Neurodegenerative Diseases (Palop, J., Chin, J., & Mucke, L. (2006) A network dysfunction perspective on neurodegenerative diseases, *Nature, 443*, 768-773)

* Main point: cognitive symptoms associated with neurodegenerative diseases likely not due solely (or at all) to neuronal loss 🡪maybe synaptic loss
* People suffering from neurodegenerative diseases have fluctuations in cognitive capabilities
  + These fluctuations can’t be only due to decrease in neurons🡪the number of neurons never goes back up so why do people have moments of lucidity?
* May be more caused by neuronal dysfunction than neuronal loss
* Abnormal proteins suspected of causing neurodegenerative disorders impair integrity or function of presynaptic terminals and postsynaptic specializations🡪hurt plasticity
* Synaptic plasticity Accounts partially for the fact that neurodegenerative disorders don’t become cognitively apparently until long after the molecular symptoms have started
  + Brain rewiring itself to work around the messed up areas
* Synaptic loss correlated with cognitive decline better than most other symptoms in most neurodegenerative diseases
  + So neurodegenerative diseases may be less disorders of neural loss, and more disorders of synaptic loss causing the inability to produce LTP

General info

* Chronic, progressive dementia disorder
* 4.4% of people over 65 affected
* 9.7% of people over 70 affected
  + doubles in prevalence for each 5 years over age 65
* Two Types of AD
  + Late-onset AD (95%) (LOAD)
  + Early Onset AD (EOAD)
    - Younger than 60
* Always preceded by mind cognitive impairment (MCI)
  + MCI doesn’t always develop into AD
  + Difficulty in performing >1 task at a time
  + Difficulty solving problems
  + Forgetting of recent events or conversations
* Cognitive symptoms of AD
  + Forgetfulness🡪loss of memory function
  + Emotional behavior
  + Personality change
  + Language difficulties
  + Perception difficulties
  + Judgment impairment
  + Anhedonia
  + Difficulty performing complex cognitive tasks
  + Anomia
  + Misplacing things
  + Disrupted sleep
  + Incontinence
  + Difficulty swallowing
  + Delusions, hallucinations
  + Depressed mood
  + Agitation
  + Decreased ability to recognize danger

Brain issues

* Degeneration of cells mostly in frontotemporal association cortex
* 45% loss of synapses

Amyloid Plaques

* Accumulation of beta-Amyloid protein between neurons in the brain🡪formation of amyloid plaques
* A-β usually produced by enzymatic cleavage of amyloid precursor protein (APP)
  + Accumulation of misfolded amyloid β peptides in the form of oligomers and fibrils in brain🡪AD
* Proposed functions of Aβ:
  + Kinase activation
  + Facilitation of gene transcription
  + Cholesterol transport regulation
  + Pro-inflammatory actions and antimicrobial activities
* After use fragments degraded in healthy brain
* In AD protein fragments (esp. Aβ42) accumulate to form plaques. 3 plaque types:
  + Senile/neuritic plaque—core of amyloid protein surrounded by abnormal neuritis (dendrites/axons)
  + Diffuse deposits of amyloid with no neuritis surrounding the core
  + Dense core of amyloid without neuritis
    - Long term outcome
  + Figure 21.10 from non-julian textbook
* Monomers tend to aggregate and form Aβ oligomers which eventually produce A β fibrils (picture)
* Assumed that fibrillar state required for neurotoxicity
* Oligomer structure actually probably the toxic structure (stable in that structure, not converting to fibrils)
  + Exposure of hippocampal slices to fibril-free oligomer preparations completely inhibits LTP (Lambert et al., 1998; Wang et al., 2002)
    - Confirmed in vivo too
* Deff bind nonrandomly (like totally bind to hippocampal cells)
* Specifically target synapses
* Three hypotheses as to what happens in the synapses after oligomers attach:
  + Oligomers generate ion flux via transmembrane pores
  + Oligomesr could generate synaptically localized oxidative damage
  + Binding to specific toxin receptors could lead indirectly to a downstream impact on signaling pathways

Neurofibrillary Tangles (NFTs)

* Fibrous inclusions that are abnormally located in the cytoplasm of neurons
* Pyramidal neurons most susceptible to NFTs
* Tau: primary component of NFTs. Protein associated with microtubules (filaments that maintain cellular structure and participate in axonal transport)
* Tau abnormally phosphorylated
  + Aβ 🡪increase in RCAN1.
  + RCAN1 inhibits PPP3CA, which dephosphorylates tau
  + RCAN1 stimulates production of GSK3β 🡪tau phosphorylation
  + Therefore increase in RCAN1🡪decreased dephosphorylation and increased phosphorylation of tau
* Other proteins (ex. Ubiquitin) also found in NFTs
* Accumulates through trans-synaptic spread
* In early AD found in entorhinal cortex🡪disease progresses into hippocampus and neocortex

