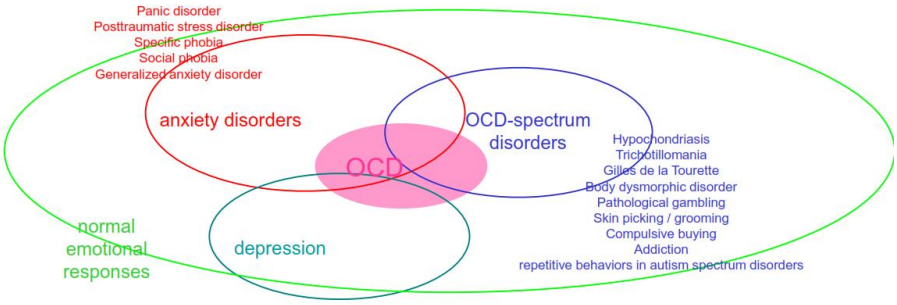
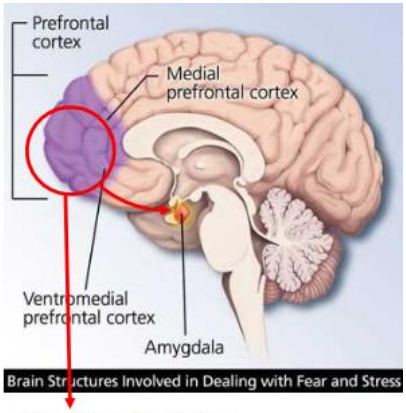
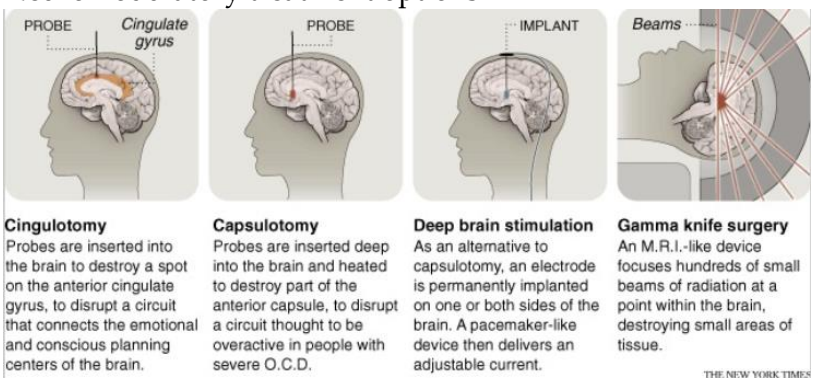
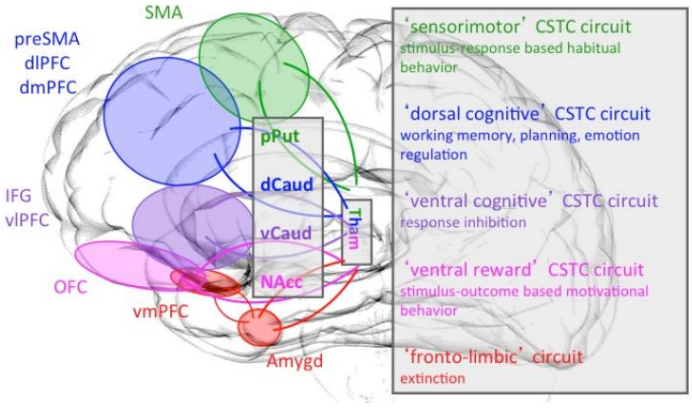
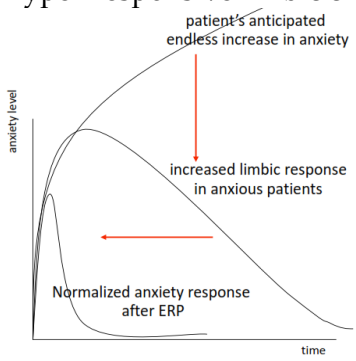
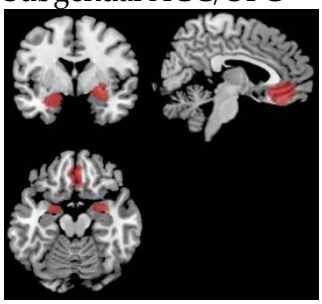
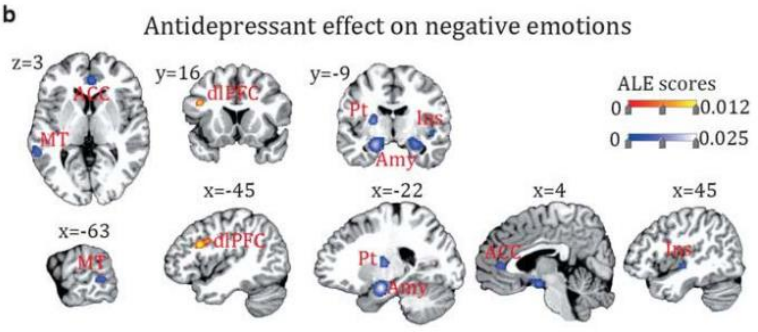
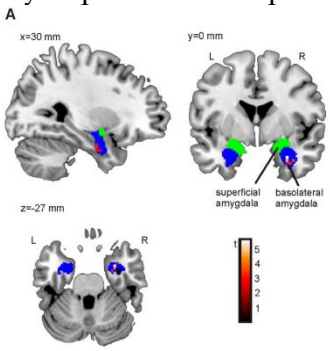
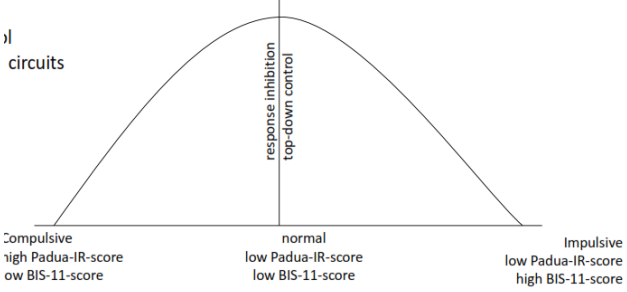
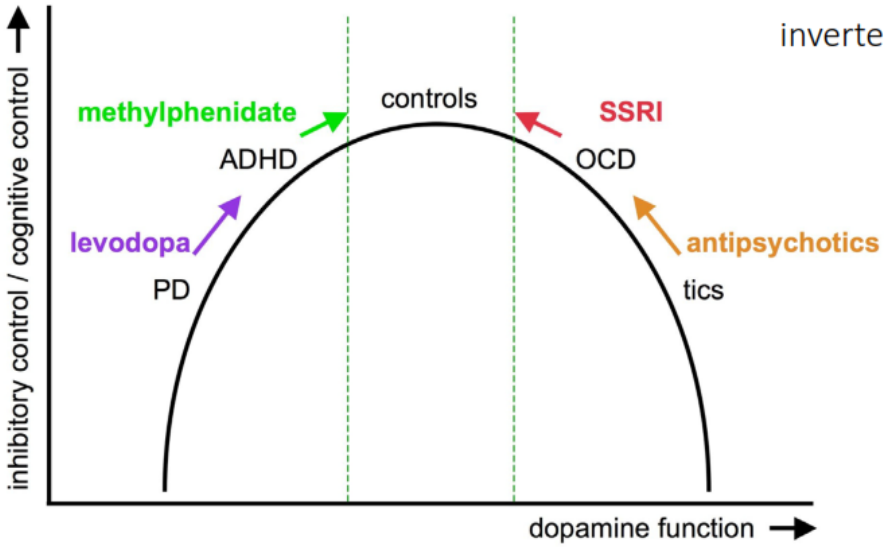
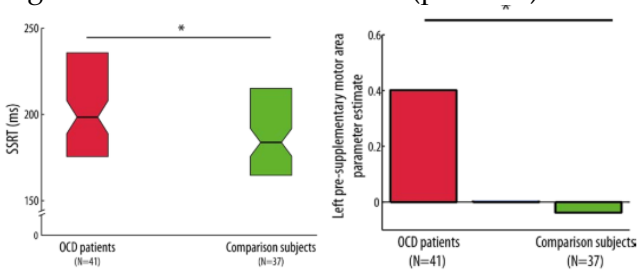
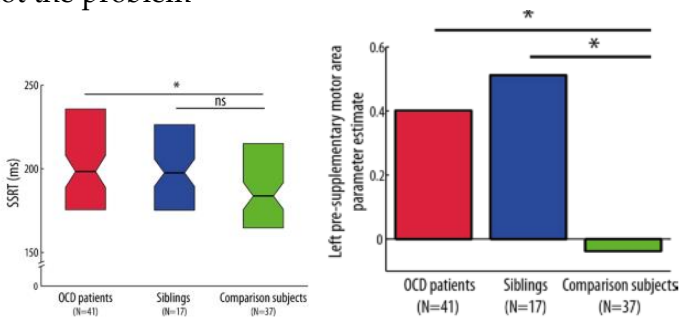
8a. Obsessive-compulsive disorder; translating between patient experience, disease models, brain imaging and therapy response (van den Heuvel)

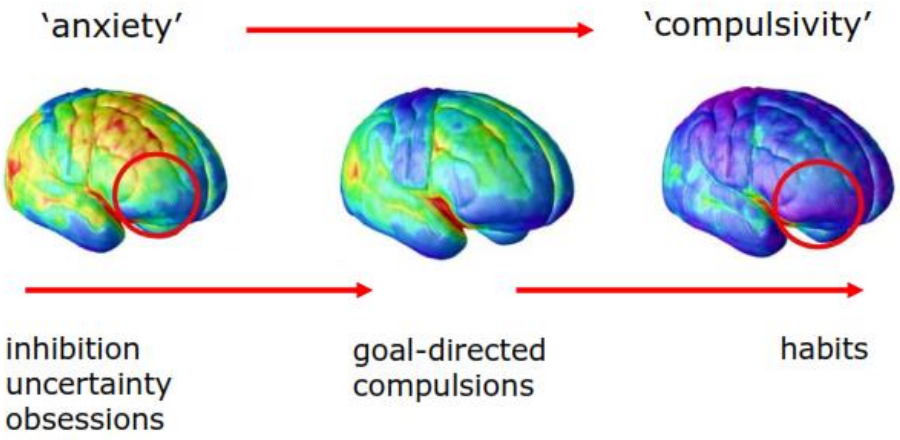
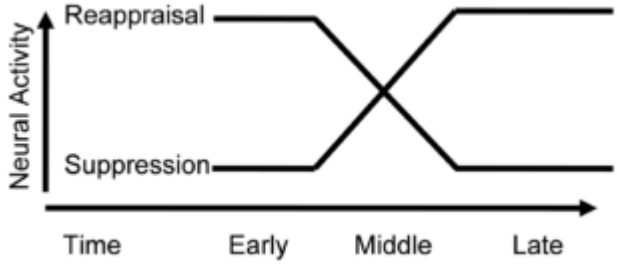
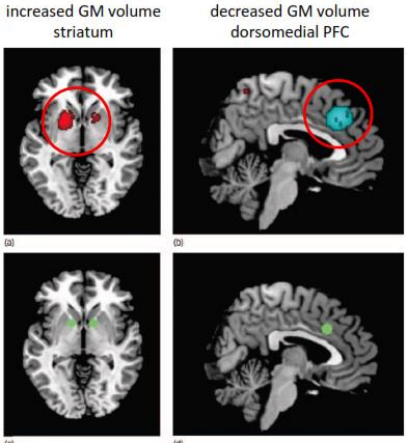
What are common behaviors of OCD patients?	OCD - Various symptoms Intrusive thoughts and repetitive behavior - Washing rituals, symmetry, counting and mental compulsions, hoarding, checking behaviors It is often disguised socially, the patient expresses the behavior alone at home
What is the overall epidemiology of OCD?	Epidemiology of OCD 1-3% of people Most often diagnosed in young adulthood Chronic and heterogeneous disorder
Which disorders does OCD overlap with?	OCD is often overlapping with other disorders 
What are the common treatment options for OCD?	Treatment guideline Cognitive behavior therapy - Exposure in vivo with response prevention Anxiety drops after a while Antidepressants (mainly serotonergic) - SSRIs, higher doses compared to depression, long term treatment before evaluation, side effects (sexual drive decreases)
What is the supposed underlying mechanism for psychotherapy in OCD?	Psychotherapy underlying mechanism Extinction learning - Exposure in-vivo

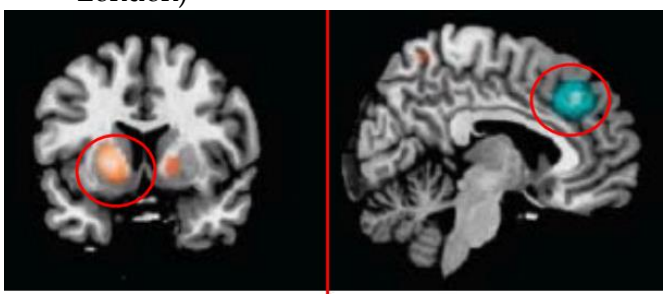
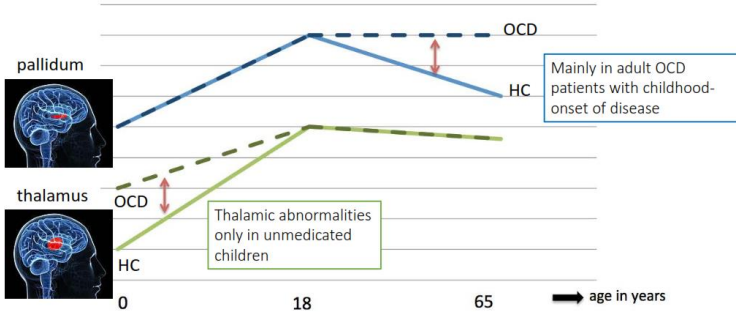
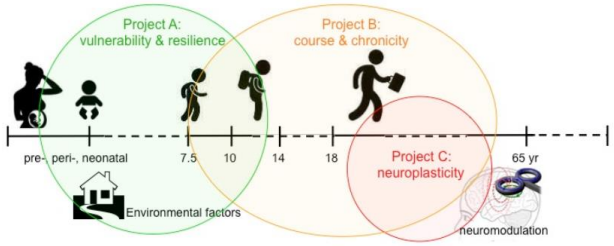
	 extinction learning (exposure-in vivo with response prevention ERP) mPFC inhibits amygdala Cognitive reappraisal - Dorsal PFC
What are the neuromodulatory treatment options for OCD?	Neuromodulatory treatment options  Non-invasive stimulation is currently being developed (Transcranial Magnetic stimulation)
What is the biological reason that OCD symptoms seem so diverse?	Disease models for OCD - Many circuits are involved, model varies with symptoms  The more habitual the problem is -> more involvement of sensory motor regions

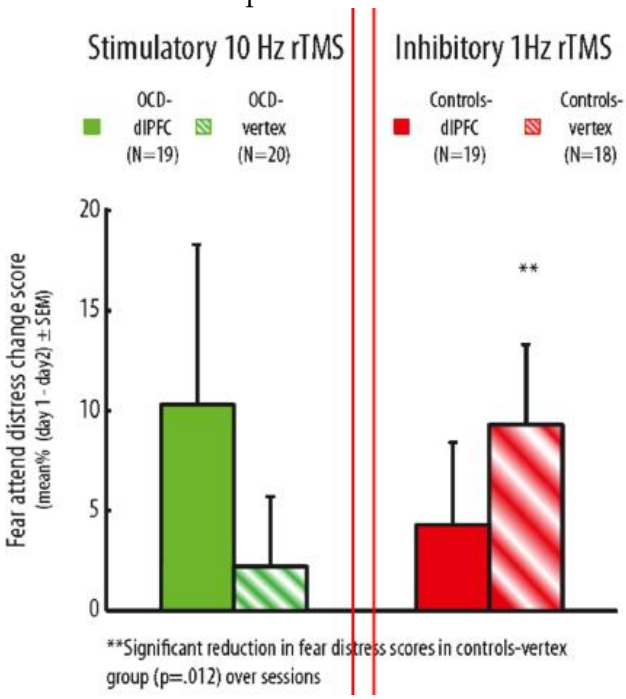
Why is OCD often considered an anxiety disorder?	OCD has always been considered an anxiety disorder • Harm avoidance/doubt/uncertainty • Anxiety/stress • Hyper-responsive limbic circuitry  Anxiety drops after a while
In an fMRI, which brain regions are overactivated in OCD patients?	Meta-analysis of symptom provocation in OCD • Symptom provocation • Emotional faces • Other - Emotional strop test Results: Increased activation of: • Bilateral amygdala - Mainly for disease specific stimuli (unmedicated > medicated) • Right putamen • Subgenual ACC/OFC 
What is the effect of SSRIs in OCD patients?	Effects of SSRIs - Reduction of amygdala activation 

Why is medication commonly used in OCD, when CBT seems to be more effective?	An hour is not enough for anxiety to drop, at least not in the first few sessions - Ventromedial PFC in OCD patients is less able to extinct In the Netherlands, there is a lack of CBT therapists - Medication is more commonly prescribed CBT is as effective as medication - They are not commonly prescribed at the same time
Describe the Bergen 4-day format for OCD treatment.	The Bergen 4-day format (1 patient: 1 therapist)  Day 1: Psychoeducation Day2-3: Exposure with response prevention (Lean into anxiety technique) Day 3 end: Lessons learned with family and friends Day 4: Prepare for maintainence at home Overall results: All patients are in remission after a week
How can we predict which OCD patients will respond to what treatment?	Challenge: Prediction of treatment response Try to predict which patients will respond from each treatment  Use of fMRI and machine learning
Describe how OCD could be in an impulsive-compulsive spectrum, rather than an anxiety disorder?	OCD as an impulsive-compulsive spectrum (not an anxiety disorder) More like addiction - Impaired response inhibition 

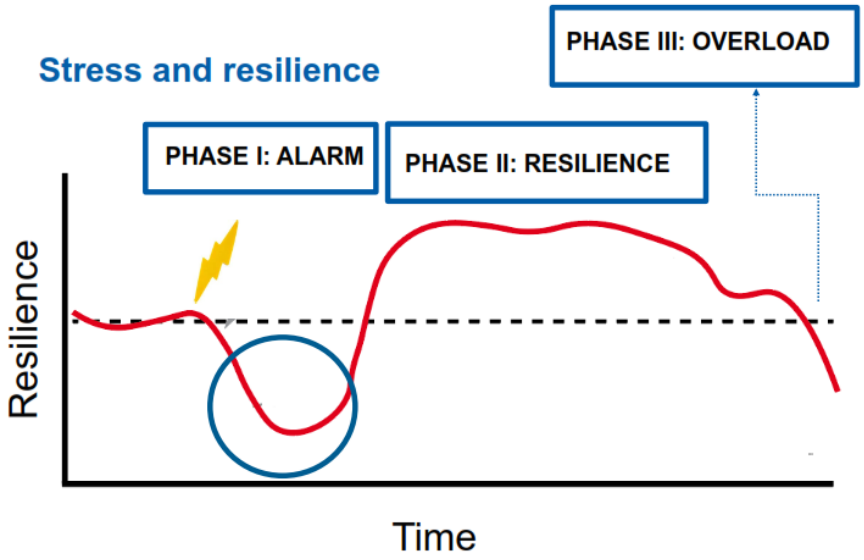
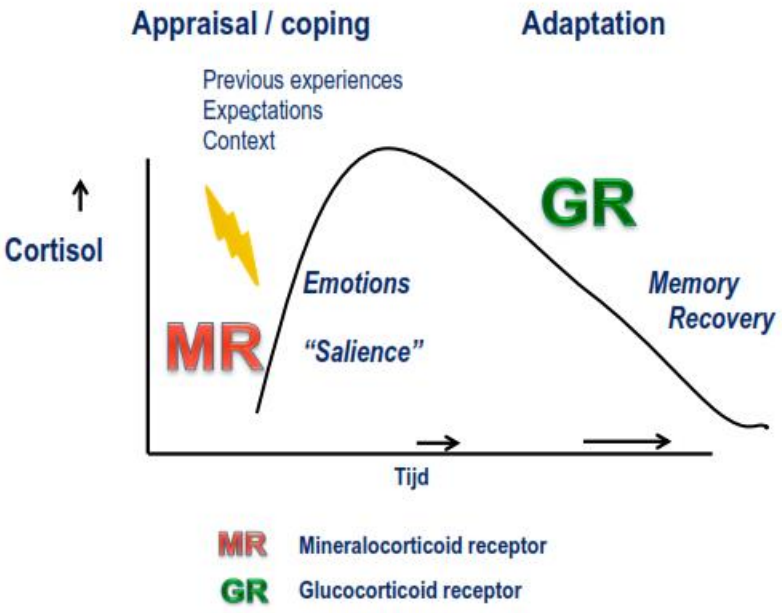
	Analogy: Response inhibition in psychiatric Too much or too little dopamine is problematic 
Why brothers and sisters of OCD patients work well as controls in fMRI experiments?	Response inhibition example Stop signal task - Left and right arrow (red X - inhibit signal) OCD patients are late Higher activation of motor area (preSMA)  Including healthy brothers and sisters.- Conclusion that preSMA is not the problem  This was replicated with other cognitive function - Avoids spurious associations

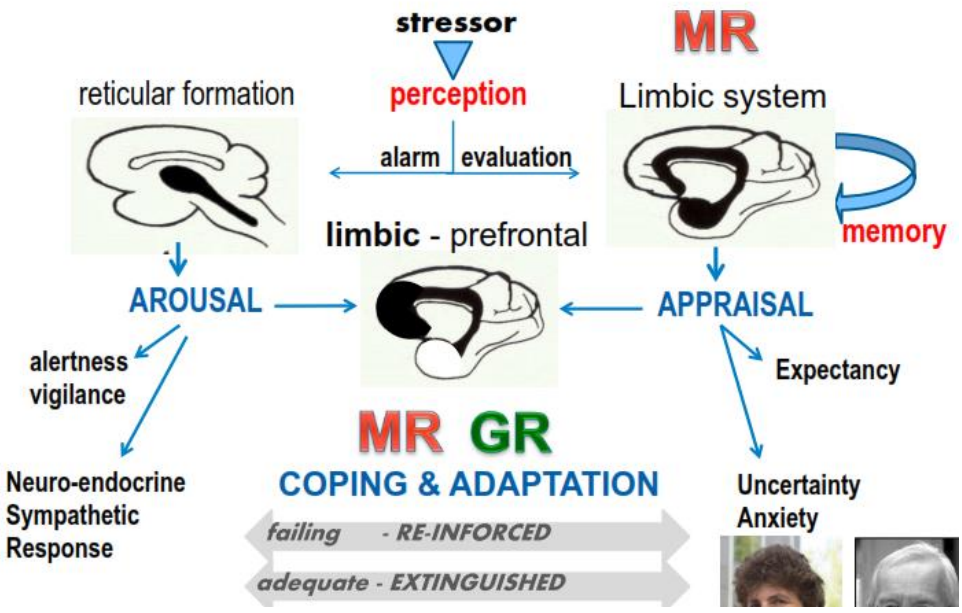
Describe the common progression of OCD.	OCD is not a static disease - Transiction between anxiety and compulsivity  Initially goal-directed -> Becomes habitual (compulsion)
Why is emotional regulation important for an OCD patient during treatment?	Emotion regulation Reappraisal - Proactive mindset  PFC cannot suppress amygdala if it is too active, it needs to be activated before amygdala (proactive state of mind)
Which brain regions are smaller/bigger in OCD patients compared to the general population?	VBM studies in OCD OCD - Bilateral insula and dorsal medial PFC is small than patients that suffer from other diseases 

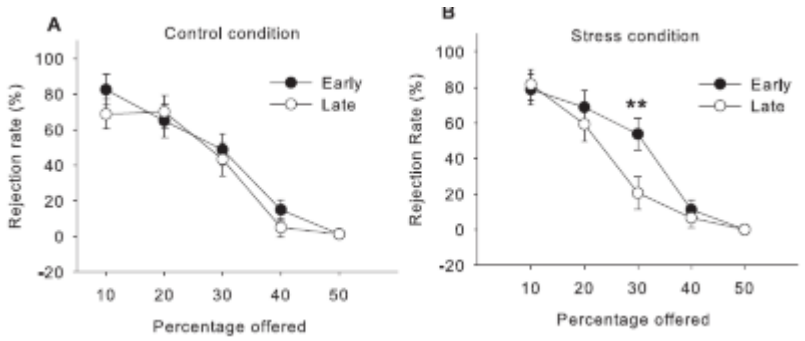
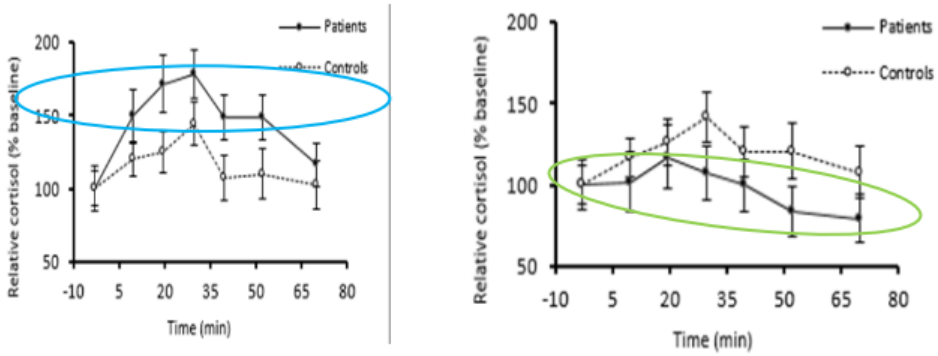
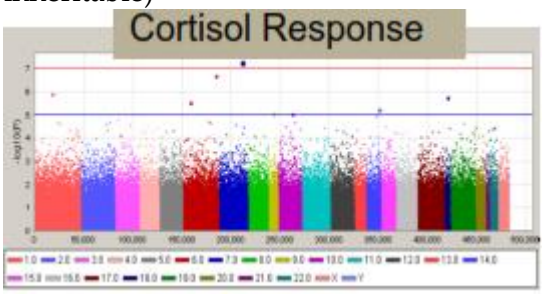
	Bigger striatum - Typical for OCD; since it is active the whole day, it does not decrease (analogy taxi driver's hippocampus in London)  Increased ventral circuitry - Compulsivity Decreased dorsal circuitry - Emotional regulation/Executive function
What is the difference between childhood OCD and adult OCD?	A child OCD brain is not an adult's OCD brain Adult - Smaller brain volume, chronic disease, you cannot assess causes of disease, only consequences Adult - Bigger striatum, smaller hippocampus (Comorbidity with depression); Thinner cortex Child - Larger thalamus; Decreased surface area of cortex  Findings are only significant in medicated patients - There are no longitudinal studies that assess long-term effects of these medications
Why is a lifespan approach important to study complex diseases like OCD?	Lifespan approach (Generation R study) - Scans of the same people throughout life since birth (decreased variability, show disease progression) 

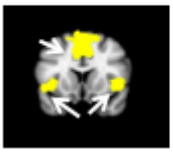
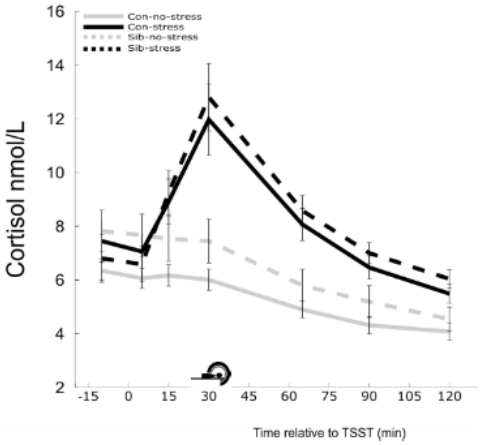
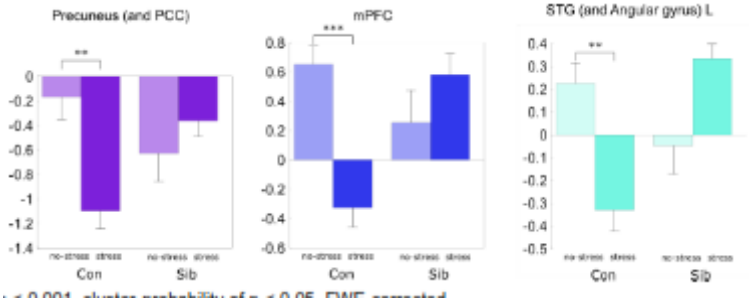
Describe what is transcranial magnetic stimulation and how it can be used to treat OCD patients.	Transcranial Magnetic Stimulation Magnetic coil produced electric stimulation in the brain Can inhibit or enhance neuron activation Experimental: Stimulus provocation  Repeated exposure to the same stimulus - Habituation, less anxiety Striped lines - Controls Future: Combine TMS with Cognitive Behavior Therapy

8b. Stress and neuropsychiatry (Christian Vinkers)

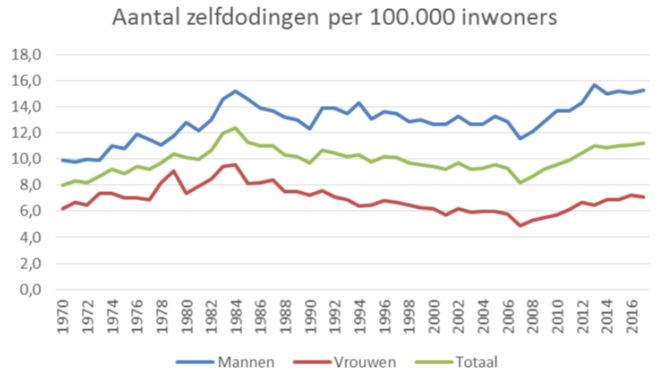
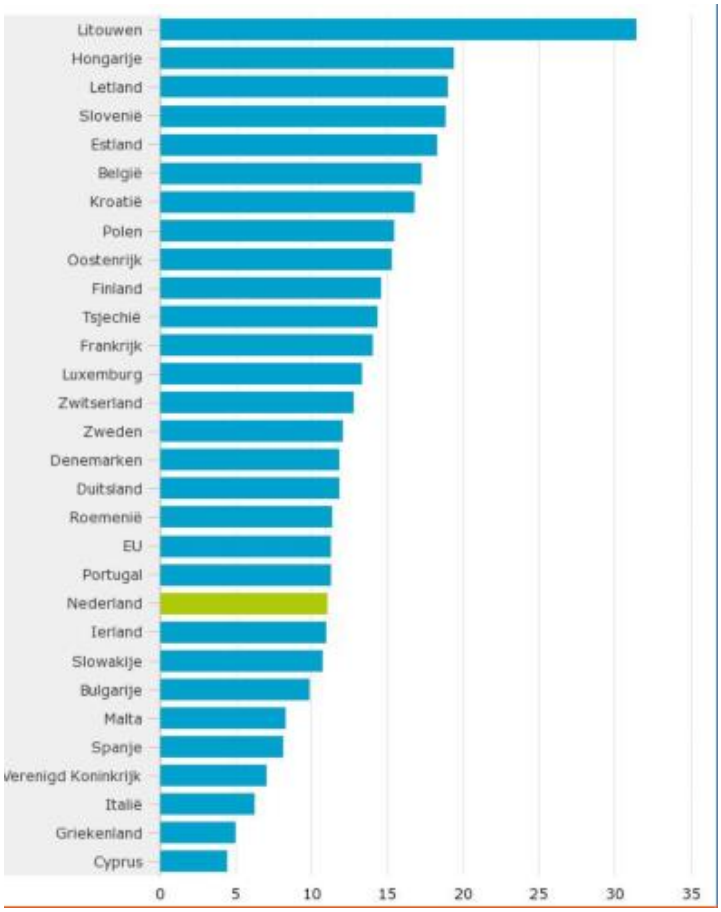
What is stress and resilience?	Stress and resilience  Resilience - Stress resistance/ability to recover from stress Stress is not necessarily bad - Excess and total lack of stress are equally bad If the stress system stays on for too long - Overload (molecular adaptation)
Which are the receptors that cortisol binds to?	HPA-axis - Hypothalamic-pituitary-adrenal gland (end products: cortisol) Cortisol binds to two different receptors: Mineralocorticoid and glucocorticoid receptor
Describe the interplay of cortisol and MR/GR receptors in response to stress.	

