# 1a. Sleep and Brain Disease (Ysbrand O. Van der Weif)

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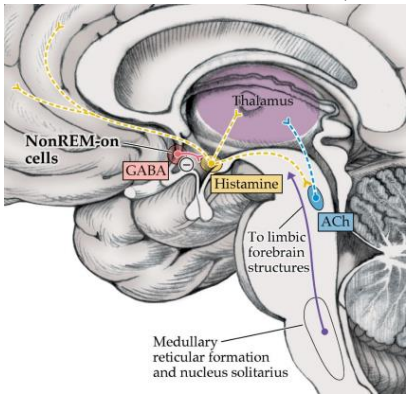
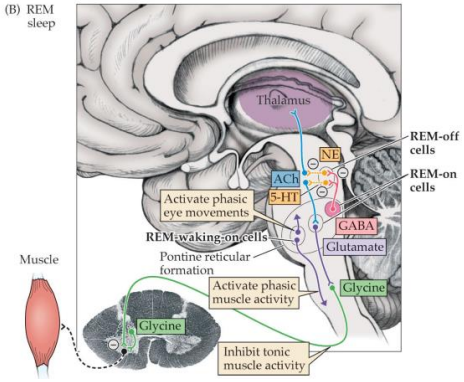
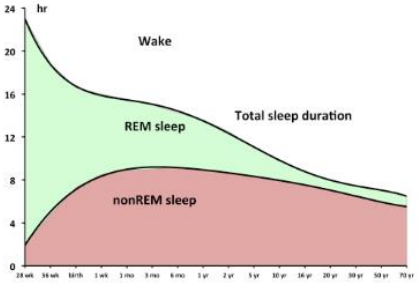
| **What is sleep?** | What is sleep?<br>State of brain - specific position, reduced reaction, relative inactivity, reversible, perceived comfort |
| **What is the difference in neurotransmitter transmission between non-REM sleep and REM sleep?** | Sleeping is a brain function<br>NonREM-on cells - GABA, histamine, acetycholine<br>  <br>REM on cells - Acetylcholine and serotonin to the thalamus<br>  <br>Glycine inactivates muscle |
| **What happens with REM and non-REM sleep throughout life?** | Sleep changes throughout life<br>Fetus sleep 100% of the time before birth<br>  <br>REM sleep is reduced throughout life |

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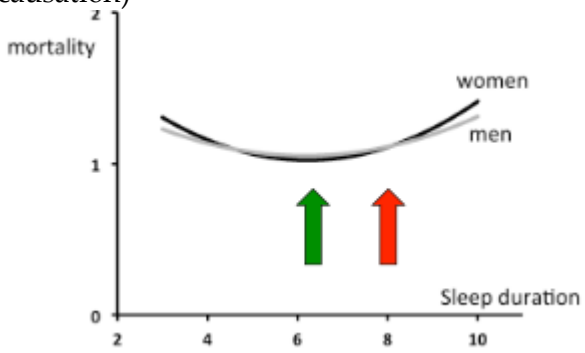
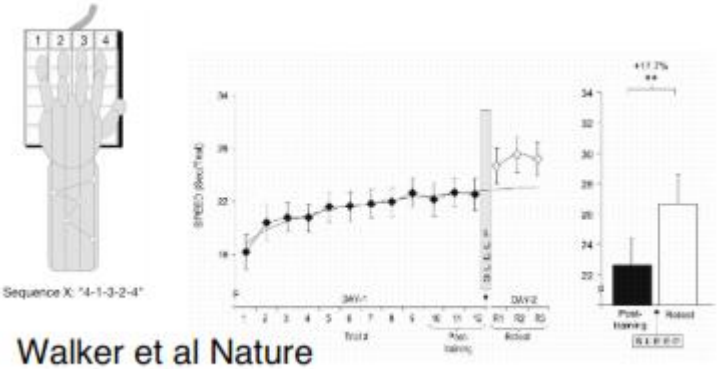
| **What is the optimal amount of sleep for maximum longevity? What is the limitation of this piece of information?** | Duration of sleep for survival changes<br>Optimal: 6 to 6 and half hours (correlation does not imply causation)<br>  |
| **What are the functions of sleep?** | Functions of sleep<br>Physical restorative - Release of hormones<br>Synapses undergo change<br>Energy function<br>Cognitive function<br>Emotional function<br>Immune function<br>Brain rising - Does not have lymphatic system, glial cells shrink and allows CSF to flow more freely |
| **Describe the main finding of Walker et al 2003?** | Sleep and memory (Walker et al 2003)<br>  <br>People improve in a motor task after sleeping<br>During sleep, you consolidate memories formed throughout the day |
| **How many sleep disorders are there?** | Sleep disorders - Over 60 different<br>• Too little sleep - Insomnia, restless legs, narcolepsy, apnea<br>• Too much sleep - Excessive daytime sleepiness, narcolepsy, hypersomnia |

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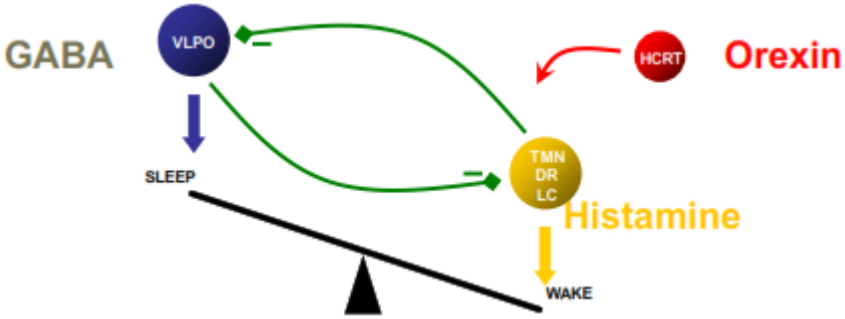
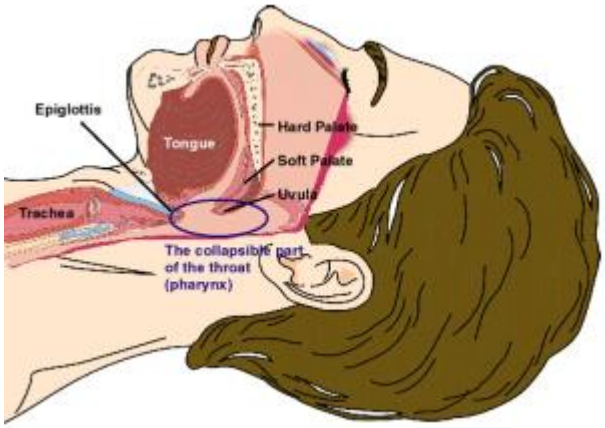
| **How is insomnia defined? What is its prevalence in the population?** | Insomnia - The biggest disorder in the world (10% of the world population)<br>• Defined by three months complaint at least two days a week<br>• Has effects on awake functioning<br><br>Causes<br>• Alzheimer's, Parkinson's, MS<br>• Primary or Psychophysiological insomnia - No other diseases are associated<br>• Psychiatric disorders - Depression, anxiety, addiction |
| **What is the molecular mechanism for narcolepsy?** | Narcolepsy<br>• Excessive sleepiness during daytime<br>• Sometimes associated with cataplexy<br>• REM sleep during the day - Hypnagogic hallucination<br>• Result of hypocretin/orexin<br>  <br><br>Flip-flop switch -> loss of orexin |
| **What are the current available treatments for apnea?** | Apnea<br>  <br><br>• Snoring<br>• Breathing stops<br>• Hypersomnolence<br>• Cognitive complaints |

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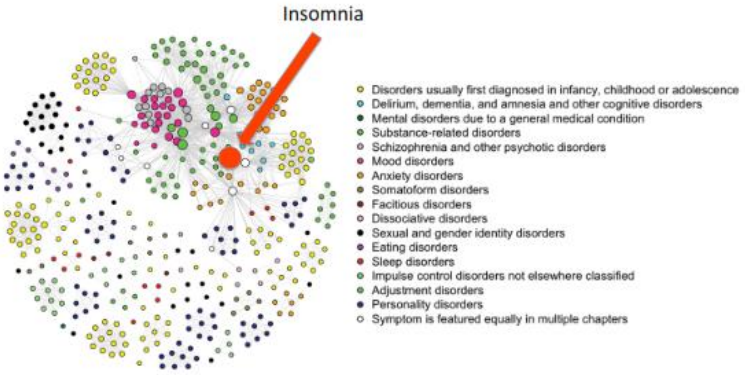
| | • Headache, impotence<br><br>Sleeping on your side helps<br>Typical: Male, overweight, short neck<br>Treatment - Weight loss, continous positive airway pleasure, somnoplasty (remove fat from airway) |
| **What are the problems with benzodiazapines for sleeping?**<br><br>**What is the main advantage with Z-drugs when comparing with benzodiazapines?** | Sleep medication<br>GABA - A and B<br>Inhibits Histamine and Monoamines<br>Promote melatonin<br><br>Benzodiazapines - Most common drugs after contraceptive<br>Reasonably safe, except if you combine it with other drugs (like alcohol)<br>Highly addictive<br>Half-life determines side effects<br><br>New generation of benzodiazapines - Z drugs<br>Sleep onset medication<br>Enhance the inhibitory effect of GABA<br>Rapid effect - The patient can take the drug once he cannot fall asleep for a while |
| **What are some non-pharmacological sleep therapy options?** | Non-medicated sleep therapy<br>Sleep restriction<br>CBT<br>Sleep hygiene<br>Exercise<br>Body temperature manipulations |
| **What is the most common symptoms among psychiatric disorders?** | Poor sleep as a central symptoms in psychiatry - Borsboom et al 2001<br>  <br><br>Imnosia is the most common complaint in psychiatry |

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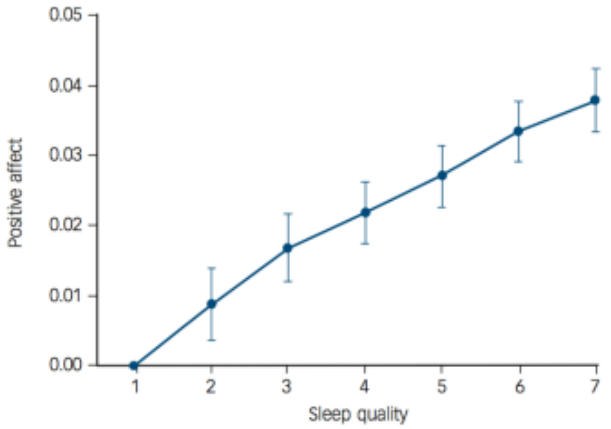
| **What does it mean to say 'good sleep predicts positive affect'?** | Good sleep predicts positive affect<br>  <br><br>The better you sleep, the better you feel |
| **What is the main finding of Baglioni et al 2011?** | Poor sleep mediates depressed mood (Baglioni et al 2011)<br>First you sleep poorly, then you have depression<br><br>Model: Factors that lead to insomnia that leads to depression (downward spiral) |
| **What is a possible conclusion since insomnia is involved in many different psychiatric diseases?** | Poor sleep mediates PTSD/Psychosis/Bipolar disorder<br>Not all people with a traumatizing event develop PTSD<br><br>Sleep mediates emotional processing<br>How does sleep mediate all these different diseases? We don't know |
| **What happens to sleep in older people?** | Sleep and Ageing<br>The older you are, the more trouble you have maintaining and falling asleep<br>Fragmentation of sleep-wake rhythms |
| **Why is elderly restlessness important for the rate of institutionalization?** | Sleep and Dementia<br>In demented elderly, nocturnal restlessness is a primary cause for institutionalization<br>The partner is not able to provide for the elder during day and night<br>Maintenance of function of the circadian rhythms |
| **What is the effect of light therapy in Alzheimer's patients?** | Light helps sleeping problems and cognition in Alzheimer's - Blue-enriched (similar to daytime light)<br>Increases cognition<br>Ameliorates depressive symptoms |

# Pills and Potions (Chris Vriend)

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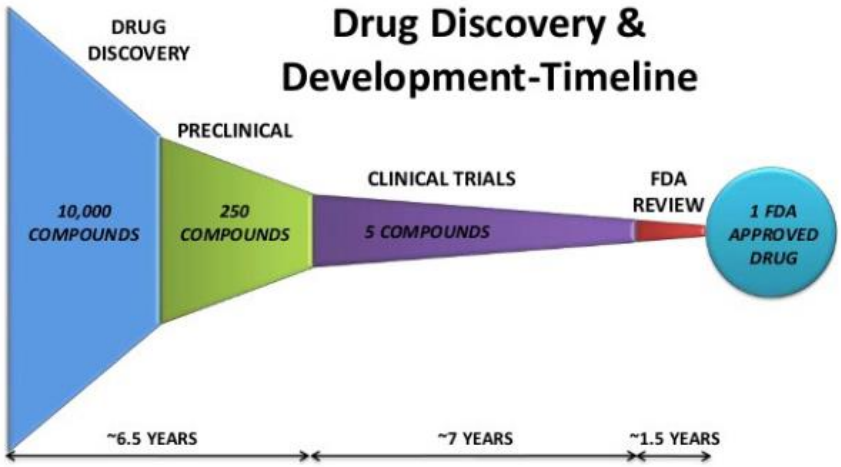
| | Two major classes of treatments: Pharmacological |
| **What are the downsides of pharmacological approach to disease treatment?** | Pharmacological approach<br>Neurological disorders - Have little to no effect on disease progression, almost all available treatments are symptomatic<br>Psychiatric disorders - Chronic treatment is necessary, many patients are treatment-resistant |
| **What are the challenges of drug development?** | **Challenges of pharma**<br>Takes 12-15 years and one billion dollars to make a drug<br>  <br><br>Many pharmaceutical companies have opted out to develop new drugs for neurological disorders - It takes too much time and it is a risky investment |
| **Define Rational drug design** | **Rational drug design** - Based on the known binding properties of the biological target to achieve a therapeutic effect<br>Since the 90's - Advances in imaging techniques and computer models |
| **Define how serendipity played a role in drug discovery in the past** | **Traditionally** - Trial and error, in vitro, cell cultures, animal models<br>Serendipity - Penicillin in 1928, Viagra in 1998<br>Researchers found an Alzheimer treatment while research diabetes<br><br>Downfall of serendipity - Rise of rational drug design, less time for clinicians to observe effects of drugs, reliance on double-blind placebo control trials |
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| **What are five reasons pharmaceutical companies are not incentivized to produce drugs for neurological disorders?** | Five reasons<br>1. Lack of understanding of disease mechanisms<br>2. Non-representative animal models<br>3. Lack of biomarkers<br>4. Subjectivity of endpoint measures<br>5. Regulatory restrictions |
| **Define two problems of 'Lack of understanding of disease mechanisms' in drug discovery** | **1. Lack of understanding of disease mechanisms**<br>• **Etiology (largely) unknown for almost all brain disorders**<br>• **Multifactorial, involving polygenic and environmental risks** (and their interaction) |
| **Define five problems of 'Non-representative animal models' in drug discovery** | **2. Non-representative animal models**<br>Basic anatomy and physiology<br>Pharmacokinetics<br>Pharmacodynamics<br>Toxicity<br>• Very hard to mimick human disease in animal models |
| **Define two problems with 'Lack of biomarkers' in drug discovery** | **3. Lack of biomarkers**<br>Not all patient with the same diagnosis have the same disease<br>Neurological diseases significantly overlap in pathophysiology<br>This is the object of precision medicine |
| **Define three problems with 'Subjectivity of endpoint measure' in drug discovery** | **4. Subjectivity of endpoint measure**<br>Clinical evaluation and questionnaires are often not an objective measure of reality<br>• Test-retest effect<br>• Inter-rater variability<br>• Disconnect with real-life functioning |
| **Define two problems with 'Regulatory restrictions' in drug discovery** | **5. Regulatory restrictions**<br>• **Complex and inconsistent regulations within and among agencies**<br>• **Negative pre-clinical findings are not published** |
| **What is the 'sad summary' of current** | **Sad summary**<br>• No disease curative treatments for brain disorders - Except relapsing-remmiting MS |

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| **pharmacological disease treatment? What are four things that may help improve the situation?** | • High cost and disappointing results discouraged investments from pharmaceutical companies<br><br>**Glimmer of hope**<br>• Shared data resources<br>• Reproducible and transparant science<br>• Abandon animal models (poor translation) - Use humans directly for validation<br>• Stratification and trials in homogenous subgroups |
| **Cite six non-pharmacological treatments to disease.** | **Non-pharmacological treatments**<br>Booming field - Bright light therapy, CBT, neurostimulation, music therapy, acupunture, nutrition |
| **What are two non-pharmacological treatments with a known pathophysiological intervention?** | **Only a few are based on known pathophysiology**<br>Deep brain stimulation for Parkinson's disease or Obsessive Compulsive Disorder<br>Bright light therapy - Seasonal affective disorder (winter depression) |
| **What are the advantages and disadvantages of non-pharmacological treatments?** | **Benefits**<br>Less adverse effects<br>Patients are part of their treatment<br>Generally cheaper<br><br>**Disadvantages**<br>Generally not disease-modifying<br>Effortful: Patients need to be willing, motivated and healthy enough |
| **What is the current interplay between pharmacological and non-pharmacological treatment?** | **Pharmacological vs non-pharmacological**<br>Very scarce direct comparasion studies<br>Non-pharmacological are used as an adjuvant<br>Non-pharmacological exclusively are used in treatment-refractory patients |
| **What is the limitation from the inference from two meta-analysis** | Meta-analysis - Exercise has more benefits than pharmacological interventions<br>Pharmacological - 0.3 standard deviation away from control<br>Exercise - 0.98 standard deviation away from control |

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| **that exercise is more effective than pharmacological treatment?** | Limits: These are different studies, the comparision of the statistics of one against another is not possible in principle |
| **What is the physiology principle behind bright light therapy?** | **Bright light therapy in Parkinson's disease**<br>Circadian system - Approximately 25 hours on its own<br>Input - Blue light captured by ganglion cells -> connects to suprachiasmatic nucleus and adjusts<br>Pacemaker - Some cells in hypothalamus<br>Output - Release of hormones<br><br>Less light leads to lack of sleep<br>• PD have lower temperature<br>• Increase cortisol<br>• Lower expression of clock gene BMAL1 in PD<br><br>**Neurobiological mechanism**<br>Melatonin is high during night and low during the day - Takes about 1 or 2 hours to increase or decrease<br>  <br>Bright light therapy decreases melatonin |
| **Describe the study design of Bright light therapy for Parkinson's disease.** | **Study design**<br>30 minutes<br>83 diagnosed patients<br>6 month follow up |

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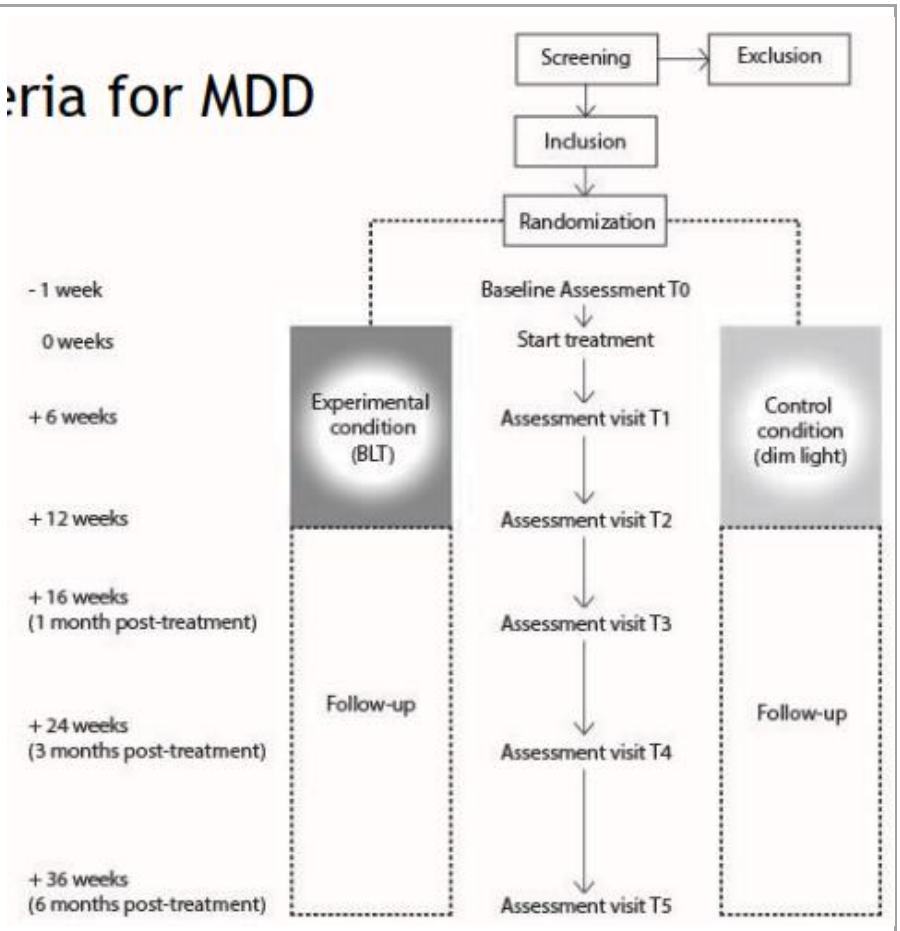
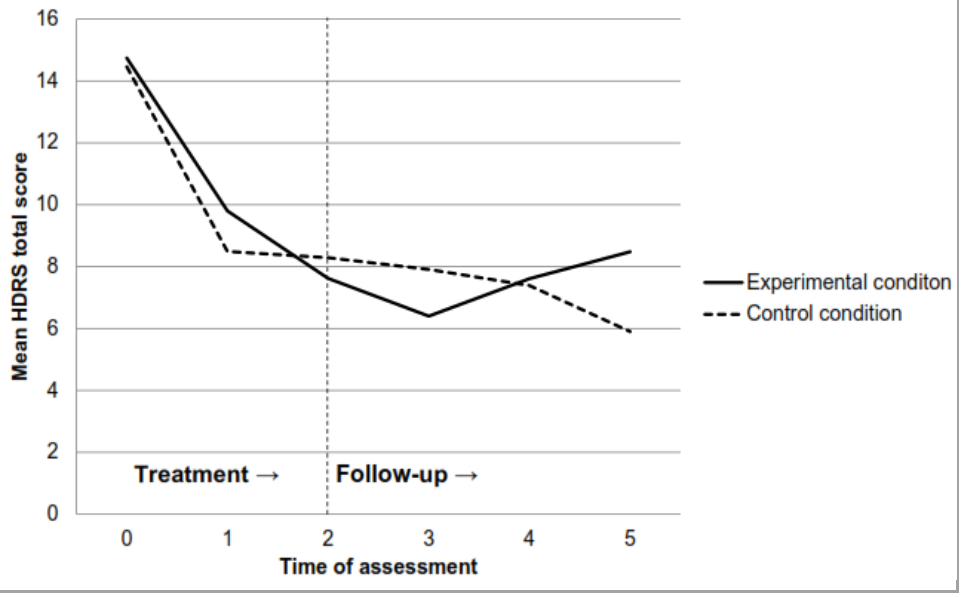
| |  <br>Control - Dim light<br>Experimental - Blue light |
| **What were the main finding of the bright light therapy study for Parkinson's disease?** | Subjective sleep quality increased in the blue light group<br>Cortisol levels were decreased in the blue light group<br>  |

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| **What is the current state of affairs for non-pharmacological interventions?** | Summary of non-pharmacological treatment<br>Many studies are being published<br>Equally or more effective than drugs<br>Little side effects<br>Non-disease modifying -> Not curative<br>Cognitive behavior therapy have been shown to be really sucessful in treaments of depression |

What do you need to know from this lecture?

- Knows the treatment arsenal for neurological and psychiatric disorders
- Understands the challenges and opportunities of pharmacological treatment
- Can name advantages and disadvantages of non-pharmacological treatment

# Development of the central nervous system (D.P.Bakker)

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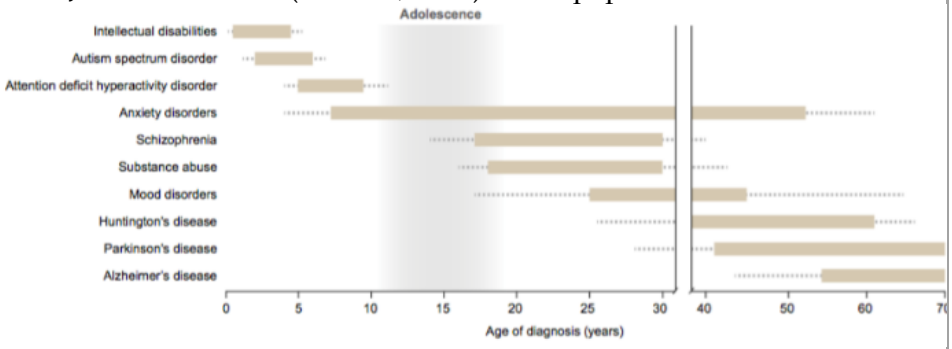
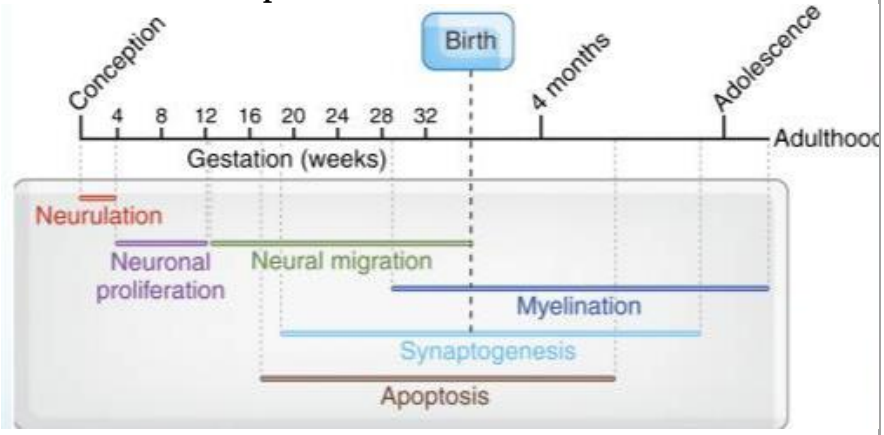
| **In which week of development does the cerebral cortex cover the midbrain?**<br><br>**In which week of development does the cortex fill with gyri and sulci?** | **Overview of development of the central nervous system**<br>Four weeks after conception - Neural plate forms the nerual tube<br>Forebrain - Cerebral cortex<br>Midbrain - Relay station of information<br>Hindbrain - Control basic physiological process<br><br>**8-26** - Cerebral cortex covers the midbrain<br>**28-40** - Brain fills with gyri and sulci<br>Premature babies born before this have smooth brains |
| **How many neurons does the neocortex have?** | • Neocortex has 16 billion neurons<br>• 175000 km of myelinated axons<br>• Brain consumes 18% of body oxygen |
| | **Psychiatric and neurological disorders age of onset**<br>John C. Silbereis (Neuron, 2016) - read paper<br>  |
| **Describe the main events that occur during brain development + when they occur during gestation and after birth.** | **Timeline of brain development**<br>  |

