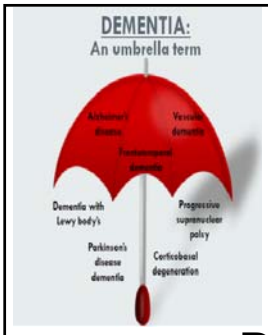
Dementia

Clinical Neuroscience
26.03.2018



Term «dementia»

lat. demens = insane, mad
lat mens, mentis = mind, meaning

Dementia is a SYNDROME

There are different defintion

In DSM-5 *dementia* «is no more»

"DSM" American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), VA 2013.

delirium = acute confusion disturbance state

Definition dementia «Core»

- impairment must be acquired and represent a significant *decline* from a previous level of functioning
- The cognitive deficits *must interfere with independence in everyday activities*
- The disturbances are not occurring exclusively during the course of *delirium*
- The disturbances are not better accounted for by another mental disorder (eg Depression)

Dementia: ICD-10-Definition (F00-03)

- disease of the brain
- usually of a chronic or progressive nature
- duration > 6 month

- in which there is disturbance of multiple higher cortical functions:

- memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement

- Consciousness is not clouded

- The impairments of cognitive function are commonly accompanied, and occasionally preceded by:

deterioration in emotional control, social behaviour, motivation.

Syndrome «dementia» DSM-5-criteria

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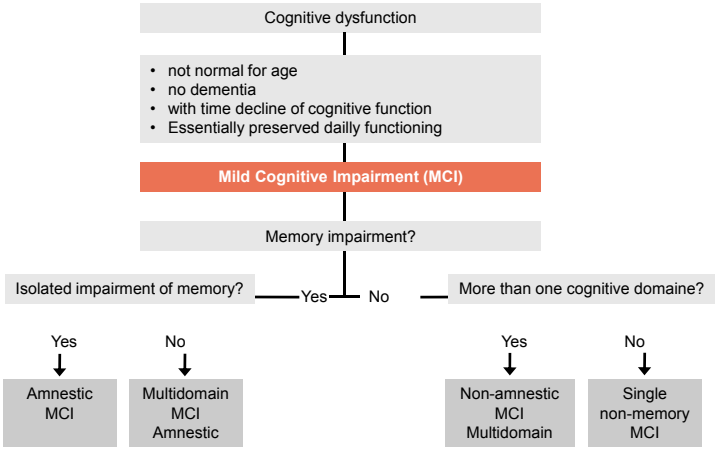
DSM-IV and DSM-5 criteria for dementia

DSM-IV criteria for dementia	DSM-5 criteria for major neurocognitive disorder (previously dementia)
A1. Memory impairment	**A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
A2. At least one of the following: - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning	
B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning	**B.** The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively during the course of delirium	**C.** The cognitive deficits do not occur exclusively in the context of a delirium
	D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

"DSM" American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), VA 2013.

The intermediate state
Mild Cognitive Impairment

an intermediate state between normal cognition and dementia



[nach Winblad 2004]

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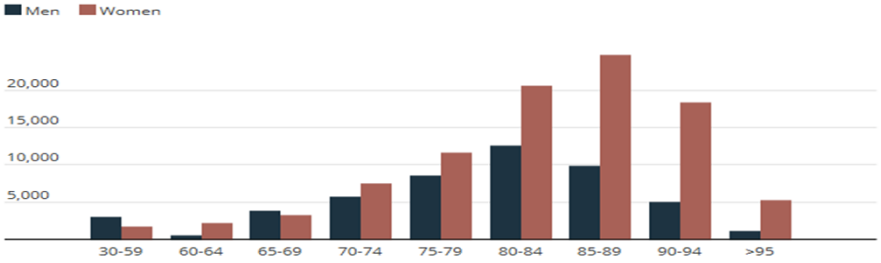
Dementia cases on the rise: 300 000 cases by 2040

Statistics show far more people with dementia in Switzerland than previously thought, with the number expected to more than double over the next 25 years.

In 2016, some 144,000 people living in Switzerland had a form of dementia, according to new numbers from the non-profit organisation Alzheimer Switzerland. Last year, the group estimated that it was "only" about 120,000, based on information from the Federal Statistical Office, which had put the figure at 110,000 in November 2016.

144,000 people with dementia in Switzerland (2016)



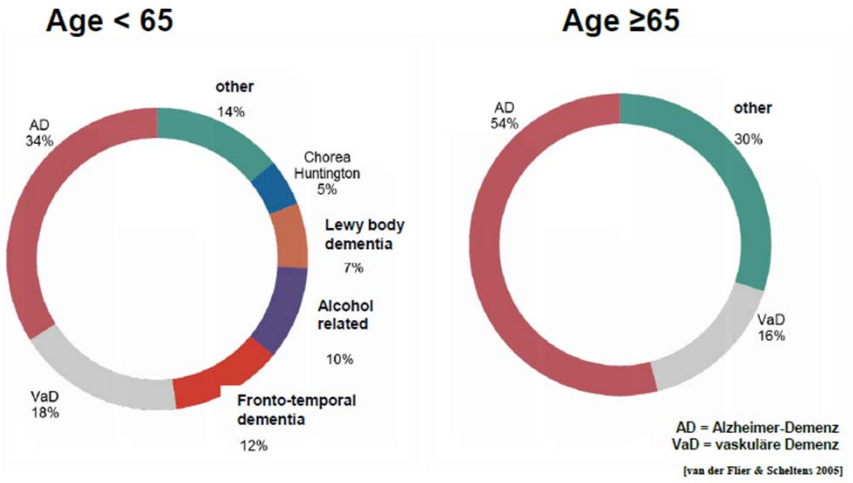
Source: Federal Statistical Office Get the data

