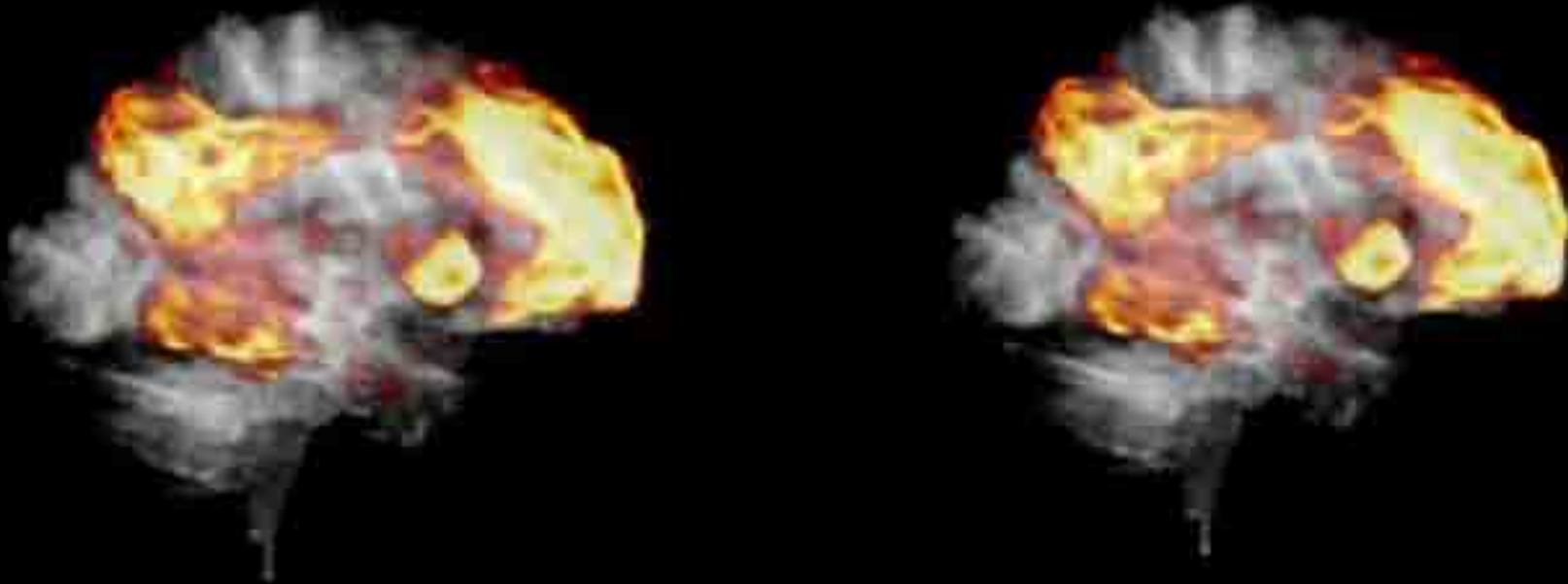


# Biologische Grundlagen der Alzheimer Krankheit und deren Prävention



Prof. Dr. rer. nat. Tobias Hartmann  
Neurobiology & Neurodegeneration, Saarland University



Alzheimer ist eine Demenz.

Eine fortschreitende  
Beeinträchtigung der  
kognitiven  
Leistungsfähigkeit

# Alzheimer ist ...

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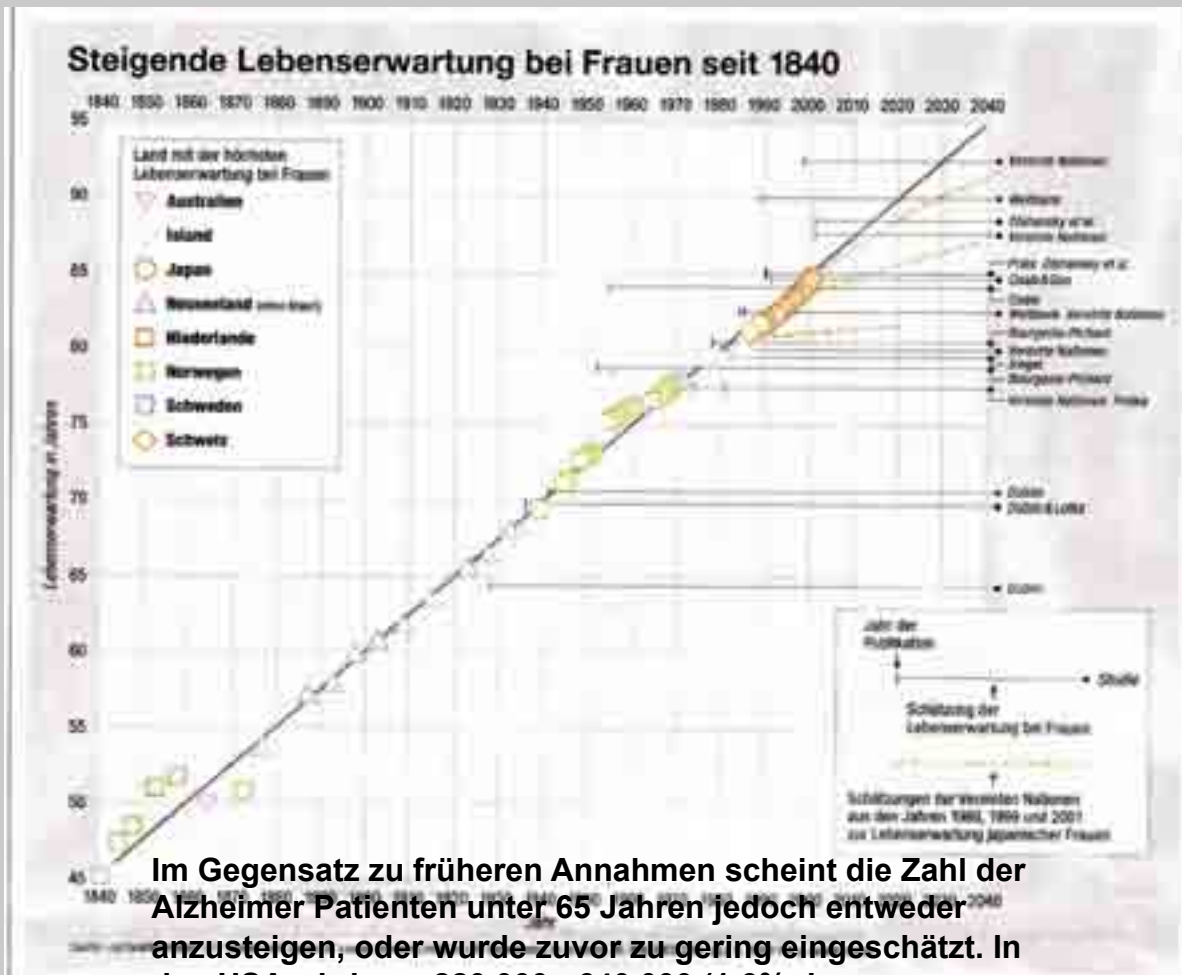
- Alzheimer ist keine Altersdemenz
- Alzheimer ist keine Verkalkung
- Alzheimer ist keine Altersfolge
- Alzheimer ist keine normale Alterserscheinung
- Alzheimer ist eine Stoffwechselkrankheit

# Themen

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- Demographie
- Symptome
- Histologie
- Molekulare & zelluläre Grundlagen
  - APP
  - Sekretasen
  - Erbfaktor
- Grundlage zukünftiger Behandlungsoptionen
- Kurzschrift: [www.neuro-saarland.de/Hartmann](http://www.neuro-saarland.de/Hartmann)
- Weitere Infos: <http://www.ipa-online.org/neurosite/index.asp>
-

# Alzheimer Risiko & Demographie



The risk to develop Alzheimer's disease is strongly age correlated. With 80+ years of age 20-35% have Alzheimer's disease. With 95+ years most people have Alzheimer's disease.

In most european countries life expectancy increases rapidly.

Each decade life expectancy increases by two years. Or for the 5 hours you may have spent at this conference your life expectancy has increased by 1 hour.

# Alzheimer Risiko & Demographie

## Glückwünsche des Bundespräsidenten zum 100. Geburtstag

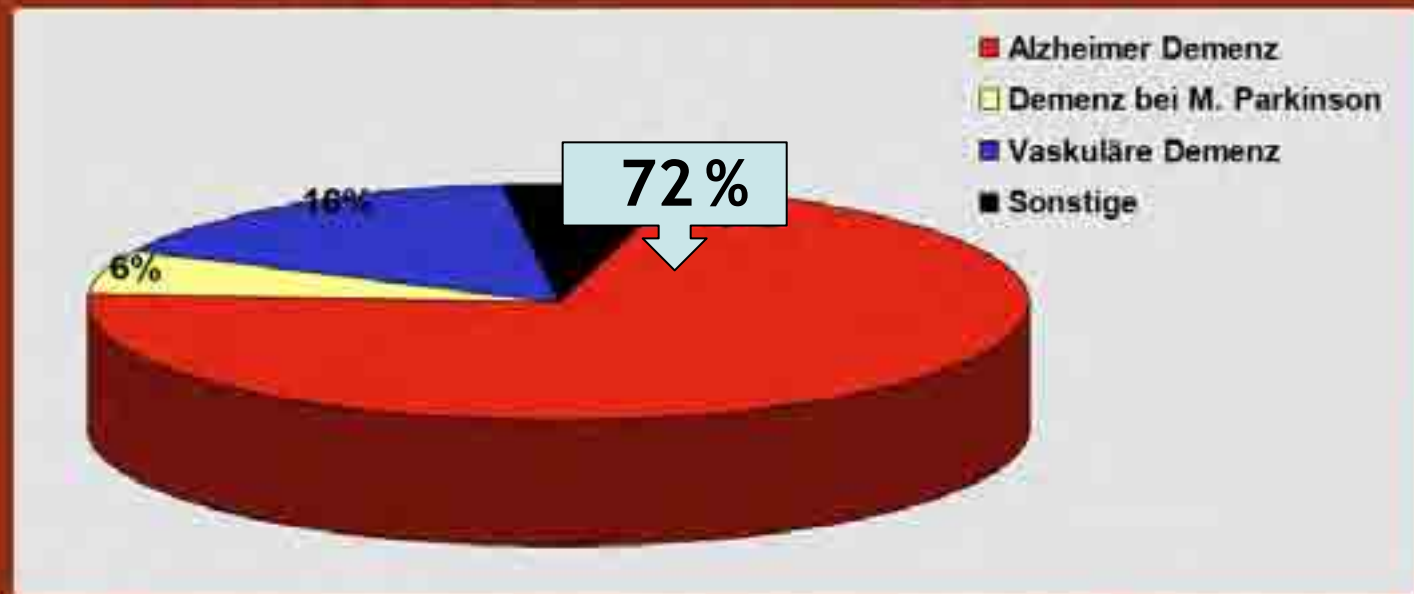


• einschließlich neuer Bundesländer  
Zerfass 2008

# Alzheimer Risiko & Demographie

## Häufigste Demenzform: Alzheimer Krankheit

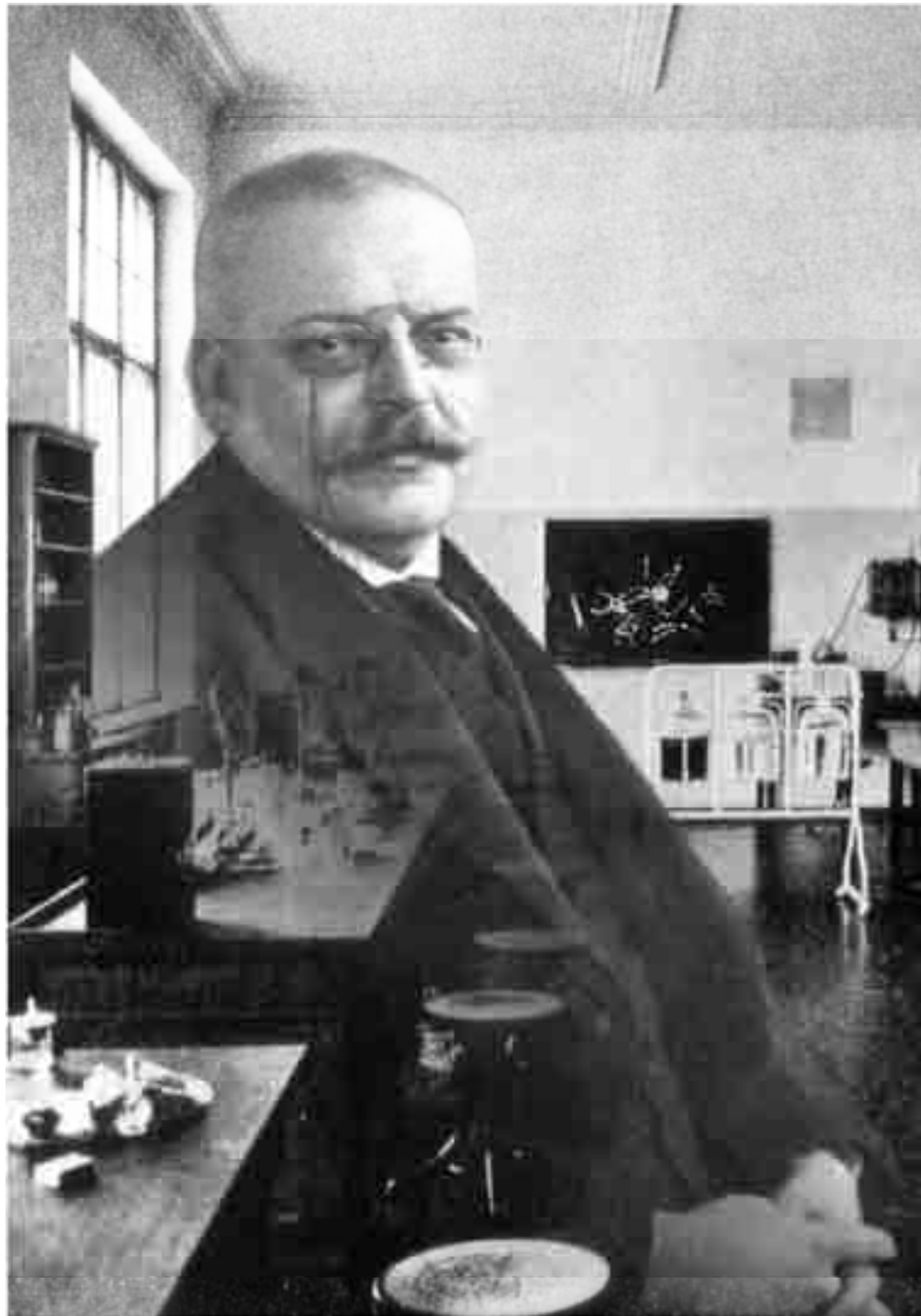
7.528 untersuchte Patienten (55 - 106 Jahre):  
Demenz: n = 474; davon Alzheimer Demenz n = 339



Quelle: Ott A, et al. Prevalence of Alzheimer's Disease and Vascular Dementia: Association with Education. The Rotterdam Study. British Medical Journal 310, 970-973 (1995)

# Symptome

---



## Alois - der Irrenarzt

### II. Vereinsbericht.

#### 37. Versammlung südwestdeutscher Irrenärzte in Tübingen am 3. und 4. November 1906.

Bericht von Dr. Flieckh (Tübingen).

