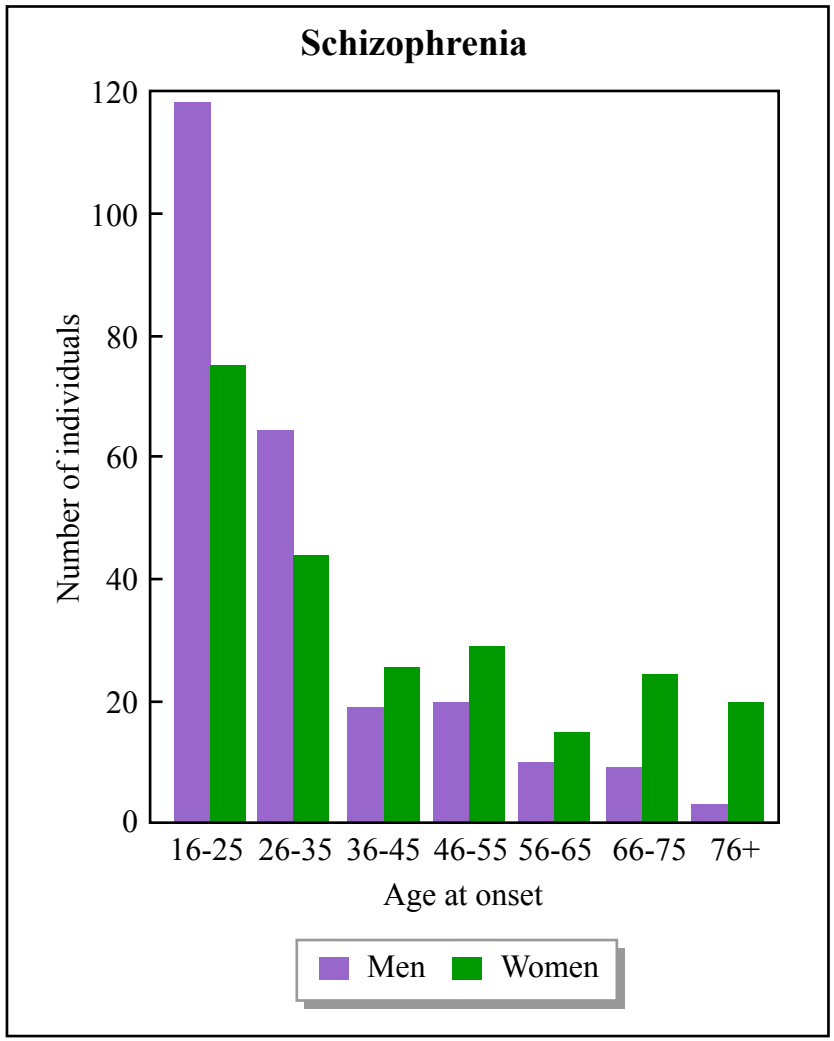
9.98 Neuropharmacology
January (IAP) 2009

Schizophrenia

Chronic disorder that occurs in 1% of the population.

It affects both men and women but the onset is different according to the gender



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Symptoms:

Illogical thinking

Inability to recognize reality

Hallucinations (voices insulting or commanding)

Absence of emotions, lack of feelings

Symptoms change over time

Functional Imaging studies revealed:

Decreased activity in the prefrontal area (hypofrontality)

Activation of cortical areas during hallucinations

Increased activity also in subcortical areas: i.e.limbic system

Positive symptoms:

Hallucinations

Disorganized speech

Treated with antagonist of D2 receptors, aggravated by increasing DA transmission

Negative symptoms:

Reduced speech

Social withdrawal

Intellectual impairement

Loss of motivation/ emotions

Treated with the “atypical antipsychotics”

Etiology of schizofrenia

Genetic components and environmental factors

Anatomical studies

There is an enlargement of the ventricles that is NOT caused by cell death. It is rather due do defects in development that preceed the onset of the symptoms

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Figure 18.12 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Also, there are changes in cellular structure non accompanied by gliosis. This suggests that the abnormalities occurred in the developmental process.

