

Schizophrenia: What Do We Know? Where Do We Go From Here?

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Objectives

Participants will be able to:

- Understand the clinical signs and symptoms of Schizophrenia
- Learn about the clinical course, epidemiology, pathophysiology, and unmet needs in Schizophrenia

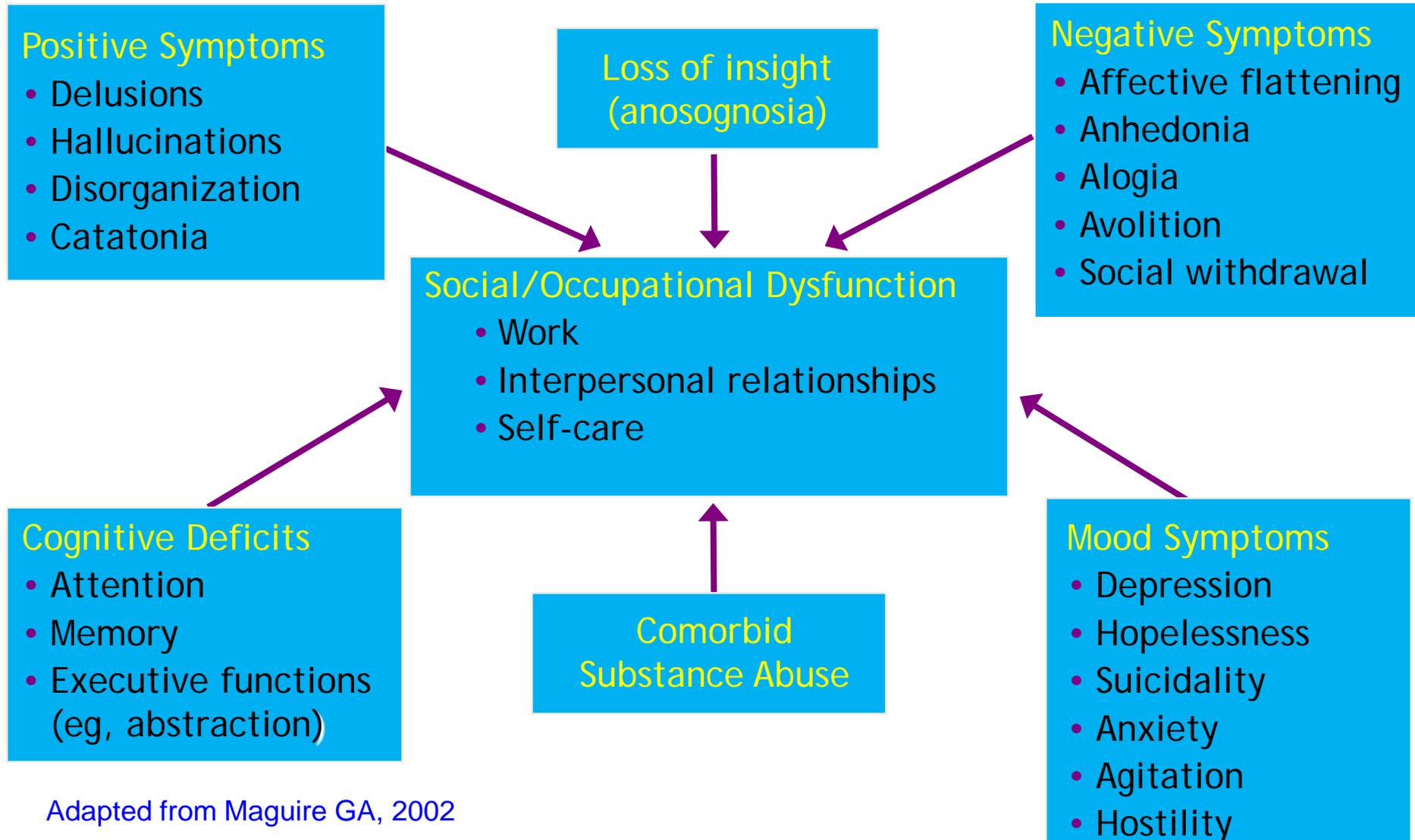
Diagnosis of Schizophrenia: DSM-5

- A. 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 (freq. derailment or incoherence)
 - 4) Grossly disorganized or catatonic behavior
 - 5) Negative symptoms (i.e., diminished emotional expression or avolition)

Diagnosis of Schizophrenia: DSM-5

- B. Social/occupational dysfunction
- C. Duration: Continuous signs for at least 6 months (psychosis + prodrome + residual sx)
- D. Schizoaffective and psychotic mood disorder have been excluded
- E. Not attributable to substance or general medical condition
- F. Not a manifestation of a pervasive developmental disorder

Features of Schizophrenia





Epidemiology of Schizophrenia

- Lifetime prevalence: 0.5 – 1.0%
 - DSM-5: 0.3 - 0.7%
- Average age of onset:
 - Males: teens to mid-20' s
 - Females: early to late 20' s
 - Range: Early childhood to 50' s/60' s
- Male slightly > female

Prodrome

- Highly variable in quality and duration
- May last from weeks to years
- May include cognitive, negative, attenuated positive, and various other symptoms

Morbidity and Mortality

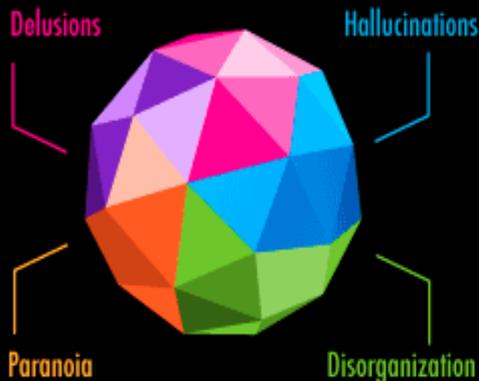


Leads to suicide in ~10% of cases,
especially in first decade of illness

Did You Know? Schizophrenia Stats



What Is Schizophrenia?