QUESTIONS

Risk factors for AD

* Advancing age and family history of AD
* Diabetes, obesity, untreated hypertension, high cholesterol, stress, and a sedentary lifestyle
* History of head trauma, hypoxic brain injury, depression, bipolar disorder, PTSD

Genetics of Mendelian AD (EOAD)

* Deterministic genes- genes that can directly cause the disease
  + Genes for APP on chromosome 21
  + Presenilin 1 (PS-1) on chromosome 14
  + Presenilin-2(PS-2) on chromosome 1
    - PS1 and PS2 proteins part of the structure of ϒ(upsilon)secretase (enzyme involved in creating Aβ)
  + Mutations🡪autosomal dominant Alzheimer’s disease
  + Symptom onset likely to occur before age 60
  + These genes found in > 80% of EOAD patients

Genetics of LOAD

* >200 genes suggested for LOAD🡪no major LOAD locus
* Risk genes—may contribute to development of the disease
  + Apolipoprotein E (ApoE)
    - Component of very low density lipoproteins (VLDL)
    - VLDLs remove excess cholesterol from the blood and carry it to the liver for degredation
    - E4 form (APOE ε4) 🡪 increased risk of AD
    - APOE may be involved in amyloid processing
  + Other risk genes🡪proteins that would normally interact with previously mentioned proteins
  + Alpha-2 macroglobulin (A2M) gene🡪protease that normally contributes to the degradation and clearance of the Aβ protein
  + UBQLN1 gene🡪ubiquitin 1, which promotes the accumulation of uncleaved PS-1 and PS-2 proteins, which are part of the structure of ϒ(upsilon)secretase (enzyme involved in creating Aβ)
  + Sortilin-related receptor 1 (SORL1) is neuronal receptor for ApoE. Decreased in people with AD
    - Decreased SORL1 correlated with increased Aβ load in brain
  + AlzGene.org
    - Summarizes scientific literature on topic
    - Provides results of allele-based meta-analyses for most polymorphisms
      * Highlight >20 diff potential AD genes
    - Show the class how cool this is
* AD closely linked to trisomy 21 (down syndrome)
  + By 30-40 years old most people with DS develop plaques and tangles associated with AD
  + Maybe because DS have 3 copies of APP (on chromosome 21)
  + Not all DS patients develop AD

Epigenetics in AD

* Histone acetylation and DNA methylation implicated in etiology of AD
  + Amyloid plaques formed by deposition of Abeta peptides
  + Abeta peptides formed by cleavage of APP by beta and gama secretase
  + This cleavage also generates an APP intracellular domain which can interact with the histone acetyltransferase TIP60 and coact as a transcriptional activator can🡪 increased APP transcription
  + So therefore also AD associated with increase in histone acetylation
  + Hypomethylation of promoter region of PSEN1🡪 increase presenilin expression and enhanced Abeta formation
    - Presinilin are part of the structure of upsilon secretase (enzyme involved in creating Aβ)

QUESTIONS

Diagnosing AD🡪imaging studies

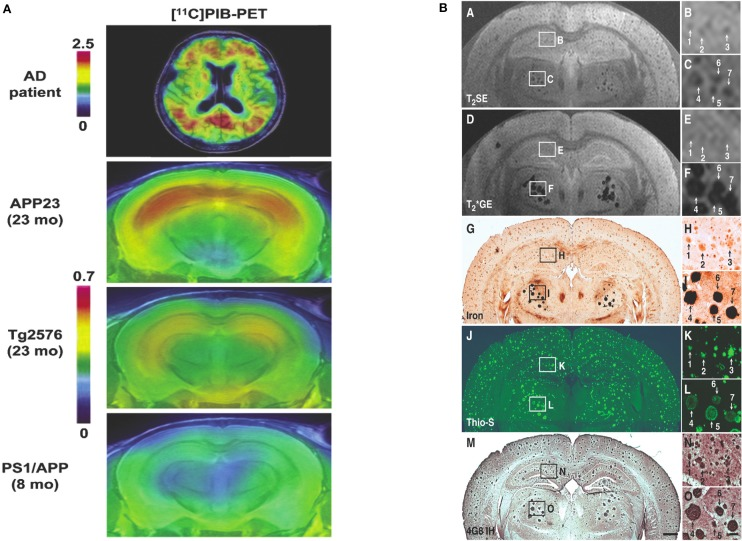
* Defined by changes that happen in the brain during degenerative processes🡪can’t see that without direct observation of the brain
* Rule out other things in order to give diagnosis of AD to a living person
* Amyvid: An 18F tagged molecule that binds β-amyloid. Used with a PET scan to examine people that already have cognitive decline
* Florbetaben: another imaging technique using PET scan. Has significant false-positive risk🡪only used with people who already show cognitive decline
* 18F flutemetamol🡪 a tagging molecule that accumulates in amyloid plaques
* postmortem analysis looks for NFTs and amyloid plaques
* 