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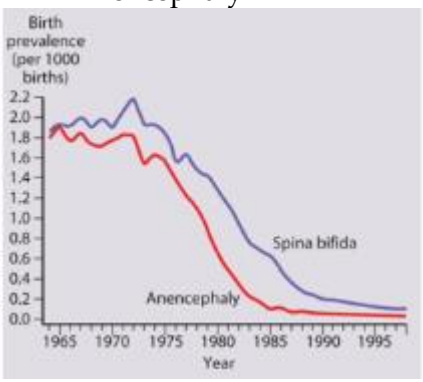
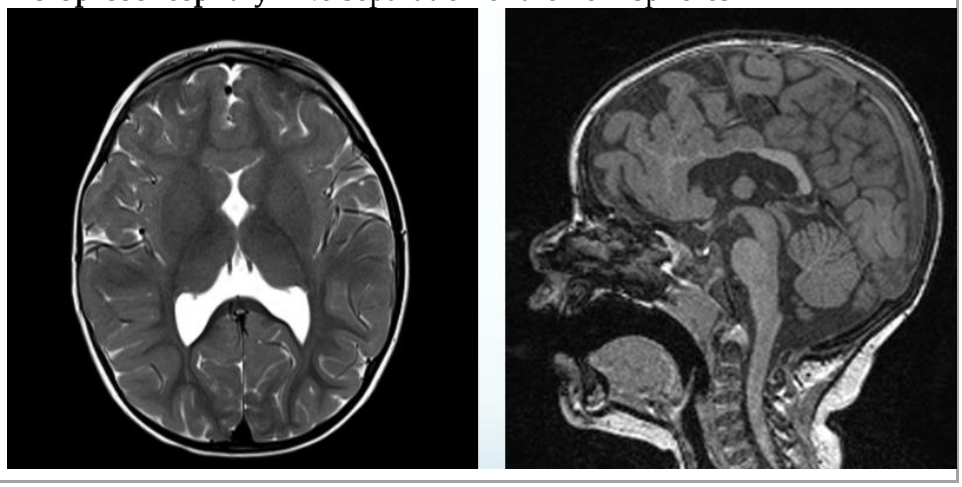
| **What are the main processes that cause head growth in children?** | **Head circumference** - Measurement of brain size in children<br>Microcephaly<br>Macrocephaly<br><br>Head growth is caused by myelination and neuron proliferation |
| **What were the two main technological discoveries that reduced the birth of babies with neural tube formation disorders?** | **Neurulation**<br>Neural plate invaginates and forms the neural tube<br><br>Disorder from neural tube formation - Often caused by environmental reasons (lack of folic acid; in the 80's, with the advances of ultrasound technology, these fetus were often aborted)<br>○ Spina bifida<br>○ Anencephaly<br>  <br> |
| **What are the main genes involved in brain regionalization?** | **Regionalization of brain regions**<br>Sonic hedgehog (Shh) - Vertical<br>Hox, FGF - Horizontal |
| | **Holoprosencephaly** - No separation of the hemispheres<br>  |

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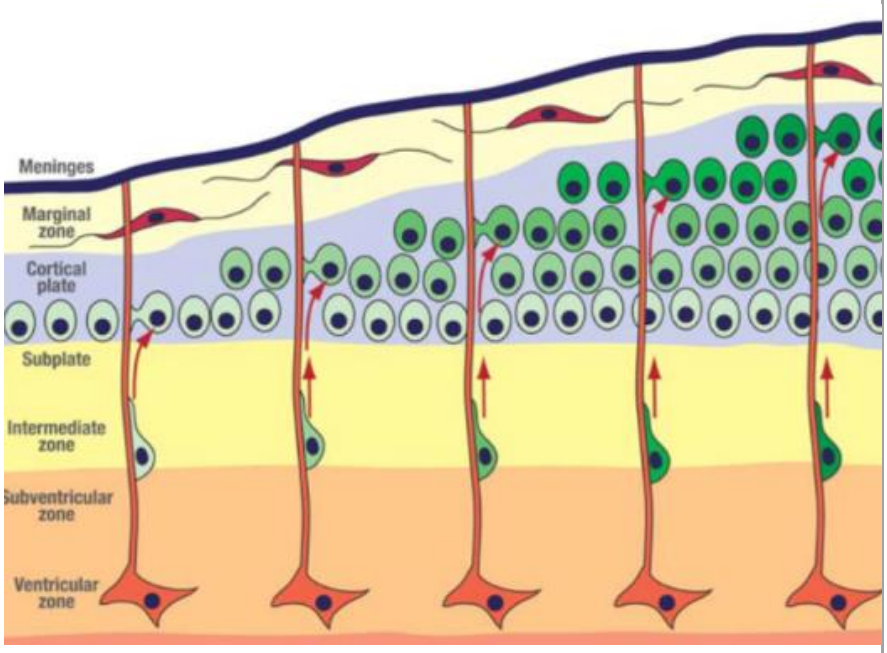
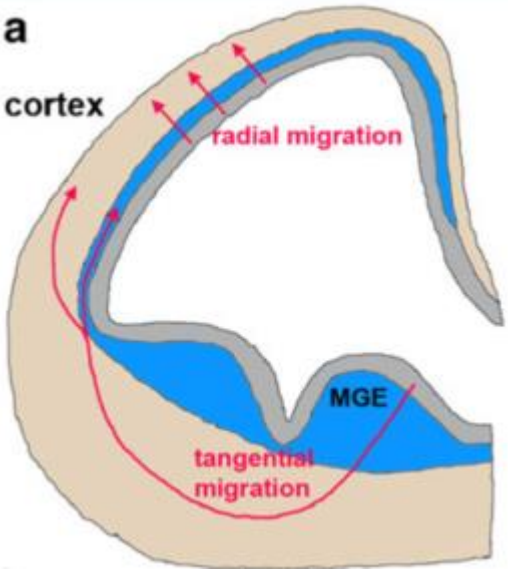
| **Which layers do neurons go through to reach the cortical plate during neural migration?** | **Neuronal migration** - Occur from the ventricular zone to the outer most layers<br>  <br><br>Goes through the subventricular zone and the intermediary zone |
| **What is the difference between radial and tangential neuronal migration?** | **Types of migration**<br>Radial - From different cortical layers<br>Tangential - Within the same cortical layer<br>  <br> |
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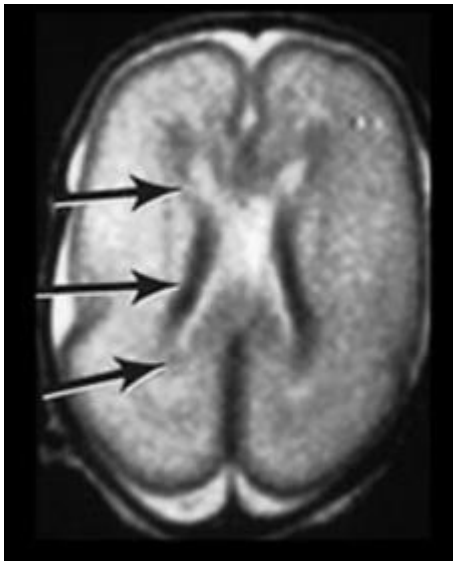
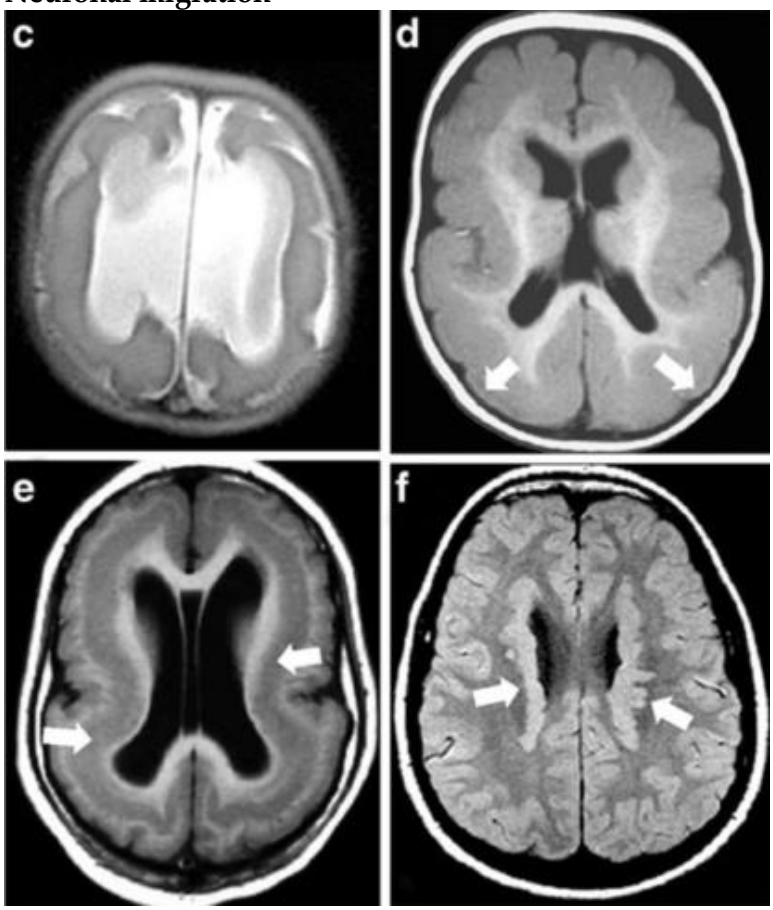
| **What is the germinal matrix?** | **Germinal matrix (25 weeks)**<br>  <br>Definition: Dense proliferation of neurons next to the ventricles - (intensity of grey matter)<br>High blood supply - Prone to bleeding |
| **Look at the image to the right. What is represented in: C/D/E/F?** | **Neuronal migration**<br>  |

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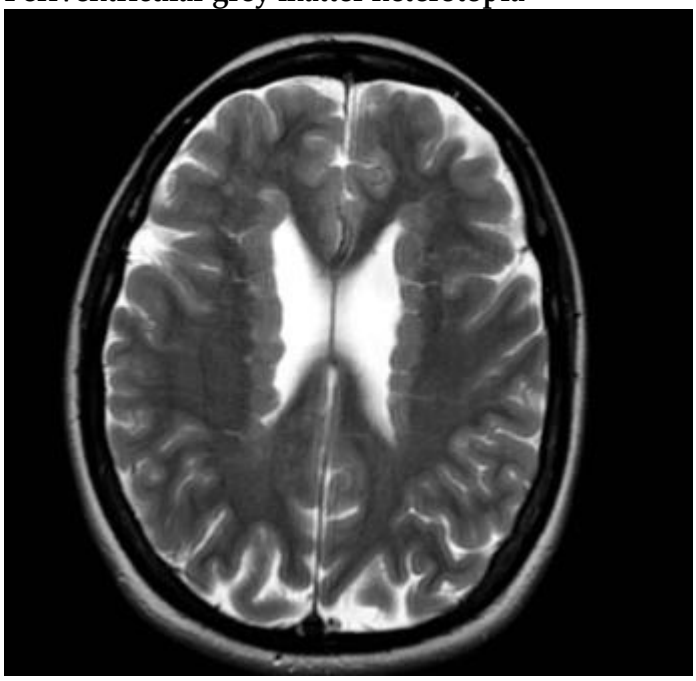
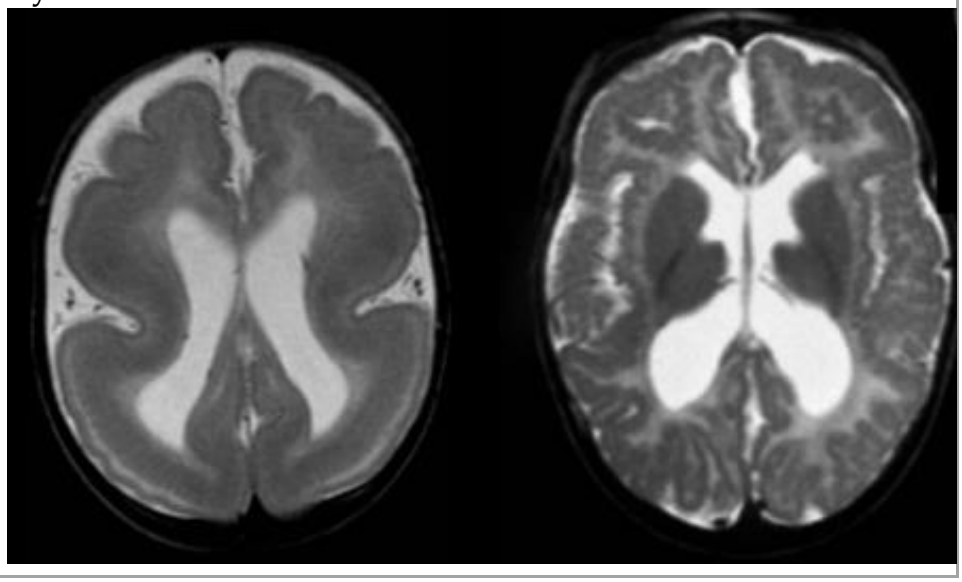
| | F. Older child - Gyri and sulci already defined (heterotopia)<br>E. Younger - Less gyri and sulci, ventricles quite big (double cortex syndrome)<br>D. Cortex too thick (pachygyria)<br>C. Lisencephaly and agenesis<br>Children survive, but they have developmental problems (cognitive impairments, epilepsy) |
| **What are the visual characteristics of brains with periventricular grey heterotopia?** | **Periventricular grey matter heterotopia**<br>  <br>Cells from the germinal matrix did not migrate properly |
| **What are the visual characteristics of brains with:**<br>**a. Lisencephaly**<br>**b. Polimicrogyria** | **Gyration abnormalities**<br>  |

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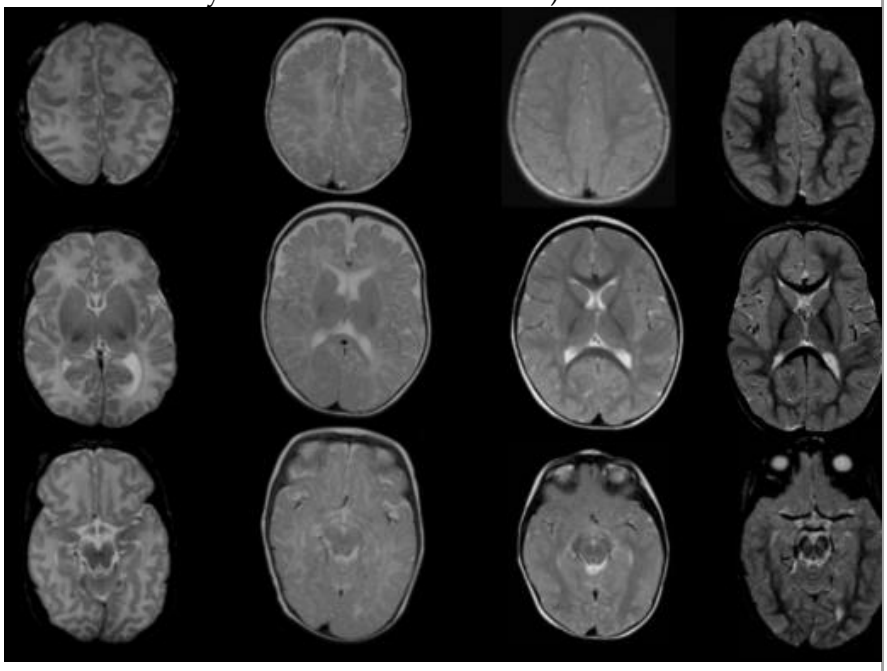
| | Left. Lisencephaly<br>Right. Polymicrogyria - Small cauliflower-like gyri |
| **When does synaptogenesis start during development?** | **Synaptogenesis**<br>Starts 6 months after conception<br>*Mnemonic: Six-Synaptogenesis both start with s* |
| **Which brain structures are myelinated first during development? What is the evolutionary reason for that?** | **Myelination**<br>Myelin is black - Motor cortex, brainstem (most important functions are myelinated first -> heart rate)<br>  <br>0 months: Myelin only in the posterior gyrus (motor)<br>24 months - Basic myelination process is finished<br>The longer your neurons are, the longer it takes to myelinate - Head balance comes first, walking comes later |
| **What is one possible reason that different age groups are susceptible to different diseases?** | **Spatiotemporal dynamics of human brain transcriptome** - Different brain regions express different genes at different times |

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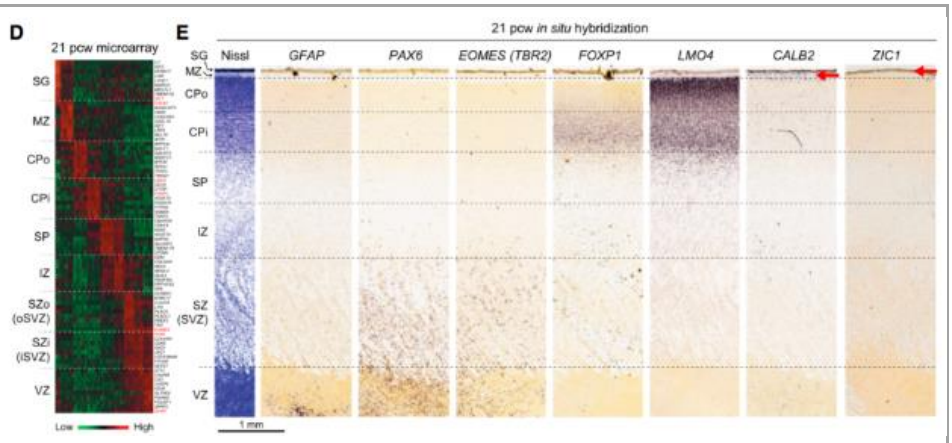
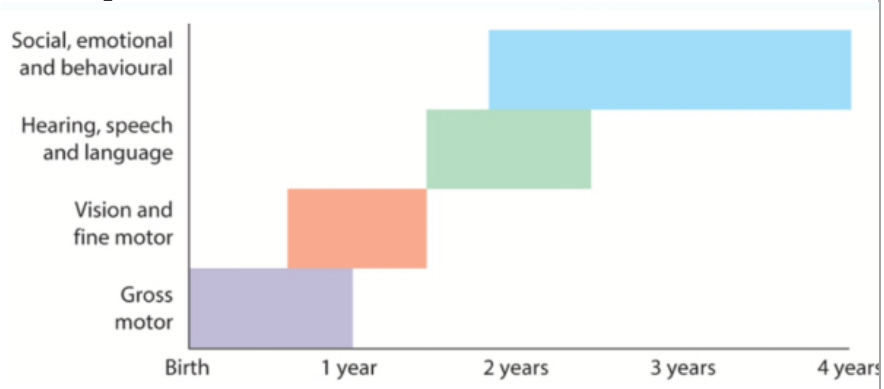
| |  <br>Might explain why some ages are more susceptible to some diseases |
| **When do the main complex CNS behaviors start to emerge in humans after birth?** | **Child development**<br>  <br>Gross motor - Walking, pinching, sucking motion |

# Brain imaging methods (Menno M. Schoonheim)

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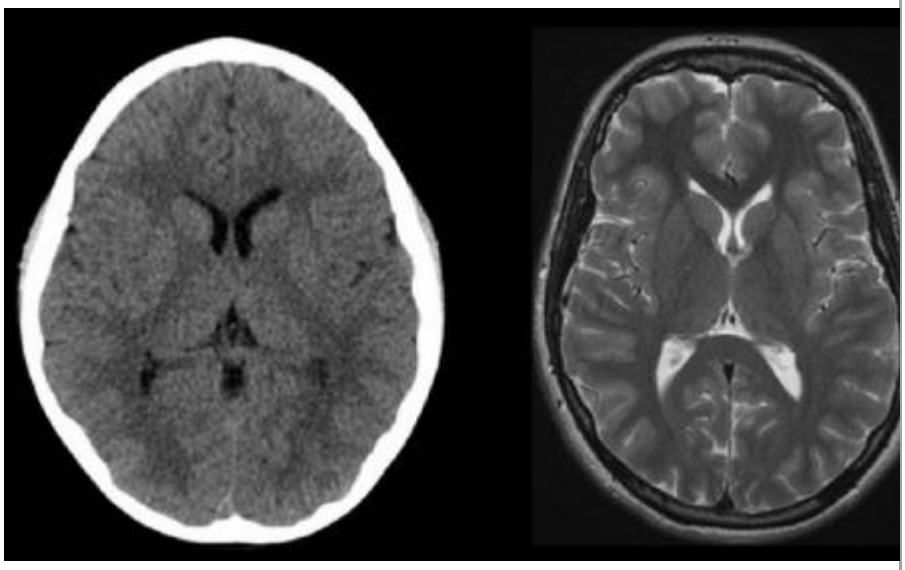
| **How do you differentiate CT and MRI?** | Skull is visible on a CT, not MRI<br>MRI outline - Skin<br>  |
| **How does an MRI work?** | Human body is mainly built of 26 elements<br>Hydrogen is very simple - Only a single proton<br>In a strong magnetic field - the protons align<br>Radio waves are transmitted - The waves jostle the proton of their original axis<br>Radio waves are turned off and when the protons come back, **they release energy** - which is measured by the head coil |
| **What is a voxel?** | **Voxel** - 3d cube<br>Magnetization of a region of tissue<br>MRI is a summary measure of all voxels - The higher the resolution, the better image quality |
| **What are the advantages of MRI?** | **Advantages of MRI**<br>Non-invasive<br>Non-ionising radiation<br>High soft-tissue discrimination |
| **What are the disadvantages of MRI?** | **Disadvantages of MRI**<br>Time consuming<br>Contraindication of fMRI<br>Noise from the machine<br>More advanced staff to operate |

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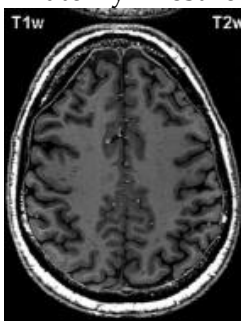
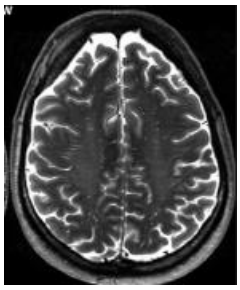
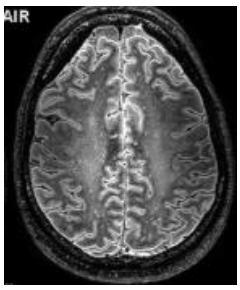
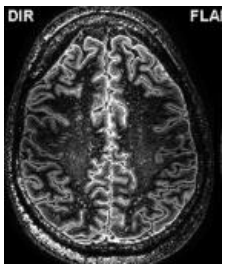
| **What are the main techniques of MRI? What is the most common use of each one?** | **Main techniques - How you measure the return to normal**<br>T1 - Sensitive to fat, not sensitive to water<br>Myelin is white, ventricles are black<br>Anatomy - Best for studying atrophy<br>  <br>T2 - Sensitive to water, not to fat<br>White matter is dark<br>Good to assess lesions - Water will pool into the lesion<br>  <br>Flair - T2 with the water signal reduced to 0<br>Fluid atenuated inversion recovery<br>Difference from T1 lesions will become white<br>  <br>DIR - Supress signal from the white matter<br>Double inversion recovery<br>  |

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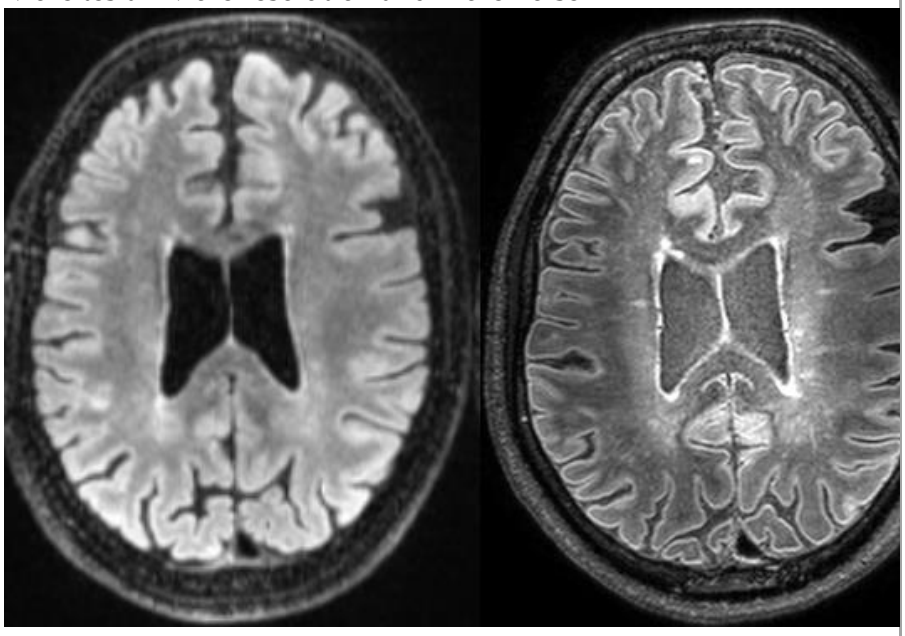
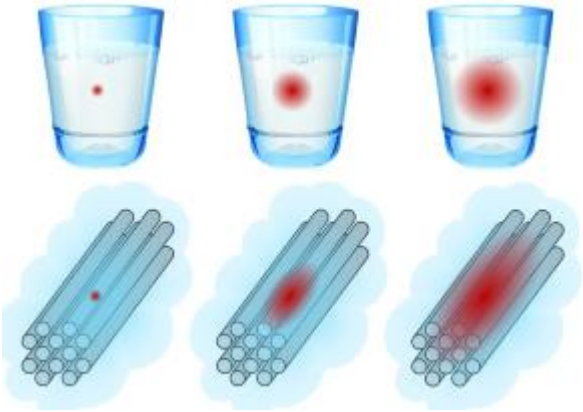
| **What is the T1 contrast enhancement MRI? What is its main advantages over non-contrast MRI?** | **T1 contrast enhancement - Gadelinium**<br>Does not normally cross the BBB<br>With a disease like MS, the BBB becomes leakier<br><br>Differentiate old and new lesions - This method only detects new lesions |
| **What is the downside of increasing resolution in an MRI?** | More tesla - More resolution and more noise<br>  <br>3T vs 7T |
| **What is diffusion weighted imaging and what does it measure?** | **Diffusion weighted imaging (DTI/DWI)**<br>Aim: Visualize structure connection in vivo<br>Look at proton movements - Movement is restricted by axons and dendrites<br>  <br>Isotropic - Random<br>Anisotropic - Limited in direction |

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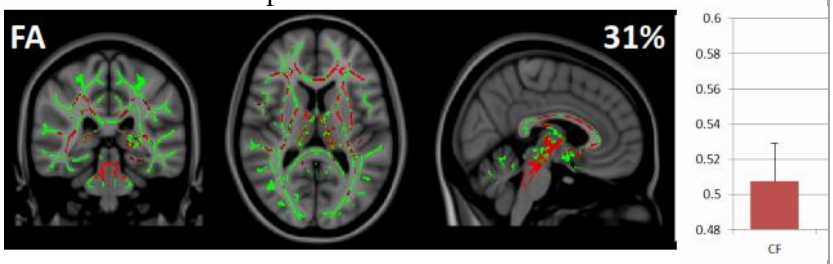
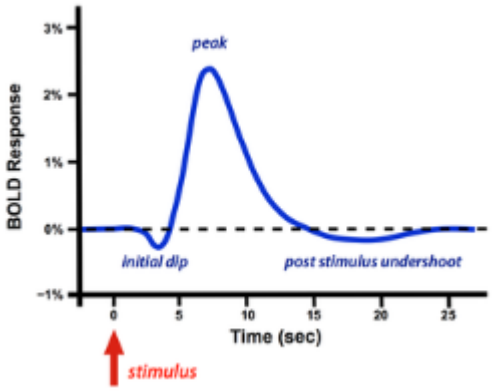
| | 1. Axial diffisuvity - Along axons<br>2. Radial diffusivity - Across axons<br>3. Mean diffusivity<br>4. Fractional anisotropy<br><br>Example:<br>Man and women are wired differently<br>Men are more prone to MS<br>  |
| **What is fMRI and what is it measuring?**<br><br>**What are the main downsides of fMRI?** | **Functional fMRI**<br>  <br>BOLD - Blood oxygenation level dependent imaging<br>Possible because haemoglobin disturbs the magnetic field<br>Increased neuronal activity -> More oxygen is required<br><br>In fMRI there is always a delay of six seconds<br>Multiple scans are needed |
| **What is the default mode network?** | **Functional connectivity - Coactivation of different brain areas**<br>Indication that the regions are connected |