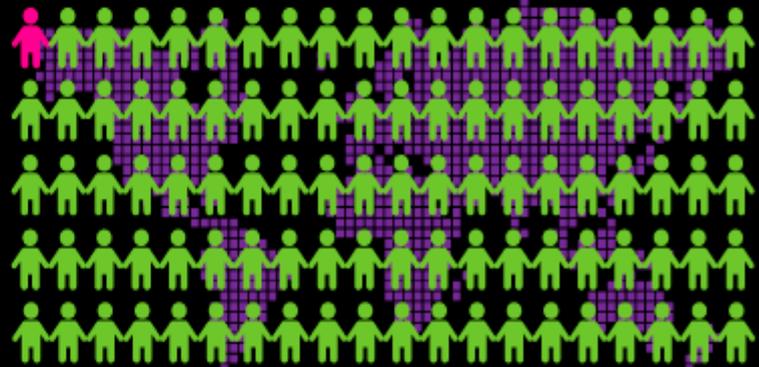


Schizophrenia is a complex, multifaceted mental illness that features many symptoms, including those above and many more. Sufferers deal with anxiety, depression, dissociation, synesthesia, etc.

What is the Age of Onset?

Symptoms begin for males and females at varying times through life. The graph below shows the typical age of onset.

Who Has Schizophrenia?



Schizophrenia affects roughly one percent of the general population...



1%

...that's 70 million people worldwide!



Etiology and Pathophysiology of Schizophrenia

Etiology and Pathophysiology

- Genetics
- Neuropharmacology
- Neuroanatomy
- Neural circuit dysfunction

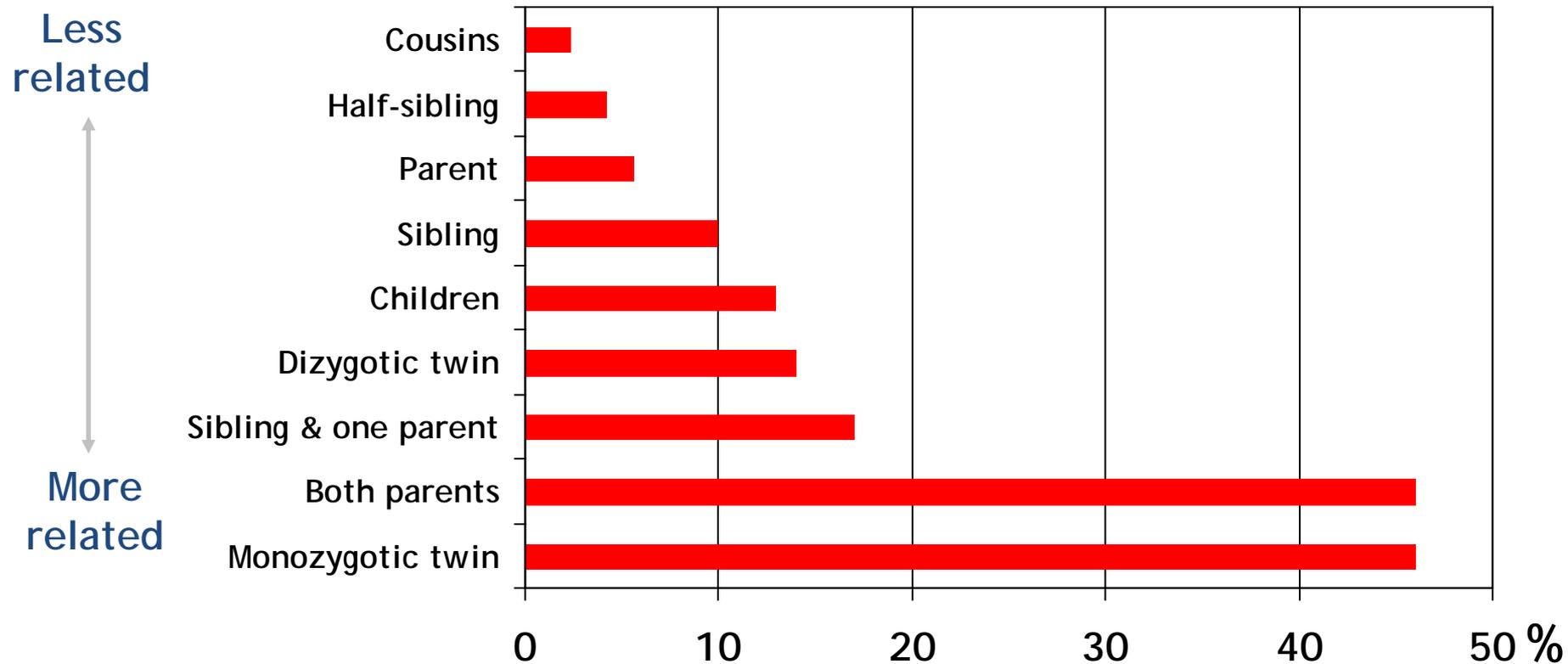


Genetics

Genetic vulnerability +
environmental factors
(intrauterine, post-natal)
= Schizophrenia