Alzheimer (München): Ueber eine eigenartige Erkrankung der Hirnrinde.

A. berichtet über einen Krankheitsfall, der in der Irrenanstalt in Frankfurt am Main beobachtet, und dessen Zentralnervensystem ihm von Herrn Direktor Sioli zur Untersuchung überlassen wurde.

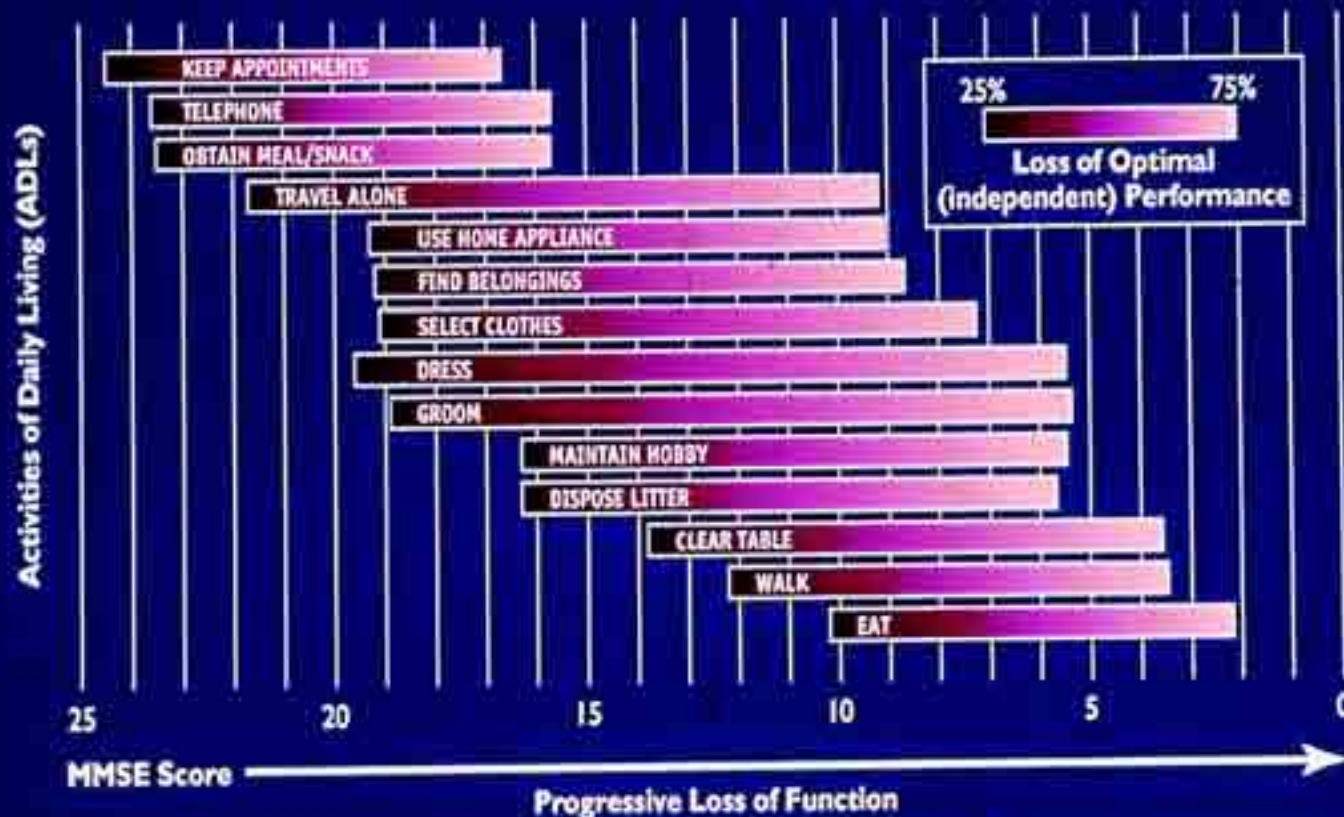
Er bot schon klinisch ein so abweichendes Bild, dass er sich unter keiner der bekannten Krankheiten einreihen liess, anatomisch ergab er einen von allen bisher bekannten Krankheitsprozessen abweichenden Befund.

Eine Frau von 51 Jahren zeigte als erste auffällige Krankheitserscheinung Eifersuchtsideen gegen den Mann. Bald machte sich eine rasch zunehmende Gedächtnisschwäche bemerkbar; sie fand sich in ihrer Wohnung nicht mehr zurecht, schleppte die Gegenstände hin und her, versteckte sie, zuweilen glaubte sie, man wolle sie umbringen und begann laut zu schreien.

In der Anstalt trug ihr ganzes Gebahren den Stempel völliger Ratlosigkeit. Sie ist zeitlich und örtlich gänzlich desorientiert. Gelegentlich macht sie Aeusserungen, dass sie alles nicht verstehe, sich nicht auskenne. Den Arzt

first "Alzheimer" publication by A. Alzheimer 1907

# Lower MMSE scores correlate with increased difficulty performing activities of daily living (ADLs)



# Cognitive Loss in Alzheimer's

## Disease

An father who at in heaven better be  
than <sup>me</sup> King down

$$\begin{array}{r} 879 \\ 79 \\ \hline 7841 \\ 6146 \\ \hline 69301 \end{array}$$



FIG. 4. Patient's graphic abilities early in the AD progression.

Before

# Cognitive Loss in Alzheimer's

## Disease

An father who at in heaven better be  
than <sup>me</sup> King down

$$\begin{array}{r} 879 \\ 79 \\ \hline 7841 \\ 6146 \\ \hline 69301 \end{array}$$



FIG. 4. Patient's graphic abilities early in the AD progression.

Louise Perann

Man Maperan

M 56

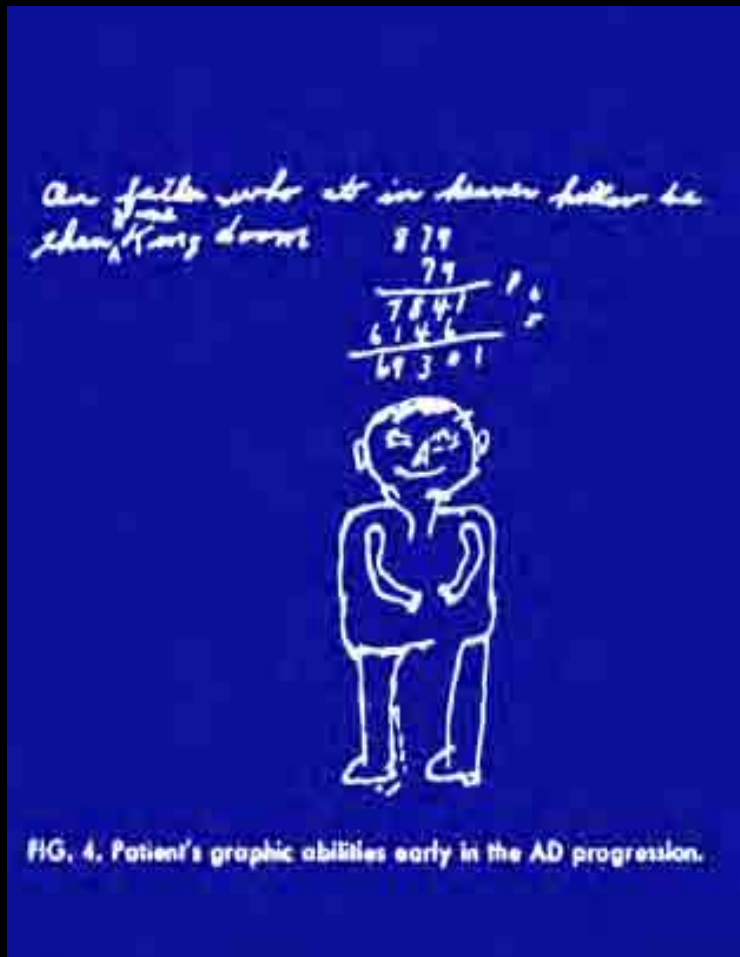
Co. 5



Early Stage

Before

# Cognitive Loss in Alzheimer's



Early Stage

Late Stage

Before

# Horn Paintings

*an artists AD history*



- before
- “MCI”
- mild
- moderate
- severe
- end stage



# Histologie & Organveränderungen



KODAK SAFETY FILM COPY 854028 L

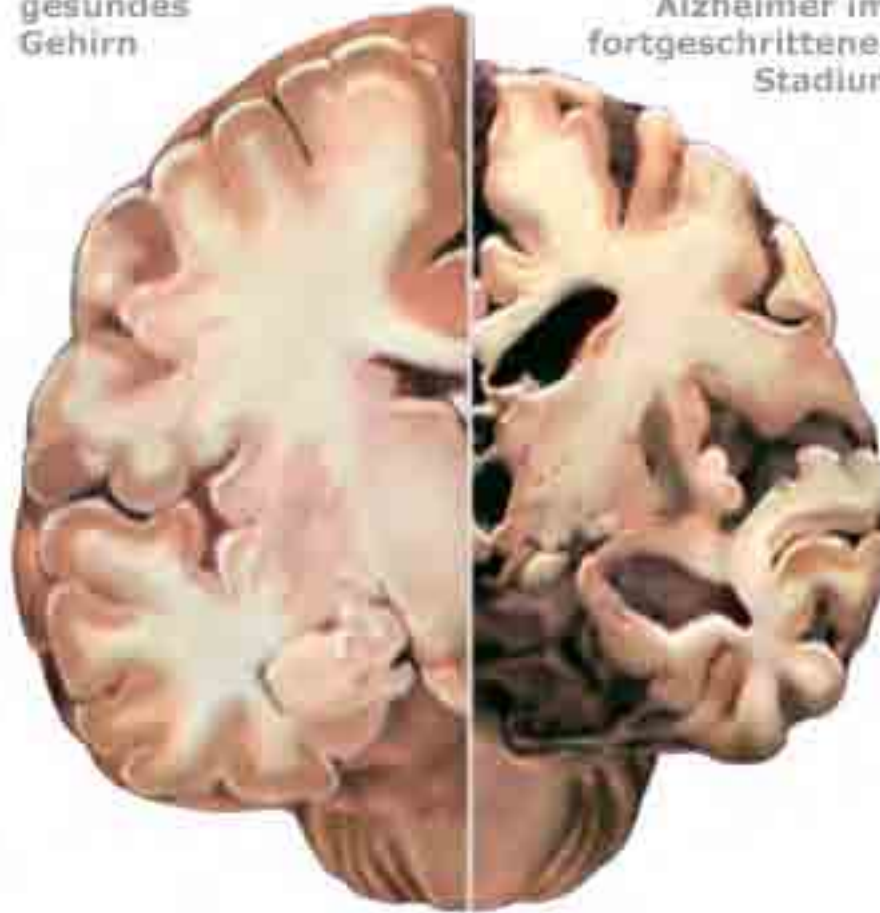
H. J. SIMPSON

# Massive neurodegeneration



**Normal**

gesundes  
Gehirn



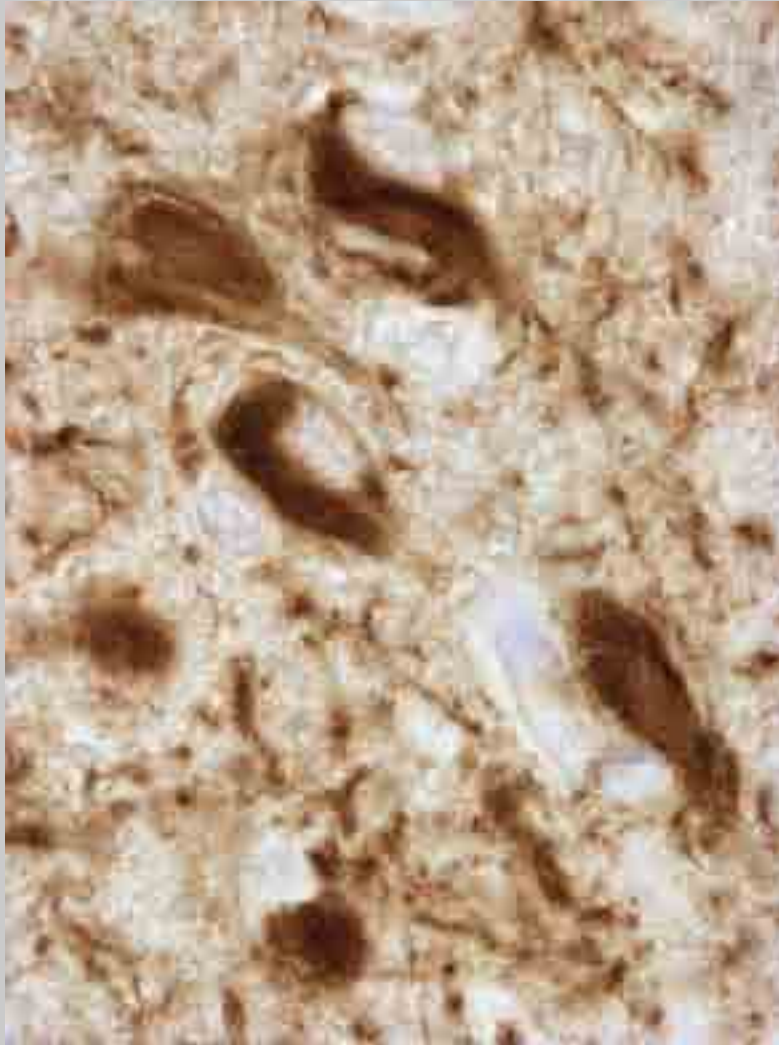
Alzheimer im  
fortgeschrittenen  
Stadium