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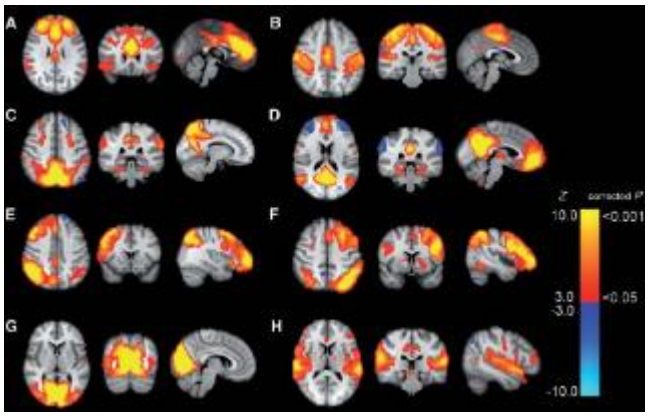
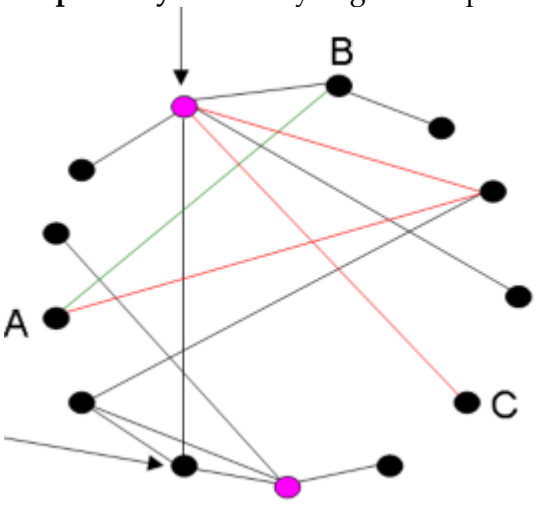
| |  <br>D. Default mode network - Active during rest<br>Biggest hubs of the brain |
| **What is magnetoencephalography and what does it measure?** | **Magnetoencephalography** - Recording of electromagnetic fields produced by the eletric currents in the brain |
| **What is a possible explanation that thalamus connectivity increases in MS?** | **Thalamus connectivity** - In Multiple Sclerosis, there is an increase in connectivity is related to cognitive impairment<br>Damage to interneurons? |
| **In graph analysis, what are nodes, edges and clusters?** | **Graph analysis** - Analysing the shape of the graph<br>  <br><br>Examples: Shortest path between A and C = 3<br>Cluster - Nearby nodes that are connected to each other -> indicates local information processing |

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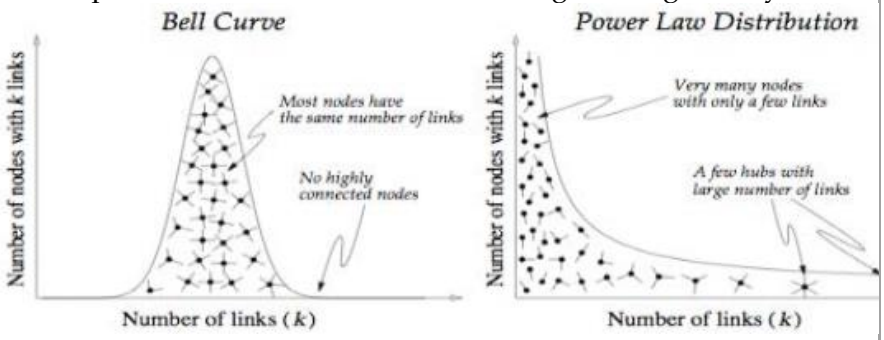
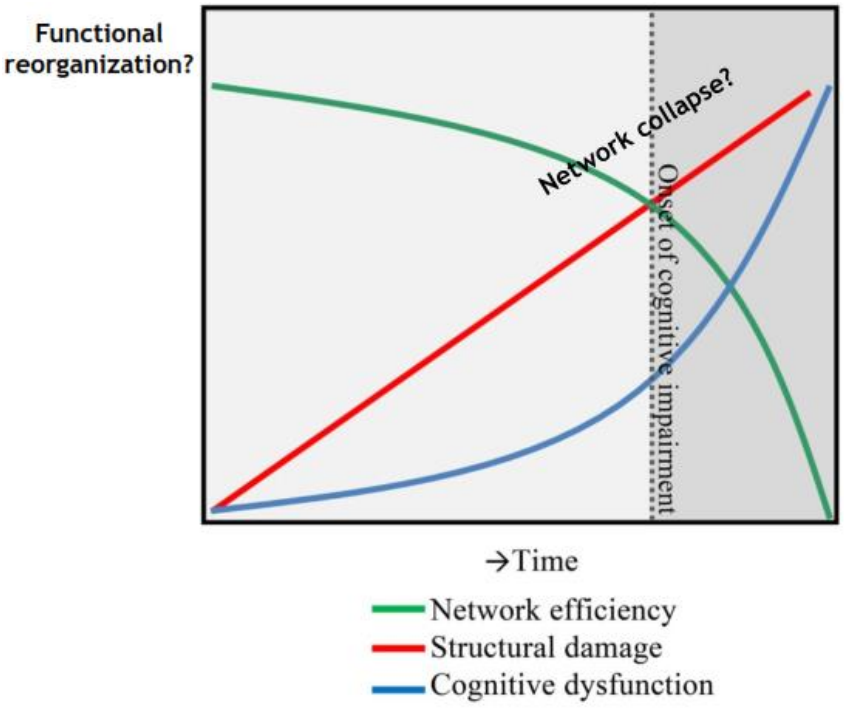
| **Why is graph theory useful in Neuroscience?** | Why is this used?<br>It quantifies how fast information can go through the system<br>  <br><br>Bell curve - Nodes have the same number of links<br>Power Law distribution - Many nodes with only a few links, few hubs with a high number of links<br>More efficient<br><br>In Neuroscience - Diseases often change the connectivity between different brain regions<br>  <br> |

# Neuro-oncology Masterclass (Linda Douw)

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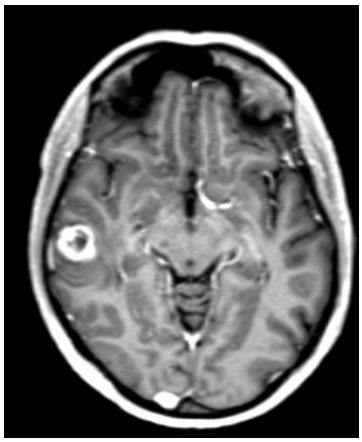
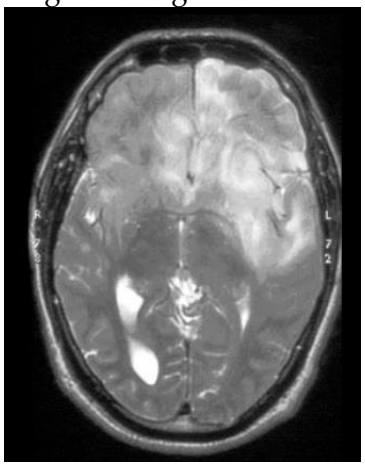
| **How come is it possible that a grade IV cancer generates no observable symptoms and a grade II cancer may lead to very severe symptoms?** | Three example cases:<br>Mrs. M<br>60 year old female<br>Generalized seizure<br>Glioblastoma multiforma<br>  <br>Symptoms: Severe anosognosia (you do not realized you are severely ill), major personality change, no deficits on neuropsychological assessment<br>Mr. V<br>34 year old male<br>Seizures<br>Oligodendroglioma - Generalized, but grows really slowly<br>  <br>Symptoms: Only minors cognitive deficits picked up on NPA<br><br>Mr. K<br>51 year old male<br>Anaplastic astrocytoma |

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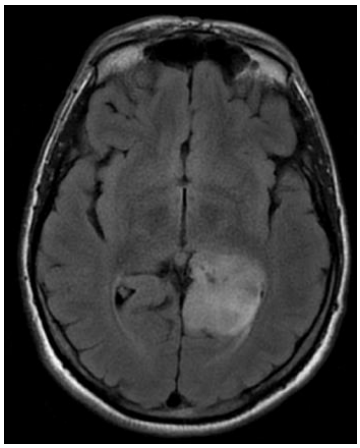
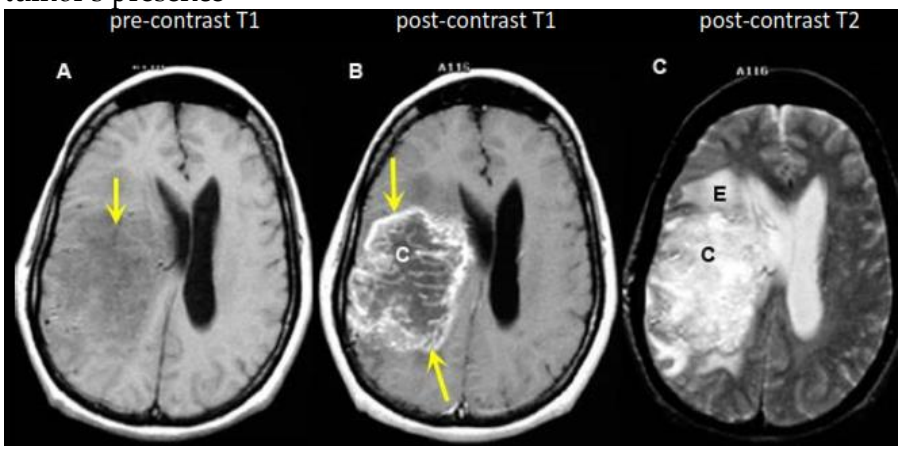
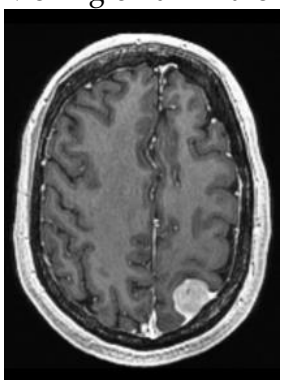
| |  <br>Symptoms: Severe cognitive impairment, catatonia<br><br>Conclusion: The severity of the cancer not always is correlated with the severity of the symptoms |
| **What is the current standard of diagnosis of CNS cancer today?** | Current stardard of diagnosis:<br>MRI - A contrast (Gadolonium) must be used to prove a brain tumor's presence<br>  <br>If contrast doesn't light up the lesion - The BBB is intact, means the lesion is old |
| **What is a meningioma? What grade is it?** | Meningioma - In the head, not the brain<br>  |

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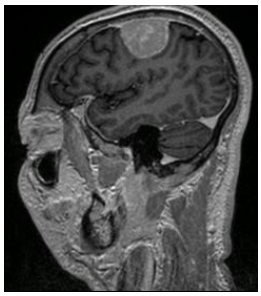
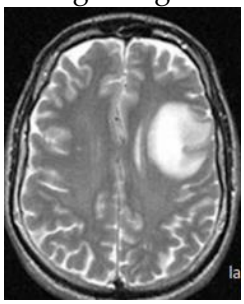
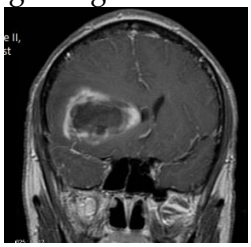
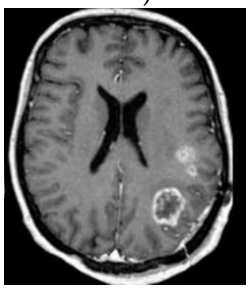
| |  <br>Grade I - Does grow and does not cause problems<br>Hyperintense after gadolinium injection |
| **What is a low grade and high grade glioma?** | Low-grade glioma<br>  <br>Grade II - Always grows, often slowly |
| **What is the difference between grade III and grade II cancers?** | High-grade glioma<br>  <br>Grade III - Largely identitical to grade II, but with more contrast enhancement |
| **What is glioblastoma multiforme? Why does it have this name? What are the visual characteristics observable in an MRI?** | Glioblastoma multiforme (impossible to determine which glial cells they came from)<br>  <br>Grade IV - Ring-shaped contrast enhancement, necrosis, edema<br>Often cross to the other hemisphere |

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| **What is the current prognosis for CNS cancers grade I-IV?** | Current prognosis of CNS cancer<br>WHO grade I<br>meningioma, astrocytoma, oligodendroglioma, oligoastrocytoma, rare tumors<br>mostly "benign", no treatment or resection<br><br>WHO grade II<br>astrocytoma, oligodendroglioma, oligoastrocytoma<br>variable prognosis **3-12 years**, resection + RT or wait<br><br>WHO grade III<br>astrocytoma, oligodendroglioma, oligoastrocytoma<br>variable prognosis **3-10 years**, resection + RT or XT<br><br>WHO grade IV<br>glioblastoma multiforme<br>prognosis **14 months or less**, resection + combined RT/XT |
| **What are the symptoms of low-grade and high-grade glioma?** | Symptoms<br>Low-grade glioma - Epilepsy, cognitive deficits<br>High-grade glioma - Increased intracranial pressure, paralysis, paresis<br><br>Glioma patients perform worst in every test - Not only related in the brain region lesioned |
| **What are the current treatment options for CNS cancer?** | Treatment options<br>• Wait and scan - Only if resection is not possible<br>• Surgery (tumor resection) - Completely resection is never possible<br>◦ Optimization - Resect as much of the tumor as possible, keep functional areas intact (awake craniotomy)<br>• Chemotherapy<br>• Radiotherapy<br>• Combination |
| **What is the problem with chemotherapy for brain cancer? What is the primary and secondary chemotherapy** | Chemotherapy<br>Most drugs do not reach the brain - Blood brain barrier<br>Temozolomide (primary treatment) - Alkylating agent, binds to methyl group in DNA, induces cell loss<br>PCV combination (secondary treatment) - Procarbazine, lomustine, vincristine |

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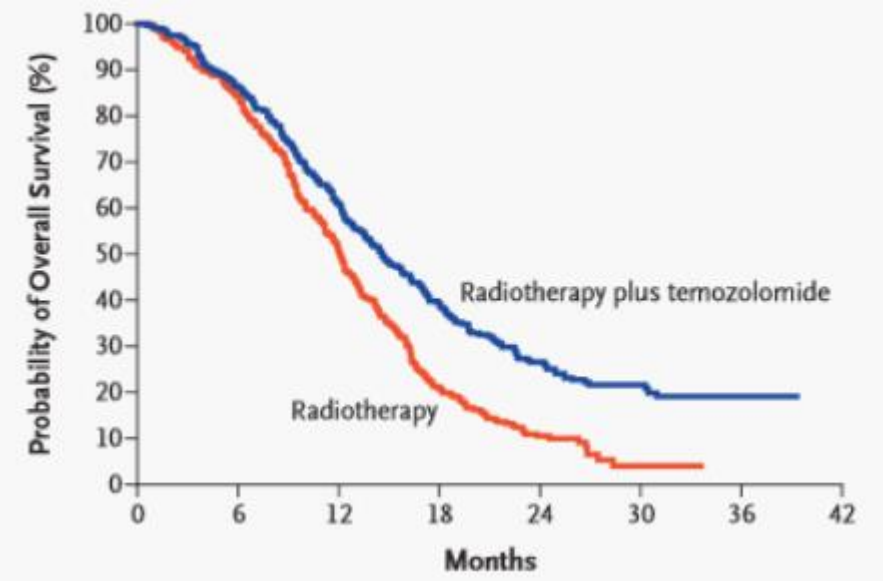
| **options available today?** | |
| **What is the problem with radiotherapy for brain cancer?**<br><br>**What are the long-term effects of radiotherapy for brain cancer?** | Radiotherapy<br>Damages DNA<br>Radiation focuses on the tumor, but it is never 100% specific<br><br>Delayed radiotherapy effects on cognition<br>No difference in six years<br>Executive functioning, attention and information processing speed decreases in twelve years |
| **What was the result of combination therapy of radiotherapy + temozolomide for glioblastoma treatment?** | Combination therapy in glioblastoma<br>  <br><br>Radiotherapy<br>Radiotherapy + temozolomide - Median survival went up 12 months |
| **What is the supposed mechanism of action of tumor-treating fields?** | Partially sucessful - Tumor-treating fields<br>Machine that delivers alternating currents to the brain<br>Cancer cell is constantly dividing - Machine interfers with cell division |

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| |  <br>5-month survival benefits<br><br>There was no placebo in this study<br>Could damage glial cell division<br><br>Improves survival and quality of life |
| **What is the problem with health-related quality of life as an endpoint measure?** | Health-related quality of life<br>Primary endpoint of studies - A life one month longer may not be worth if the treatment causes suffering<br>Subjective - Done with questionaires |
| **What does HRQoL take into account?** | Quality of life - Measured by HRQoL<br>Tumor and treatment<br>Side effects<br>Symptoms<br>Benefits - Amiliorate symptoms<br><br>Outcomes measures in neuro-oncology<br>Patients with cognitive impairments have higher subjective quality of life<br><br>There is no objective better questionnaire |
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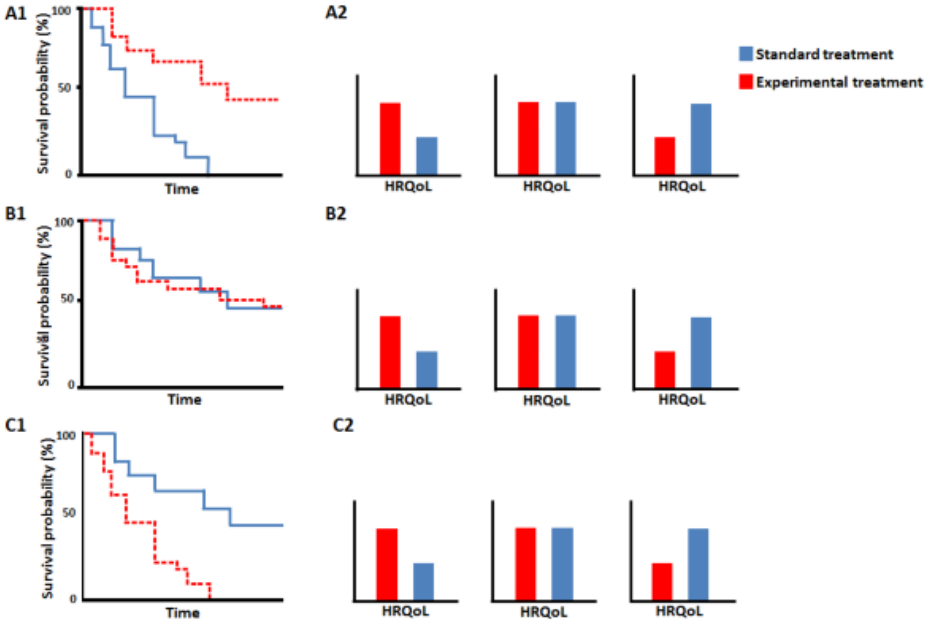
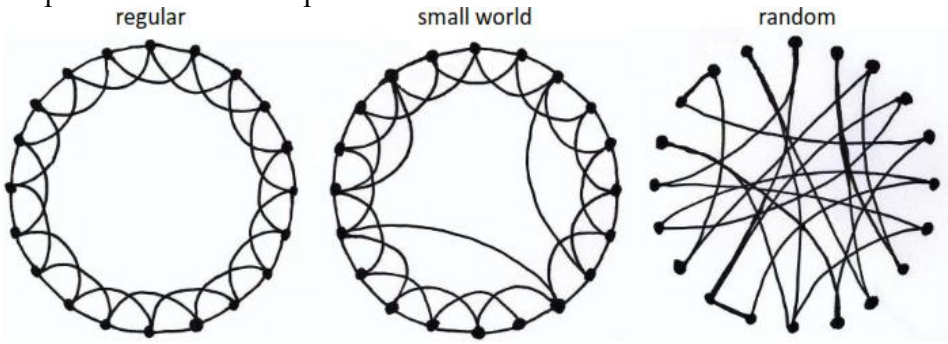
| **What are the possible outcomes of a drug in terms of survival and quality of life?** | Survival and quality of life<br>  <br><br>Treatment can prolong, shorten or maintain survival<br>Treatment can increase, decrease or maintain quality of life |
| **What are the limitations in assessing quality of life?** | Limitations in assessing quality of life<br>Some patients are not able to fill out these forms<br>Low compliance - Patients forget<br>Statistical significance vs clinical relevance |
| **What is the current understanding of the neural correlates of cognition?** | Neural correlates of cognition<br>1830 - Frenology<br>1995 - fMRI (frenology-like)<br>Today - Cognition is the result of large scale connections between different brain regions |
| **In graph theory, what is a I) regular graph; II) small world graph; III) random graph?** | Graph theoretical concepts<br>  <br><br>Regular - High clustering, high path length<br>Small world - High clustering, low path length |

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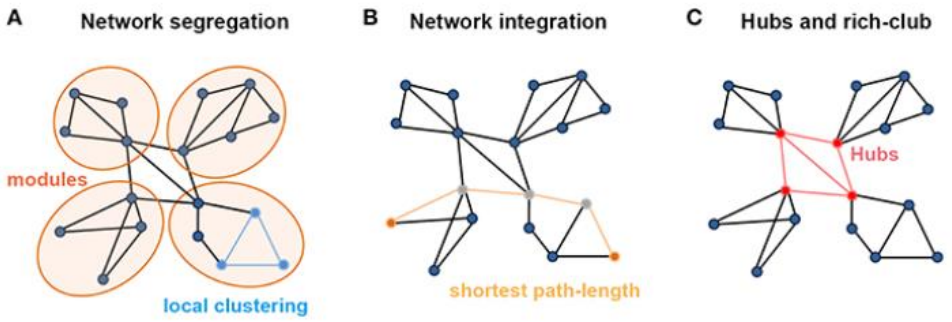
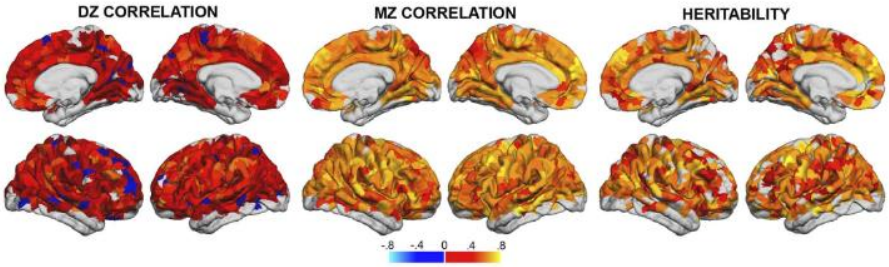
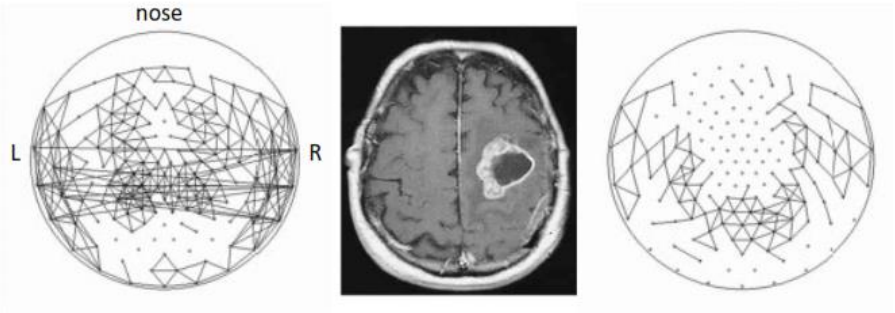
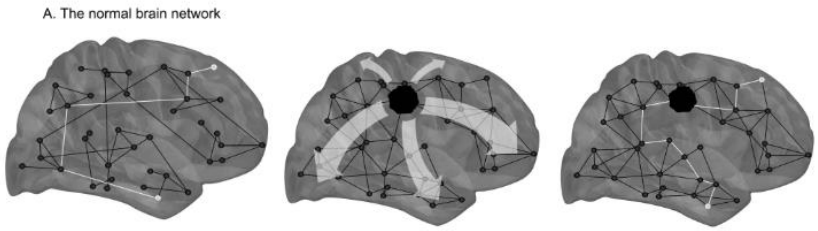
| | Optimal balance between connections and efficiency<br>Random - Low clustering, low path length |
| **Define what is**<br>**I. Network segragation**<br>**II. Network integration**<br>**II. Hubs and rich-club** |  <br>Network segregation - Local clustering<br>Good for resilience - each node is not much important<br>Network integration - Measured by the shortest path length<br>Hubs and rich-club - Nodes connected to the rest of the graph<br>Most important regions in the brain<br>Hubs are connected to each other, but not to non-hubs (rich becomes richer effect) |
| **How is connectomics studied today?** | Connectomics<br>White matter connections via diffusion MRI<br>FMRI and EEG/MEG - Correlation between time series<br>  <br>The connectome is heritable - 80% of connectomics is equal in identitical twins |
| **What is the consequence of diseases that disrupt connectivity in the brain?** | High IQ is related to small-world networks<br>Pathologies such as Parkinson's, MS have disrupted default mode network (increased connectivity all over the brain) |




Local connections form due to the tumor disruption of the network (release of glutamate from the tumor) - Maybe causes epilepsy

Local connections become less efficient - More paths to travel



# 3a. Clinical features of Multiple Sclerosis (Iris Dekker)

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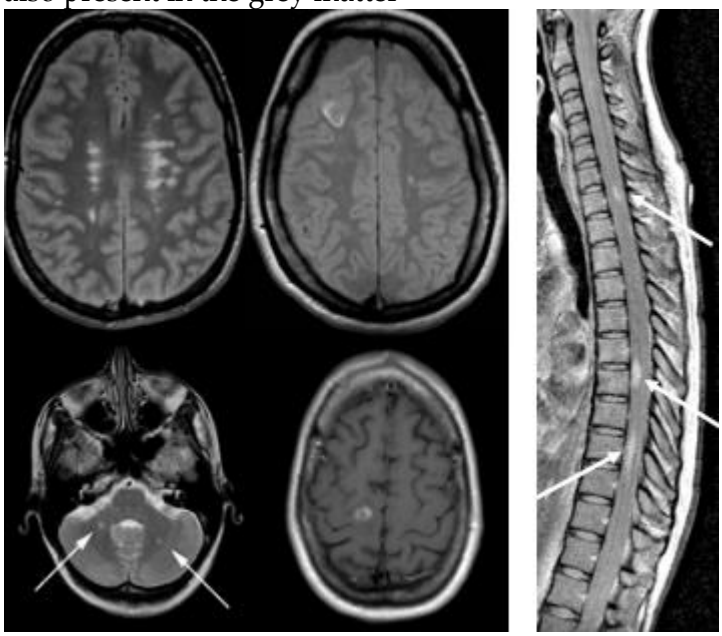
| **What is the definition of multiple sclerosis?** | Definition of Multiple Sclerosis<br>Multiple scars in CNS<br>Multifocal lesions/plaques - Mostly located in the white matter, but also present in the grey matter<br>  |
| **What is the prevalence of MS in the Netherlands?** | Prevalence: 1:1000 in the Netherlands<br>  <br>Women are 2-3 times more likely to develop MS |
| **What some possible explanations that countries in** | Prevalence increases with higher latitudes - possible contributing factor are:<br>Vitamin D levels<br>Diet |

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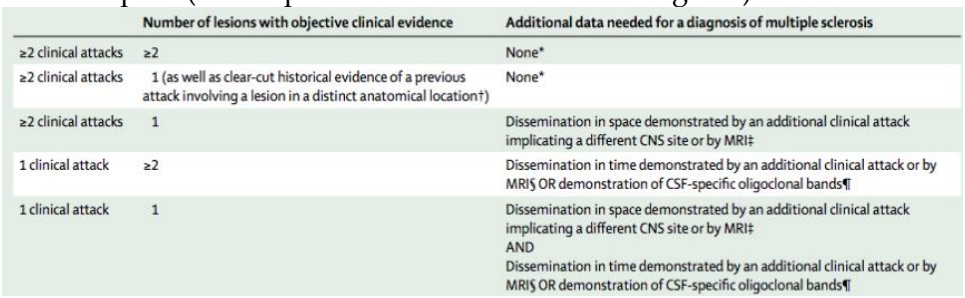
| **higher latitudes are more likely to develop MS?** | Epstein-Barr virus - Mononucleosis infectiosa<br>Smoking<br>Ethnicity<br>Genetics |
| **Which cell structure is affected by MS in the white matter and grey matter?** | Anatomy<br>Grey matter - Cell bodies are affected<br>White matter - Myelin in the axon is affected |
| **What is the pathophysiology of MS?** | Pathophysiology<br>Inflammation, demyelination, remyelination (made by oligodendrocites), scarring (gliosis)<br>Blood brain barrier leaky - Immune cells invade the CNS and attack the myelin |
| **What is the current diagnosis for MS?** | Diagnosis<br>Clinical features<br>Radiological features<br>Abnormalities in cerebrospinal fluid<br><br>• Diagnosis is made based on dissemination in time and dissemination in space (2 time points and 2 different brain regions)<br>  |
| **What is the typical MS damage seen on MRI?** | Typical MS lesions<br>Ovoid shaped<br>Perivascular orientation<br><br>Different scans<br>T2 - Disease burden<br>T1 - Irreversible damage<br>T1 contrast - Active lesions<br>Assess dissemination in time - lesions in different regions |

| | Number of lesions with objective clinical evidence | Additional data needed for a diagnosis of multiple sclerosis |
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| ≥2 clinical attacks | ≥2 | None* |
| ≥2 clinical attacks | 1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†) | None* |
| ≥2 clinical attacks | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ |
| 1 clinical attack | ≥2 | Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |
| 1 clinical attack | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡<br>AND<br>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |