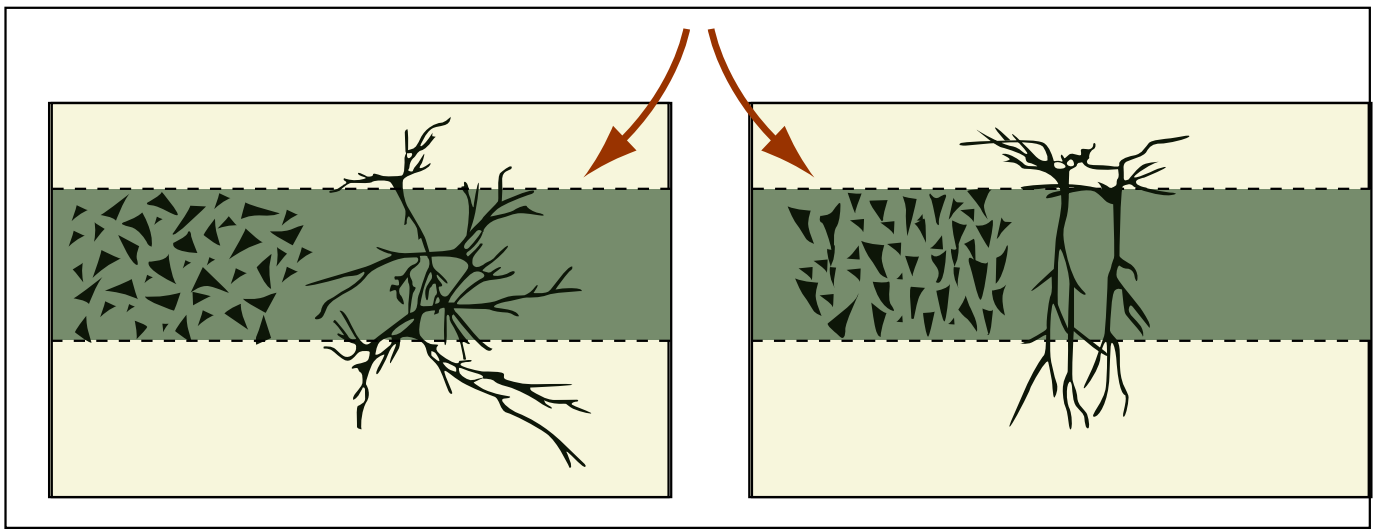

Figure by MIT OpenCourseWare.

Neurophysiological studies

Hypofrontality

EEG show that in schizofrenics, the electrical activity evoked by a stimulus is not localized, as in normal subjects, but it is widespread in the brain

Genetic studies

Linkage studies across affected individuals identified specific loci on chromosomes 13, 8, 22 and 6

Microarray analysis revealed impairments of transcripts for the presynaptic function in the prefrontal area, but also defects in glutamatergic and GABAergic Transmission, energy metabolism and growth factors

Schizofrenia is a neurodevelopmental disorder

Amphetamine-induced stereotypy used in animal models for schizofrenia

High dosage of amphetamine induce DA release

Drugs that treat the symptoms of schizofrenia (neuroleptics)
can cause motor impairment (catalepsy)

Gate hypothesis: schizofrenics fail to “gate” the stimulus they receive
(as measured by PPI)