Dementia – facts and figures

Someone in the world develops dementia *every 3 seconds*
(World Alzheimer report 2015)

Global estimates of dementia prevalence are up to *7% of individulas above the age of 65 y*
(8-10% in developed countries due to longer life spans)

Epidemiology



Two broad categories of disease:

Neurodegenerative originally called „irreversible“	**Non-neurodegenerative** originally called „reversible“
Alzheimer dementia	Vascular dementia
Frontotemporal lobar degeneration	Normal pressure hydrocephalus
Dementia with Lewy bodies, Parkinson’s Disease	Metabolic causes, Vitamin deficiency
Multiple system atrophy / **PSP** / Huntington disease / Wilson disease / Dentatorubral-pallidoluysian atrophy; motor neuron disease	Autoimmune causes Neoplastic / paraneoplastic causes
	Depression («pseudo-dementia»)
Alcoholic cognitive impairment / Chronic traumatic encephalopathy	Infectious causes trepinoma pallidum, syphillis
Prion disease	Toxic causes (lead, arsenic, pesticides)

ask when did it start, abrupt or progressive
did same occur in family earlier,
does it fluctuate (for some diseases fluctuation is a criterium, like
min to min or throughout the day etc),
also ask about all neurocognitive performances

is it caused by something else maybe?
also can do CSF testing (not main way to do though)

Evaluation and Diagnosis

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1) Thorough **clinical history**

2) Neurological examination, with emphasis on the **assessment of mental status**

3) Selective **labs** to screen for selected metabolic/physiologic abnormalities

4) Structural (functional) brain scan

Diagnostics

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Laboratory testing: TSH, Vitamin 12, others (e.g. Syphilis given a suggestive history); CSF (cells, protein, (p)Tau, β-Amyloid)

Genetical testing: The use of genetic testing for AD in patients with dementia is controversial because of the potential for both false positives and false negatives (e.g. Apolipoprotein E epsilon 4 allel)

Exclusion of treatable causes

The diagnostic process requires pattern recognition.

Diagnostics

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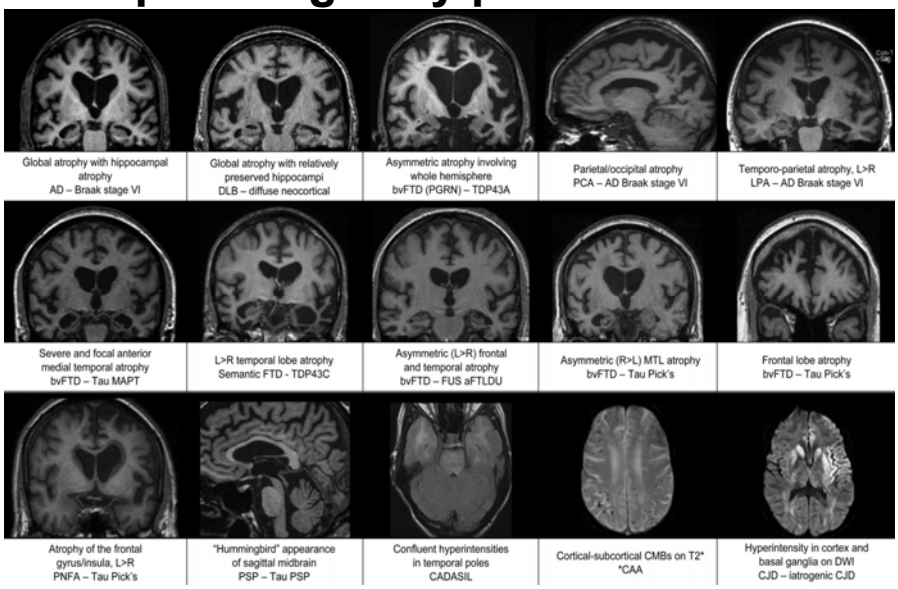
	Alzheimer's disease	Frontotemporal dementia	Vascular dementia	Dementia with Lewy bodies
History	memory loss, spatial disorientation, language failure	early personality change stereotyped behaviour	mental and physical decline	confusion, physical slowness
Neurology	myoclonus akinesia, rigidity (late)	early primitive reflexes occasional akinesia, rigidity	pyramidal weakness, ataxia pseudobulbar palsy	akinesia, rigidity, myoclonus
Memory	severe amnesia	variable loss	variable loss	variable loss/amnesia
Language	aphasia	adynamic speech, mutism	dysarthria	incoherent, rambling
Visuo-spatial function	spatial disorientation	preserved	preserved	spatial disorientation
Perception	primary recognition failure	preserved	preserved	misperceptions
Conduct	appropriate concern	inappropriate unconcern	appropriate concern	appropriate concern
Mental effort	high	low	slow	slow
Motor skills	impaired spatial configuration	impaired sequencing	impaired sequencing	impaired sequencing/ spatial configuration
CT/MRI	hippocampal atrophy	severe anterior atrophy	prominent white matter change/lacune	atrophy
SPECT	posterior	anterior	patchy	posterior
EEG	slow	normal	slow	grossly slow

