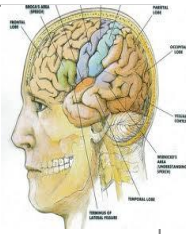


Schizophrenia



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Etiology



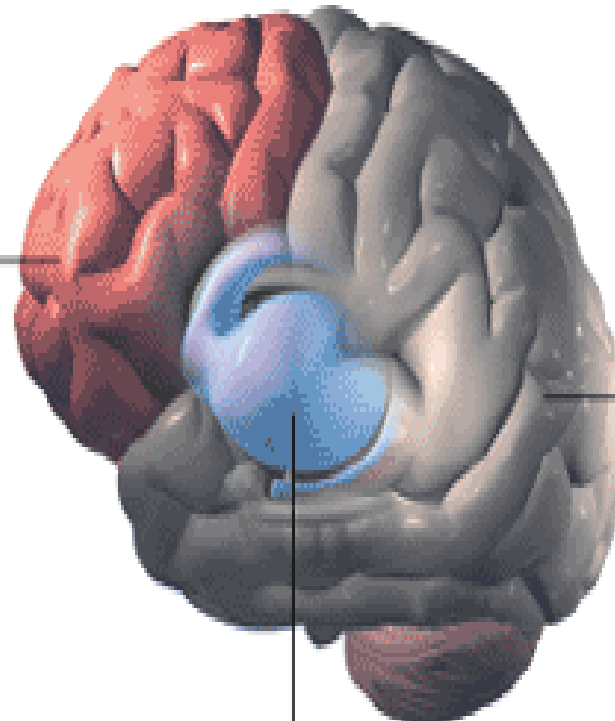
Exact etiology is **unknown**.

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.

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 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.

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

ALFRED T. KAMAJIAN

THE BRAIN IN SCHIZOPHRENIA

MANY BRAIN REGIONS and systems operate abnormally in schizophrenia, including those highlighted below. Imbalances in the neurotransmitter dopamine were once thought to be the prime cause of schizophrenia. But new findings suggest that

impoverished signaling by the more pervasive neurotransmitter glutamate—or, more specifically, by one of glutamate's key targets on neurons (the NMDA receptor)—better explains the wide range of symptoms in this disorder.

BASAL GANGLIA

Involved in movement and emotions and in integrating sensory information. Abnormal functioning in schizophrenia is thought to contribute to paranoia and hallucinations. [Excessive blockade of dopamine receptors in the basal ganglia by traditional antipsychotic medicines leads to motor side effects.]

FRONTAL LOBE

Critical to problem solving, insight and other high-level reasoning. Perturbations in schizophrenia lead to difficulty in planning actions and organizing thoughts.

LIMBIC SYSTEM

Involved in emotion. Disturbances are thought to contribute to the agitation frequently seen in schizophrenia.