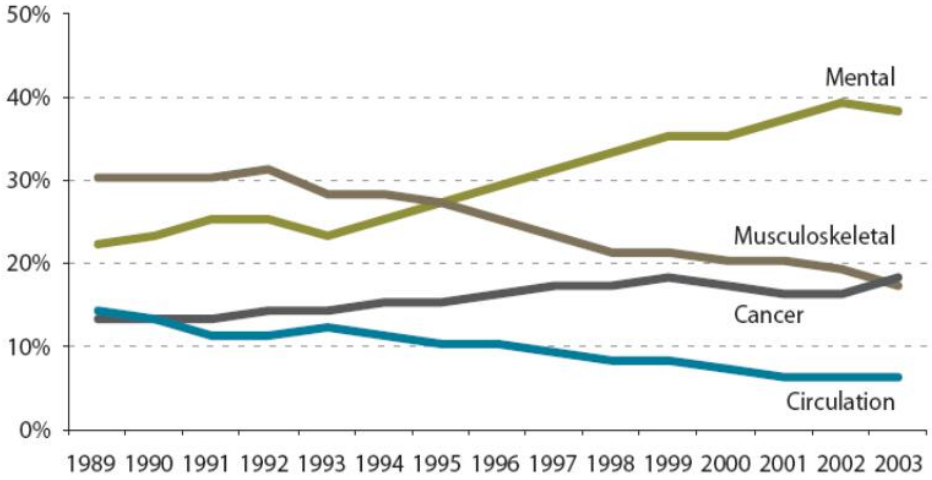
	MR is expressed in the limbic system High affinity for cortisol Activation level depends on previous experiences, expectations and context GR works when cortisol levels are high - 20 or 30 minutes after stress Low affinity for cortisol Memory associated with stress event Expressed throughout the brain Responsible for the decline of cortisol in the bloodstream - Modulation of gene transcription
What makes an experience stressful?	What makes an experience stressful: Context Predictability Control
What is the role of reticular formation, limbic system and prefrontal cortex during a stressful event?	Brain response  Drugs as coping mechanisms for stress Stress reduces dopamine reward system!
Why is timing important in stress research?	The importance of context and timing in stress research (do a presentation with no verbal or social cues) Initially after stress - Cortisol stays up after two hours
What is the main finding of the	Offer money (10 euros) - Unequal division (*"If you do not accept my offer, we both do not get money"*)

relation between stress and cooperativeness?	 30% (7:3 euros) - Your stress levels are quite important for your decision
What is the difference between the response of cortisol from man and women with MDD?	Sex in stress research  Men with MDD - Increased response to cortisol Women with MDD - Decreased response to cortisol Less research done with women (hormone complications)
What is the consistent locus associated with MDD in GWAS?	Epigenetic changes and childhood trauma DNA methylation - Persists throughout adulthood (may be inheritable)  Study: 4 loci significant regarding stress response (1 consistent: KITLG: KIT ligand, stem cell factor)
How does stress change neuronal networks?	Stress-induced shift in neuronal networks Salience network - Up-regulated during stress,down-regulated after cortisol administration

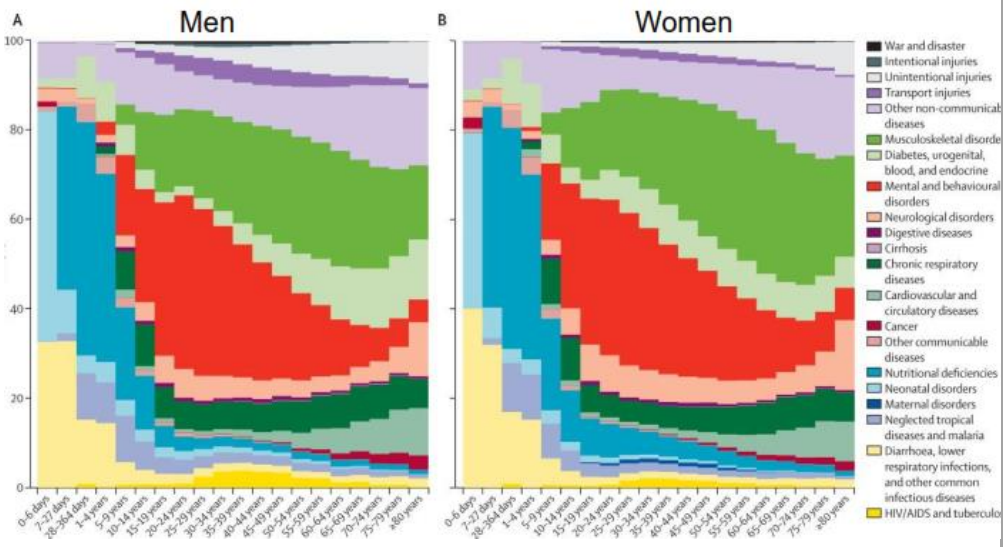
	Salience network (SN)  Default mode network - Self-referential processes, suppressed during cognitively demanding tasks (stress interferes with suppression) *Default mode network* 
Why is measuring cortisol from saliva probably not a good representation of stress?	Study Increase cortisol levels persist for 140 minutes  Not the whole picture - Cortisol in saliva does not translate directly to brain activation Whole-brain analysis - Siblings of schizophrenic siblings = no effect of stress (30 minutes later) 

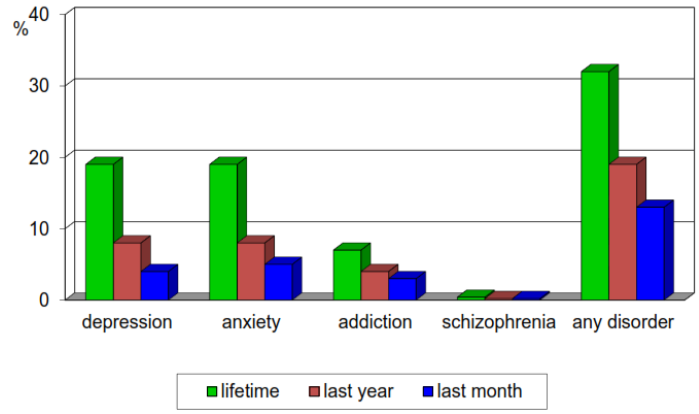
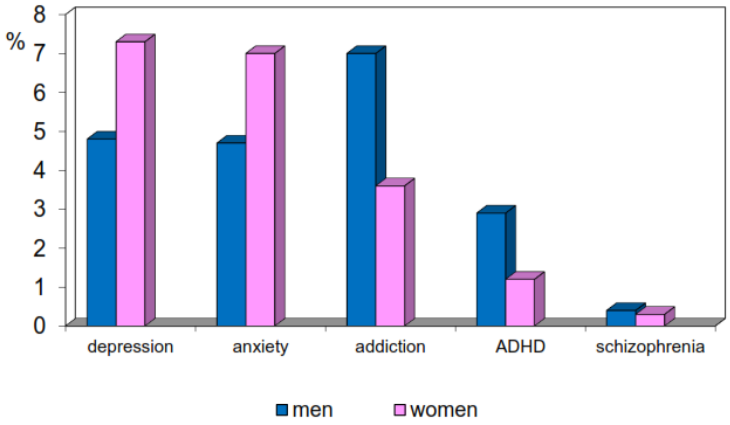
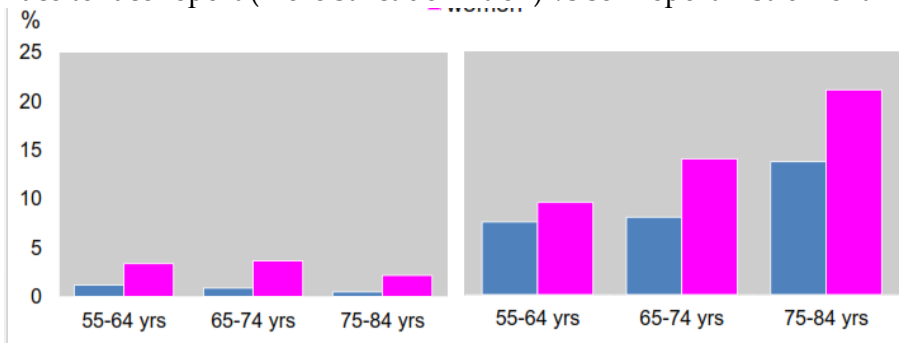
8c. If ever there was a good time to start a career in psychiatry (Aartjan TF Beekman)

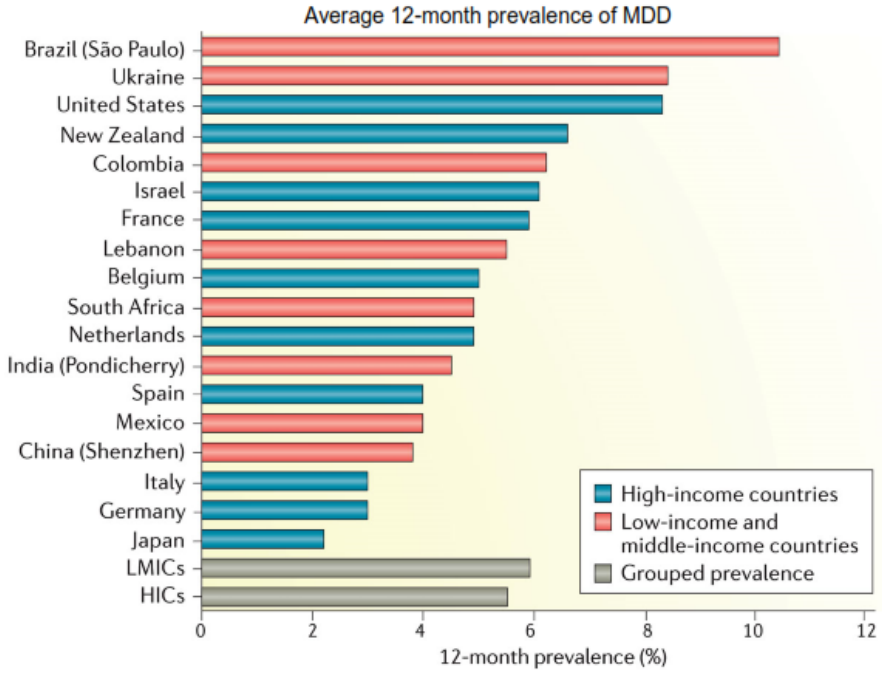
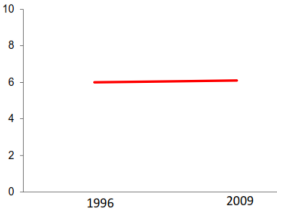
What are the suicide rates of males and females in the Netherlands?	Suicide number per 100000 in Netherlands Males are more likely to commit suicide 
What are important predictors for suicide rate?	Alcoholism is an important predictor for suicide - not socioeconomic status 

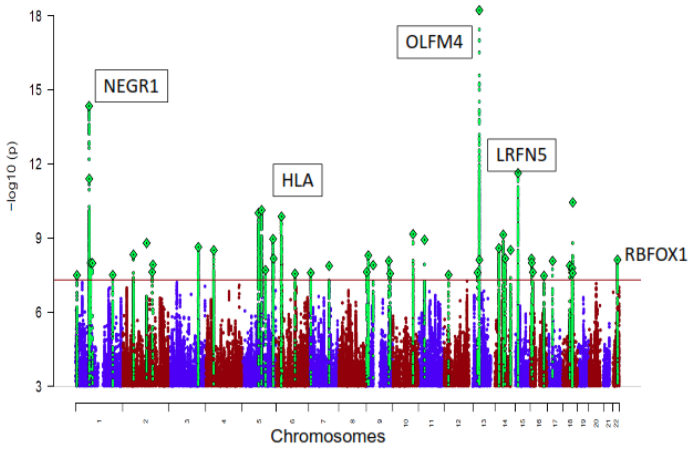
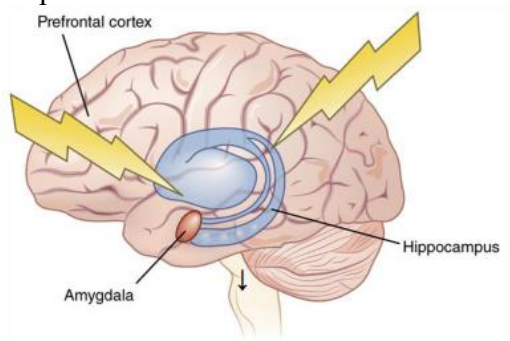
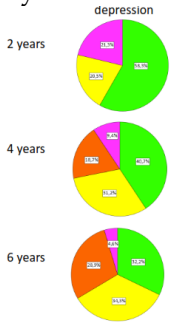
What is the main cause for early retirement today?	Causes for early retirement - Mental disorders have an enourmous economic impact 
What is the current state of affairs in the Netherlands regarding suice rates?	State of affairs Effective treatments Availability of treatment is very good in NL But • No effect prevalence psychopathology • Effects mental illness on public health unchanged
Why is evidence based prevention important?	Automobile accidents - Illustrates the potential of scientific research influence (evidence based prevention)

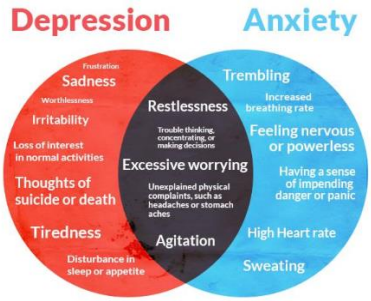
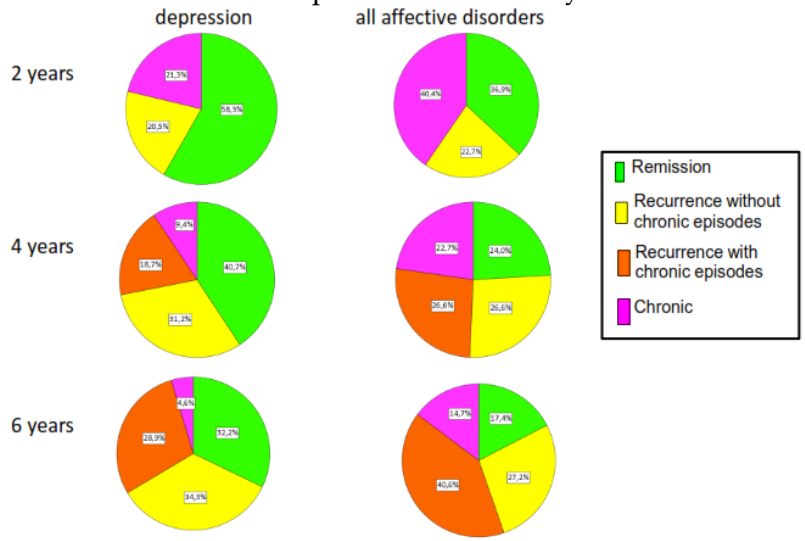
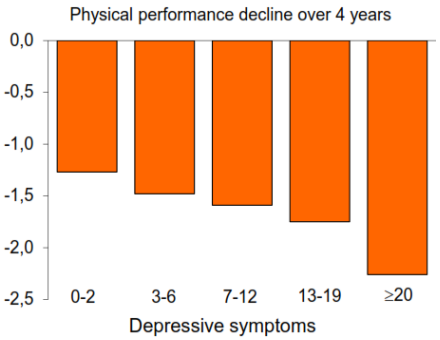
8d. Ins and outs of depression (Brenda W.J.H. Penninx)

Why is the prevalence of depression so high in young people compared to other diseases?	WHO disease burden Mental and behavioral disorders - Peak at 20-24 (means that young people are less prone to other diseases)  Depression takes second place in western society
How is depression diagnosed today?	What is depression? Over 5 symptoms, chronic & impact on daily life: • Sad/depressed mood • Little interest in doing things (anhedonia) • Increase or decrease in sleep • Increase or decrease in appetite/weight • Fatigue/no energy • Feeling of worthlessness • Concentration problem • Psychomotor retardation or agitation • Suicidal thoughts
Why is the impact of depression so big?	Impact of depression High prevalence - 6% of Dutch people in the previous year (2009) Chronicity Impact early in life Impact on functioning Interaction with somatic health
What determines	Prevalence estimate of depression - Depends on time frame, characteristic of population and instrument of measurement

prevalence estimate?	Time frame (Are you depressed? Have you been depressed in the last year, Have you been depressed in your life?)  Characteristic of population (sex, age, setting)  Men are prone to addiction/ADHD, women are more affected by depression/anxiety Measurement instrument Face to face report (more strict definition) vs self report instrument 

Is depression correlated with income?	Depression prevalence worldwide Not correlated with income 
Is there a depression epidemic today?	Depression epidemic? There is no change in depression prevalence in the Netherlands between 1996 and 2009 
If our daily life stress had increased in the last years and stress is correlated with depression, how come the rates of depression have remained stable over the	Importance of environmental factors Work stress - Increased Many other environmental factors have decreased 

last few decades?	
What is the heritability of depression?	Genetic vulnerability  Heritability - 37%
What changes depression causes in the brain?	Depression - Brain disorder  Structural - Decrease in hippocampus, amygdala, prefrontal cortex Connectivity - Increase of DMN, decrease of selience and central executive functions Functional activation: Striatum
Why is it important to follow depressive patients after they overcame the disease?	2 years after initial depression diagnosis - 58% remission 4 years - 40% remission 6 years - 32% remission 

What is the comorbidity percentage between depression and anxiety?	Comorbidity between depression and anxiety - 70% 
What are the remission rates when taking into account all affective disorders?	Remission levels with depression and anxiety  Only 17% after 6 years *With chronic episodes - More than two years*
What is the mean age of depression onset?	Impact early in life - Average age of onset of depression is 28 years
What is the relationship between depression and physical performance?	Impact on functioning  Physical performance decline over 4 years

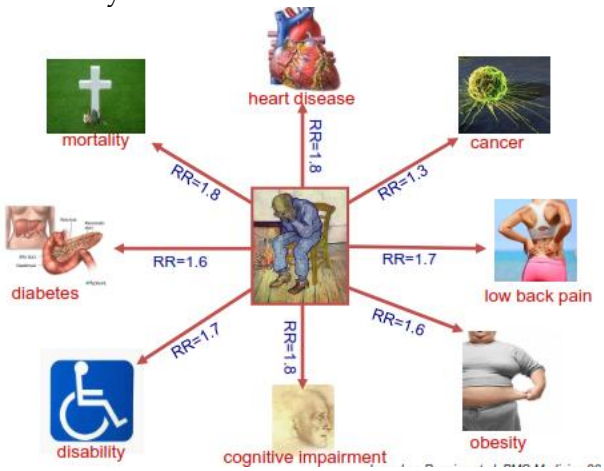
What is the economic impact of depression in work environments?

Absenteeism - People with depression lose 23 days per year less
Presenteism - People with depression lose 30 days per year less (in terms of productivity)

Which diseases are correlated with depression?

Depression is correlated with many diseases

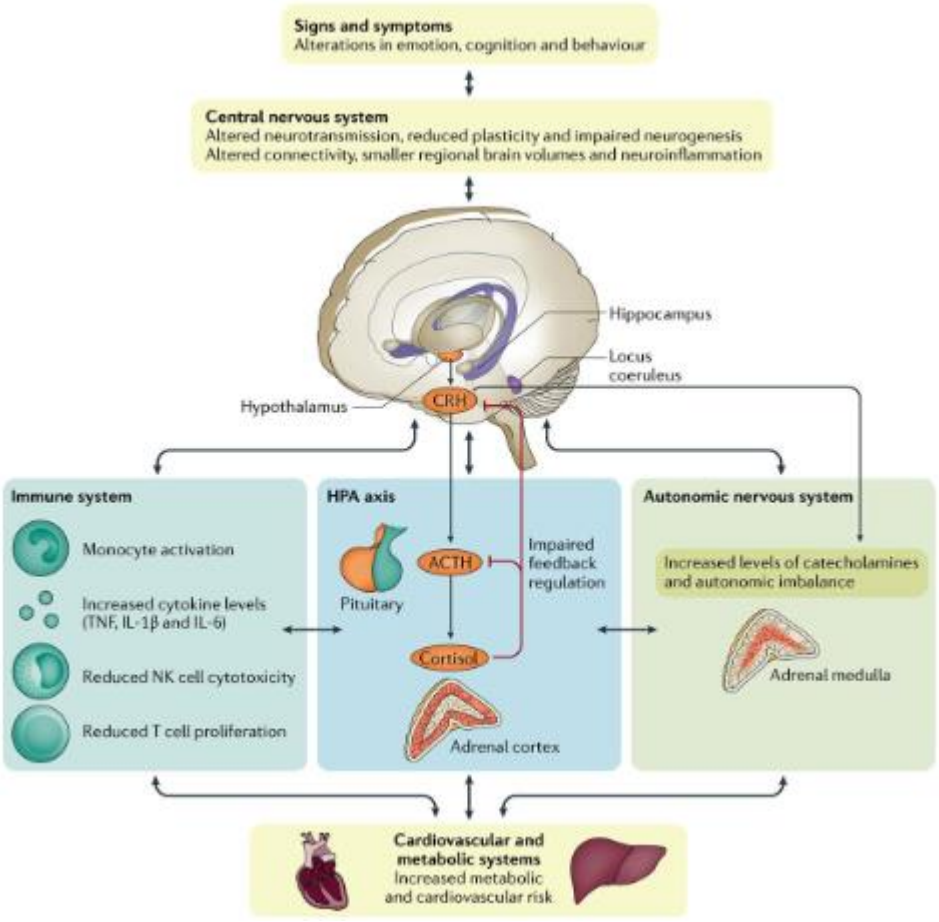
- Cardiovascular disease
- Obesity
- Cancer
- Diabetes
- Disability



What are main lifestyle differences between depressed and non-depressed people?

Life style between depressed people and healthy people

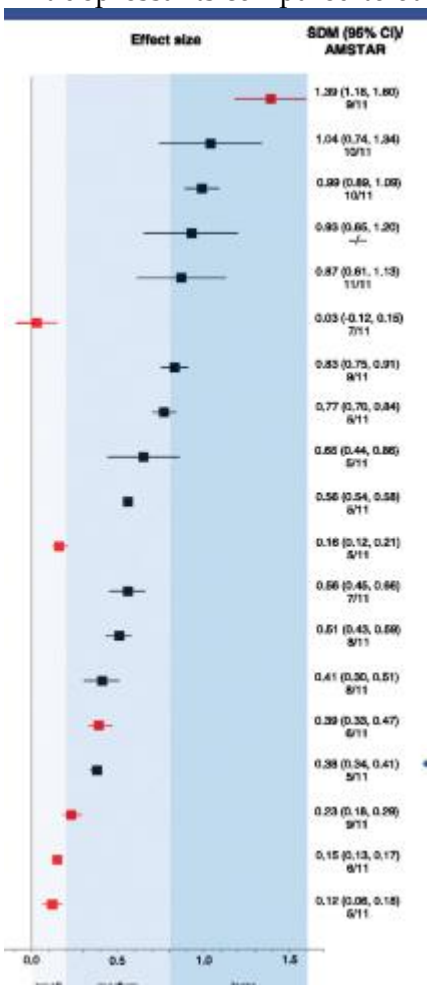
	Healthy controls n=524	Depressed patients n=1075	p
Physical inactivity	12.8%	21.1%	.001
Regular sports activity	57.5%	37.0%	.001
Alcohol dependence	1.4%	9.1%	<.001
Smoking - moderate	21.9%	27.8%	<.001
- heavy	4.1%	17.4%	
Body Mass Index	25.1	25.9	.01
Medication adherence	28.8%	40.4%	<.001

How does depression affect the body's stress system?	Depression affect biological stress system  Autonomic nervous system - Increased heart rate HPA axis - Hyperactive; Increase cortisol (increased metabolism and cardiovascular risk) Immune system - Chronic low grade inflammation
What is the average effect of placebo, antidepressants and psychotherapy for depression?	Placebo difference from antidepressant Increase in 20% response There is still an effect of antidepressants compared to placebo Efficacy of antidepressants increases with increasing depression severity Combination of antidepressants and psychotherapy is best - 50% of patients

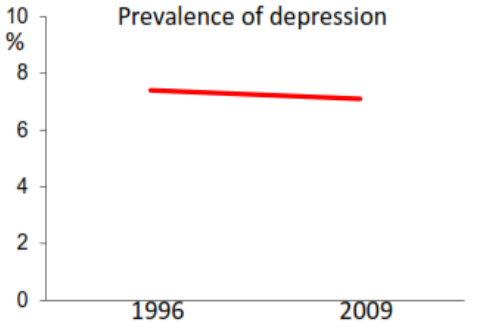
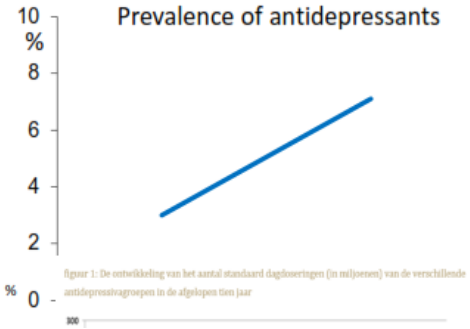
Facts	Bewijs
1. Yes, there is a placebo-effect	with placebo: ~20% response
2. In mild depression, antidepressants not very effective	
3. In moderate to severe depression, antidepressants work (on top of the placebo-effect)	Effect size~0.4
4. In moderate to severe depression, psychotherapy works (on top of the placebo-effect)	Effect size~0.35
5. The combi of antidepressants and psychotherapy is best	Hedges 'g=0.43
6. Efficacy of antidepressants increases with increasing depression severity	
7. There is large variation in the effectiveness of treatments	In ~50% there is no response

If medication has such a small effect compared to placebo, why is it still being used?

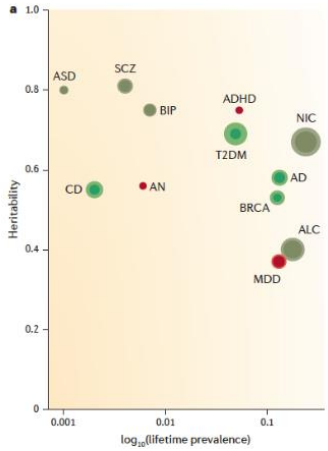
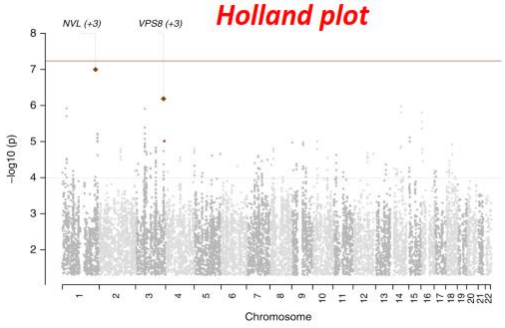
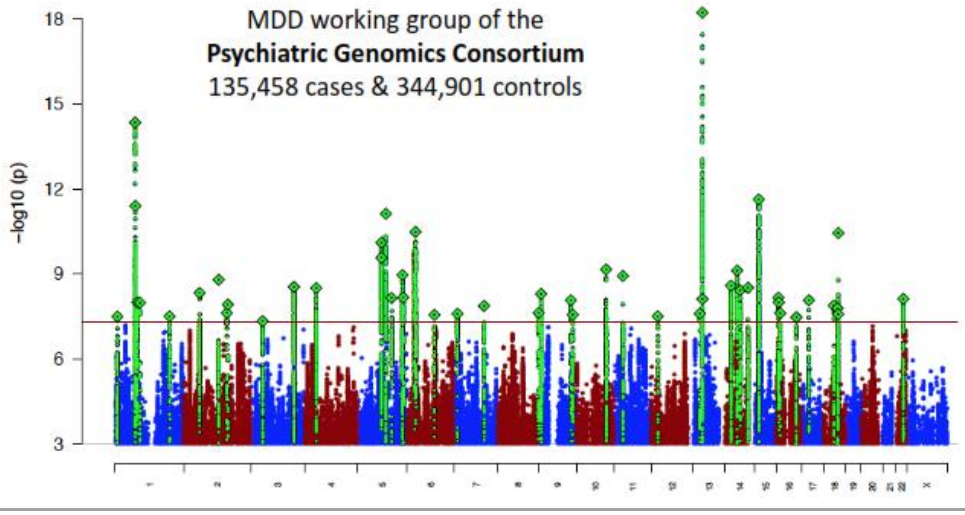
Antidepressants compared to other pharmacological treatments?

