Schizophrenia

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Case of Mr.Schi

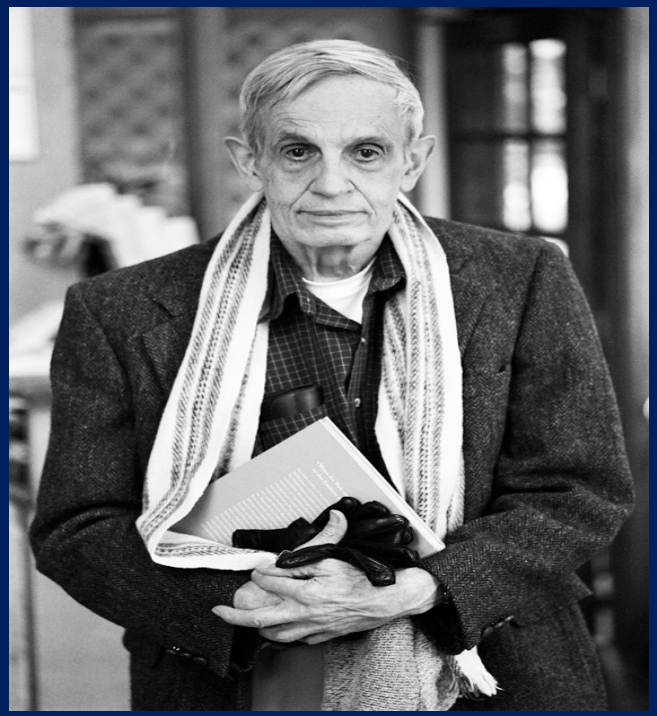
- Mr. Schi is a 28 year-old single male who was brought to Emergency room by his family because of gradual changes in his behavior started 9 months ago. Since then, he became agitated; eat only canned food but not cooked food made by his family, afraid of being poisoned. He talks to himself and stares occasionally on the roof of his room.

Case of Mr.Schi

- He had two brief psychiatric hospitalizations in last 3 years that were precipitated by anger at his neighbor and voices commenting about his behavior.
- His personal history indicated that he was a healthy child, but his parents reported that he was a bed wetter and seemed slower to develop than his brothers and sisters.
- Schi smokes tobacco frequently to calm himself. During his early adolescence he used to smokes Hash heavily plus occasional use of amphetamine. He stopped both Hash and Amphetamine use 5 years ago.

Both has schizophrenia

Lives at group home for the mentally ill



Won Nobel prize

Intended Learning objectives

- By the end of this lecture, a student should be able to:

❖ Appreciate that schizophrenia is a serious, brain illness that needs early intervention and comprehensive management approach.

❖ Enhance his knowledge of schizophrenia including epidemiology, etiology, diagnosis and management.

❖ Acquire preliminary skills to evaluate and intervene adequately to manage schizophrenic patients.

Schizophrenia

- It is not a single disease but a group of disorders with heterogeneous etiologies.
- Found in all societies and countries with equal prevalence & incidence worldwide.
- A life prevalence of 0.6 – 1.9 %
- Annual incidence of 0.5 – 5.0 per 10,000
- Peak age of onset are 10-25 years for ♂ & 25-35 years for ♀

Features of Schizophrenia

http://image.slidesharecdn.com/schizophrenia1-090716160801-phpapp02/95/schizophrenia1-5-728.jpg?cb=1247760507

Etiology

Exact etiology is unknown.

1- Stress-Diathesis Model:

- Integrates biological, psychosocial and environmental factors in the etiology of schizophrenia.
- Symptoms of schizophrenia develop when a person has a specific vulnerability that is acted on by a stressful influence.

2- Neurobiology

* Certain areas of the brain are involved in the pathophysiology of schizophrenia: the limbic system, the frontal cortex, cerebellum, and the basal ganglia.