AUDITORY SYSTEM

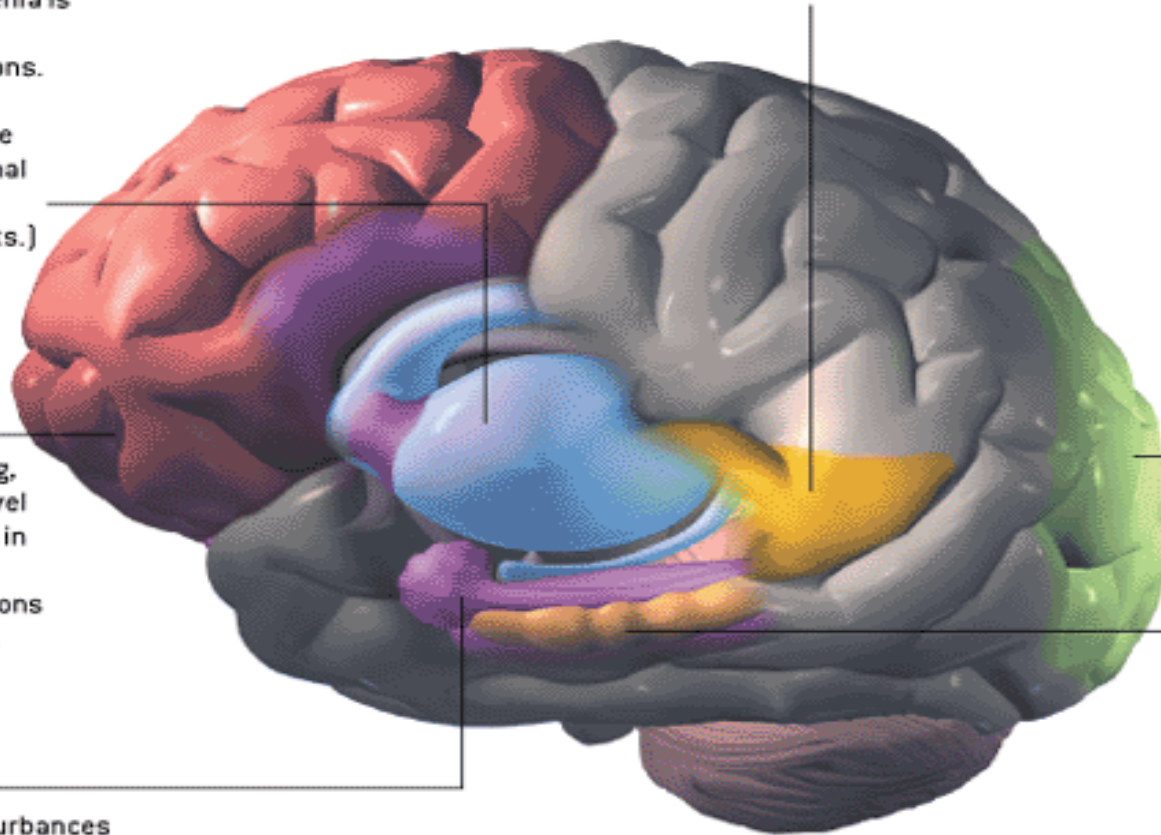
Enables humans to hear and understand speech. In schizophrenia, overactivity of the speech area (called Wernicke's area) can create auditory hallucinations—the illusion that internally generated thoughts are real voices coming from the outside.

OCCIPITAL LOBE

Processes information about the visual world. People with schizophrenia rarely have full-blown visual hallucinations, but disturbances in this area contribute to such difficulties as interpreting complex images, recognizing motion, and reading emotions on others' faces.

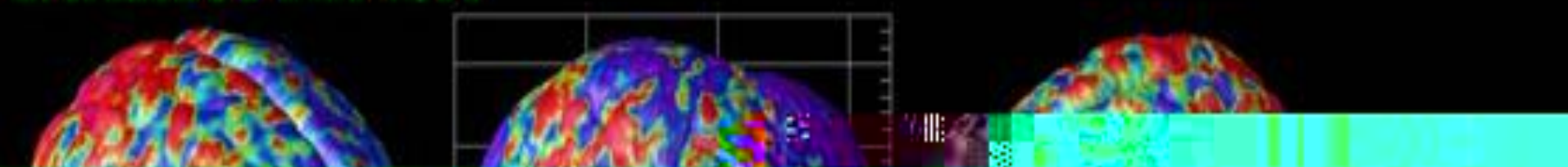
HIPPOCAMPUS

Mediates learning and memory formation, intertwined functions that are impaired in schizophrenia.



