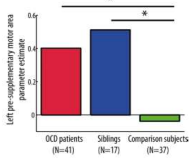
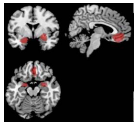
Obsessive-compulsive disorder; translating between patient experience, disease models, brain imaging and therapy response

Brothers and sisters of OCD patients work well as a control group - Genetic similarity often reveals that the same brain areas are active, even though they do not present symptoms



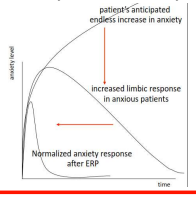
- OCD has an early and a late form
  - Adult OCD - Bigger striatum, smaller hippocampus (Comorbidity with depression); Thinner cortex
  - Child OCD- Larger thalamus; Decreased surface area of cortex

- Symptom provocation of OCD in an fMRI activates



  - Bilateral amygdala - Mainly for disease specific stimuli (unmedicated > medicated)
  - Right putamen
  - Subgenual ACC/OFC

- OCD is commonly considered an anxiety disorder

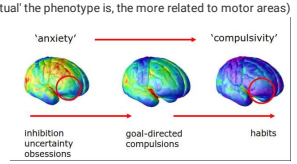


  - Harm avoidance/doubt/uncertainty
  - Anxiety/stress
  - Hyper-responsive limbic circuitry

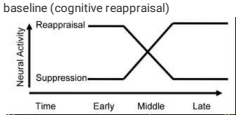
- OCD entails intrusive thoughts and repetitive behavior -> phenotypes are varied (washing rituals, checking locks, etc.)

- 1-3% of people are affected - diagnosis often occur in early adulthood. Often disguised socially (patients present their symptoms when they are alone)

- OCD has major overlap with anxiety and depression - It starts as an anxiety disorder, then becomes compulsive (- The more 'habitual' the phenotype is, the more related to motor areas)



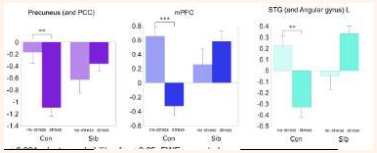
- Cognitive behavior therapy works when the patients mPFC learns to inhibit the amygdala; dPFC learns to bring emotion back to baseline (cognitive reappraisal)



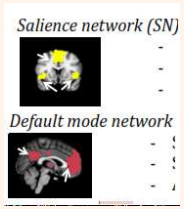
  - Reappraisal depends on a proactive mindset - the PFC must be active before the amygdala
  - Future - CBT + TMS (activate dPFC)

Stress and neuropsychiatry

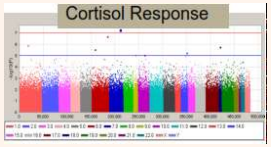
Cortisol is usually measured from saliva samples, which is not a good representation of brain stress and may lead to incorrect conclusions



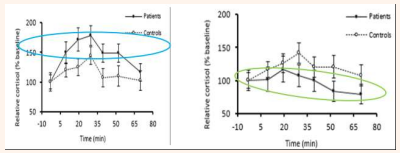
- Stress increases Salience network (during the stressful event, it decreases after administration of cortisol) and Default Mode Network (during cognitively demanding tasks)



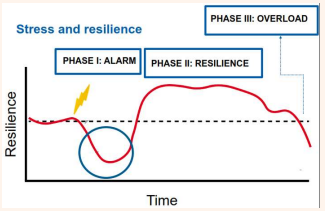
- Epigenetic changes may persist due to childhood trauma (GWAS -> KITLG, which is a stem cell factor)



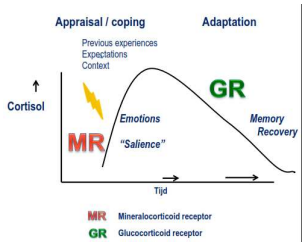
- Men with depression have increased levels of cortisol; women with depression have decreased levels of cortisol



- Stress = Bodily response to a stimulus; Resilience = Ability to recover from stress

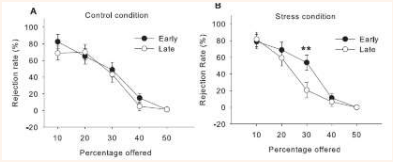


- Cortisol binds to two different receptors in the CNS: Mineralocorticoid and glucocorticoid



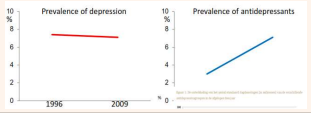
- MR is expressed in limbic system and has a high affinity for cortisol - Important in appraisal (your initial stress depends on your experience) and coping
- GR is expressed in the whole brain and has a low affinity for cortisol - it decreases cortisol in the bloodstream by modifying gene expression. Important for adaptation.