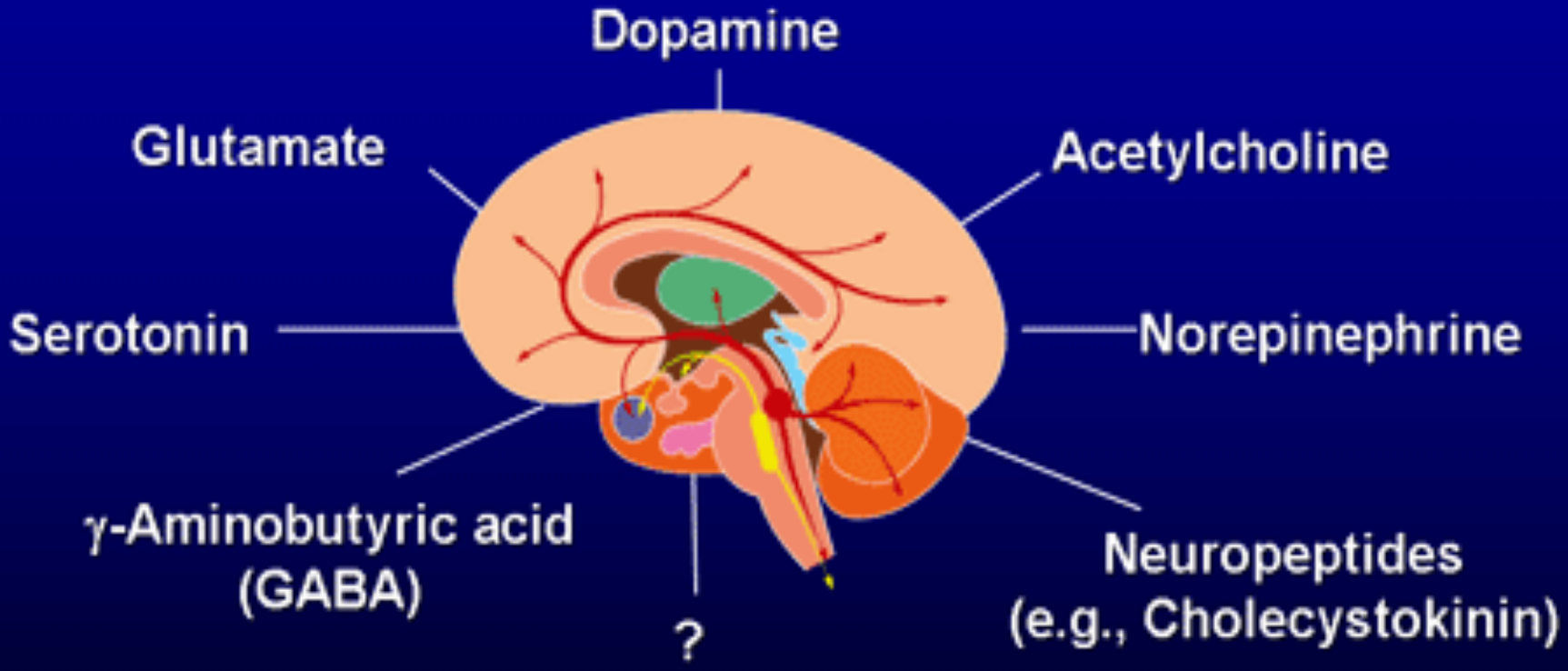
a- Dopamine Hypothesis;

Too much dopaminergic activity (whether it is ↑ release of dopamine, ↑ dopamine receptors, hypersensitivity of dopamine receptors to dopamine, or combinations is not known).

b- Other Neurotransmitters;

Serotonin, Norepinephrine, GABA, Glutamate & Neuropeptides

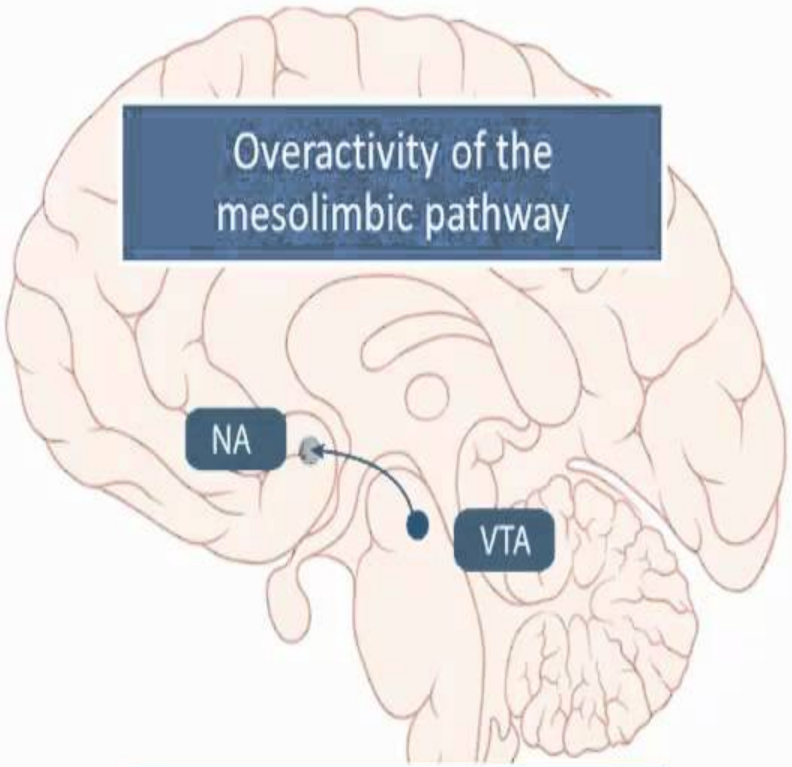
Neurotransmitter Systems Implicated in Schizophrenia