Table 2. Clinical, neuropsychological and imaging characteristics of Alzheimer's, frontotemporal, vascular and Lewy body dementias

Pattern recognition

Characteristic atrophy in several forms of pathologically proven dementia



Lorna Harper et al. J Neurol Neurosurg Psychiatry 2014;85:692-698

Classification

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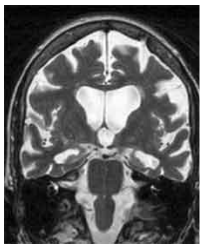
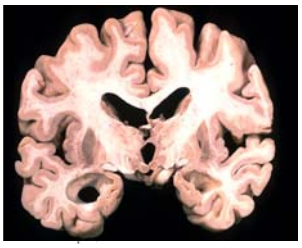
clinically
- cortical
- subcortical
- frontal

pathology
- degenerative
- vascular
- toxic
- infectious

staging
- MMST 20-25: mild
- MMST 10-19: moderate
- MMST 0-10: severe





Classification

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Cortical	Subcortical	Cortico-subcortical
• Alzheimer's disease • frontotemporal degeneration	• vascular dementia • progressive supranuclear palsy • multiple system atrophy • Huntington's disease • multiple sclerosis • hydrocephalus	• dementia with Lewy bodies • Creutzfeldt-Jakob disease • corticobasal degeneration

Cortical dementia

→impairment of higher cortical functions
- aphasia
- memory impairment
- impairment of orientation, spatial dysfunction
- apraxia
- reduced ability to judge, reduced intellectual power

Classification

Cortical	Subcortical	Cortico-subcortical
• Alzheimer's disease • frontotemporal degeneration	• vascular dementia • progressive supranuclear palsy • multiple system atrophy • Huntington's disease • multiple sclerosis • hydrocephalus	• dementia with Lewy bodies • Creutzfeldt-Jakob disease • corticobasal degeneration

Subcortical dementia

- memory impairment
- general slowing
- impairment of attention
- apathy
- diffuse cognitive deficits

Classification

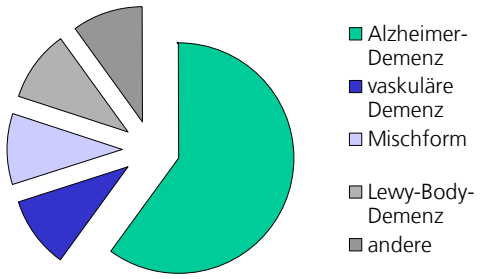
Cortical	Subcortical	Cortico-subcortical
• Alzheimer's disease • frontotemporal degeneration	• vascular dementia • progressive supranuclear palsy • multiple system atrophy • Huntington's disease • multiple sclerosis • hydrocephalus	• dementia with Lewy bodies • Creutzfeldt-Jakob disease • corticobasal degeneration

Frontal dementia

- changes in character and affection
- decrease or increase of impulse
- impairment of thinking: abstraction, planning, judgement
- memory impairment

Dementias
Differential diagnosis

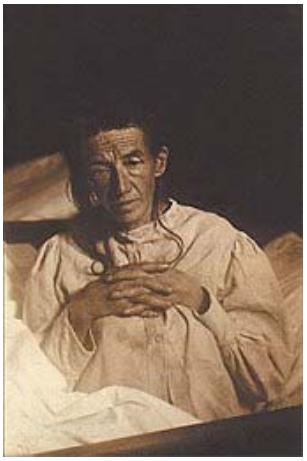
Highest prevalence in the elderly
=> Alzheimer‘s dementia (2/3)



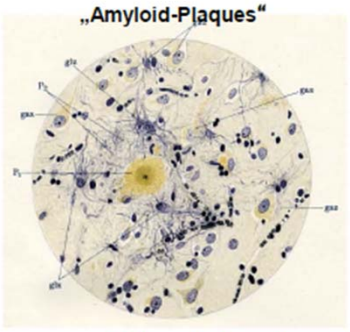
Alzheimer‘s disease

Clinical course
- **chronically progressive**
- **median survival 8-12 yrs**

Symptoms (cortical dementia)
- ***memory***
- ***spatial thinking***
- **speech**
- **apraxia**
- **agnosia**
- **attention, perception**
- **physical assessment often normal**

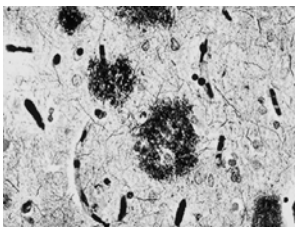


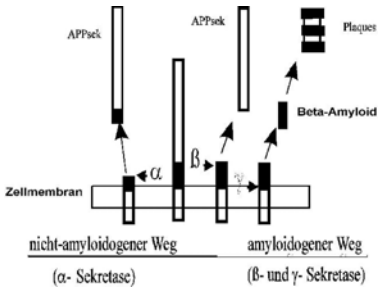
Two neuropathological hallmarks in AD



original drawings by Alzheimer on the histopathologic hallmarks

Amyloid plaques

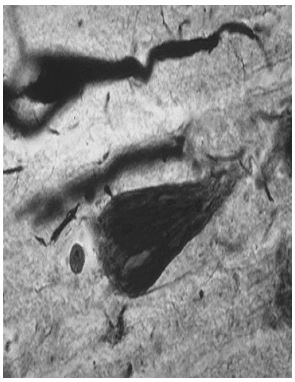




<u>Non-amyloidogeneous pathway:</u> APP is degraded via α-secretase.

