Neurological disorders (2)

Degenerate disorders (14.9)

- Transmissible spongiform encephalopathy (e.g. Bovine spongiform encephalopathy) (B.S.E = mad cow disease) Creutzfeldt- Jakob disease, scrapie (animals only)
  - Sporadic: can be infectious or genetic
  - Cause by protein infectious agents (prions) found in neural membranes, important for synaptic functions and myelin. Normal amino acid composition, but misfolding.
  - Symptoms similar to Alzheimer’s, but faster and deadlier
  - No known treatments in human. Genetic manipulation in mice.

- Scrapie can be treated by late onset destruction on (normal) prions. Prions are useful for development. Treatment involves a prion- destructive protein produced after 12 weeks (mice)
  - Possible genetic therapies. Selective activation of cell death, in infected cells only. Use caspases: Enzyme that triggers cell death (a.k.a. apoptosis)

- Parkinson’s disease: classified as movement disorders
  Symptoms:
  - Rigidity, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and making abnormalities, bradykinesia, and akinesia.
  - Initially, little intellectual impairments as it progresses: speech impairments, decreased short term memory, slower problem solving and slower visual spatial skills.
  - Mood changes, including depression. Anxiety also common
  - In general, not hereditary. Sporadic. Affects 0.5% of adult population, slow progression (~20 yrs.)
  - No single cells (genetic, strokes, tumors, infections... ) no cure.

Degeneration of the basal ganglia

- 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 (14.11)**

- Lack of dopamine
- Nigro- Striatal dopaminergic neurons almost gone.
- Lewi bodies: protein ‘growth’ within dopamine cells
- Possibly due to detect on chromosome 4: the protein (synuclein) produced is misfolded.
- Toxic gain of function: production of a toxic protein by a 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

Ubiquitin + misfolded protein $\rightarrow$ (Parkin) tagged misfolded protein $\rightarrow$ proteasomes $\rightarrow$ amino acids

**Parkinson’s disease**

- 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 movement)
  - Pall idotomy: precise lesions of the Globus pallidus:

Sub- Nigra (dopamine) $\rightarrow$ Glob. Pall. $\rightarrow$ (-) motor systems

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\downarrow

(+)
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Subthalamic nucleus

**Current research on PD**

- Gene therapy: modified virus that inhibits STN $\rightarrow$ increase activity in supplemental motor area $\rightarrow$ decrease PD symptoms
- Neuroprotective agents- chemicals that protect the brain. Control α- synucleins.
- 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 on set.
- 1630’s 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) Prefrontal Cortex (motor cortex) → (+) motor activity / plans
- Treatment:
- No treatment: 1/10,000 people. Management therapies
- Gene is identified, and tests exists to determine whether it’s present
- Research focuses on gene therapy

**Alzheimer’s disease**
- Symptoms:
- Affects 10% of the > 65 years old population, 50% if > 85 years old
- 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. Basals)
  - degeneration of the hippocampus, frontal and temporal cortices, raphe nucleus and locus coeruleus

**Alzheimer’s disease (14.15)**
- Neural substrate:
- Development of: B- Amyloid plaques: accumulation of B- amyloid… cell death
- Neuro fibrillary tangles. Dead microtubules. Also in down syndrome

Skip: figures 14.16- 14.18 and page 380 (starting at app) – 382 (before ALS)
- Treatment: no cure. Causes unclear. Gene mutation on 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 on set) no dementia
- Mostly sporadic cases (1,200,000)
- In some cases, related to chromosomes 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