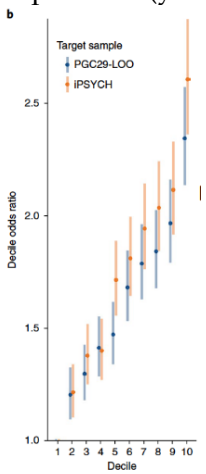
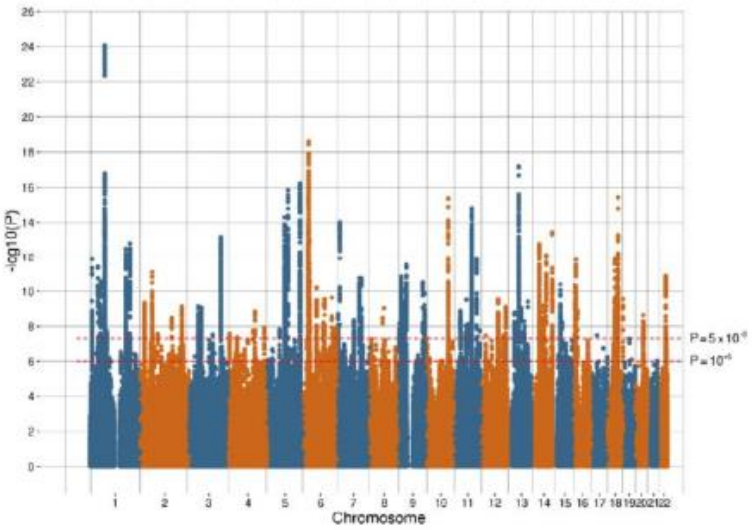


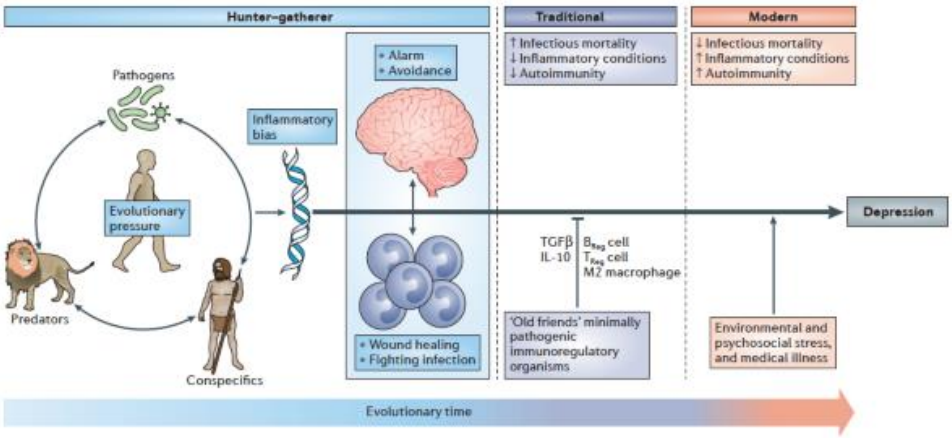
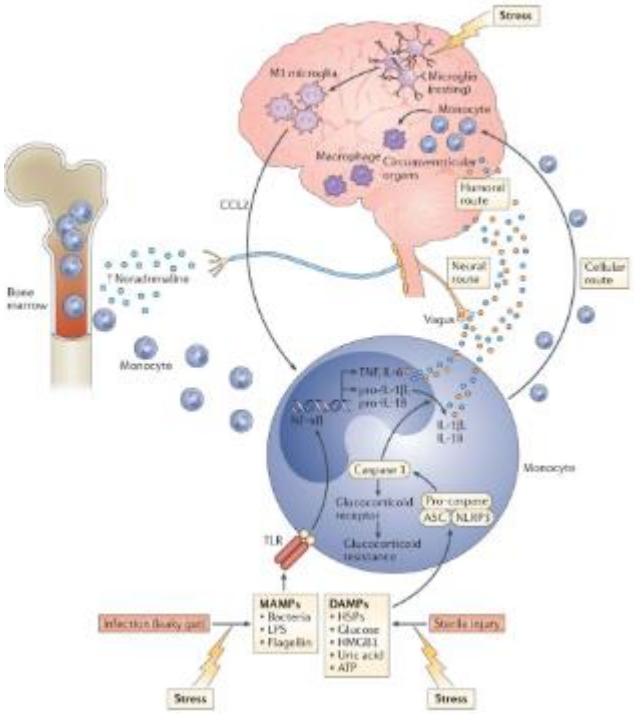
Medium effect - But is not the worst treatment option

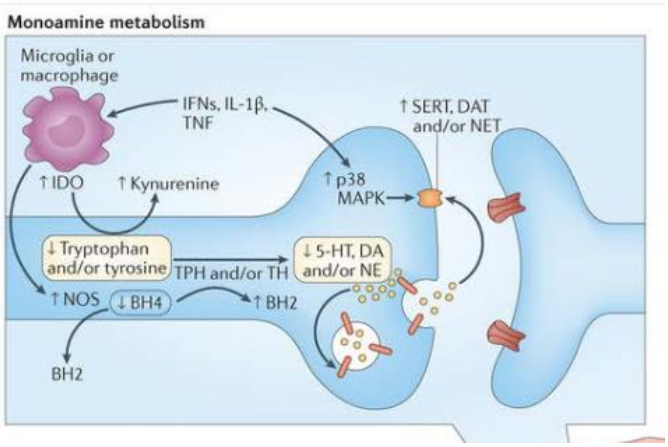
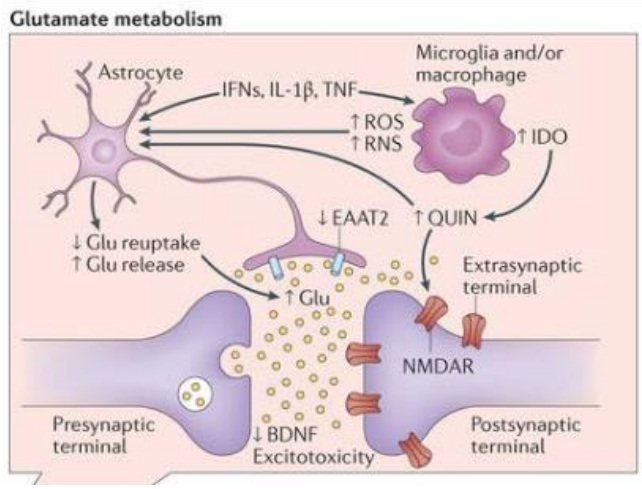
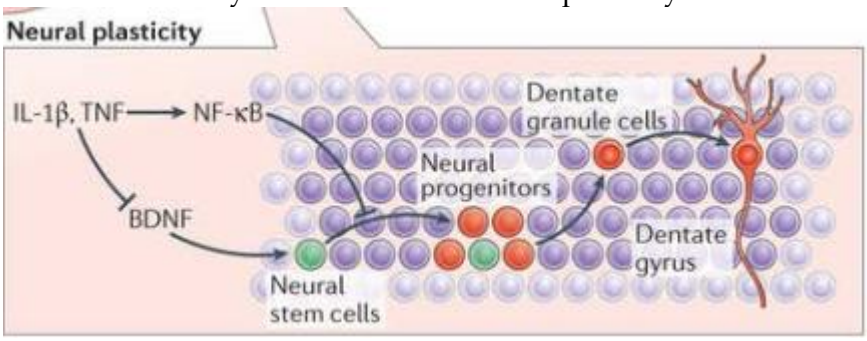
Why is the increase in antidepressant use not correlated with a decrease in depression rates?	Prevalence of depression - Stable Prevalence of antidepressants - Increases over time   • Prescribed does not mean that it is used • Antidepressants are not only used for depression • More and more chronic users • Efficacy of antidepressants is not great (especially over long term) • Adequacy of antidepressants: difference in efficacy and true effectiveness
What are some non-pharmacological options for depression treatment/	Alternative strategies • Mindfulness • Internet psychotherapy • Running therapy • Behavioral activation • Collaborative care • Transcranial stimulation • ECT • Deep brain stimulation
How can depression be prevented at a population level?	Prevention Attention to the offspring of people with depression E-health courses - Reduction of risk of developing actual full depression Relapse prevention cognitive therapy

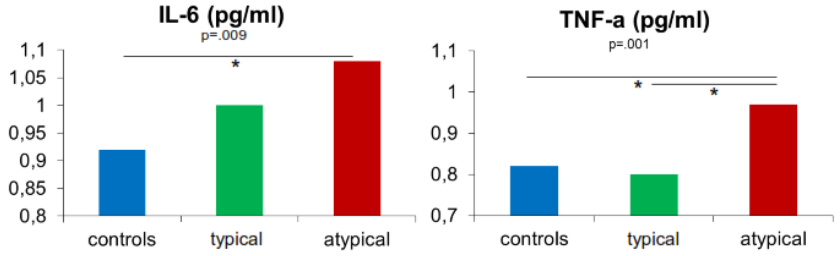
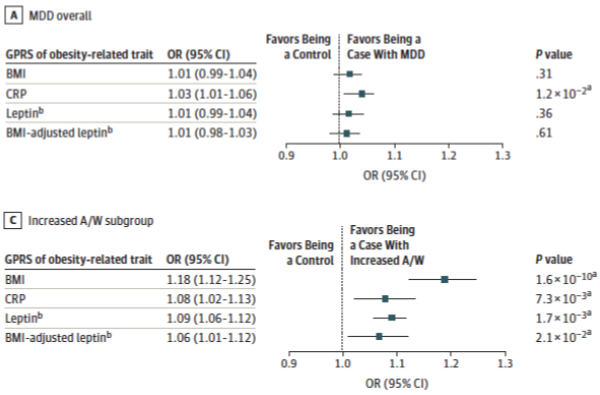
9a. Biological pathways of MDD (Yuri Milaneschi)

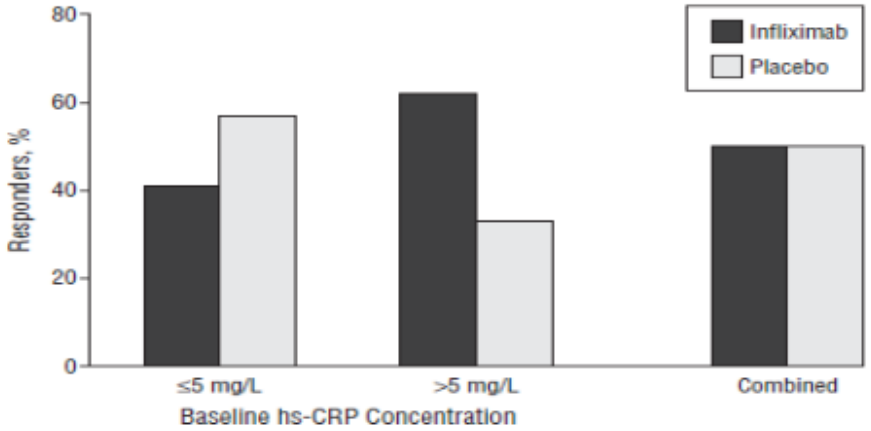
What is the average heritability of MDD?	Genetics of Major Depressive Disorder  **h² ~ 0.4** Heritability - 0.4
Why did the first GWAS for depression not find any hits?	No hits in GWAS ***Holland plot***  Underpowered sample size - Each locus has a very small effect size Clinical heterogeneity - Maybe there are different phenotypes that we call 'depression'
How many risk variants are associated with depression?	GWAS meta-analysis 2018 

	44 risk variants associated with depression Mostly expressed in the brain (gtexportal.org/home) Pathway analysis: Neuronal pathway and cytokine production/inflammation
What is a polygenic score?	Polygenic score Score of each genetic variant for a specific trait The higher the polygenic score, the higher the chance of developing depression (y-axis - another sample)  Conclusion - MDD is highly polygenic
What is the SNP heritability for MDD?	SNP-heritability - proportion of phenotype captured by all SNPs Heritability of SNPs - 0.09
Why are tools like Biorxiv important for research today?	Biorxiv - Submission of data before publishing  Way to collect data more quickly - 250000 patients and 500000 controls

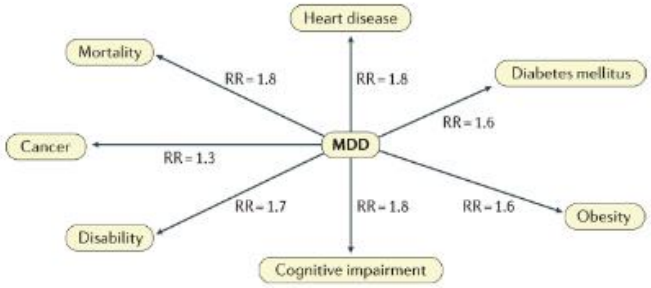
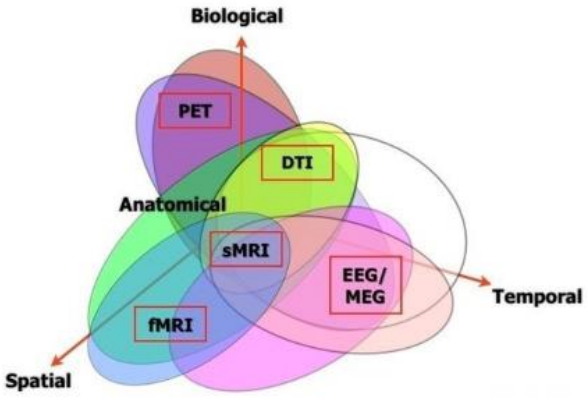
What is a evolutionary hypothesis for the association between inflammation and depression?	Inflammation and MDD  Mismatch between our hardwired inflammatory response and current standards of living - Nowadays it is triggered by other stimulus (psychosocial -> chronical influences) Depression behavior - Sickness related (social withdraw, reduction of activity)
What is the cycle of inflammation and depression?	Immune System  Inflammasome - Capture signal from inflammation and transfers it to the brain Cycle - Inflammation triggers depression (inflammasome), depression triggers inflammation (activation of HPA axis)

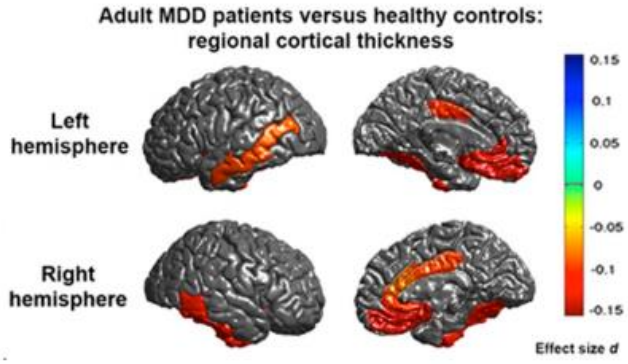
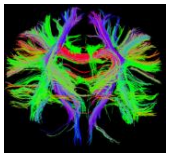
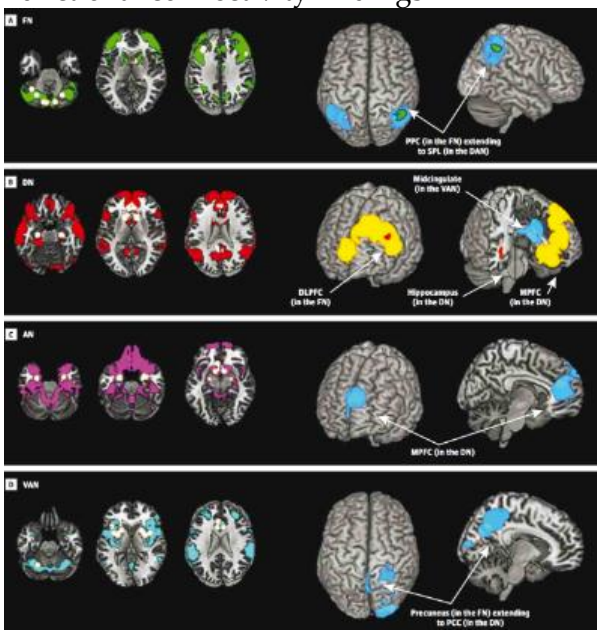
What is the evidence that depression is related to inflammation?	Evidence that depression may be related with inflammation Autoimmune diseases + early infections increase risk of mood disorders The use of inflammatory drugs induce depression Inflammation markers increase in depression
What are the hypothesis that explain the relationship between depression and inflammation?	Hypothesis Inflammation may interfere with the metabolism of monoamines - Lack of tryptophan  Inflammation may increase availability of glutamate  Inflammation may interfere with neuronal plasticity 

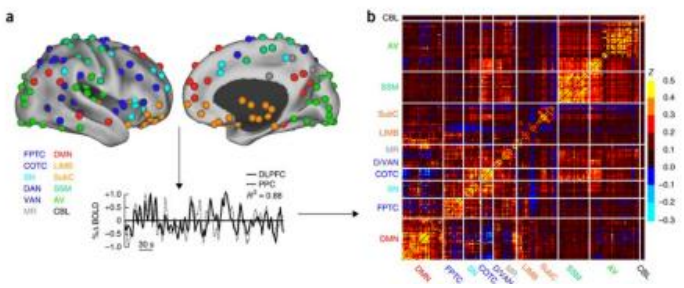
What is the problem with MDD's heterogeneity?	The heterogeneity of MDD is: Hindering research - Inconsistent finding Hindering treatment - Small effect sizes
What are the two probable subtypes for depression/	Depression subtypes "Atypical depression" (immunometabolic) - Inflammation plays an important role Symptoms: Hyperfagia, weight gain, hypersomnia, fatigue, leaden paralysis Typical depression - Inflammation does not play an important role (correlates better with hyperactivity of HPA-axis)
What suggests that there may be three depression subtypes?	Data-driven symptom classes  Classification in three major subgroups - Moderate, sereve typical, severe atypical
What is the major link between typical and atypical depression?	Link between atypical symptoms and inflammatory pathways Appetite symptoms - During depressive episodes, weight and appetite either increased or decreased
What may be the benefit for researchers to consider different depression subtypes?	Polygenic risk scores  The strength of the association between depression and obesity related genetic variance increases when you analyze a subgroup of patients

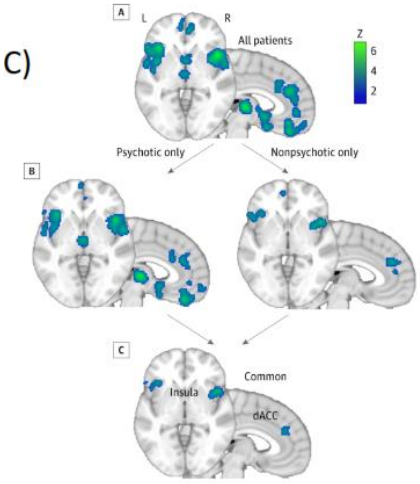
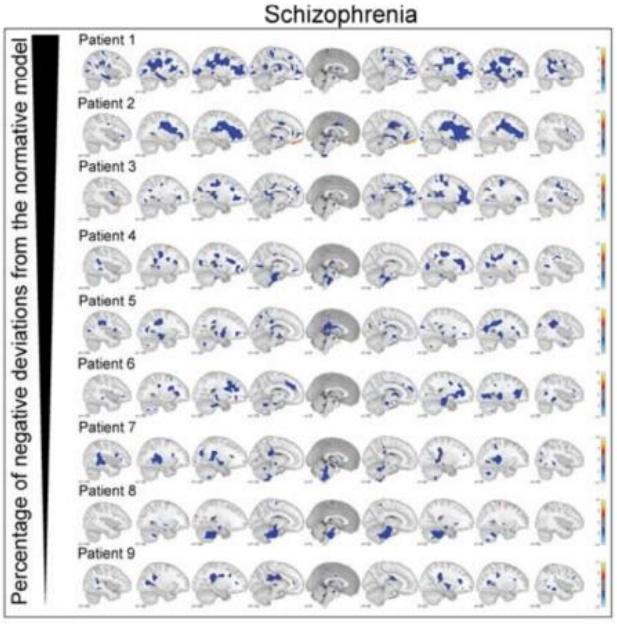
	PhD study Inflammatory pathways play a large role in depressive patients that present hyperfagia Pattern of hyperfagia or hypofagia is stable over different depressive episodes  The significance of new pathways was only discovered when anaylizing a subgroup of patients
What is the clinical application for the establishment of different depression phenotypes?	Clinical applications Stratification of patients - Creation of separate and specific treatments for different subtypes of depression Difference in initial inflammation levels - Difference in efficacy of treatments

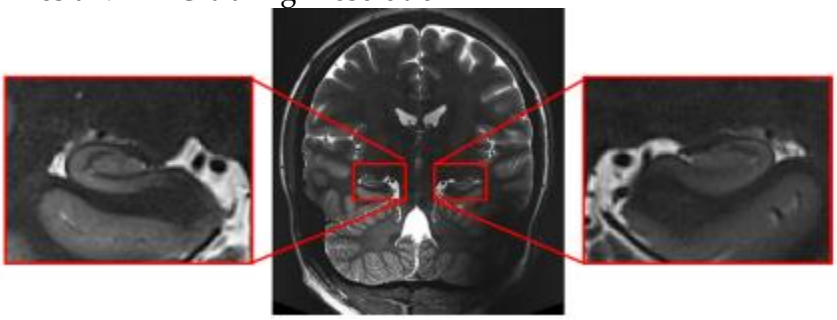
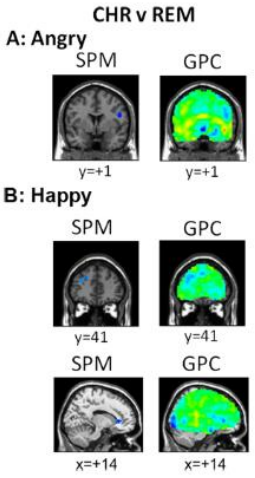
9b. Neuroimaging in Depression (Laura Nawijn)

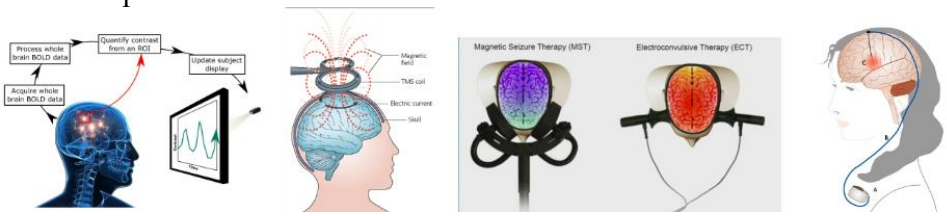
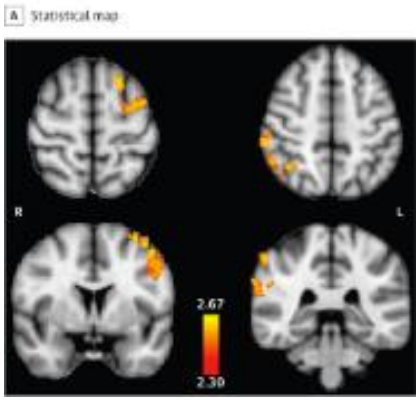
What is the prevalence of depression?	Prevalence of depression: 20% during lifetime 227 combinations of symptoms Subtypes: Anxious distress, melancholic features, atypical features
Why is depression such a heterogeneous disease?	Heterogeneity in clinical features Severity and functional impairment Age of onset Number and duration of episodes Treatment resistance
What conditions are associated with depression?	Comorbidity High psychiatric Comorbidity with anxiety (50%), drug abuse (15%) 
What is the environmental vulnerability aspects for depression?	Environmental vulnerability Stress: Trauma, daily-stress Social: Support network Lifestyle: Physical exercise, nutrition, sleep
What is the main problem with imaging studies for depression?	Neuroimaging of MDD 

	Replication problems - Heterogeneity in disease and method (small sample sizes and small effect sizes) -> creation of consortia (ENIGMA)
What are the characteristics of the brain structure of depressed patients?	Brain structure - MRI findings Altered brain volume - Decrease in OFC, ACC, PCC, insula, temporal lobes, hippocampus (small effect size); Increase in amygdala volume  DTI  Decrease in fractional anisotropic (decrease in overall connectivity) Increase in mean diffusivity and fractional diffusivity (structural disconnectivity)
What are functional connectivity changes in depressed patients?	Functional connectivity findings 

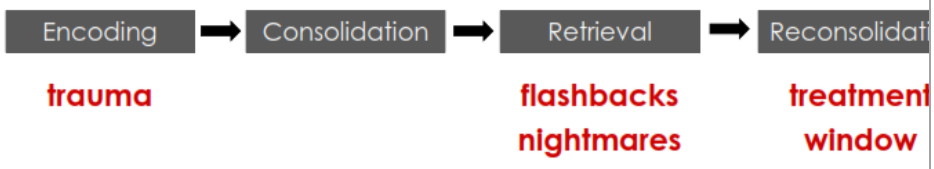
	Decrease in : • frontoparietal network • affective network • ventral attention network Increase in default mode network
What did task based fMRI not get significant differences between depressed and non-depressed people?	Task based fMRI - No difference between depressed patients and controls Different tasks are done differently by different groups - yield different results PFC seems to be over reactive to negative stimuli and underreactive to positive stimuli
What are the elements of lack of convergence in task-based fMRI?	Meta-analysis of task based fMRI - No difference between MDD and controls (lack of spatial convergence) Lack of convergence in meta-analysis Different inclusion criteria Heterogeneity of experiments - Faces only vs all experiments Study quality (small sample size) ROI (specific brain regions - inflates chance of finding spurious significant results) vs whole brain
What are two promising avenues for MDD imaging?	Promising avenues in MDD Imaging Tackling heterogeneity and comorbidity: Large sample sizes (patients with MDD, bipolar, schizophrenia); Clinical features (medication, severity of disorder) Mega-analysis (raw data from every single experiment) - Machine learning
What is the problem with the anhedonic/anxiety subtypes for depression?	Subtyping Anhedonia - Fronto striata and orbitofrontal connectivity impaired Anxiety - Limbic  **Posterior studies failed to replicate this finding**

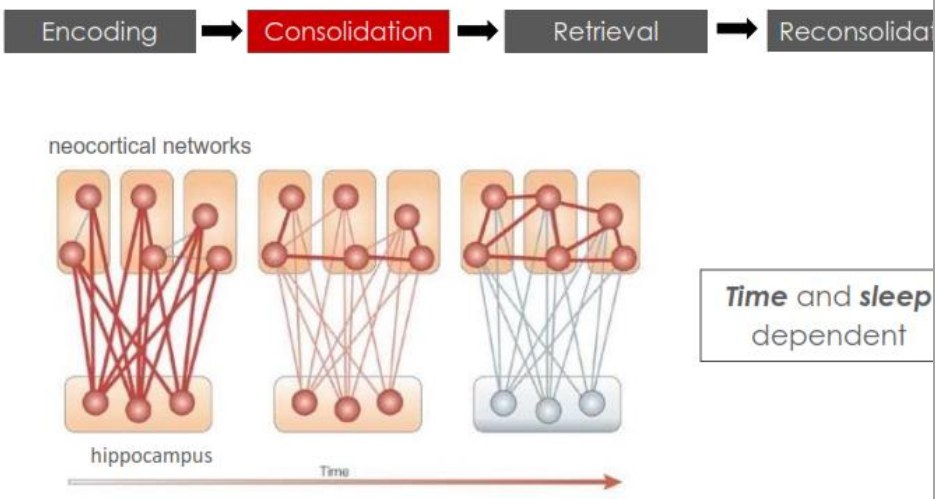
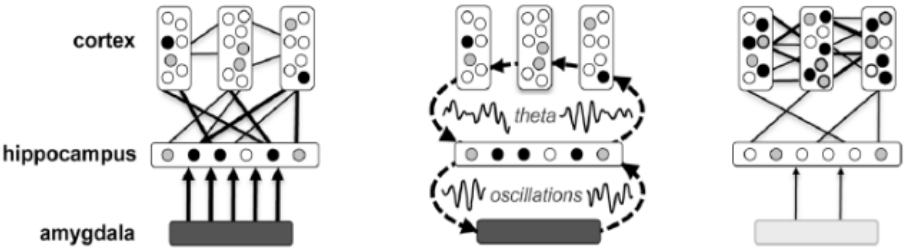
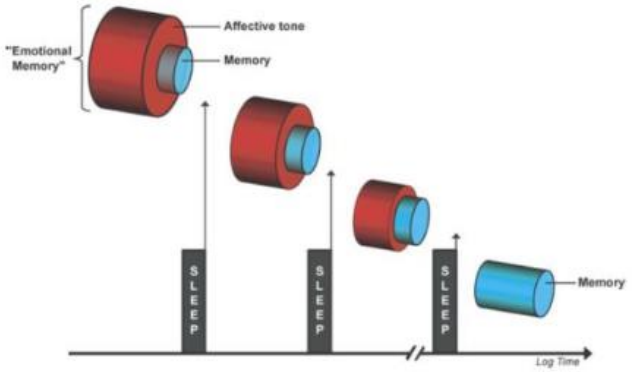
What are the common aspects of brain functional between all affective disorders?	Cross-disorder meta-analysis  Schizophrenia, bipolar, depression, OCD, anxiety Common: Decreased gray matter volume and insula (associated with decreased executive function) Internalizing (depression and anxiety): Decrease hippocampus and amygdala volume P-factor - Common genetic underpinnings for these diseases
Why is it problematic to take averages in achieving the goal of a personalized treatment?	There is no average patient  Case-control studies may disguise inter individual differences All patients show different deviations from an average scan “Idea of the average patient is a non-informative construct” - Mean is informative for groups, not for individuals

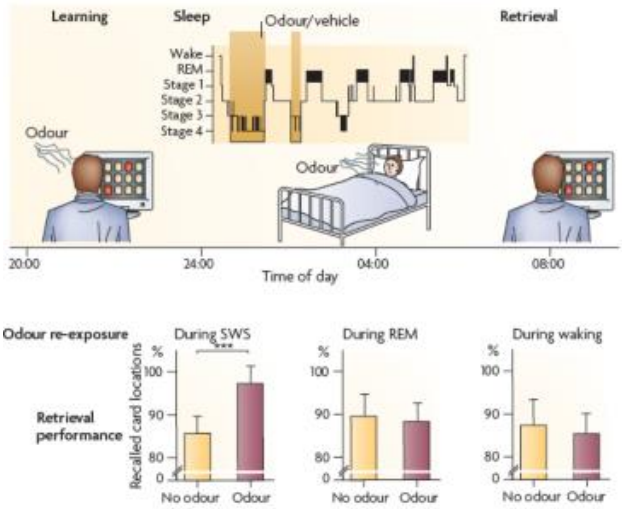
Why 7-Tesla MRI may help us discover new things?	7 Tesla MRI - Ultra-high resolution  May yield new findings that were not observable before
What is the 'age' difference of depressed people compared to healthy controls?	Brain aging in MDD Structural brain features can be used to estimate chronological age People with depression show a “year older” brain than controls
Why neuroimaging may be useful to develop new treatments for depression?	Usefulness of Neuroimaging in MDD 30% of patients do not respond Treatment response takes long Recurrence is high Personalized medicine Machine learning: Prediction of treatment response, relapse, chronicity
How well does machine learn predict chronicity in MDD?	Predicting chronicity fMRI to predict 2-year MDD chronic course  Emotional faces: 73% accuracy Clinical features: 69% accuracy Other fMRIs (resting state, executive task, structural MRI) did not predict above chance