<u>Amyloidogeneous pathway:</u> APP is degraded via β-secretase and γ-secretase. Generation of β -amyloid.

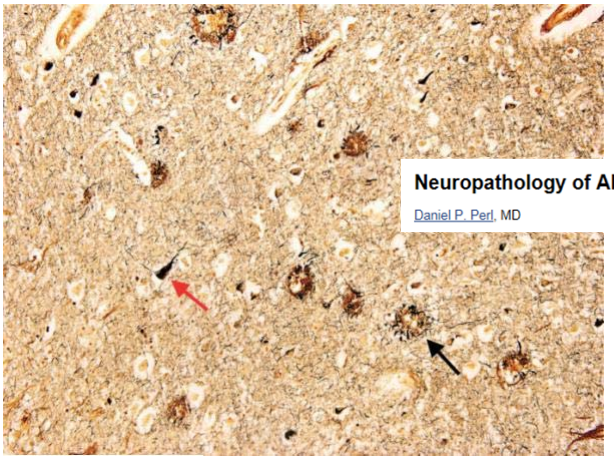
Neurofibrillary tangles



Neurofibrillary tangles: Aggregation of hyperphosphorylated tau-protein.

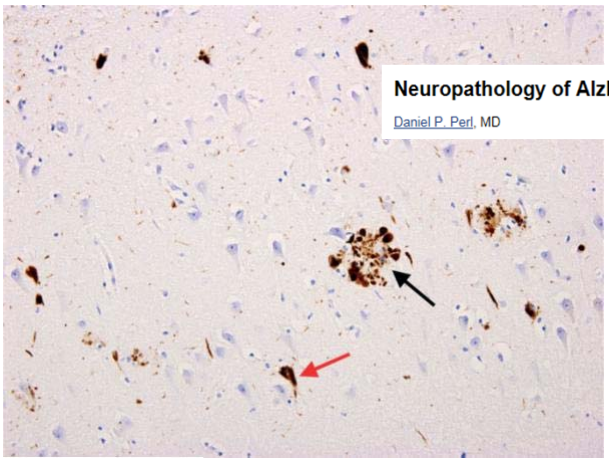
Tau binds mikrotubuli and regulates the structure of the cytoskeleton.

Neuropathology of Alzheimer's Disease

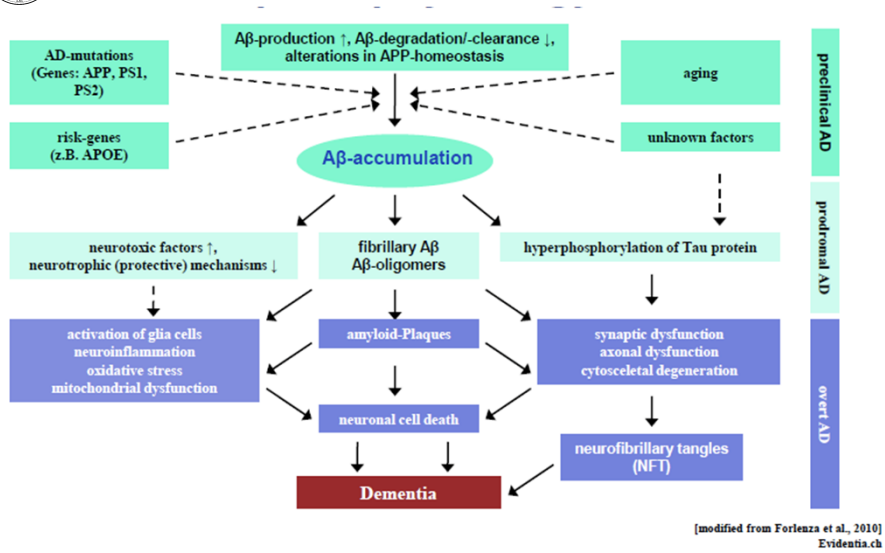


Photomicrograph of the temporal cortex of a patient with Alzheimer's disease (modified Bielschowski stain; original magnification, 40×). Numerous senile (neuritic) plaques (black arrow) and neurofibrillary tangles (red arrow) are shown.

Neuropathology of Alzheimer's Disease

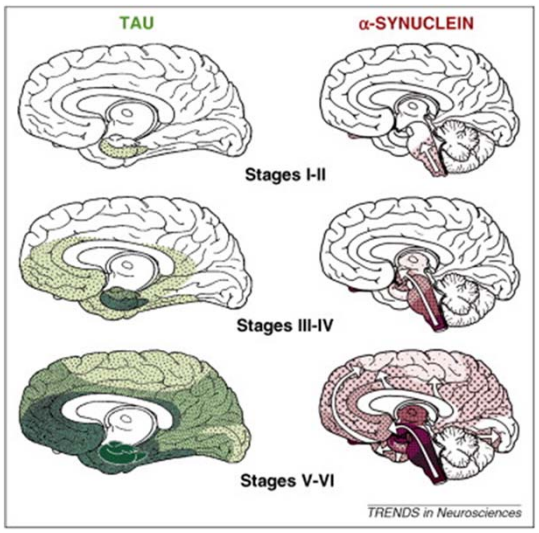


Temporal cortex of a patient with Alzheimer's disease (immunohistochemical stain; original magnification, 100×):
the microscopic appearance of an immunohistochemical preparation using an antibody directed against abnormally phosphorylated tau
This antibody prominently decorates neurofibrillary tangles (red arrow) and swollen dystrophic neurites (neuronal processes)
that form the outer rim of the senile (neuritic) plaques (black arrow).