Lifetime expectancy for schizophrenia in relatives of schizophrenics

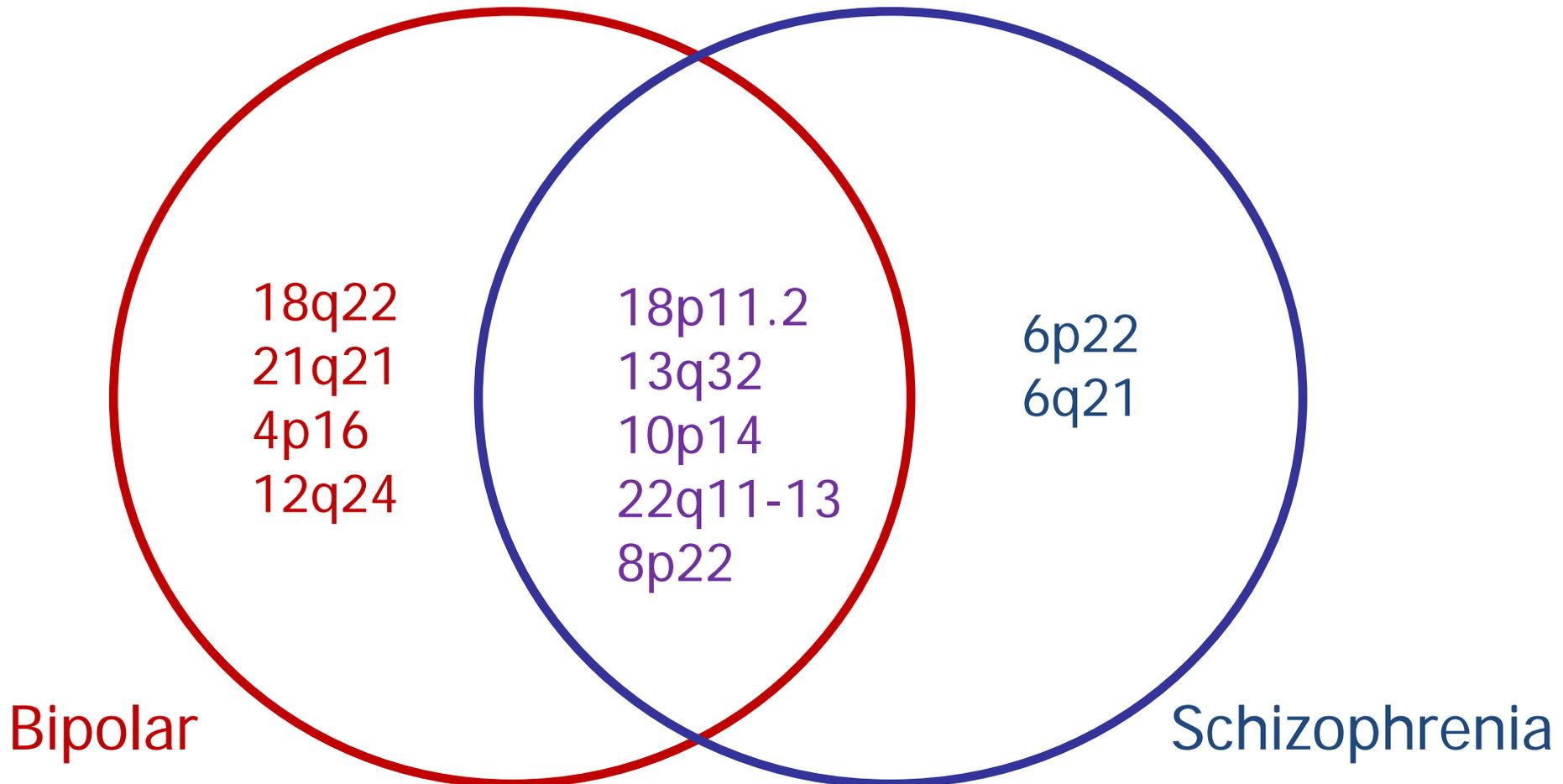


Candidate vulnerability genes

- Polygenic; widely distributed across genome
- Putative roles in:
 - Neurodevelopment & neuroprotection (dysbindin, BDNF, DISC-1)
 - Glutamate function (neuregulin-1)
 - Monoamine function & receptors (dysbindin, COMT, MAOA)
 - White matter
- Copy number variants (deletions & repeats)

Linkage Analysis Studies

Linkage Analysis: A gene hunting technique that traces patterns of disease in high-risk families, in an attempt to locate a disease-causing gene by identifying genetic markers of known chromosomal location that are co-inherited with the illness.





Neuropharmacology

Neuropharmacology

- Major hypotheses:
 - Dopamine
 - Glutamate
- Minor: serotonin, GABA, other



Dopamine Hypothesis

- Psychotomimetic effect of dopaminergic drugs
- Antipsychotic medicines cause parkinsonian symptoms & block dopamine (D_2) receptors



Dopamine Hypothesis

- Mesolimbic hyperdopaminergia
 - Positive symptoms
- Mesocortical hypodopaminergia
 - Negative/cognitive symptoms