- In a game of unequal division of money, your levels of cortisol play an important role in your decision



Ins and outs of depression

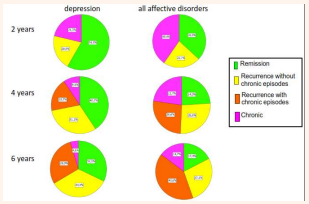
- The prevalence of depression has remained the same while the use of drugs for depression has significantly increased
  - Prescribed does not mean that it is used
  - Antidepressants are not only used for depression
  - More and more chronic users
  - Efficacy of antidepressants is not great (especially over long term)
  - Adequacy of antidepressants: difference in efficacy and true effectiveness



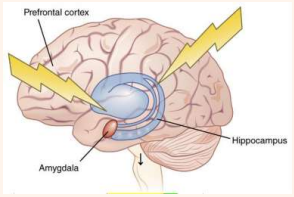
- The effect of psychotherapy is quite modest (0.35 compared to 0.2 of placebo) - this has led to a ressurgence of non-pharmacological treatment options
  - Mindfulness
  - Internet psychotherapy
  - Running therapy
  - Behavioral activation
  - Collaborative care
  - Transcranial stimulation
  - ECT
  - Deep brain stimulation

- Depression has a big impact on the economy - People with depression lose 30 productivity working days every year (including not going to work or going to work while feeling unwell)

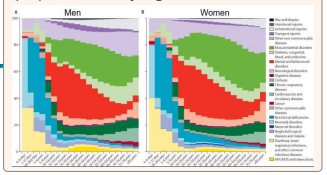
- It is important to follow up patients after remission - After 6 years, only 17% of patients do not have a relapse episode



- Physical alterations in the brain due to depression:
  - Structural - Decrease in size of hippocampus, amygdala, prefrontal cortex
  - Connectivity - Increase of DMN, decrease of salience and central executive functions
  - Functional activation: Striatum



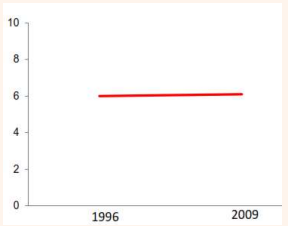
- Depression peaks at a young age because young people are less likely to get other diseases



- Depression is characterized in the DSM-5 by having 5 chronic symptoms:
  - 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

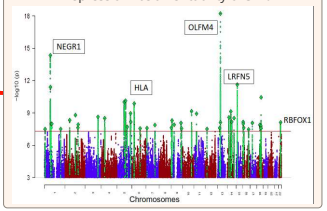
- The prevalence of depression depends on how you measure it:
  - Timeframe: "Have you ever been depressed?" vs "Were you diagnosed with depression last 5 years?"
  - Characteristic of population (females are more prone to have depression/anxiety)
  - Measurement instrument - Self-report vs professional diagnosis

- There is no depression epidemic in the Netherlands - Rates of the disease have remained stable over the last 20 years



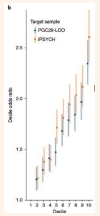
- Even though stress has increase, other risk factors have gotten better

- Depression has a heritability of 37%

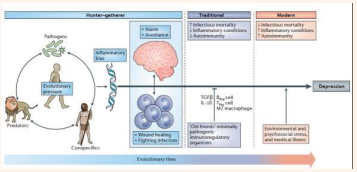


Biological pathways of MDD

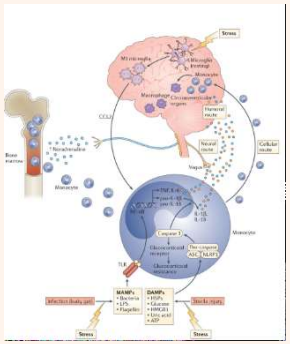
- Depression is a highly polygenic disorder