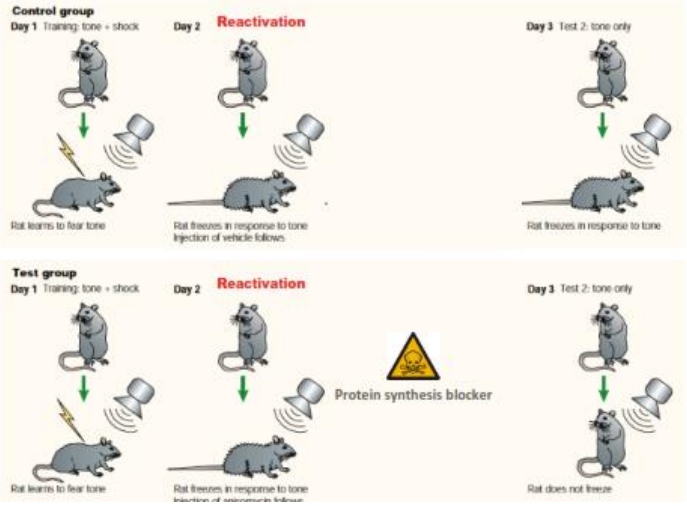
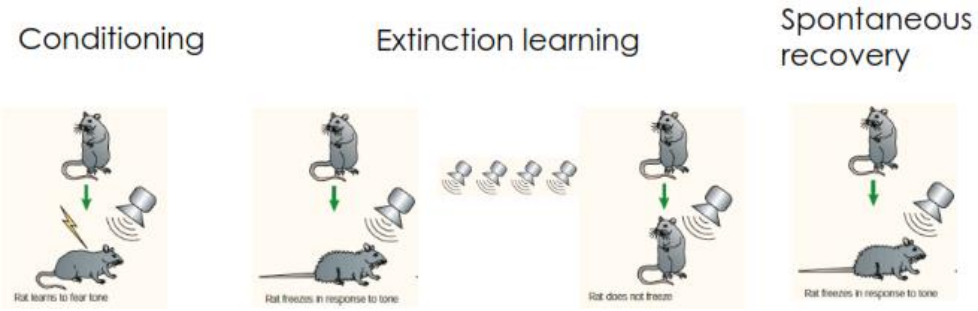
How well does machine learning predict treatment response?	Predicting treatment response Imaging data - 82% accuracy Better when using multiple data types - Clincal data + Biology Publication bias, lack of replication in most findings
What are current options for therapeutic neuromodulation ?	Therapeutic neuromodulation Neurofeedback Non-invasive brain stimulation Electroconvulsive therapy/Magnetic seizure therapy Deep brain stimulation 
What is the efficacy of brain stimulation in treating depression?	Brain stimulation efficacy High variation - Most patients prefer active treatment over fake treatment  Decrease amygdala activation during faces task Increase of task performance and activation of the dorsolateral prefrontal cortex
Why machine learn may help patients even before we discover the underpinning mechanisms for depression?	Is depression a brain disease? Genetic findings suggests that yes How it works? We don't know. ○ Imaging techniques are still crude ○ With machine learning, we don't need to understand the mechanism to have an accurate prediction

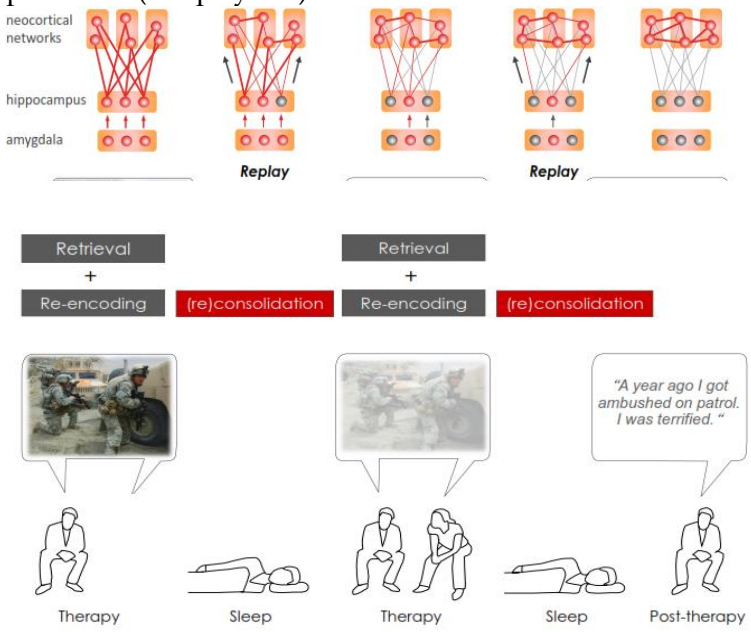
9c. Sleep and traumatic memory in PTSD (Hein van Marle)

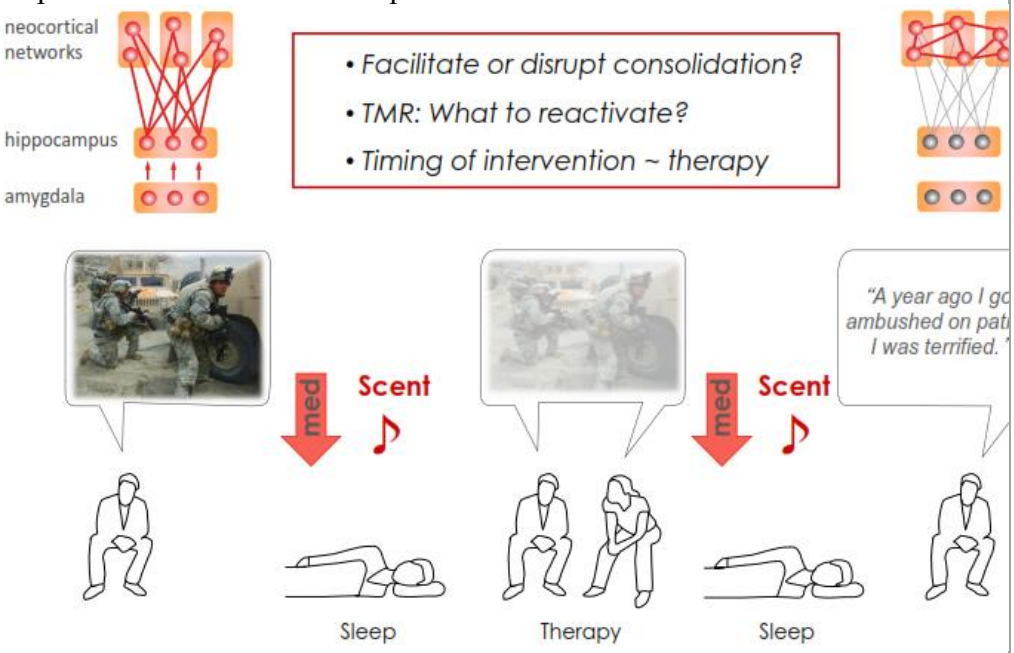
What is the DSM-5 criteria for the diagnosis of PTSD?	Case study - Justin (American Veteran)  DSM-5 criteria: • Exposure to stressor • Intrusions (memories, flashbacks) • Avoidance • Negative alteration in cognition and mood • Alterations in arousal and reactivity • Lasts more than a month • Significant distress/dysfunction • Some patients develop dissociative subtype
Describe the process of PTSD as a memory disorder.	PTSD as a memory disorder Encoding - When a traumatic event occurs Consolidation -> Integration of initial labile memory into long-term storage Retrieval - Flashbacks/nightmares Reconsolidation - treatment window -> possibility to modify memory  Traumatic memory trace is at the basis of disorder
What happens when memories are consolidated in our brain?	System level consolidation theory When you acquire a memory, it is represented by connections between neocortical models and hippocampus Consolidation - Disconnected at a hippocampal level

	 Memory becomes abstract and biographical
When we have an emotional memory, which brain area is most active?	Emotional memory - More memorable than neutral memories (theta oscillations)  Amygdala - Works to alert the brain that there is a threat Cortisol and norepinephrine act at the level of the amygdala
What is a proposed hypothesis for the function of sleep and emotion?	Emotional memory and sleep One of the main functions of sleep is emotional memor consolidation  ***Decoupling** of **emotion** and **memory*** Blue - What happened Red - What you felt

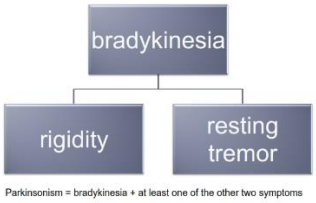
Describe the experiment that discovered the mechanism of neuronal replay.	Mechanism behind consolidation Neuronal replay - Memories are repeated during sleep Mice walking in a triangular maze - Place cells in hippocampus activate at particular points When the mice slept - Same pattern was observed in the hippocampus Different mechanism are necessary for neuronal replay
Describe the experiment that used smell during sleep. What was its main finding?	Target memory reactivating to boost memory  Visual task associated with smell When patients were sleeping, smell was presented again (during deep sleep) Memory was improved in smell patients compared with controls (not REM sleep or wake)
Why is sound advantageous and problematic as a targeted memory during sleep?	Memory stabilization with targeted deactivation during human slow-wave sleep Sound: More options than smell, more likely to wake patients up
What is a hypothesis for the difference between neutral memories and	Hypothesis of lack of consolidation Neutral memory - No amygdala • Abstract, verbally accessible • Voluntary retrieval Traumatic memory - Amygdala involved • Linked to sensory, emotional and autonomic markers

traumatic memories?	• Not verbally accessible • No autobiographical context • Involuntary retrieval
What was the main finding of Nader 2000?	Memory reconsolidation - When you reactivate a memory, it changes  Nader 2000 - Rat freezes due to fear conditioning Anisomycin - Blocks protein synthesis in the amygdala -> fear is extinguished
What happens at a neuronal level during the process of extinction learning?	Extinction learning - Analogous to exposure therapy  Tone is presented multiple times without negative stimulus - Second memory is formed, the first memory is still present Patients can have relapses when in the same context
What are possible strategies to change a memory during the reconsolidation window?	Reconsolidation window - 10 minutes and 6 hours. Eliminate memory trace - Not possible in humans ECT has similar effects Disrupt old memory trace - Propranolol, inhibits norepinephrine (diminishes negative memory coding) Update old memory trace - When timed in the reconsolidation window -> update and extinguish fear memory Strengthen old memory trace - Cortisol

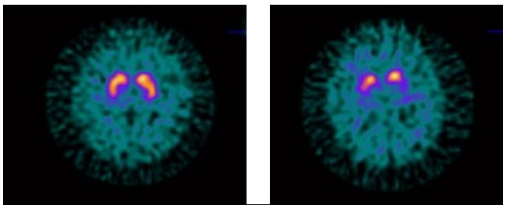
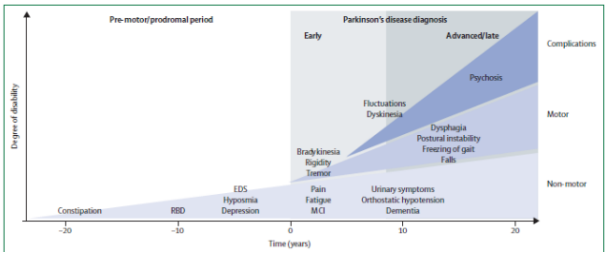
What is the proposed mechanism behind the effectiveness of psychotherapy for PTSD treatment?	PTSD treatment Exposure therapy - Reactive traumatic memory, re-encode fearful memory in a positive context Memory gets more neutral overtime - Multiple reconsolidation processes (sleep cycles) 
What types of pharmacological interventions can be used for PTSD? What is their intended effect and application in the clinic?	Medication treatment - SSRI Not linked to memory consolidation/reconsolidation Treatment augmentation - Therapy and medication together Enhancing memory drug (D-cycloserine) - Given to treatment after therapy session MDMA is not an established drug for PTSD
Why is sleep deprivation not a definitive solution for patients who just suffered a traumatic experience?	Immediate intervention after trauma Sleep deprivation - Only postpones the problem, since the patient has to sleep at some point

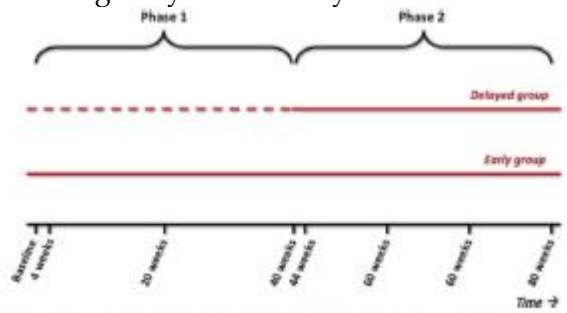
How can target memory/sleep be used as an experimental treatment for PTSD?	Experimental treatment - Sleep  Music and smell during therapy - Exposure to the same music or smell during sleep -> promotes faster reconsolidation of the memory

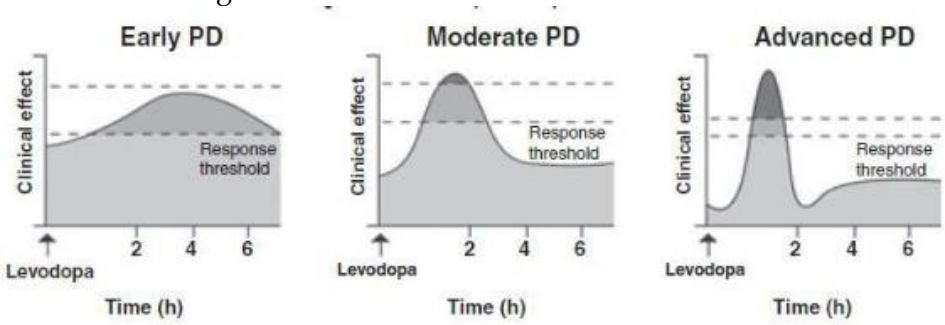
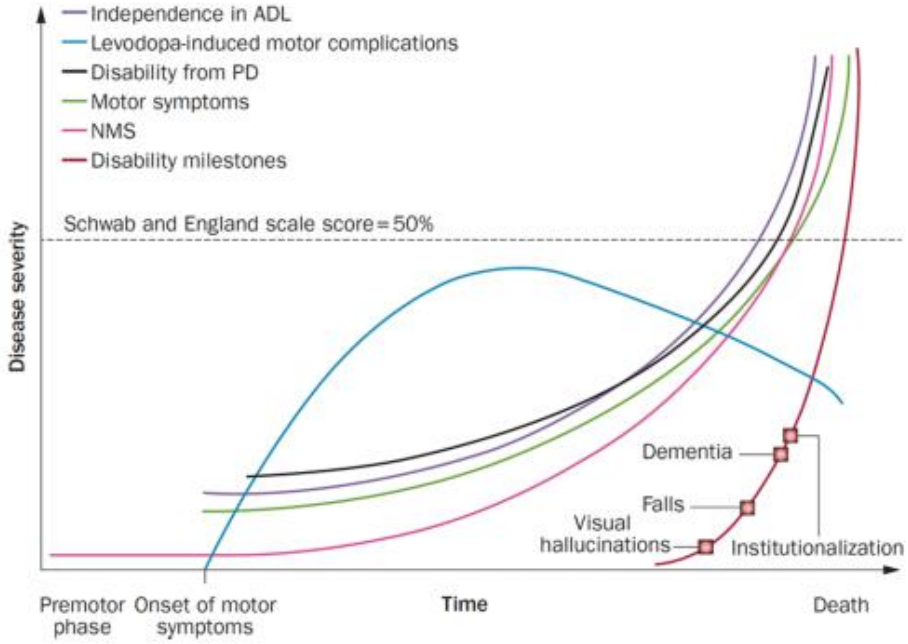
10a. Movement Disorders: Parkinson's Disease

What is the prevalence of Parkinson's Disease?	Epidemiology of Parkinson's Disease Prevalence of 1/800 1% of people over 65 years Mean age of onset = 70 years Man > Women (60-40)
Why are we in a 'Parkinson Pandemic'?	Parkinson Pandemic Increase in lifespan of the population - Increase in incidence of Parkinson's
What are potential risk /protective factors for PD?	Risk factors Aging - Increases risk Herbicides/pesticides - Increases risk Coffee - May be protective Nicotine effect - May be protective Head trauma - *Unclear evidence*
Why do PD patients usually go to the clinic in the first place?	Clues for the initial diagnosis of PD The patient often does not know they have Parkinson - They present muscle cramps, loss of smell (hyposnya), forgetfulness, dizzyness
What are the main signs of Parkinson's disease?	Signs of Parkinson Hypomimia - Unable to express emotions  Parkisonism = Bradykinesia + rigidity or resting tremor  **Bradykinesia** - Decrement in amplitude and frequency of movement **Rigidity** - Velocity independent resistence to passive movement Lead pipe resistance **Resting tremor** - 4-6 hz in resting limb

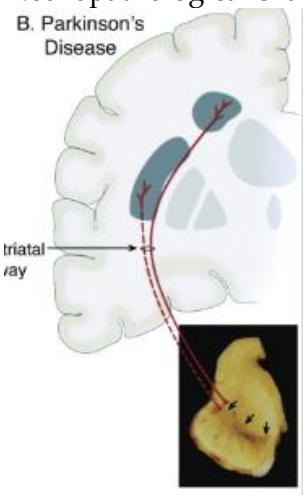
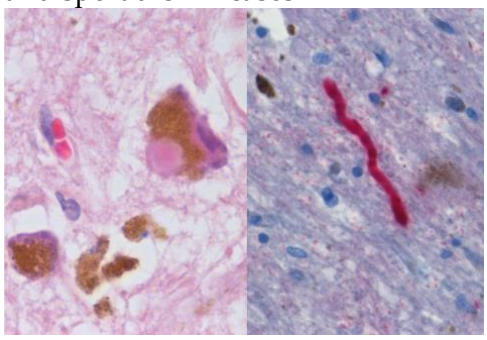
	25% of patients do not have resting tremor Essential tremor difference - Happens during movement
What is the general diagnostic criteria for PD?	Diagnostic criteria Clinically established • Two supportive criteira, no red flags Clinically probable
What are the supportive criteria for PD diagnosis?	Supportive criteria ◦ Responsible to levodopa - Effects within 30 minutes ◦ Hyposmya - Loss of smell (substantia nigra loss degenerates olfactory bulb) ◦ Resting tremor
What are the exclusion criteria for PD diagnosis?	• Exclusion criteria ◦ Cerebellar abnormalities ◦ Downward vertical gaze palsy - Suggests PSP, another type of parkisonism ◦ Frontotemporal dementia ◦ Lower limb parkisonism ◦ Drug induced parkisonism ◦ Cortical sensory loss ◦ Normal presynaptic dopaminergic imaging
What are red flags for PD diagnosis?	• Red flags ◦ Rapid progression of gait impairment ◦ Complete absence of motor symptom progression (more than 5 years) ◦ Early bulbar dysfunction ◦ Inspiratory respiratory dysfunction ◦ Severe autonomic failure early in disease ◦ Disproportionate anterocollis ◦ Symmetric parkisonism - Typical PD is lateralized
Why MRI is useful for the diagnosis of PD?	MRI - Used to determine if the symptoms is caused by other diseases Parkinson cannot be diagnosed by MRI
What is DAT-SPECT?	DAT-SPECT - Analyse dopaminergic neurons Tracer binds dopamine transporters in the presynaptic neurons Proxy for the integrity of the dopaminergic system

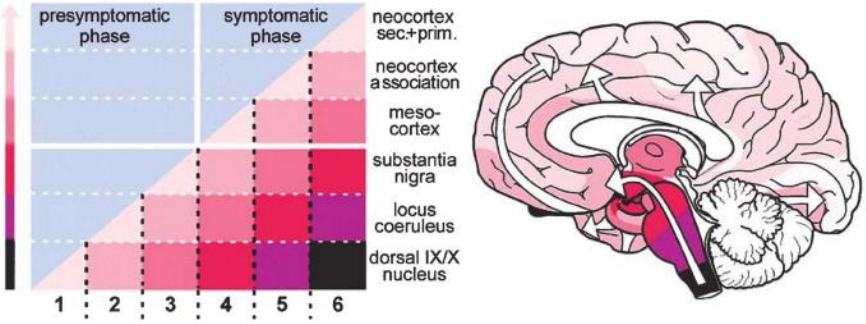
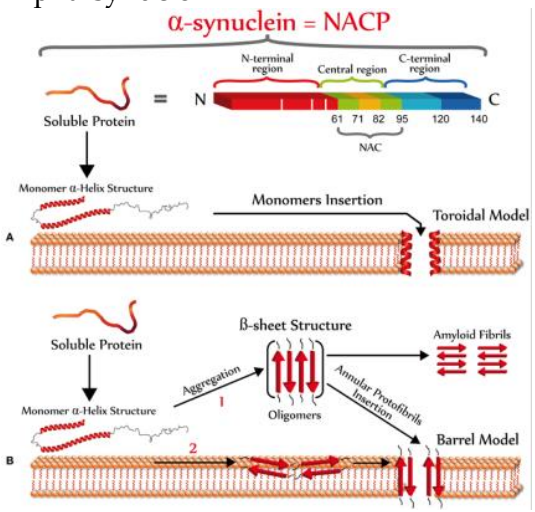
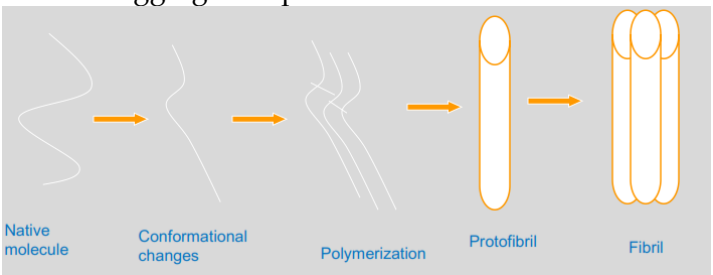
	 Red - Caudate nucleus/putamen PD - No dopamine in caudate (notice assymetry)
What other diseases have Parkinson-like symptoms?	Differential diagnosis Drug induced Vascular parkisonism - Exclusively motor Atypical parkisonism MSA - Multiple system atrophy PSP - Progressive supranuclear palsy DLB - Dementia with Lewy Bodies CBD - Cortical basal degeneration
Which brain systems do PD affect?	PD affects all systems - Not only dopamine Acethylcholine, serotonin, endocannabinoid
What are the non-motor symptoms for PD?	Non-motor symptoms Depression - 80% of patients Anxiety Cognitive disturbances/dementia Psychosis/visual hallucination Impulsive control disorder - Only medicated patients (15-35%) Sleep disturbance - Insomnia, excessive daytime sleepiness, REM-sleep behavior disorder, restless legs Autonomic disfunction - orthostatic hypotension, urine incontinence, impotence Other - Smell impairment, pain, tiredness
What is the prevalence of non-motor symptoms in PD patients?	Almost all PD patients present non-motor symptoms ▫ Prevalence: 60-97% 

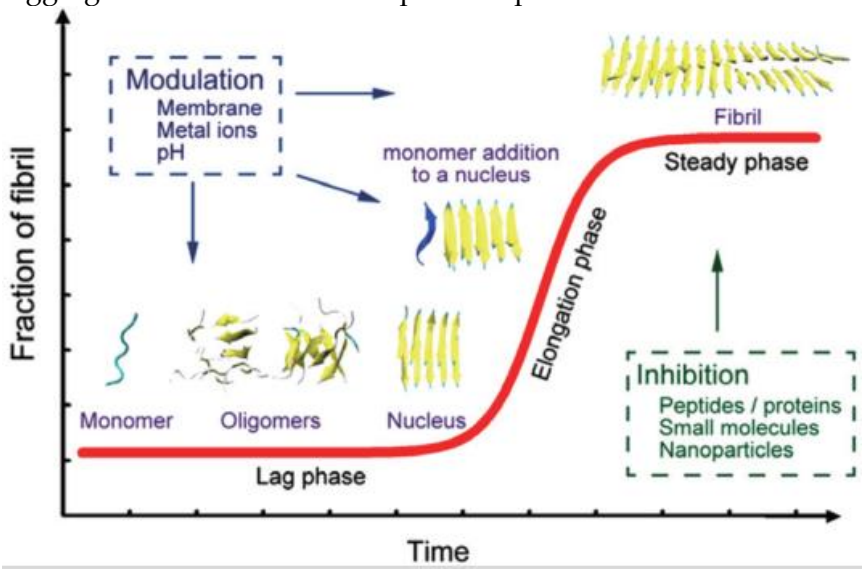
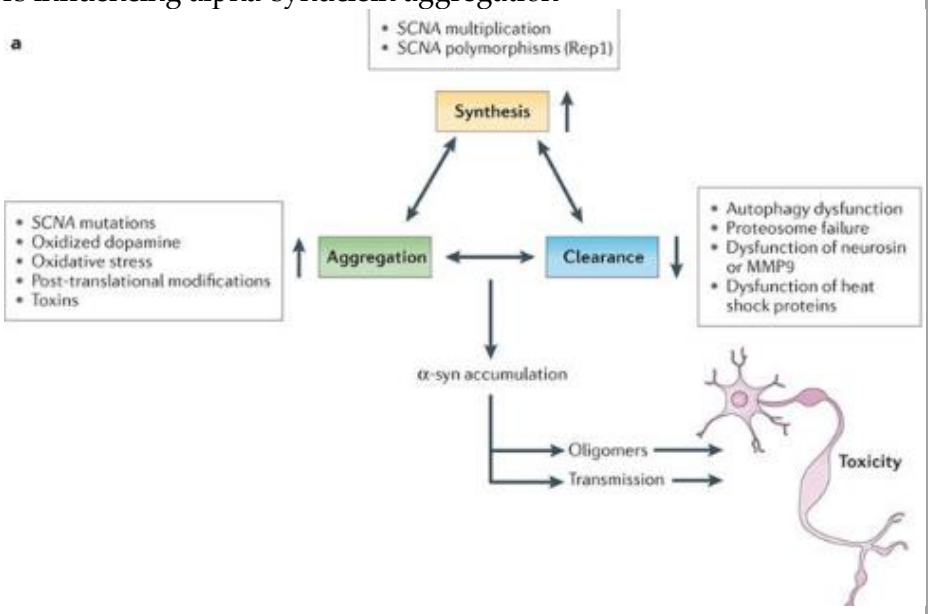
What are the main forms of treatment for PD?	Treatments - Are symptomatic, not disease modifying Dopaminergic - MAO B inhibitor (enzyme that destroys dopamine), dopamine agonist, levodopa Advanced therapy - Continuous infusion of levodopa (subcutaneous, intrajejunal), deep brain stimulation in cortical thalamical
What is the main side effects of levodopa in the treatment of PD?	Side effects Impulsive control disorder - Higher chance when using dopamine agonist Inconstipation
What is the honeymoon phase of PD treatment? How long does it last?	Honeymoon phase - Drugs work quite well in the first 5 to 10 years End of dose effect - Treatment stops being effective
What is the main research question of the LEAP study?	LEAP study - Starting early or later may be more beneficial in the long run  Fig. 1 Delayed-start design. Studies with a delayed-start design investigate two agents: active treatment (*solid line*) and controlled treatment (*dashed line*). In phase 1, patients are randomised to either active (levodopa) or controlled (placebo) treatment. In phase 2, both groups receive First stage: Levodopa or placebo Second stage: Levodopa
Describe the problem that traditional PD treatment has related to therapy fluctuation?	Therapy fluctuation 

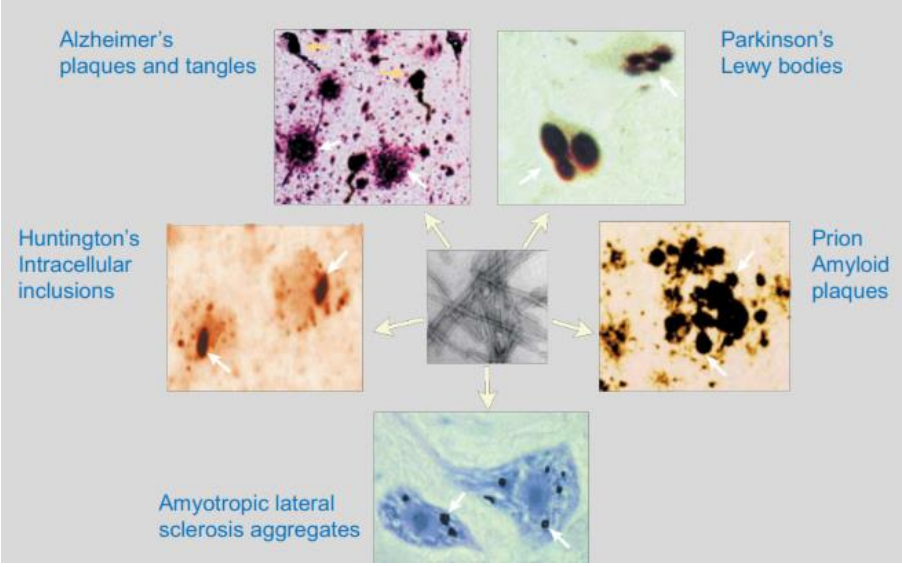
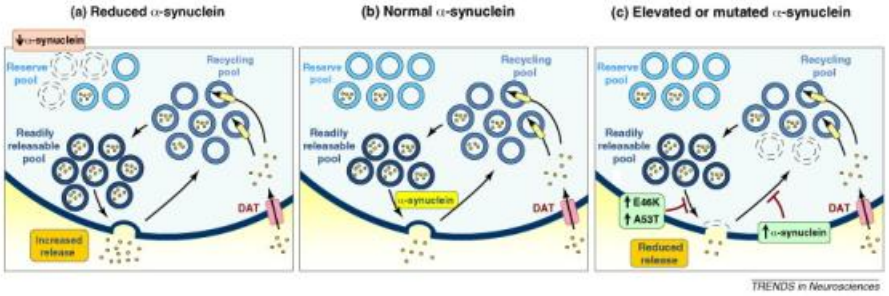
	Pill form - High increase when taking the drug, rapid decrease (On-off fluctuations) Gets worse in later stages - Patients needs more levodopa, clinical effect time gets shorter 
Describe the main disabilities milestones of PD.	Disability milestones  Levodopa effects is an inverted u-shape - Dopaminergic neurons are degenerated and the drug cannot act as well