Glutamate, GABA and the NMDA receptor

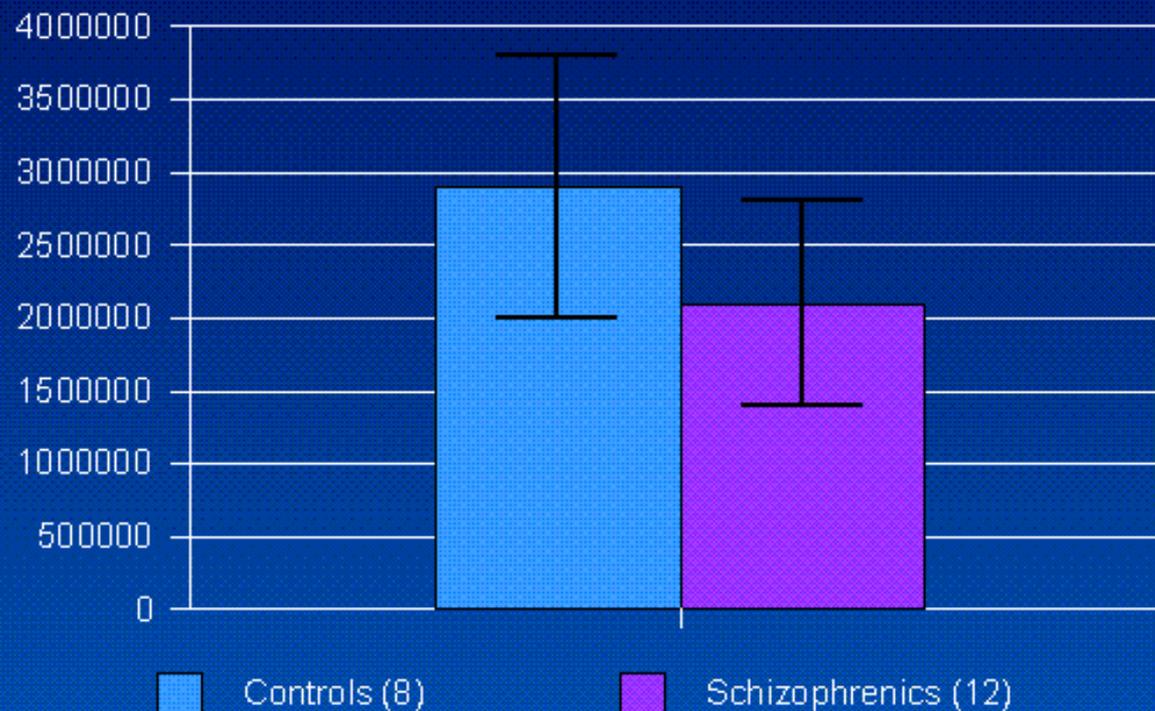
- Psychotomimetic effect of PCP (NMDA antagonist)
- Abnormalities in glutamate levels, release, receptors in schizophrenia



Neuroanatomy:
Microscopic

Neuronal Number

Medial Dorsal Nucleus

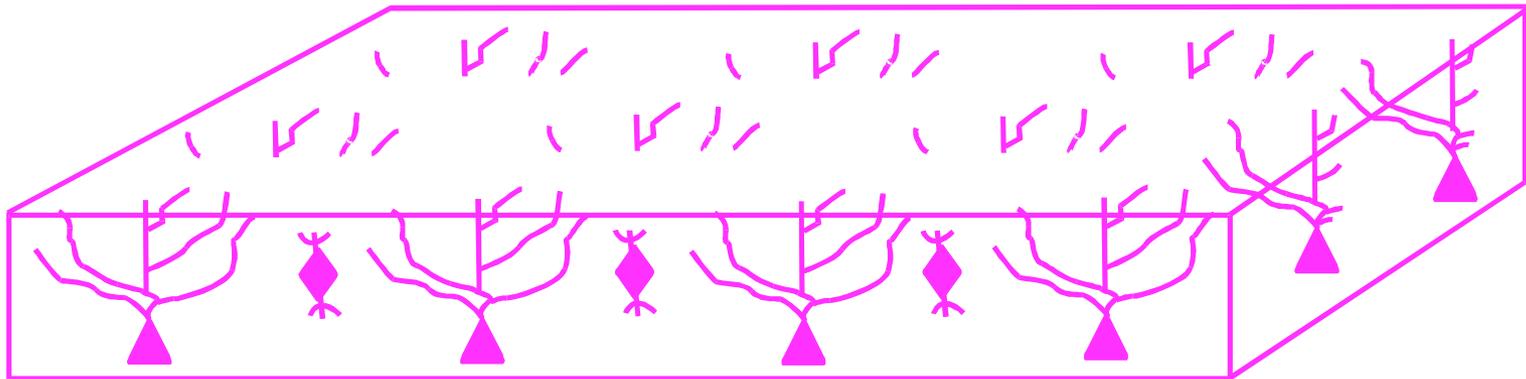


$P = .032$

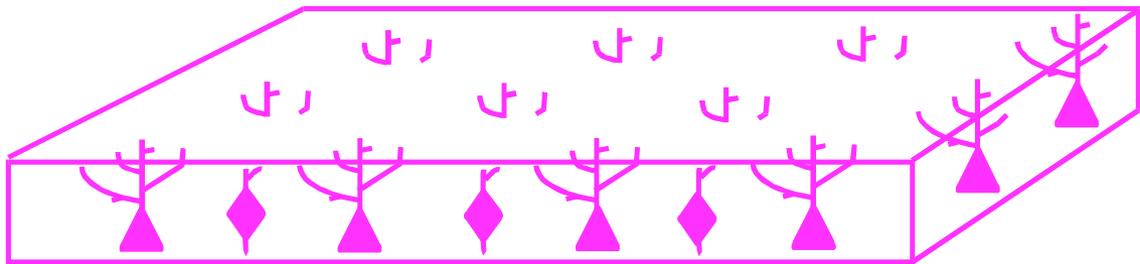
Present Study	3,000,000 neurons with 28% reduction
Popken et al (2000)	3,000,000 neurons with 27% reduction
Young et al (2000)	2,000,000 neurons with 35% reduction
Pakkenberg (1990)	5,000,000 neurons with 40% reduction