Early and Late Gray Matter **Deficits** in Schizophrenia

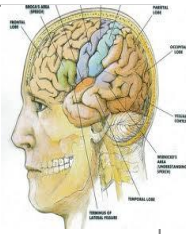
EARLIEST DEFICIT



5 YEARS LATER (SAME SUBJECTS)

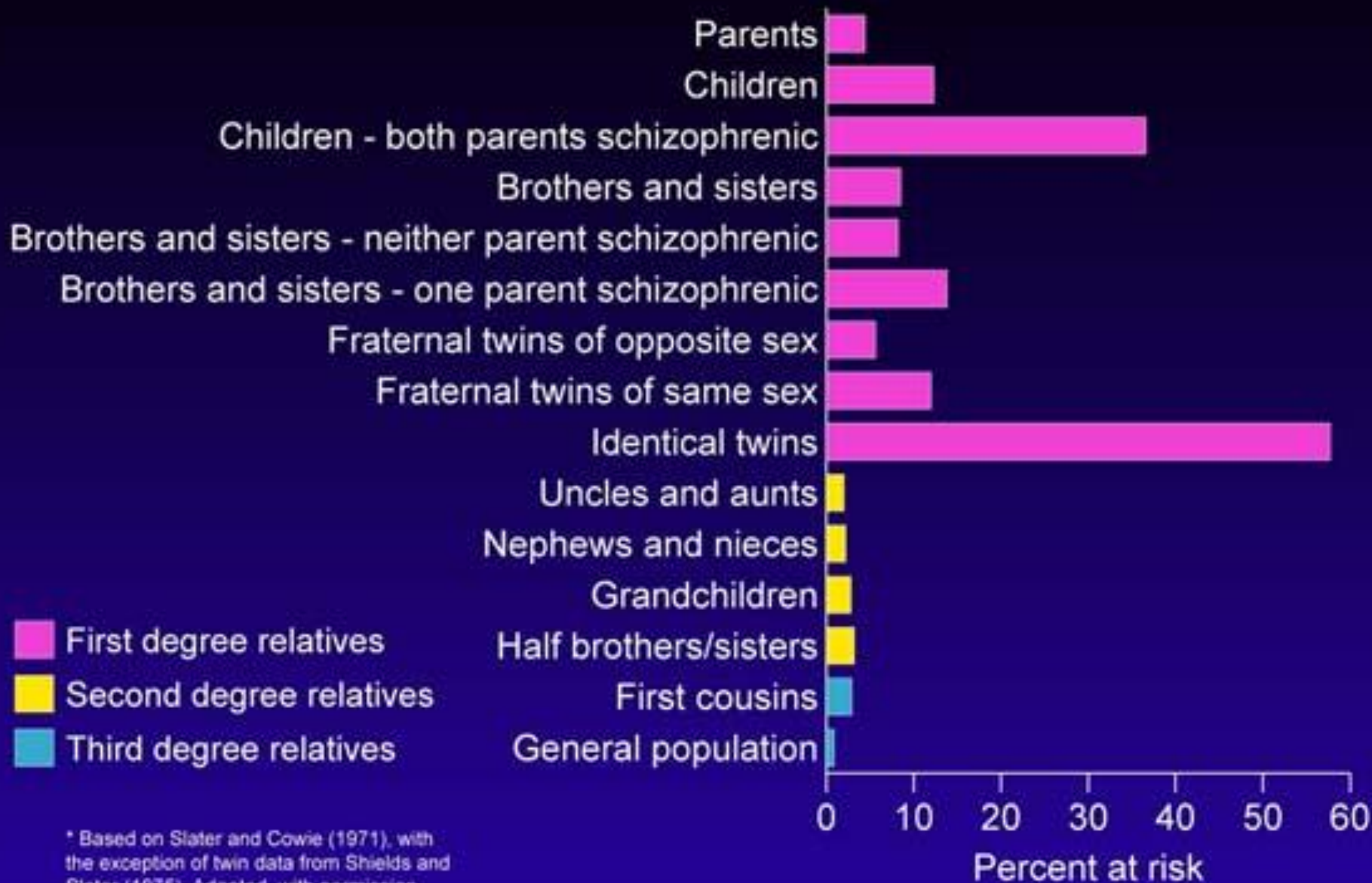


3- Genetic Factors



- A wide range of genetic studies strongly suggest a genetic component to the inheritance of schizophrenia that outweighs 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 Vandermeij (1980).

