Announcements: Thursday 12/1

- Readings: chapter 16- p.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 Dec. 8th from 5-7pm in Modern Languages 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

Degenerative Disorders Continued

- **Amyotrophic Lateral Sclerosis (Lou Gehrig’s disease)**
  - Symptoms: stiffness of movement, exaggerated reflexes, muscular atrophy, paralysis, terminal disease (5-10 year after onset). No dementia
  - Mostly sporadic cases (1/20,00)
  - In some cases, related to chromosome 21 (misfolding of protein, toxic gain of function)
  - Neural substrate: degeneration of spinal cord neurons and cranial nerves. Excitotoxicity
  - Treatment: no cure. Drug that decrease glutamate release, improve symptoms. Gene therapy.

- **Multiple Sclerosis**
  - Symptoms: complex and very diverse. Slowly evolving. Not hereditary, not contagious. More women than mend (20-30 y/o) 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 (mosquitoes, or STDs), bacterial, fungi
    - Encephalitis: affect the whole brain
    - Meningitis: affects the 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 break-out 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:** headache, stiff neck → convulsion, death. Infection of meninges, damage resulting in impaired blood/CSF circulation.
  Cranial nerve damage. Treatable by antibiotics. Vaccine.
Class 26: Schizophrenia affective (and anxiety) disorders

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 (larger 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 (persecution, contact with aliens, grandeur)
  - Hallucinations: sensory perceptions mal-function (auditory…)
- Chlorpromazine blocks D2 receptors, and eliminate positive symptoms
- L-Dopa, cocaine, amphetamine: agonists increase the positive symptoms
  - Dysfunction of the meso-limbic dopaminergic system: ‘too much dopamine’
  - VTA → nucleus accumbens + amygdala
- The more D2 receptors are blocked, the largest the anti-schizophrenic effect
• **Negative symptoms: brain damage**
  
  o **Absence of certain behaviors:** flat affect, flat motivation, unusual facial expression, social inhibition, anhedonia, poor eye pursuit, deficit in eye blink reflexes…
  
  o **Enlarged ventricles**
    
    ▪ Large lateral (and third) ventricles → less gray matter (temporal, frontal lobes…)
  
  ▪ **Hypofrontality: evidence from physiology**
    
    • Decrease of activity in (dorso-lateral) frontal cortex
    
    • Due to decrease in dopamine release
    
    • Brain images shows reduced frontal lobe activity
    
    • Frontal lobe dysfunctional (neurons do not fire as much as they should)
    
    • Not enough dopamine in frontal cortex
  
  ▪ **Hypofrontality: evidence from animal studies**
    
    • Animal models: PCP (angel dust) or Ketamine produce schizophrenic-like symptoms: indirect NMDA antagonists → decrease neural activity and dopamine modulation in prefrontal cortex
    
    • Lack of prefrontal activity/dopamine results in perseverating behaviors
    
    • Clozapine increase dopamine in prefrontal cortex and alleviate symptoms
Evidence from anatomy: the loss of brain tissue (cortical gray matter) is progressive after onset. More loss in schizophrenic patients

- Gray matter = cell bodies

**Treatment**

- 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 triggers 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 (e.g. clozapine, aripiprazol)
  - \( \Rightarrow \) Agonist in PFC
  - \( \Rightarrow \) Antagonist in Nuc. Accumbens

- Alleviate all symptoms of schizophrenia

**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 causes**
  - 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 have 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 mechanism 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