Failure of normal cellular organization in prefrontal cortex



Normal



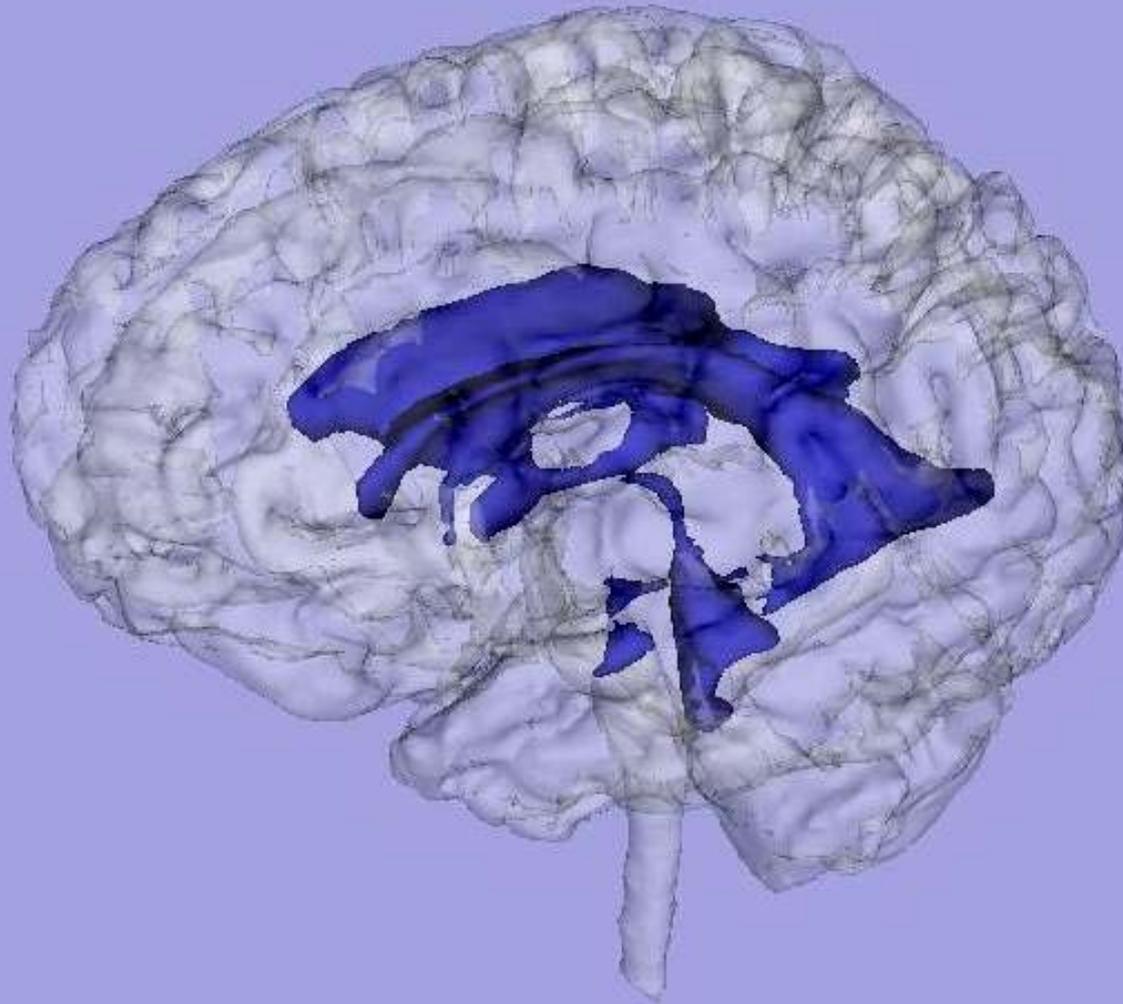
Patients with schizophrenia

Selemon et al. *Arch Gen Psychiatry* 1995; 52:805



Neuroanatomy:
Gross & Regional

Ventricles





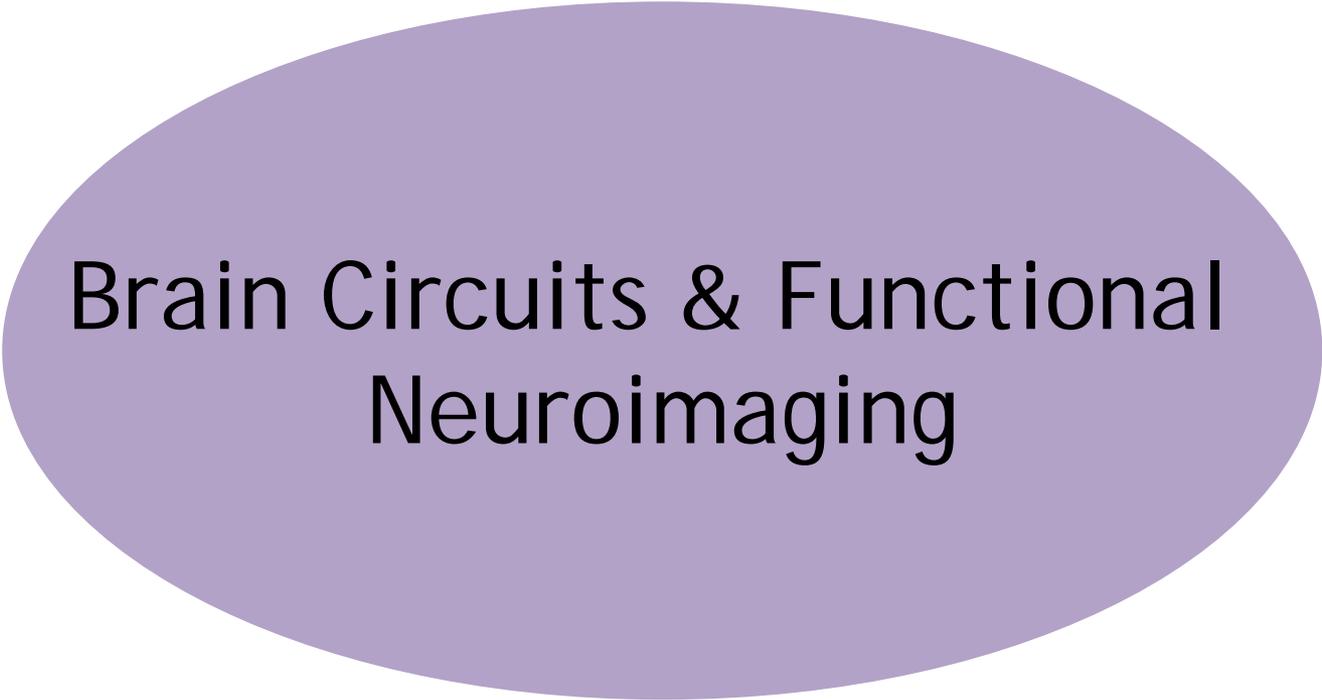
Schizophrenia: Structural Imaging Findings

- Enlarged ventricles and sulci
- Reported in 1927 (pneumoencephalography)¹
- Replicated early in CT era²
- Replicated ~ 100 times since then with CT³ and MRI⁴
- Associated with poor prognosis, negative sx, cognitive deficits

¹Jacobi W, Winkler H. *Arch Psychiatr Nervenkr*, 1927; ²Johnstone EC, et al. *Lancet*, 1976; ³Andreasen NC, et al. *Arch Gen Psychiatry*, 1990; ⁴Andreasen NC, et al. *Arch Gen Psychiatry*, 1990