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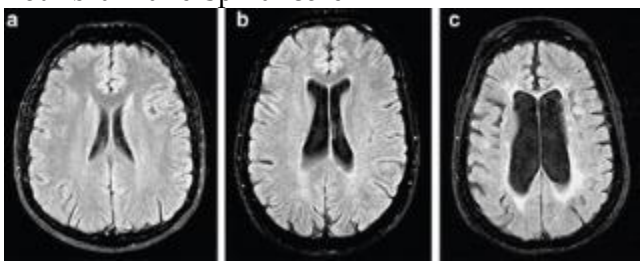
| | MS lesions: periventricular, cortical, infratentorial and spinal cord<br>Two different regions: Dissemination in space |
| **What is the biological explanation for brain atrophy?** | Atrophy<br>Widening ventricles<br>Later disease stages<br>Both brain and spinal cord<br>  <br><br>Independent from white matter damage |
| **What are three diseases that look similar to MS in an MRI analysis? How can the differential diagnosis be made?** | MRI in MS<br>Other diagnoses: Vascular disease, Neuromyelitis optica, Sarcoidosis<br>  <br><br>If the diagnosis cannot be assessed:<br>CSF can be used to assess dissemination in time<br>Oligoclonal bands |
| **Define:**<br>**a. RRMS**<br>**b. SPMS**<br>**c. PPMS**<br>**d. PRMS** | Relapses |

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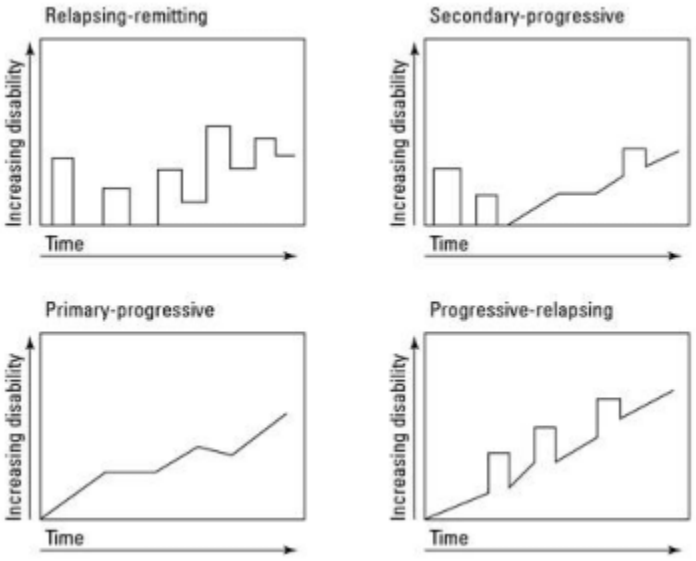
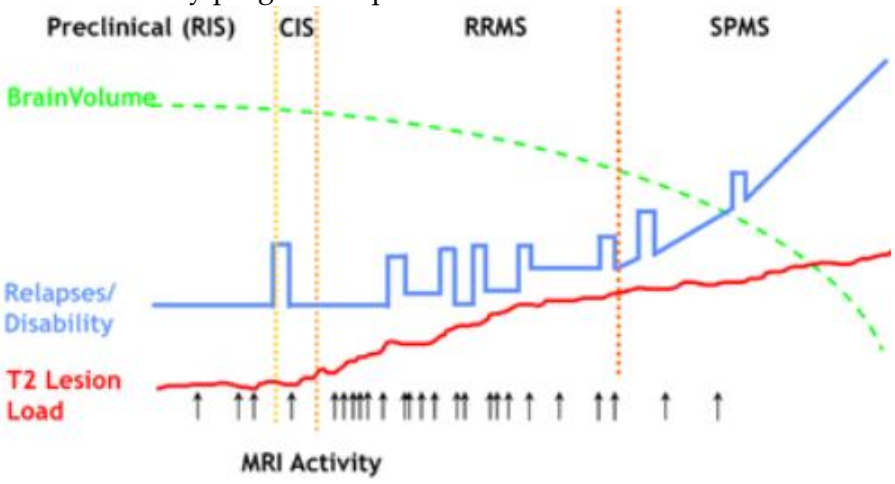
| |  <br>Relapsing-remitting MS - 85%<br>Secondary progressive - 80%<br>Primary progressive - 10-15%<br>Progressive-relapsing |
| **What is the disease progression in MS?** | Disease progression<br>Radiological isolated syndrome - People with MS lesions but no observable symptoms<br>Clinically isolated syndrome<br>Relapsing remitting MS<br>Secondary progressive phase<br>  |
| **What are the main symptoms of MS?** | Main symptoms of Multiple Sclerosis<br>👁 Visual problems<br>🚶♂ Pyramidal Symptoms<br>😞 Sensory disturbances |

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| | 🚽 Bladder/Bowel/Sexual problems<br>⚖ Coordination problems<br>🤯 Cognitive problems<br>😕 Fatigue |
| **What are the visual problems in MS?** | Visual problems - Optic neuritis (decreased color vision, pain in the optic nerve, scotoma) -> though it is a common first symptom, not deterministic |
| **What are the pyramidal symptoms in MS?** | Pyramidal symptoms - Paresis, spasticity, abnormal reflexes |
| **What are the sensory disturbances in MS?** | Sensory disturbances - Tingling, painful sensations, numbness, lack of sensory feedback (ataxia), Symptom of Lhermitte (when they bend forward, they feel a painful sensation) |
| **What are the bladder/sexual problems in MS?** | Bladder/bowel/sexual problems - Incontinence, urine retention, frequent urinary tract infections, sexual problems |
| **What are the coordination in MS?** | Coordination problems - Ataxia, tremor, balance |
| **What are the cognitive problems in MS?** | Cognitive problems - Memory, concentration, attention, difficulties organizing |
| **What is the cause of fatigue in MS?** | Fatigue - No good treatment, unknown cause, high prevalence |
| **What are the important secondary symptoms of MS?** | Other - Depression (50% during disease course),suicide (7-8), don't walk independently after 25 years (50%), |
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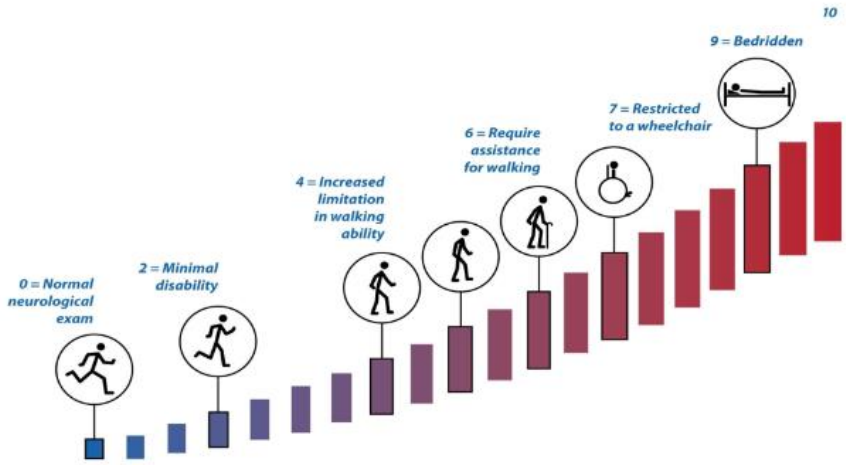
| **What are the three disability outcome measures?** | Disability outcome measures<br>Expanded disability-status scale (EDSS) - 10 is death due to the disease<br>  <br><br>9-hole peg test<br>25-feet walk test |
| **How is the efficacy of treatment measured in MS?** | Efficacy measures<br>Relapses - Annualized relapse rate<br>Disability - Outcome measures<br>MRI - Gadolinium enhancing lesion, new or enlargin T2 lesions, atrophy<br><br>No Evidence of Disease Activity (NEDA) - No relapses, no MRI activity, no EDSS progression<br>No Evidence of Progressive Disease Activity (NEPDA) - Using 25-feet walk test or 9-hole peg test |

# 3b. Neuroradiology of MS (Anand J.C. Eijlers)

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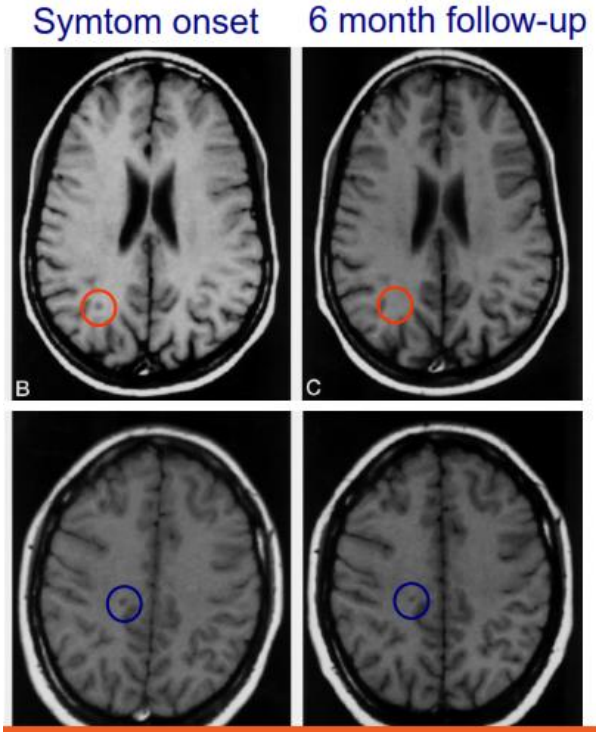
| **Why do we use imaging in MS?** | Why do we use imaging in MS?<br>Diagnose<br>Monitor disease and treatment effect<br>Research |
| **What is the imaging hallmark of MS?** | Hallmark of MS - White matter lesions<br>T2-weighted MRI<br><br>Sensitive in the detection of MS lesions<br>Lack of histopathologic specifity (old and new lesions look the same)<br><br>T2 MS lesions<br>Relapsing-remaining - Many lesions<br>Secondary-progressive - Many lesions<br>Primary progressive - Few lesions<br><br>Spinal cord - Frequent in all of them |
| **What does T1 imaging show in MS?** | T1 in MS<br>Shows edema and reabsorption of edema<br>If a lesion stays for more than 6 months, it is more severe<br>  |

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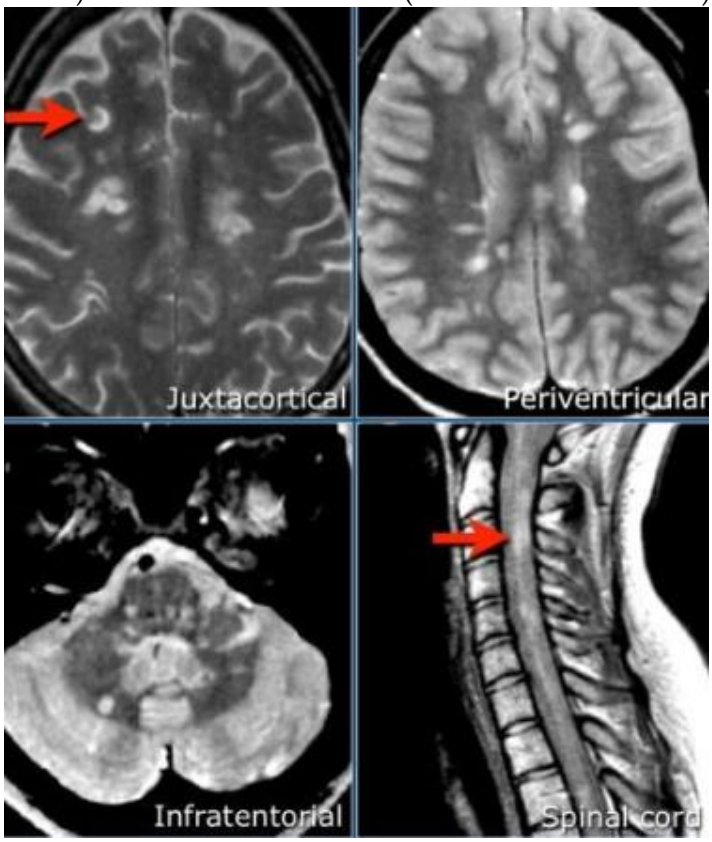
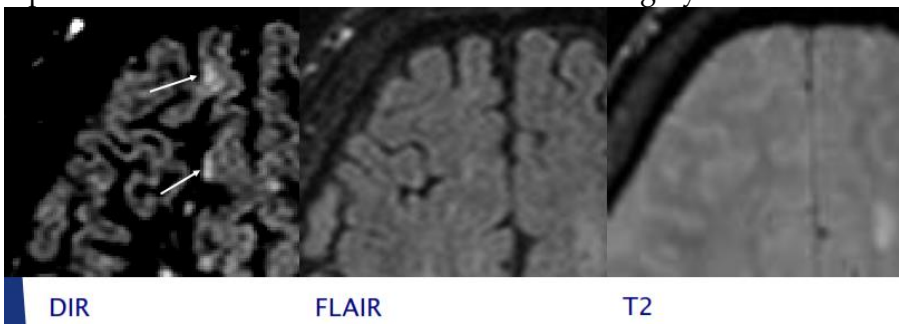
| **Why is an active lesion distinct in a contrast MRI from a non-active lesion?** | Active lesion - Current inflammation<br>Measure with T1 contrast - Blood brain barrier is only leaky in a currently active lesion |
| **What are the four main categories of MS lesion?** | McDonald criteria for MS - Dissemination in space (lesions in different brain areas) + dissemination in time (more than two attacks)<br>  |
| **Why is DIR useful for MS diagnosis?** | Double Inversion Recovery<br>Optimized for more difficult to see lesions in the grey matter<br>  |

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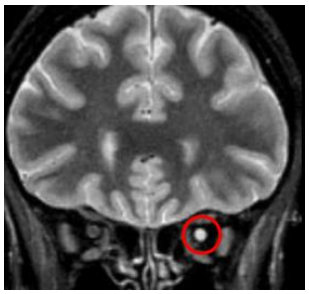
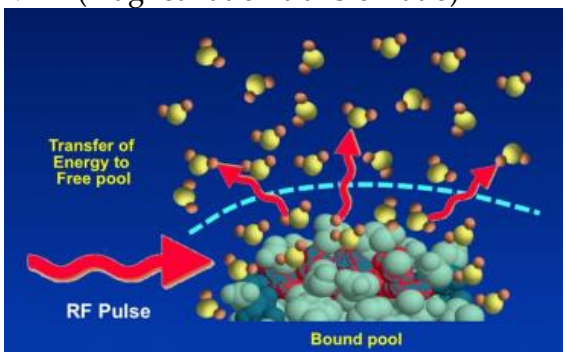
| **How come MS is a CNS disease and it affects one of the cranial nerves (optic nerve)?** |  <br>Optic nerve is part of the CNS, different from the rest of the cranial nerves |
| **Define the clinico-radiological paradox. What might be some possible explanations for that?** | Clinico-radiological paradox<br>Patients with many lesions do not have to be severely impaired<br>Patients with few lesions can be severely impaired<br><br>Cognitive deficits are more difficult to measure<br>Small lesions are not picked up by MRI<br>Lesions are not related to neurodegeneration (atrophy) |
| **What is being damaged due to brain atrophy?** | What is causing atrophy?<br>Both grey and white matter - Cell bodies in grey matter and axons in white matter<br>Measure: 3-dimensional T1-weighted images<br>Automated segmentation techniques - Not used in the clinic yet |
| **How does Magnetization transfer imaging work?** | Quantitative MRI - MTI and Diffusion weighted imaging<br>Resonance properties of tissue<br><br>MTI (Magnetization transfer imaging)<br>1. RF pulse applied to protons bound to macromolecules<br>2. Magnetization partially transfer to free water protons<br>3. Another RF directed at water protons<br>4. Difference between signals with and without off-resonance pulse = MTR (magnetization transfer ratio)<br>  <br> |

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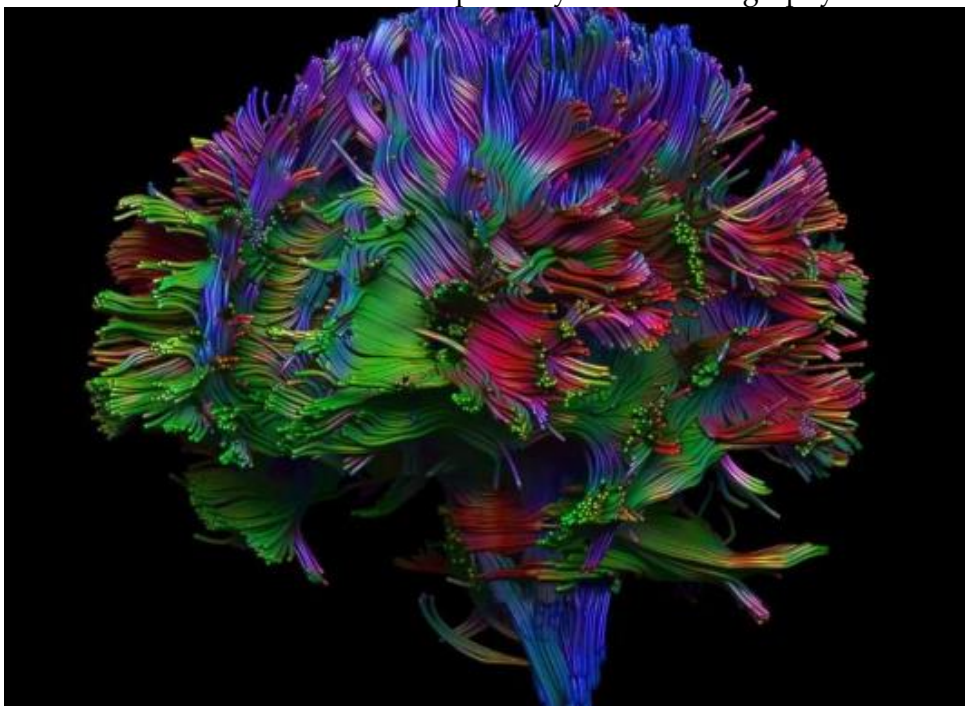
| **How does diffusion weighted imaging work?** | Diffusion weighted/tensor imaging<br>Isotropic vs anisotropic diffusion<br>• Isotropic - Ventricles<br>• Anisotropic - Along the axons<br><br>You can use this to tract an axonal pathway - Fiber tractography<br>  <br>An individual line is not an axon |

# 3c. Multiple Sclerosis: Etiological mechanisms and neuropathology (Geert Schenk)

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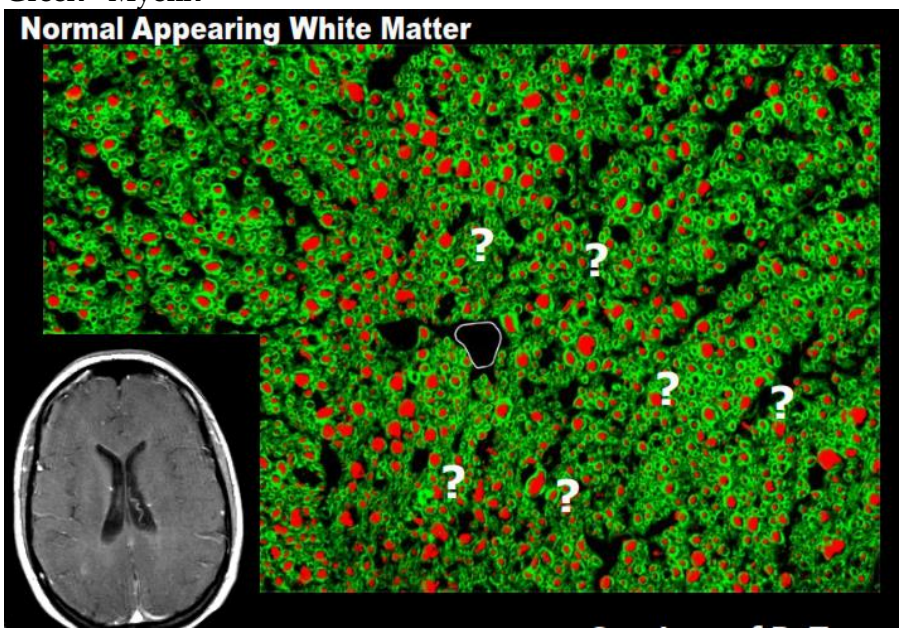
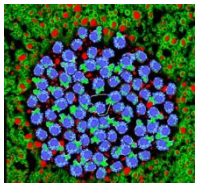
| **Where MS lesions usually occur in the brain?** | Normal appearing white matter<br>Axons - Red<br>Green - Myelin<br>  <br>A lesion will often form close to a blood vessel<br>MS generates network abnormalities before lesion formation, axonal damage, blood brain barrier alterations |
| **What is the difference between:**<br>**a. Active white matter lesion**<br>**b. Chronic active lesion**<br>**c. Chronic inactive lesion** | Active white matter lesion<br>Immune cells eat the myelin<br>  <br>Chronic active Lesion<br>The blood brain barrier is recovering the center of the lesion<br>Immune cells still destroying myelin |

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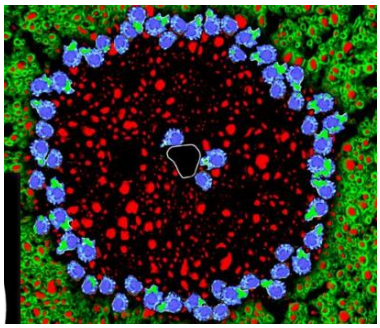
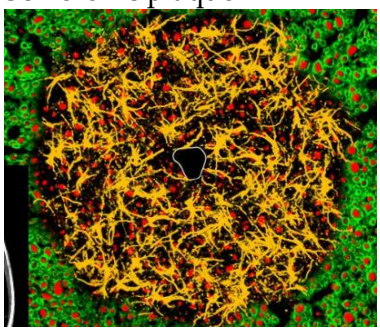
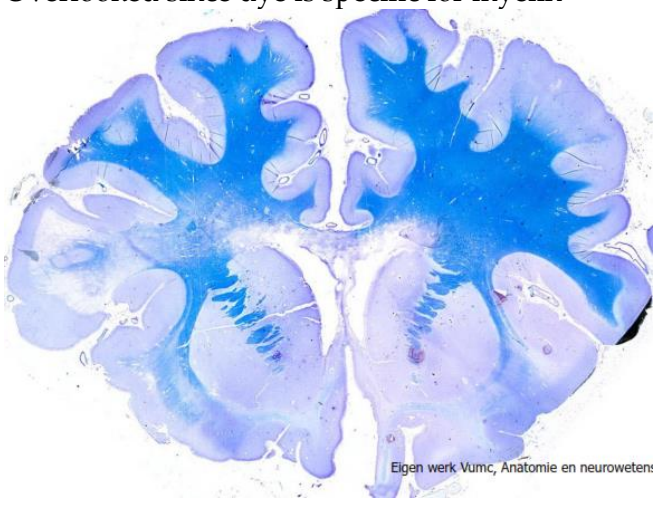
| |  <br>Chonic inactive lesion<br>The immune cells left the lesion site<br>Schleronic plaque<br>  |
| **What can be observed microscopically in MS brain tissue?** | Microscopy<br>Demyelination<br>Leukocyte infiltration<br>Foamy microphages<br>Perivascular infiltrates<br>Axonal damage<br>Axonal loss (silverstain) |
| **Why was grey matter pathology overlooked for many years in MS?** | Grey matter pathology<br>Overlooked since dye is specific for myelin<br>  |

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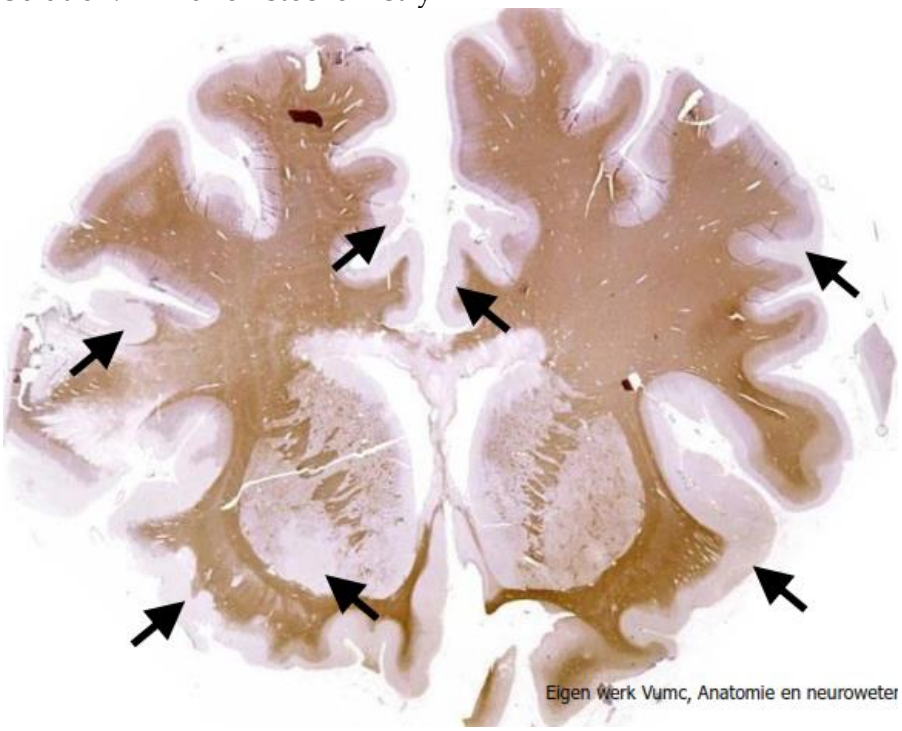
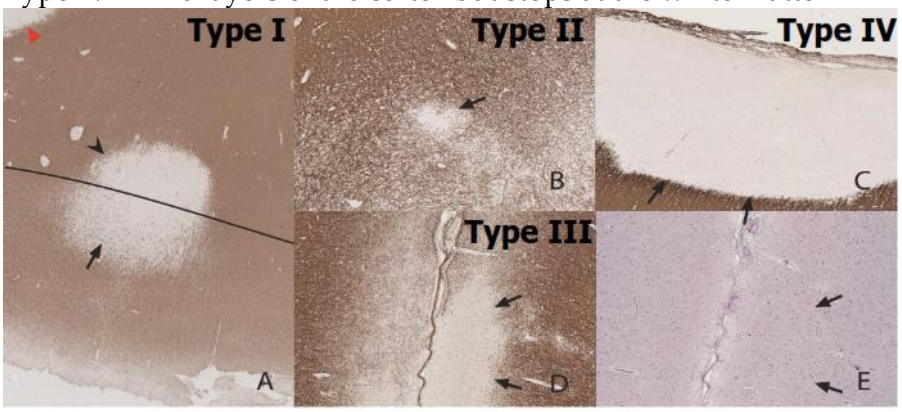
| | Solution: Immunohistochemistry<br>  <br><br>Demyelination can be observed in all brain structures |
| **What are the four different categories of MS lesions?** | Cortical MS lesions **(exam)**<br>Type I - Layers VI and V + white matter<br>Type II - Intracortical (surrounded by grey matter)<br>Type III - Superficial layers (I-III); most common<br>Type IV - All 6 layers of the cortex but stops at the white matter<br>  <br><br>Hypothesis:CSF or white matter damage first |
| **What is the difference between white matter and grey** | Clinical relevance of GM damage<br>Grey matter damage is more severe than white matter ones<br><br>Major differences with white matter lesions<br>Classified based on anatomical location |

