Notes for PSY 302
Neurological Disorders II

Readings: Chapter 15 (Skip Figure 14.16-14.18 and p. 380 starting at APP-382 before ALS)
Final: Dec. 9th, 1:00 PM-3:00 PM
Review Session: Dec. 8th, 5-7 PM Modern Languages #311

- Developmental Disorders
  - Inherited metabolic disorders: deficiency in the production of an enzyme
    - Genetic bases
    - PKU (Phenylketonuria): deficit in phenylalanine—tyrosine conversion (chemical reaction)
      - Lack of myelination (consequence of deficit of the conversion)
      - Metabolism error
      - Mental retardation if untreated
      - Detectable at birth; preventable by appropriate diet (low protein—high protein content causes chemical reaction to occur)
  - Lack of vitamin B6: damage to thalamus and cerebellum
  - Lack of glucose metabolism (Galactosemia): damage to cerebellum and cortex
    - Inability to process galactose (glucose in milk); if left untreated, can have harmful effects
  - Tay-Sachs disease: inability to breakdown cellular waste products
    - Accumulation of waste, brain swelling (due to the space that the extra waste products take), death
    - Eastern European Jewish population (retinal diagnosis)
      - No need for blood tests or genetic testing (characterized by cherry spot in the middle of the retina)
  - Down Syndrome: congenital (‘born with’)
    - 1/700 children
    - 350,000 people in the US
    - Extra chromosome 21 in mother’s ovum; over-expression of genes; can be detected before birth
      - Trisomy 21
    - 10% less brain; less neurons in frontal lobe and superior temporal gyrus (Wernicke’s area)
    - Milk to severe mental retardation; can learn to have almost normal lives; no cure
    - Research: focused on avoiding associated diseases (heart condition, epilepsy, hearing/vision deficits…); determine gene over-expression pattern
      - Exactly the pathway from the genes to the phenotypes
Degenerative Disorders

- Transmissible Spongiform Encephalopathy
  - E.g. Bovine Spongiform Encephalopathy or BSE=’mad cow disease’, Creutzfeldt-Jakob disease, scrapie (animals only)
    - Called spongiform because pathology tissue example has holes in it like a sponge (someone with BSE)
  - Sporadic: can be infectious or genetic
    - Happens in very sparse populations; opposite of epidemic
  - Caused by protein infectious agents (prions); found in neural membranes, important for synaptic function and myelin; normal amino acid composition, but error in the folding
    - Proteins need to look right; cannot be mis-folded or dysfunctional or they won’t work right
  - Symptoms similar to Alzheimer’s, but faster and deadlier
  - No known treatments in human; genetic manipulations in mice

- Scrapie (in animals only)
  - 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: selection activation of cell death in infected cells only
    - Use Caspases: enzyme that triggers cell death (also known as apoptosis)
      - Cascade reaction that causes cell to die (trigger apoptosis)
      - Only kill cells that are dysfunctional (not healthy cells)

- Parkinson’s Disease: classified as movement disorder
  - Symptoms:
    - Rigidity, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia, and akinesia
    - Initially, little intellectual impairments; as it progresses: speech impairments, decreased short term memory, slower/problem solving and slow visual spatial skills
    - Mood changes, including depression; anxiety also common
    - In general, not hereditary; sporadic; affects 0.5% of adult population; slow progression (over about 20 years)
    - No single causes (genetic, strokes, tumors, infections, etc.) and no cure
  - Muhammad Ali before and after, with Parkinson’s Disease
  - Degeneration of the Basal Ganglia
    - Neural structures affected:
      - Degeneration of Pars Compacta region of the Substantia nigra—basal ganglia
      - Caused by cell death of dopamine neurons
Decreased activity of 4 areas that receive inputs from the basal ganglia:
- Motor cortex (tremors), oculomotor (eye movement) and associative areas, limbic system (higher level thinking), orbitofrontal cortex

**Physiological Mechanism 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: protein alpha synuclein produced is misfolded
- Toxic gain of function: production of a toxic protein by faulty gene
- Mutation on chromosome 6: Parkin gene
- Ubiquitin tags faulty/misfolded protein
- Tagged proteins are destroyed by proteasomes
- 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
  - Misfolded protein + Ubiquitin—Parking—‘tagged’ misfolded protein—proteasomes—amino acids
  - Parkin attaches molecules of ubiquitin to misfolded protein, targeting it for destruction by the proteasome
  - Proteasome breaks misfolded protein into its constituent amino acids

**Treatments:**
- MAO inhibitors (e.g. deprenyl): prevents the destruction of monoamines; slows down progression of PD
- L-Dopa: promote 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 globus pallidus
- Substantia nigra—dopamine—globus pallidus—motor systems
  - Subthalamic nucleus also goes to globus pallidus
- Deep brain inhibitory stimulation of subthalamic nucleus (STN)

**Current Research on PD:**
- Gene therapy: modified virus that inhibits STN—increase activity in supplemental motor area—decrease PD symptoms
  - The more you inhibit, the ‘better’ you are as far as decreased symptoms goes
- Neuroprotective agents—chemicals that protect brain; control alpha synuclein
- Stem cells—increase dopamine secretion

○ Huntington’s Disease:
  - Symptoms:
    - Uncontrollable and excessive movements; uncoordinated activation of motor programs
      - Opposite of PD
    - Rare, associated with dementia; symptoms appear after 35 years old, death after 15 years from onset
    - Terminal disease; hereditary (dominant gene, C4); misfolded protein (Huntingtin) accumulation; toxic gain of function
    - 1630’s Witches of Bures (UK)
      - Evidence that some patients were mistakenly taken for witches, because they had Huntington’s disease (it wasn’t known as Huntington’s); burnt alive
  - Neural substrate: degeneration of caudate and putamen; affect GABA and Ach cells in basal ganglia; enlarged ventricles
  - Venezuela patients: Huntington
    - Share strong gene pool
      - In this family, an average of 1 out of 4 die from Huntington’s
      - Cells right in the middle of the brain begin to die
        - Enlarged ventricles in the middle of the brain due to death of brain tissue
      - No way of telling who is carrying disease until the symptoms appear (then it is too late)
      - Huntington’s disease may become preventable if the gene is found
  - Caudate putamen—GABA—prefrontal cortex, motor cortex—motor activity/plans
    - GABA is not as localized as dopamine
  - Treatment:
    - No treatment; 1/10,00 people; management therapies
    - Gene is identified; tests exists to determine whether it is present
    - Research focuses on gene therapy

○ Alzheimer’s Disease
  - Symptoms:
    - Affects about 10% of 65 yo or greater, 50% of 85 yo or greater
    - 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 (nucleus basalis)
- Degeneration of hippocampus, frontal and temporal cortices, raphe nucleus, and locus coeruleus
- Development of: beta-amyloid plaques: accumulation of beta amyloid…cell death
- Neurofibrillary tangles; dead microtubules; also in Down Syndrome
  - Treatment: no cure, causes unclear; gene mutation on chromosome 21 (amyloid gene)