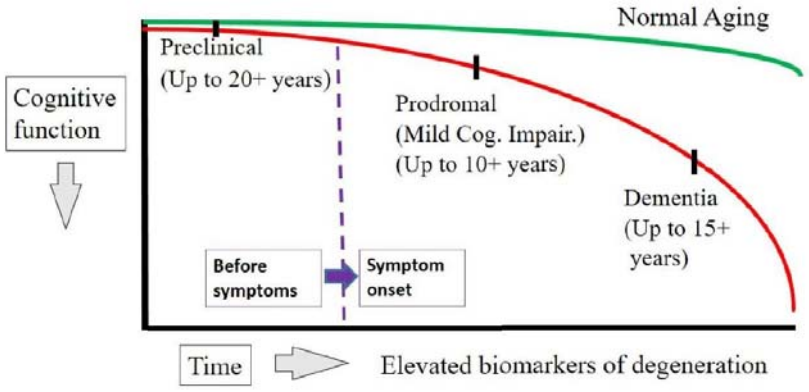


[modified from Forlenza et al., 2010]
Evidentia.ch

Temporospatial spreading of tau-positive neurofibrillary and α-synuclein-positive lesions



The Continuum of Alzheimer Disease (AD)



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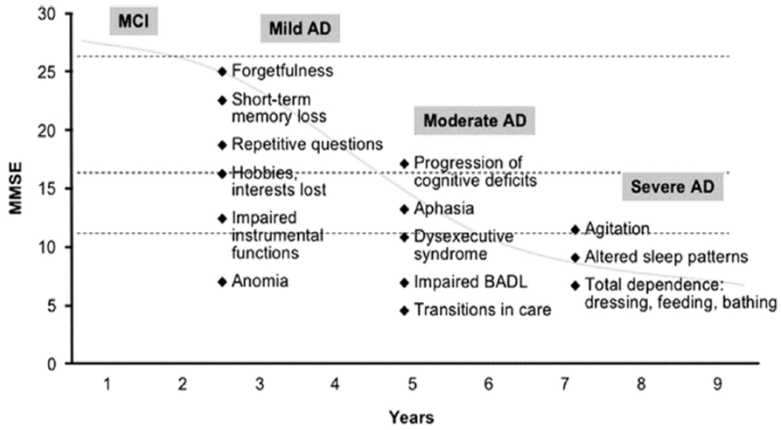
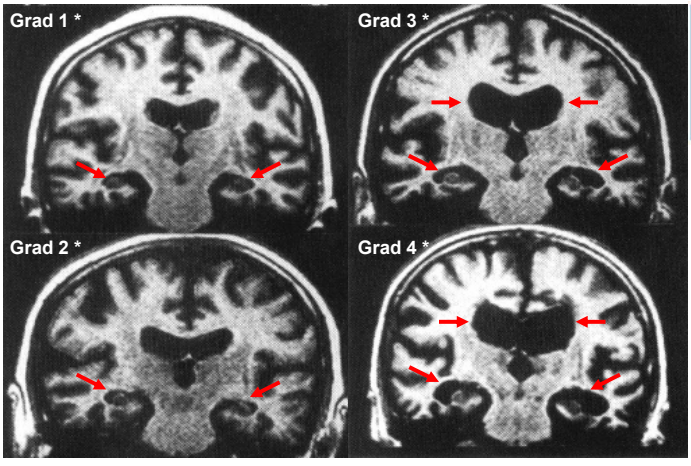
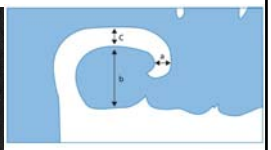
Clinical course



H. H. Feldman, and M. Woodward Neurology 2005;65:S10-S17

Alzheimer's Disease: cMRI



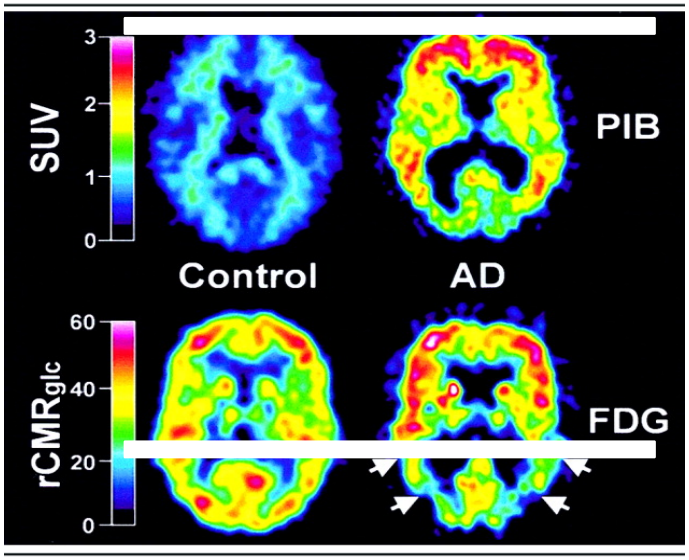


a = width of temporal horn
b = hippocampal hight
c = width of fissura choroidea

Grade	a	b	c
0	N	N	N
1	N	N	↑
2	↑	↓	↑↑
3	↑↑	↓↓	↑↑↑
4	↑↑↑	↓↓↓	↑↑↑

[nach Scheltens et al., 1995]