Schizophrenia: genes plus stressors

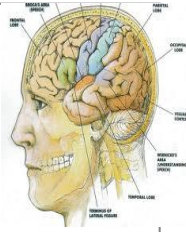


TABLE.
Susceptibility Genes for Schizophrenia

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	

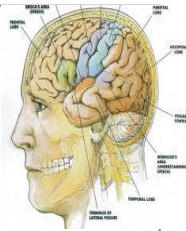
DISC-1=disrupted in schizophrenia-1; DAOA=D-amino acid oxidase activator (G72/G30); DAAO=D-amino acid oxidase; RGS4=regulator of G-protein signalling 4; COMT=catechol O methyl transferase; CHRNA7= α -7 nicotinic cholinergic receptor; GAD1=glutamic acid decarboxylase 1; GRM3=glutamate receptor, metabotropic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

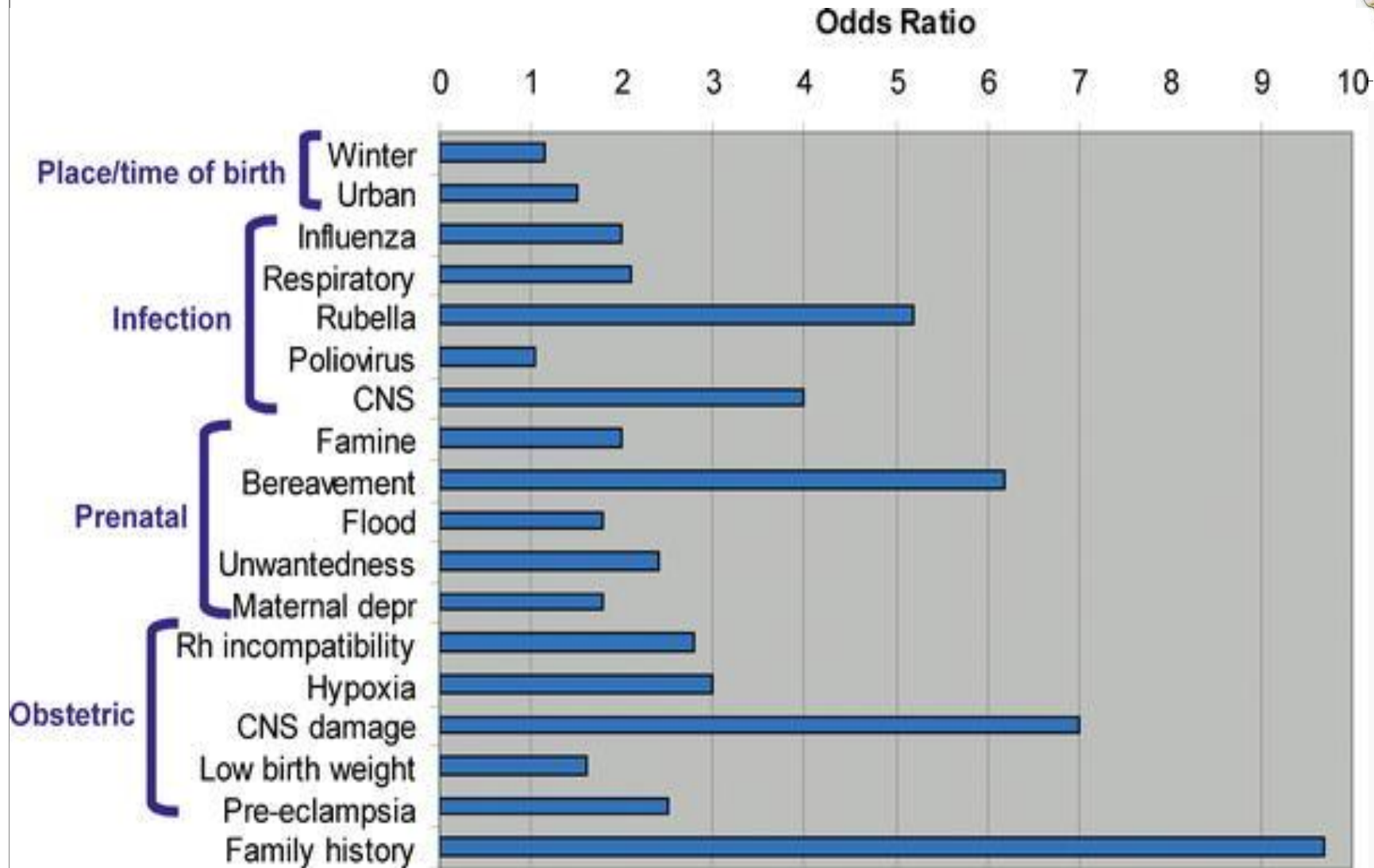
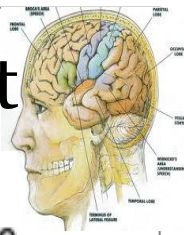
*Stephen M The Genetics Of Schizophrenia
Converge, Upon, The NMDA Glutamate Receptor, CNS Spectr.
2007*