**Alzheimer**



# Neurofibrilläre Tangles (Bündel/Knäuel)

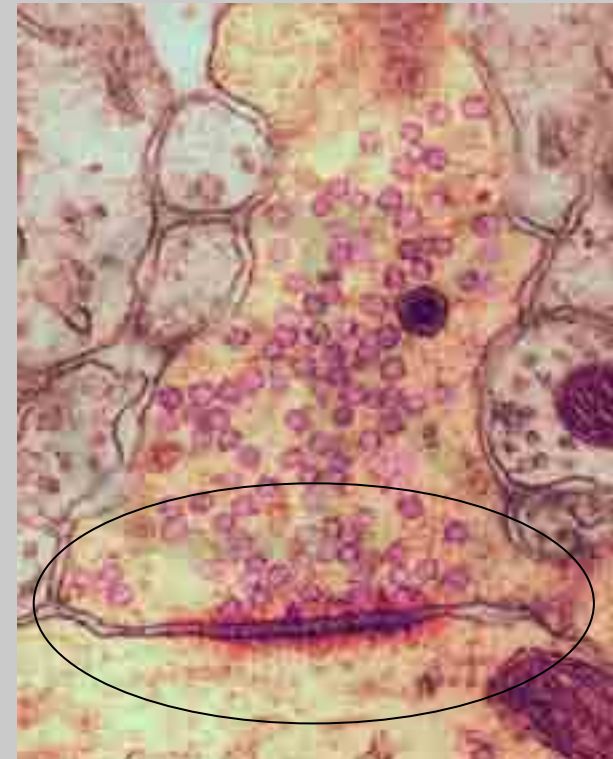
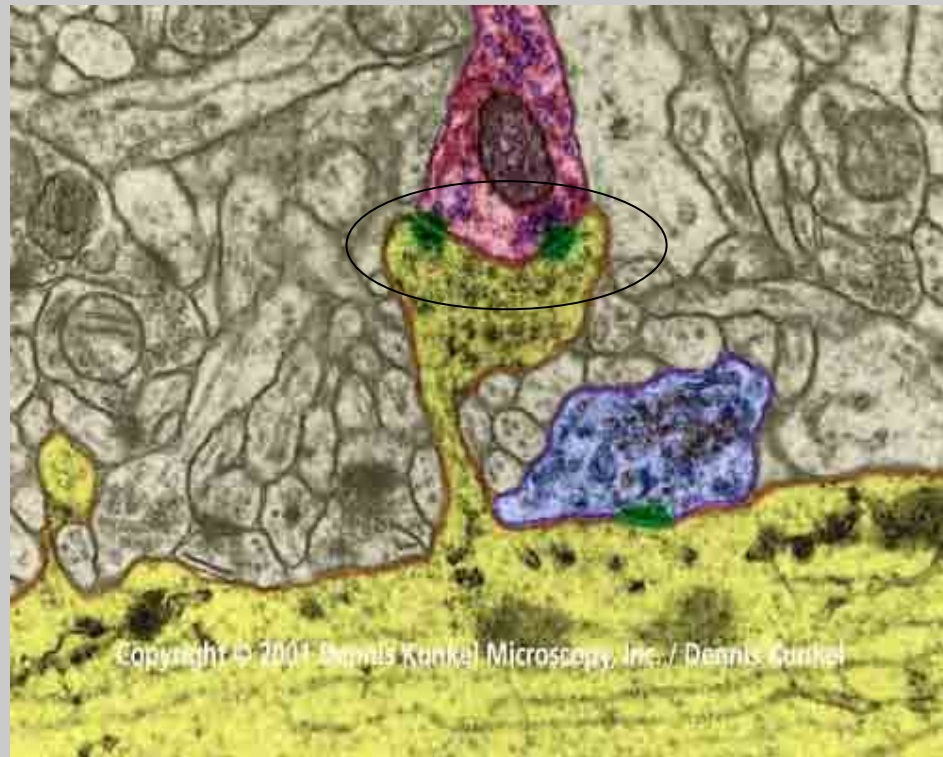
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- Major lesion of Alzheimer's disease and other neurodegenerative diseases found inside neurons
- Paarige, helikale Filamente welche aus abnormalem Phospho-Tau-Protein bestehen.

# Synapsen, Schalter der Information

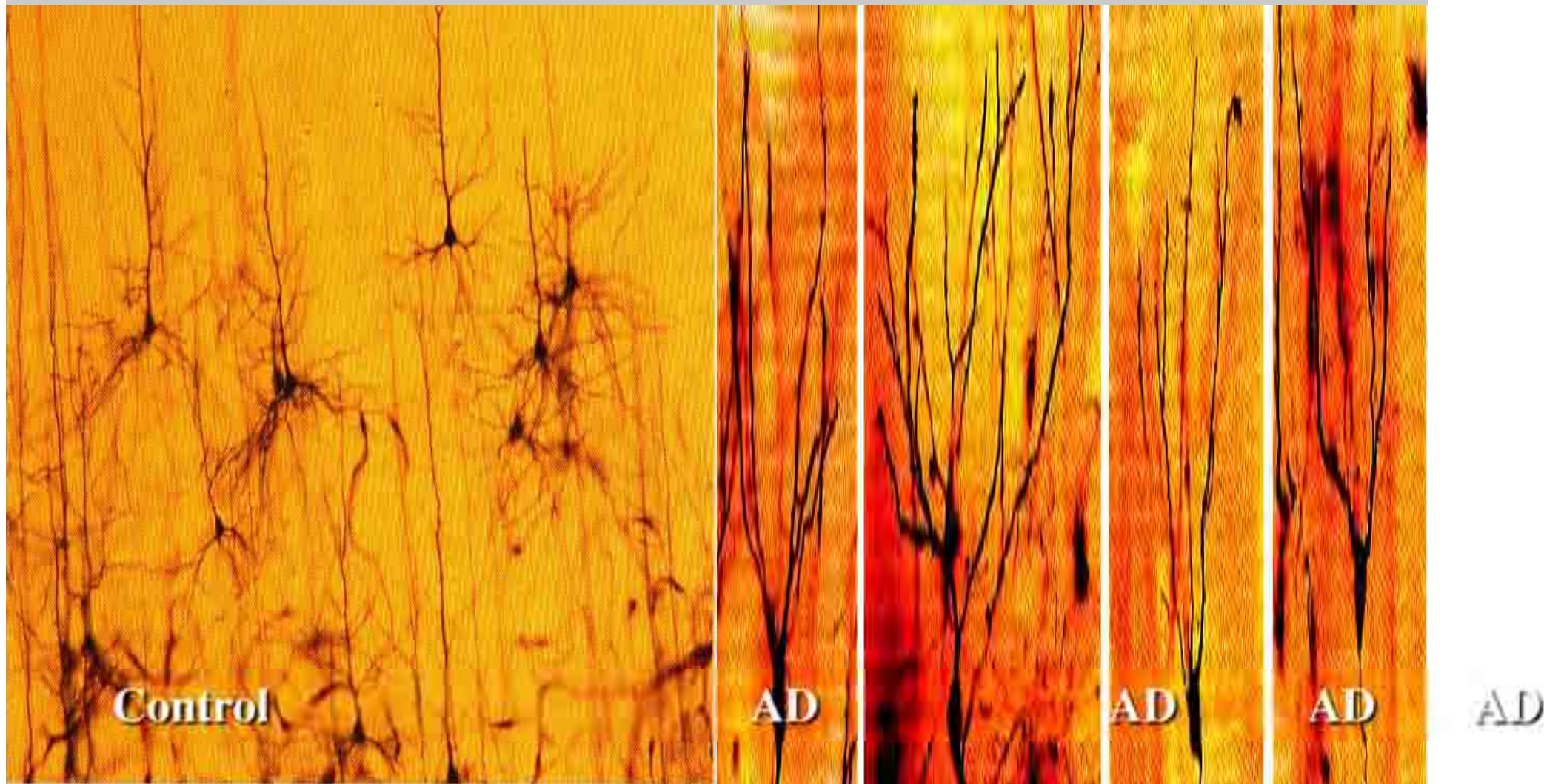
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# Neurodegeneration bei der AD

## Die Verzweigungen/Synapsenanzahl nehmen ab

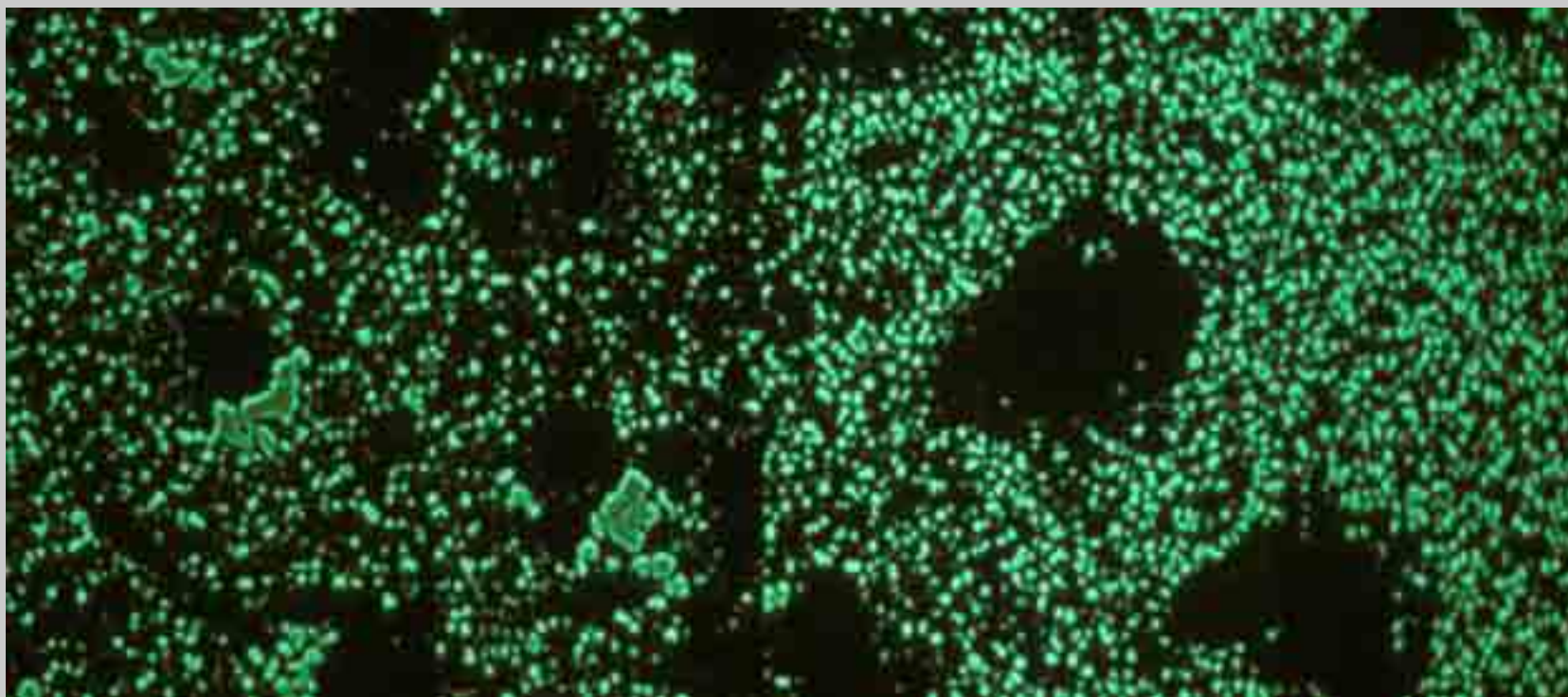
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# Neurodegeneration bei der AD