Other structural abnormalities

- Decreased volume:
 - Medial temporal (limbic) structures (hippocampus, e
 - Prefrontal cortex
 - Thalamus, esp. mediodorsal nucleus
- White matter abnormalities
- Striatal changes
- Deviations from normal asymmetry



Brain Circuits & Functional
Neuroimaging

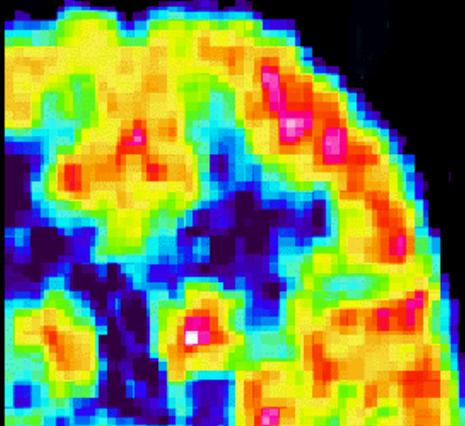


Prefrontal cortex: Functional Imaging Findings

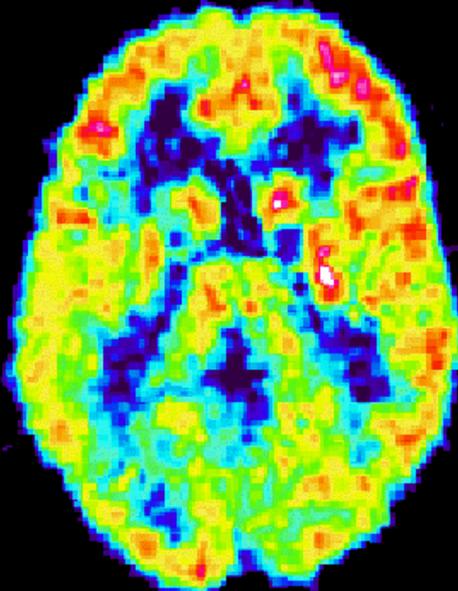
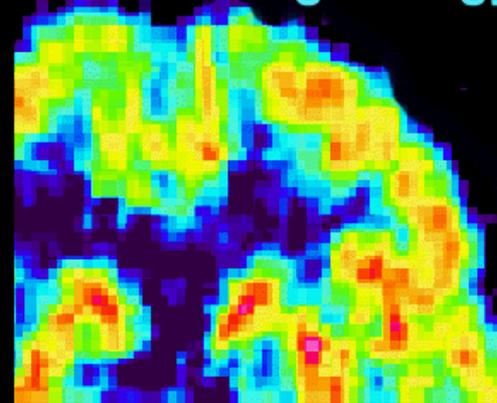
- Hypoactivity of the frontal lobes, esp. DLPFC (“hypofrontality”)
- Inconsistent at rest, but robust during prefrontal task (e.g., Wisconsin Card Sorting Test)



