Announcements:

- Readings: CH.16 up to pg.428
- Final: Friday Dec 9th, 1:00pm-3:00pm. No Make ups.
- Registered DRC students will take the Exam, at the DRC.
- Review session: Thursday December 8th from 5-7pm in Modern Languages Rm.311.
  **Remember to bring your extra credit sheet the day of the final**
- If you get an A in the class … Consider becoming a preceptor for 302 next fall.
- Final Exam Covers: **Ch. 2,4-15 Not 1,3,16**

Last Lecture:

Degenerative Disorders

**Amyotrophic Lateral Sclerosis (Lou Gerhigs Disease)**

Symptoms: Stiffening of movement, exaggerated reflexes, muscular atrophy, paralysis terminal disease (5-10 years after onset). No dementia

- Most sporadic cases (1/20000)
- In some cases, related to chromosome 21 (Misfolding of protein, toxic gain of function
- Neural substrate: Degenerative of spinal cord motor neurons and cranial nerves. Excitotoxicity

**Treatment:** No cure. Drugs that decrease glutamate release. Improve symptoms.
Gene therapy

**Multiple Sclerosis (MS):**

**Symptoms:** Complex and very divers. Slowly evolving. Not hereditary, not contagious. More women then men (20-30yo). Loss of motor coordination, tremor, numbness...

**Neural substrate:** Autoimmune disease. Degeneration of myelin and formation of sclerotic plaques.

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

Encephalitis and Meningitis

Symptoms:

- Fever, irritability, nausea -> convulsion, delirium.
- 10% is terminal, 20% results in permanent brain damage. Deafness.

Neural substrate:

- Viral infections
- Encephalitis: Affect the whole brain
- Meningitis affects the meninges

Treatment (Encephalitis): None in general

- Herpes Simplex: cold sores. Virus that lives in spinal ganglion and "breakouts" periodically along the sensory nerves. Encephalitis results from break-out to the brain (rare), frontal and temporal lobes. Treatable (acyclovir). But no cure.

- Polio: damage to all moto 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 Ca\(^{2+}\) through NMDA receptors (excitatory. Hippocampus and cortex

Treatment: (Meningitis): None in General

Schizophrenia

1% total world population. Complex disease. Not strictly degenerative.

3 types of symptoms:

- Negative symptoms (lack of some behaviors)
- Cognitive symptoms (disorder of information processing)
- Positive symptoms (additional abnormal behaviors)
**Physical traits:** Mild Facial (longer heads, wide-set eyes, low ears) + finger signatures

- **Late onset:** 20’s

- **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
- Hallucinations: Sensory perception mal-function (auditory..)

- Chlorpromazine blocks D2 (dopamine) receptors, and eliminate positive symptoms

- L-Dopa, cocaine, amphetamine: Agonists increase the positive symptoms

- A dysfunction of meso-limbic dopaminergic system: “too much dopamine”
  - VTA ---> Nucleus Accumbens +Amygdala

- The more D2 receptors are blocked, the largest the anti schizophrenic effect... this is only for positive symptoms

**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 (especially in the temporal and frontal lobes)

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

- **Hypofrontality:** Evidence from physiology
  - Decrease of activity in (dorso-lateral) frontal cortex
  - Due to decrease in dopamine release
  - Reduced frontal lobe activity
Hypofrontality Evidence from animal studies
  o Animal models: PCP (angle dust) or ketamine produced schizophrenia-like symptoms: Indirect NMDA antagonists \(\rightarrow\) decrease neural activity and dopamine modulation in the prefrontal cortex.
  o Lack of prefrontal activity/dopamine results in perseverating behaviors (inability to change strategies)
  o Clozapine increases dopamine in prefrontal cortex and alleviate symptoms. (individuals are able to switch strategies)

Treatment

Summary:

Towards an explanation and an effective treatment for the positive and negative symptoms.

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

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

*** Not enough DA in frontal cortex, too much DA in Nuc. Accumbens ***

Treatment: Partial competitive DA agonist: high affinity, but less efficient than DA. Atypical antipsychotic (ex: Clozapine, aripiprazol).
  - Agonist in PFC *
  - Antagonist in Nuc. Accumbens *
  - Alleviate all symptoms of schizophrenia. Doesn’t cure but makes the patient way better.

Causes:

Viral cause:
  - Epidemiology: Study of disease at the population level.
  - Latitude effect: Increase risk in birth occurs far from the equator.
  - Seasonality effect: Late- winter/ Early –spring births.
  - Birth after a flu epidemic on 2\textsuperscript{nd} 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 cause:**

- 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 increase 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 areas?: No clear neural correlates or mechanisms found yet.

**Affective Disorder: Mania and Depression**

- **Bipolar disorder:** Cycle between depression and mania.

- **Depression:** 3x longer then mania.

- Mania by itself is rare

- Depressions (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.