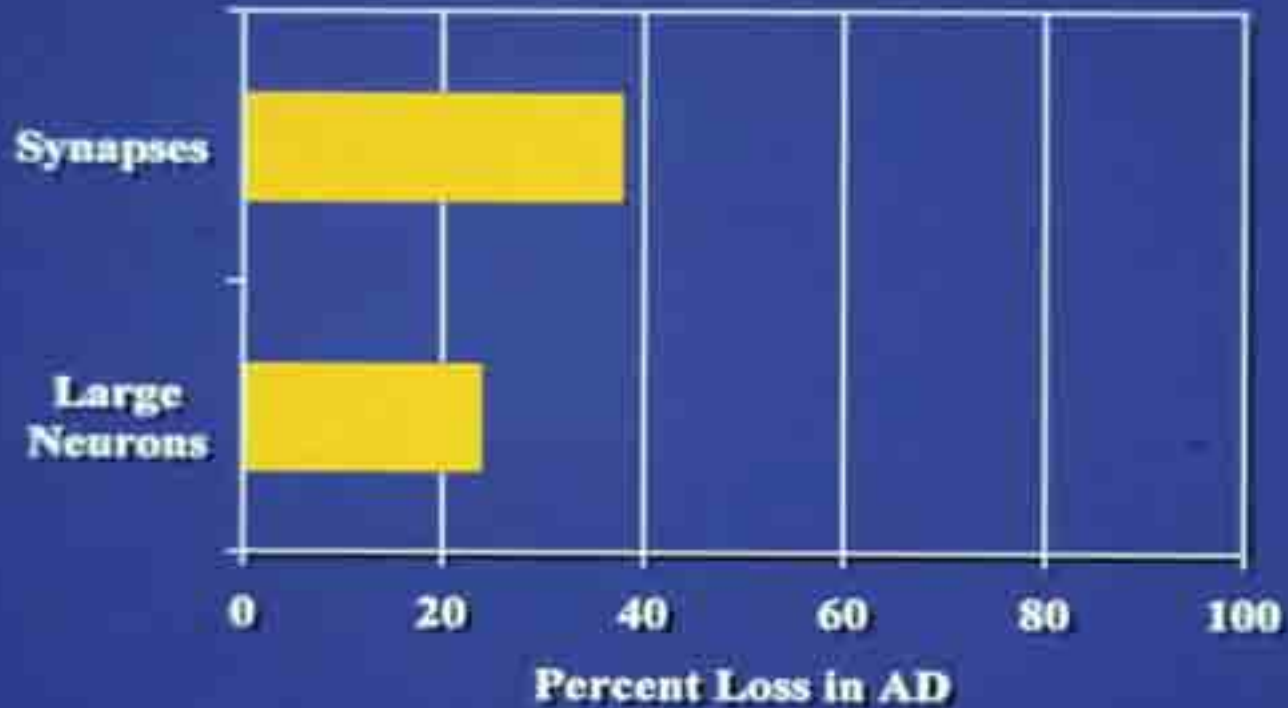
## Die Synapsenanzahl ist reduziert

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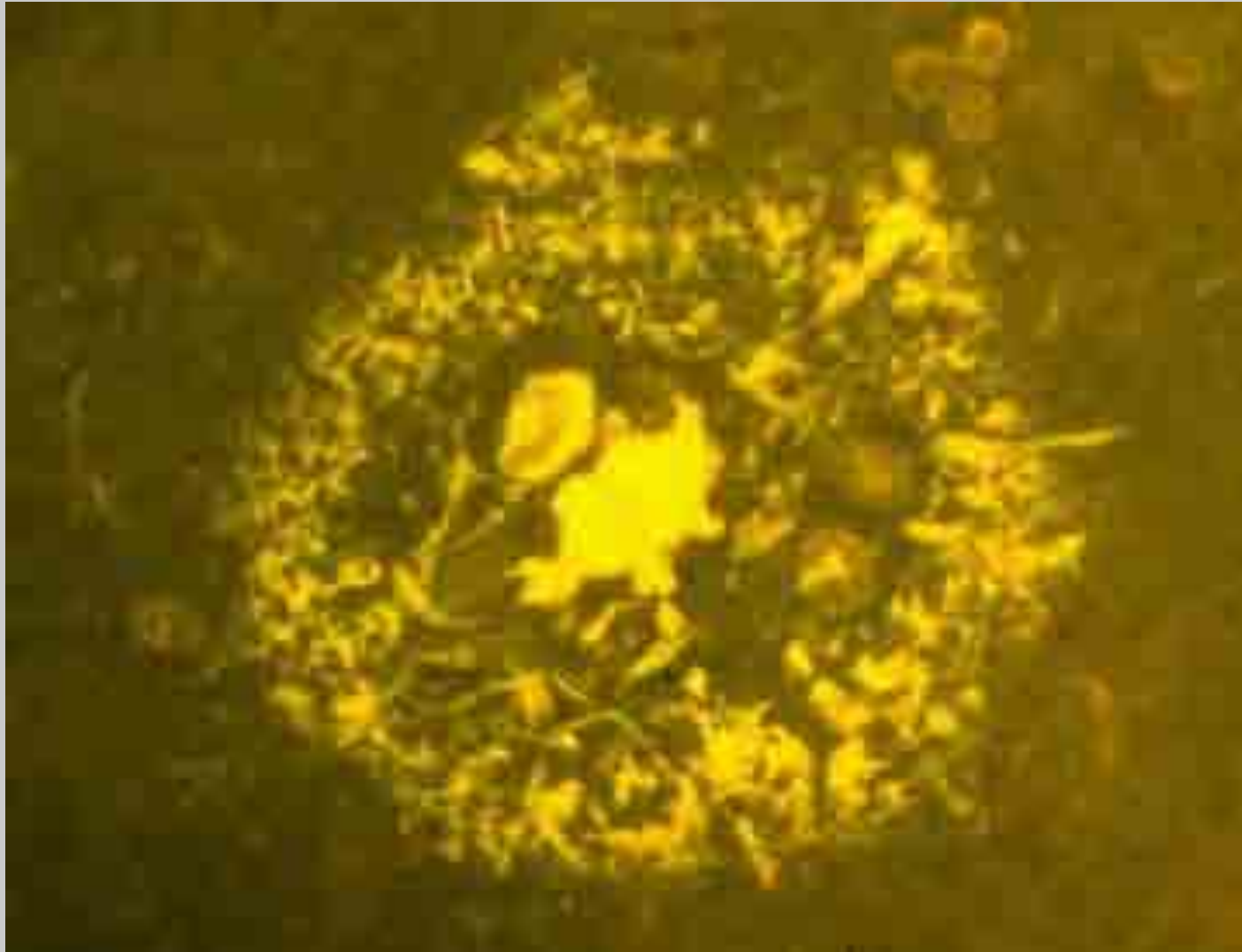
Confocal images with anti-synaptophysin: normal cortex on right, AD on left. Each green granule is a presynaptic body.

## Cortical Synapse Loss Exceeds Neuron Loss in AD

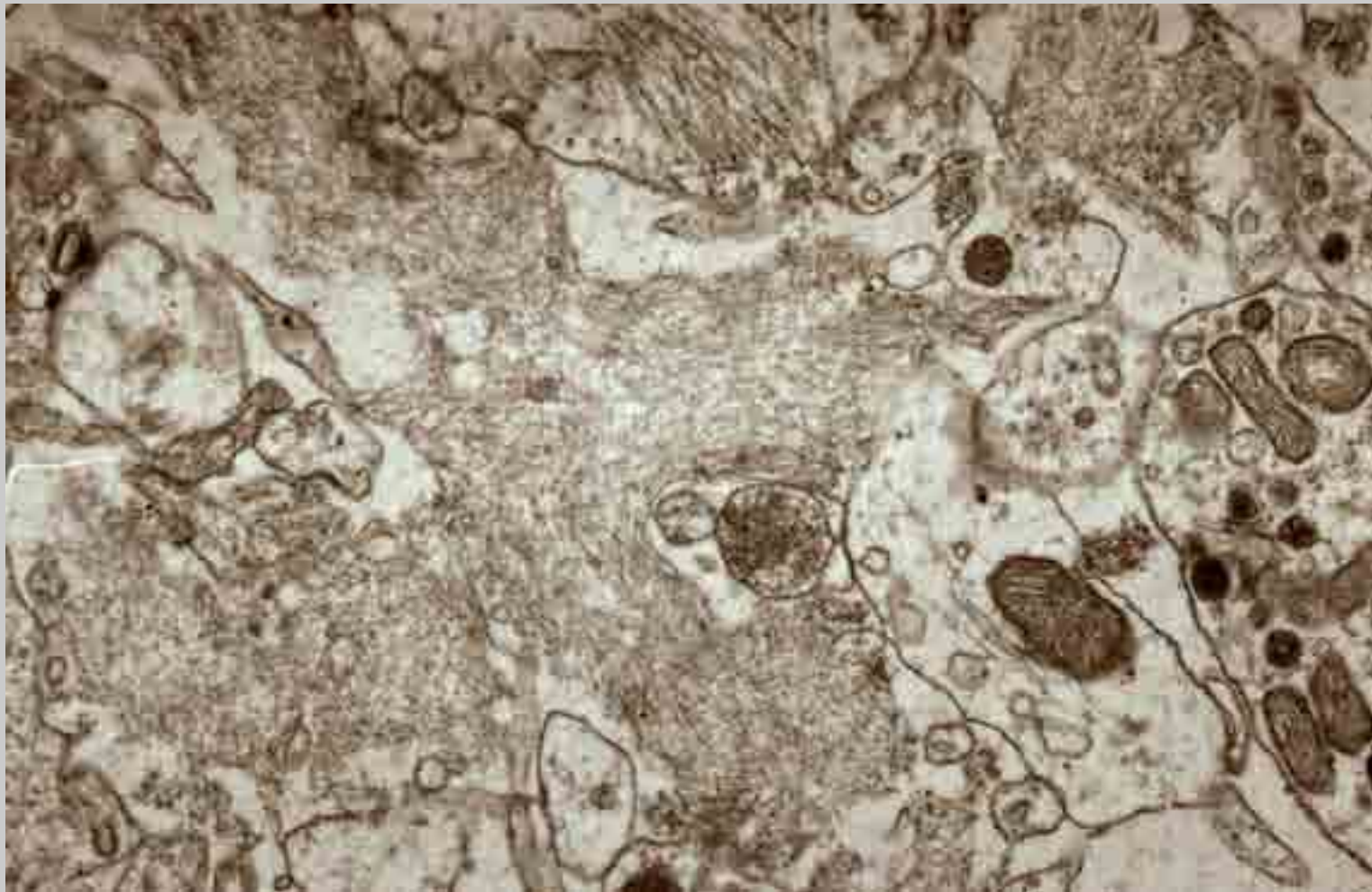


15 AD cases, 9 controls  
Neurons counted by image analysis  
Synapses by microdensitometry of  $\alpha$  synaptophysin

The proportion of synapse loss is greater than that of neuron loss. Synapses go first.



The thioflavin stain. Typical plaque with amyloid core and dystrophic neurites.

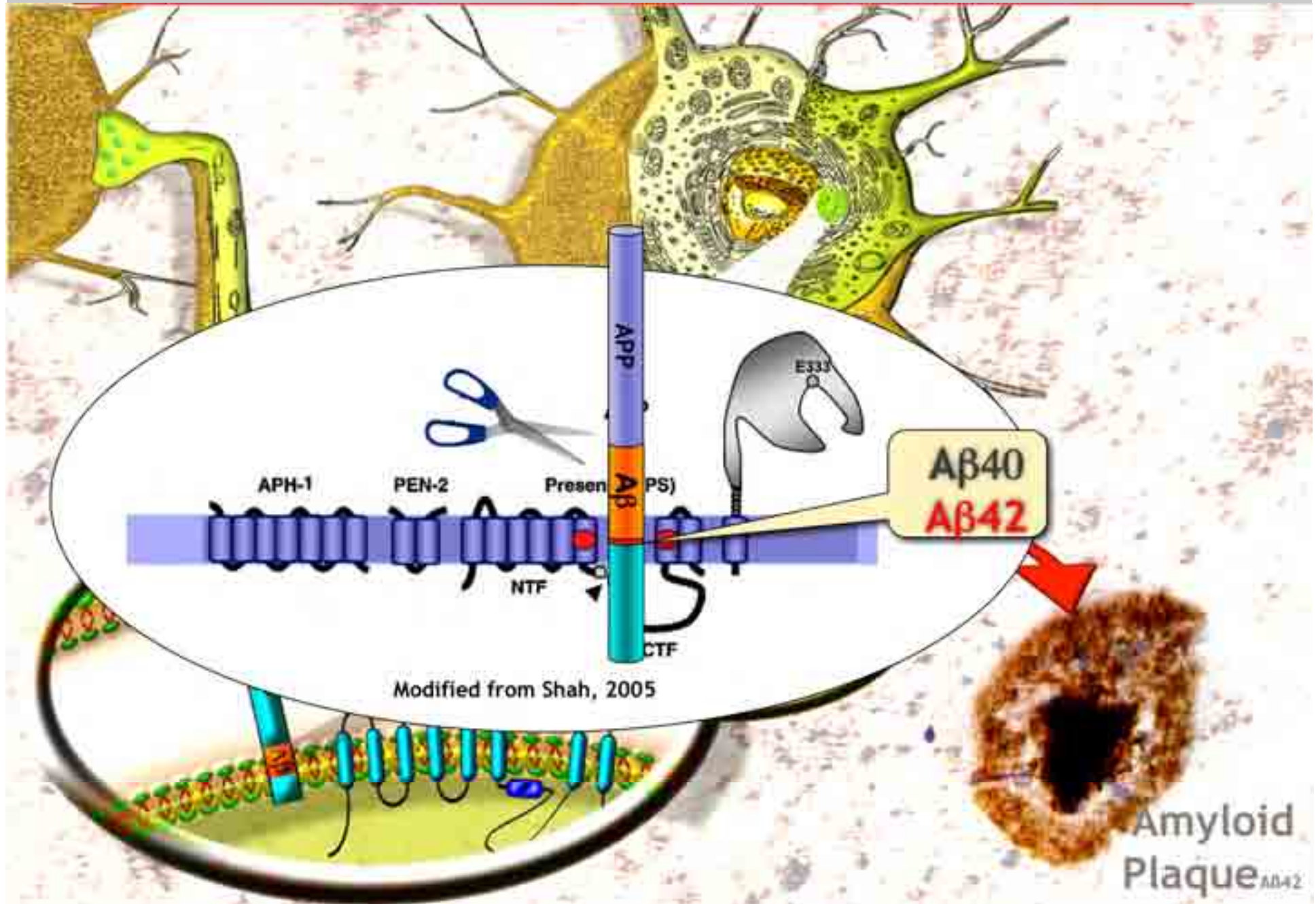


Plaque amyloid is fibrillar and extracellular.