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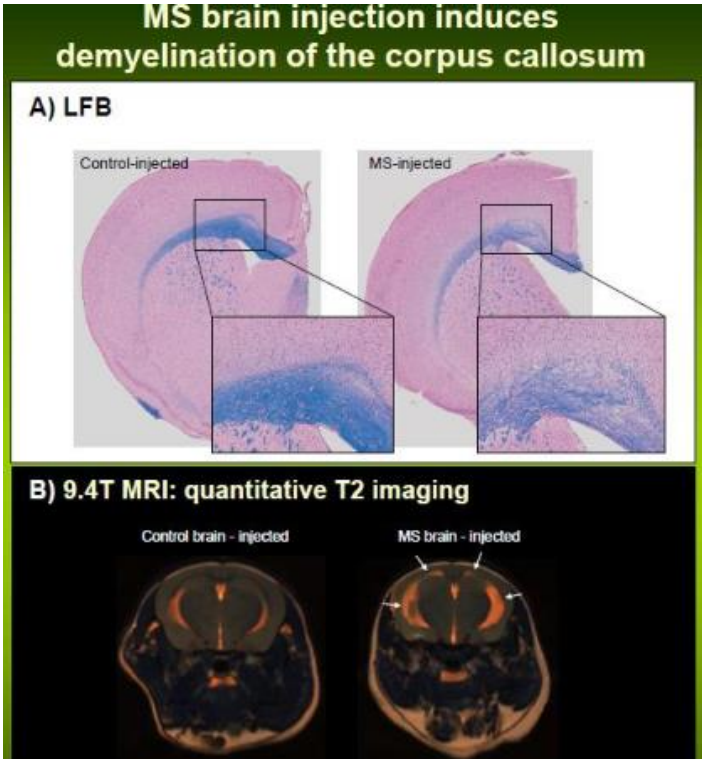
| **matter lesion in MS?** | Virtually no leukocyte infiltrates<br>Sporadic activated microglia/astrocytes<br>No signs of blood brain barrier breakdown |
| **What are some unanswered questions and controversies regarding grey matter pathology in MS?** | Remaining questions with regard to GM pathology<br>1. Cause of demyelination - is it a primary or secondary event?<br>2. Why do grey matter lesions lack most of the white matter changes?<br>3. What is the mechanism underlying neuronal injury and loss?<br>4. Involvement of meningeal inflammation<br>Controversies<br>Leukocytes infiltrate the grey matter<br>Shadow plaques are supposed to represent remyelination - how to differentiate that from weak demyelination? |
| **What is the definition of an autoimmune disease? Why is MS considered an autoimmune disease?** | Pathogenic triggers<br>Autoimmune disease - Need to be transmissible<br>There are animal models to MS<br>MS as a transmissible protein misfolding disorder - Prion disease<br>It is possible to transmit MS from a human brain to the rat model<br>  <br><br>CNS extrinsic model - Immune event in the periphery will start to attack the brain |

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| **Define the difference between outside in and inside out models for MS.** | Outside in vs inside out models<br>Outside in - 90% of the literature supports<br>Inside out - 10% of literature<br><br>Outside-in model - Oligodendrocyte event is a primery event in MS<br>Inside-out model - Neuro-axonal injury is a primary event in MS (due to mitochondrial defects) |

# 3d. Cognition and Multiple Sclerosis

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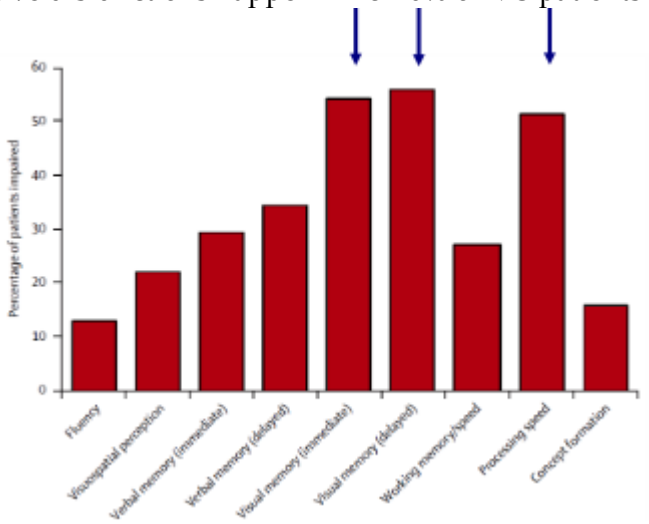
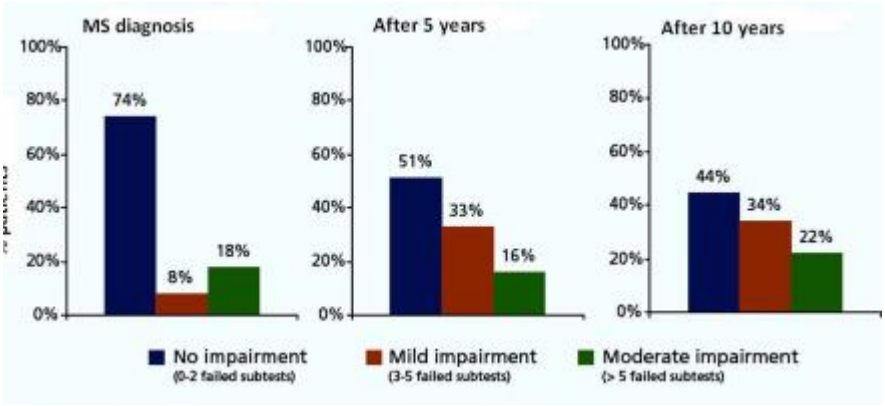
| **What is cognition?** | Cognition - Set of mental abilities and processes related to knowledge<br>Memory<br>Attention<br>Information processing<br>Executive functioning |
| **Which cognitive functions are most commonly affected in MS? Which are usually unaffected?** | Cognitive disfunctions happen in 43-70% of MS patients<br>  <br><br>Visual memory and processing speed are most commonly affected<br>Almost never affected: Simple attention (repeating digits), verbal abilities (naming, comprenhension)<br><br>Usual clinical problems are quite subtle<br>General intelect is intact - dementia is rare |
| **Why is there such a great variability of percentage of cognitive decline between studies?** | Cognitive decline in MS<br>  <br><br>There is no single definition of cognitive impairment - each study uses a different definition |

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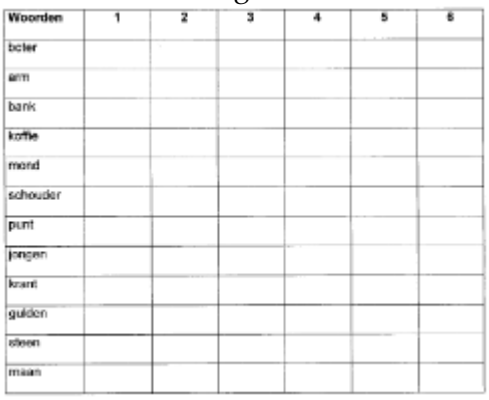
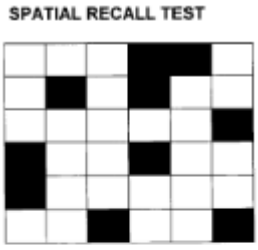
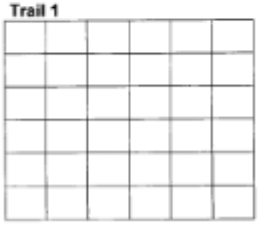
| **Which are the most important predictors of current cognitive decline? And future cognitive decline?** | Predictors of cognitive decline<br>Deep grey matter volume - Mainly deep grey structures (thalamus)<br>Education - Higher cognitive reserve?<br>MS phenotype<br>Sex<br>Age<br><br>Predictors of future cognitive decline<br>Cortical grey matter |
| **Which tests are usually to detect cognitive problems?** | How do we detect cognitive problems?<br>Neuropsychological tests - Standardized, scientifically validated, clinical setting (different tests are used depending on what you want to know and their limitations) |
| **Which tests are used in the BRB-N?** | BRB-N - Brief repeatable battery of neuropsychological tests<br>Selective reminding test - Verbal memory<br>  <br>10/36 spatial recall test - Spatial memory<br>  <br>  <br>Symbol digit modalities test - Attention and information processing |

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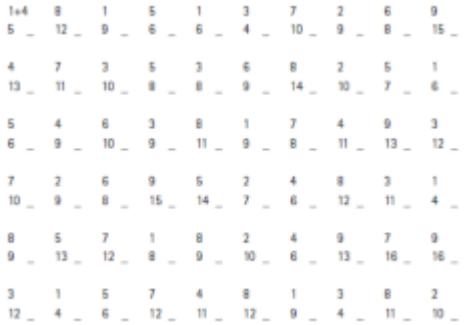
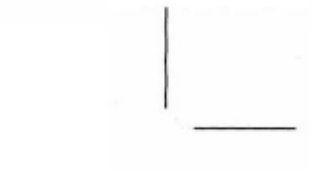
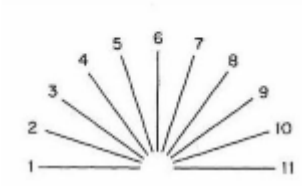
| |  <br>Paced auditory serial addition test - Working memory and attention<br>  <br>Word List Generation - Verbal fluency and memory retrieval<br>MS patients perform as healthy controls |
| **Which tests are included in the MACFIMS?** | MACFIMS - Minimal assessment of cognitive function in MS; Same tests as BRB-N + 3 others<br>Judgement of Line Orientation Test<br>  <br>  <br><br>Brief visuospatial memory test |

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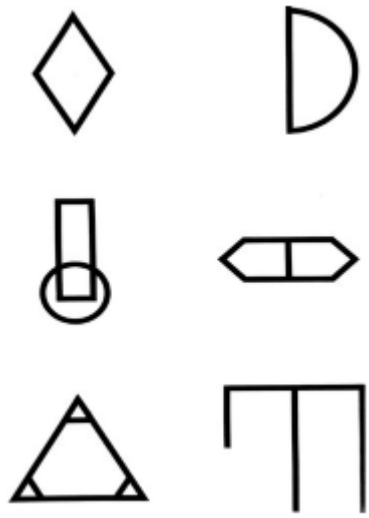
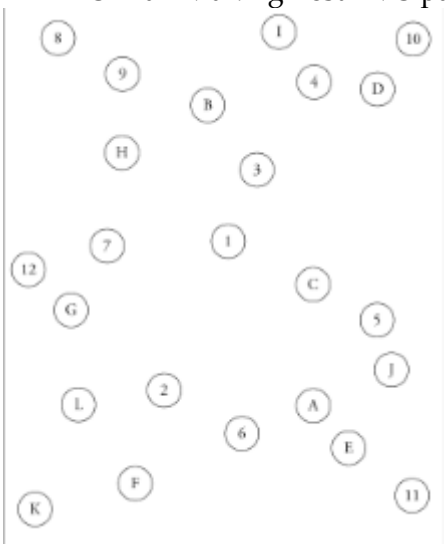
| |  <br>D-KEFS Trail Making Test - MS patients are slower<br>  |
| **What are the advantages and disadvantages of using BRB-N over MACFIMS?** | BRB-N vs MACFIMS<br>• BNB-N is shorter |

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<tr><th></th><th>BNB-N</th><th>MACFIMS</th></tr>
<tr><td>Speed of processing</td><td>PASAT<br>SDMT</td><td>PASAT<br>SDMT</td></tr>
<tr><td>Memory</td><td>10/36 SRT<br>B-SRT</td><td>BVMT-R<br>CVLT-II</td></tr>
<tr><td>Executive Functioning</td><td>-</td><td>K-DEFS ST</td></tr>
<tr><td>Visuospatial Processing</td><td>-</td><td>JLO</td></tr>
<tr><td>Language</td><td>COWAT</td><td>COWAT</td></tr>
<tr><td>Premorbid Intelligence</td><td>-</td><td>-</td></tr>
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<ul><li>MACFIMS tests executive functioning, visuospatial processing and it is more extensive</li></ul>
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<tr><td>Which tests are used in BICAMS?</td><td>Brief International Cognitive Assessment for MS<br>Short - Screening only
<table>
<tr><th></th><th>BRB-N</th><th>MACFIMS</th><th>BICAMS</th></tr>
<tr><td>Speed of processing</td><td>PASAT<br>SDMT</td><td>PASAT<br>SDMT</td><td><br>SDMT</td></tr>
<tr><td>Memory</td><td>10/36 SRT<br>B-SRT</td><td>BVMT-R<br>CVLT-II</td><td>BVMT-R<br>CVLT-II</td></tr>
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<tr><td>Which confounders need to taken into consideration when doing psychological tests?</td><td>Confounders<br>Learning effects<br>Age<br>Medication<br>Fatigue</td></tr>
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# 4a. Current therapy of Multiple Sclerosis (Brigit de Jong)

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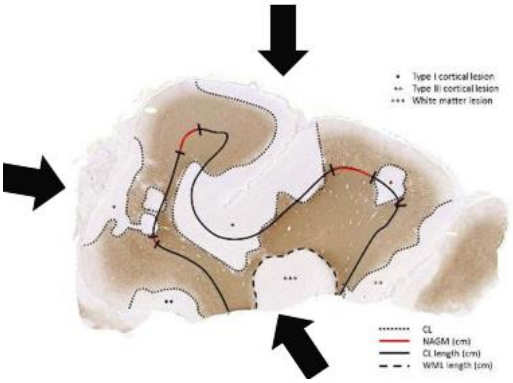
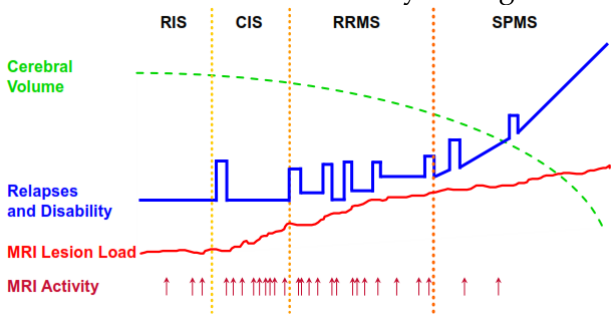
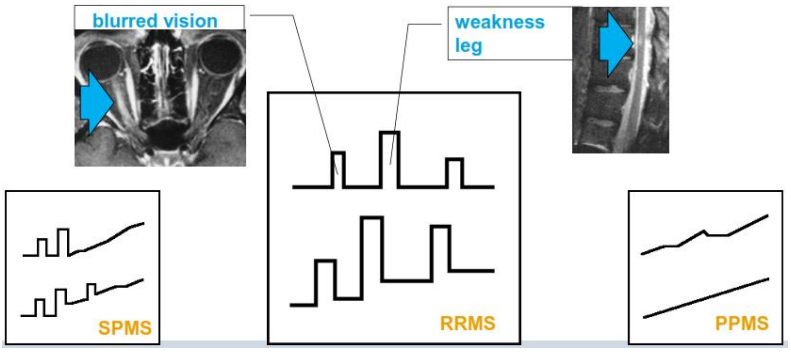
| **What is MS?** | Multiple sclerosis<br>Organ-specific autoimmune disorder<br>Demyelination of grey and white matter<br>  |
| **Describe the disease progression in MS.** | Clinical and MRI disease activity throughout MS<br>  |
| **How are the MS lesions characterized?** | Dissemination in space and time<br>  |

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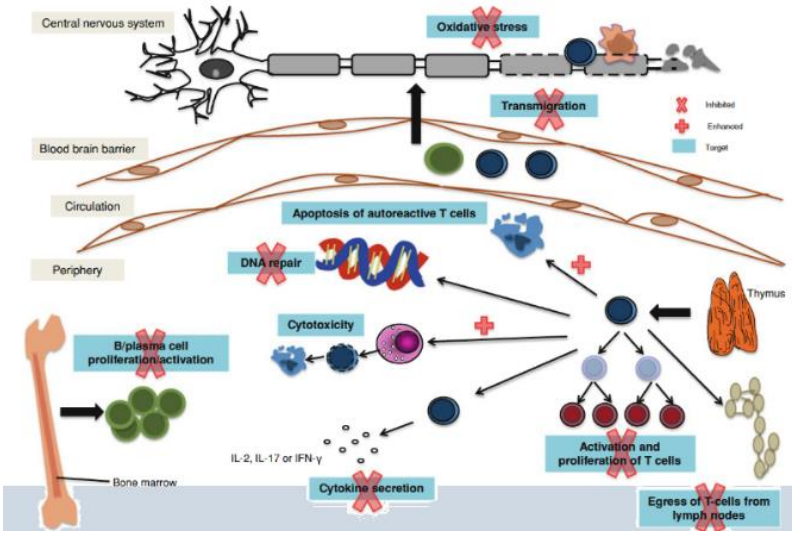
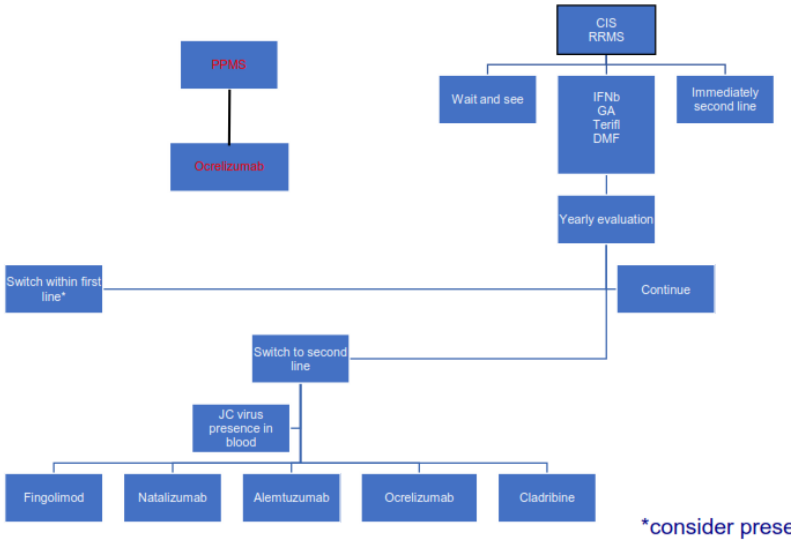
| **What are possible targets for MS drugs?** | Targets for MS drugs<br>  <br><br>Act on the periphery - Block lymphocyte entrance to the CNS<br>Act on the CNS |
| **What are the possible treatments for clinically isolated symptoms of MS?**<br><br>**What is the most efficient treatment available for PPMS?** | Available drugs<br>  <br><br>CIS/RRMS - Wait and see (one isolated case, quality of life untouched), first line drugs (IFNb, DMF), second line drugs (if the lesions are really active)<br>Evaluation after one year<br>PPMS - Ocrelizumab (immunomodulating drug; monoclonal antibodies that block receptors in B cells)<br><br>• First drug - Interferon-beta (1995)<br>• Before that - Steroids after relapses |

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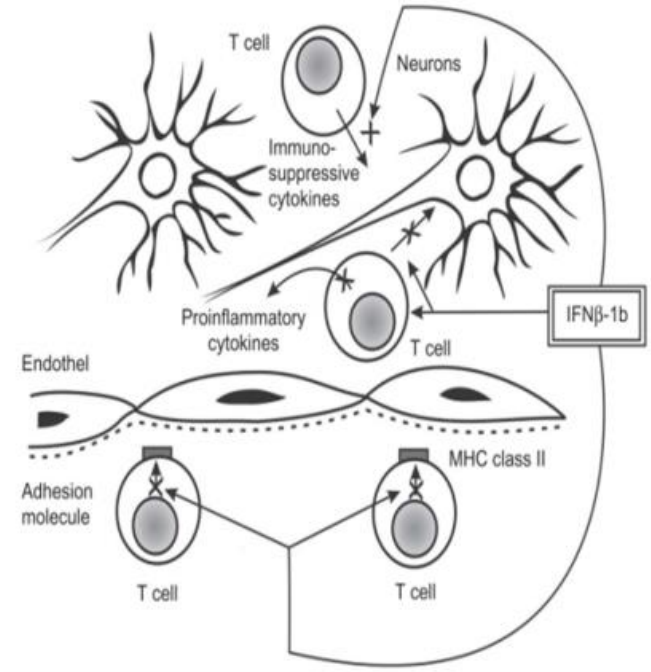
| **Describe the main advantages and disadvantages of interferon beta as a treatment for MS.** | Interferon-beta (cytokin)<br>Four IFNb products in the market<br>Injectable<br>Average 30% reduction of relapses<br>Does not increase chance of infections/cancer<br>Side effects: skin reactions, flu-like symptoms |
| **What is the mechanism of action for interferon beta?** | Mechanism of action of Interferon-beta<br>  <br><br>Reduction in T-cel activation<br>Reduction of pro-inflammatory cytokines<br>Th1 switch to Th2 |
| **Describe the main advantages and disadvantages of glatiramer acetate as a treatment for MS.** | Glatiramer acetate<br>Pool of peptides composed of random sequences of four amino acids<br>Used for RRMS<br>Daily injections<br>Average 30% reduction of relapses<br>Side effects: skin reactions |
| **How does glatiramer acetate compare against interferon beta?** | Comparison interferon-beta and glatiramer acetate |

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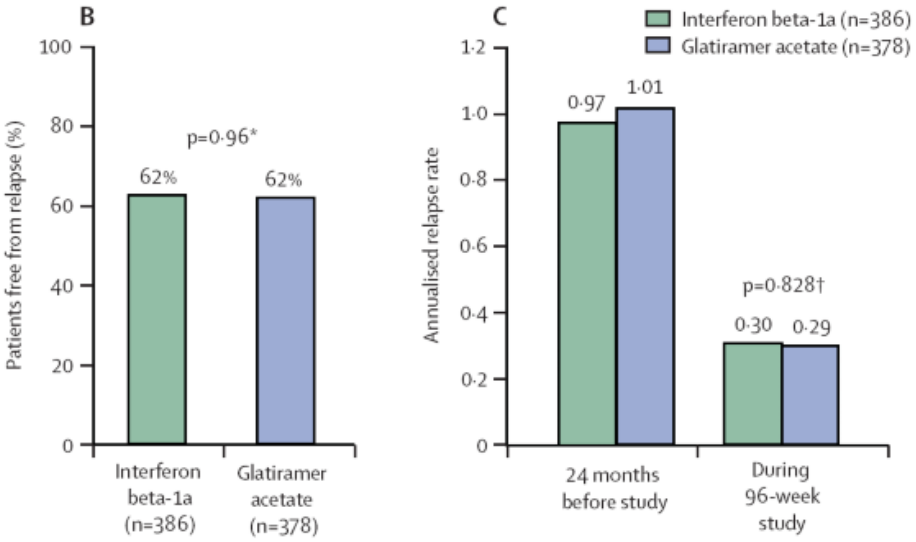
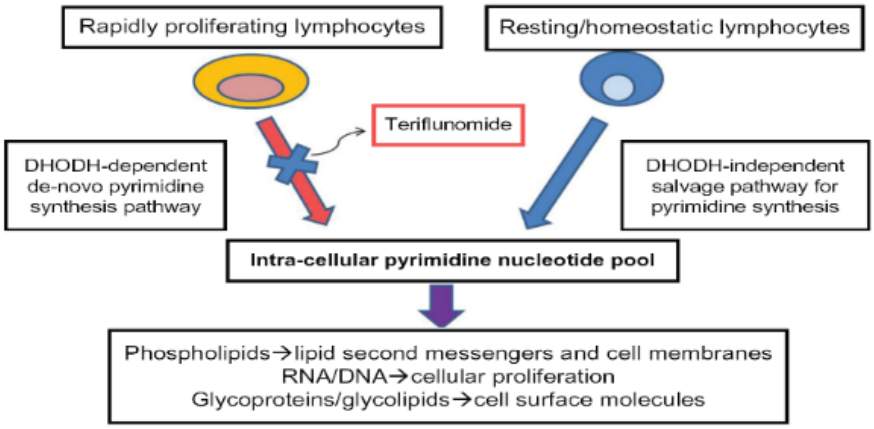
| |  <br>Quite similar effects |
| **What is the mechanism of action for teriflunomide?** | Teriflunomide<br>Oral<br>  <br>Mechanism of action - Active lymphocytes are more susceptible to the drug |
| **What is the mechanism of action for dimethylfumarate ?** | Dimethylfumarate<br>Oral<br><br>Mechanism of action - Modulates Krebs Cycle<br>Side effects: Flushing, gastrointestinal events |
| **What is the main advantage regarding quality of life in using Natalizumab?** | Natalizumab<br>68% reduction in relapse rate<br>54% reduction in disability progression<br>Improves quality of life<br>Infusion once every four weeks |

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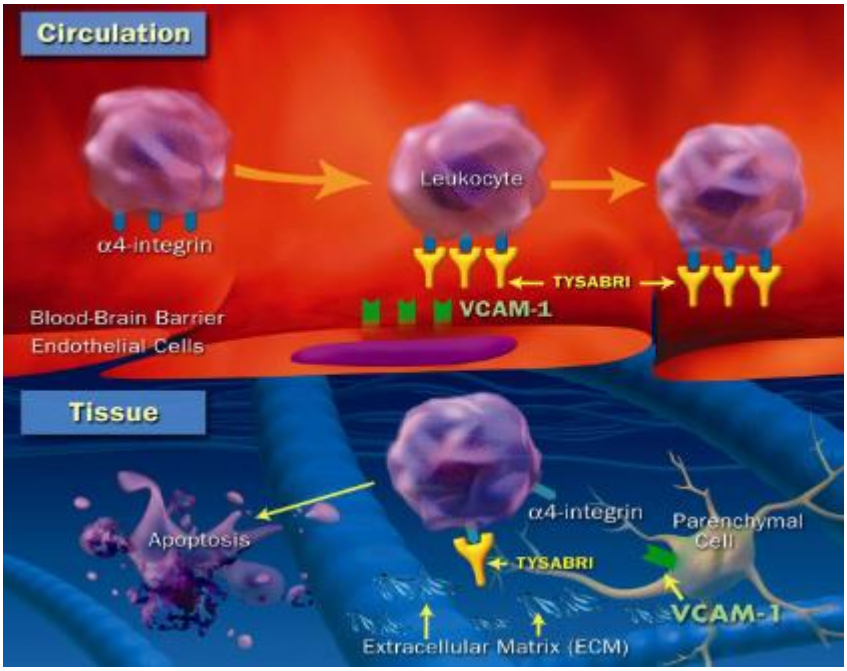
| **What is the mechanism of action for natalizumab?** | Mechanism of action of Natalizumab<br>  <br><br>Block passage of immune system into the blood brain barrier |
| **What is the main risk of using Natalizumab?** | Natalizumab increases the risk of developing PML<br>John Cunningham-virus<br>50% of people have this virus - In healthy people, it is kept in check<br>When people are immunodeficient - PML (MS caused by JCV)<br>Natalizumab associated PML: 24% lethal<br><br>If someone is JCV-negative, Natalizumab is the best second line treatment |
| **What is the mechanism of action for fingolimod?** | Fingolimod<br>Oral<br>50-60% reduction in relapse rate<br><br>Mechanism of action of Fingolimod |