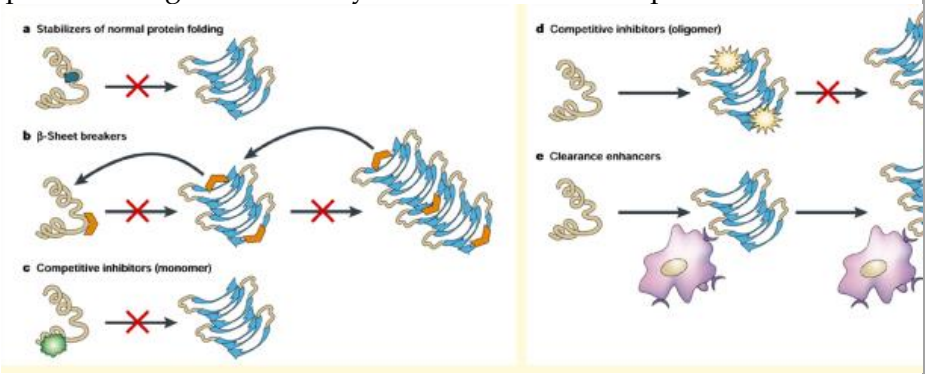
10b. Pathogenesis of movement disorders: Protein misfolding and protein aggregation (Micha Wilhelmus)

What is 'sporadic PD'?	Parkinson's disease Progressive neurodegenerative disorder 95% sporadic (we have no idea why)
What are the neuropathological characteristics of PD?	Neuropathological characteristics  Degeneration of dopaminergic neurons Formation of Lewy Bodies
What is the main component of Lewy Bodies?	Alpha-synuclein is the major component of Lewy Bodies in both familial and sporadic PD cases 
What are pieces of evidence for the role of alpha-synuclein in PD?	Evidence for the relationship between alpha-synuclein and PD Point mutations in alpha-synuclein gene cause rare forms of PD Transfection of human alpha-synuclein genes induce morphological and clinical symptoms of PD in animal models

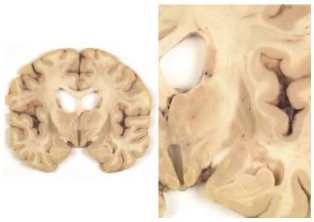
Describe Braak stages for Parkinson disease.	Braak stages  First stage - Smell becomes impaired - damages to olfactory bulb End stage - Spread throughout all over brain, except cerebellum
Describe the molecular characteristics of alpha-synuclein. What is the proposed mechanism for its cytotoxicity?	Alpha-synuclein  16 kD highly conserved Monomer, hydrophilic, alpha coil Binds to membranes in alpha structure Binds to other alpha-synuclein monomers in beta sheet - Creating amyloid fibrils Possibility - They form holes in the membrane, causing cell death
What happens to alpha-synuclein's solubility when it aggregates?	Putative aggregation process  More aggregations - decrease solubility Toxic variant is still unknown

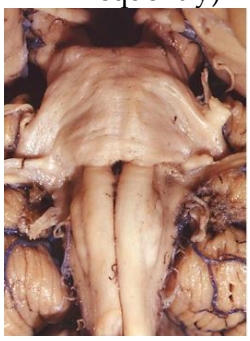
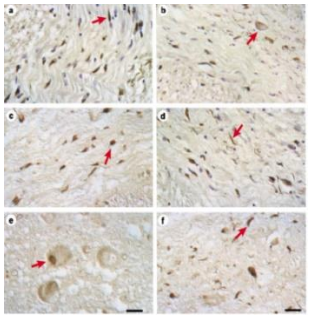
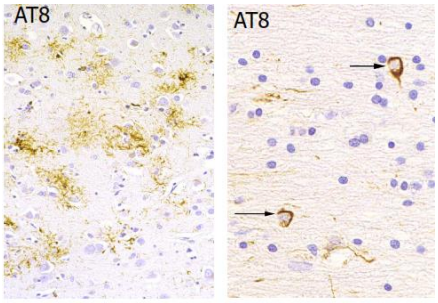
What physical aspects of the cell influence aggregation of alpha-synuclein?	Aggregation is a nucleation dependent process  Depends on concentration and modulation of monomer (ions, alter pH)
What are the three main factors that influence alpha-synuclein aggregation?	Factors influencing alpha-synuclein aggregation  Clearance - Seems to be dependent on aging
Which CNS diseases are alpha-synucleopathies ?	Alpha-synucleopathies PD Dementia Multiple system atrophy Neurodegeneration with brain iron Immunoreactive lesions

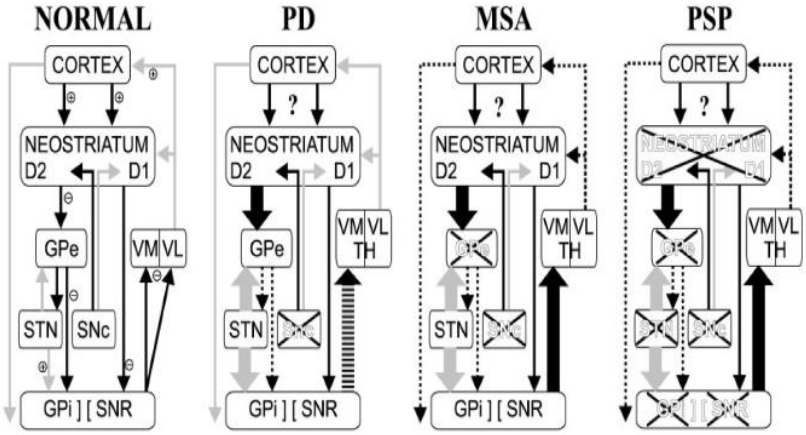
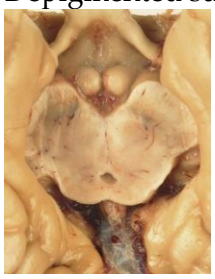
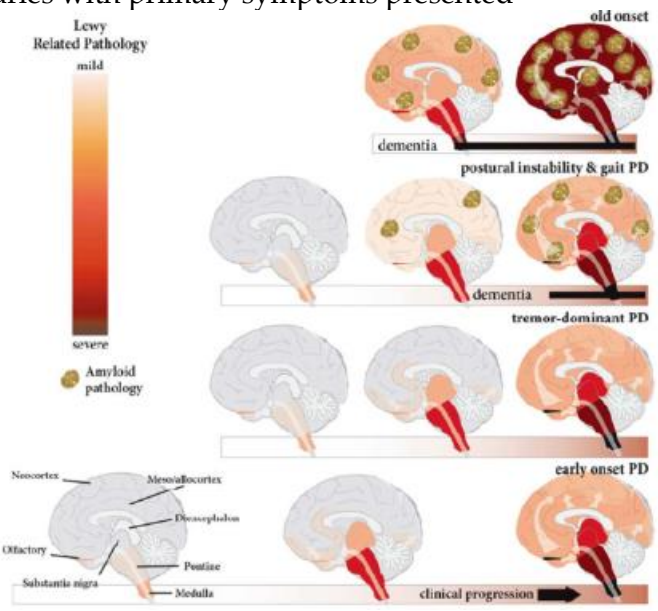
What are five CNS diseases related to protein aggregation?	Is protein aggregation unique for PD? Alzheimer's disease - Plaques and tangles (nobody knows the function of amyloid); there are many version (not only AB1-40, AB1-42) Examples of diseases caused by protein aggregation: • Alzheimer's • Parkinson's • Huntington's • Prion Disease • Amyotropic lateral sclerosis (ALS) 
What are intrinsically disordered proteins?	Intrinsically disordered proteins (IDP) Lack of rigid 3D structure under physiological conditions Probable reason: Flexibility of interactions with different substrates under different conditions Hypothesis: These diseases are caused not only protein misfolding, but also protein misindification and missignaling
What is the neuronal effect of alpha-synuclein defects?	Disturbed phospholipid membrane binding  Decreased vesicle budding

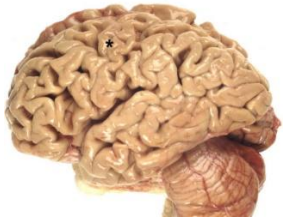
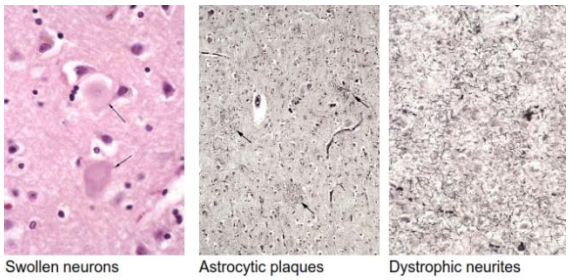
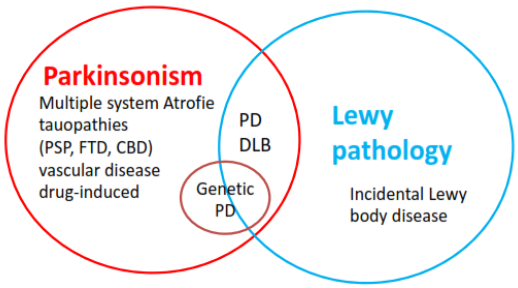
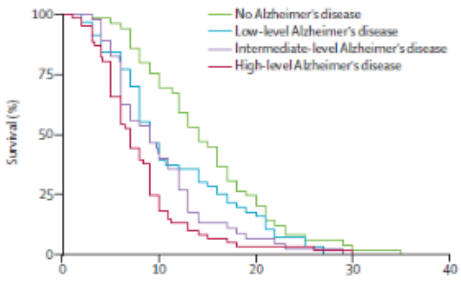
What are possible strategies to deal with Intrinsically Disordered Protein diseases?	Therapeutic strategies - Currently not one of these is implemented  E.g. Beta-sheet breakers, amyloid inhibitors (possible protective mechanism of nicotine)

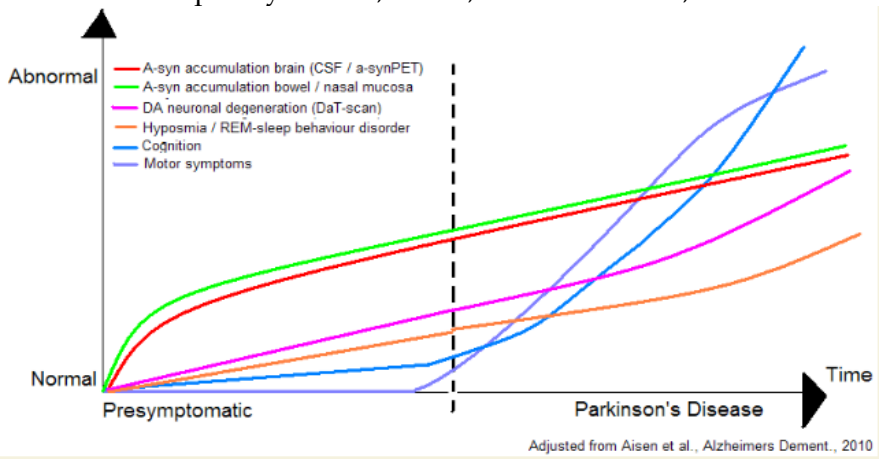
10c. Parkinson's disease: clinical heterogeneity, differential diagnosis and biomarkers (van de Berg)

When were Lewy bodies discovered? And when was alpha-synuclein discovered?	Lewy bodies - Discovered in 1912 Alpha-synuclein - Discovered in 1997
What are eight conditions that mimic Parkinson's symptoms? What is their main difference from idiopathic PD?	Diseases that mimic Parkinson (and their differences) PD = Idiopathic Parkinson's Disease - Typical symptoms, unknown cause **Essential tremor** - Different amplitude of tremor, less progressive **Progressive supranuclear palsy** - Tauopathy (different areas from Alzheimer's Disease); patients tend to fall (affects balance regions of the brain) **Vascular Parkinsonism** - Symptoms depend on the affected brain region **Multiple System Atrophy** - Facial problem, more symetrical, do not respond well to levodopa **Drug induced Parkinsonism** - Propanolol **Incidental Lewy Body disease** - Due to normal aging (lesser concentration than PD) **Inherited Lewy Body disease** - Mutations of alpha-synuclein gene are very rare but it is always causal. E.g. LAC2/Glucoseroxidase (50% of population in the Netherlands) **Dementia with Lewy body** - Clinical symptoms are memory, personality change
What are the neuroanatomical differences between MSA and Parkinson's	**Multiple System Atrophy** • Shrinked putamen (striatonigral degeneration) 

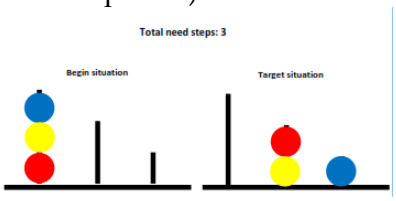
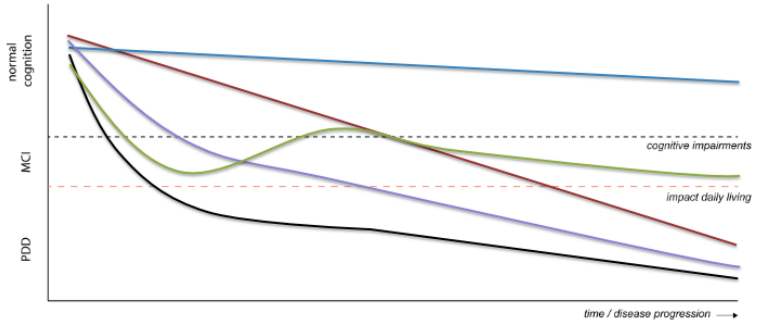
	• Olivopontocerebellar atrophy (problems with balance - patients fall frequently)  • Glial inclusions in oligodendrocytes in MSA 
If you wanted to differentiate PD and PSP, which test could you do?	Progressive supranuclear palsy - Neurofibrilary tangles in motor cortex (tau) 'Spider-like' staining - **Hyper**phosphorylated tau (high accumulation in the brain, low accumulation in the CSF)   Tufted Astrocytes Coiled bodies (white matter)

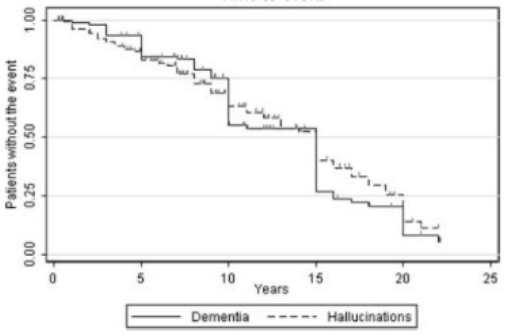
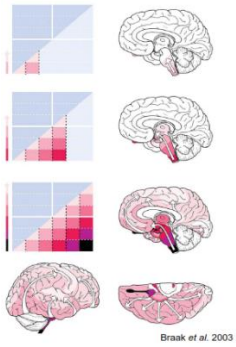
Describe in great anatomical detail how PD, MSA and PSP differ from a normal brain.	Model of PD vs other parkisonisms 
What is the difference between PD patients and patients with DLB?	Dementia with Lewy Bodies Depigmented substantia nigra in DLB  AD pathology is frequently present 30% of DLB cases have vascular abnormalities
Describe the four Braak stages (including their names) in PD.	Braak stages Varies with primary symptoms presented 

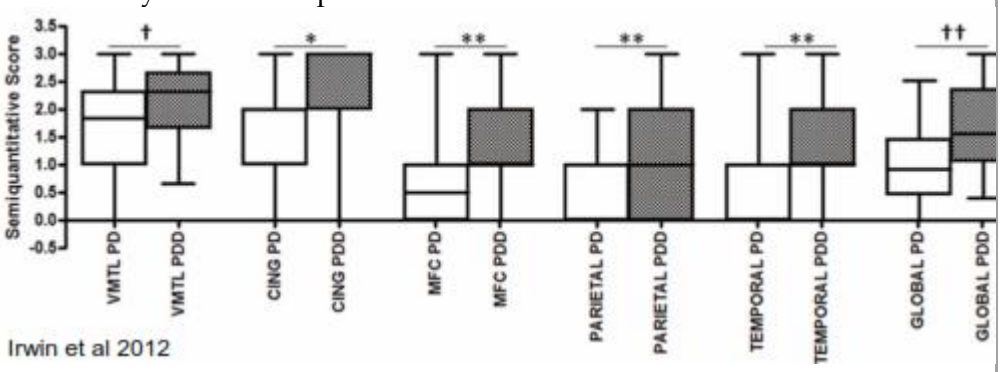
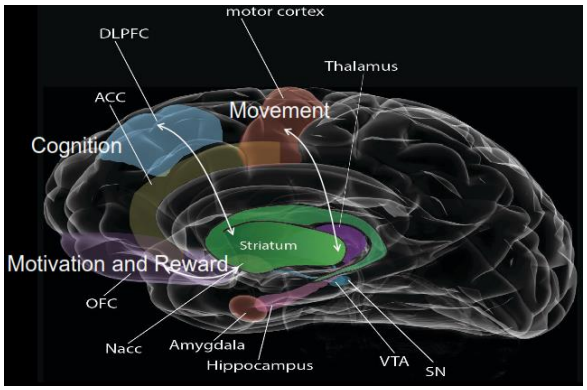
How is corticobasal degeneration defined anatomically?	Corticobasal degeneration - Atrophy of post-central gyrus Dilation of ventricular system   Swolen neurons - Tauopathy
Describe how parkinsonisms overlap with Lewy body pathology.	Parkisonism in common in many disorders  Parkinsonism - No Lewy body Lewy pathology - No motor symptoms
What is Lewy body disease correlated with in PD patients?	Lewy body disease is associated with longer disease duration, dementia at death  More AD pathology - Shorter disease duration

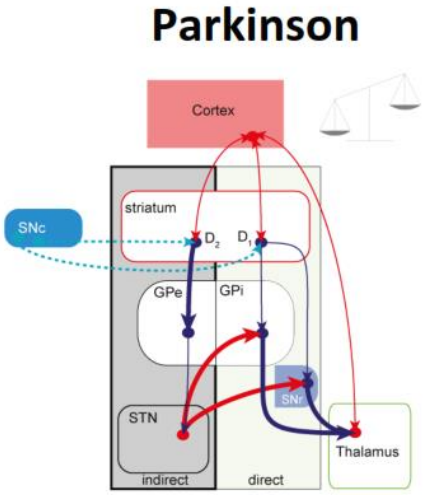
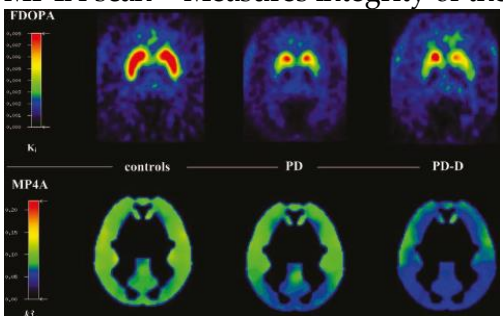
What happens with soluble and truncated alpha-synuclein in the CSF of PD patients?	Quantification of Lewy body concentration: Soluble • Total alpha-synuclein - Does not change • Phosphorylated alpha-synuclein - Increased in CSF of PD patients Aggregates/Truncated alpha-synuclein • Not detectable in controls • Present in Lewy body diseases 70 antibodies - Differentiate all alpha-synucleopathies with a 98% accuracy
What should we expect for the future of diagnosis of PD via biomarkers?	Conclusion - Many biomarkers are need to get an accurate diagonostic tool Candidates: Alpha-synuclein, Gcase, AD biomarkers, neurofilament 

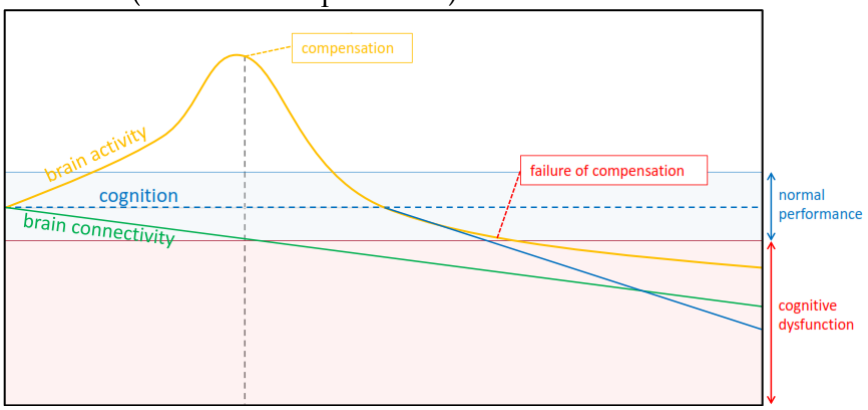
11a. Cognition and Parkinson's disease - epidemiology, disease mechanisms and possible treatments

What percentage of PD patients suffer from cognitive impairments?	50% of PD patients suffer from cognitive impairments 20-25% already have the problem at the time of diagnosis
What are the most common cognitive impairments in PD patients? Which tests could you use to test them?	Cognitive impairments • Executive functions • Attention • Working memory • Visuospatial function • Semantic memory (episodic memory usually not affected) ◦ Disfunction is shown in the tower of London test (planning is impaired) •  • Later stages: ◦ Hallucination/psychosis ◦ Considerable morbity ◦ Decreases independence, increases hospitalization
What are the three threshold of cognitive decline? Where does subjective cognitive impairment fit?	Stages of cognitive decline  MCI and dementia - Differ by impact in daily living Subjective cognitive decline - Normal cognition in tests, but there is a subject effect in daily living

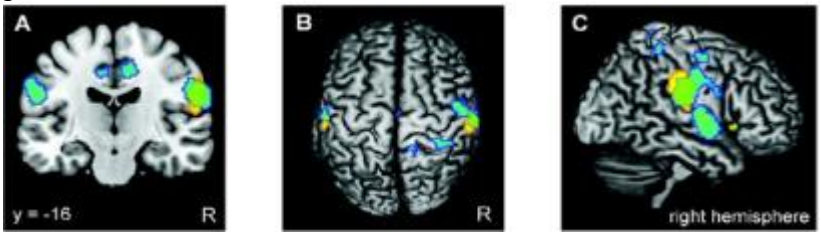
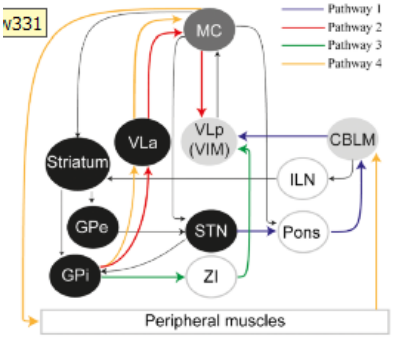
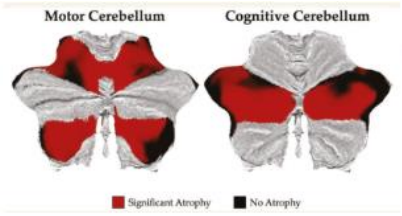
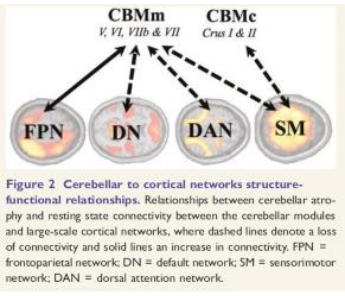
What percentage of PD patients develop Dementia after 20 years?	80% of all PD patient develop Parkinson's Disease Dementia in 20 years 
What is the Dual syndrome hypothesis for PD?	Dual syndrome hypothesis - There are two PD phenotypes: Frontal dysfunction and Cortical posterior deficits
What are the differences between Frontal Dysfunction and Cortical posterior deficits phenotypes for PD?	**Frontal dysfunction** • Executive problems (planning) • Working memory • Partly responsive to dopaminergic treatment • Tremor-dominant phenotype • MCI **Cortical posterior deficits** • Visuospatial dysfunction • Disturber semantic fluency • Akinetic motor phenotype • Rapid decline to PDD • (more alike AD)
What happens in the third Braak stage for PD?	Disease mechanisms PD pathology  Alpha-synuclein reaches cortex - Degeneration and dementia

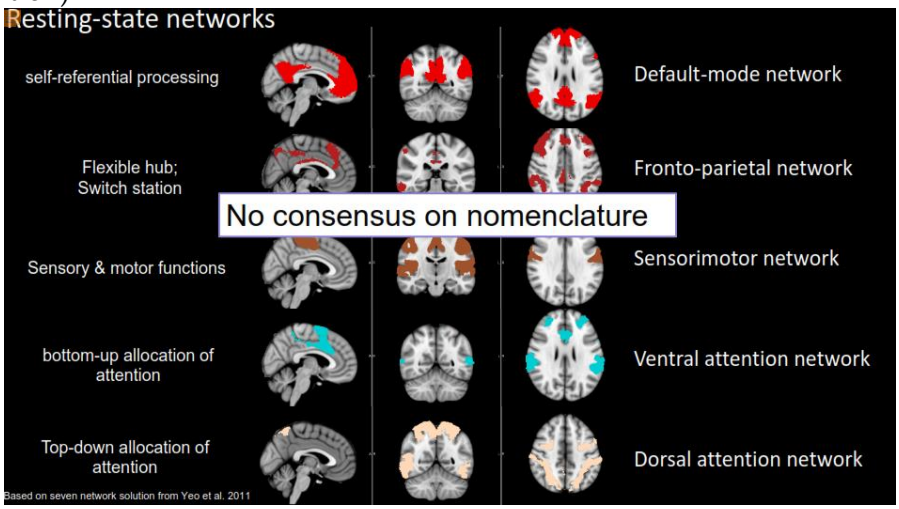
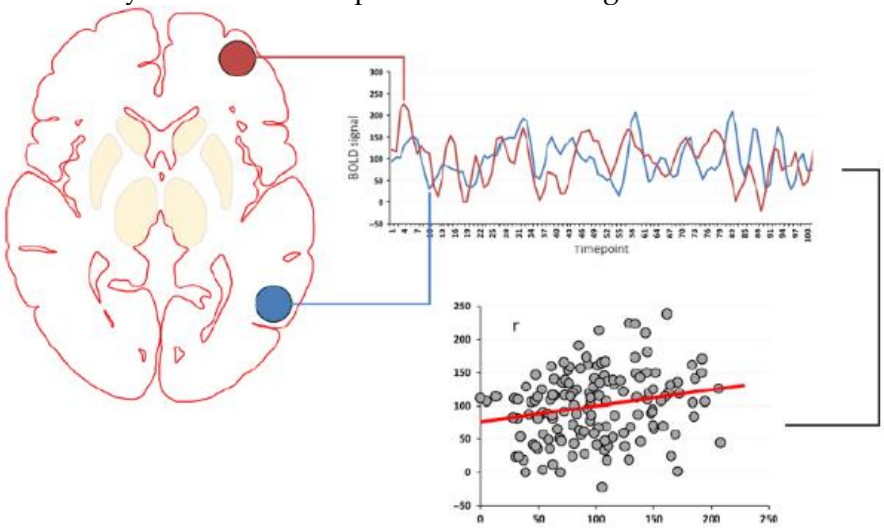
What is the neuropathology of degeneration and dementia in PD?	Neuropathology Neurocortical Lewy bodies is determinant for cognitive impairment • Mainly frontal and parietal cortices  Irwin et al 2012 Other hypothesis: Interplay of amyloid, tau and alpha-synuclein; vascular changes may be important
What is the current state of affairs regarding biomarkers in vivo for PD diagnosis?	Neuropathology in vivo CSF biomarkers - Negative correlation of AB42 and cognitive functions Alpha synuclein - Increases in early stages and decreases in later stages Molecular imaging biomarkers - A-beta pathology is not common with PDD; but when it happens, it is related to worse cognitive declines No predictive biomarkers thus far
Describe three brain regions affected by dopaminergic degeneration in the substantia nigra and their effects.	Neurotransmitters Dopamine - Produced in substantia nigra and VTA, projects to striatum and cortex Connections of striatum  Putamen - Movement Caudate nucleus - Cognition Nucleus accumbens - Motivation and reward When dopamine degenarates - the circuits get stuck ('dopamine is the oil of the machine')

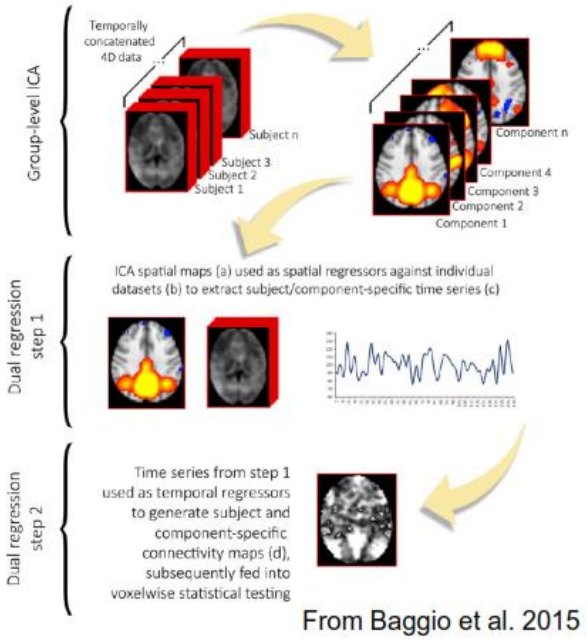
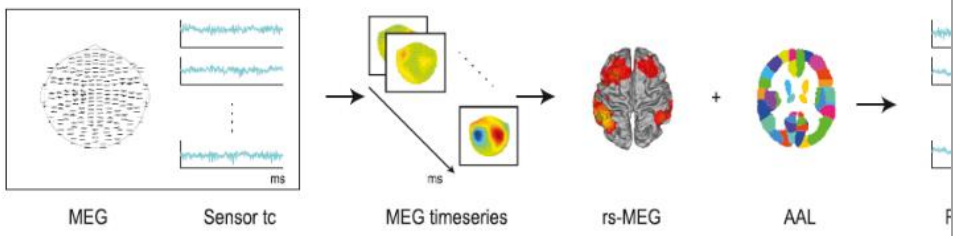
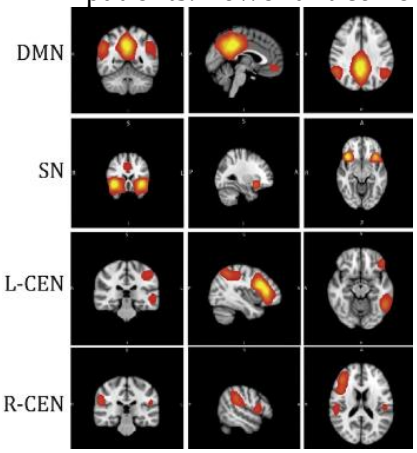
Describe how brain pathways are affected in PD.	Pathways affected in PD Direct - 'gas' Indirect - 'break' Dopaminergic pathways mediates 'stoping or going' D1 - Excitatory D2 - Inhibitory  Parkinson - D2 is less inhibited, it becomes more active
How is the cholinergic system affected in PD patients?	Cholinergic system in PD - Impairments in functional and structural remodeling Levodopa scan - Measures integrity of the dopaminergic system MP4A scan - Measures integrity of the cholinergic system  Cholinergic system is affected throughout cortex in PDD
Describe three genetic risk factors for PD.	Genetic risk factors SNCA (alpha-synuclein)- Mutation causes familial PD + cognitive impairment + increased risk of PDD APOE (apoliprotein E) - Associated with PDD GBA (Glucosylceramidase - glucose metabolism) - Associated with subject cognitive complaints
What are pharmacologic	Treatments • Cognitive impairment (for frontal phenotype) -