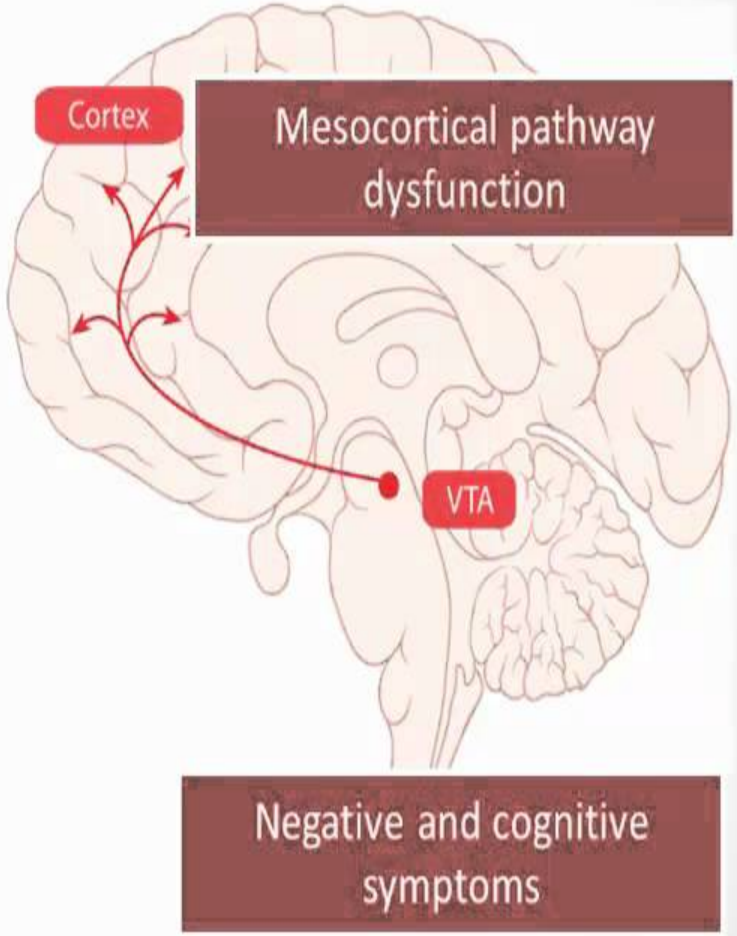


Schizophrenia Probably Involves Multiple Neurotransmitter System Abnormalities[1, 2]

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

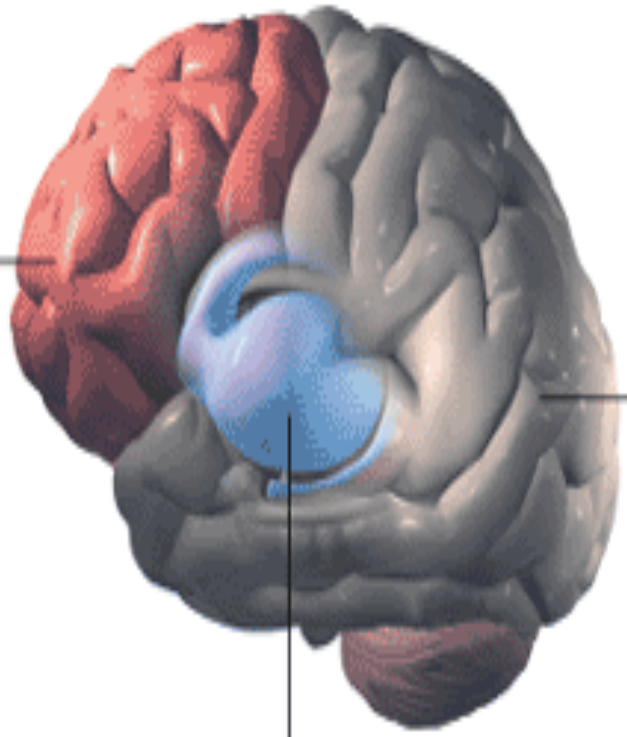
Dopamine Pathways Relevant to Schizophrenia Symptoms





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.

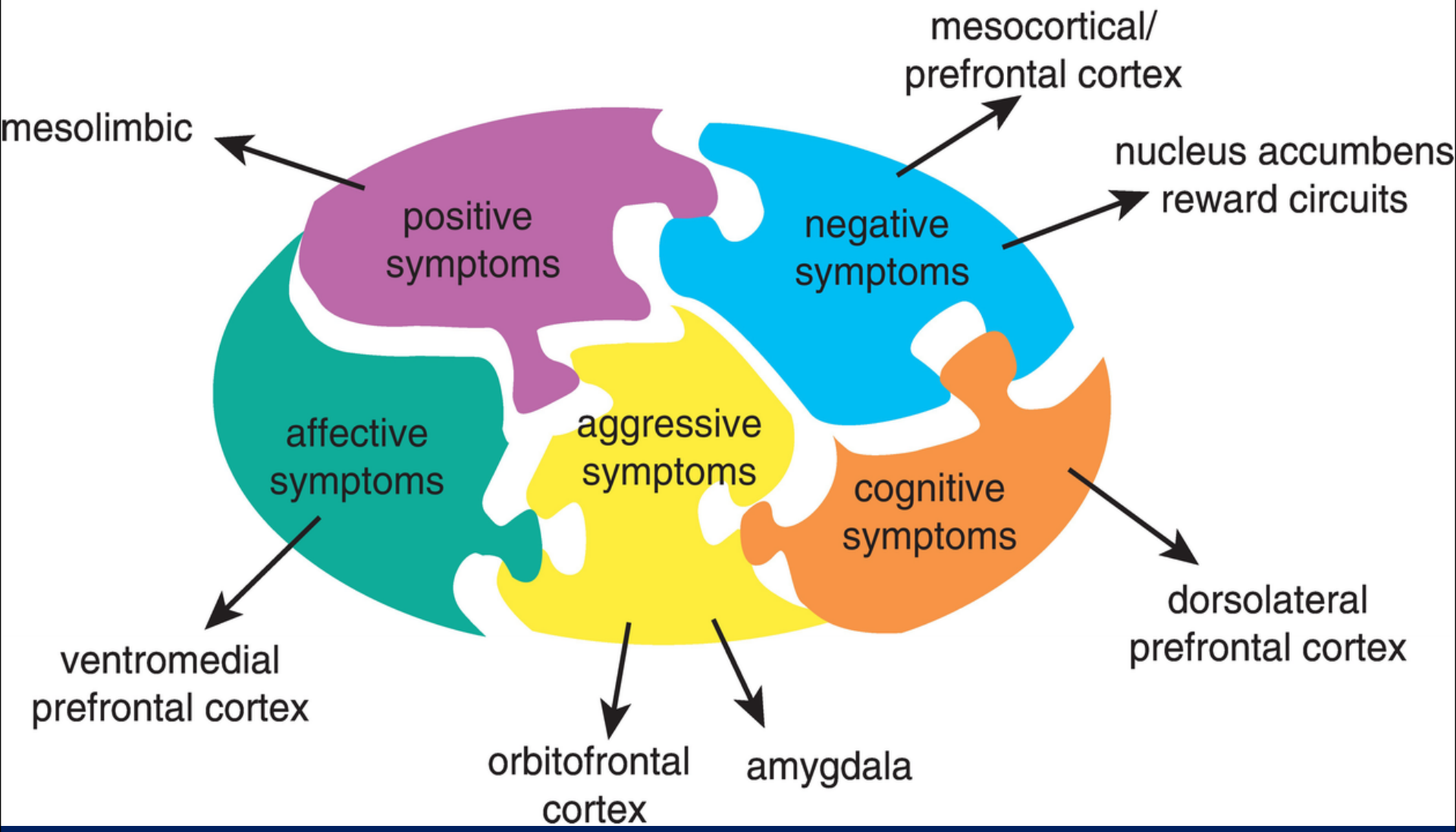
IN THE BASAL GANGLIA, where dopamine normally inhibits cell firing (by acting on D2 receptors on nerve cells), glutamate's stimulatory signals oppose those of dopamine; hence, a shortage of glutamate would increase inhibition, just as if too much dopamine were present.