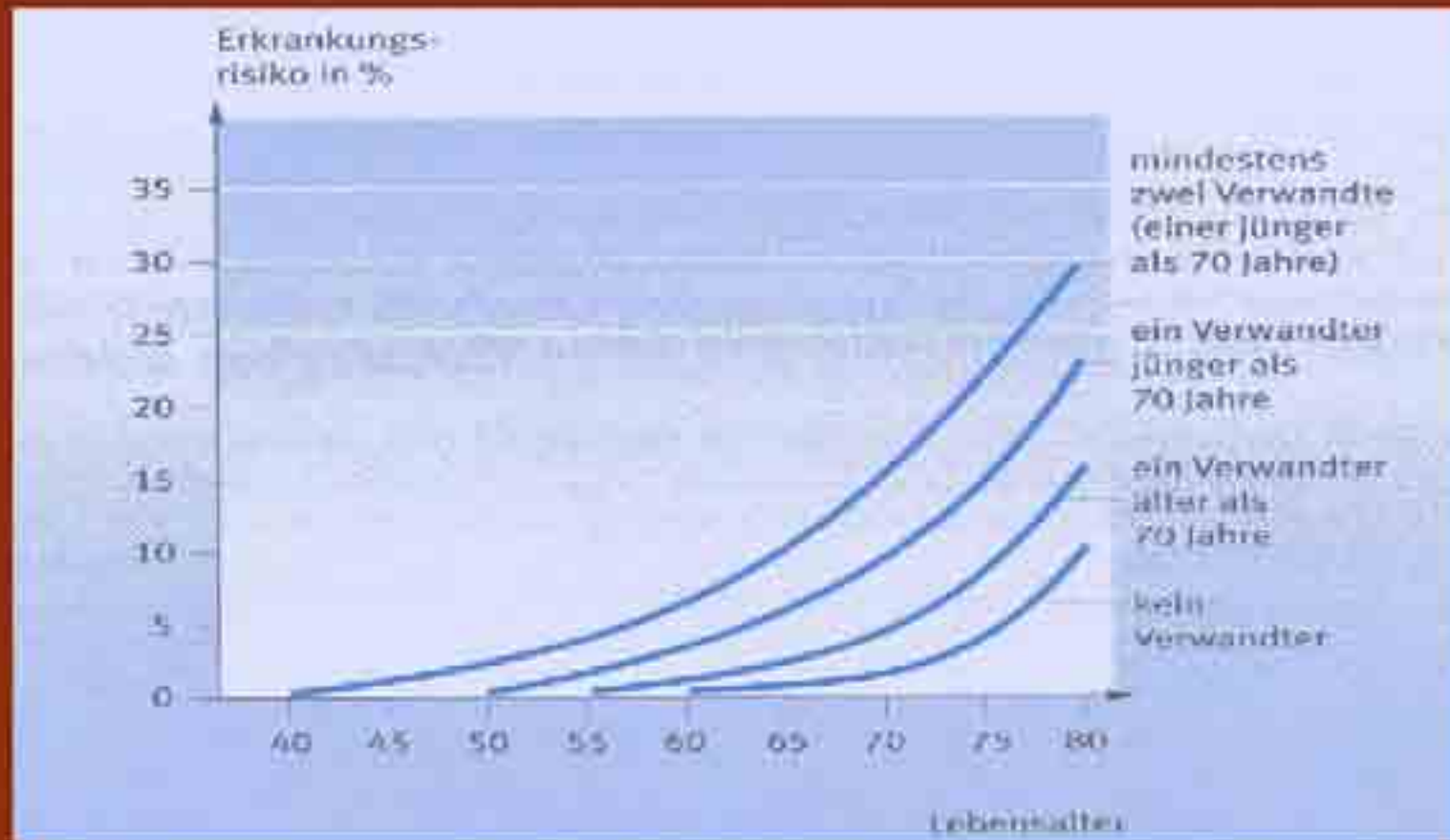
# Molekulare Grundlagen

---

# Der $\gamma$ -Secretase Komplex

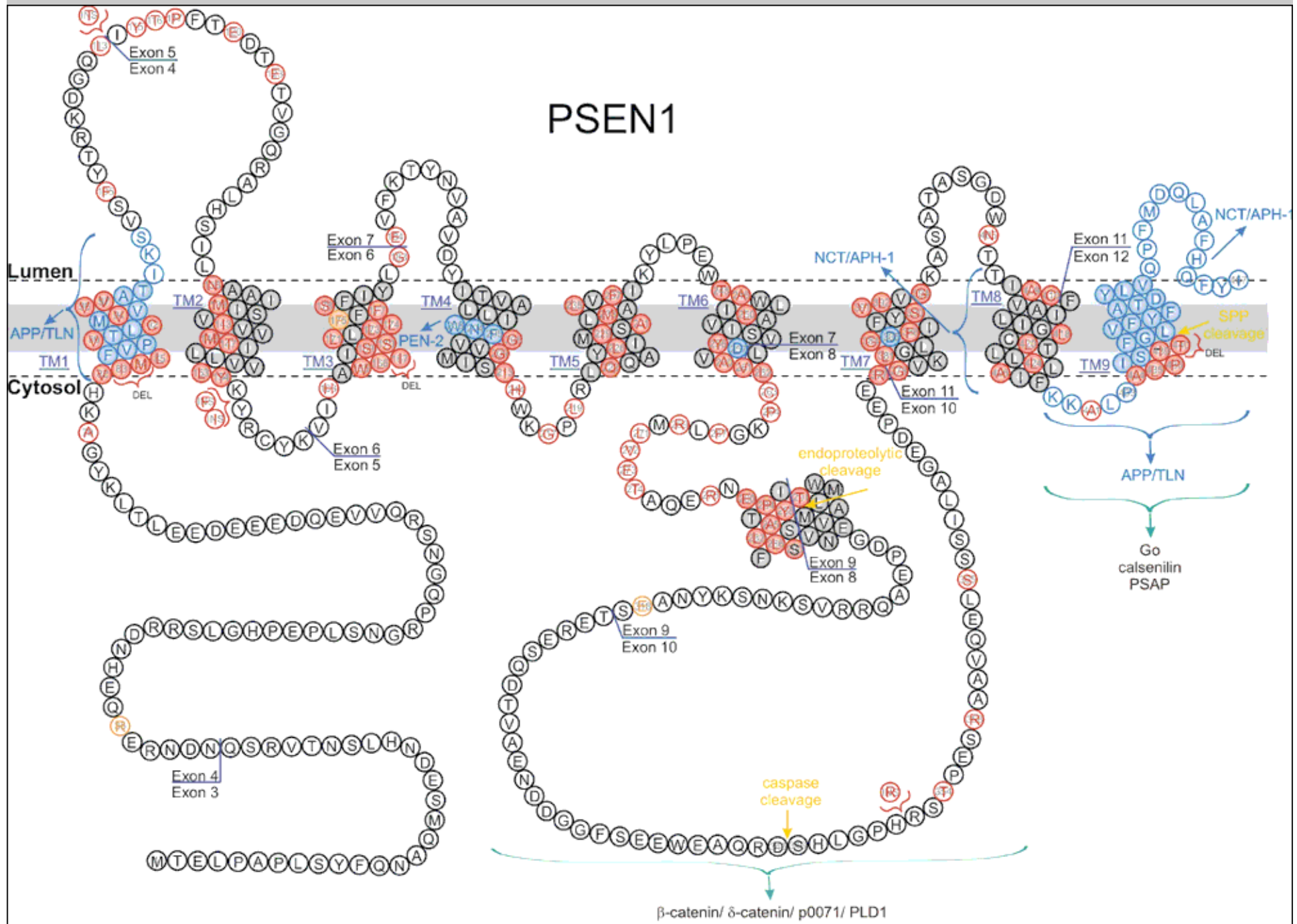


# Ist Alzheimer vererbbar ?

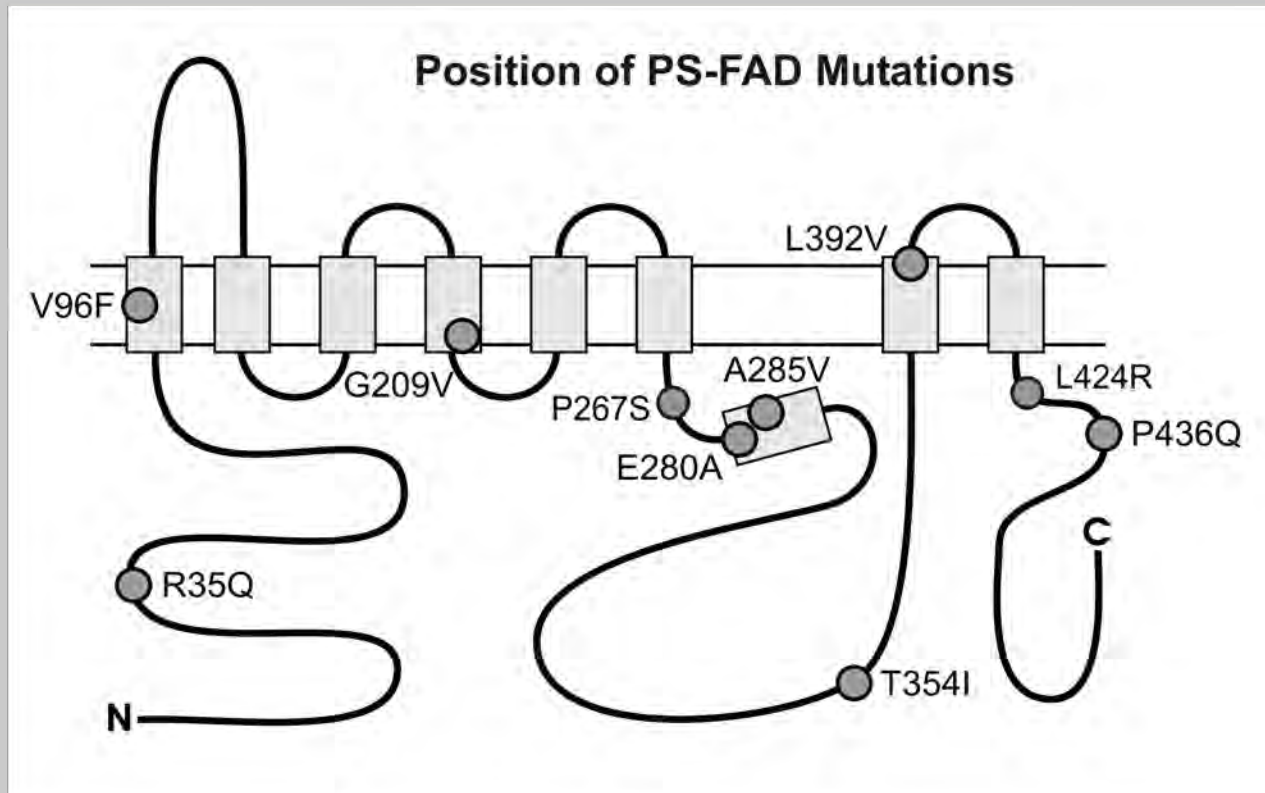


⇒ Vererbungsgrad: Eineiige Zwillinge 40-60%, zweieiige Zwillinge 10%

# PSEN1



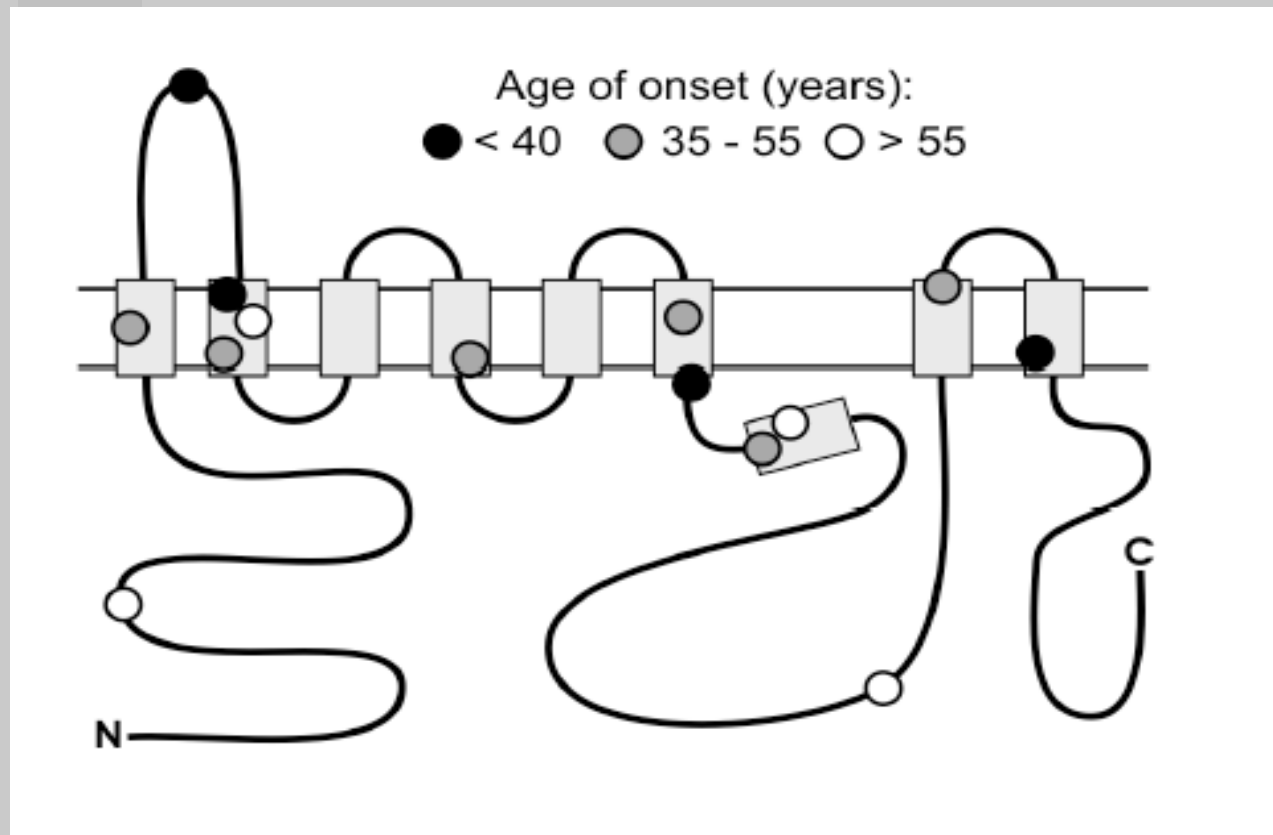
# PS-FAD-Mutations



PS-FAD mutations show an increased Aβ42:Aβ40 ratio

# disease onset age prediction (PS-FAD)

Comparison of FAD mutation specific disease onset age with A $\beta$ 42 levels, corrected for A $\beta$ 40



Mean age of disease onset

**The correlation is highly significant:**

- Linear Regres.  $p < 0,001$
- ANOVA:  $p < 0,001$

**The explanatory power is high:**

96% of the variance in mean age of onset is determined by the variance in A $\beta$ 40/42-ratio