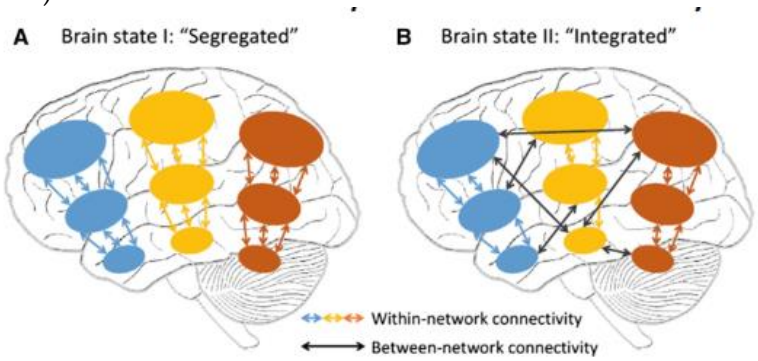
al treatments for PD?	• Levodopa - Dopaminergic system, patients become more attentive within 30-45 minutes • Rivastigmine - Cholinergic system (blocks Ach breakdown), only used in more severe cases (severe side effects)
What are the limitations for transcranial stimulation treatments for PD?	Transcranial magnetic stimulation (TMS) - Effects last for one hour in the beginning, duration increases with treatment progression Transcranial direct-current stimulation (tDCS) - Device has to be wore continuously Both influence activity in certain brain areas
What is the limitation for strategy training for PD?	Strategy training - Coping for cognitive impairment Only works for patients that are mildly affected
Describe the hypothesized model of cognition for PD.	Function training Model of cognition - Brain activity of PD patients is higher than controls (compensation); after pathology builds up, cognition decreases (failure of compensation)  Most function training program offered today has not been studied
What is COGTIPS? What are its main goals?	Project goals (COGTIPS) - Increase compensation training of PD patients by playing cognitively enhancing games. • Improve cognitive function • Delay cognitive decline • Understand neural mechanism of cognitive training Difficulty adapts to the player's ability Why is it a game? It needs to be fun to increase adherence

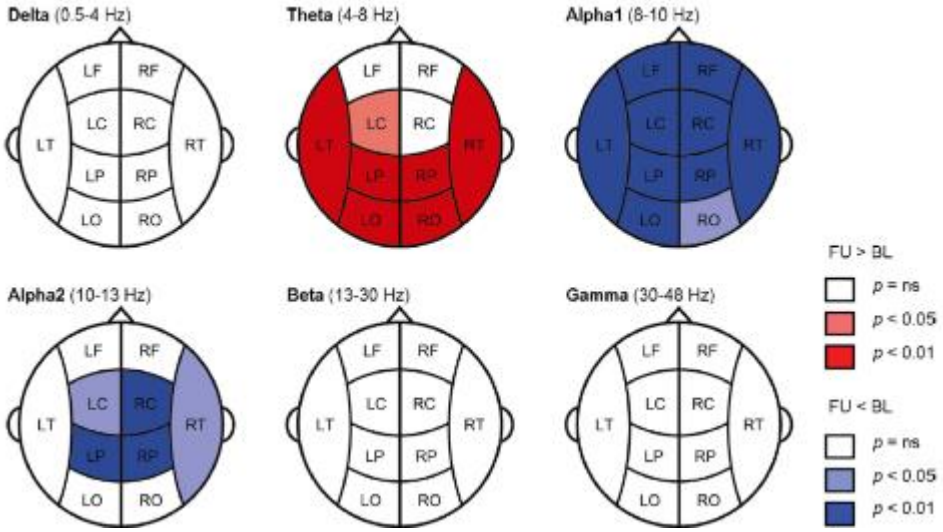
11b. Brain connectivity and Parkinson's Disease

What are two main connectivity changes in PD patients?	Connectivity of posterior putamen with motor cortex is decreased in PD patients  Anterior putamen with frontal areas of brain - Connectivity is decreased
What happens to the cerebellum in PD patients?	Cerebellum - Often overlooked in PD pathology  Cerebello-thalamo-cortical circuit - Increased in PD patients Parkinson's tremor - Triggered by basal ganglia Dopamine reduces tremor -> Inhibits the cerebellar thalamus
What are connectivity changes in the cerebellum in PD patients?	Motor cerebellum - Increased connectivity with fronto-parietal network, decreased con with sensomotor, default network and dorsal attention network Cognitive cerebellum   **Figure 2 Cerebellar to cortical networks structure-functional relationships.** Relationships between cerebellar atrophy and resting state connectivity between the cerebellar modules and large-scale cortical networks, where dashed lines denote a loss of connectivity and solid lines an increase in connectivity. FPN = frontoparietal network; DN = default network; SM = sensorimotor network; DAN = dorsal attention network.

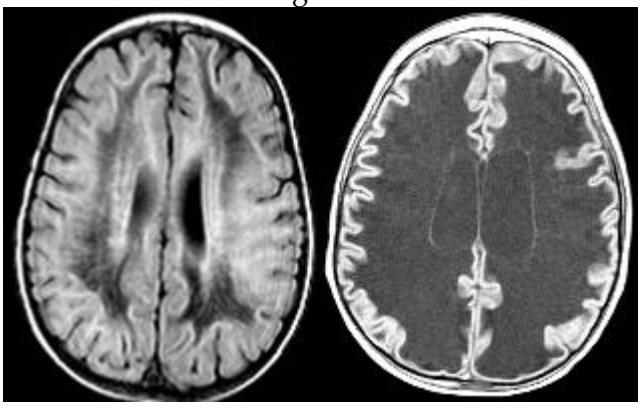
What are five resting state networks and their proposed functions?	Resting state networks - No consensus on nomenclature (pay attention to the definition) 
Describe three methods to calculate connectivity in the brain.	Methods to calculate connectivity Connectivity of one area compared to another region 

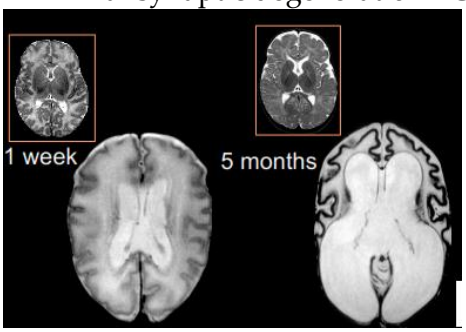
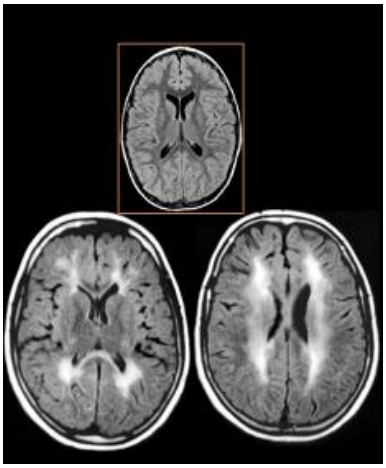
	Creation of 4d spatial maps  From Baggio et al. 2015 Atlas placed on functional scan to extract time series 
What happens in the Default Mode Network of PD patients?	Parkinson versus healthy controls In healthy patients: DMN is anticorrelated with SN and CEN In PD patients: Lower anticorrelation (failure to suppress DMN activity) 

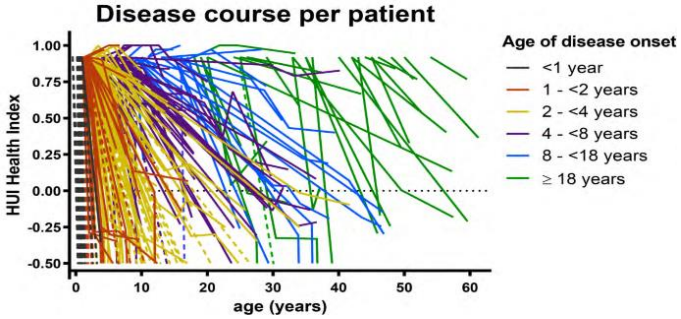
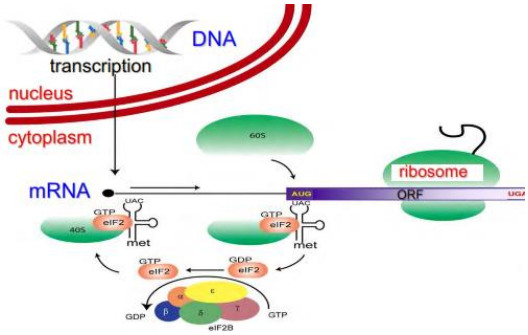
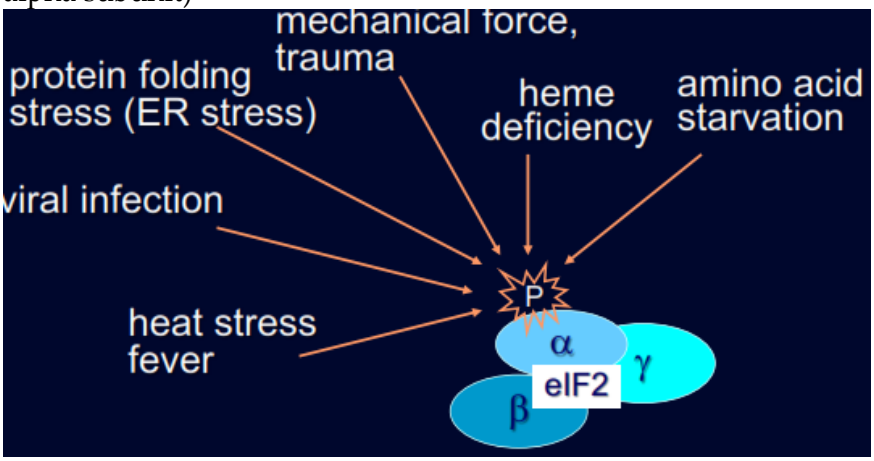
What happens to the efficiency of connections in PD patients?	Graph analysis - Based on the strength of connections PD patients have less global efficiency of connections • Other results are still being discussed
Describe segregated vs integrated brain states. What happens with these networks in PD patients?	Dynamic connectivity - 5 to 10 minutes scanned are analysed in smaller chunks -> analysis of differences of connectivity measures Sliding window approach - Chunks are overlapped (increased sample size)  Segragated vs Integrated brain states • Segragated - Focused • Integrated - Diffuse Motor symptom severity is higher -> patients change states more often (fragmented resting state network) • This may be a problem with all brain disorders
What are two ways to study structural networks?	Structural networks Structural covariance - Gray matter volume compared to volume of other brain regions  Tractography - White matter tracts  Studies with these techniques have shown that PD patients - Less global efficiency, global clustering coefficient higher or lower

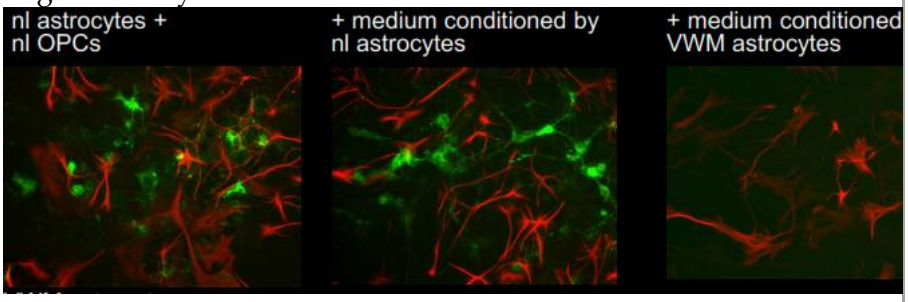
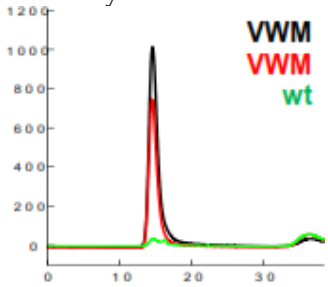
What does structural MRI tell about PD?	Structural MRI Loss of tissue in frontal and parietal cortices (PDD vs cognitively normal PD) Cognitive decline is associated with thinning of cortex Regions of decreased volume have higher accumulation of Lewy Body pathology
What does functional MRI tell about PD?	Functional MRI Lower functional resting state connectivity Higher default mode network - Associated with cognitive impairments Reduced ability to switch between networks Decreased functional connectivity is correlated with cognitive decline
What does electrophysiology tell about PD?	Electrophysiology  Slowing of oscillatory brain activity correlates with cognitive decline Alpha band (8-10 hz) - shifts towards theta bands (4-8 hz) Red - Increased, blue - decrease

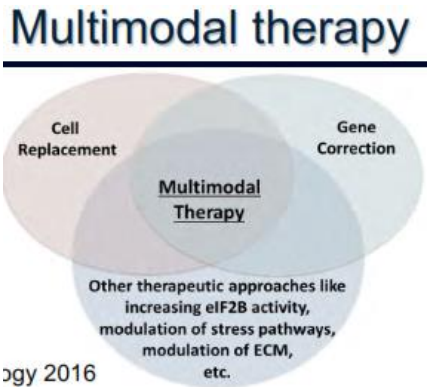
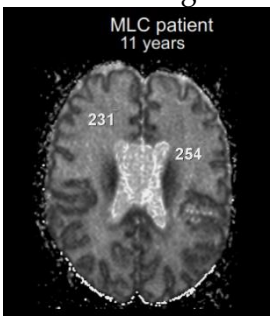
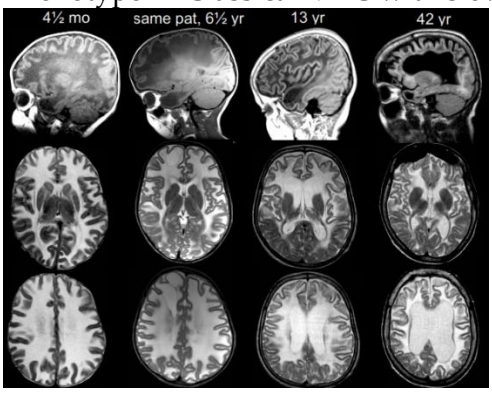
12a. Childhood white matter disorders

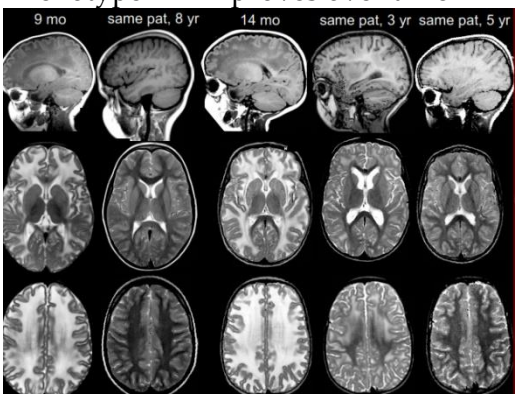
How can lesions in the white matter appear in a FLAIR?	Lesions in FLAIR Show up as white - If it is solid Show up as black - Fluid abnormalities (CSF)
What are the common clinical features of white matter disorders?	Clinical features of white matter disorders Motor problems - Ataxia, spasticity(Axonal degeneration only affects the distal part of the neuron) Cognitive problems less clear No or mild epilepsy - Cortex is intact
What are the common clinical features of grey matter disorders?	Clinical features of grey matter disease disorders Early cognitive problems Motor problems (apraxia and loss of dexterity) Epilepsy
What is the current standard of diagnosis for white matter disorders?	MRI pattern recognition to diagnose white matter disorders 60% of patients with CWMD cannot be diagnosed by MRI - This is improved by using MRI + clinical features
What would you observe in an MRI of a patient with Vanishing white matter disorder?	Novel disorders White matter is turning into CSF  Cystic white matter - No myelin Disease: Vanishing white matter
What is the common disease progression for VWM?	VWM disease progression Chronic neurological deterioration (ataxia) Stress-sensitive disease -> Gets worse with head trauma or infections

Which part of the Netherlands is more commonly affected by VWM? Why?	Many vanishing white matter patients came from the east of Netherlands More isolated population EIF2B1-5 - Recessive mutations in all 5 genes cause VWM
What are the two phenotypes for VWM?	Phenotypic variation Severe Antenatal/early infantile onset - Microencephaly, growth retardation, death within a few months Transynaptic degeneration - Causes cerebellar atrophy  Mild Migraines Epilepsy Cognitive problems Motor deterioration 
Why is VWM a early onset problem, not a congenital problem?	You are not born with a myelinated brain This happens within 2 years of birth

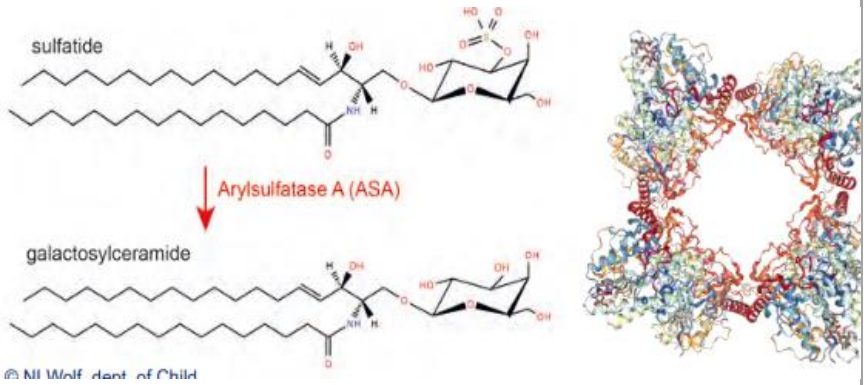
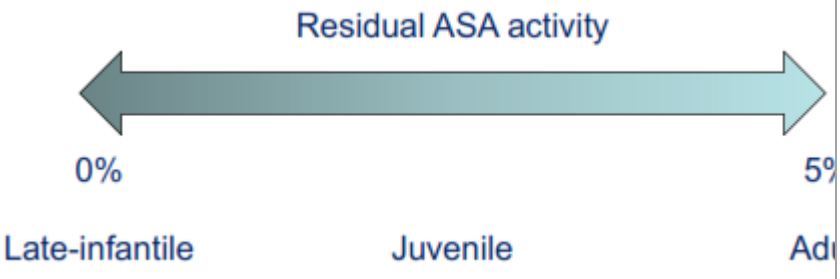
What determines disease severity in VWM?	What determines disease severity Number/Severity of mutations The later the onset of disease, the greater the variability of disease severity  Four years or more of disease onset - Speed of disease progression is the same
What is the role of eIF2B? Where is it expressed?	eIF2B - Exchanges GDP for GTP in the initiation complex in the process of translation  This becomes a problem during early childhood -> A lot of protein synthesis is happening
What are examples of cellular stress responses? What do they do with eIF2?	Cellular stress response - Hampers eIF2 function (phosphorylation of the alpha subunit)  Leads to inhibition of protein synthesis

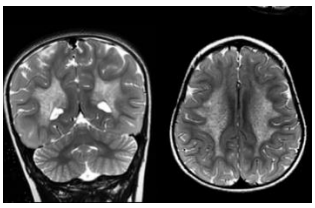
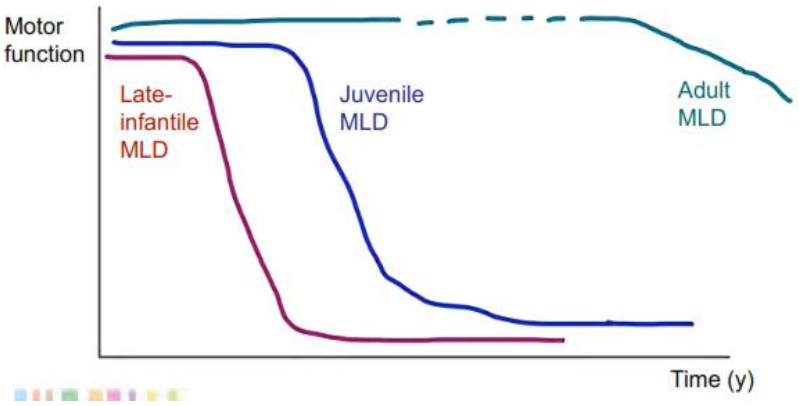
Why is there no scarring due to myelin loss in VWM patients?	VWM pathology Cystic WM - No scar Neurons are normal, astrocytes and olygodendrocytes are abnormal (remain immature) Lack of myelin Lack of gliotic scar - There are just holes in the MRI, no obvious damage
What is the role of astrocytes in VWM?	OPCs - Oligodendrocyte precursors cells Myelin can be used as a maturation proxy - Only mature oligodendrocytes produce myelin Medium of VWM astrocytes inhibits maturation of oligodendrocytes 
What is the molecule produced by astrocytes in VWM?	Astrocytes produce high molecular rate hyaluronan -> Inhibit oligodendrocyte maturation 
What are treatment options for VWM?	Treatment Avoid stresses - Fever, infections, head trauma Not enough - Patients still die Curative options Increase eIF2B activity - Works in mice Modulate extracellular matrix - Prevent astrocyte inhibition Gene therapy Stem cell therapy Probable future: multimodal therapy

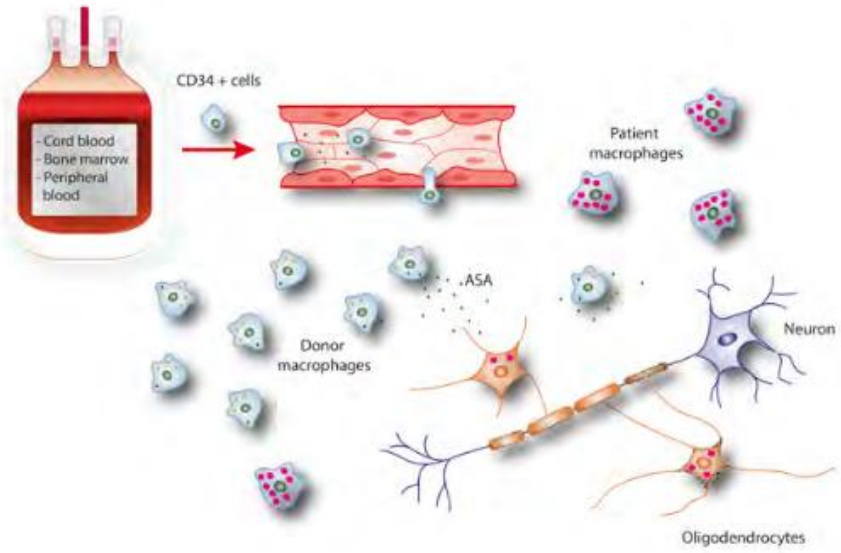
	
What are clinical features of MLC?	Disease - Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC) Macrocephaly Epilepsy Wheel-chair dependent as a teenager Autosomal recessive
What can be observed in DWI in MLC patients?	Diffusion weighted imaging  • MLC patient has higher water content and increased ventricles
What is the main genetic risk factor for MLC?	Genetic linkage study MLC1 - 70-80% of patients
What is MLC phenotype I?	Phenotype I - Classical MLC with slow deterioration 

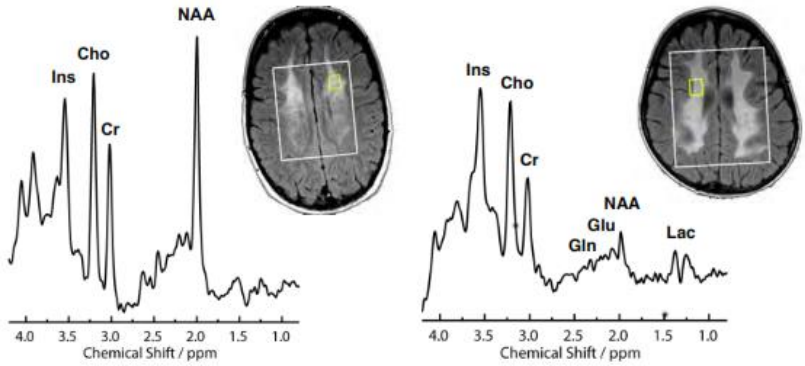
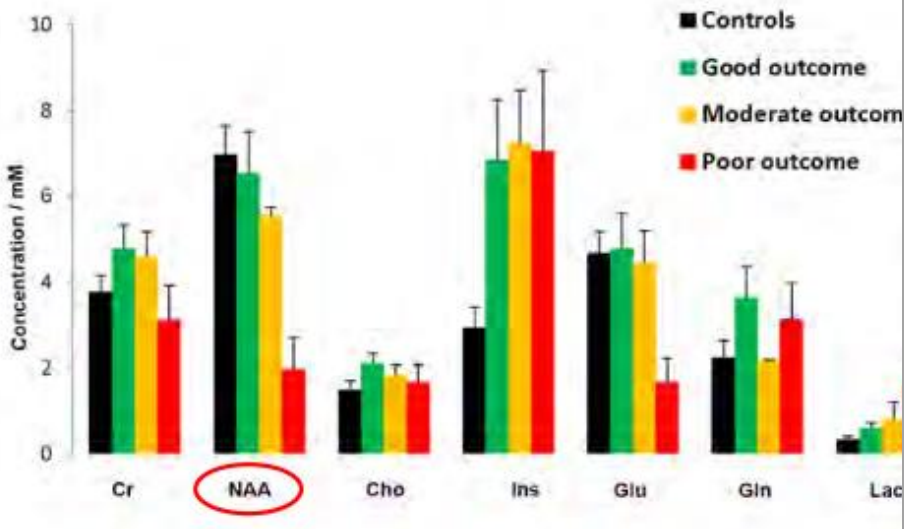
What is MLC phenotype II?	Phenotype II - Improves over time  Clinically improving Macrocephaly may or may not persist
How was the relation between GlialCAM and MLC established?	Protein-protein interaction assay GlialCAM - Discovered to be the second gene associated with the disease Phenotype I - 2 GlialCAM mutation Phenotype II - 1 GlialCAM mutation
What is the effect of glialCAM mutation?	GlialCAM - Located around blood vessels Costating - Only present in the endfeet astroglial processes (CSF blood brain barrier) GlialCAM is a chaperone for MLC1
Why is MLC1 and GlialCAM not part of traditional prenatal screenings?	This disease is not present in neonatal screening - There is no treatment options!