Alzheimer's Disease: Amyloid PET



[aus Klunk et al., 2004]

Alzheimer's Disease: etiology

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Autosomal dominant

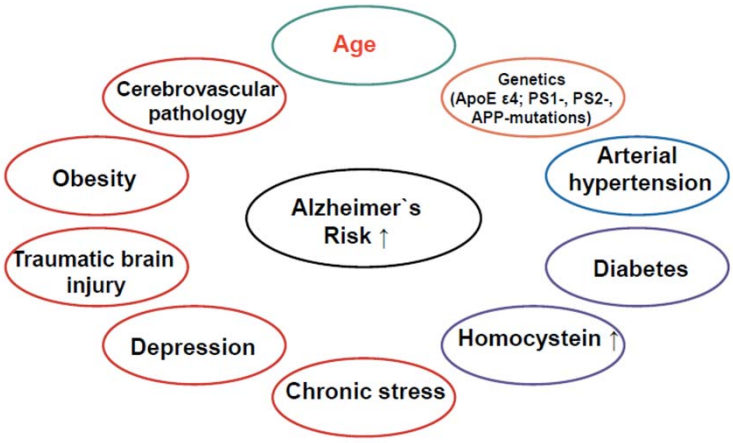
Mutations of β-APP or presenilin (part of γ-secretase):
<1% of cases

Sporadic: risk factors

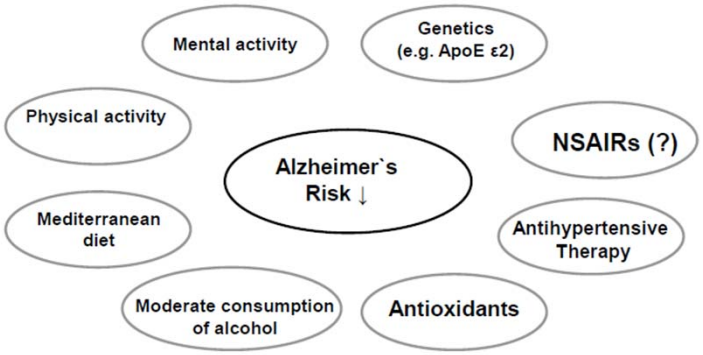
presence APO E epsilon 4-allele
- **1 allele: risk 2-3x; 2 alleles: risk 10x**
- **frequency of carriers: 20%**

low level of education
hyperhomocysteinemia
diabetes m., lipoprotein profile

Alzheimer's Disease
Potential risk factors



Alzheimer's Disease
Potential protective factors



Alzheimer‘s Disease: pathophysiology

- amyloid-plaques (extrazellular / perivascular)
- neurofibrillary tangles
- axonal/ neuritic degeneration
- loss of synapses
- loss of neurons (temporal-mediobasal and hippocampal atrophy)
- cholinergic deafferentiation, degradation of N. basalis Meynert
- glutamatergic exzitotoxicity
- immunologic processes, e.g. activation of microglia

Alzheimer‘s Disease pharmacological treatment

Symptomatic treatment

Core symptom cognition

- Acetylcholinesterase-Inhibitors
- NMDA-Rezeptor-Antagonists

Neuropsychiatric symptoms (e.g. Depression, Delusion, etc.)

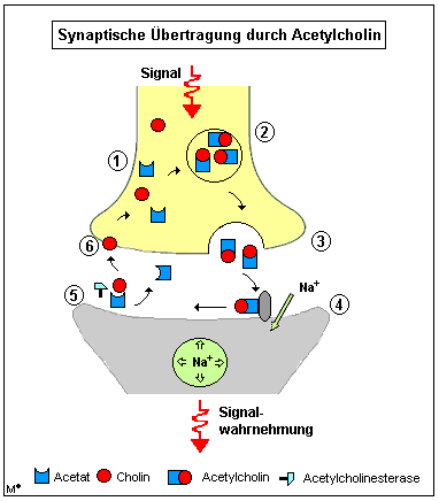
- Acetylcholinesterase-Inhibitors
- NMDA-Rezeptor-Antagonists
- Antidepressants
- Atypical neuroleptics
- Mood-Stabilizer
- Etc.

Causal treatment

„disease modifying“ (within clinical trials!!!)

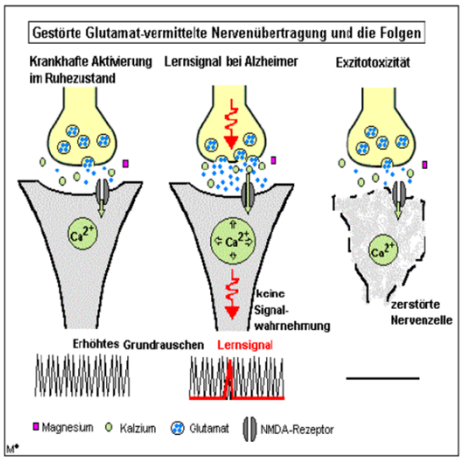
- Aβ-modifying therapies
- Tau-modifying therapies
- Antioxidants
- Neuroprotective therapies
- Anti-inflammatory treatments, etc.

