Pathophysiology of Schizophrenia

Epidemiology:
- Lifetime prevalence = 1.0%
- Prevalence remarkably similar among all cultures
- Onset: most often late teens or early twenties
  - Rare prior to adolescence or over 40 years old
- Prevalence equal among males and females
  - Mean age of onset = 6 years later in females
  - Females often have milder course of illness
- First admission for males = age 15-24; females 25-34
- Most do not return to baseline functioning
- Suicide rate is 10-15%
  - Similar to rate for depressive illness
- >75% of patients are smokers
- Increased incidence of substance abuse
- Lifespan of an individual with schizophrenia is about 10-15 years less than general population
  - May be related to lifestyle: poor nutrition, lack of exercise, smoking, substance abuse, decreased access to medical care and higher suicide rate

DSM-V Diagnostic Criteria for Schizophrenia:
- ≥ 2 of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one should include 1-3:
  1. Delusions
  2. Hallucinations
  3. Disorganized speech
  4. Grossly disorganized or catatonic behavior
  5. Negative symptoms
- Decline in social and/or occupational functioning since the onset of illness
- Continuous signs of illness for at least 6 months with at least one month of active symptoms
- Schizoaffective disorder and mood disorder with psychotic features have been ruled out
- The disturbance is not due to substance abuse or medical condition

Course and Prognosis:
- Typically the symptoms begin in adolescence
- The onset of the disturbing symptoms may seem to have been precipitated by a social or environmental change, such as moving away to college, an experience with substances, or death of a relative
- The prodromal syndrome may last a year or more before the onset of overt psychotic symptoms
- After the first psychotic episode, the patient has a gradual period of recovery, which can be followed by a lengthy period of relatively normal functioning
- Relapse usually occurs
- The general pattern of illness that is evidenced in the first five years after the diagnosis is usually predictive of the course that the patient follows
- Each relapse of the psychosis is followed by a further deterioration in the patient’s baseline functioning
- Positive symptoms tend to become less severe with times, however the negative symptoms may increase in severity
- A reasonable estimate is that:
  - 20-30% able to lead somewhat normal lives
  - 20-30% continue to experience moderate sx
  - 40-60% remain significantly impaired by their disorder for their entire lives

Dopamine Pathways:

Mesolimbic
- Projects from ventral tegmental area of brainstem to limbic system
- Pathway important for positive sx, motivation, pleasure and reward
- Increase dopamine release in this pathway (including via drugs) can cause psychosis
  - Antipsychotics block D2 receptors in this brain region → treat positive symptoms
- This pathway may also play a role in aggressive and hostile sx
- Led to dopamine hypothesis of schizophrenia
  - Hypothesis evolved from 2 observations:
    - Antipsychotics treat psychosis
    - Amphetamines & cocaine can mimic paranoid schizophrenia
  - However, hypothesis doesn’t explain the negative sx of schizophrenia

Mesocortical
- Projects from ventral tegmental area of brainstem to prefrontal cortex
  - Branches of this pathway into the dorsolateral PFC are hypothesized to regulate cognition and executive functions
    - Cognitive and some negative sx may be due to a deficit of dopamine activity in projections to DLPIFC
  - Branches of this pathway into the ventromedial PFC are hypothesized to regulate epione and affect
    - Affective and other negative sx may be due to deficit of dopamine activity in projections to VMPIFC
- Therapeutic dilemma: how do you increase dopamine in the mesocortical pathway, while at the same time, decrease dopamine activity in the mesolimbic dopamine pathway?

