Psychosis

A symptom of mental illness characterized by the loss of contact with reality

Manifestations: hallucinations, disorganized thoughts and speech, emotions exhibited in an abnormal manner

Causes of psychosis
• Functional: schizophrenia, manic phase of bipolar disorder, psychotic depression
• Organic: Alzheimer's disease and other causes of dementia, brain tumors
• Drug abuse: cocaine, amphetamine, PCP ("angel dust")

Epidemiology

Lifetime prevalence	1% in US and worldwide
Onset	Most commonly in young adults
Sex	Equally prevalent in men and women
Frequency	More frequent in people born in cities and born between January and April and in the northern hemisphere
Suicide	~ 15%

Structural Abnormalities

Decreased cortical thickness in the absence of gliosis	⇨ Gliosis (proliferation of the glial cells) occurs as a compensatory change in the degenerative disease in the brain (typically happens later in life)
Reduction in volume of the frontal lobe, medial temporal lobe, thalamic and hippocampus	⇨ increased ventricular size

Decreased blood flow and glucose metabolism in the frontal lobe and left temporal lobe

Abnormal (excessive) synaptic pruning	⇨ decreased number of glutamanergic dendritic spines in PFC in individuals with schizophrenia
	⇨ Synaptic Pruning: the process of synapse elimination that occurs between age 2 and onset of puberty

Multiple NT systems interact in a particular way to cause the signs and Sx of SZ

Structural Abnormalities (cont)

Functional abnormalities are related to alterations in:	Dopamine, Glutamate, Serotonin

New Research: a person's risk of schizophrenia is increased if they inherit specific variants in a gene related to synaptic pruning
*⇨ **Complement Component 4 (C4)**: plays a role in the immune system, as well as brain development*

Pathogenesis of SZ | DOPAMINE

Hypothesis	SZ results from dysregulation of the mesolimbic and mesocortical pathways
Reasons	Drugs that block dopamine receptors are used in the Tx of SZ
	Drugs that increase dopaminergic activity (ie. amphetamines) can cause psychosis

Pathogenesis of SZ | SEROTONIN

▶ Serotonergic neurons originate in the raphe nuclei and project extensively to all regions of the cortex, basal ganglia, limbic system, hypothalamus, cerebellum and brain stem

▶ **High density of 5-HT-2A receptors in the cerebral cortex⇨ 5-HT-2A Receptors modulate the release of DA, glutamate, NE, GABA, and ACh** ⇨ regulation of cognitive processes, working memory, and attention

Serotonin 5-HT-2A receptor blockers (*2nd generation antipsychotic agents*) are used in the Tx of SZ

▶ = NORMAL

Clinical Manifestations

Definition	a chronic disorder of thought and affect with the individual having a *significant disturbance* in interpersonal relationships and *ability to function* in society on a daily basis
Symptomology	Often occur in **cycles**, alternating periods of improvement (**remissions**) with periods of psychosis (**relapses**)
	During acute psychotic episodes, the pt loses touch with reality
	Impaired psychosocial functioning during remissions

Although the course of illness is variable, the long-term prognosis is poor

Grouped into positive, negative, and cognitive symptoms

Positive	Delusions (often paranoid)
	Hallucinations (most often auditory)

Clinical Manifestations (cont)

	Thought Disorder (disorganized speech, loose associations)
Negative	Poverty of speech and speech content
	Flattening of emotional responsed
	Withdrawal from social contacts
Cognitive	Impaired attention, working memory, and executive function

Positive sx correlate with abnormalities in limbic pathways in the brain
⇨ Hyperactivity of Mesolimbic DA pathways ⇨ positive sx

Negative and cognitive sx can be associated with prefrontal lobe dysfunction
⇨ hypoactivity of mesocortical DA pathway ⇨ negative and cognitive sx

Positive sx typically respond to tx, while negative and cognitive sx often persist and contribute to chronic disability

Negative Symptoms

Alogia & Poverty of Speech	May speak very little or speech may have little meaningful content
	May have long delays between words and sentences, as if the connections between thoughts and speech were interrupted or blocked
Flattening or blunting of affect	May have reduced emotional expression
	May not smile or frown in response to happy or sad events
	Their voices may not change tone or pitch
	May not maintain eye contact or other kinds of emotional links with other people
Anhedonia and Avolition	May seem to lose interest in and energy for pleasurable activities and achievements
	Avolition = lack of desire, drive, or motivation to pursue meaningful goals
Catatonia and Posturing	May seem to freeze into unusual body positions or stop moving entirely

Negative Symptoms (cont)

	Catatonic pt's will sometimes hold rigid poses for hours and will ignore any external stimuli
	May also show stereotyped, repetitive movements

COGNITIVE SYMPTOMS

Lack of Motivation and Social Withdrawal	Contribute to poor-self care skills, difficulties maintaining employment, and living independently
Impaired Attention	Trouble focusing or paying attention
Impaired Working Memory	Ability to use information immediately after learning it
Poor executive function	Ability to understand information and use it to make decisions