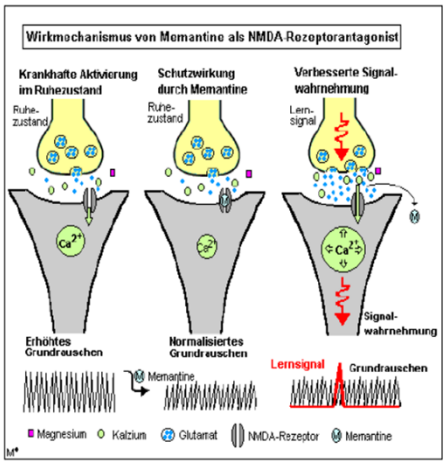
Acetylcholinesterase-Inhibitors



www.medizininfo.de

Memantine





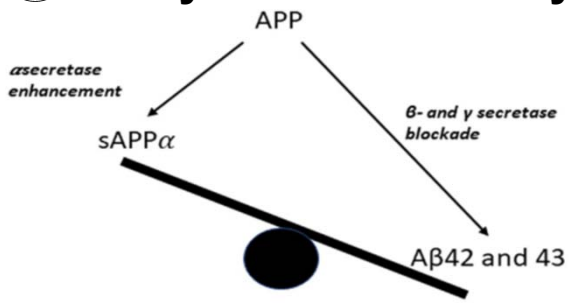
Pathologic continuous release of glutamate
-> background noise
-> leraning signal is lost in background noise

Memantine blocks NMDA-receptors
-> background noise is reduced
-> learning signal can be transmitted

Alzheimer's Disease: therapy current developments

Strategy	Examples
Modulation of neurotransmitters (*beyond Ach-I and NMDA-antagonists*)	• MAO-Inhibitors • AMPA-Receptor-modulators
Modulation of Amyloid-production	• β-secretase-inhibitors • γ-secretase-inhibitors & γ-secretase-modulators
Modulation of Amyloid-aggregation	• Diverse peptide- and non-peptide-based inhibitors of aggregation
Modulation of Amyloid-clearance	• Active immunization against Aβ • Passive immunization: IVIG, anti-Aβ antibodies
Modulation of Tau-Pathology	• Inhibitors of Tau-aggregation • Inhibitors of Tau-Hyperphosphorylation (e.g. kinase-inhibitors) • Anti-Tau/Anti-pTau-antibodies
Antiinflammatory drugs	NSAID / COX-inhibitors
Antioxidants	Vitamine C & E; MAO-B-inhibitors (Selegilin)
Lipid-lowering drugs	HMG-CoA reductase inhibitors
Neuroprotection/-regeneration	e.g. neuronal growth factors