ALFRED T. KAMAJIAN

c- Neuropathology;

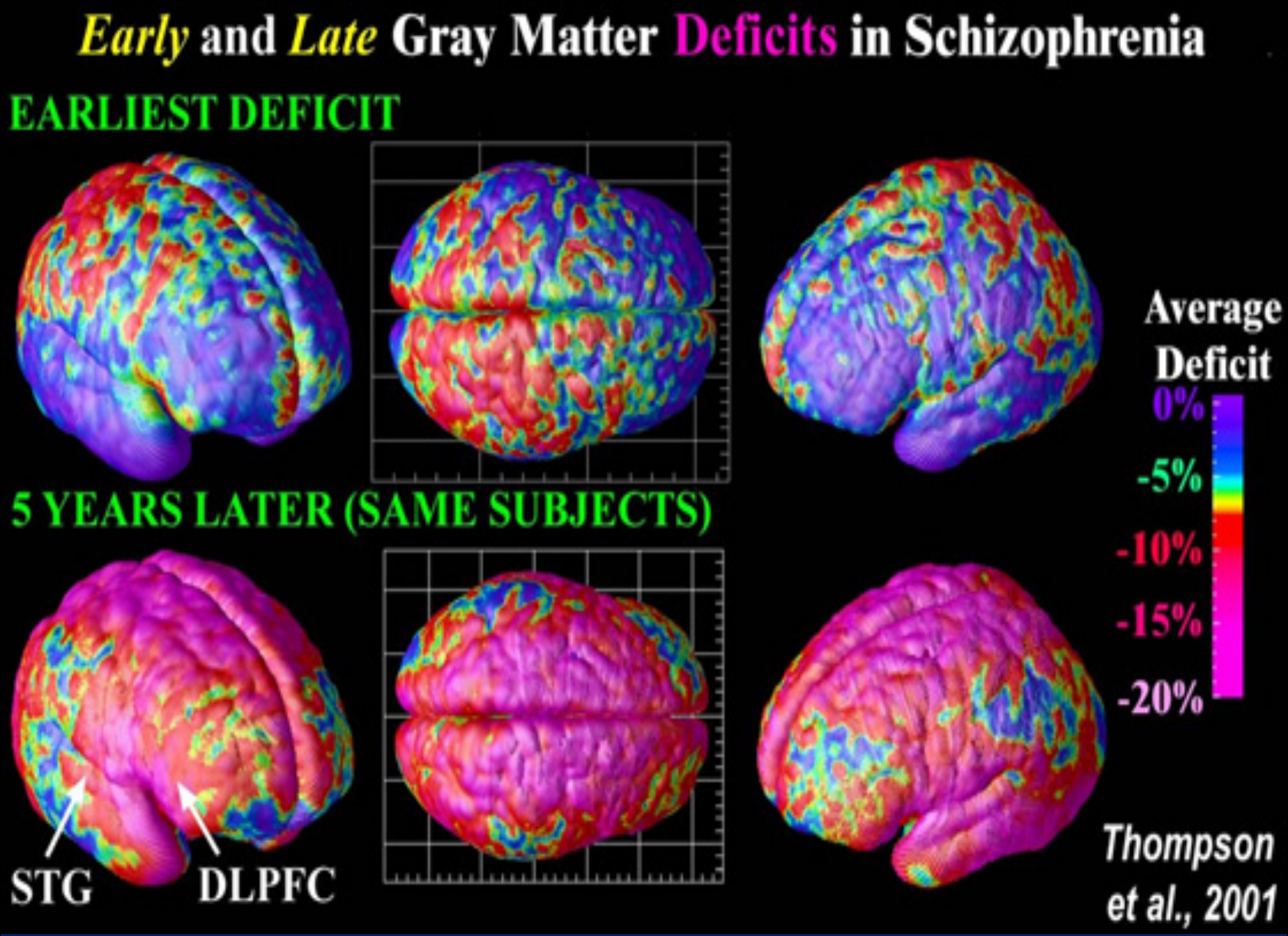
Neuropathological and neurochemical abnormalities have been reported in the brain particularly in the limbic system, basal ganglia and cerebellum. Either in structures or connections.

