Schizophrenia: Affective (and Anxiety) Disorders

Degenerative Disorders

- **Multiple Sclerosis (MS)**
  - **Symptoms**: Complex and very diverse. Slowly evolving. Not hereditary, not contagious. More women than men (20-30 years old) Loss of motor coordination, tremor, numbness...
  - **Neural substrate**: Autoimmune disease. Degeneration of myelin and formation of sclerotic plaques

  ![Sclerotic Plaques](image)

  - **Treatment**: Genetic component (Gypsies and Asians low risk), environmental component (childhood cold climates are high risk). Influencing the immune system. No cure. Partial recovery.

Infectious Diseases

- **Encephalitis and Meningitis**
  - **Symptoms**:
    - Fever, irritability, nausea --> convulsion, delirium
    - 10% if terminal, 20% results in permanent brain damage. Deafness.

  - **Neural Substrate**:
    - Viral infections (mosquitoes or STDs), bacteria, fungi
    - Encephalitis: affect whole brain
    - Meningitis: affects meninges

  - **Treatment**: none in general

  - **Herpes simplex**: cold sores. Virus that lives in spinal ganglion and breaks out periodically along the sensory nerves. Encephalitis results from breakout to
the brain (rare), frontal and temporal lobes. Treatable (acyclovir), but no cure.
- **Polio**: damage to all motor neurons (brain + spinal cord) Vaccine (Jonas Salk)
- **Rabies**: fever, headaches --> convulsions, seizures, death within a week. Affects cerebellum and hippocampus. Vaccine
- **AIDS (not HIV)**: Brain damage in 75% of cases if untreated. Due to excess of Ca2+ through NMDA receptors (excitotoxicity). Hippocampus and cortex
- **Meningitis**: headaches, stiff neck --> convulsions, death. Infection of meninges, damage resulting from impaired blood/CSF circulation. Cranial nerve damage. Treatable by antibiotics. Vaccine.

**Schizophrenia**
- 1% total world population. Complex disease. Not strictly degenerative.

**3 Types of Symptoms**
- **Negative** Symptoms: lack of some behaviors
- **Positive** Symptoms: disorder of information processing
- **Cognitive** Symptoms: additional abnormal behaviors

- Physical traits: Mild facial (larger heads, wide-set eyes, low ears) + finger signatures
- Late onset: 20s
- Symptoms appear gradually within 5 years of onset. Positive symptoms appear last.

**Positive Symptoms: Dopamine**
- All positive symptoms may be preceded by short-lived elation/euphoria
- Thought disorders: irrational, disorganized thinking
- Delusions: non factual beliefs (persecution, contact with aliens, grandeur)
- Hallucinations: sensory perception malfunction (auditory...)

- Chlorpromazine blocks D2 receptors, and eliminate positive symptoms
- L-Dopa, cocaine, amphetamine: agonists increase the positive symptoms

A dysfunction of the meso-limbic dopaminergic system: "too much dopamine"

VTA --> Nucleus Accumbens + Amygdala
D2 Binding and Potency

The more D2 receptors are blocked, the largest the anti-schizophrenic effect.

Negative Symptoms: Brain Damage

- **Absence of certain behaviors:** flat affect, flat motivation, unusual facial expressions, social inhibition, anhedonia, poor eye pursuit, deficit in eye-blink reflexes
- **Enlarged ventricles:** large lateral (and third) ventricles --> less gray matter (temporal, frontal lobes...)

Schizophrenia (Evidence from Anatomy)

- The loss of brain tissue (cortical gray matter) is progressive after onset. More loss in schizophrenic patients.

Negative Symptoms: Brain Damage

- Hypofrontality: Evidence from physiology
  - Decrease of activity in (dorso-lateral) frontal cortex
  - Due to decrease in dopamine release

  --> Reduced frontal lobe activity

  [Concentration and attention task --> normal vs. schizophrenic]

Hypofrontality: Evidence from animal studies

- Animal models: PCP (angel dust) or Ketamine produce Schizo-like symptoms:
  - Indirect NMDA antagonists --> decrease neural activity and dopamine modulation in prefrontal cortex

- Lack of prefrontal activity/dopamine results in perseverating behaviors

  Task: reaching behind a barrier

  Perseverance: inability to change strategy

- Clozapine increases dopamine in prefrontal cortex and alleviate symptoms
Towards an explanation and an effective treatment for the positive and negative symptoms

-Step 1: Hypofrontality
  - Less NMDA and DA release in prefrontal cortex --> less PFC activity
  - Negative symptoms
  - Alleviated by indirect NMDA agonists

-Step 2: Too little activity in PFC triggers less inhibition of VTA
  - More DA release in Nuc. Accumbens
  - Positive Symptoms
  - Alleviated by D2 antagonists

Not enough Dopamine in Frontal Cortex, too much Dopamine in Nuc. Accumbens

Treatment: Partial competitive DA agonist: high affinity, but less efficient than DA. Atypical antipsychotic (clozapine, aripiprazol)
  - Agonist in PFC
  - Antagonist in Nuc. Accumbens (partial agonist displaces neurotransmitter)
  - Alleviate all symptoms of Schizophrenia (partial agonist binds with receptors)

Schizophrenia: Multiple Causes

- Viral Cause
  - Epidemiology: Study of disease at the population level
  - Latitude effect: increase risk if birth occurs far from the equator
  - Seasonality effect: late-winter/early spring births
  - Births after a flu epidemic on 2nd trimester of pregnancy
  - Births in cities: 3x more schizophrenia. Easy transmission of viruses.

- Other Risk Factors
  - Vitamin D deficiency (lack of sunlight or milk)
  - Smoking and alcohol consumption during pregnancy

- Developmental Causes
  - Lack of sociability and psychomotor skills in childhood are associated with schizophrenia
  - Monozygotic twin studies: if twinning occurs before day 4 --> separate placenta --> decrease likelihood of both twins developing schizophrenia

- Genetic Cause
  - Parental schizophrenia increases the risks of children developing schizophrenia by a factor of 10
- Twins fingerprints correlates with their concordance for schizophrenia
- Identical twins from 2 schizophrenic parents: only 45% chance that both develop schizophrenia (should be >75%) --> more than one gene involved, or other factors
- Multiple genes involved

- **Cognitive Symptoms: brain Damage**
  - Attention deficits
  - Slow reaction time (fingers, legs)
  - Deficit in learning and memory
  - Poor planning and problem solving
  - Deficit in abstract thinking

Brain: no clear neural correlates or mechanisms yet

**Affective Disorders: Mania and Depression**
- Bipolar disorder: cycle between depression and mania
- Depression: 3x longer than mania
- Mania by itself is rare
- Depression (major depressive disorder) by itself is 2-3x more likely in women (7%) than men (3%)
  MDD: unworthiness, guilt, low energy, difficulty to fall asleep
- Suicide attempts: 15% unipolar, 30% bipolar
- Accompanied by sleep disorder: less SWS, more stage 1, earlier REM onset
- Hereditary: one direct parent --> 10x increase in risk. No single genes.
- Seasonality effect: birth in May/June/July --> high risk for suicide