- Depressive behavior (social withdraw, reduction of activity) may be an evolutionary response for sickness. It may be the case that our current world triggers this response by psychosocial means



- Inflammation triggers depression (inflammazome enters brain), depression triggers inflammation (overactivation of the HPA axis)

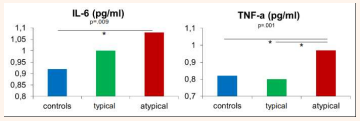


Supporting evidence: Autoimmune diseases + early infections increase risk of mood disorders

The use of inflammatory drugs induce depression

Inflammation markers increase in depression

- Depression subtypes

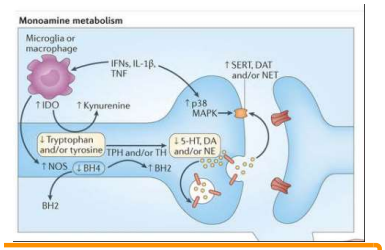


Atypical - Inflammation plays an important role. Symptoms: Hyperfagia, weight gain, hypersomnia, fatigue, leaden paralysis

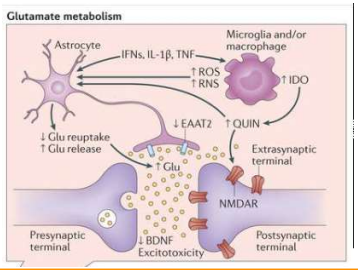
Typical - Inflammation doesn't play an important role. Symptoms: Decreased appetite, weight loss

- Three hypothesis:

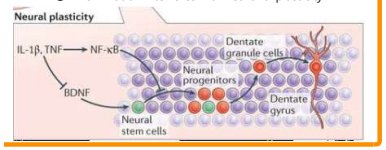
Inflammation interferes with the production of monoamines



Inflammation increases availability of glutamate

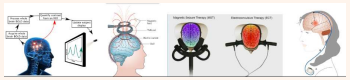


Inflammation interferes with neuronal plasticity



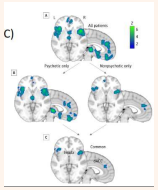
Neuroimaging in Depression

- Current treatment options for therapeutic neuromodulation:
  - Neurofeedback
  - Non-invasive brain stimulation
  - Electroconvulsive therapy/Magnetic seizure therapy
  - Deep brain stimulation

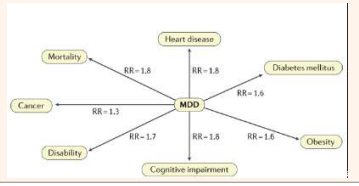


- Depression is highly heterogenic: Age of onset, treatment resistance, number and duration of episodes, severity and functional impairment. There are 227 combinations of symptoms to define 'depression'
  - Promising avenues to deal with this: Meta-analysis with more and more patients; mega-analysis (raw data from each experiment + machine learning)

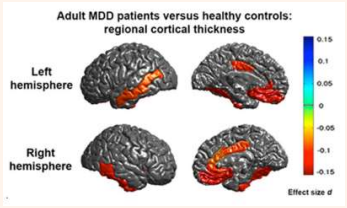
- Common problems among all affective disorders: Decreased gray matter volume and insula (associated with decreased executive function)



- Depression has a high comorbidity with other disorders

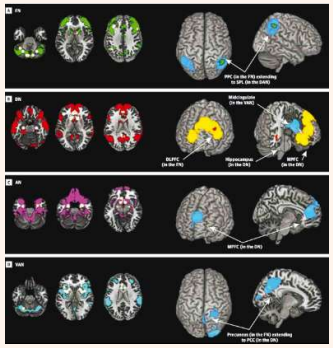


- MRI findings: Altered brain volume - Decrease in OFC, ACC, PCC, insula, temporal lobes, hippocampus (small effect size); Increase in amygdala volume

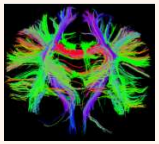


- Task-based fMRI has contradictory results for MDD. Possible explanations:
  - Different inclusion criteria
  - Heterogeneity of experiments - Faces only vs all experiments
  - Study quality (small sample size)
  - ROI (specific brain regions - inflates chance of finding spurious significant results) vs whole brain

- Functional connectivity findings: Decrease in frontoparietal network, affective network, ventral attention network; Increase in default mode network



