PSY 302: Neurological Disorders II

Degenerative Disorders
- **Transmissible Spongiform Encephalopathy**
  - E.g.: Bovine Spongiform Encephalopathy (BSE = ‘mad cow disease’), Creutzfeldt-Jakob disease (in humans), scrapie (animals)
  - Sporadic (random): can be infectious or genetic
  - Caused by ‘protein infectious agent’ (prions). Found in neural membranes, important for synaptic function and myelin. Normal aminoacid composition, but misfolding.
  - Symptoms similar to Alzheimer’s (loss of memory/dementia), but faster and deadlier
  - No known treatments in human. Genetic manipulations in mice
  - Scrapie can be treated by late onset destruction of (normal) Prions. Prions are useful for development. Treatment involves a prion-destructive protein produced after 12 weeks (in mice)
  - Possible genetic therapies: Selective activation of cell death in infected cells only. Use Caspases: Enzyme that triggers cell death (aka apoptosis)
- **Parkinson’s Disease**: classified as movement disorder
  - Symptoms:
    - Rigidly, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia (slow movements), and akinesia
    - Initially, little intellectual impairments. As it progresses: speech impairments, decreased short term memory, slower problem-solving and slower spatial skills
    - Mood changes, including depression. Anxiety also common
    - In general, not hereditary. Sporadic. Affects 0.5% of adult population, slow progression (~20 years).
    - No single causes (genetic, strokes, tumors, infections . . .). No cure
  - Neural structures affected:
    - Degeneration of Pars Compacta region of Sub. Nigra – Basal Ganglia
    - Caused by death of dopamine neurons
    - Decreased activity of 4 areas that receive inputs from the basal ganglia:
      - Motor cortex
      - Oculomotor and associative areas
      - Limbic system
      - Orbitofrontal cortex
  - Physiological Mechanisms of PD:
    - Lack of dopamine
Nigro-striatal dopaminergic neurons almost gone
- Lewy bodies: protein ‘growth’ within dopamine cells
- Possibly due to a defect on Chromosome 4: The protein (a-synuclein) produced is misfolded
- Toxic gain of function: production of a toxic protein by a faulty gene
- Mutation of chromosome 6: Parkin gene
  - Ubiquitin + misfolded protein – (Parkin) – ‘Tagged’ misfolded protein – Proteosomes – Amino acids
  - Ubiquitin tags faulty/misfolded protein
  - Tagged proteins are destroyed by proteosomes
  - Parkin gene helps in ubiquitin tagging
  - Mutation – loss of Parkin function
- Not only genetic: other possible mechanisms include decreased mitochondrial activity and iron build-up

Treatments:
- MAO inhibitors (e.g., deprenyl): prevents the destruction of monoamines
  - Slows down progression of PD
- L-Dopa: promote the production of dopamine. Side effects (hallucinations)
  - Effects are temporary. Eventual complete destruction of dopamine neurons
- Direct fetal dopamine cell transplantation in Basal Ganglia. Side effects (involuntary movements)
- Pallidotomy: Precise lesions of the Globus Pallidus:
  - Sub Nigra – (inhibited by dopamine) – Glob. Pall. – (inhibitory) – Motor Systems
  - Destroy Glob. Pall. – no more inhibition of motor systems (no rigidity)
  - Deep brain inhibitory stimulation of Subthalamic Nucleus (STN) – Target Subthalamic nucleus (has excitatory connection to Glob. Pall.)
- Current research on PD:
  - Gene Therapy: modified virus that inhibits STN – increase activity in Supplemental Motor Area – Decrease PD symptoms
  - Neuroprotective agents – chemicals that protect brain. Control a-synuclein
  - Stem cells – increase dopamine secretion

Huntington’s Disease
- Symptoms:
- Uncontrollable and excessive movements. Uncoordinated activation of motor programs
- Rare, associated with dementia. Symptoms appear after 35 years old, death 15 years after onset
- 1630s Witches of Bures (UK)

  - Neural Substrate:
  - Degeneration of caudate and putamen: affect GABA and Ach cells in the Basal Ganglia. Enlarged ventricles
  - Caudate Putamen – (GABA, inhibitory) projection is damage, lack of inhibition, more excitation – Prefrontal Cortex, Motor Cortex – Motor activity/plans

  - Treatment:
  - No treatment. 1/10,000 people. Management therapies
  - Gene is identified and test exist to determine where it is present
  - Research focuses on Gene therapy

  - Alzheimer’s Disease
  - Symptoms:
  - Affects 10% of the >65 yo population, 50% of >85 yo population
  - Not entirely hereditary
  - Progressive: depression, loss of memory and mental function (dementia). Resemble anterograde amnesia of declarative memory
  - Down syndrome develops sometimes into Alzheimer’s
  - Terminal disease

  - Neural substrate:
  - Degeneration of Ach center (nuc. Basalis)
  - Degeneration of the hippocampus, frontal and temporal cortices, raphe nucleus and locus coeruleus
  - Development of:
    - B-Amyloid plaques: accumulation of B-Amyloid ... cell death
    - Neurofibrillary tangles. Dead microtubules. Also in Down Syndrome

  - Treatment:
  - No cure
  - Causes unclear
  - Gene mutation chromosome 21 (amyloid gene)

  - Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)
  - Symptoms:
- Stiffness of movement, exaggerated reflexes, muscular atrophy, paralysis, terminal disease (5-10 years after onset). No dementia
- Mostly sporadic cases (1/20,000)
- In some cases, related to chromosome 21 (misfolding of protein, toxic gain of function)

- **Neural Substrate:**
  - Degeneration of spinal cord motor neurons and cranial nerves.

Excitotoxicity

- **Treatment:** no cure. Drug that decrease glutamate release, improve symptoms.
  Gene therapy

- **Multiple Sclerosis (MS)**
  - Symptoms:
  
  - **Neural Substrate:**
    - Autoimmune disease. Degeneration of myelin and formation of sclerotic plaques
  
  - **Treatment:**
    - Genetic component (Romani 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 (mosquitos or STDs), bacteria, fungi
    - Encephalitis: affect the whole brain
    - Meningitis: affects the meninges only

  - **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