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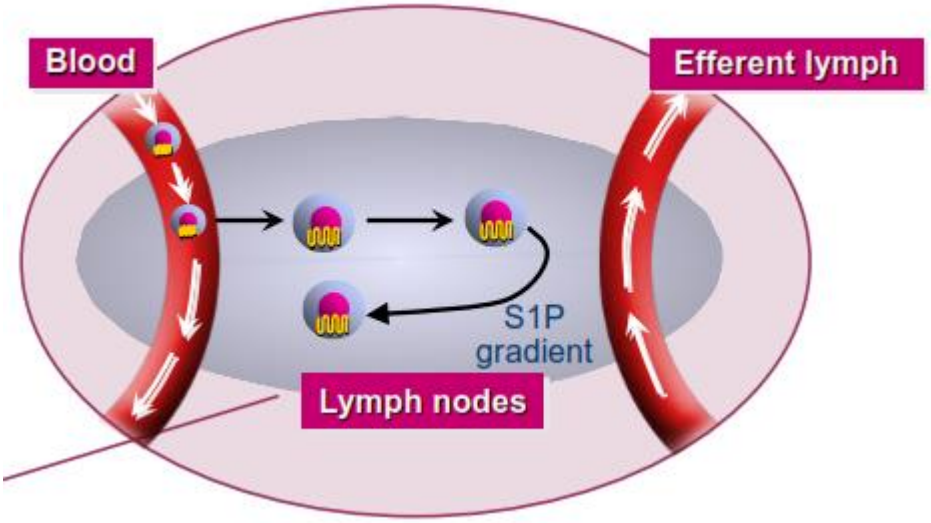
| |  <br>Block passage of lymphocytes from the lymph node to the blood stream |
| **What are the clinical effects of using Alemtuzumab?** | Alemtuzumab<br>Humanized mAb<br><br>90% infusion relations reactions<br>22% secondary autoimmune disease |
| **What are the clinical effects of using Ocrelizumab?** | Ocrelizumab<br>Humanized mAb - CD20 receptor (present in B cells and T cells)<br><br>50% relapse reduction compared to interferon-beta<br><br>Side effects: Herpes infection |
| **What are the clinical effects of using Cladribine?** | Cladribine<br>Immunosupressant that crosses the BBB<br>Inhibits proliferation and induces apoptosis of microglia<br><br>Does not affect disease progression over time<br>75% reduction of new T2 lesions |

# 4b. MS Animal Models (Anne-Marie van Dam)

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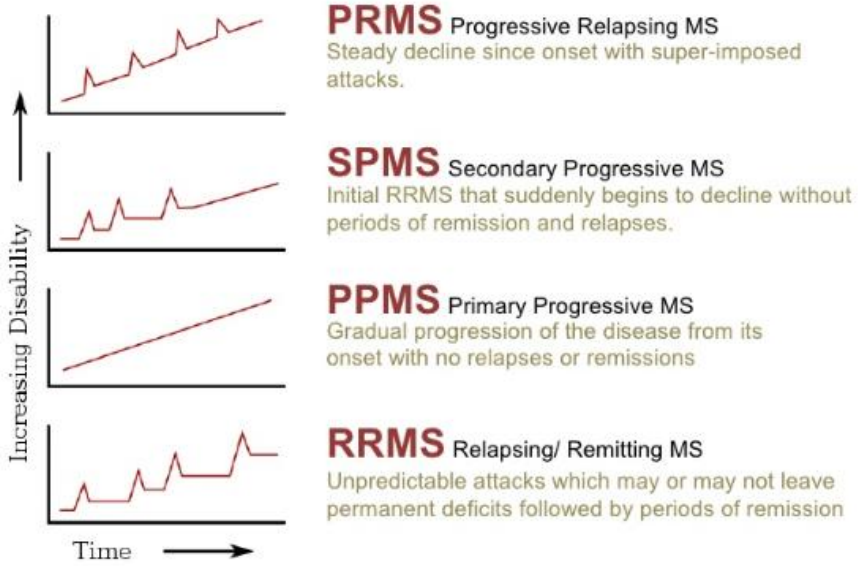
| **Define the four types of MS with relation to disability progression.** | Classification of multiple sclerosis<br>  <br> |
| **Why is it impossible to have one perfect animal model for all aspects of MS?** | The model needs to fit the research question<br>MS is a very heterogeneous disease, it needs a very ponctual research question<br>Reproducibility<br>Predictibility |
| **What is face validity and predictive validity?** | Model vailidity<br>Face validity - The model mimicks the disease<br>Predictive validity - Effectiveness of research results to predict future results |
| **What are three types of animal models commonly used for MS studies?** | Animal models<br>Transgenic mice - Sponteneous demyelination (gene overexpression), theiler virus-mediated demyelination<br>Experimental autoimmune encephalomyelitis - Non-human primates or mice<br>Acute - Myelin peptide + adjuvant<br>Create motor symptoms<br>Adoptive transfer - myelin specific CD4+ cells from other model mice injected in control mice<br>Nowadays it is thought that CD8+ and B cells play a more important role in MS development |

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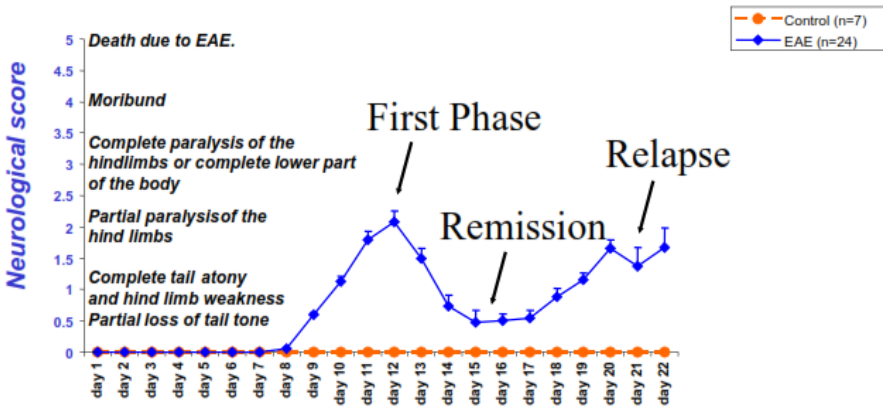
| | Chronic - Myelin peptide + adjuvant (Relapsing remitting model)<br>Difference between acute and chronic - Genetic background of the animals<br>Demyelinating models - Activation of glial cells and consequent demyelination<br>Cuprizone - Oral<br>Lysolecithin - Local |
| **Describe what is the ethical problem with chronic relapsing model in DA rat.** | Chronic relapsing EAE in DA rat<br>Model for grey matter pathology - MOG + cytokines icv generates cortical demyelination<br><br>Graph of disease progression - Relapsing-remitting<br>The animals are sacrificed after day 22, the model is not reproducible (sample sizes change from experiment to experiment)<br>  |
| **What are the microscopy results of chronic relapsing EAE in DA rat?** | Results of Chronic relapsing EAE in DA rat<br>Monocyte invasion |

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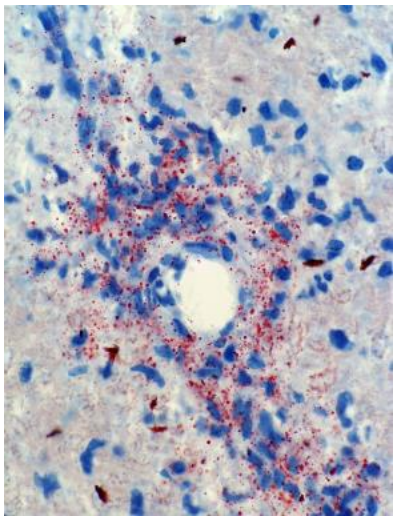
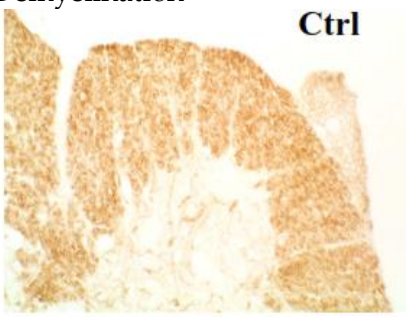
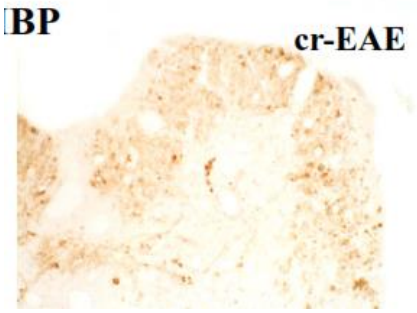
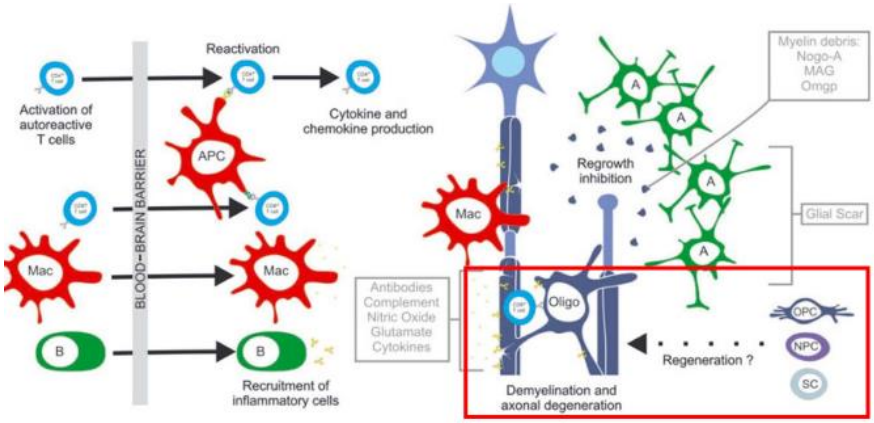
| |  <br>Demyelination<br>  <br><br>  <br> |
| **Why transglutaminase may be an interesting drug target for MS treatment?** | TG2 is present in myeloid cells in rat model for MS<br><br>Inhibition of TG2 reduces neurological scores during cr-EAE<br>Inhibition of TG2 reduces monocyte invasion and demyelination<br>Tissue TG2 may play a role in remyelination |




Validity: TG2 is present in infiltrating immune cells in active human MS lesions

Cuprizone model - Focus on demyelination

Observable processes of demyelination and remyelination when the intake of drug stops

TG2 knockout have slower remyelination processes

# 4c. Are you connected? Functional connectivity changes in MS (Kim Meijer)

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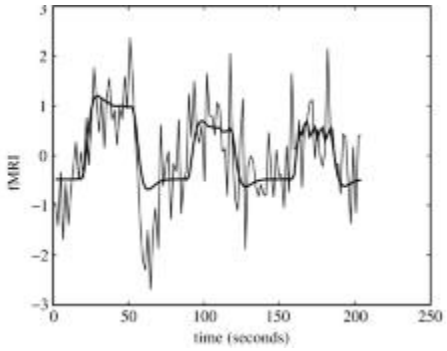
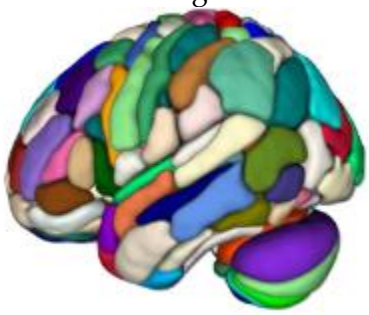
| **How to investigate brain function?** | How to investigate brain function?<br>Activation patterns<br>Connectivity patters<br><br>During rest<br>During a specific task<br>Activation of motor cortex may be a confounder |
| **Why study brain function?** | Why study brain function?<br>It reflects behavior<br>Study the effect of brain damage on brain function |
| **What is the difference between activation patterns and functional connectivity?** | From activation to connectivity<br>Activation patterns - Which brain regions are involved in certain kinds of behavior<br>Functional connectivity - Interaction between brain regions |
| **How to study structural connectivity?** | Structural connectivity<br>Histology - Tract tracing<br>DTI - Tractography<br>It is currently not possible to do in MS patients (white matter lesions cause algorithm to stop) |
| **How to study functional connectivity?** | Functional connectivity<br>Rs-fMRI - Extract functional information of brain regions over time<br>  <br><br>  <br>Correlation of time series - Create connectivity matrices |

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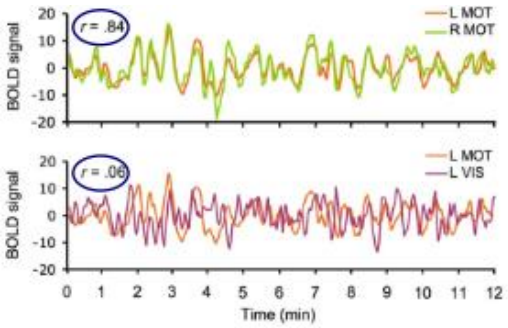
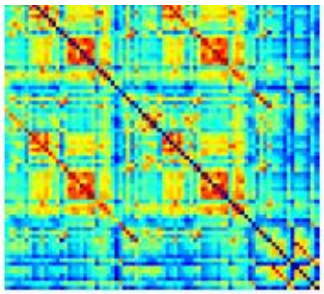
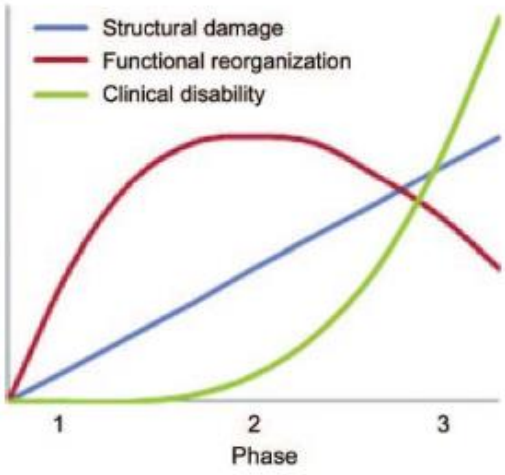
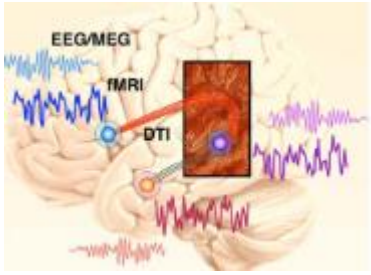
| |   |
| **Is increased connectivity a good or bad thing in MS?** | fMRI: Resting State Network<br>RRMS causes increased connectivity<br>SPMS causes decreased connectivity<br>  <br>Increase in activation and connectivity is "good"<br>Increased functional connectivity - not good or bad<br>Local functional compensation<br>Maladaptive reasons<br>Epiphenomenon caused by atrophy |
| **In neuroscience, what is a node or a link?** | Graph theory<br>Nodes: brain areas<br>Links: white matter tracts<br>  <br>Balance between integration and segregation |

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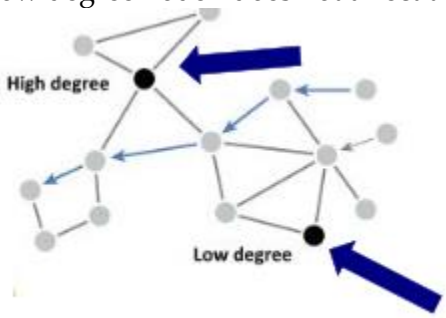
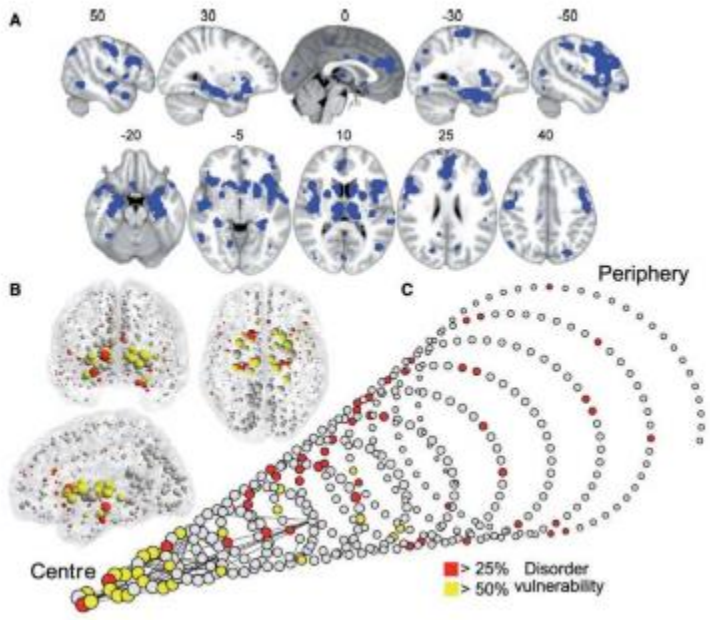
| **What is a high degree node and a low degree node?** | High degree node - affect the direct pathway<br>Low degree node - does not affect the direct pathway<br>  |
| **Why are long-range connections more prone to damage than short-range connections?** | Long-range connections are more prone to damage than short-range connections<br>Hubs have more long-range connections<br><br>Hub regions<br>Highly interconnection of signals<br>Integration of signals<br><br>More prone to damage because it is connected to many other regions - Hub overload? |
| **Where in the brain are the hubs most commonly shared among neurological diseases?** | Hubs across neurological diseases<br>  <br>Almost all hubs are in the center of the brain - Thalamus |

# *5a. Pathogenesis of Dementia

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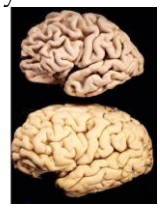
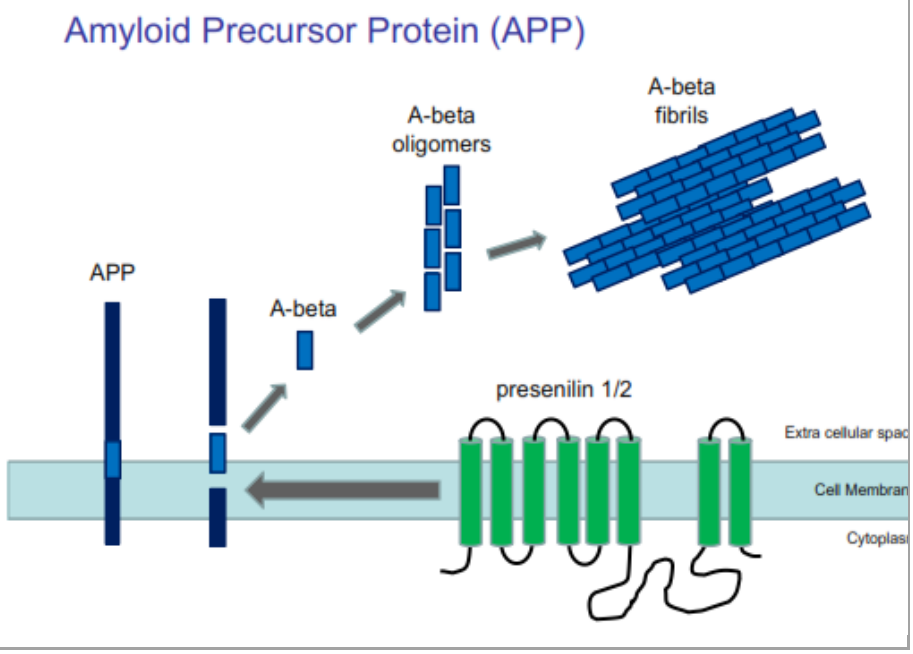
| **Which conditions cause dementia?** | More than 100 conditions impair memory, behavior and thinking<br>Alzheimer's<br>Dementia with Lewy bodies<br>Parkinson's<br>Frontotemporal dementia<br>Prion disease |
| | Alzheimer's<br>Discovered by Alois Alzheimer in 1906<br>  <br>Alois Alzheimer<br>1906<br>Atrophy of neuronal tissue - Increased space between gyri<br>  <br>Auguste D. 51 yr.<br>  <br>Fisher (1907) - Corona of abnorml neurites and glial cells<br>Today we know - Amyloid beta deposits |
| **How does amyloid beta accumulate in the brain?** | Amyloid Precursor Protein<br>  |

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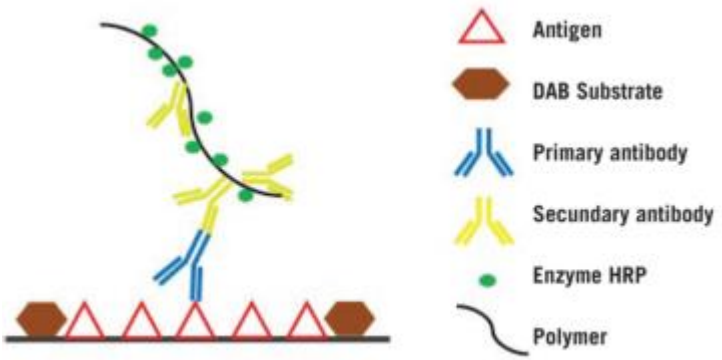
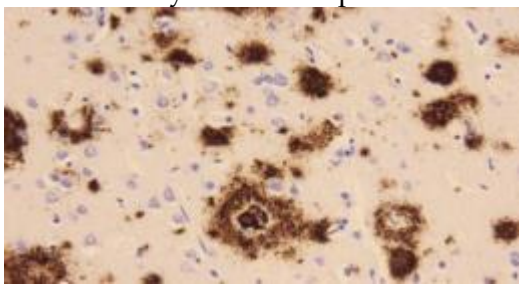
| | APP -> Amyloid-beta (cleaved by presenilin 1/2)<br>Amyloid-beta units form oligomeres and fibrils<br>Hydrophobic proteins tend to clump together<br>These long fibrils are cytotoxic and promote cell death<br><br>A-beta is rapidly removed in a healthy brain |
| **How can immunohistochemistry be useful in AD studies?** | Immunohistochemistry<br>  <br>Primary antibody against A-beta<br>Secondary antibody with an enzyme for detection<br><br>Different amyloid beta deposits in the brain<br>  <br>Around cappilaries - Indicates that there is something wrong with the blood brain barrier<br><br>Detection of Abeta in the brain - more present in the grey matter |
| **What neurofibrillary tangles are observed?** | Neurofibrillary tangles - present inside the neurons<br>Composed of tau proteins |
| **What is tau? What happens in AD regarding tau accumulation?** | Tau - Microtubule-associated protein tau<br>Essential for stability of microtubules (there are many other proteins with this function, so tau is not an essential protein)<br>Length - Around 400 amino acids<br><br>In AD - Increase Tau kinases or decrease of Tau phosphatases |

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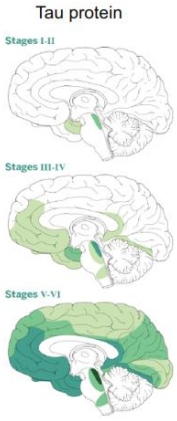
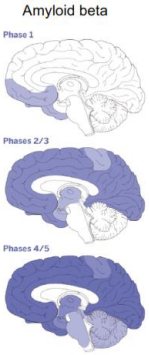
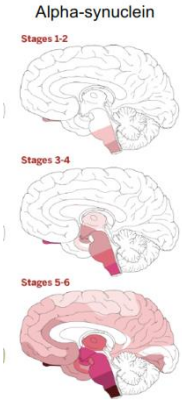
| | Tau binds more to itself and less to the microtubules |
| **Describre the spread of tau?** | Spreading of phosphorylated tau in AD brain<br>Starts near the hippocampus - Entorhinal region<br>  <br>*Why the cerebellum is not effect? Neurons that evolved later are more prone to AD (more connections, higher chances of tau transmission)* |
| **Describe the spread of amyloid beta.** | Spread of Amyloid beta<br>Hippocampus is initially not affected<br>  |
| **Describe the spread of alpha-synuclein.** | Spread of alpha-synuclein<br>  |

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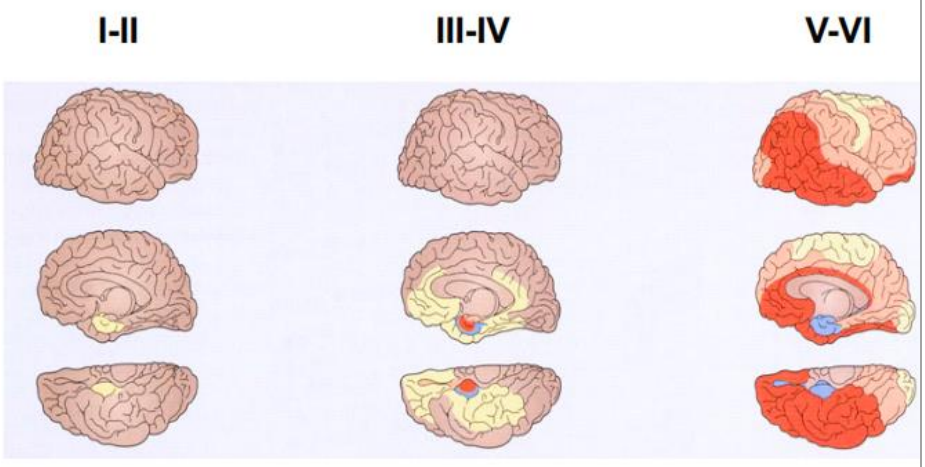
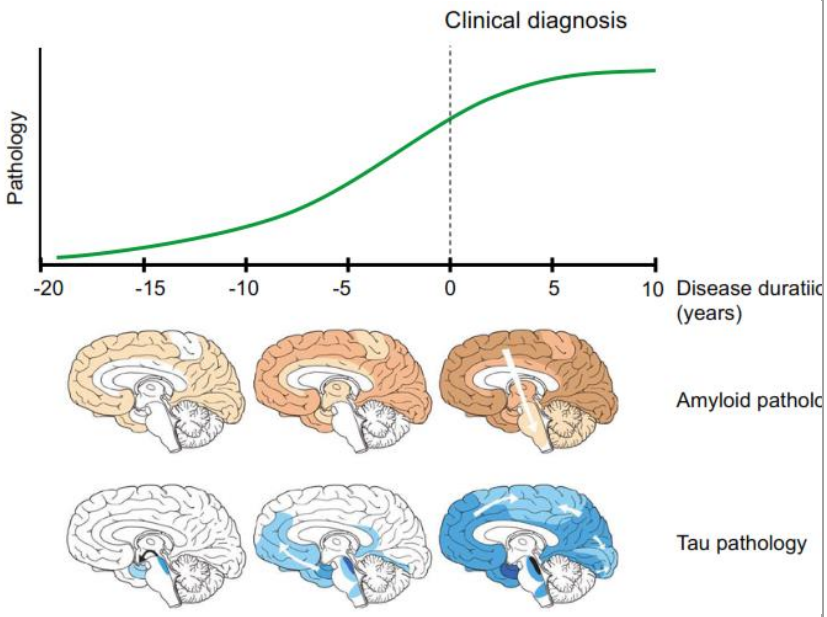
| **Describe braak stages for AD pathology.** | Braak stage for AD pathology<br>  <br>I-II - Transentorhinal region<br>III-IV - Entorhinal and transentorhinal layer (pre-alpha)<br>V-VI - All areas of isocortex |
| **Which accumulation correlates better with disease pathology in AD: AB or tau? Why?** | Disease duration and dementia<br>  <br>Tau-pathology correlates better with cognitive decline<br>Amyloid beta happens before cognitive decline -> tau-pathology happens later |
| **What does the rare familial-type AD suggests regarding AB?** | Familial-type of Alzheimer's disease - Suggests that amyloid beta accumulates first<br>Counterpoint: Frontotemporal dementia - Tau accumulates, amyloid beta don't<br>Suggests that amyloid alone is not enough to explain AD |