- DTI findings: Decrease in fractional anisotropic (decrease in overall connectivity)
  Increase in mean diffusivity and fractional diffusivity (structural disconnectivity)

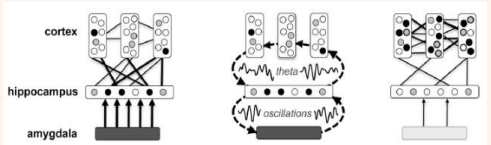


PTSD

- PTSD is defined in the DSM-5 by:
  - 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

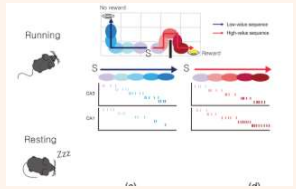
- PTSD can be considered a memory disorder (ECRR)

- When you consolidate a memory, it loses its emotional content.
  Problem with PTSD: Activation of amygdala reactivates hippocampus (patients relive a memory)

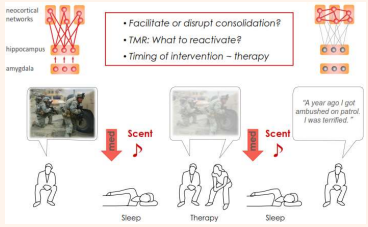


  - Linked to sensory, emotional and autonomic markers
  - Not verbally accessible
  - No autobiographical context
  - Involuntary retrieval

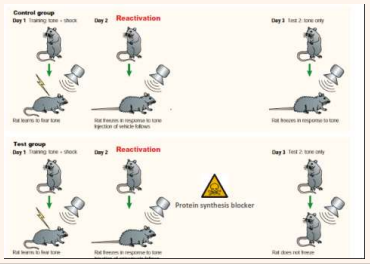
- Sleep plays an important role in memory consolidation - Neuronal replay (may be the function of dreams)



- Smell/sounds can be used to enhance memories during sleep - possible alternative treatment (smell during therapy session, present the same smell during sleep)

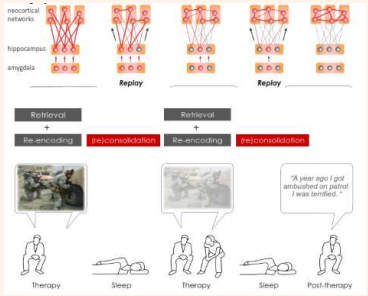


- Memory reconsolidation - Every time you remember something, the neuronal connection changes (anisomycin can block fear conditioning)



- Extinction learning - Old memory is still present, patients learns to ignore it

- What you can do to manipulate reconsolidation window (10 minutes to 6 hours)

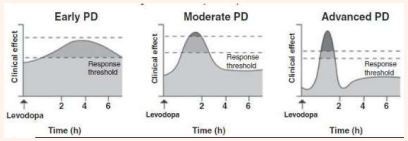


  - Eliminate memory trace - Not possible in humans
  - Disrupt old memory trace - Propranolol, inhibits norepinephrine (diminishes negative memory coding)
  - Update old memory trace - update and extinguish fear memory
  - Strengthen old memory trace - Cortisol

- Pharmacological interventions for PTSD
  - SSRI - Not linked to memory consolidation/reconsolidation
  - MDMA is not an established drug for PTSD - Patient feels good
  - Enhancing memory drug (D-cycloserine) - Given to treatment after therapy session

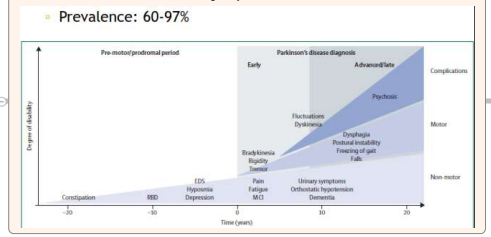
Parkinson's

- Levodopa treatment becomes less effective over time (end of honeymoon phase)

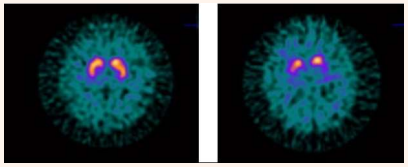


- The main side effect for levodopa treatment is the development of impulsive control disorder

- Non-motor symptoms of PD include
  - 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



- DAT-SPEC - Shows assymetry in dopaminergic degeneration (red = caudate nucleus + putamen)

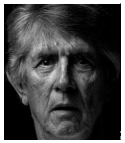


- Red flags:
  - Rapid progression of gait impairment
  - Complete absence of motor symptom progression (more than 5 years)
  - Early bulbar dysfunction
  - Inspiratory respiratory dysfunction
  - Severe autonomic failure early in disease
  - Disproportionate anterocollis
  - Symmetric parkisonism - Typical PD is lateralized

- Parkinson's disease has a high prevalence for people over 65 years of age (1%). The number of Parkinson patients will increase over due to an increase in overall lifespan.