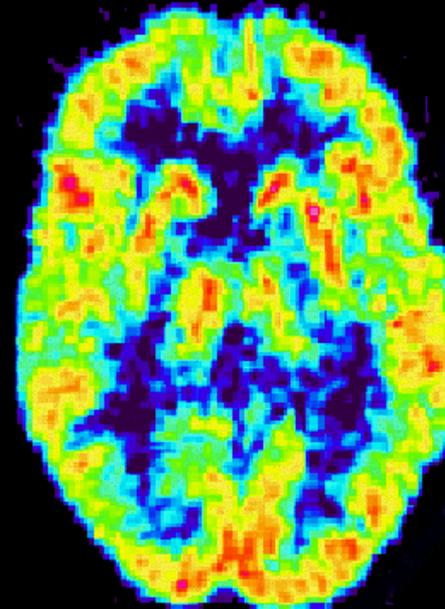
**active in
frontal cortex**



**less active in
frontal lobe and
cingulate gyrus**



**Normal
control**



**Schizophrenia
patient**



Aberrant neurodevelopment
and neuroprotection

Neurodevelopmental hypothesis

Aberrant neurodevelopment present at birth, but does not manifest symptoms until normal neuromaturational events occur in teens/early adulthood

Neurodegeneration

- Clinical progression
- Direct imaging evidence

Delusions

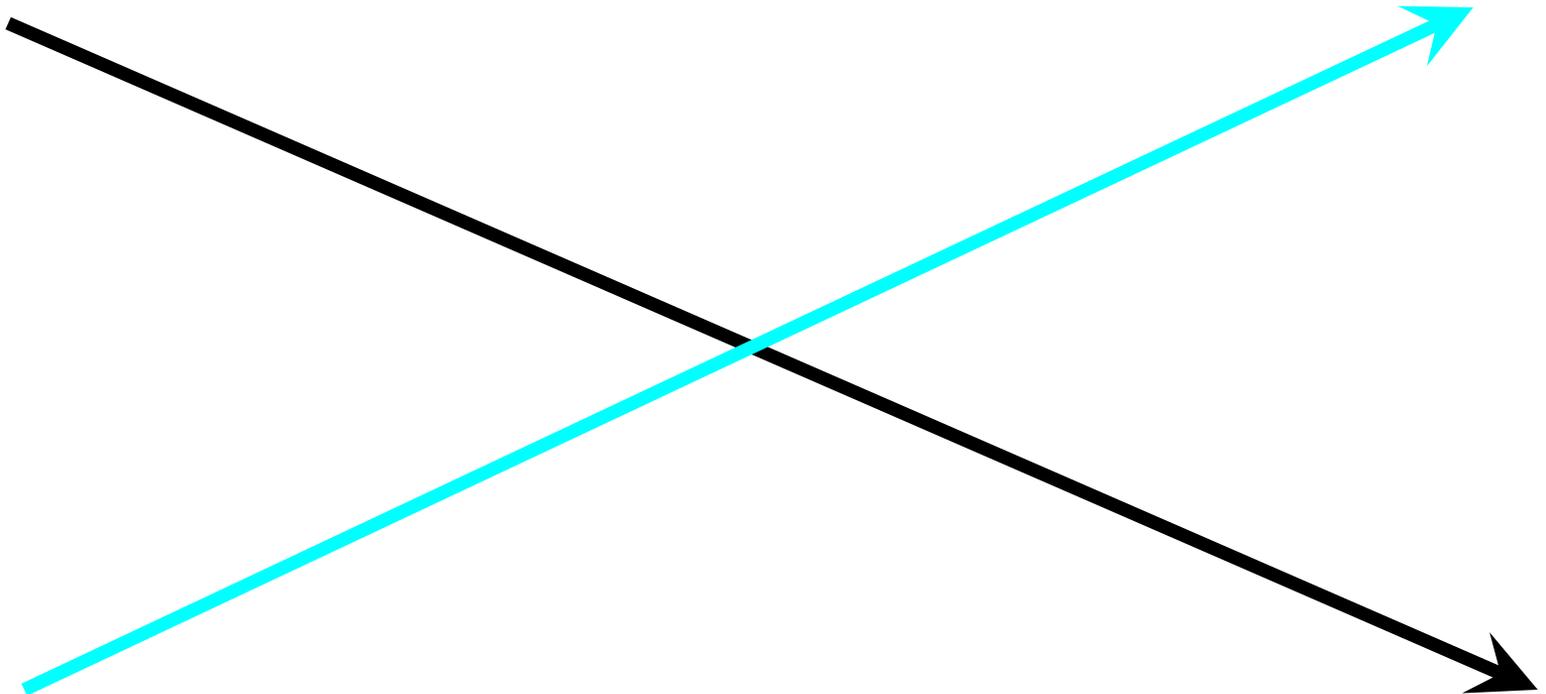
Hallucinations

Strong affects

Negative symptoms

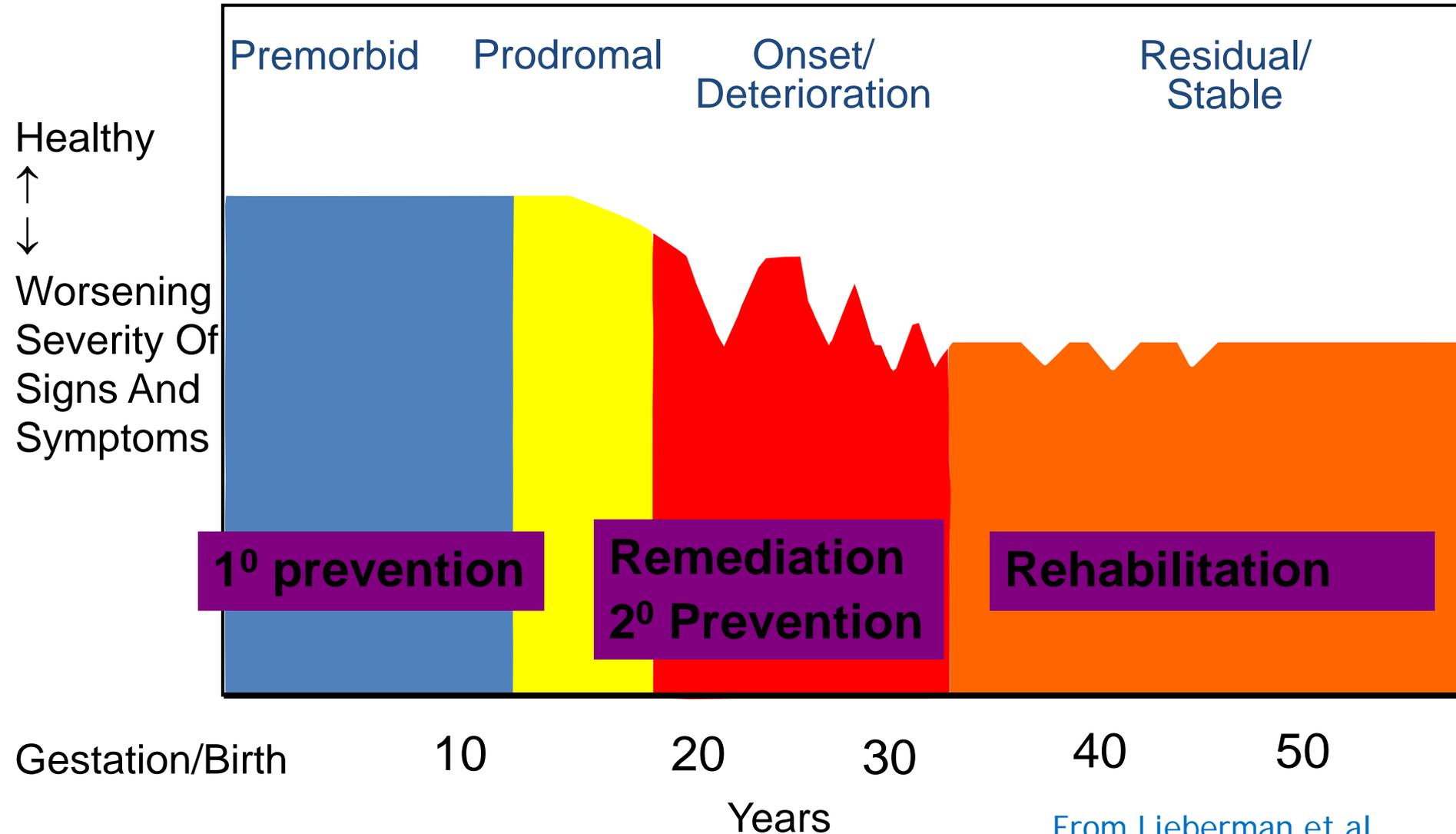
Cognitive symptoms

Thought Disorder



Natural History of Schizophrenia

Stages Of Illness



Other psychotic disorders

- Schizophreniform
- Brief Psychotic
- Schizoaffective
- Delusional
- Substance-induced Psychosis
- Psychosis d/t gen' l medical disorder
- Other
 - Persistent AH
 - Attenuated psychosis
 - Overlapping mood/delusions
 - Partner of delusional pt.
- Unspecified



Schizophreniform Disorder

- A. Criteria A, D, & E of schizophrenia are met
- B. Episode (including prodromal, active, residual phases) lasts ≥ 1 month but <6 months
- C. “Provisional” if waiting for 6-month point
- D. Specifiers: w/ vs w/o good prognostic features;
w/ catatonia



Brief Psychotic Disorder

- A. Presence of ≥ 1 of: delusions; hallucinations; disorganized speech; grossly disorganized/catatonic behavior
- B. Duration of sx: ≥ 1 day, < 1 month; full return to premorbid function