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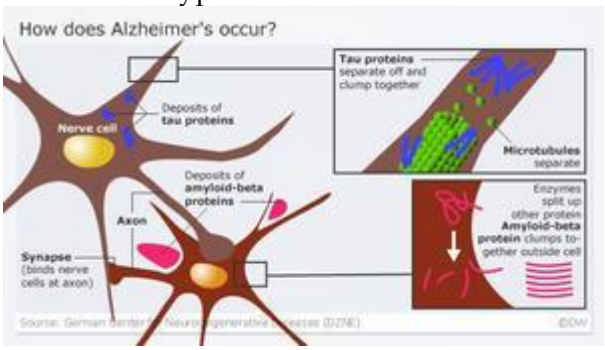
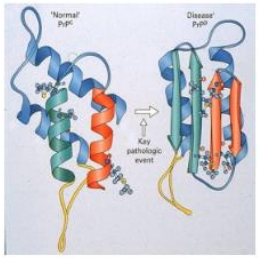
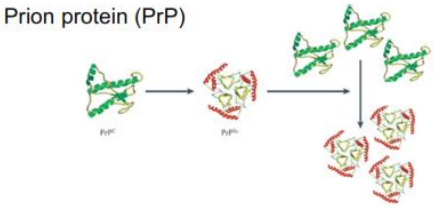
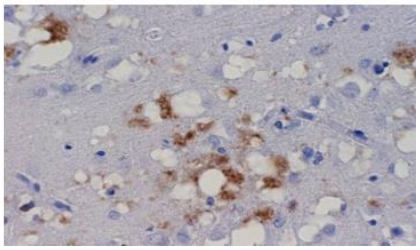
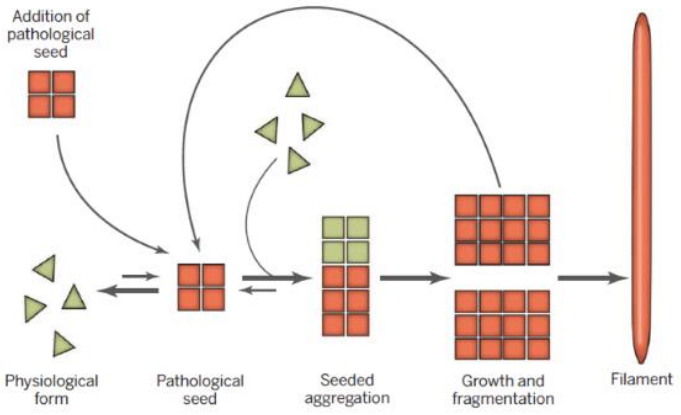
| **Describe the amyloid cascade hypothesis** | Amyloid cascade hypothesis<br>  <br>Amyloid beta plaques causes neurotoxicity, recruits microglia which damage neurons and promote tau accumulation |
| **How do prion diseases propagate?** | Prion diseases<br>  <br>  <br>  <br>A lot of cells in the body express PrP - Function is not known<br>Disease: Alpha helices are replaced with beta-sheets (more hydrophobic) -> causes another normal PrP to misfold as well ->forms deposits |
| **How do misfolded protein diseases propagate?** | Prion-like spreading of misfolded proteins<br>  <br>Pathological seeds -> lead to the formation of filaments |

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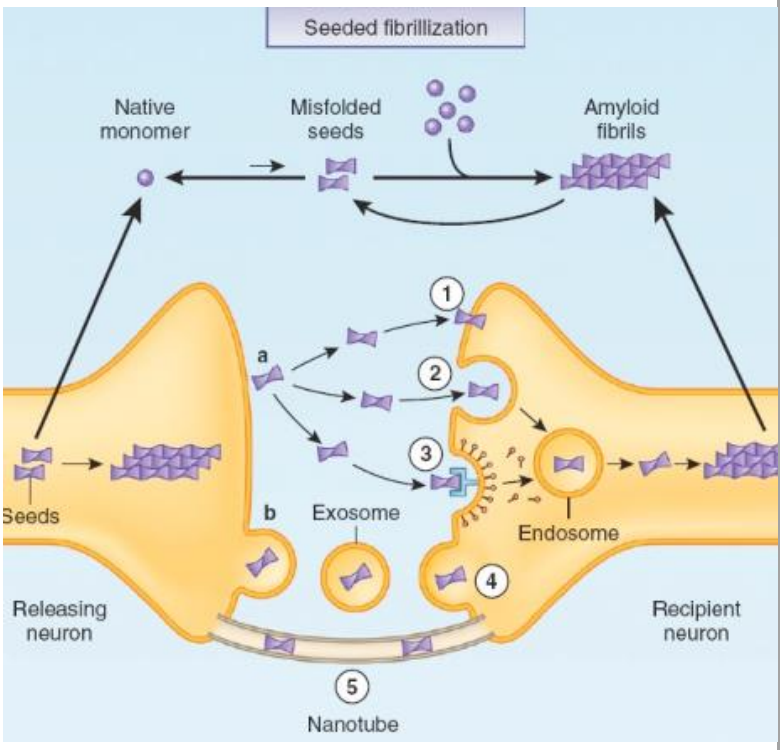
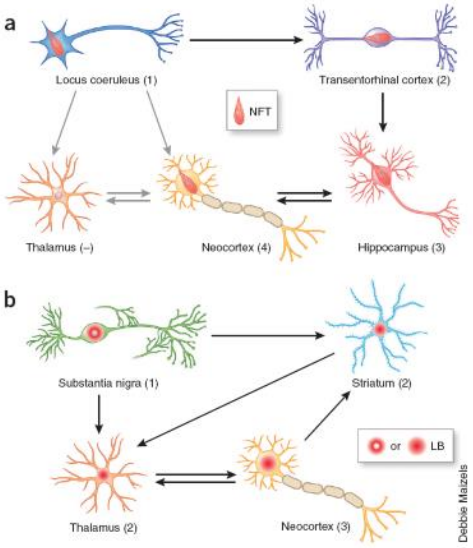
| **How is tau pathology transmitted between cells?** | Transmission of tau pathology<br>Brain homogenates from human induce tau inclusions in the mouse brain<br>Same is true for alpha-synuclein and amyloid beta<br><br>Potential mechanisms for cell-to-cell transmition<br>  <br><br>Via synpases - Direct contact? |
| **What is the hypothetical neuronal model which could explain AD?** | Hypothetical neuronal model<br>  <br> |

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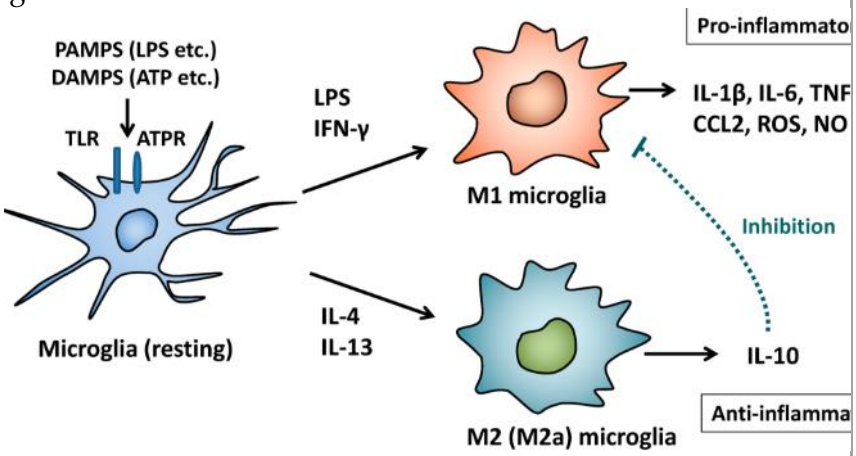
| **What is the difference between neurodegenerative and neuroinflammatory?** | Inflammation in the CNS<br>Neurodegenerative: Innate immune system<br>Neuroinflammatory: Adaptative immune system<br>Image |
| **What happens with microglia in AD?** | Microglia<br>Maintainence of tissue homeostasis<br>Synaptic remodelling<br>Secretion of neurotrophic factors<br><br>In AD: Overactivation of microglia -> clustering |
| **What do M1 and M2 microglia do?** | Microglia activation in AD<br>  <br>M2-like - 'Good side' of microglia<br>M1-like - 'Bad side' of microglia<br>Damage neurons with free radicals after they are not able to kill the source of inflammation |

# 5b. Maintaining cognitive health during aging: the 100-plus study

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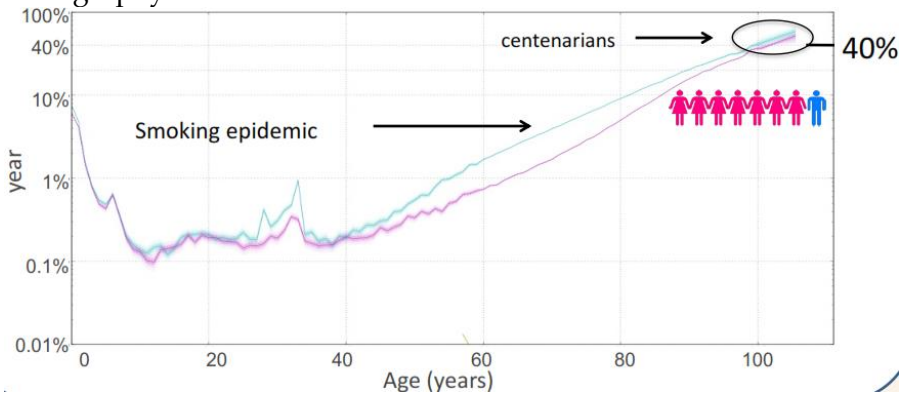
| **What was surprising about the brain of the oldest dutch woman?** | 115 year-old woman<br>  <br>No cognitive decline - Brain equivalent to a 60 year-old at 114<br>Tau-staining - Stage II<br>No beta-amyloid plaques<br>No neurovascular disease<br><br>It is possible to live a very long life without dementia |
| **Why most people that were born in the beginning of the 20th century did not live very long?** | 1912 demography<br>  <br>Peak of mortality - World war II<br>After - Natural decline (the chance to die increases exponentially with aging)<br>During aging, we lose the capability to oppose damage to the body<br>Only one in eight centanarians is male - Probably explained by smoking epidemic<br><br>Extrapolating the data - The chance of dying is larger than the chance of getting dementia at 100 years old |

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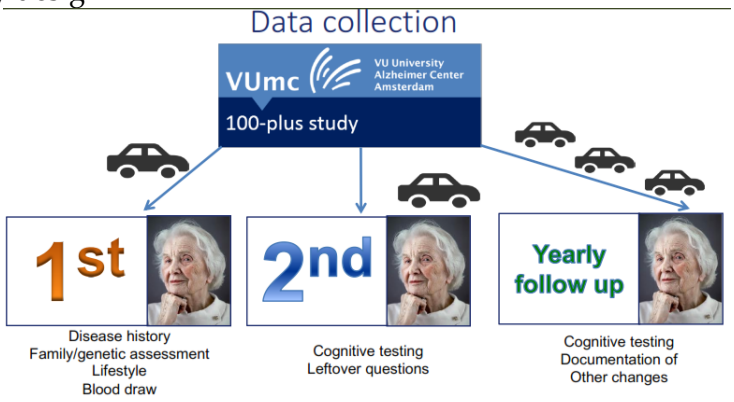
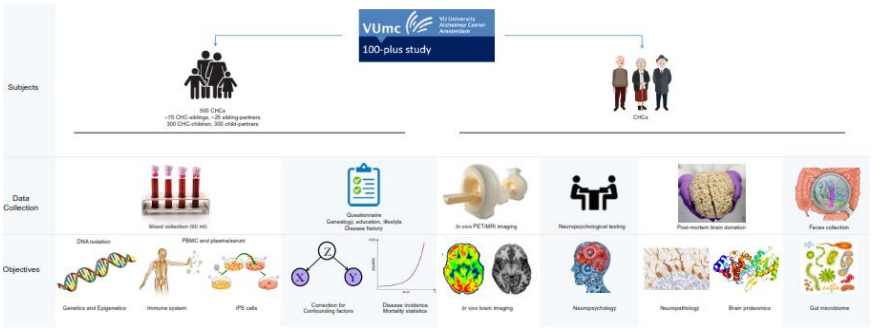
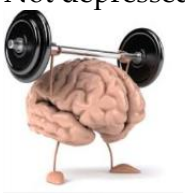
| **What percentage of centenarians are demented?** | Cognitively healthy centenarians<br>1/4 of centenarians is not demented<br>60-80% of Alzheimer risk is hereditary<br>Are there protective genetic variants? VUMC study (since 2013) |
| **What was the study design of the Vumc centenarian study? What data did they collect?** | Study design<br>  <br>  |
| **What were the main characteristics of centanarians observed in the Vumc study?** | Characteristics<br>Good hearing<br>Good vision<br>Mobile<br>Not depressed<br>  <br>lucid<br>  <br>Slightly more children<br>  <br>Higher educated<br>  <br>stout persons<br>Have more children than their parents<br>Higher educated<br>Maintain a level of activity after they stop working<br>Stout persons - Not extremely thin |

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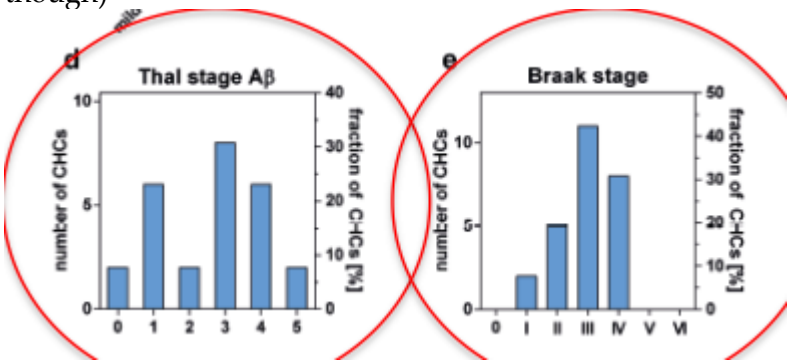
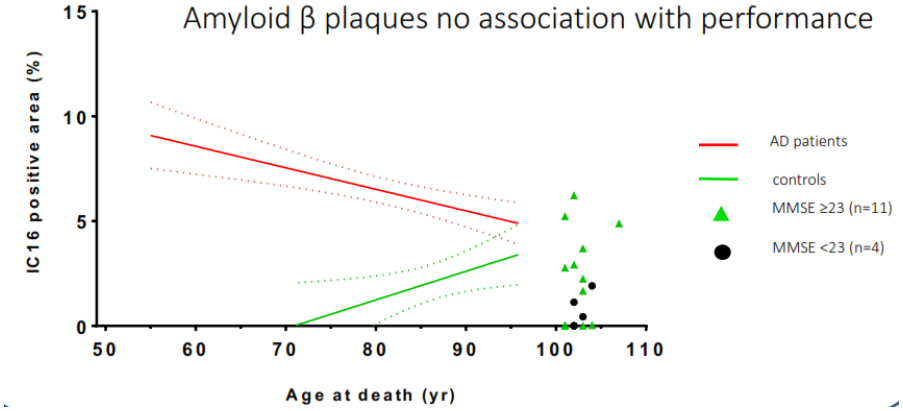
| **What was the relationship between amyloid plaques in centenarians brains and cognitive decline?** | Pathology results<br>Centenarians - Present pathologies (not the most extreme versions though)<br>  <br>AB plaques show no association with cognitive performance at older ages<br>  |
| **What does it mean to say that centenarians are 'delayers' or 'escapers'? What are the possible reasons for that?** | Centenarians are delayers or escapers:<br>Delayer - Delay onset of dementia<br>Escaper - Once a person is 100, they do not show signs of dementi for the rest of their lives<br><br>Hypothesis<br>1. Slower build-up of pathologies - Lifestyle<br>2. Better removal of pathologies - E.g. APOE2, more reactive microglia<br>3. Cognitive reserve - Larger brains, more connections<br>4. Resilience to pathologies - Combination? |
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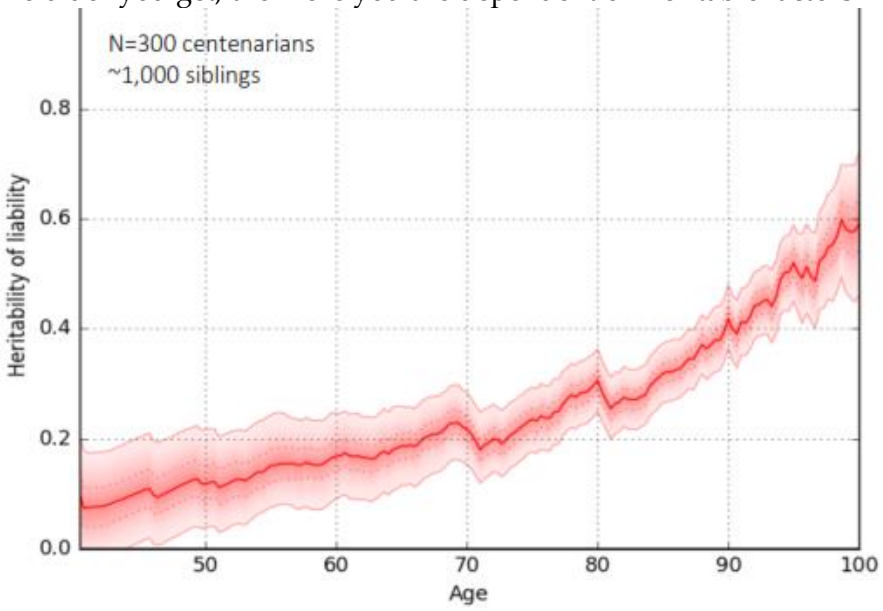
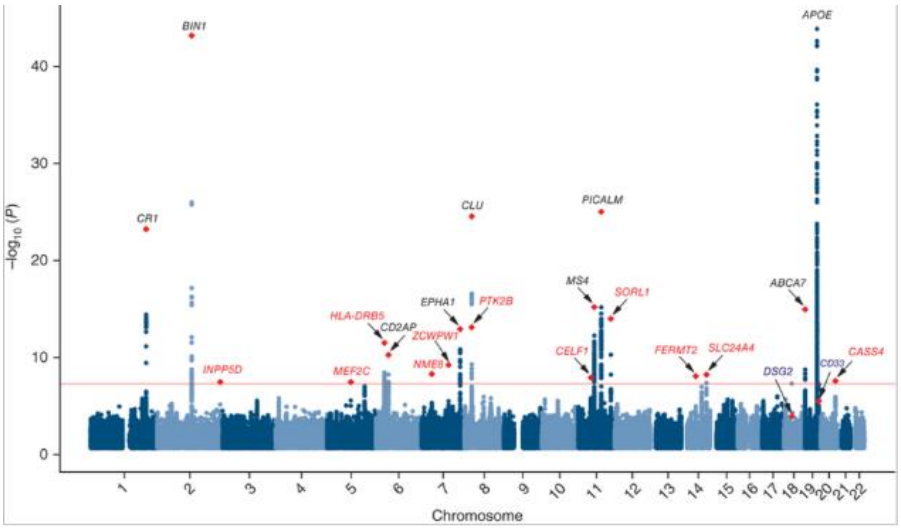
| **What was discovered from the proteomic profiling of centenarians?** | Proteomic profiling to identify differences<br>The older you get, the more you are dependent on heritable factors<br>  |
| **Which loci are important risk factors to develop AD?** | GWAS studies<br>Small effect size for each individual locus<br>  <br>APOE4 - 30% of Alzheimer's risk is attributable to this variant alone<br><br>PSEN1 PSEN2 APP SORL - Large effect but low contribution to overall AD risk<br><br>Objective of these studies: Predict who is at risk - treatment needs to start before dementia occurs; Personalized treatments |
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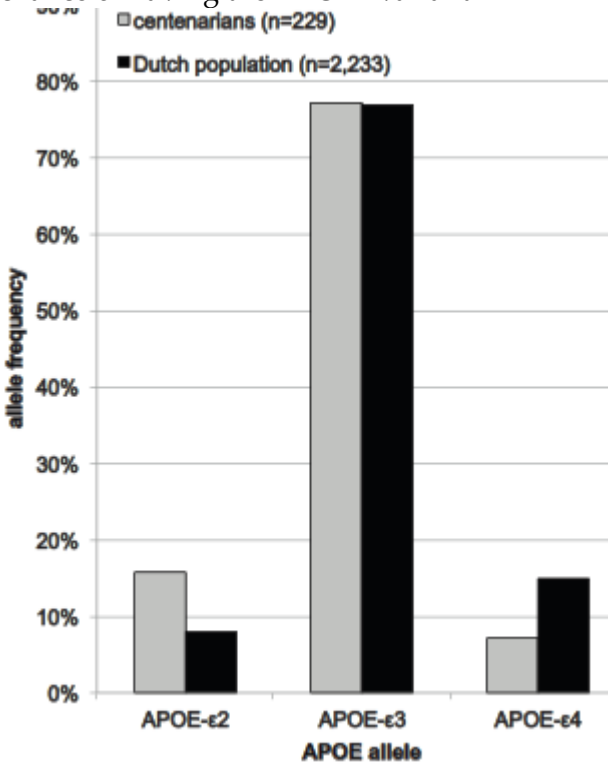
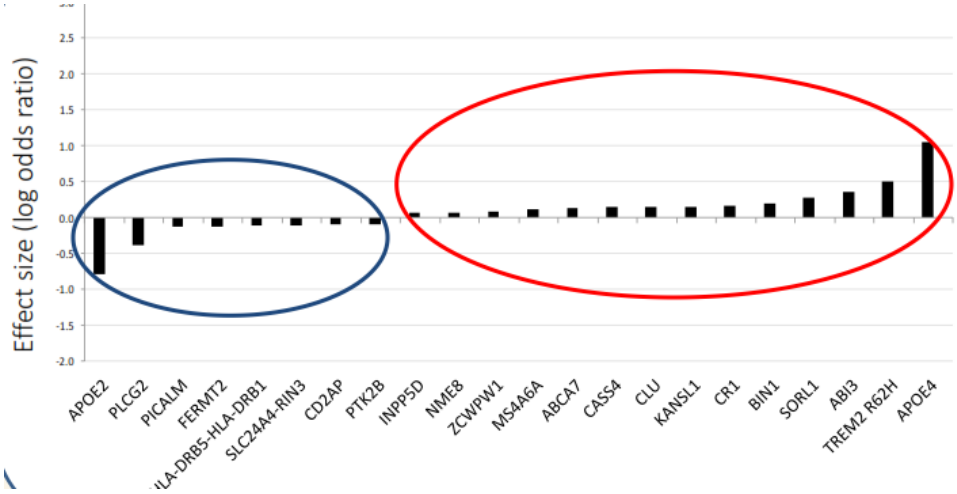
| **What was the difference in allele frequence of the APOE locus between the general population and the centenarians?** | Centenarians have higher chance of having the APOE2 variant and low chance of having the APOE4 variant<br>  |
| **Which alleles are protective against AD and which are risk factors?** | Decreased risk and increased risk of AD<br>  <br>Difference between early onset AD patients and centenarians<br>PLCG2 - Part of inflammatory response |

# 6a. Neuropsychology of dementia (C. Schreuder)

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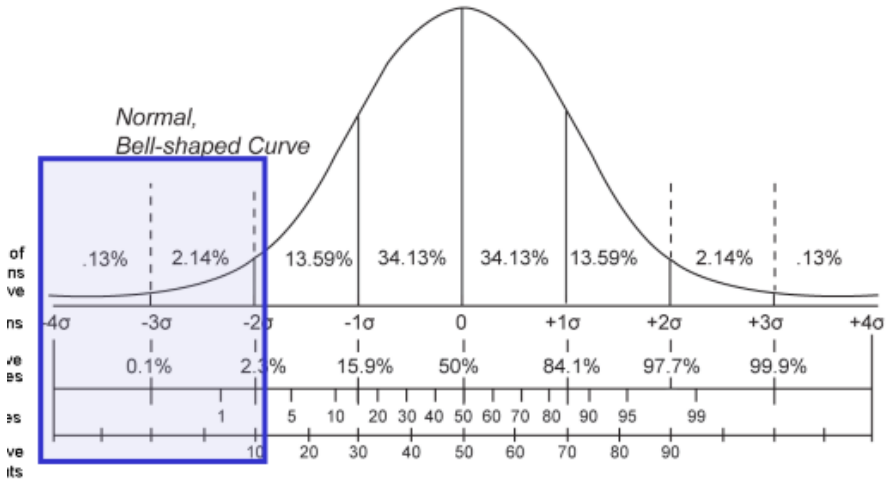
| **What is the current definition of dementia?** | Dementia is a syndrome<br>Possible underlying causes: Alzheimer's, vascular dementia, Lewy body dementia, other<br>Criteria: Two or more cognitive disorders<br>Memory<br>Attention<br>Executive Functioning<br>Visuospatial abilities<br>Language<br>Praxis<br>Speed of processing<br>Changes in personality and behavior |
| **What is the statistical definition of dementia regarding the NPA?** | Neuropsychological Assessment (NPA) measures cognitive decline of the brain<br>Interpretation - Two standard deviations below the mean = cognitive disfunction<br>  |
| **What is the difference between disorder and dementia?** | Disorder: A very low score on multiple tests within one domain<br>Dementia: Disorders in more than two domains |
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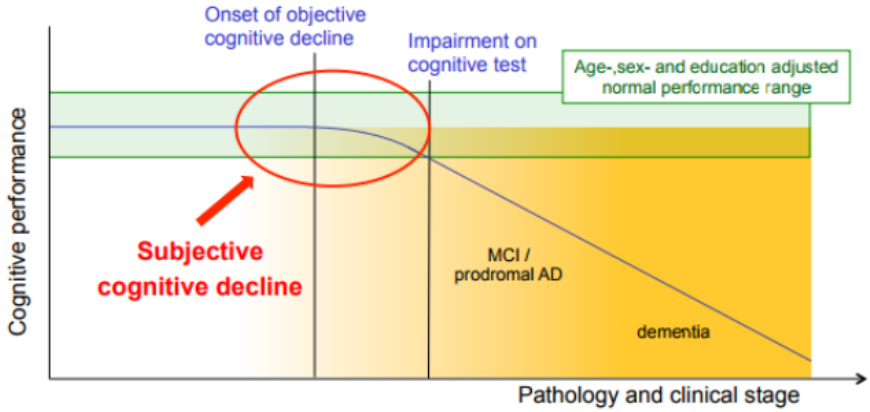
| **What are the three stages of disease progression in dementia?** | SCD, MCI, Dementia<br>  <br><br>Subjective cognitive decline - Patients complains, but tests do not show cognitive decline<br>Mild cognitive impairment - One domain is compromised<br>Dementia |
| **What is implied if a CSF profile shows low amyloid beta and high tau?** | Case: Miss P, age 60<br>Progressive memory complaints in the last six months - Forgetting names, forgetting appointments, getting lost in common environments<br>'cognitive impaired impression'<br>positive head turning (check with partner to confirm answers)<br>normal mood<br><br>Discussion<br>Memory disorder at NPA<br>MTA score 3, Global cortical atrophy 1<br>CSF profile: low amyloid-beta (implies accumulation in the brain), high tau and p-tau<br><br>Conclusion: Moderate cognitive impairment due to Alzheirmer's Disease |
| **What are the NPA tests for attention/concentration?** | NPA tests for attention/concentration<br>• WAIS digit span - Repeat digits to the examiner - average<br>Column 1<br>Forward test<br>(3) 2-6-5<br>(4) 1-5-2-3<br>(5) 2-4-7-6-1<br>(6) 4-2-1-9-3-7<br>(7) 3-6-4-8-5-2-9<br>(8) 7-5-8-2-9-6-1-3<br>(9) 5-8-6-4-2-7-3-9-1<br>Backward test<br>(2) 2-1<br>(3) 5-8-4<br>(4) 4-8-9-1<br>(5) 6-8-7-2-1<br>(6) 5-8-1-7-4-6<br>(7) 8-5-3-6-7-2-9<br>(8) 1-7-4-3-8-9-5-2 |

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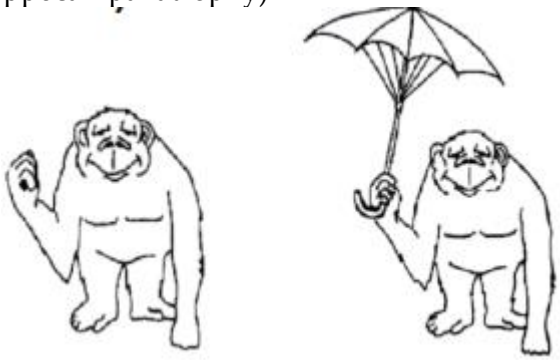
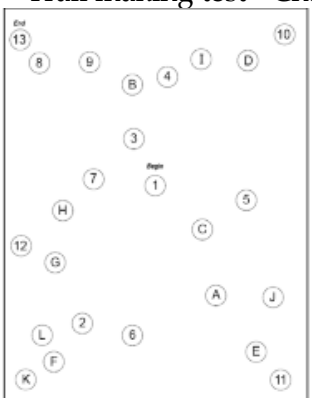
| | • Trail making test - connect numbers in increasing order<br>  |
| **What are the NPA tests for memory?** | NPA tests for memory<br>• Rey Auditory Verbal Learning Test (15-words) - Determine if words are on a list<br>• Visual Association Test - Image with associations then recall - patient had an average score followed by a very low score (typical for AD patients; patients can remember some items, but it surpasses a threshold, the patient cannot remember anymore, due to hippocampal atrophy)<br>•  |
| **What are the NPA tests for executive function?** | NPA tests for executive function<br>• Trail making test - Changing from numbers to letters<br>  |