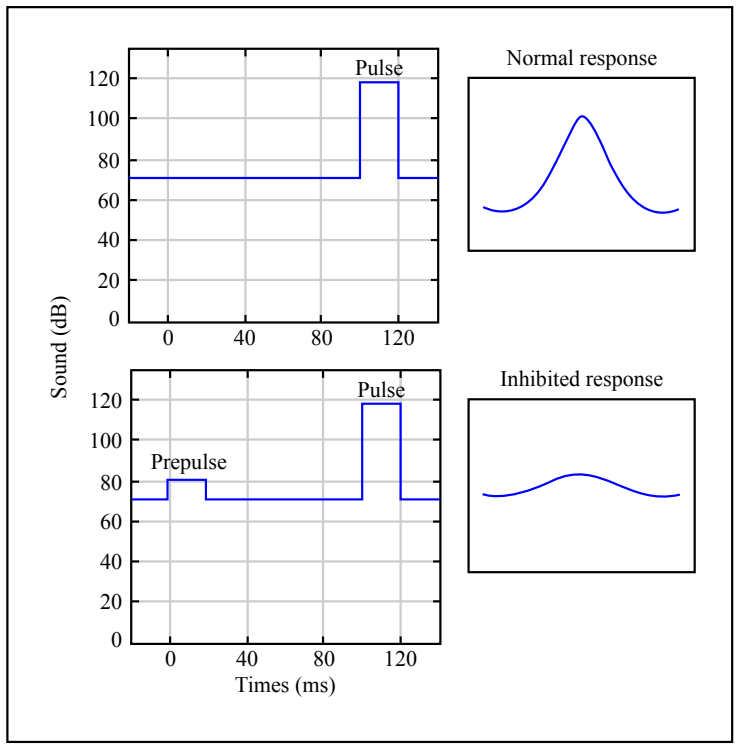

Figure by MIT OpenCourseWare.

The second generation drugs reduce the negative symptoms,
they have reduced side effects

Drugs that treat the symptoms of schizofrenia (neuroleptics)
can cause motor impairment (catalepsy)

There are evidences of a reduced glutamatergic function (on DA neurons)

Some studies have found no differences in DA transmission in schizofrenics

The second generation drugs reduce the negative symptoms,
they have reduced side effects

PPI is a measure of the “gate”
It is disrupted by systemic administration of DA agonists and reinstated by DA receptor-blocking antipsychotic drugs

PPI is also disrupted by systemic administration of serotonin agonists and Glutamate antagonists

Partial list of commonly used traditional and atypical antipsychotic drugs and their side effects (Part 1)

Generic name (trade name)	*Sedation*	*Autonomic side effects* [a]	*Hypotension* [b]	*Motor disorders*
Typical antipsychotics				
Chlorpromazine (Thorazine)	High	High	High	Moderate
Prochlorperazine (Compazine)	Moderate	Low	Low	High
Trifluprom azine (Vesprin)	High	Moderate	Moderate	Moderate
Thioridazine (Mellaril)	Moderate-high	Moderate-high	Moderate-high	Low
Trifluoperazine (Stelazine)	Low-moderate	Low-moderate	Low	High
Fluphenazine (Prolixin)	Low	Low	Low	High
Perphenazine (Trilafon)	Low-moderate	Low	Low	High
Mesoridazine (Serentil)	High	Moderate	Moderate	Low
Thiothixene (Navane)	Low	Low-moderate	Low	Moderate-high
Haloperidol (Haldol)	Low	Very low	Low	High-very high
Loxapine (Loxitane)	Moderate	Low	Low	Moderate
Molindone (Moban)	Moderate	Low	Very low	Low-moderate

[a] Includes blurred vision, dry mouth, reduced gastric secretion and motility, urinary retention, and constipation.
[b] Drop in blood pressure upon standing upright (orthostatic), dizziness, faintness, or blacking out.

Partial list of commonly used traditional and atypical antipsychotic drugs and their side effects (Part 2)

Generic name (trade name)	*Sedation*	*Autonomic side effects* [a]	*Hypotension*[b]	*Motor disorders*
Atypical antipsychotics				
Clozapine (Clozaril)	Moderate-high	Moderate	Moderate-high	Low
Olanzapine (Zyprexa)	Moderate	Low	Moderate	Very low
Risperidone (Risperdal)	Low-moderate	Very low-low	Moderate	Low
Quetiapine (Seroquel)	Moderate	Moderate	Moderate	Very low
Ziprasidone (Zeldox)	Low	Low	Moderate	Very low

[a] Includes blurred vision, dry mouth, reduced gastric secretion and motility, urinary retention, and constipation.
[b] Drop in blood pressure upon standing upright (orthostatic), dizziness, faintness, or blacking out.

The mechanisms of action are not clear