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

Early and *Late* Gray Matter Deficits in Schizophrenia



d- Psychoneuroimmunology;

↓ T-cell interlukeukin-2 & lymphocytes, abnormal cellular and humoral reactivity to neurons and presence of antibrain antibodies.

These changes are due to neurotoxic virus ? or endogenous autoimmune disorder ?

e- Psychoneuroendocrinology;

Abnormal dexamethasone-suppression test

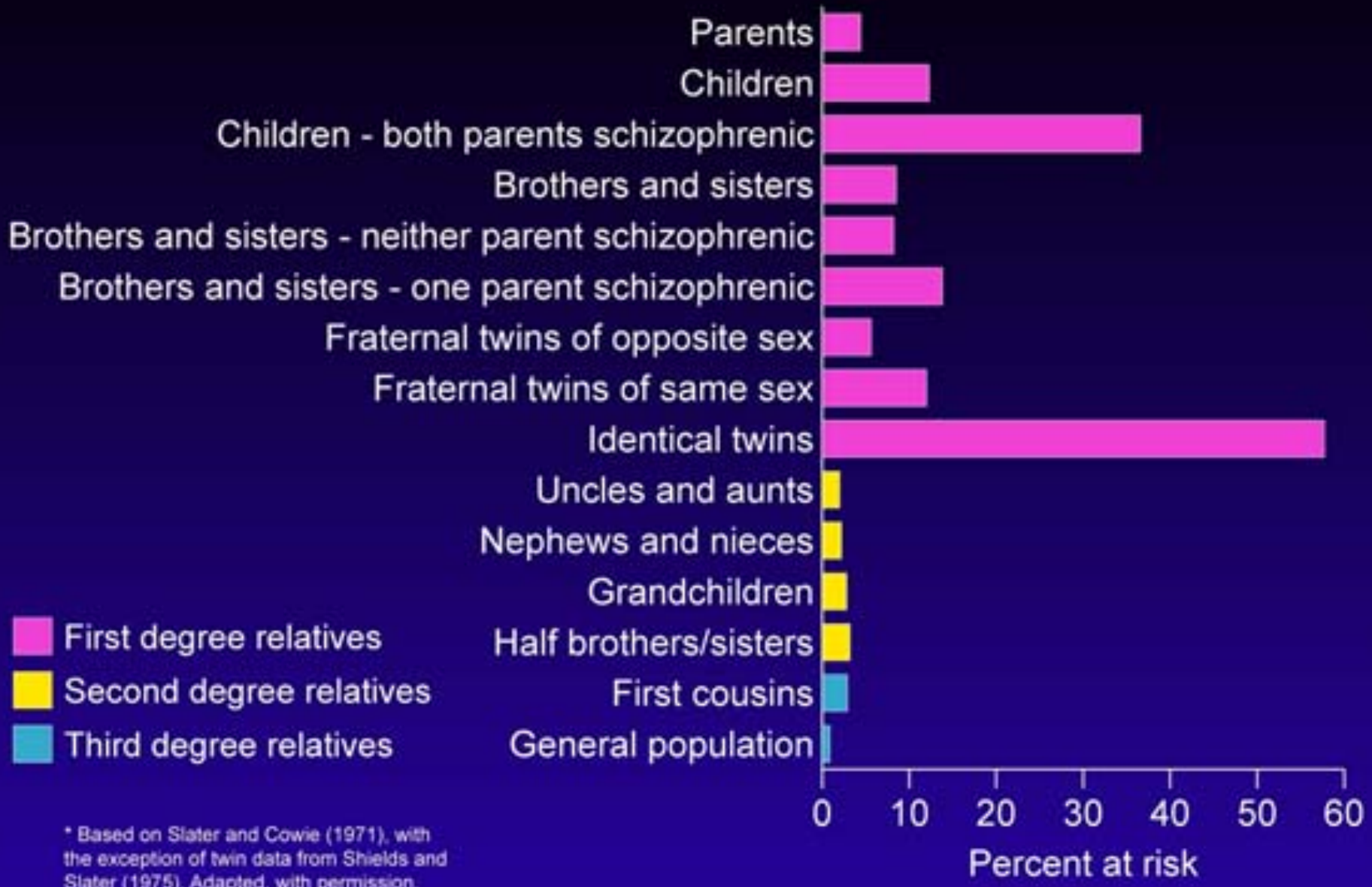
↓ LH/FSH

A blunted release of prolactin and growth hormone on stimulation.

3- Genetic Factors

- A wide range of genetic studies strongly suggest a genetic component to the inheritance of schizophrenia that outweights the environmental influence.
- These include: family studies, twin studies and chromosomal studies.