4- Psychosocial Factors;

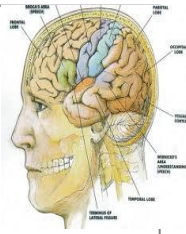


- In family dynamics studies, no well-controlled evidence indicates specific family pattern plays a causative role in the development of schizophrenia.
- High Expressed Emotion family : increase risk of relapse.

Weight of different RF: Family history comes first



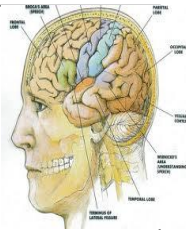
Diagnosis



DSM-IV-TR Diagnostic Criteria for Schizophrenia:

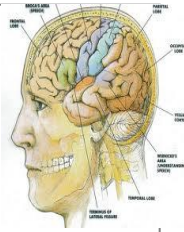
A- \geq two characteristic symptoms

- 1- Delusions
- 2- Hallucinations
- 3- Disorganized speech
- 4- Disorganized behavior
- 5- Negative symptoms



- B- Social / Occupation dysfunction
- C- Duration of at least 6 months
- D- Schizoaffective & mood disorder exclusion
- E- Substance / General medical condition exclusion
- F- Relationship to pervasive developmental disorders

Subtypes of Schizophrenia



Paranoid type

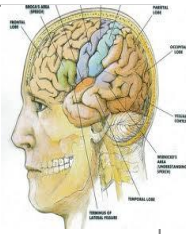
Disorganized type

Catatonic type

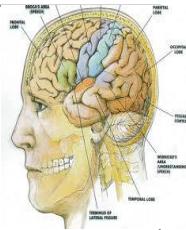
Undifferentiated type

Residual type

Clinical Features

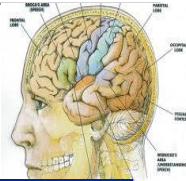


- ❑ No clinical sign or symptom is pathognomonic for schizophrenia
- ❑ Patient's history & mental status examination are essential for diagnosis.
- ❑ Premorbid history includes schizoid or schizotypal personalities, few friends & exclusion of social activities.
- ❑ Prodromal features include obsessive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

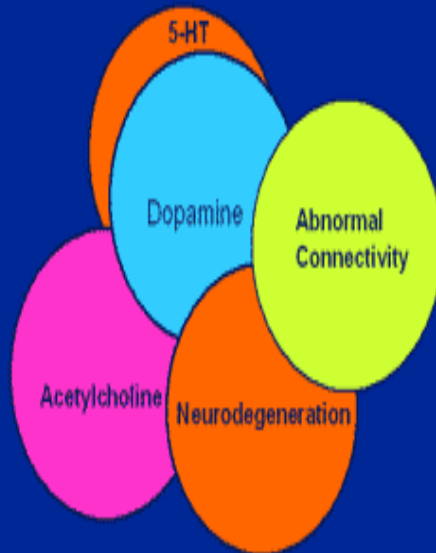


- Picture of schizophrenia includes positive and negative symptoms.
- Positive symptoms like: delusions & hallucinations.
- Negative symptoms like: affective flattening or blunting, poverty of speech, poor grooming, lack of motivation, and social withdrawal.

