Exercises Biol-480 "Neuroscience I" – Alzheimer's disease

1) Where in the brain does Alzheimer's disease (AD) start?

Entorhinal cortex

2) "Braak and Braak" staging:

- What is "Braak and Braak" staging?
  From MCI to fully developed AD
- What pathology is it based on?
  Tau
- What is the relationship between "Braak and Braak" staging and the MMSE?
  Inverse correlation

3) Neurofibrillary tangles:

- Explain the deleterious effects of neurofibrillary tangles.
  Microtubule destabilization
- What are neurofibrillary tangles? What are the biochemical steps that lead to their production?
  Tangles are fibrillized forms of tau oligomers, which in turn are tau proteins that have been hyperphosphorylated

4) Amyloid pathologies:

- What is the amyloid cascade hypothesis? Explain all steps involved.
  APP->B-secretease->y-secretase->Ab42->oligomers->fibrils->plaques
- Which genes are mutated that lead to aberrant amyloid processing?
  APP, PSEN1, PSEN2
- In relationship to the first detectable symptoms of AD, when does the amyloid pathology start in the brain?
  Up to 10-15 years before

5) What is the difference between familial and sporadic AD?
   FAD: monogenetic (mendelian cause), early onset; SAD: no clear genetic cause, late onset

6) Name at least three risk factors for sporadic AD.
   Obesity/hypertension/low educational attainment/diabetes/age/ApoE genotype/inactivity/smoking/depression

7) What is the cognitive reserve hypothesis? What evidence is it based on?
   People with higher education at lower risk for developing AD; epidemiological studies

8) What is the LEARn model of AD?
   Multiple-hit hypothesis of AD, reaching to prenatal life

9) What is the commonality between AD, PD and ALS? What are the key proteins involved in these diseases?
   Protein misfolding/spreading; amyloid/tau; synuclein; TDP-43

10) Name at least two problems when using mouse models of Alzheimer's.

There is not a single mouse model that fully recapitulates all pathological symptoms of AD;
Mouse models are based on genetic mutations, and hence predominantly target FAD, which only makes up 5% max. of the entire AD population.