Rates of Schizophrenia Among Relatives of Schizophrenic Patients*



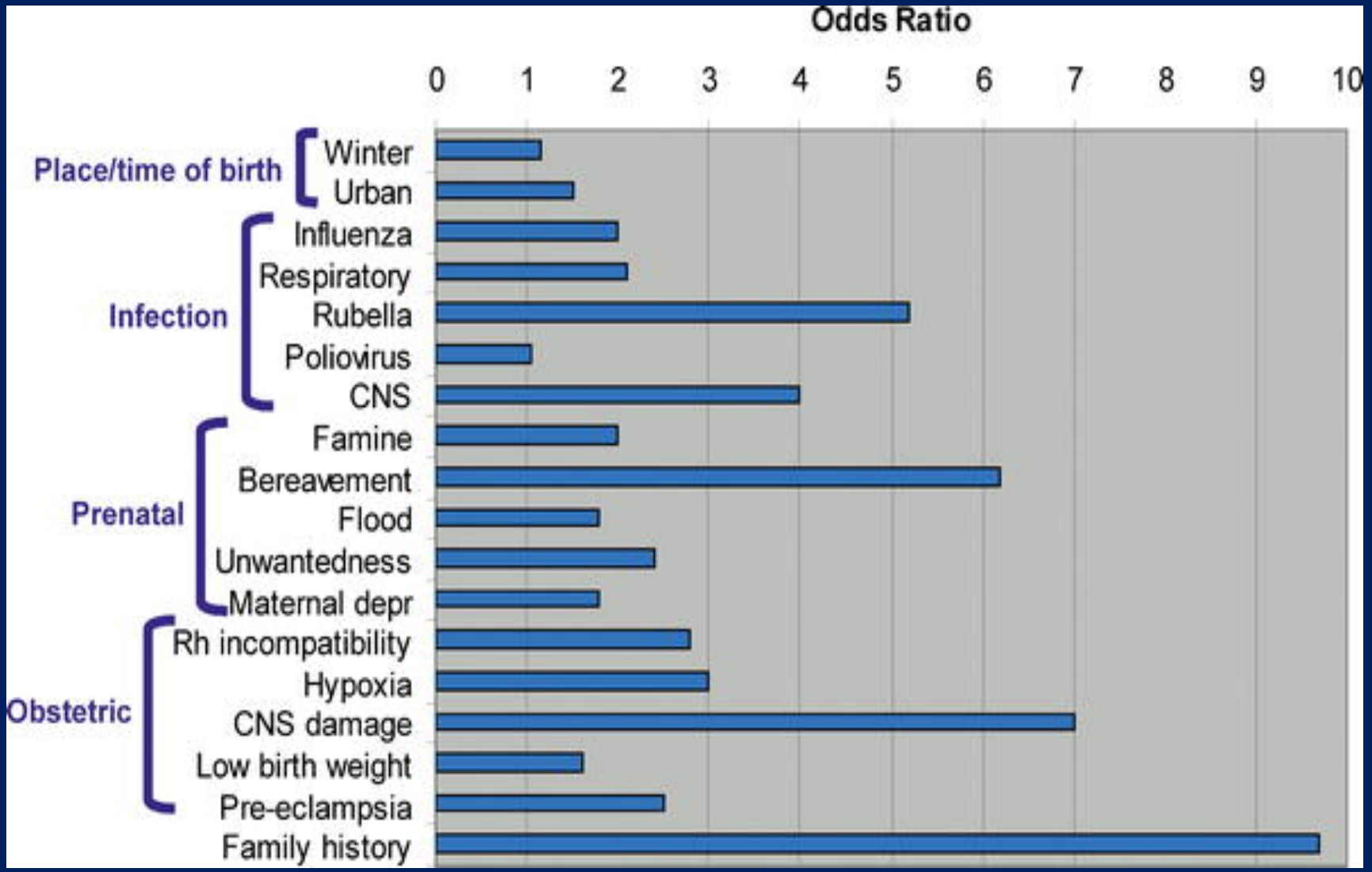
* Based on Slater and Cowie (1971), with the exception of twin data from Shields and Slater (1975). Adapted, with permission, from Tsuang and Vandermey (1980).

4- Psychosocial Factors:

- In family dynamics studies, no well-controlled evidence indicates specific family pattern plays a causative role in the development of schizophrenia.

- High Expressed Emotion family : increase risk of relapse.

Weight of different RF: Family history comes first



PLOS Medicine

Schizophrenia's strongest known genetic risk deconstructed

Suspect gene may trigger runaway synaptic pruning during adolescence (Nature, Feb 2016)

ARTICLE

doi:10.1038/nature16549

Schizophrenia risk from complex variation of complement component 4

Aswin Sekar[1,2,3], Allison R. Bialas[4,5], Heather de Rivera[1,2], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,2], Katherine Tooley[1,2], Jessy Presumey[5], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,2], Samuel A. Rose[2], Robert E. Handsaker[1,2], Schizophrenia Working Group of the Psychiatric Genomics Consortium*, Mark J. Daly[2,6], Michael C. Carroll[5], Beth Stevens[2,4] & Steven A. McCarroll[1,2]

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (*C4*) genes. We found that these alleles generated widely varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele associating with schizophrenia in proportion to its tendency to generate greater expression of *C4A*. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

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 and excessive pruning of neuronal connections) 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

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.

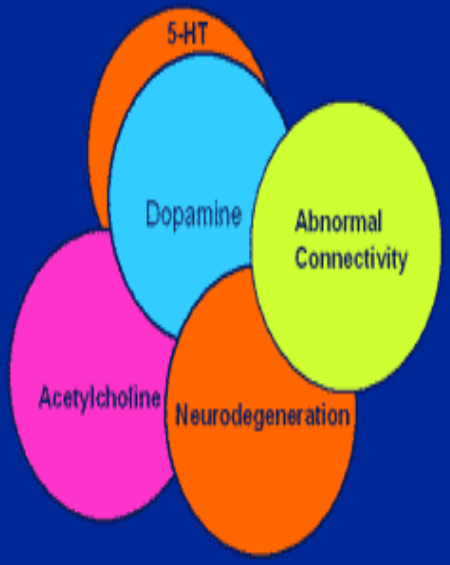
Clinical Features

- 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.