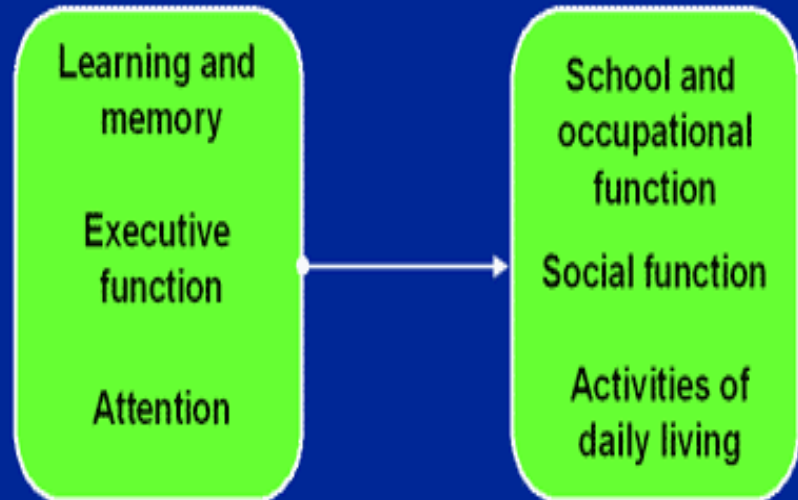
Cognitive deficits in schizophrenia



Multiple Mechanisms for Cognitive Dysfunction in Schizophrenia

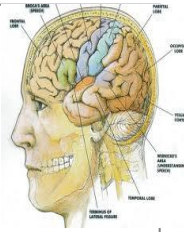


Cognitive Deficits Predict Functional Outcomes



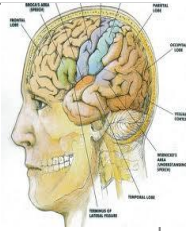
Green 1996; Velligan et al 1997

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

Prognosis



Good 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

Poor P.F

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

Nonpsychiatric disorders:

Substance-induced disorders

Epilepsy (TLE)

CNS diseases

Trauma

Others

Psychiatric disorders:

Schizophreniform disorder

Brief psychotic disorder

Delusional disorder

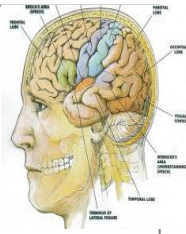
Affective disorders

Schizoaffective disorder

Personality disorders (schizoid, schizotypal & borderline personality)

Malingering & Factitious disorders

Treatment



What are the indications for hospitalization?