ISBN 978-3-70-01-8540-2



# Alzheimer Krankheit - Therapie Von den Grundlagen zur Behandlung

W. J. SIMPSON

# Therapieansätze

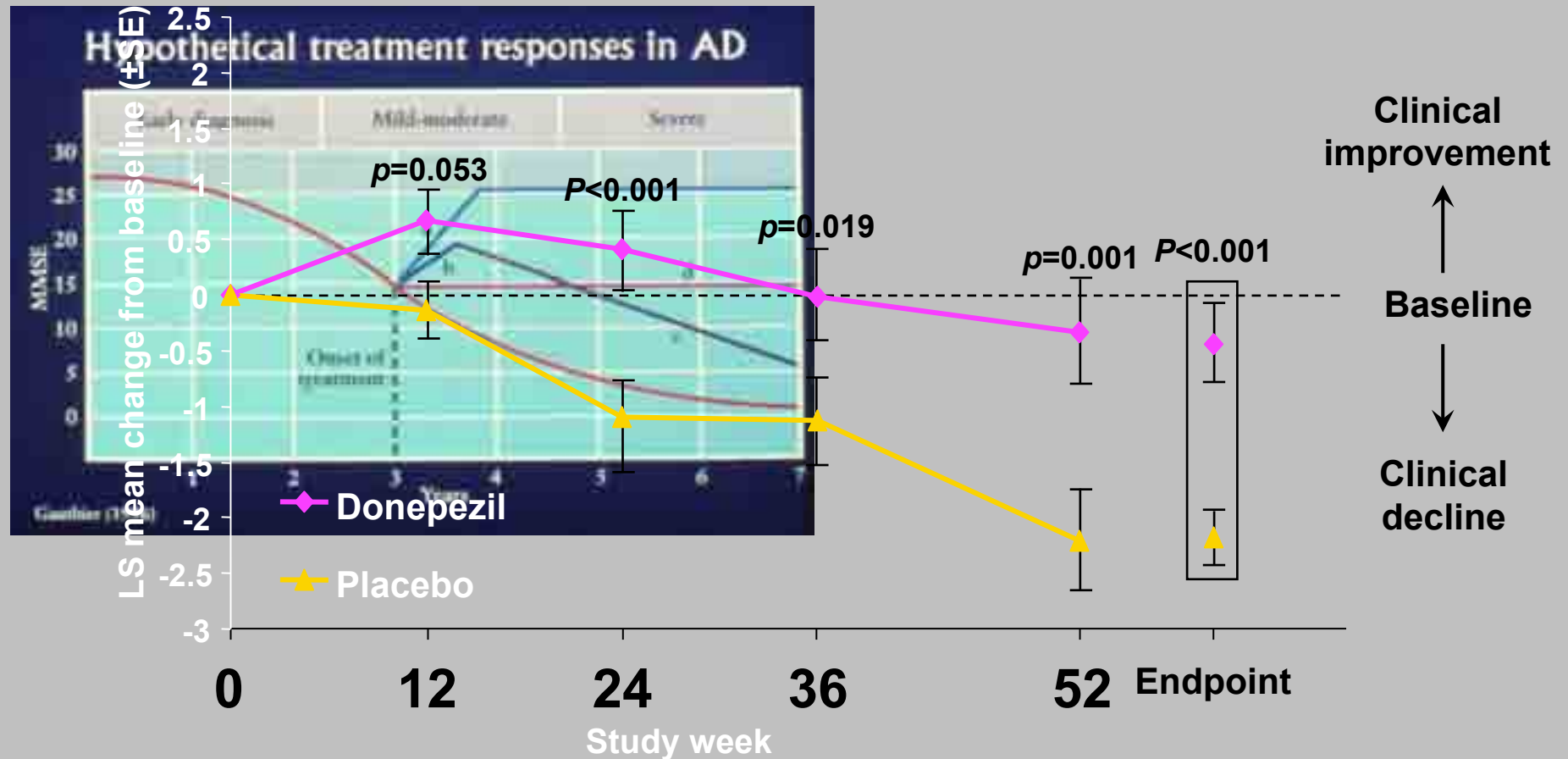
Medikamente  
gegen Alzheimer -

**bis 2008:  
>150 klinische  
Studien**



# Acetylcholinesterase Hemmung

## Mini-Mental State Test (MMST)

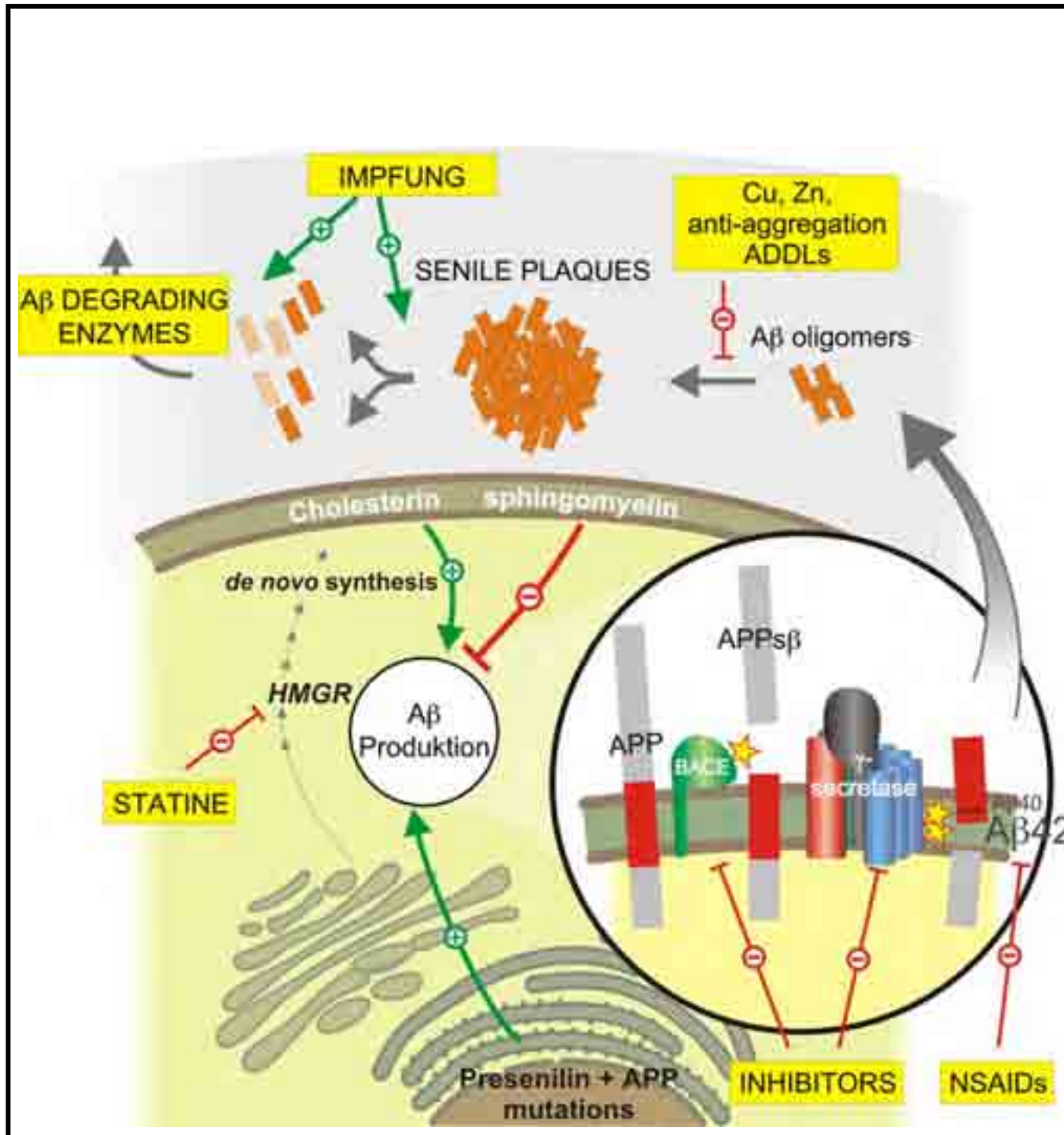


Donepezil /placebo (Winblad et al. Neurology 2001; 57: 489-495)

# Therapieoptionen

Kein Mangel an  
Auswahlmöglichkeiten?

Und Wunder  
dauern etwas  
länger...



# Amyloid entfernende Substanzen I

---



## **Brain to Plasma Amyloid- $\beta$ Efflux: a Measure of Brain Amyloid Burden in a Mouse Model of Alzheimer's Disease**

**Ronald B. DeMattos,<sup>1,2,3\*</sup> Kelly R. Bales,<sup>5\*</sup> David J. Cummins,<sup>5</sup>  
Steven M. Paul,<sup>5,6†</sup> David M. Holtzman<sup>1,2,3,4†</sup>**

The deposition of amyloid- $\beta$  (A $\beta$ ) peptides into amyloid plaques precedes the cognitive dysfunction of Alzheimer's disease (AD) by years. Biomarkers indicative of brain amyloid burden could be useful for identifying individuals at high risk for developing AD. As in AD in humans, baseline plasma A $\beta$  levels in a transgenic mouse model of AD did not correlate with brain amyloid burden. However, after peripheral administration of a monoclonal antibody to A $\beta$  (m266), we observed a rapid increase in plasma A $\beta$  and the magnitude of this increase was highly correlated with amyloid burden in the hippocampus and cortex. This method may be useful for quantifying brain amyloid burden in patients at risk for or those who have been diagnosed with AD.

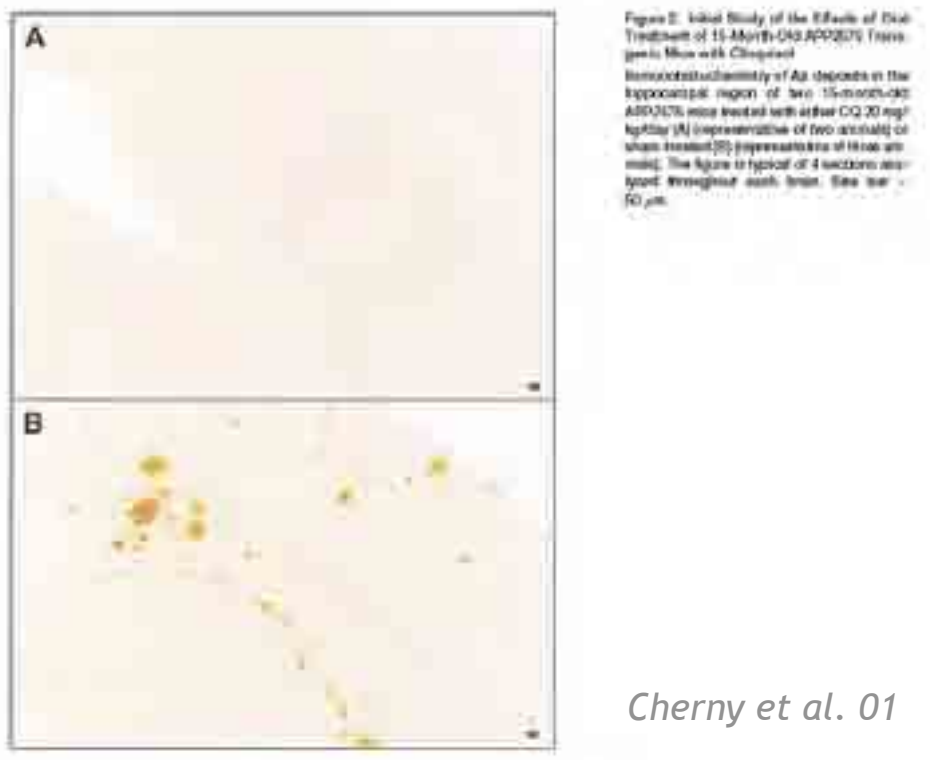
### *Hauptvorteil:*

Viele A $\beta$  bindende Substanzen sind bekannt. Möglicherweise sehr gut verträglich.

### *Nachteile:*

Keine klinischen oder epidemiologischen Daten vorhanden. Effektstärke unbekannt.

# Amyloid entfernende Substanzen II



## **Hauptvorteil:**

**Bisher einziger Zugang um auch im fortgeschrittenem Stadium Amyloidablagerungen aufzulösen.**

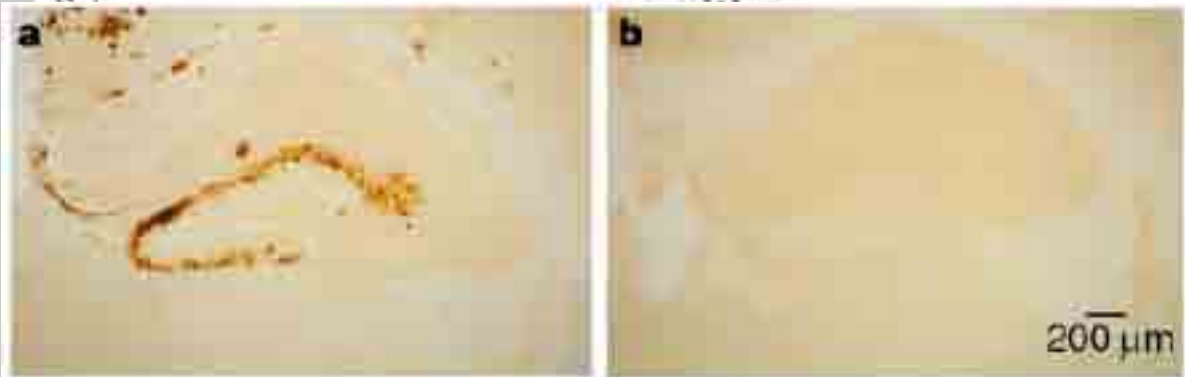
## **Nachteile:**

**Es entstehen intermediär kleine A $\beta$ 42 Oligomere die wahrscheinlich wesentlich gefährlicher sind als die Amyloidplaques. Nebenwirkungen des Chelators wahrscheinlich.**

# Impfung

2001 Natl.

## Amyloid $\beta$ vaccination: reduced plaques and improved



amyloid plaques.

$\beta$  A $\beta$  aggregates in AD and Alzheimer target  $\beta$  A $\beta$  immunization in AD.

unbehandelt

behandelt

Transgene Alzheimer Mäuse

from Schenk et al. 99

invariably found in the brains of AD patients. Amyloid plaques are composed primarily of abnormally phosphorylated  $\tau$  protein. The major protein component of senile plaques is the amyloid  $\beta$  protein (A $\beta$ ), a product of proteolytic cleavage of the amyloid  $\beta$  protein precursor (APP). Most A $\beta$  has 40 amino acids (A $\beta$ <sub>40</sub>) but a minor, slightly longer form (A $\beta$ <sub>42</sub>) is believed to be the major pathogenic species in AD. Three studies, published in the 21/28 December issue of *Nature* by Clark et al., Jansen et al.<sup>1</sup> and Morgan et al.<sup>2</sup>, provide new evidence that

These models overexpress mutant forms of APP, such as Swedish (SWE) or Dutch (DNL) APP, which cause early onset familial AD. This overexpression causes an age-dependent accumulation of A $\beta$  plaques that are quantitatively and qualitatively similar to those of the AD brain, but does not reproduce the complete phenotype observed in the human AD brain, as neurofibrillary tangles do not develop and there is considerably less neuron and synapse loss. The current AD transgenic models are an excellent tool for evaluating therapies that target A $\beta$ , and they can be used to determine if age-dependent

Meningeal deposits in Tg2576 transgenic mice which overexpress mutant APP can be reversed by A $\beta$  vaccination.

78

NATURE MEDICINE • VOLUME 7 • NUMBER 1 • JANUARY 2001

# Impfung

## Set back to Alzheimer vaccine studies

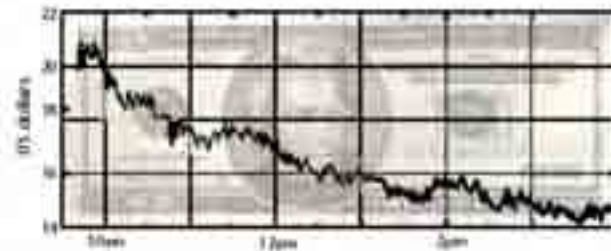
Elan, the Ireland-based biotechnology company that had taken the lead in developing a potential vaccine to treat Alzheimer disease, has suffered a double set back. Within days of announcing that trials of its therapeutic vaccine AN-1792 had been suspended, the company's share value plummeted by over 70% amid concerns over accounting practices and calls for Elan directors to resign.

AN-1792 was undergoing Phase IIa trials in Alzheimer 360-patients, which were supported by the large vaccine manufacturer, Wyeth-Ayerst. However, five subjects (four in France and one in Switzerland) showed signs of inflammation of the central nervous system. Presently it is not known how

ules. This will give the comm time to find out whether the deed the cause, and will not trial if the vaccine is given the

One theory for the cause disease—the inflammation that deposits of  $\beta$ -amyloid elicit immune response that croglia to become autotoxic surrounding neurons, result tive decline.