Nigrostriatal
- Projects from substantia nigra area of brainstem to basal ganglia or striatum
- Controls motor movement
- Dopamine deficiency in this pathway causes movement disorders
  - Rigidity, akinesia, bradykinesia, tremor, dystonia, akathisia
- Antipsychotics can produce these movement disorders
  - Chronic blockade of D2 receptors in this pathway may result in tardive dyskinesia

Tuberoinfundibular
- Projects from hypothalamus to anterior pituitary
- Normally, these neurons are active and inhibit prolactin release
  - Blockade of D2 receptors on the lactotrophs of the anterior pituitary results in a rise in prolactin levels
  - Symptoms associated with elevated prolactin: galactorrhea, amenorrhea, sexual dysfunction, reduced bone density

Dopamine Hypothesis of Schizophrenia:
- More precisely = mesolimbic dopamine hypothesis of positive psychotic symptoms
  - Over-activity in this dopamine pathway mediates positive sx of psychosis
- The basic theory does not elaborate on whether the dopaminergic hyperactivity is due to:
  - Too much releases of dopamine
  - Too many dopamine receptors
  - Hypersensitivity of the dopamine receptors to dopamine
  - Some combination of these mechanisms
- The original hypothesis fails to take into account and adequately explain the negative sx
- Although dopamine is the neurotransmitter that has received the most attention in schizophrenia research, other neurotransmitters are certainly involved
  - Serotonin, norepinephrine, GABA, glutamate

Other Hypotheses of Schizophrenia:
- NMDA receptor hypofunction (cortico-brainstem glutamate projection) hypothesis
  - Results in mesolimbic dopamine hyperactivity & mesocortical dopamine underactivity
- Neurodegenerative hypothesis = progressive loss of neuronal function through loss of dendrites, destruction of synapses, or neuronal death may underlie the symptoms and progression of schizophrenia
  - Causes include genetics, fetal insults (ex: anoxia, infection, toxins, maternal starvation) and glutamate excitotoxicity
- Excitotoxicity hypothesis = neurons degenerate because of excessive neurotransmission at glutamate neurons
  - Calcium activation of intracellular enzymes producing free radicals → neuronal death
- Many more ...
**CLINICAL FEATURES:**

- No sign or symptom is a pathognomonic of schizophrenia
- Prior history of schizotypal or schizoid personality traits or disorder are often present
- Many symptoms of schizophrenia are categorized as either positive or negative
  - However, affective, aggression and neurocognitive dysfunction are gaining acceptance as terms to describe symptom dimensions of schizophrenia

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<thead>
<tr>
<th>Positive symptoms (mesolimbic)</th>
<th>Hallucinations</th>
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<tr>
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<td>Delusions</td>
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<td>Disorganized speech and behavior</td>
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<td>Thought disorder characterized by loose associations, tangentiality, incoherent thoughts, neologisms, thought blocking, thought insertion, thought broadcasting, and ideas of reference</td>
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<td>Catatonic behavior</td>
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<th>Negative symptoms (mesocortical PFC)</th>
<th>Poverty of speech (alogia) or poverty of thought content</th>
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<td>Anhedonia</td>
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<td>Flat affect</td>
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<td>Loss of motivation (avolition)</td>
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<td>Attentional deficits</td>
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<td>Associality</td>
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<th>Affective symptoms (ventromedial PFC)</th>
<th>Depressed mood</th>
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<td>Anxious mood</td>
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<td>Guilt</td>
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<td>Tension</td>
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<td>Irritability</td>
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<td>Frequent worry</td>
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<th>Aggressive symptoms (orbitofrontal cortex, amygdala)</th>
<th>Impulsive control (ex// sexual acting out)</th>
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<tr>
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<td>Verbal or physical abusiveness</td>
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<td>Frank violence (ex// assault)</td>
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<td>Self-injurious behaviors including suicide</td>
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<th>Cognitive impairment (dorsolateral PFC)</th>
<th>Problems maintaining goals</th>
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<td>Problems with attention</td>
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<td>Problems prioritizing</td>
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<td>Problems modulating behavior</td>
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<td>Problems with learning</td>
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<td>Impaired verbal fluency</td>
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<td>Difficulty with problem solving</td>
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<td>Problems with memory</td>
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- The presence of tactile, olfactory or gustatory hallucinations may indicate an organic etiology such as complex partial seizures
- Sensorium and memory are usually intact
- Insight and judgment frequently impaired