- C. Not d/t mood, other psychotic disorder or substances or gen' l med. Condition
- D. Specifiers: w/ vs w/o marked stressors; postpartum



Schizoaffective Disorder

- A. Period of illness w/ either mania or major depression *and* criteria A of schizophrenia
- B. During *same episode as above*, delusions or hallucinations $\times \geq 2$ weeks w/o mood sx
- C. Prominent mood episodes throughout total duration of illness
- D. Not d/t substances, gen' l med. Condition
- E. Specifiers: Bipolar/Depressive type



Delusional Disorder

- A. Delusion(s) of ≥ 1 month duration
- B. Criteria A of schizophrenia never fully met
- C. Behavior & function not markedly impaired except as affected by delusions
- D. Total duration of mania or depression brief relative to duration of delusions
- E. Not d/t substances or gen' l med. condition
- F. Specifiers: Erotomanic, grandiose, jealous, persecutory, somatic, mixed; bizarre

Other causes of psychosis

Psychiatric illness

- Major depression
- Mania
- OCD
- Dementias
- Personality disorders (esp BPD)
- Dissociative disorders
- Substance use

Non-psychiatric illness

- Epilepsy (TLE)
- Mass intracranial lesions
- Metabolic disorders
- Encephalopathies
- Infection
- Autoimmune
- Nutritional
- Drugs & toxic states

What do we do?

Early intervention is important

Psychoducation

Pharmacogenomic testing

CBT-P

Assisted Outpatient Probate (?)

Medications

Medication Overview:

Oral agents

Long Acting Injectables

AND ABOVE ALL ELSE,

-----NEVER, EVER GIVE UP HOPE

Thank you for your kind attention.....



Questions?