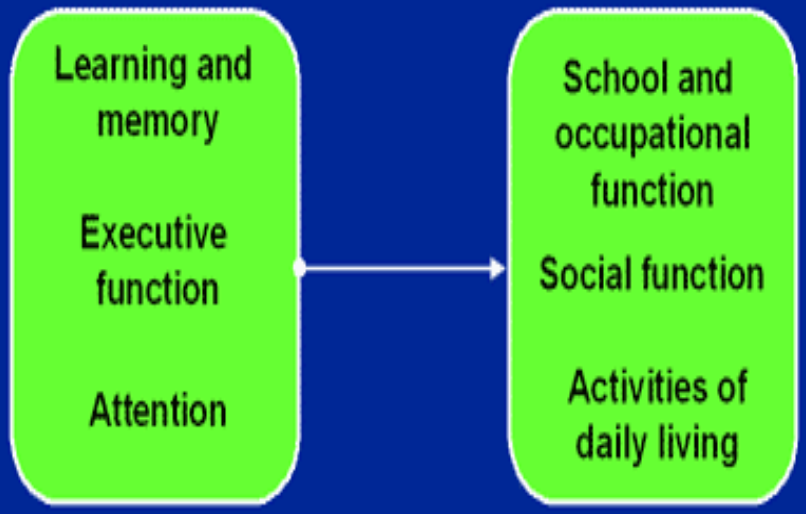
- Picture of schizophrenia includes positive and negative symptoms.
- Positive symptoms like: delusions & hallucinations.
- Negative symptoms like: affective flattening or blunting, poverty of speech, poor grooming, lack of motivation, and social withdrawal.

Cognitive deficits in schizophrenia

Multiple Mechanisms for Cognitive Dysfunction in Schizophrenia



Cognitive Deficits Predict Functional Outcomes



Green 1996; Velligan et al 1997

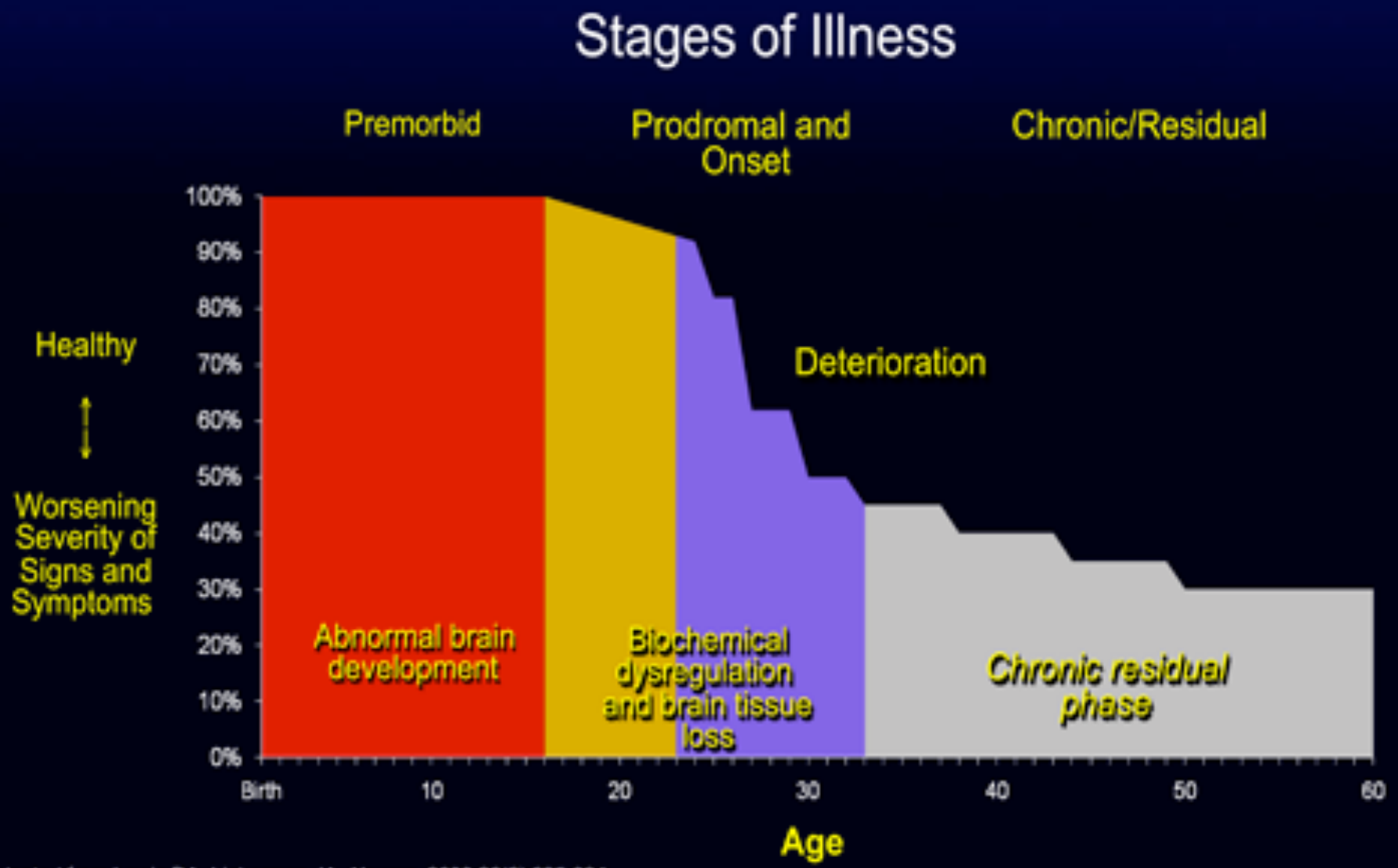
Mental status examination

- Appearance & behavior (variable presentations)
- Mood, feelings & affect (reduced emotional responsiveness, inappropriate emotion)
- Perceptual disturbances (hallucinations, illusions)
- Thought: Thought content (delusions)
  Form of thought (looseness of association)
  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

