L19

Normal Aging	Alzheimer's	Parkinson's
• Mild shrinkage of brain volume and weight • Enlargement of ventricles • Decreased dendridic density in cortex • No dramatic decline in neuron number, except for notor neurons • Memory worsens due to declines in hippocampal function • Loss of synapses, changes in dendritic morphology and myelination in the prefrontal cortex	• Progressive disease – initial, intermediate, and advance stage leading to death • Widespread neuronal death leading to significantly reduced volume and weight of brain • Amyloid plaques • Neurofibrillary tangles	• Bradykinesia (slowness in executing movement) • Tremors at rest • Unstable posture • Akinesia (lack of movement) • Reduced blinking • Increased risk of dementia • Progressive neuronal degeneration – especially in the Substantia Nigra (resulting in loss of dopaminergic projections from substantia nigra to basal ganglia to modulate motor movement)

- Neurofibrillary tangles: paired helical threads of proteins observed in the neurons of patients with Alzheimer's – mostly in pyramidal neurons; first occur in the rhinal cortex
    - The proteins involved in the tangles are *hyperphosphorylated tau proteins*
    - The number of tangles usually correlates with the severity of symptoms

- <u>Progressive stages of Alzheimer's:</u>
    1. **Initial stage**:
        - Characterized by decline in explicit memory, attention deficits, and subtle personality changes
    2. **Intermediate stage:**
        - Characterized by confusion, irritability, deterioration of speech, delusions, and hallucinations
    3. **Advanced:**
        - Patient becomes virtually mute; terminal disease that leads to death

- <u>Main areas of widespread neuronal death</u>:
    - Rhinal cortex
    - Hippocampus
    - Neocortex
    - Basal forebrain (source of cholinergic (ACh-releasing) neurons)
    - Striatum
    - Thalamus

- **Amyloid Plaques**: peptides arranged in sheets that surround dying axons observed in patients with Alzheimer's
    - Amyloid plaques are most prevalent in neurons of the rhinal cortex, hippocampus, and neocortex

- **Neurofibrillary tangles:** paired helical threads of proteins observed in the neurons of patients with Alzheimer's – mostly in pyramidal neurons; first occur in the rhinal cortex
    - The proteins involved in the tangles are *hyperphosphorylated tau proteins*
    - The number of tangles usually correlates with the severity of symptoms
    - Proliferation (increase) of tangles also mimics the development of **dementia:**
        - Debilitating deterioration in more than one cognitive function *(perception, attention, executive function, memory, and planning)*

- Medications to treat Alzheimer's:
    - It's important to note that *no* medication offers substantial benefits and only help memory function in the early stages of the disease
        - There are two types of medications available:
            1. **Acetylcholine esterase inhibitors**: inhibit the action of acetylcholine esterase to keep acetylcholine in the synapse as long as possible
                a. ACh has implications in memory function
            2. **NMDA receptor partial antagonists**: block NMDA receptors to reduce calcium influx
                a. Reducing the influx of calcium is supposed to protect pyramidal neurons from overstimulation and death via complex cellular mechanisms
- Basal Ganglia and Parkinson's
    - The basal ganglia acts as a *modulatory* motor movement regulator (ie. Adjusting grip)
        - Receives inputs from the cortex, subthalamic nuclei, and the ***substantia nigra – source of dopaminergic projections***
        - Has *inhibitory GABAergic* outputs to the entire cerebral cortex via the thalamus and to brainstem nuclei
            - Inhibitory projections are what modulate motor movement
                - When you get rid of these inhibitory projections, you induce Parkinson's – like syndromes
                    - In order to excite these GABAergic, modulatory neurons, a dopaminergic synapse must occur from the substantia nigra
                        - Thus when you sever the source of dopamine, you lose the inhibition/modulation and you induce Parkinson's symptoms

        - Thus, Parkinson's is the result of *too little dopamine* in the basal ganglia

L20

- **Schizophrenia**: 2 types; most schizophrenics have both types
    - Type I: characterized by positive symptoms (aka *active* symptoms; more stereotypical)
        - Can be treated by neuroleptics
    - Type II: characterized by negative symptoms (symptoms similar to depression)
        - Poor response to neuroleptics
- **Symptoms:** 3 classes

Negative Symptoms	Positive Symptoms	Cognitive Symptoms
• Affective flattening – *R/A emotional response* • Alogia – *R/A speech* • Avolition – *R/A motivation* • Anhedonia – *R/A pleasure* **R/A = "reduction or absence of"*	• Delusions of: o Grandeur o Persecution o Reference (taking public things personally) • Hallucinations • Incoherent speech • Odd behavior	• Memory deficits (especially working memory) • Deficits in executive function (planning skills)

- **There are no unequivocal etiological factors:** there's no definite understanding or mechanism explaining schizophrenia; only theories and ideas
    - **Genetic Factors:**
        - Schizophrenia might be a genetic disorder involving a large number of genes and environmental factors
        - 50% concordance rate in monozygotic twins implies that there is some evidence for genetic inheritance, but the fact that it is not 100% indicates that genetics is not the only thing involved
    - **Environmental factors that might be involved:**
        - Paternal age
        - Malnutrition in mothers during pregnancy
        - Early infections
        - Autoimmune reactions
        - Birth complications
    - Inheritance of schizophrenia might be exacerbated by:
        - Stress
        - Alcohol
        - Cannabis
- **Observed neuroanatomical abnormalities** in patients with schizophrenia:
    - Thinning of the prefrontal cortex (especially *dorsolateral area*: the area implicated in working memory)