Figure 2

* A)
  + 1. PET scan of Axial view of human AD patient tagged with PIB (which images beta amyloid plaques)
  + 2-4. PET scans of coronal views of diff transgenic mouse models
* B) MRI scans of an APP/PS1 AD transgenic mouse brain (24 months)
  + A&D: different ways to capture images on an MRI. Different pulse sequences
  + G: DAB enhanced iron staining
    - Possible iron accumulation in AD plaques
  + J: thioflavine S amyloid staining
  + M: anti-Abeta peptide immunohistochemistry

Animal Models of AD

* APP/PSδ(delta)E9 and APPswe/PS1δE9 models: mutations on APP gene🡪memory deficits, increased in Aβ42 and amyloid deposits
* SAMP8- early learning and memory deficits, incrased Aβ proteins, oxidative damage, and tau phosphorylation
* Aged beagles have learning and memory deficits and cortical atrophy, neuron loss, lack of neurogenesis, and Aβ plaques

“Treatments”

* Cholinesterase inhibitors
  + Inhibit reuptake of ACh
  + Deficits in functioning of ACh secreting neurons correlated with cognitive impairments in AD
    - Patients with severe AD have ACh levels 60-85% below normal
  + Improve cognition by increasing the presence of ACh in synapse
  + Can slow memory decline
  + Ex. Cognex, Aricept, donepezil, Exelon
  + Mild improvements in cognition with horrible side effects
    - Nausea, diarrhea, abdominal cramping and anorexia
* Mostly only effective in mild🡪moderate AD
* NMDA glutamate receptor antagonist
  + Damaged neurons release lots of glutamate🡪 excitotoxicity
  + drugs (such as memantine) to prevent further excitotoxic neurodamage
  + Block current flow through NMDA receptor🡪prevent increase in firing
  + Memantine🡪moderate-affinity noncompetitive NMDA receptor antagonist🡪decreased cognitive deterioration in moderate🡪severe AD
    - No undesirable side effects
    - Doesn’t decrease agitation
    - Efficacy questioned
    - Combine AChE-I and memantine🡪improved cognition and functioning
    - At high doses it inhibits glutaminergic mechanisms of synaptic plasticity🡪actually hurts memory
    - Gotta keep it at low doses
  + Chemo drug epothilone D decreases the presence of tau protein tangles in mice
* Alzheimer’s vaccine
  + Combat Aβ buildup
  + AN1792🡪antibody response🡪functional decline
    - Decreased Aβ plaques
    - Decreased tau protein
    - But also leads to a T-cell response to Aβ which 🡪 meningoencephalitis
    - But discontinued cuz bad
  + CAD106 vaccine uses fragment of Aβ (Aβ1-6)
    - Decrease plaques in mice
    - Antibodies with no T-cell activation
    - Decrease amyloid deposit
    - No encephalitis
* Antiamyloid drugs often used but amyloid deposition might actually happen way before any cognitive impairments arise🡪anti-amyloid formation drugs used after cognitive impairment useless
  + So we need to discover biological markers as early as possible

Drugs in the works (alz.org)

Solanezumab (alzforum.org)

* Humanized monoclonal Immunoglobulin G 1 (IgG1) antibody
* Directed at the soluble monomeric Abeta peptide (not fibrillar Abeta)

MK-8931 (verubecestat)

* Disrupts Beta-secreatase (BACE) which is the enzyme that cuts APP and makes it possible for Abeta to form
* Still in progress. May be working

AADvac1

* Vaccine that stimulates body’s immune system to attack abnormal form of tau protein that destabilizes structure of neurons

CSP-1103

* Microglial modulator aimed at reducing inflammation in the brain

Lloret, A. et al. (2011) Amyloid- β toxicity and tau hyperphosphorylation are linked via RCAN1 in Alzhymer’s disease. *Journal of Alzheimers Disease, 27*(4), 701-709.