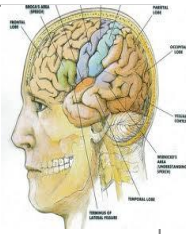
Diagnostic purpose

Patient & other's safety

Initiating or stabilizing medications

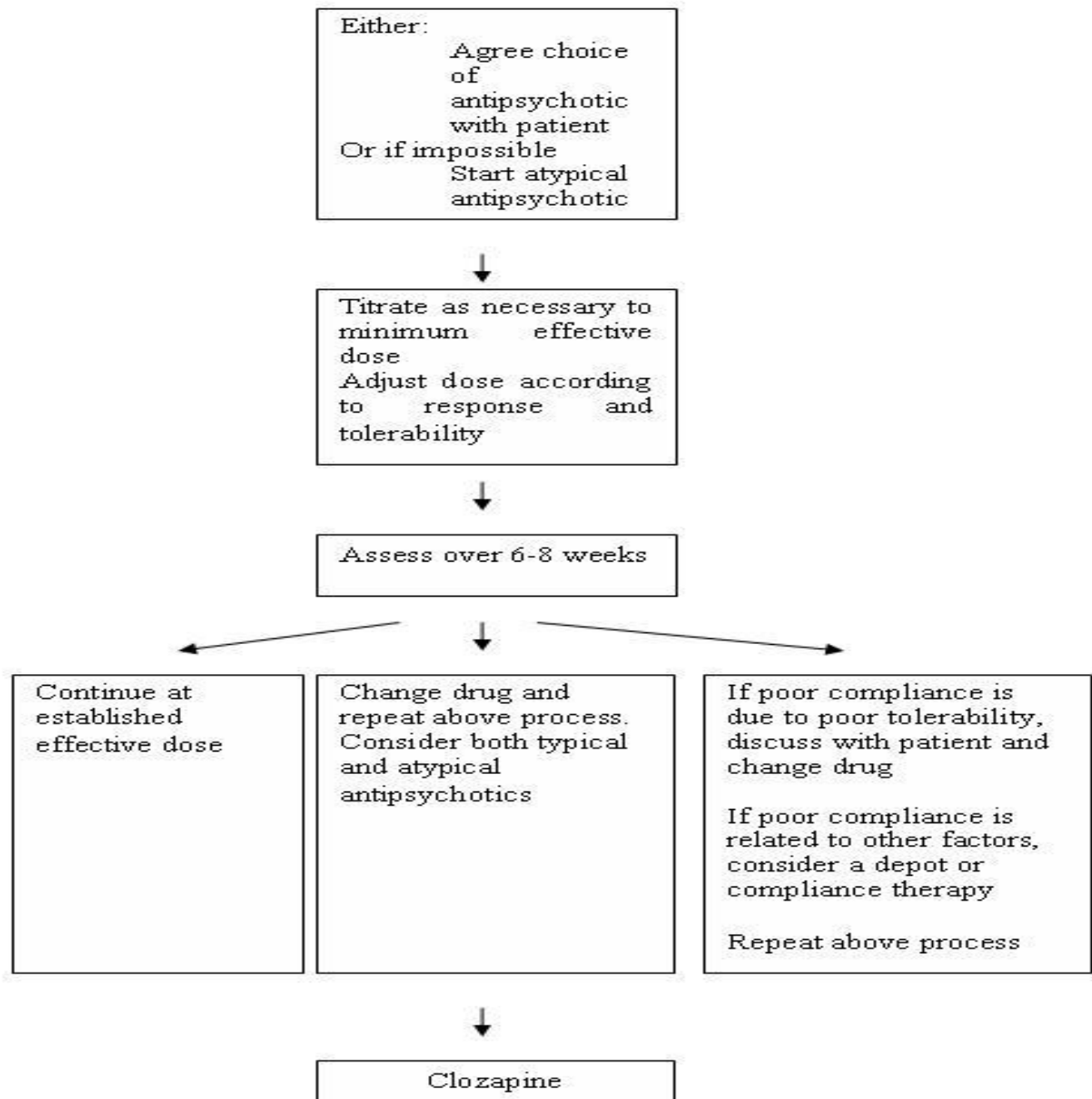
Establishing an effective association between patient
& community supportive systems

Biological therapies

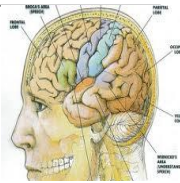


- ❑ Antipsychotic medications are the mainstay of the treatment of schizophrenia.
- ❑ Generally, they are remarkably safe.
- ❑ Two major classes:
 - Dopamine receptor antagonists (haloperidol, chlorpromazine)
 - Serotonin-dopamine receptor antagonists (Risperidone, clozapine, olanzapine).
- ❑ Other drugs:
 - Anticonvulsants
 - Lithium
 - Benzodiazepines
- ❑ 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 (Taylor et al, 2005)

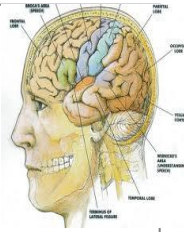


Common side effects of antipsychotic medication (Taylor et al, 2005)



<i>First generation antipsychotics</i>	<i>Second generation antipsychotics</i>	<i>Clozapine</i>
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

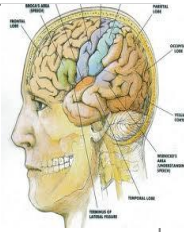
Family oriented therapies

Group therapy

Individual psychotherapy

Assertive community treatment

Vocational therapy



Thank you