- Risk factors for PD include aging and herbicides. Protective factors include nicotine and caffeine.

- Patients often do not know they have PD, then come to the clinic complaining about secondary symptoms (muscle cramps, loss of smell)



Sign of PD - Hypomimia

- Parkinsonism is defined as bradykinesia (decrease in amplitude and frequency of movements) + rigidity or resting tremor (is not present in 25% of PD patients)

- Clinically established PD requires two supportive criteria + no red flags

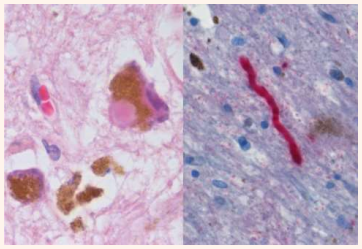
- Supportive criteria:
  - Responsible to levodopa - Effects within 30 minutes
  - Hyposmya - Loss of smell (substantia nigra loss degenerates olfactory bulb)
  - Resting tremor

- Exclusive 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

Alpha-synuclein and PD

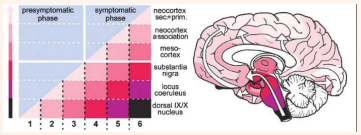
- 95% of Parkinson's disease occurrence is idiopathic/sporadic (we can't explain why)

- Alpha-synuclein is an important component of familial and sporadic PD. Evidence:



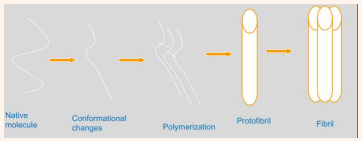
  - Point mutations in alpha-synuclein gene cause rare forms of PD
  - Transfection of human alpha-synuclein genes induce morphological and clinical symptoms of PD in animal models

- Braak stages - First affects olfactory bulb (loss of smell), then the entire brain

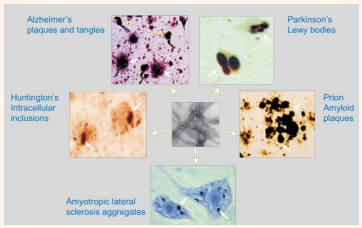


- Possible mechanism for α-synuclein damage: Pores are formed in the cell membrane, it cannot maintain homeostasis and dies

- α-synuclein aggregates forming beta-sheets - Decreases solubility, promotes a cascade of nucleation events (bad proteins converting good proteins)

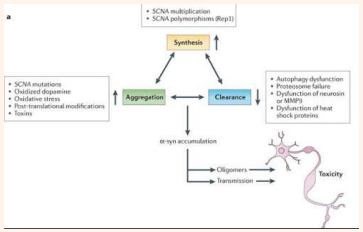


Intrinsically disordered proteins - Some flexibly shaped protein may be root of many neurological disorders

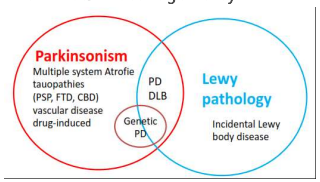


- Alpha-synucleopathies include:
  - PD
  - Dementia
  - Multiple system atrophy
  - Neurodegeneration with brain iron
  - Immunoreactive lesions

- α-synuclein depends of three factor (clearance gets worse with aging)



Clinical heterogeneity in PD



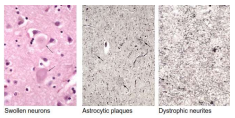
Other diagnosis

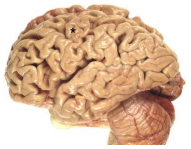
- Drug induced Parkinsonism - Propanolol
- Incidental Lewy Body disease - Due to normal aging (lesser concentration than PD)
- Inherited Lewy Body disease - Mutations of alpha-synuclein gene are very rare but it is always causal. E.g. LAC2/Glucoseroxidase (50% of population in the Netherlands)
- Dementia with Lewy body - Clinical symptoms are memory, personality change