⇨ Patients often have difficulty learning from their experiences and they can repeatedly make the same mistakes in situations requiring judgment

⇨ Poor insight into the severity of their disorder ⇨ they tend to stop therapy

Schizophrenia

A chronic psychiatric disorder characterized by impairments in the perception of realist, most commonly manifesting as disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affact, in the context of **significant social or occupational dysfunction**

Multiple emotional and cognitive functions are affects --> results in disability for a large proportion of SZ patients

Only partially effective, *symptomatic* treatment are available

• *Nothing **CURES/FIXES** the problem*

Etiology and Causes

Etiology	Unknown; cause is multifactorial
Genetics	Significant genetic component, with a complex, non-Mendelian inheritance
	The greatest risk factor is a **positive** family history
Genetic Studies	Many different genes are involved; patients inherit several risk genes
	SNPs and CNVs

Etiology and Causes (cont)

Environment	Pt's more likely to experience premature birth, low birth weight, and perinatal hypoxia
	Maternal viral infection during pregnancy (especially during the 2nd trimester)
	Early neurodevelopmental defect (brain vulnerability determines by genetic predisposition) combined with environmental factors/stressors ⇨ abnormal migration of neurons during CNS development ⇨ results in abnormal neuronal connectivity and abnormal brain circuits --> SZ

Dopaminergic Pathways in the Brain

Nigrostriatal	
	Originates in the substantia nigra ⇨ projects to the striatum
	Originates in the hypothalamus ⇨ projects to the anterior pituitary
Tuberoinfundibular	
	Part of basal ganglia ⇨ involved in the movement and pathogenesis of Parkinson's disease
	Endocrine function (dopamine inhibits prolactin secretion)
Mesolimbic and Mesocoritcal Pathways	Involved in the pathogenesis of SZ
	Both pathways originate in the ventral tegmental area ⇨ project to parts of the limbic system and the cortex
	Mesolimbic: VTA ⇨ Nucleus accumbens
	Mesocortical: VTA ⇨ Prefrontal Cortex (PFC)

Pathogenesis of SZ | GLUTAMATE

The glutamatergic system is most widespread excitatory NT system in the brain

Unlike dopaminergic neurons, glutamatergic neurons are distributed throughout the brain and play a role in sensory processing, memory, and other higher-level functions

Abnormal synaptic pruning of glutaminergic neurons ⇨ Decreased number of glutametergic dendritic spines in individuals with SZ ⇨ abnormal (decreased) neuronal connectivity

Glutamate Receptors: ionotropic (NMDA, AMPA, KA) and metabotropic glutamate receptors

▶ Normally, glutamatergic neurons inhibit dopaminergic neuronal activity in the VTA

▶ Glutamatergic neurons do NOT interact with dopaminergic neurons directly, but indirectly through GABA (*inhibitory*) interneurons

▶ When glutamatergic neuron is activated in the PFC ⇨ GABA neuron activation in the VTA ⇨ inhibition of dopamine neuron activity in the VTA

In SZ: NMDA receptor hypofunction hypothesis ⇨ glutamatergic neuronal or NMDA receptor deficiency results in dopaminergic hyperactivity ⇨ hallucinations and delusions ⇨ **hyperactivity of mesolimbic pathway**

The most important glutamate receptor is NMDA ⇨ it carries the MOST excitatory neurotransmission in the brain

▶ = NORMAL FUNCTIONS

**POSITIVE SYMPTOMS

Delusions	False beliefs that a person holds onto even when they are bizarre or could not possibly be true
	May involve fears (*paranoid delusions*), guilt, jealousy, religion, spirits, one's body and mind control
Hallucinations	A perception in the absence of external stimulus (seeing, hearing, or sensing things that are not real)

**POSITIVE SYMPTOMS (cont)	
	Most common are auditory hallucinations (*hearing voices*); voices may keep a running commentary on the person's behaviors, tell them what to do, carry on conversations about them, accuse them, or may have arguments with each other
Other Hallucinations	Visual, tactile, olfactory, gustatory
Disorganized speech, thoughts, and beliefs	May lose track of their ideas, meanings, and words (*Word Salad*)
	Thought processes are disconnected (*a sentence or phrase is not logically connected to those that occur before or after; loose associations*)
	Ideas and images may become jumbled or linked together illogically or words and meaning that should be linked instead may become disconnected
Disorganized Movement and Behaviors	May use exaggerated or repeated gestures, or may seem to be fidgeting, hyperactive, or preoccupied with meaningless physical movements

Hypothesis of SZ (Together)	
Dopamine	SZ comes from dysregulation of mesolimbic and mesocortical pathways
NMDA Receptor Hypofunction Hypothesis	Glutamatergic neuronal or NMDA receptor deficiency results in dopaminergic hyperactivity, which leads to hallucinations and delusions
	Hyperactivity of mesolimbic pathway