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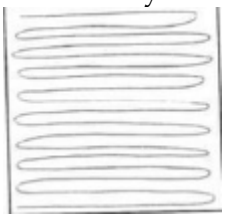
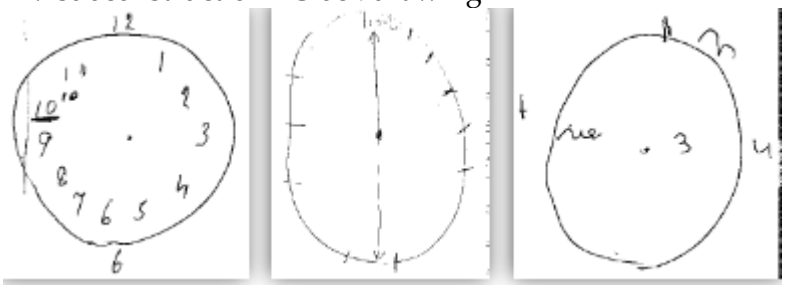
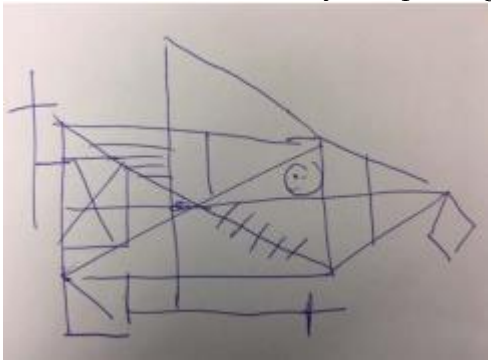
| | • Stroop color-word test<br><br>GREEN<br><br>RED<br><br>BLACK<br>• BADS key search test - Measures planning<br>  |
| **What are the NPA tests for visuospacial function?** | NPA tests for visuospacial function<br>• Visuoperception - Dot counting, incomplete letters, number location<br>  <br>• Visuoconstruction - Clock drawing<br>  <br>• Visuoconstruction - Rey complex figure (copy and recall)<br>  |

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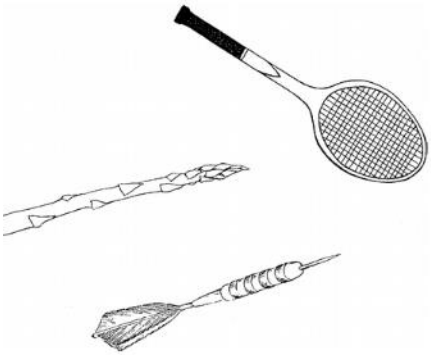
| **What are the NPA tests for language?** | NPA tests for language<br>• Naming test - Average<br>  <br>• Fluency test - Average<br>• Animal fluency - Average |
| **What are the NPA tests for praxis?** | NPA tests for praxis<br>Tests<br>• Ideational praxis - "Show how to use a hammer", average<br>  <br>• Ideomotor praxis - Average<br>  |
| **What are the general differences between dementias presented in the NPA tests?** | Differentiation between dementias<br>Alzheimer's - Mostly memory impairments<br>If it is early-onset - Less memory problems, more non-memory problems<br>Vascular dementia - Depends on the lesion, often speed and |

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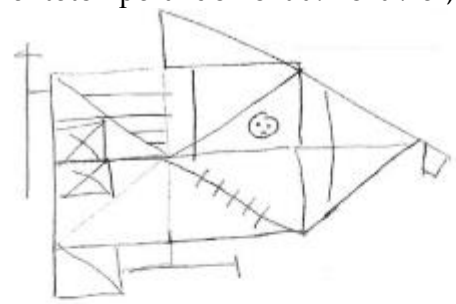
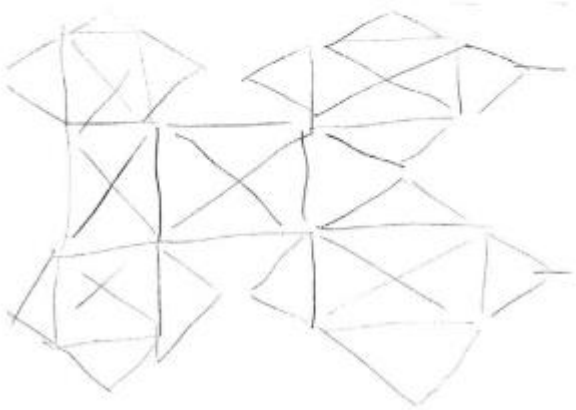
| | executive dysfunctions<br>Dementia with Lewy Bodies - Speed of processing, Executive functions, Fluctuations of attention, Visuospatial abilities<br>Frontotemporal dementia: Behavior, Executive functions, Language<br>  <br>  |

# 6b. The role of amyloid in aging and Alzheimer's Diasease (Rik Ossenkoppele)

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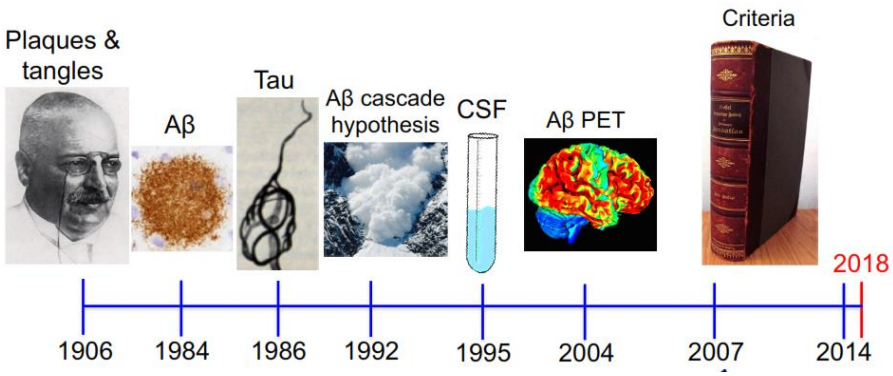
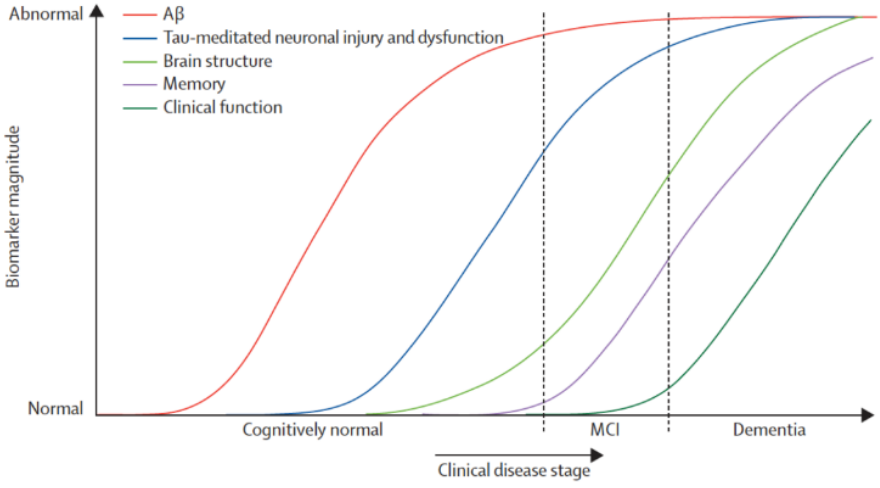
| **What are the main historical events in the history of Alzheimer's Disease discovery?** | History of Amyloid<br>  <br><br>1906: Alois Alzheimer describes plaques and tangles in the brain<br>80 years later - Discovery of amyloid and tau-proteins<br>1992: Amyloid cascade hypothesis<br>1995: Test for beta-amyloid in CSF<br>Does not correlate perfectly with brain disease (indirect measure)<br>2004: In vivo visualization of amyloid-B (PET)<br>11CPIB - Binds to extracellular amyloid beta and emits a signal<br>Image: Warmer colors -> more amyloid beta<br>Up to 2014: Six new diagnostic criteria<br>More objective measurements of the diasease |
| **What is the general biomarkers associated with AD disease progression?** | Hypothetical Biomarker Model of AD<br>  <br><br>AB accumulates first |

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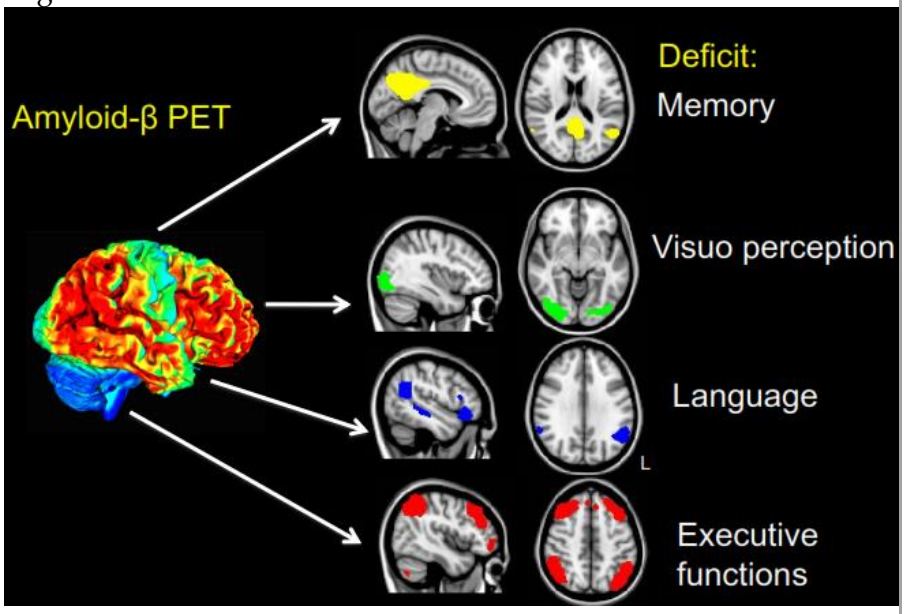
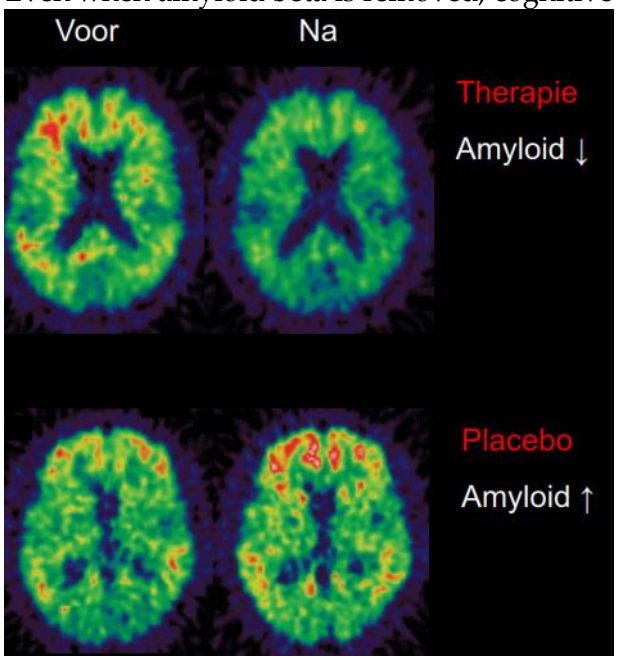
| **What are the current issues with using amyloid beta to measure disease progression in Alzheimer's?** | Current matters<br>Function of AB is still unclear<br>AB pathology is present in healthy people and non-AD dementia (Lewy bodies, frontotemporal)<br>Regional mismatch between amyloid-beta accumulation and brain degeneration<br>  <br>Amyloid is everywhere, damage is localized |
| **What happens when you pharmacologically remove most of amyloid beta from the AD patient's brain with his cognitive performance?** | Clinical trials<br>Even when amyloid beta is removed, cognitive decline still persists<br>  |

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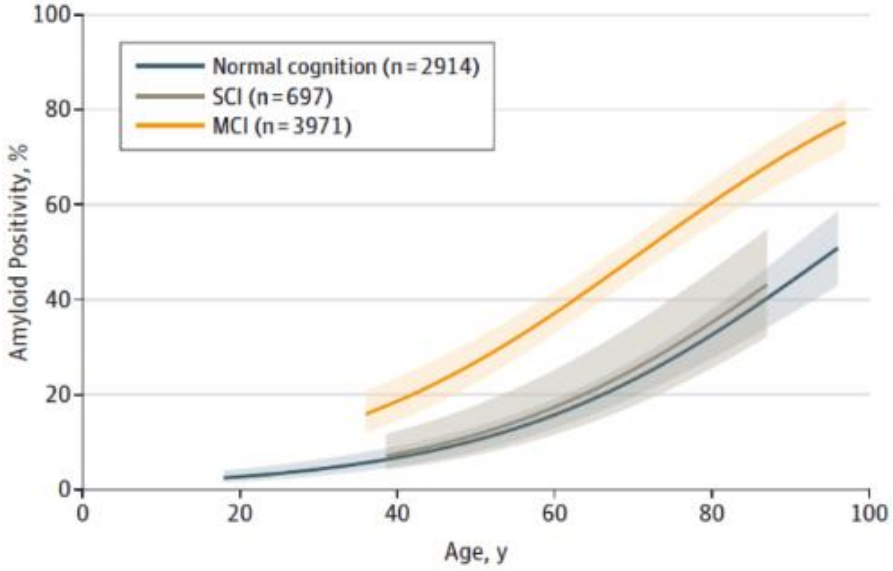
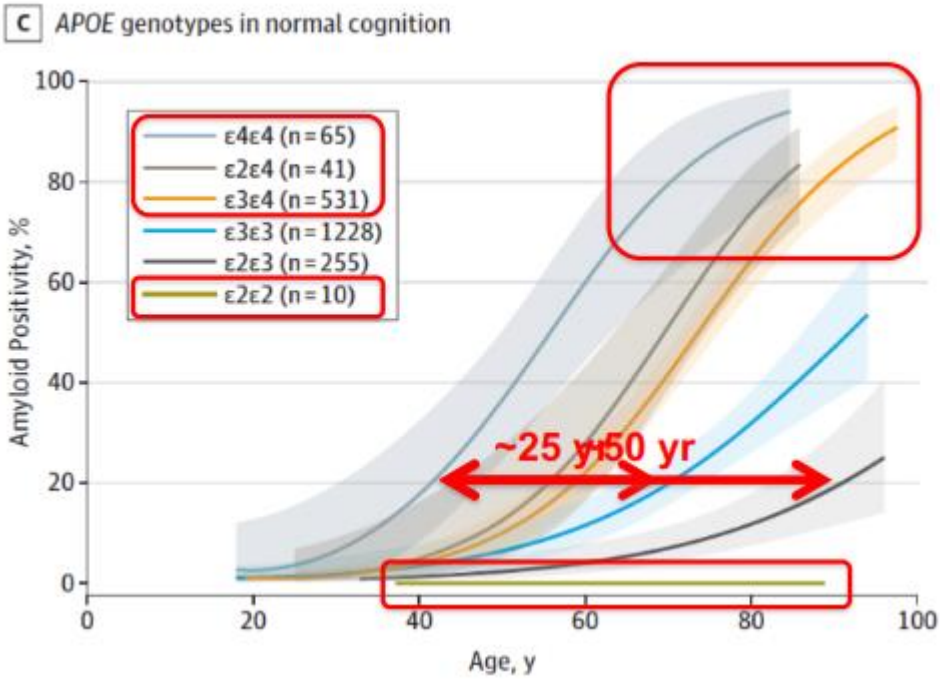
| **What is it not a problem to classify 'amyloid positivity' in a binary system, instead of looking at the concentration of AB in the patients brain?** | The role of amyloid in aging<br>Collaborative study (AB status, age, APOE genotype)<br>  <br><br>Amyloid positivity - Normal cognition and subjective cognitive impairment; moderate cognitive impairment<br>Dichotomizing works because once a certain concentration of AB passes, the concentration does not matter<br>Age is an important factor to become amyloid positive |
| | E4 gene is an important risk factor<br>  <br><br>Even healthy controls are more likely to be amyloid positive<br>E2E2 - No amyloid beta (even 90) |

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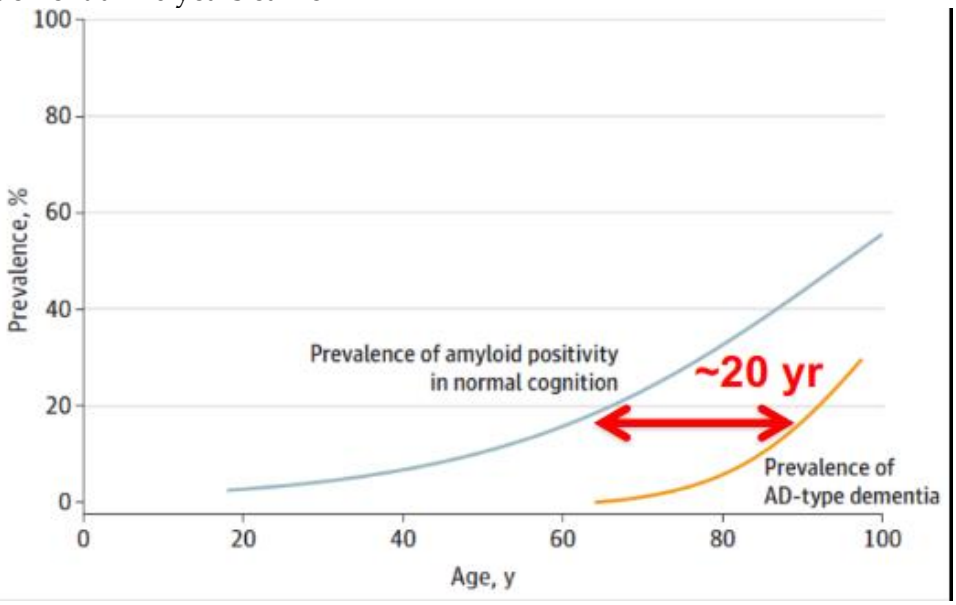
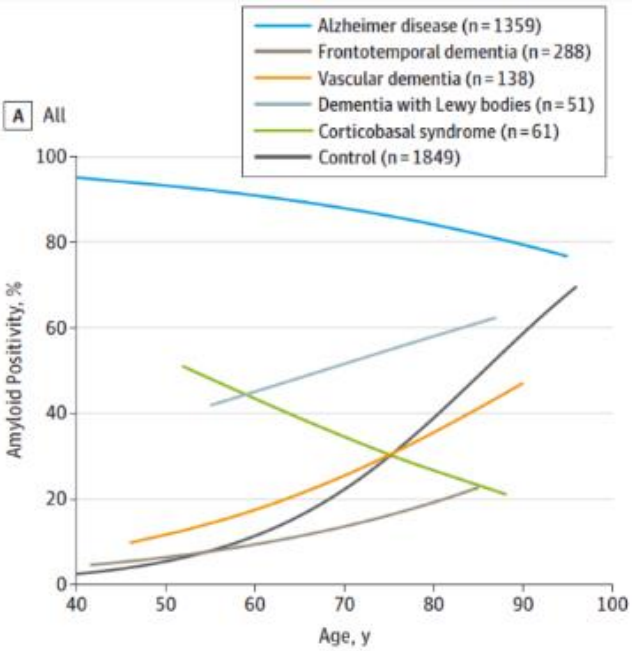
| **What is the interval in years between amyloid positivity and AD dementia?** | There is a prevalence of amyloid positivity before prevalence of AD dementia - 20 years earlier<br>  <br> |
| **Why is amyloid positivity not informative in older people?** | Implications amyloid positivity for cognition and neurodegeneration<br>  <br><br>Cross-sectional: mixed results<br>Longitudinal studies: AB show faster decline<br><br>Alzheimer's disease - Older patients have less amyloid positivity<br>Probably indicates misdiagnosis |

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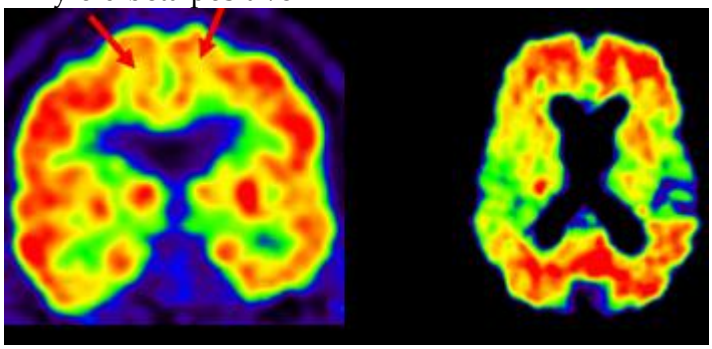
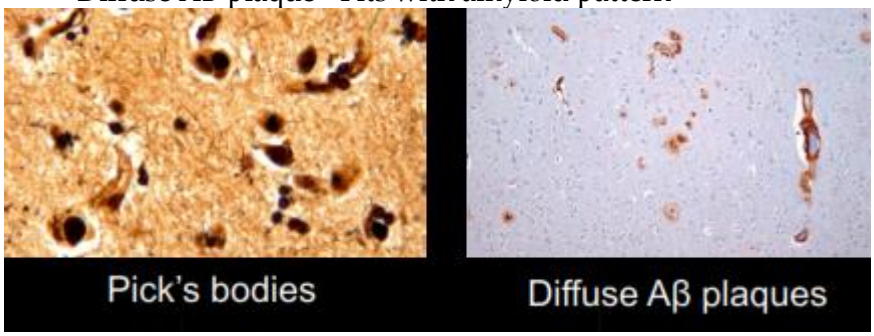
| **Why are amyloid-beta PET scans not so useful in the clinic?** | Amyloid-beta imaging in the clinic<br>Clinicals change their diagnosis frequently after PET scan results<br>PET increases diagnostic certainty<br>Patient management changes |
| **What may be the inference of a patient who is both FTD positive and amyloid positive?** | Case: Behavioral frontotemporal dementia<br>FDG PET - FTD pattern<br>Amyloid beta positive<br>  <br>Autopsy<br>• Pick bodies - Fits with FTD pattern<br>• Diffuse AB plaque - Fits with amyloid pattern<br>  <br>Presence of amyloid pathology does not mean that the person has Alzheimer's Disease |
| **When is it appropriate to use amyloid PET scans? When is it not useful?** | Appropriate use criteria for PET<br>Early onset dementia<br>Atypicial dementia<br>Persistnet or unexplained MCI<br><br>Innappropriate use criteria for PET<br>Late-onset AD - Amyloid positivity is not very informative, though a negative scan could be informative<br>Determine disease severity<br>Asymptomatic individuals - There is nothing to do, there is no literature on amyloid positivity on healthy individuals |

# 6c. The role of Tau PET in Alzheimer's Disease (Rik Ossenkoppele)

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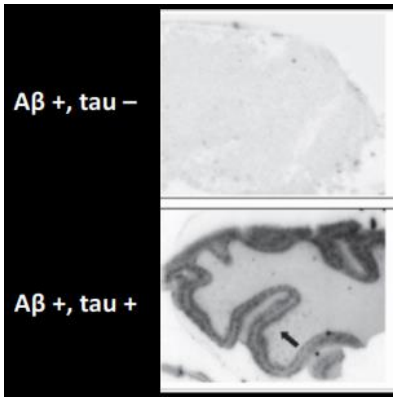
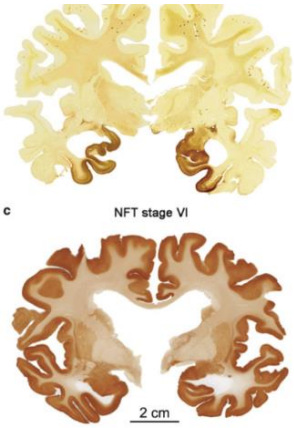
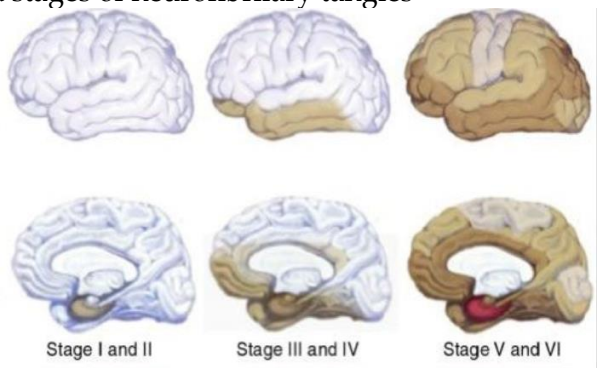
| **What is AV1451?** | AV1451: Distribution of tau in vivo<br>  <br><br>High affinity and selectivity for PHF tau |
| **What does tau correlate with in the brain?** | Abnormal tau correlates with:<br>  <br><br>disease severity and symptom progression<br>Neural dysfunction and degeneration |
| **What are the braak stages for neurofibrillary tangles?** | Braak stages of neurofibrilary tangles<br>  <br><br>Starts on entorhinal cortex, spreads to the rest of the brain |

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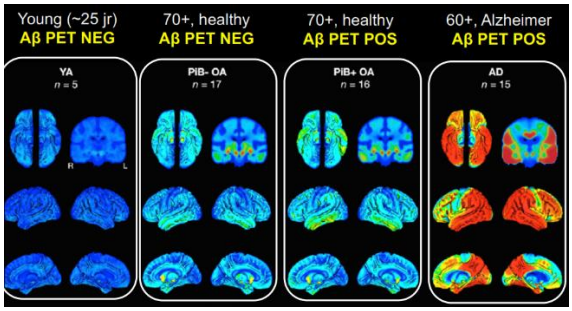
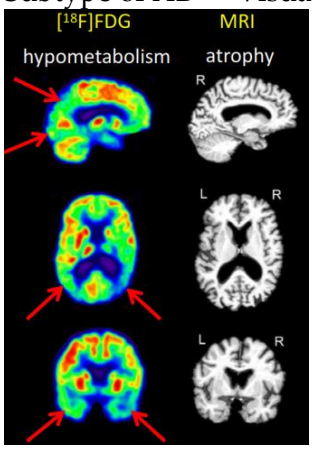
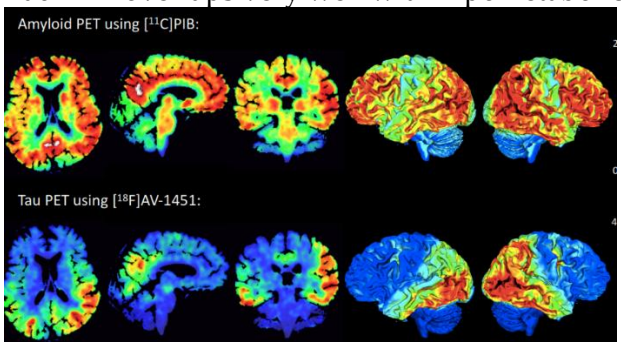
| **What are the tau PET resulsts of:**<br>**A. Young people AB negative**<br>**B. Old people AB negative**<br>**C. Old people AB positive**<br>**D. Alzheimer patients AB positive** | PET results<br>  <br><br>Yound people - Almost no tau<br>70 healthy - Some increases in tau pathology (hippocampus and entorhinal cortex)<br>70 AB pos - Similar<br>60 AB pos - Higher concentration, tau concentration correlates very well with the disease |
| **What is the relationship between hypometabolic regions and tau positivity?** | Posterior cortical atrophy<br>Subtype of AD -> Visual problems<br>  <br><br>Hypometabolism in the occipital cortex and posterior parts of the brain<br><br>Tau PET overlaps very well with hipometabolic regions<br>  <br><br>Posterior cortical atrophy - in the occipital region<br>Logopenic variant - in language region |