- Quantification of alpha-synuclein

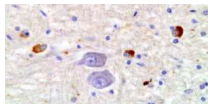
- Soluble
  - • Total alpha-synuclein - Does not change
  - • Phosphorylated alpha-synuclein - Increased in CSF of PD patients
- Aggregates/Truncated alpha-synuclein
  - • Not detectable in controls
  - Present in Lewy body diseases

Corticobasal degeneration - Tauopathy, Degeneration of motor areas in the brain, increased ventricles





Multiple System Atrophy - Facial problem, more symetrical, do not respond well to levodopa



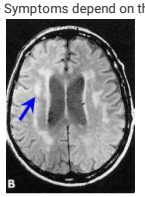
- Neuroanatomically - Olivopontocerebellar atrophy
- Glial inclusions in oligodendrocytes

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)

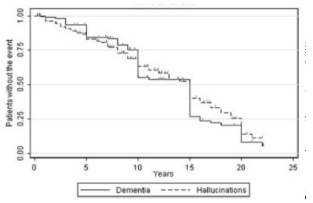
- Low phosphorylated tau in the CSF - High concentration in the brain
- Spider-like staining

Vascular Parkinsonism - Symptoms depend on the affected brain region

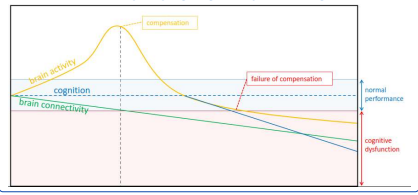


Cognition And Pd

- 50% Of Pd Have Cognitive Problems - 20-25% Already In The Time Of Diagnosis; 80% Of Pd Patients Develop Dementia Within 20 Years

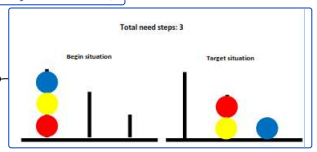


Project Goals (cogtips) - Increase Compensation Training Of Pd Patients By Playing Cognitively Enhancing Games.



- Improve Cognitive Function
- Understand Neural Mechanism Of Cognitive Training
- Delay Cognitive Decline

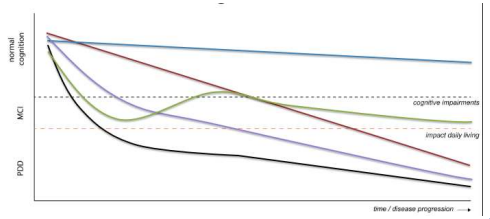
- Common Cognitive Impairments:
  - Executive Functions
  - Attention
  - Working Memory
  - Visuospatial Function
  - Semantic Memory (episodic Memory Usually Not Affected)
  - Planning - Shown In Tower Of London



- Available 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)
  - Transcranial Magnetic Stimulation (tms) - Effects Last For One Hour In He Beginning, Duration Increases With Treatment Progression
  - Transcranial Direct-current Stimulation (tdcs) - Device Has To Be Wore Continuously

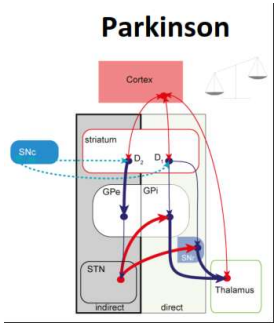
- Genetic Risk Factors Of Pd
  - Snca (alpha-synuclein)- Mutation Causes Familial Pd + Cognitive Impairment + Increased Risk Of Pdd
  - Apoe (apoliprotein E) - Associated With Pdd
  - Gba (glucosylceramidase - Glucose Metabolism) - Associated With Subject Cognitive Complaints

- Later Stages:



  - Hallucination/psychosis
  - Considerable Morbity
  - Decreases Independence, Increases Hospitalization

- Pathways Affected In Pd - D2 Is Less Inhibited, It Then Becomes More Active



- Direct - 'gas'
- Indirect - 'break'
- Dopaminergic Pathways Mediates 'stoping Or Going'
- D1 - Excitatory
- D2 - Inhibitory

- Pd May Be Subvided Into Two Phenotypes:
  - 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)