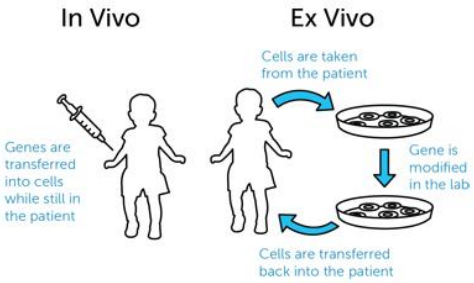
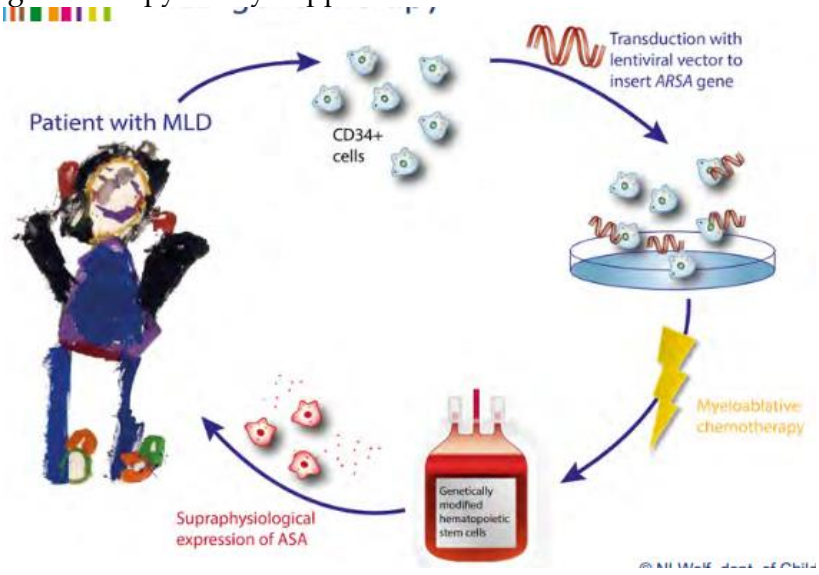
12b. Current therapy for childhood white matter disorders

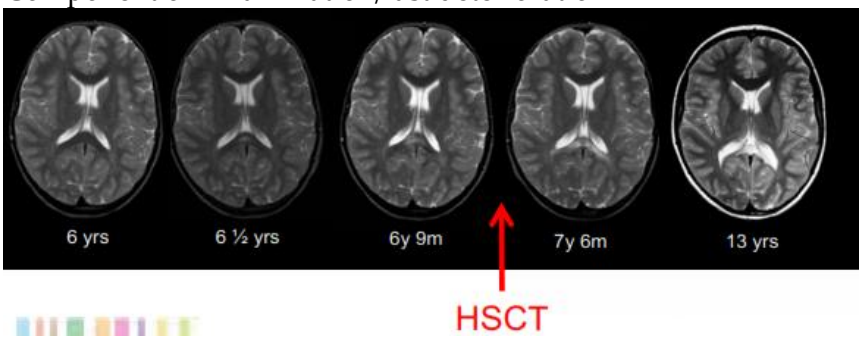
What is the underlying cause for metachromatic leukodystrophy?	Metachromatic leukodystrophy First described in 1910 by Alzheimer Autosomal recessive inheritance  Low activity of arylsulfatase A Accumulation of sulfatides in membrane and lysosome
What is the current standard of diagnosis for MLD?	Diagnosis Clinical presentation and MRI Sulfatide excretion in urine ASA activity in leukocytes ARSA mutation analysis
What are the three forms of MLD? What is their difference in symptoms?	Three forms of disease Onset < 30 - Late-infantile form 30 months - 16 years - Juvenile form > 16 years - Adult form Severity of disease depends of ASA activity  Early onset: Motor symptoms, rapid progression Late onset: Cognitive symptoms, insidious progression

What would you observe in the MRI of a patient with MLD?	MRI in MLD T2 hypointensive white matter in the center of the brain - Accumulation of sulfatide  During disease course: Atrophy of brain structures (thalamus, cerebellum)
Draw the relationship between the different phenotypes of MLD with loss of motor function.	Clinical course of MLD 
What are currently used treatments for MLD? What are some failed trials?	Strategies for treatment Hematopoietic therapy Gene replacement therapy - Delivered to the brain; Ex vivo (hematopoietic cells -> Migrate to the brain) Enzyme replacement therapy Not used due to dubious efficacy: substrate reduction therapy, neuroprotective treatment, neuronal/glial cell transplantation
What are the problems with enzyme replacement therapy for MLD?	Enzyme replacement therapy - Replace Arylsulfate A in the brain -> digest sulfatides Regular intravenous infusions - Once a week Problems: Antibodies in a subset of patients Blood brain barrier for lysozomal disorders *Drugs can be administered into the CSF space - Subvert BBB (intrathecal application)* Expensive

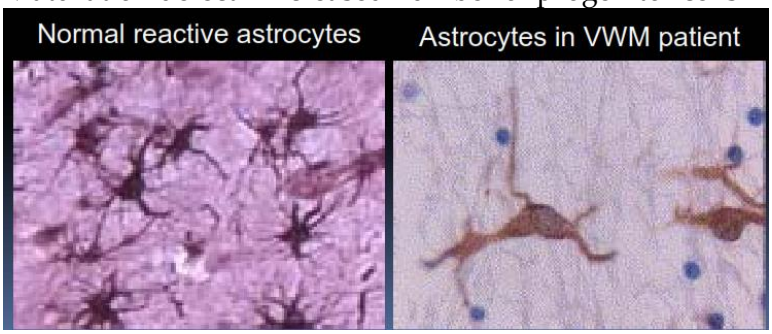
Describe how hematopoietic cell transplantation works for the treatment of MLD.	Hematopoietic cell transplantation  Enzyme reconstitution Effect on oligodendrocyte progenitors (last few slides) Macrophages start digesting sulfatides in the brain
What are some problems with HCT for the treatment of MLD?	Things to consider for HCT Intensive chemotherapy - Patient must be in isolation for 6-18 months (no immune system) Effect on peripheral organs Mortality rate of 5-10%
What is currently used to predict disease progression in MLD?	What can be used to predict disease progression? MRI - Must show no atrophy HCT - Is better for juvenile patients However, two thirds of patients are not eligible for HCT
What happens to MLD patients that successfully undergo HCT?	MRI detereoration is observed for HCT after 6 months Immunossupresion Steroids -> Modify white matter
What do MLD patients show in a H-MR spectroscopy that is different from controls?	H-MR spectroscopy in MLD

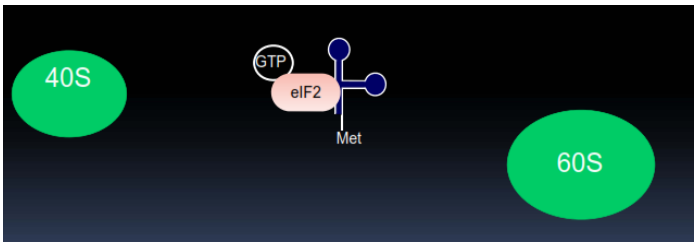
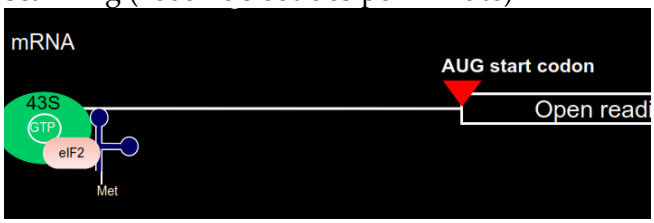
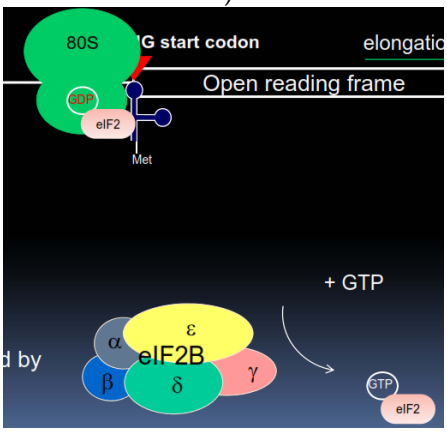
	 NAA - Marker for neuroaxonal integrity Cr - Creatine (cellular marker, constant) Cho - Choline (marker for membrane turnover) Ins - Myo-inositol More white matter abnormalities - NAA almost disappears, some Lactate is observed
Which markers can be used to decide whether or not to give HCT for MLD patients?	H-MRS can be used for prognosis  Decide to do the transplantation or not
What is the current transplantation criteria of HCT for MLD patients?	Transplantation criteria Not late-infantile MLD - Preference for stem cell therapy IQ > 85 Gross motor function normal MRI score < 17
What can be observed in the	Histopathology after HCT

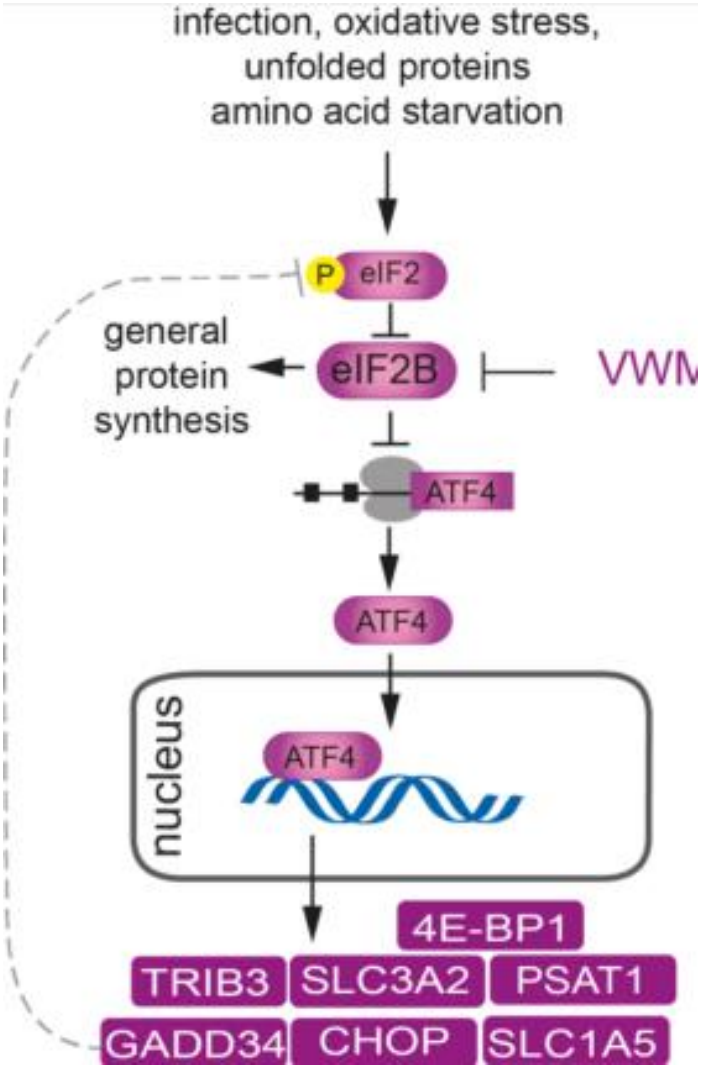
histopathology after HCT in MLD patients?	Staining for digested fatty acids - Shows that macrophages have successfully entered the brain Enrichment of donor macrophages into more affected areas - M2 or protective macrophages
What are some caviats regarding HCT for the treatment of MLD?	Open questions Peripheral neuropathy does not respond well to HCT Slow deterioration with progressive spasticity and dementia without leukodystrophy
Aside from HCT, what are the current standings for early therapy options for MLD?	Early therapy options Enzyme replacement therapy - Intrathecal is effective, intravenous is not Ex vivo gene therapy - Efficient for late-infantile patients In vivo gene therapy - Didn't work in humans 
What is the difference between gene therapy and traditional haemotopoietic cell transplant for the treatment of MLD?	MLD gene therapy - Only happens in Milan  No graft disease

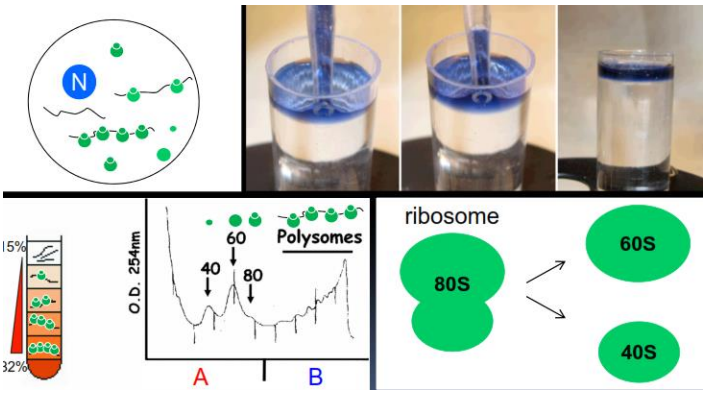
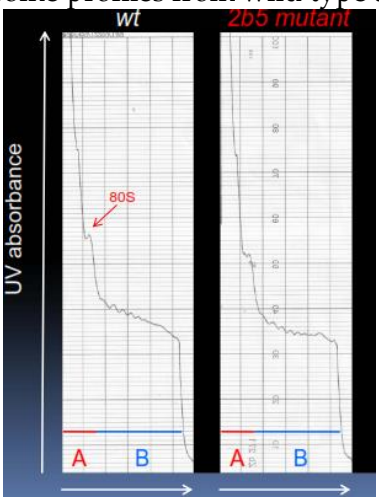
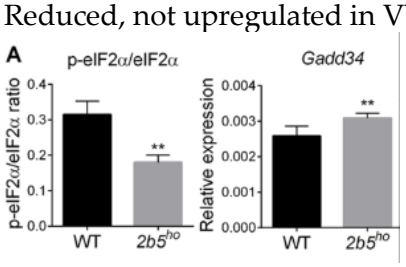
What is the underlying cause for X-linked adenoleukodystrophy?	X-linked adenoleukodystrophy Elevated long chain fatty acids Several different phenotypes
What can be observed in an MRI for X-linked adenoleukodystrophy?	MRI for childhood cerebral form Component of inflammation/fast deterioration 
What are the treatment options for X-linked adenoleukodystrophy?	Treatment options HCT (allogenic or ex vivo gene therapy) Newborn screening
What are some early promising treatments for X-linked adenoleukodystrophy?	Early treatments Antiretroviral treatment Antisense olidonucleotides Neuronal stem cell transplantation

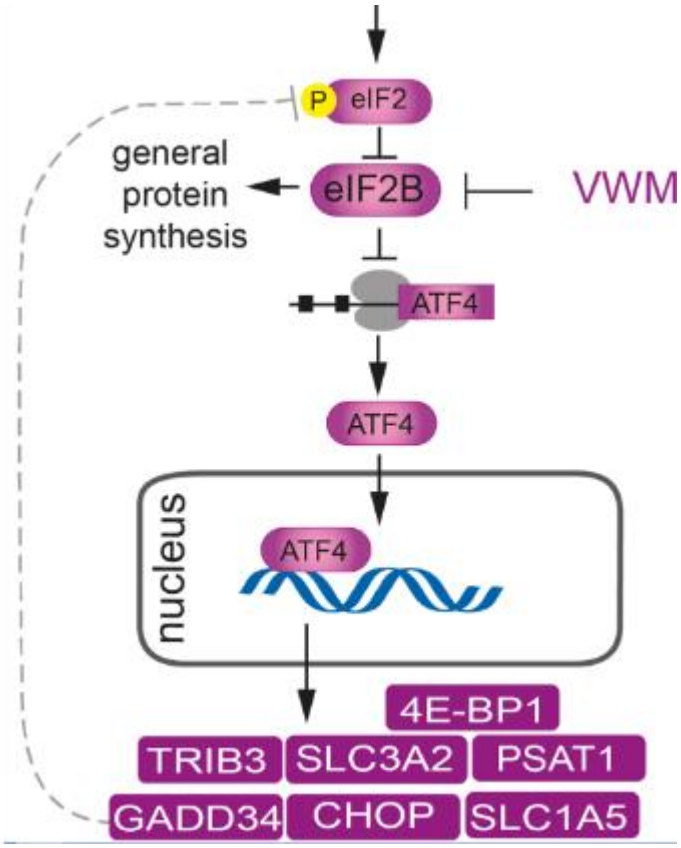
12c. Studying Disease Mechanisms (VWM as a case study)

What are the main clinical features of Vanishing White Matter disease?	VWM characteristics Most prevalent inherited childhood white matter disorder Clinical signs - Mainly ataxia Chronic and episodic neurological deterioration Episodes of major deterioration provoked by stress (e.g. fever) No dysfunction of internal organs Ovarian dysfunction in female patients Grey matter remains mostly intact
What is the morphological difference between healthy astrocytes and VWM astrocytes?	Macroglia are affected in VWM Abnormal pathology - Do not work properly Maturation defect - Increased number of progenitor cells  Reduced number of processes
What is the mutation associated with VWM?	Mutation in Eukaryotic Initiation Factor 2B EIF2B - Regenerates EIF2-GTP complex
What is the importance of eIF2B? Where is it expressed?	EIF2B - Essential for protein synthesis - housekeeping function Expressed in all cells of the body
Describe the entire process of translation initiation and how eIF2 is involved in the process.	Translation initiation: mRNA architecture  UTR - Unstranlated region (before or after ORF) Cap/poly-A tail - mRNA stabilization

	 Ternary complex - GTP-eIF2-Met - in this state, the structure has a high affinity for the ribosome's small subunit This complex in turn has a high affinity for the CAP - Starts scanning (1000 nucleotides per minute)  Large ribosome subunit joins - This process needs energy (GTP is broken into GDP)  tRNA leaves (less affinity) EIF2B replaces GTP from GDP from the eIF2
What is the function of eIF2B in the process of initiation during translation?	EIF2B regulates proteins synthesis rate EIF2B activity drives the speed of protein translation eIF2B activity is regulated by stress responses
What happens when eIF2 is phosphorylated? When does this naturally occur?	EIF2 is phosphorylated - Binds tightly to eIF2B (forms a inert complex) Integrated stress response - Very fast molecular process Phosphorylation - PERK, PKR, GCN2 and HRI ER stress, infections (protective against replication of virus), amino acid starvation (body cannot make proteins), heme deficiency

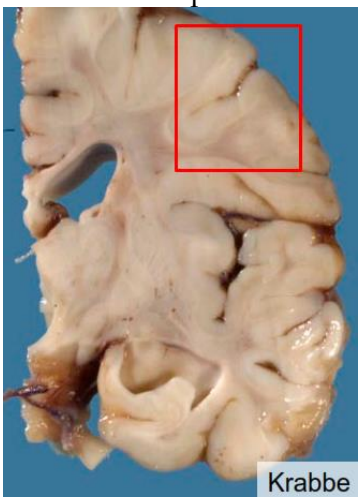
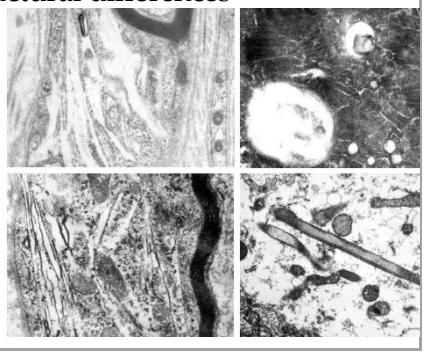
What seems contradictory in the function of ATF4?	 ATF4 - Is increased in protein synthesis (cell survival only)
What methods could you use to analyse the function of eIF2B in VWM?	Research question: How do mutations in the eIF2B gene cause VWM Analyse white matter glia throughout disease course - Animal models Mice have reduced life expectancy - Brain white matter -> less myelin, white matter vacuoles Polygonal profiling experiment
Describe how would you observe polysome in a chromatography essay.	Polysomes- mRNA associated with many ribosomes These complexes can be separated by size (sucrose gradient in brain lysate) Heavy complexes - Sink more to the bottom

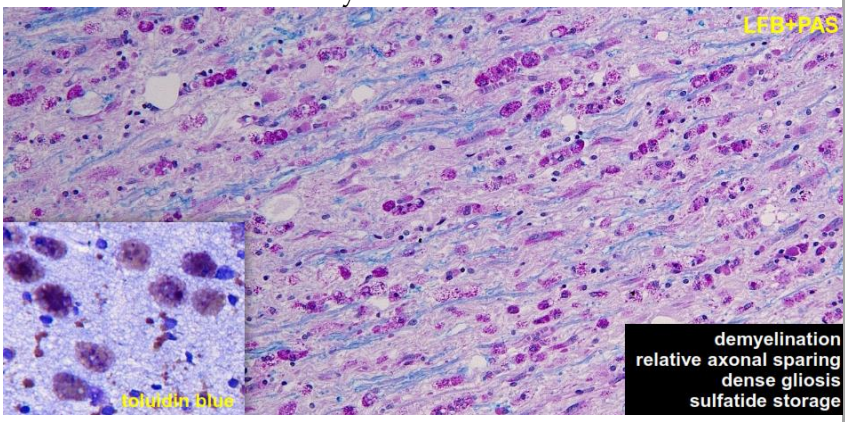
	
What was the main finding of the analysis of polysomes in VWM?	Polysome profiles from wild type and knock-down mice are similar 
Which technique could you use to identify and quantify mRNA?	Microarray- Isolate all mRNAs and polysomes Identify and quantify 176 mRNAs are differently expressed between normal mice and knockdown mice (they are upregulated in the knockdown mice!) 64 of them are regulated by ATF4 (which is usually inhibited by eIF2B) 62 of them overlap with VWM patient brain microarray
It was found that eIF2alpha was reduced, not upregulated in VWM. What may that suggest?	EIF2alpha phosphorylation in the brain Reduced, not upregulated in VWM  GADD34 - Dephosphorylate eIF2

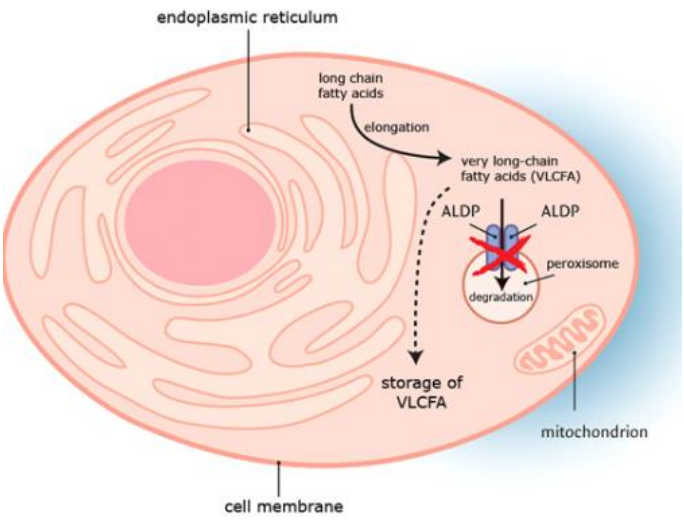
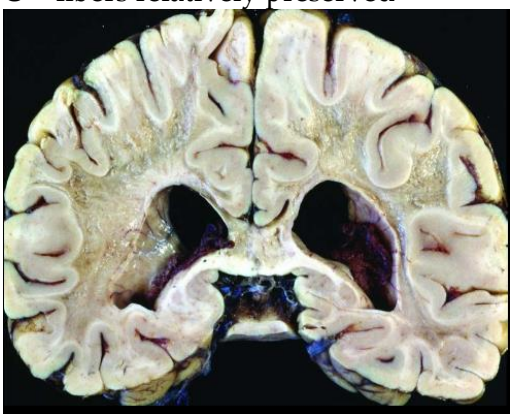
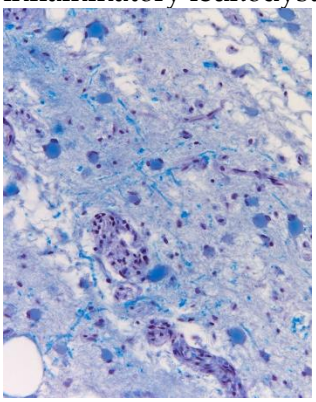


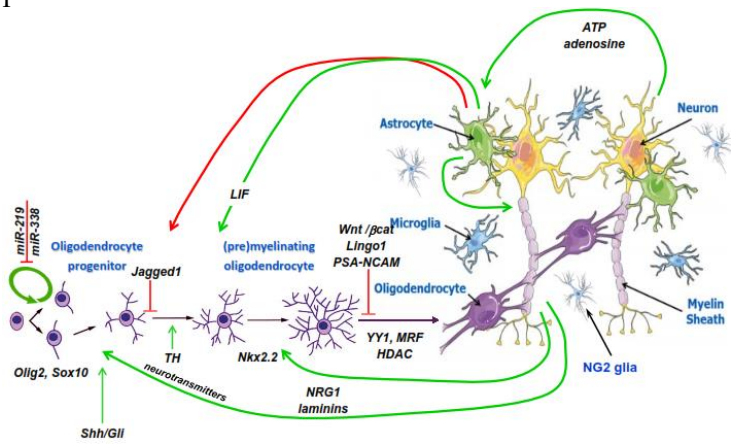
Possibly a deregulated pathway in VWM

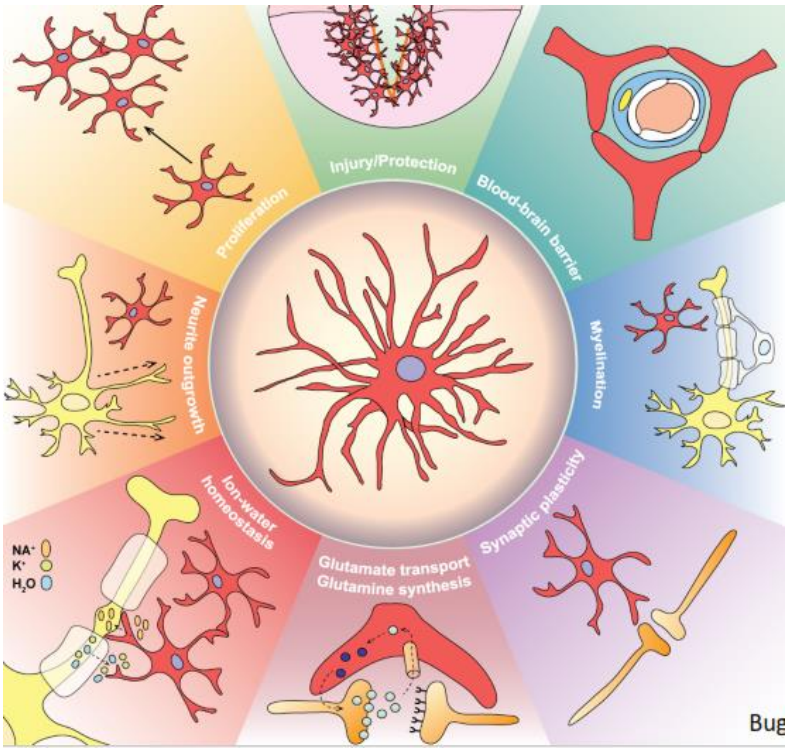
12d. History of brain white matter disorders

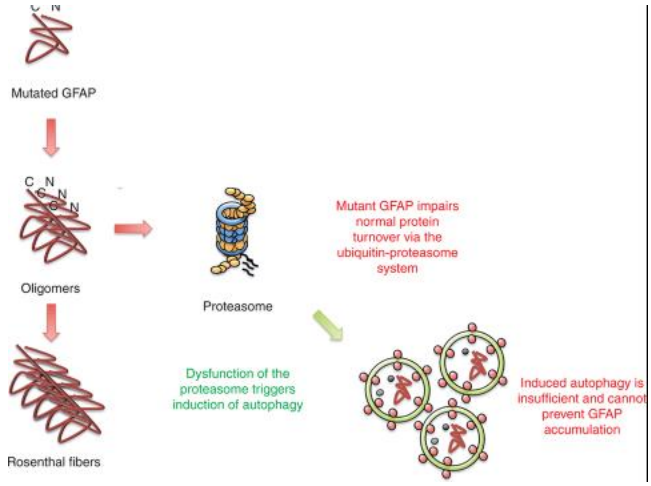
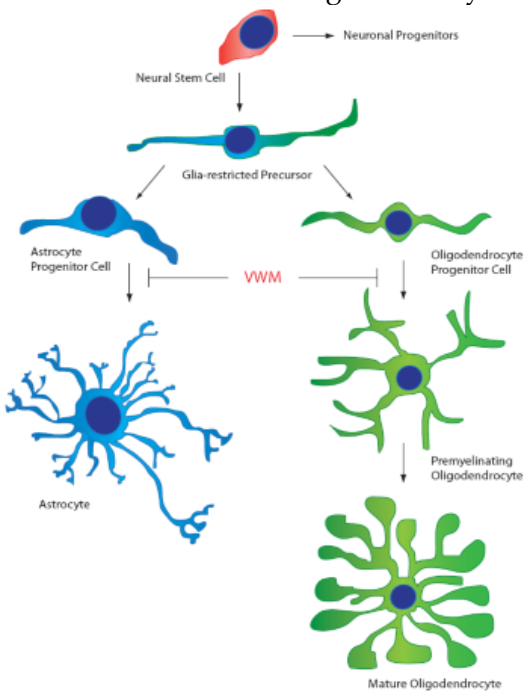
What are some common neuropathologic features of leukodystrophies?	Leukodystrophies have common gross neuropathologic features Reduced brain weight Optic atrophy Ventriculomegaly Atrophy of white matter structures 'U' fibers are spare 
What are some common leukodystrophies microscopic features?	Leukodystrophies microscopic features Reduced myelin staining Loss of oligodendrocytes Relative sparing of axons Macrophages with myelin debris Reactive astrocytosis (early) Fibrillary astrogliosis (late) Axonal loss Leukodystrophies have distintive macrophages and myelin debris Vacuolates, striated, globoid (multinuclear) Leukodystrophies have ultrastructural differences Lamellae - ALD Crystalloids - GLD Prismatic structures - MLD Rosenthal fibers - Alexander Vacuoles in myelin sheaths and mitochondrial changes - Canavan 

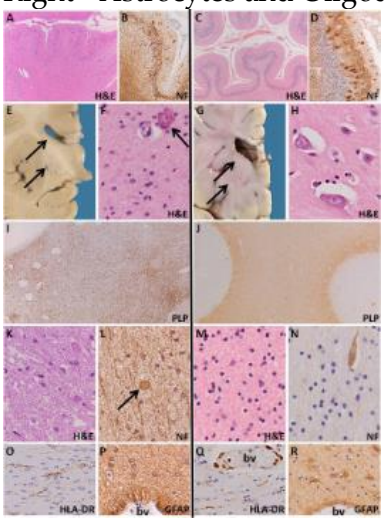
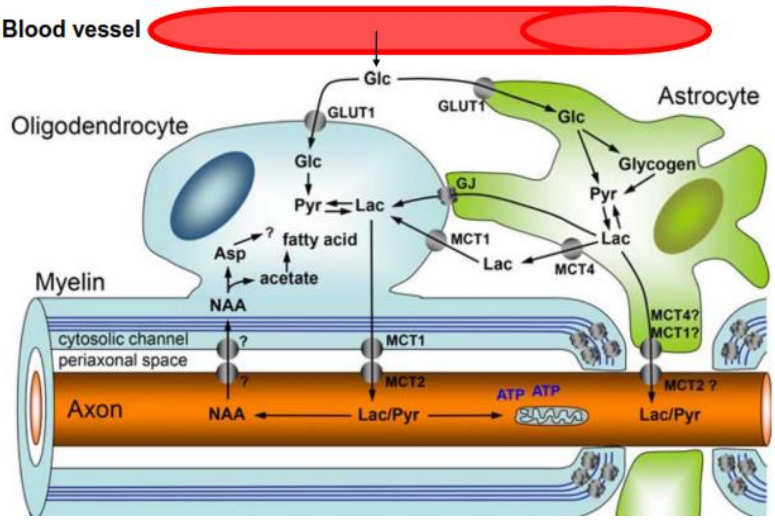
What was the early leukodystrophy definition? Why is it wrong?	Early leukodystrophy definition: Genetic progressive disorders primarily affecting myelin, either directly or through oligodendrocytes MRI had not entered clinical practice
What happens to macrophages, large axons and small axons in MLD?	Metachromatic leukodystrophy Autosomal recessive - Compound which is a substrate for myelin is not available (there is no degeneration) Accumulation of sulfatide - Toxic Macrophages stain abnormally Large axons lose myelin Small axons do not lose myelin 
Which protein is affected in X-linked adrenoleukodystrophy? What is its native function?	X-linked adrenoleukodystrophy X-linked - Affects more males Defect on ALDP Accumulation of very long fatty chain - Toxic for the cell

	
What can be observed macroscopically in the brain of a patient with X-linked adrenoleukodystrophy?	Neuroanatomy of X-linked adrenoleukodystrophy Ventricles enlarged U—fibers relatively preserved 
What can be observed microscopically in the brain of a patient with X-linked adrenoleukodystrophy?	Microscopy Inflammatory cells - Accumulate in the perivascular space (only inflammatory leukodystrophy) 

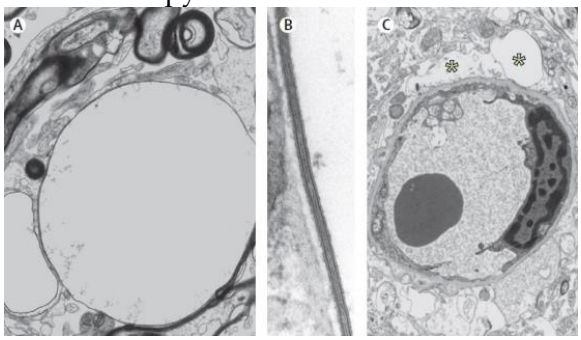
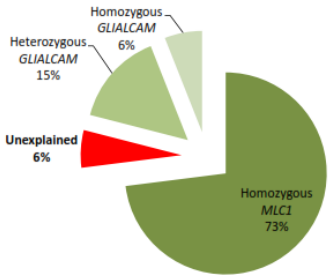
When was MRI introduced? What was a common misconception at first?	Introduction of MRI in 1980 Sensitivity was good enough for diagnosis - Completely replaced pathology as a tool Radiologists used terms for the pathology(demyelination) to define the MRI
How was MRI established as a diagnosis method?	MRI pattern recognition Some diseases can be diagnosed for sure (genetic) - If they have the same MRI pattern, clinical symptoms, then it can be used a discriminatory tool 2015: Over 80% of children receives a specific diagnosis
What promotes OPC into differentiating into mature oligodendrocytes?	Oligodendrocyte development Oligodendrocyte precursor - Present even in adults Stimulus that promote Oligodendrocyte progenitor - Action potential  Not all leukodystrophy involves oligodendrocytes/myelin
What is the current definition of leukodystrophy?	Current definition of leukodystrophy: Disease caused by defect of any of the white matter structural components
What are the five categories of leukodystrophies?	Classification of leukodystrophies Myelin disorders Astrocytopathies Leuko-axonopathies Leuko-microgliopathies Leukovasculopathies
What are some important functions of astrocytes in the brain?	Astrocytes - Diverse functions