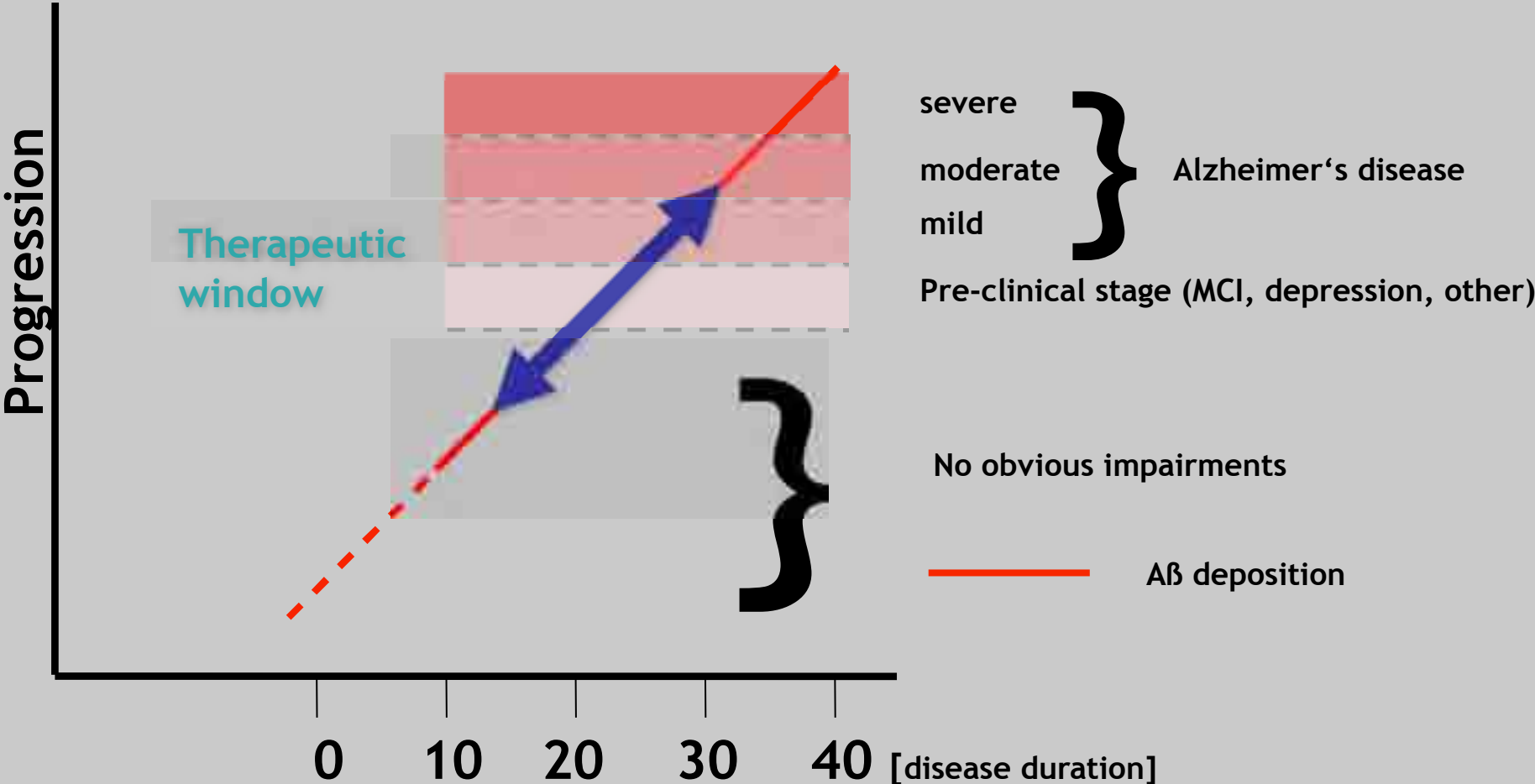
AN-1792 causes the immu create antibodies against  $\beta$ - there are currently two pote



Elan share price plummets

ne  
fec  
de  
th  
bi  
loi  
an  
th  
m

# Therapeutisches Fenster



# Risikofaktoren

- Die Risikofaktoren sind das primäre Ziel der Prävention
- Midlife – Faktoren!

## „CV/Metabolisches Syndrom“

- Alter!
- Cholesterin
- Blutdruck
- Diabetes
- CV/Stroke
- Übergewicht
- ApoE4
- + Statine
- + Behandelte Bluthochdruck
- + Körperliche Aktivität
- + NSAIDS (>18m, einige)
- + Omega-3
- + Alkohol

## Genetisch

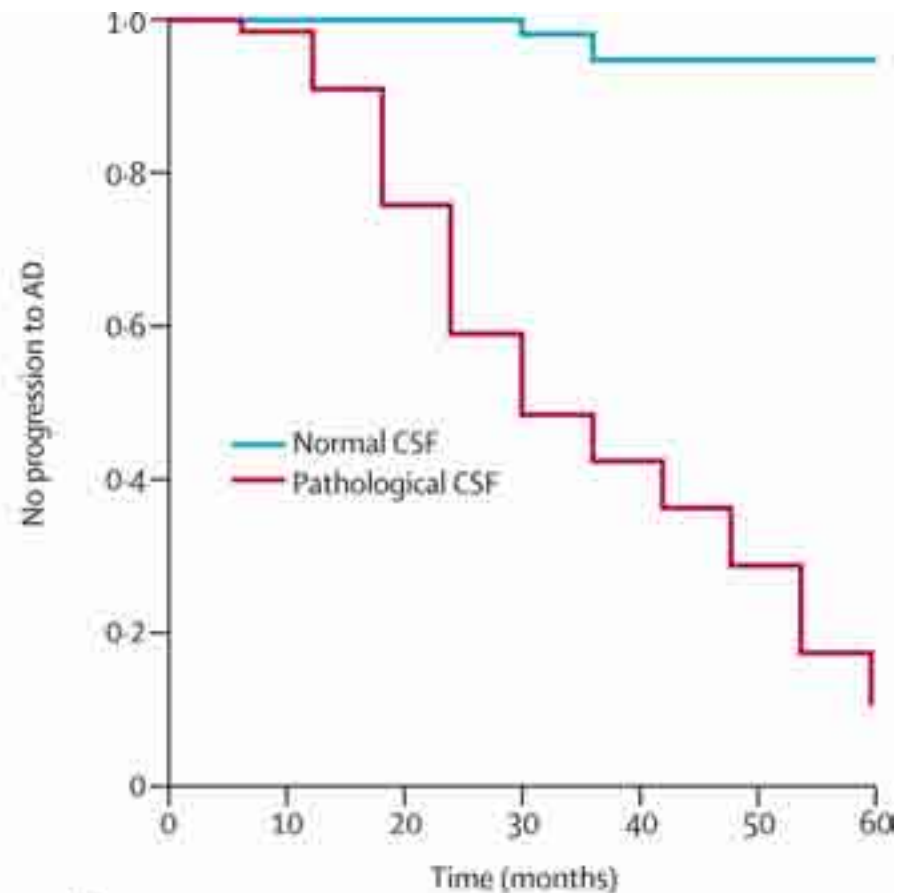
- ApoE4!
- PS
- APP
- T21
- +(Verwandte)
- + Bildung

## Andere

- Hirntrauma
- Alleinstehend
- + Midlifecrisis ohne!  
Scheidung
- + Geistige Aktivität

# Early diagnosis

## KM-Progression in 5 Jahren



Numbers at risk		0	10	20	30	40	50	60
Total	134	131	111	87	74	55	31	
Normal CSF	67	66	62	56	47	40	28	
Pathological CSF	67	65	49	31	27	15	3	

### Molecular marker

- A $\beta$ 42
- A $\beta$ 40
- P-tau
- (T-tau)

The incidence of Alzheimer's disease in MCI with pathological CSF (n=67) was 27% per year and 1% per year in patients with normal CSF (n=67).

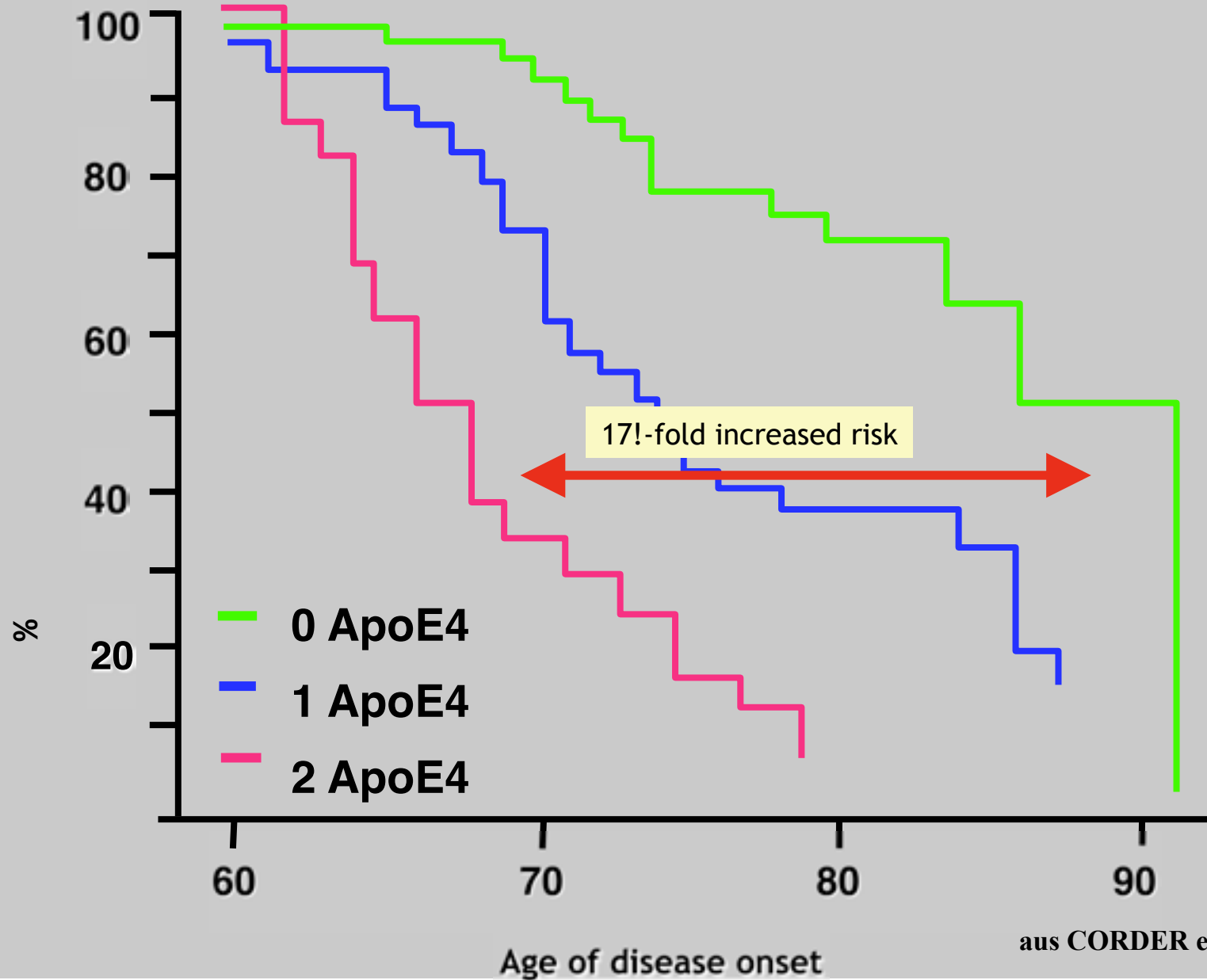
*e.g. ratio A $\beta$ 42/tau*

*Sensitivity of 95%*

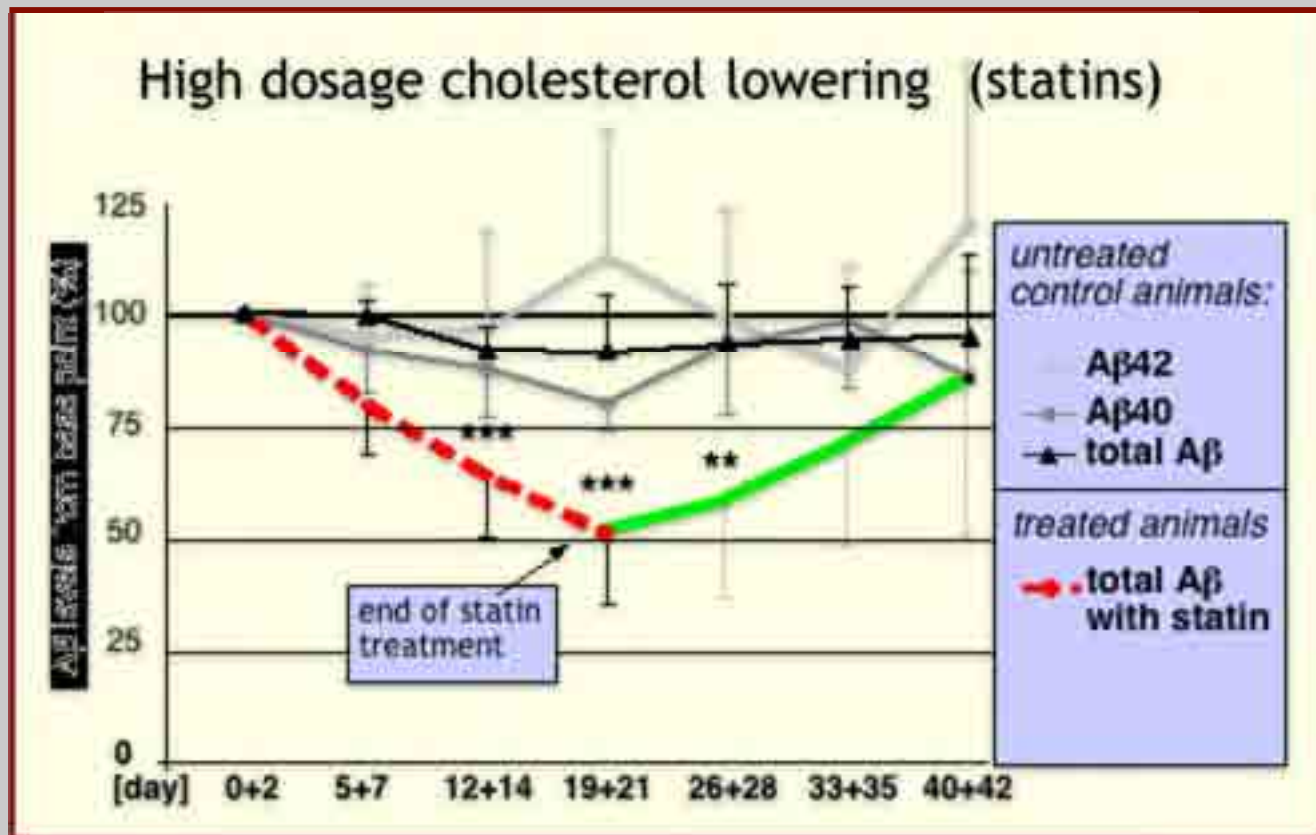
*Specificity of 83%*

Cut-off values for pathological CSF were >350 ng/L for T-tau and <530 ng/L for A $\beta$  42. Hansson et al., 2007

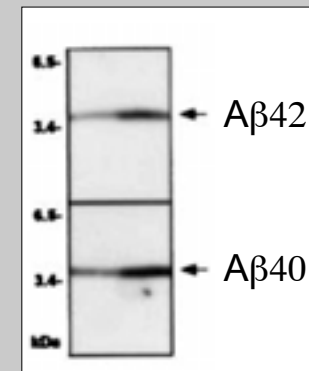
## Apolipoprotein-E: main genetic risk factor



# Cholesterol modulates A $\beta$ production



Cerebrospinal fluid

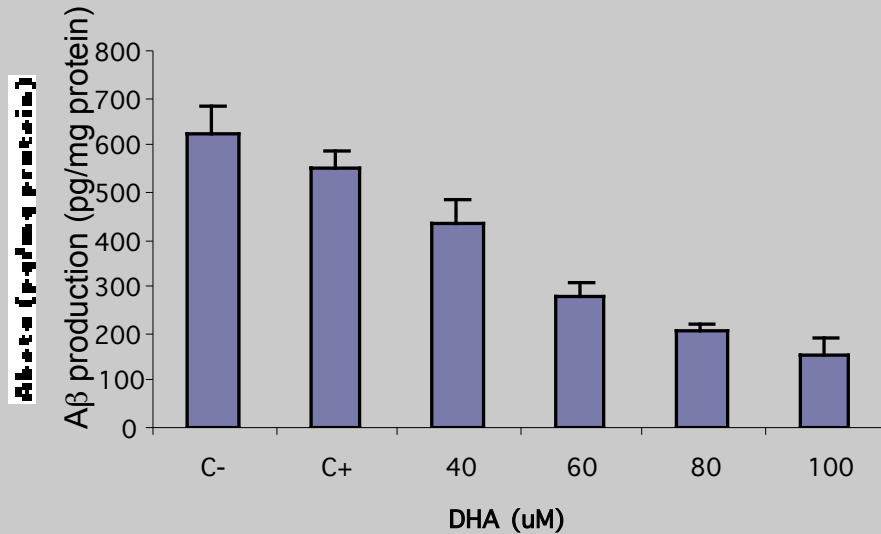


Brain tissue

Related results by Refolo, Duff, Kovacs, Sparks, ...

