F), muscle rigidity, mental status changes
- Autonomic instability and hyperthermia are the major causes of morbidity and mortality.
- Common lab abnormalities include ↑CPK or myoglobinuria, ↑WBC, metabolic acidosis
- Ensure other medical causes have been excluded.
- Management includes discontinuing antipsychotic(s), lithium, and dopamine blocking antiemetic agents and providing supportive care, most commonly in an ICU. Although older references recommend use of bromocriptine or dantrolene, more recent references show no advantage for these agents.

Psychosocial therapies

- Social skills training
- Family oriented therapies
- Group therapy
- Individual psychotherapy
- Assertive community treatment
- Vocational therapy

Thank you