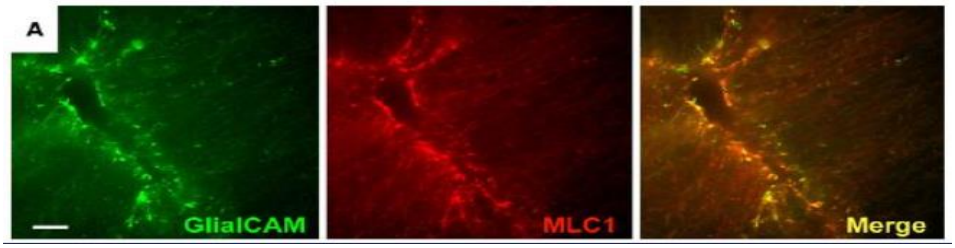
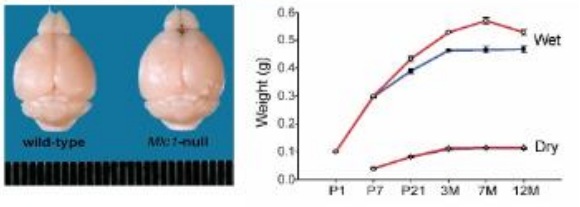
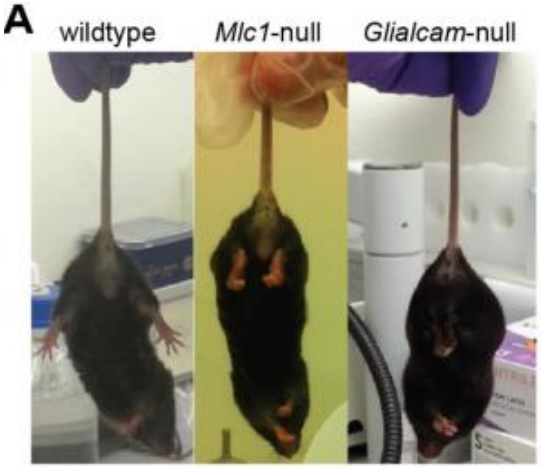
	 Maintain white matter homeostasis Blood brain barrier Control myelination Phagocytosis
Why is reactive gliosis an important process?	Reactive gliosis & glial scaring The destruction of the brain is limited to a particular area to preserve the whole Animal models - without reactive gliosis More damage than normal mice Asthenic astrocytes - Reactive gliosis does not occur (schizophrenia)
What is Alexander disease? Why is it a good example of why the original definition of leukodystrophies does not work?	Alexander disease Mutations in GFAP (intermediate filament only expressed in astrocytes) Dominant disease - GFAP accumulates (forms Rosenthal fibers), neurons cannot operate properly Oligodendrocytes are killed - no myelin is formed • There is no 'loss' of myelin, rather lack of myelin

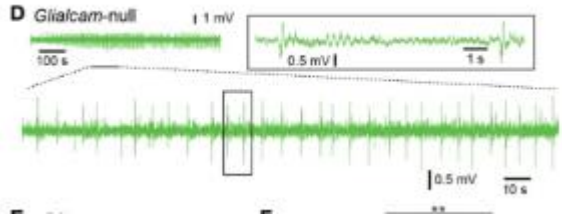
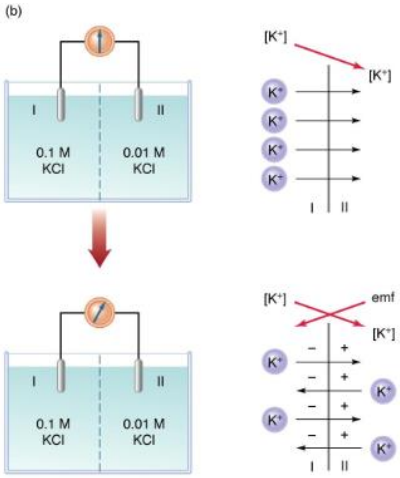
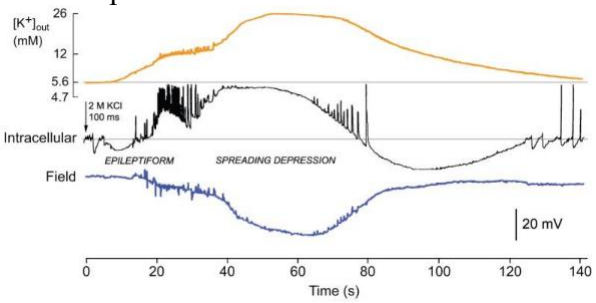
	 Astrocytes in the frontal areas of brain have more GFAP - This brain are is more vulnerable
Which part of the brain is affected in VWM? Why?	Vanishing white matter Only dorsal part of the neural tube is affected - Ventral part is not affected Astrocytes are never matured - High molecular weight hyalunoran -> prevents maturation Extracellular matrix like a fetus - Fluid (hyalunoran holds water) Proliferation of cells - Oligodendrocytes (but not mature) 

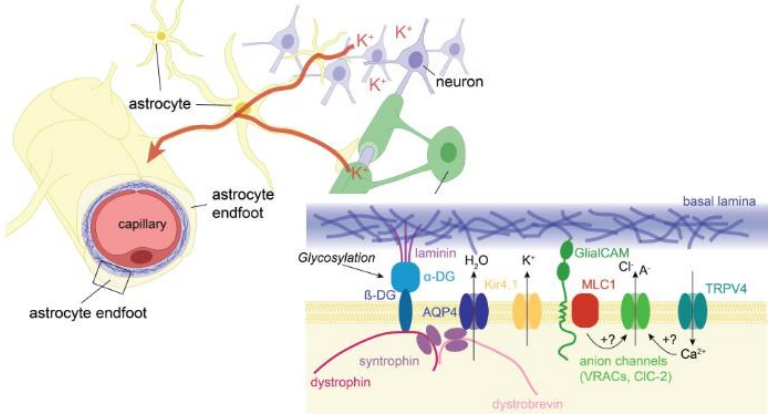
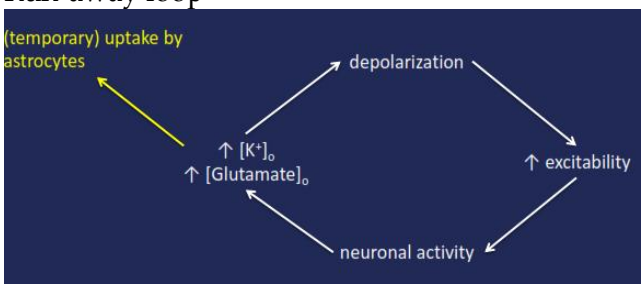
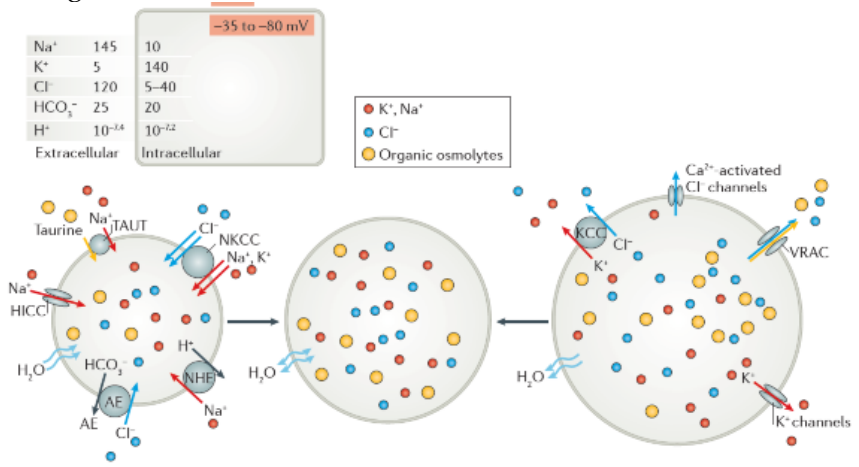
What is the underlying cause for hypomyelination with atrophy of basal ganglia and cerebellum?	Leuko-axonopathy - Hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC) Defect in beta-tubulin- Affects microtubules Probably affects axonal transport There is no myelin loss
Which cell is affected in H-ABC?	H-ABC: Two distinct neuropathological phenotypes Right - Astrocytes and Oligodendrocytes are mostly normal  Mutations - Makes Oligodendrocyte immature Same mutations in the neurons do not change anything
How do the axons of meter-long neurons get their energy?	Glial support of axonal energy Long neurons have mitochondria, not ER Glial cells give food (glucose->lactate) to the neuron 

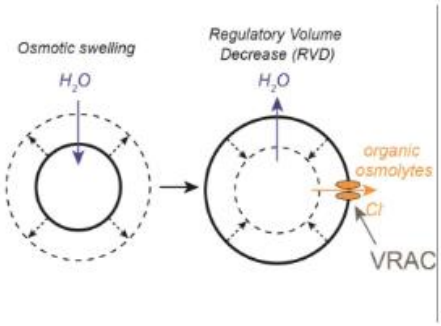
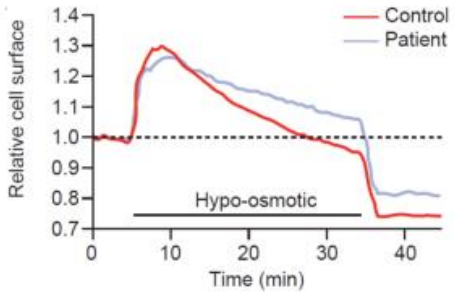
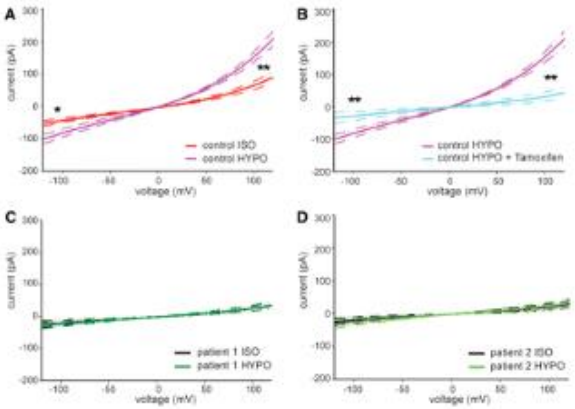
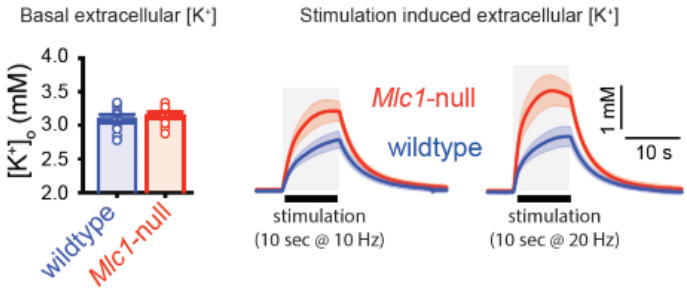
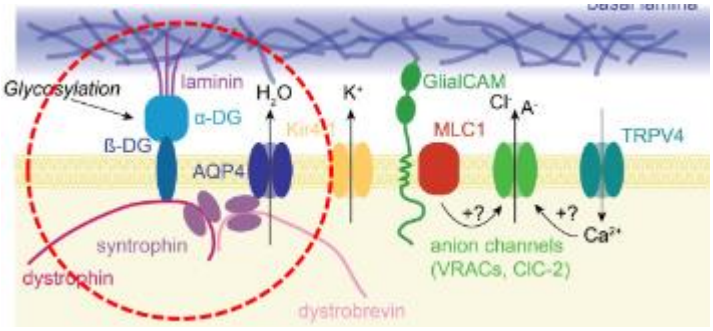
13a. Water homeostasis in white matter disease (Roger Min)

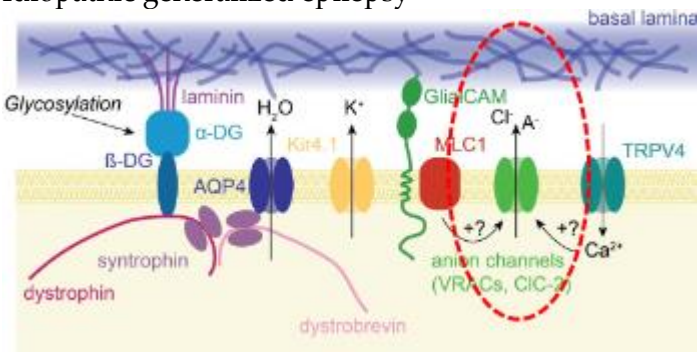
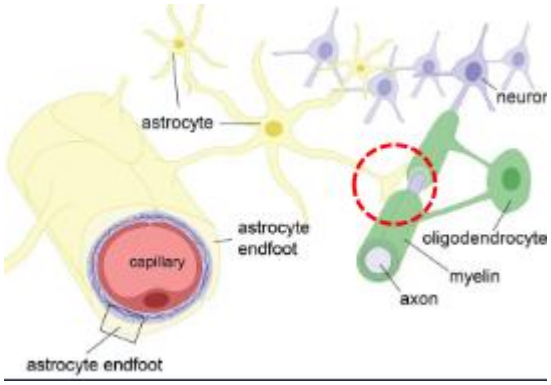
What are the main characteristics of MLC?	MLC is characterized by Macrocephaly from an early age Above 2 standard deviations from the mean White matter is swollen Mildly delayed early development Delayed onset of motor deterioration Early onset of seizures Dependency of wheel chair as a teenager Late and mild cognitive decline Epileptic seizures are frequent Head trauma as a provoking factor (55% of patients with seizures) Status epilepticus (staying in the seizure) occurs ofter (17% of patients with seizures)
What would you observe in a sample of an MLC patient under a microscope?	Electron microscopy of MLC  Endfeet of astrocytes are swollen Vacuoles between myelin sheets
What percentage of MLC patients are unexplained genetically?	MLC1 and GLIALCAM 6% of patients do not have these risk factors  Classical MLC (homozygous for MLC1 or GLIALCAM) Remitting MLC (heterozygous GLIALCAM) More often autistic

Where are MLC1 and GlialCAM localized in the neuron?	MLC1 and GLIALCAM are colocalized in astrocyte endfeet Genes are dependent on each other to reach their normal localization at the endfeet 
What is the dry and wet weight of MLC mice brain? What does this indicate?	Mouse model Dry weight of the diseased brain is the same - Proteins, fat Wet weight of the diseased brain is much heigher - Suggests accumulation of water Increased brain water content  Swelling of astrocyte endfeet Progressive vacuolization of white matter
What is the motor phenotype of MLC mice models?	Motor problems in mice model Running is the same/Amount of movement is the same BUT, when you pick up a mouse by their tail - They do not move as much  Hind limb clasping

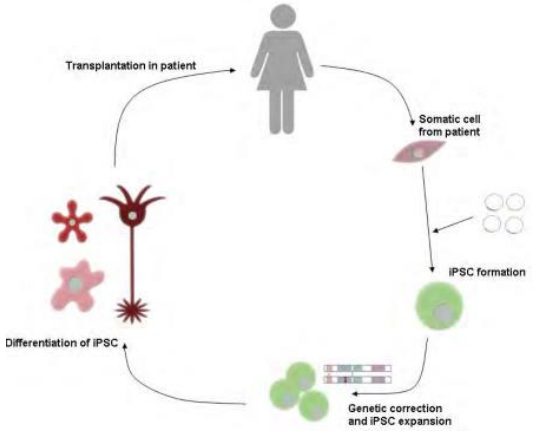
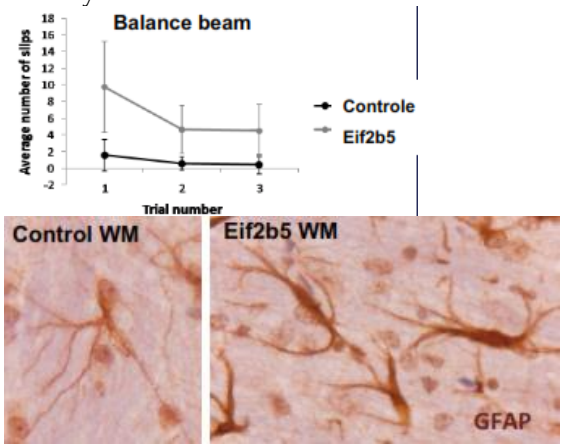
What is the difference between normal mice and MLC mice in terms of epilepsy?	Epilepsy in MLC mice MLC mice - Small discharges (interictal spikes)  MLC mice have a lowered seizure threshold
What is the importance of maintaining a specific concentration gradient in the brain?	The brain has a large amount of ion transporters to maintain a very specific concentration gradient - Spends a lot of energy When a membrane is impermeable - no concentration gradient When a membrane is semipermeable - Ions can go through (concentration gradient) Potential difference - Eletrical and chemical 
What happens if excess potassium accumulates in the extracellular space?	During neuronal activity ions and neurotransmitters accumulate in the extracellular space  Accumulation of potassium may lead to seizures (epilepsy) or spreading depression (migraine) Notice how action potentials cannot be generated during spread depression

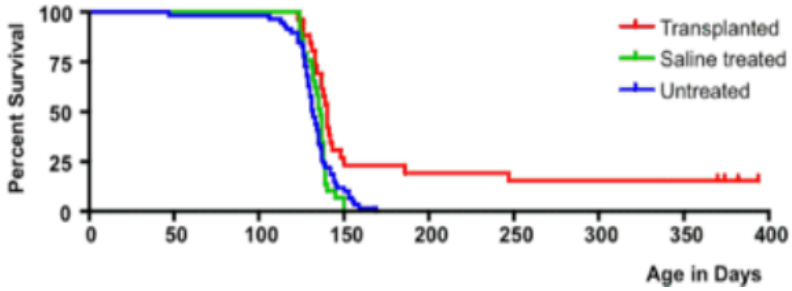
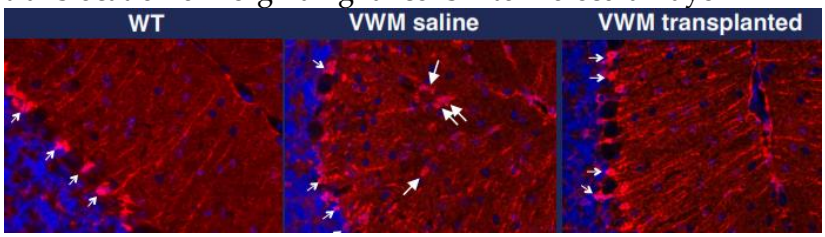
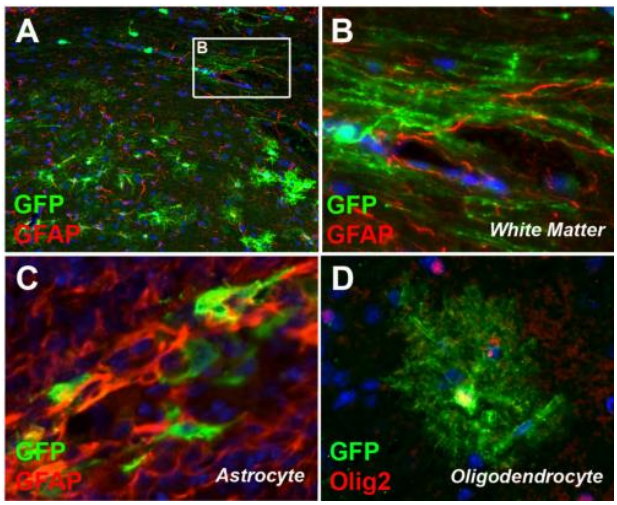
What is the importance of astrocytes in maintaining concentration gradients?	Astrocytes take up potassium from the extracellular space and redistribute it  Extrapotassium can be redirected to the blood vessels Potassium channels are clustered underneath the myelin sheet in oligodendrocytes - Flow via gap junctions to the astrocyte
Describe the run-away loop that can happen if potassium is defective.	If this is defective -> potassium accumulates and water accumulates Run-away loop 
What is RVI and RVD?	Volume regulation in mammalian cells  RVI (regulatory volume increase) - Induced when cells shrink RVD (regulatory volume decrease) - Induced when cells are swollen VRAC - Ion channels that let negatively charged molecules go through

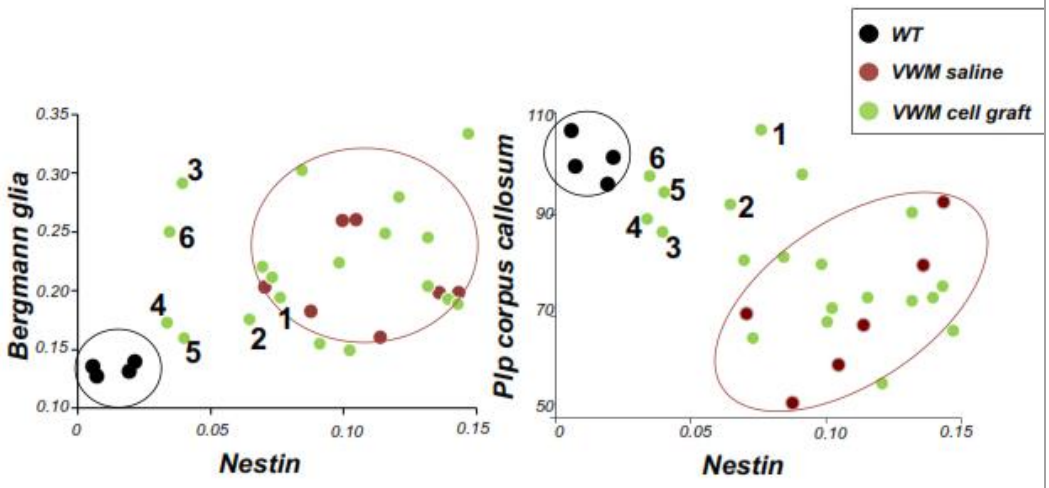
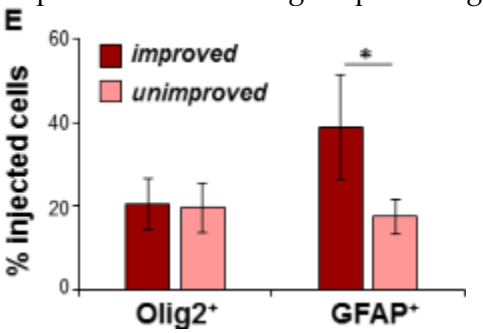
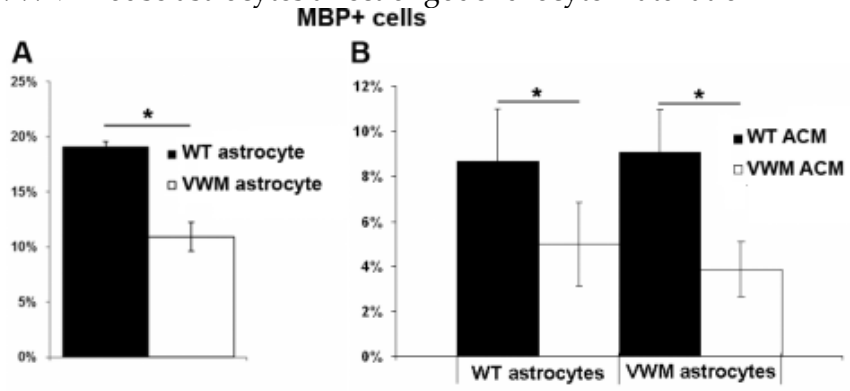
What happens with volume regulation in MLC patients? What is the root cause of that?	RVD is defective in lymphoblasts from MLC patients   Tamoxifen - Blocks VRAC channels 
What happens with extracellular potassium in MLC?	Intrinsic neuronal properties are unaltered in MLC Patch-clamp recordings from MLC mice - Action potential is normal Extracellular potassium is altered 
What are similarities and differences between Muscular Dystrophy with Brain	Balance of ions and water in the brain 

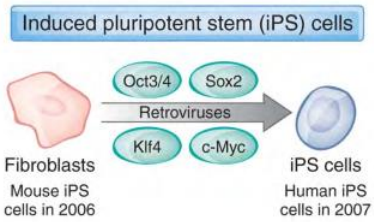
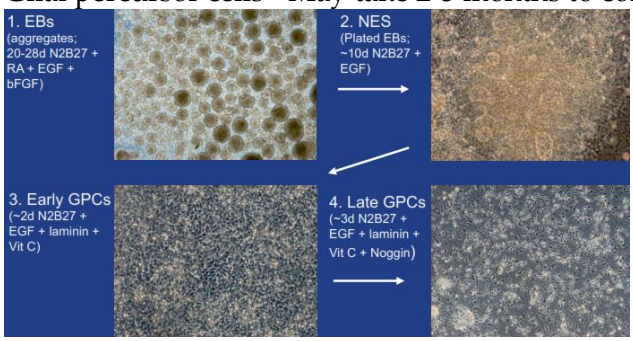
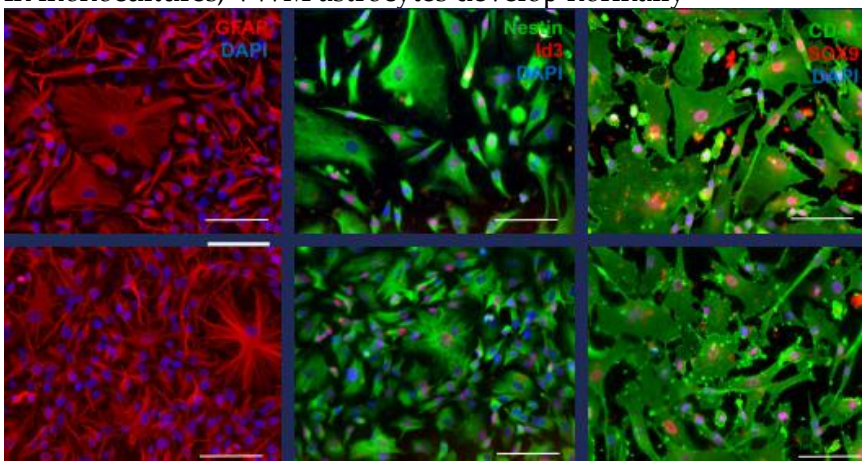
Involvement and MLC?	Muscular dystrophy with brain involvement White mater edema, subcortical cysts, myelin vacuolization MRI is virtually indistinguishable from MLC ○ Laminin is defective
What do mutations in CLCN2 induce in humans?	Idiopathic generalized epilepsy  CLCN-2 - Paper retracted due to evidence of fraud CLCN2 knockout mice- Phenotype very similar to MLC (vacuolization); expression overlaps with GlialCAM Not the case - Patients with CLCN2 mutation have very mild white matter abnormalities, patients have headaches (not seizures)
What is the molecular cause for X-linked Charcot-Marie-Tooth?	X-Linked Charcot-Marie-Tooth  Mutations in GJB1 (connexin 32) - Junctions are compromised Transient white matter edema and myelin vacuolization - Happens after exertion, high altitude or infection
	Conclusion Disruption of protein involved in ion and water homeostasis can lead to neurological disease (WMD) Expressed by glial cells - Related to redistribution of ions

13b. Stem Cell Replacement Therapies for White Matter Disorders

How can we answer pragmatic questions about stem cell research?	Cell replacement therapy - Questions Do cells recover affected areas? What types of cells need to be transplanted? Can we use patient stem cells? Advantage: Avoid rejection How many cells? When, in the disease course, do we need to transplant? Is it safe? Answered by proof-of-concept studies 
What is the mutation necessary to create a mouse model for VWM? What is its phenotype?	Mouse model for VWM Eif2B5 gene - Wobbly walk from 5 months, seizures and ataxia, dies around 7-10 months Results - Worst balance, decreased myelin gene expression, dysmorphic astrocytes 

What is the mutation in Shiverer mice? What is its phenotype? What happens when human glial precursor cells are transplated into these mice?	Proof of concept studies in mice Shiverer mouse - Not equivalent to human disorder (major deletion in MBP gene, reduction in myelin), tremor from 12 days, seizures around 30 days, death around 120-150 days Human glial precursor cells transplantation into immunodeficient Shi mice (avoid rejection)  GLC develop into astrocytes - Improves phenotype (less shivering, animals live longer)
What happens when you implant Glial Precursor Cell into eIF2B5 pups at the molecular level?	In vivo glial cell replacement studies GFP-labelled mice GPCs injected into eIF2B5 pups - Reduced nestin+ astrocytes (nestin is an indication of immaturity), decreased number of undifferentiated oligodendrocytes (2b5ho -> do not produce myelin), less translocation of Bergman glial cells into molecular layer   Cell grafts successfully differentiate into glial cells

What happens when you implant Glial Precursor Cell into eIF2B5 pups regarding phenotype?	Recovery on VWM disease markers  Discriminant analysis - Function explains 95,1% (p<0.001) Recovery on clinical phenotype Balance improves
What was the main difference between mice that had an improvement in phenotype after transplanting GPCs?	Improved mice had higher percentage of GFAP+ donor cells  Improvement may be caused by cell differentitation
What do VWM astrocytes do to affect myelintion?	VWM mouse astrocytes affect oligodendrocyte maturation  VWM astrocytes normally inhibit OPC maturation

What are the four factors necessary to produce iPS cells?	Induced pluripotent stem cell technology  Four factors: Oct3/4, Sox2, Klf4, c-Myc -> Create pluripotent stem cells (all cells except for placenta)
What are the three main applications for iPSC?	Applications for iPSC - In vitro disease modeling, drug development, cell replacement therapy Glial cells contribute to almost all neurological disorders
How long does it take to make GPC from differentiated cells? What implication does that have in the clinic?	Glial percursor cells - May take 2-3 months to complete protocol  If disorders are rapidly evolving, stem cell therapy may not be fast enough
What happens to iPSC-derived grey and white matter astrocytes?	In monocultures, VWM astrocytes develop normally  However, they proliferate more Recent studies indicate astrocyte heterogeneity -> maybe astrocytes in white matter look abnormal in VWM

	Creation of human iPSC-derived grey and white matter-like astrocytes Different markers White-matter astrocytes are more affected in VWM
How would you confirm that a cell lineage is pluripotent ?	Confirming pluripotency of stem cell lineage They are able to differentiate into all types of cell types