- Cell culture
- Neurons
- in vivo
- Epidemiology
- Clinical effects

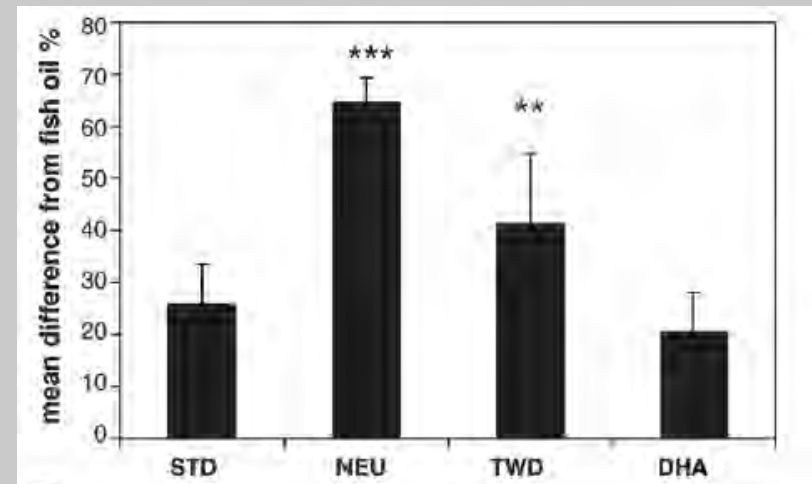
# DHA/EPA (fish oil) LipiDiet



24 hr supplementation of DHA to CHO-7PA2 cells results in a significant dose dependent decrease in Aβ production  
*De Wilde et al. 2005*

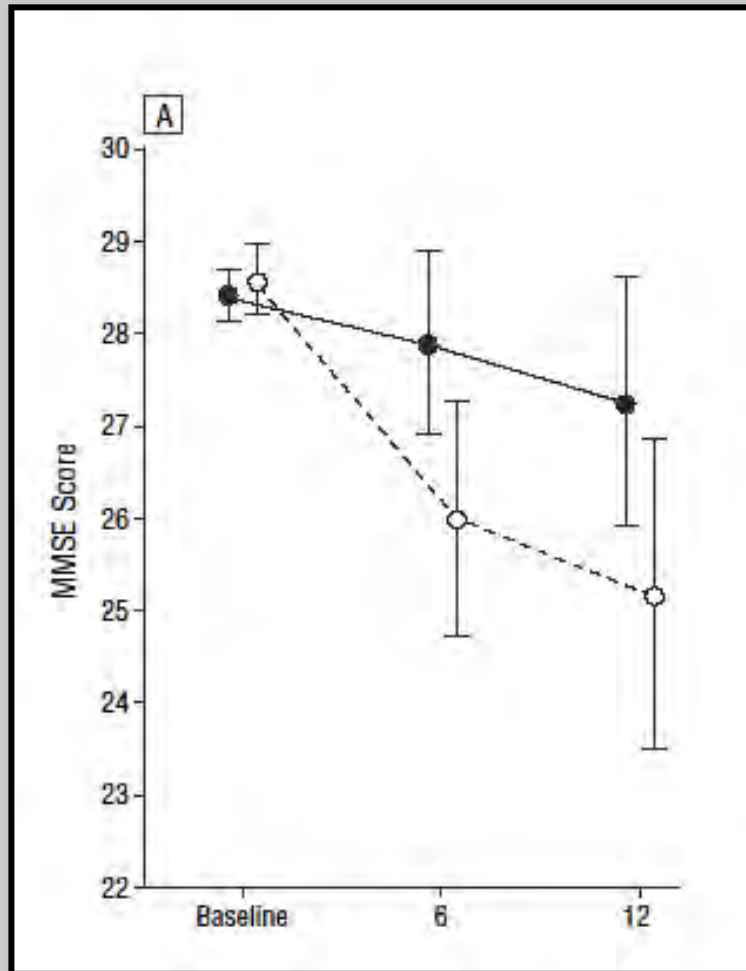
Lipid diet content	STD	NEU	TWD	DHA
DHA (C22:6 n-3) %	0	0	0	0.5
Cholesterol %	0	0	1	0
Total n-3	7	1	1	14
Total n-6	52	31	31	40
Ratio n-6/n-3	8	23	23	3
SFA %	15	44	44	19
MUFA %	22	18	18	19
PUFA %	59	32	32	54

Diets - fat blend compositions (*Lipidiet consortium*)



Fat blend effect on Aβ production (*Amtul/Oksman et al. 2006*)

# DHA/EPA (fish oil)



Freund-Levi et al. 2006 (Freund-Levi talk Sunday), n=32, very mild AD (MMSE >27), no effect in later stages. 3:1 DHA:EPA (1720:600mg)

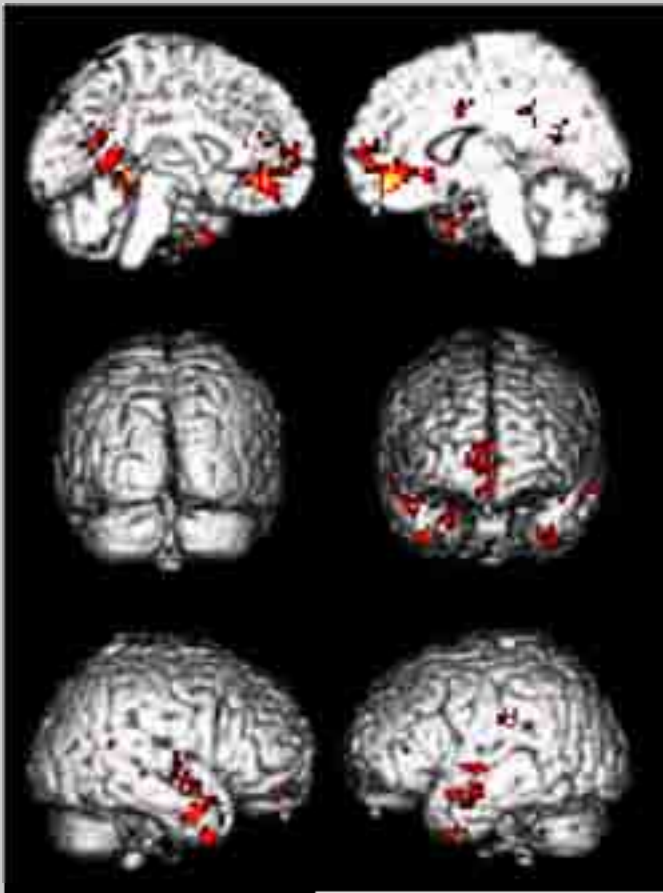
# Erhöhter! Energieaufwand bei MCI Patienten beim Lernen

Schröder et al.

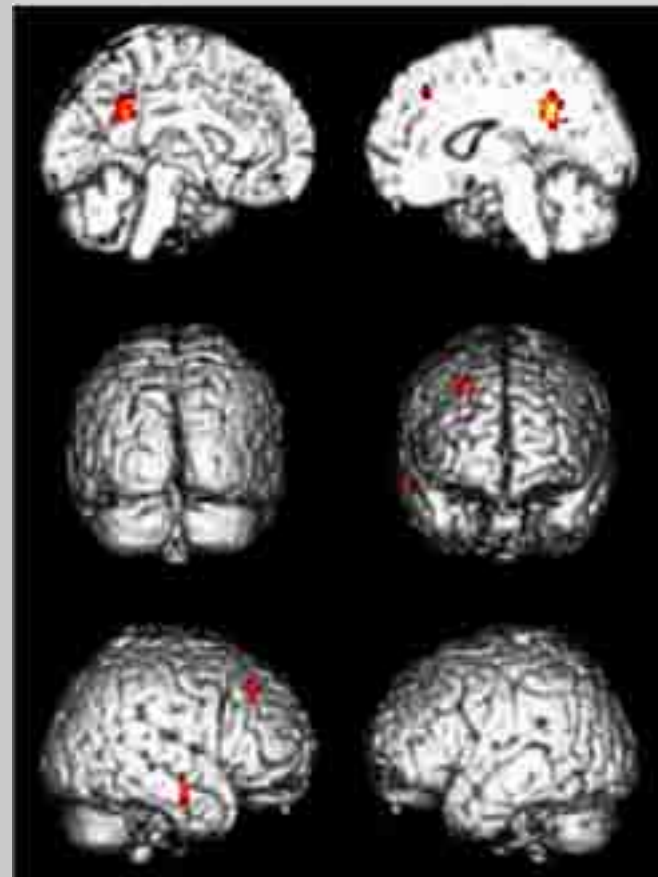
Gemessen wurde der Redoxzustand  
von Häm(oglobin) während des  
Abrufens erlernter Wortlisten

# Bevor die Wortliste trainiert wurde

Gesund

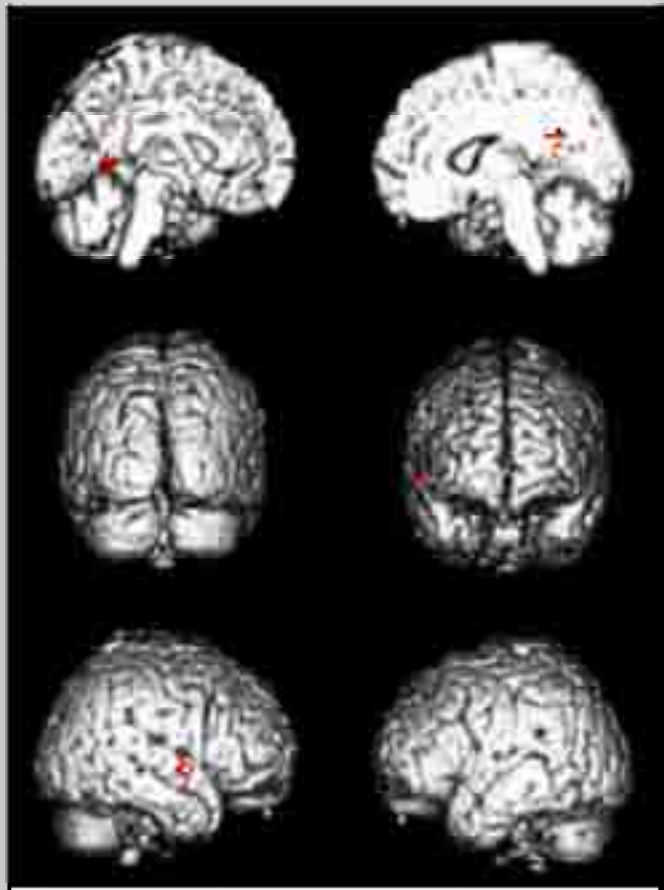


Krank



# Nachdem die Wortliste trainiert wurde

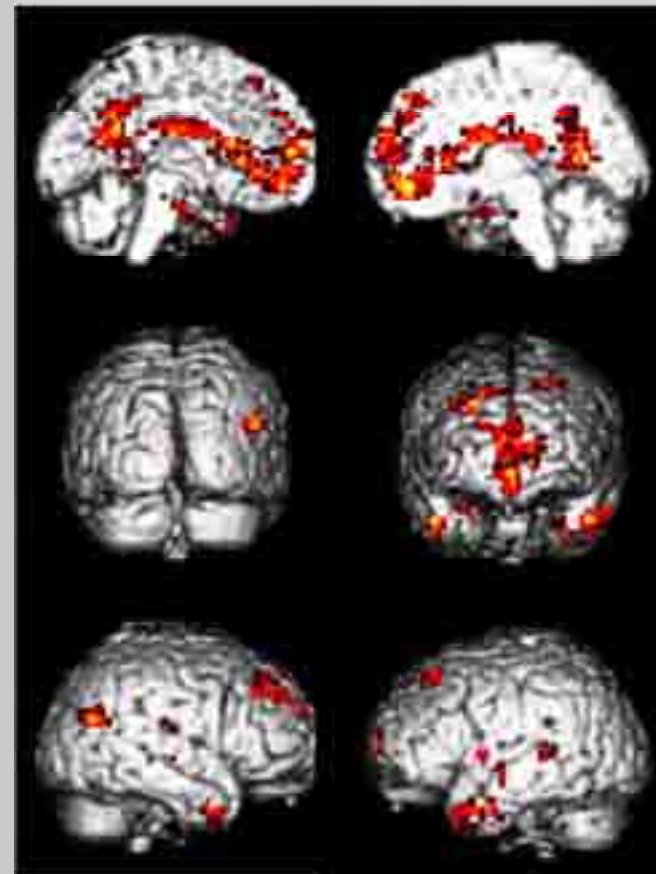
**Gesund**



*vorher*



**Krank**



*vorher*



- 
- Kurzsript (in zwei Tagen):  
[www.neuro-saarland.de/Hartmann](http://www.neuro-saarland.de/Hartmann)
  - Weitere Infos: <http://www.ipa-online.org/neurosite/index.asp>

-