Criteria of other Psychotic Disorders

- Psychotic Disorders due to another medical condition
- Substance-induced psychotic disorder

- Schizophreniform disorder ;

1-6 month of disturbance

- Brief psychotic disorder:

<1month of disturbance

- Delusional disorder(delusion only >1m)

- **Schizoaffective disorder:** An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia. There is Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode during the illness course.

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:

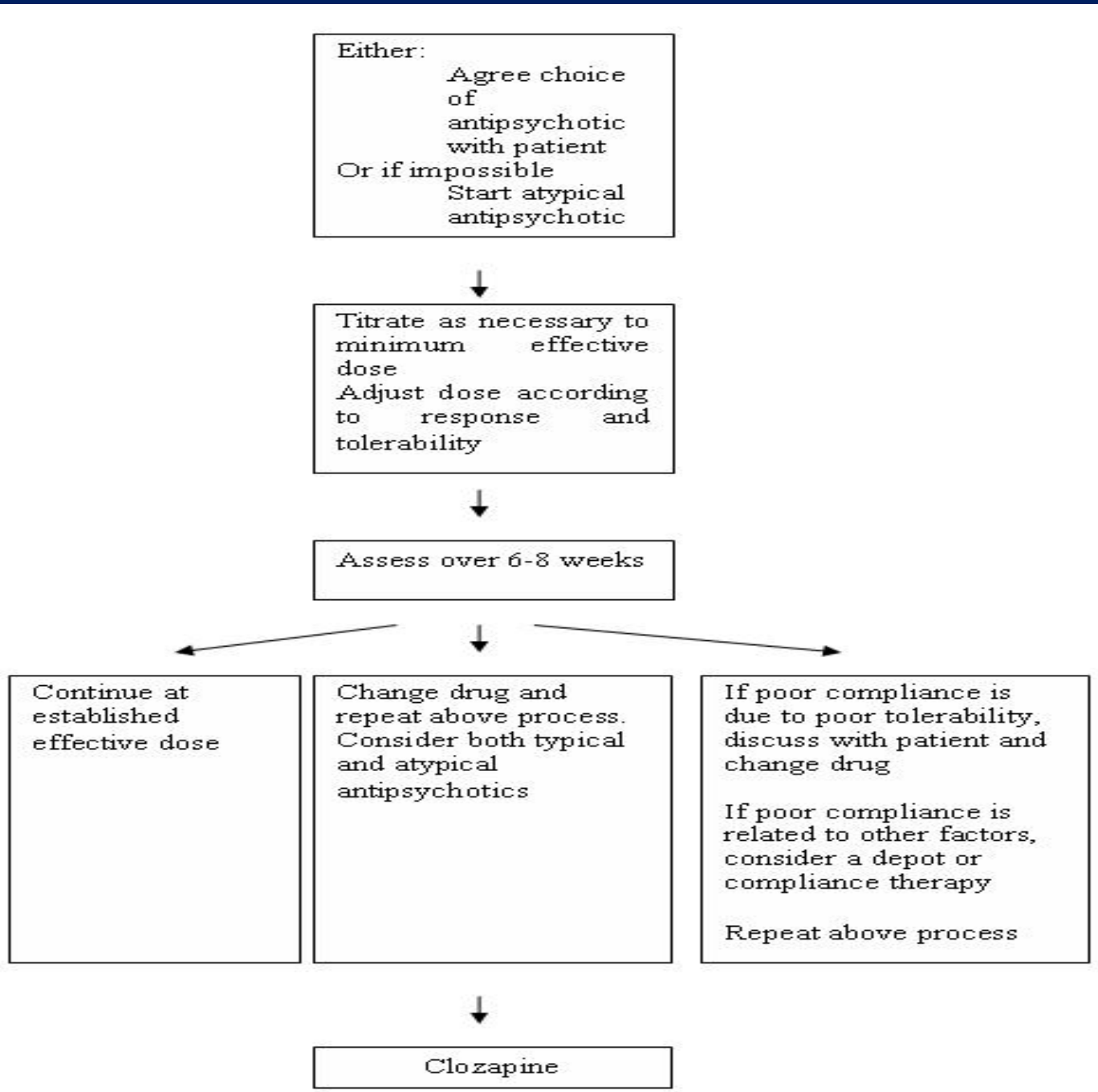
-Conventional, (1st generation) e.g. haloperidol, chlorpromazine.

-Atypical, 2nd generation (Serotonin-dopamine receptor antagonists) e.g. 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

- Pharmacological Treatment Algorithm Adapted from the Maudsley prescribing Guidelines



Side effects of antipsychotics

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-HT_{2A}	Anti-EPS (?)
5-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.

- **High Potency typical antipsychotics: Neurological side effects**
- **Low Potency typical and atypical antipsychotics: many other side effects**

Common side effects of antipsychotic medication (Taylor et al, 2005)

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

Psychosocial therapies

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

Thank you