Amyloid Cascade Hypothesis



possible therapeutic approaches

Aβ42 oligomer deposition — *Aβ clearance*

↓

Inflammatory response — *Anti-inflammatory*

↓

Oxydative damage — *Neuroprotection*

↓

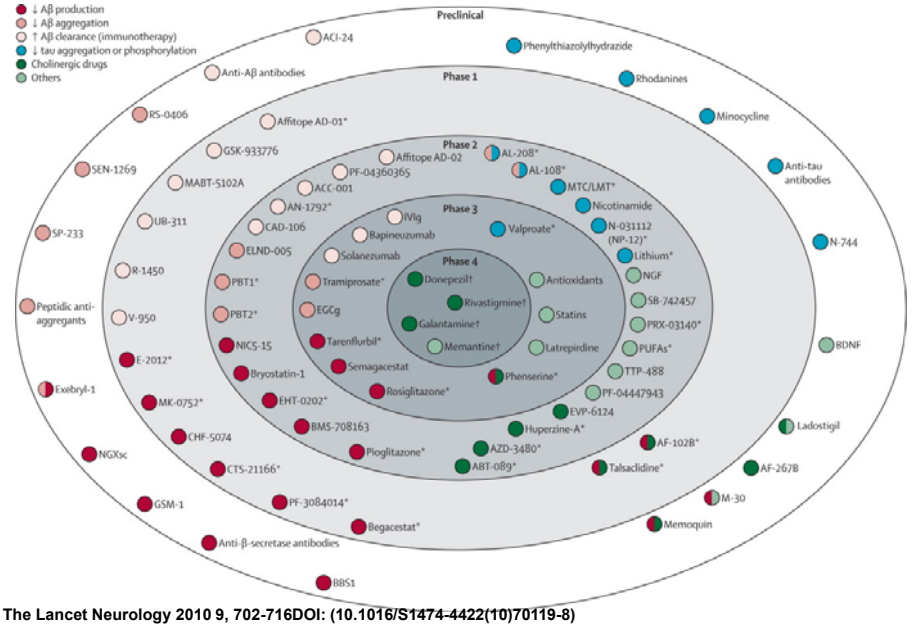
Tangle formation — *Anti-tau*

↓

Widespread synaptic dysfunction, neuronal loss, neutrotransmitter failure

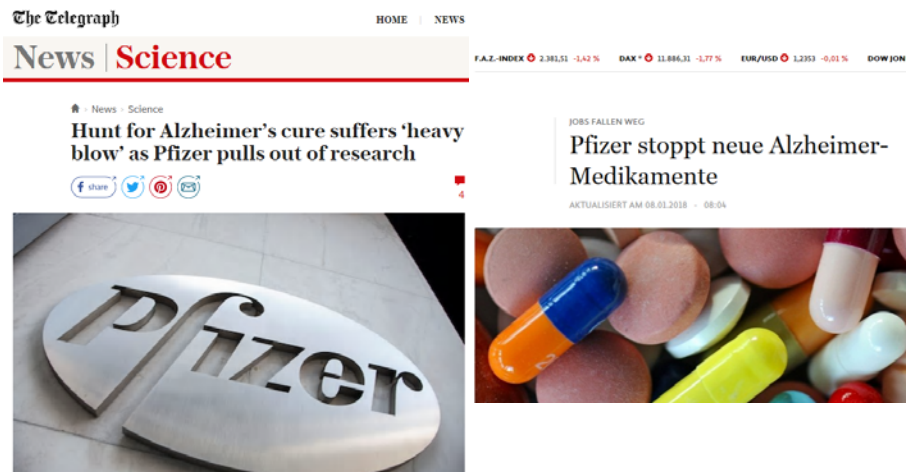
The Quest for an Alzheimer Therapy
Stefano F. Cappa

Alzheimer's Disease: therapy



The Lancet Neurology 2010 9, 702-716DOI: (10.1016/S1474-4422(10)70119-8)

Alzheimer's Disease: therapy



Alzheimer's Disease beyond drugs

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Therapeutic strategy	Description
Cognitive therapies • cognitive training • cognitive stimulation • cognitive rehabilitation • and others	→ especially in mild to moderate dementia •exercising cognitive function •memory training •giving hints to orientation in time and space
Occupational therapy («Ergotherapie»)	• Exercises to improve activities of daily living (ADL)
Physical activity	• Exercising balance, motricity, locomotion, possibly ADL
Art therapies • Music • Painting • Dance	•Improvement of neuropsychiatric symptoms •Promotion of non-verbal communication
Sensory therapies • aroma Therapy • massage • light therapy • and others	→ especially in moderate to severe dementia •use of odorous substances, e.g. in agitated patients •relaxation •communication •sleep-/wake rhythm
Family therapy	Education and training of relatives (stress reduction, symptom management)

Group of Frontotemporal Dementia

Neurodegenerative diseases linked by selective degeneration of the frontal and temporal lobe

3 distinct histologic phenotypes:

a) **Transactive responsive DNS-binding**
b) **Tau-protein**
c) **Fused-in-sarcoma**

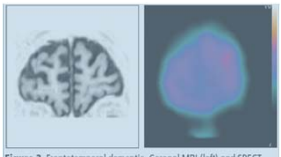

Figure 2. Frontotemporal dementia. Coronal MRI (left) and SPECT images showing severe atrophy and reduced blood flow in the frontal regions

Most common clinical syndromes

a) **behavioural-variant**
b) **Language variant (primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy)**
c) **Frontotemporal lobar degeneration and amyotrophic lateral sclerosis spectrum syndrom**

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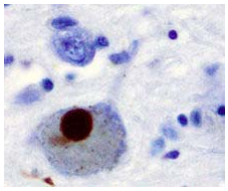
α-synucleinopathy

Several neurodegenerative diseases characterized by α-synuclein aggregates in neurons / nervous System cells

1. **Dementia with Lewy bodies**
2. **Parkinson's Disease**
3. **Multiple System Atrophy**



Positive α-Synuclein staining of Lewy body – Wikipedia

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Dementia with Lewy bodies

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Diagnostic criteria

- ***Dementia*** **plus at least two of the following:**
- **fluctuations**
- **repeated scenic hallucinations**
- **REM-Sleep Behaviour Disorder (RBD)**
- **Parkinson-symptoms (max. one year before onset of dementia)**

Supporting criteria

- **frequent falls**
- **syncopes**
- **temporary impairmpairments of consciousness**
- **intolerance of neuroleptic agents**
- **delusion, depression**
- **non-visual hallucinations**
- **sleep disorders, acting out during REM-sleep**

Vascular dementia

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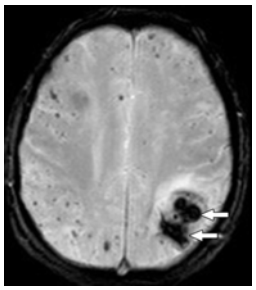
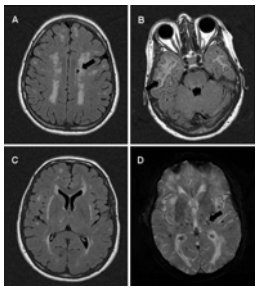
Vasculitis

Amyloid-angiopathy



CADASIL
(cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)



DEMENTIA FACTS

- Is any decline in cognition that is significant enough to interfere with independent daily functioning
- Dementia is best characterizied as an acquired syndrome with multiple possible causes rather than as one particular disease
- Global estimates of prevalence are up to 7% of individuls above the age of 65
- Advancing age, genetiv profile, and systemic vascular disease are major risk factors for developing dementia