Altern und Demenz – Therapie und Perspektiven

Josef Marksteiner

LKH Rankweil

Diskussionspunkte

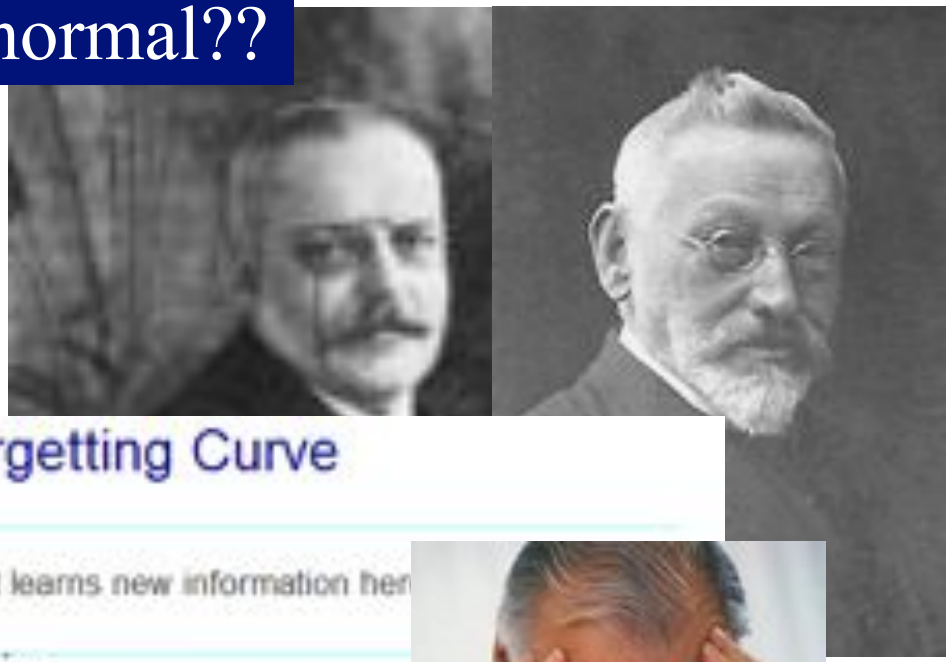
- Epidemiologie
- Pathologie
- Krankheitsverlauf
- Therapie
- Erfolgreiches Altern

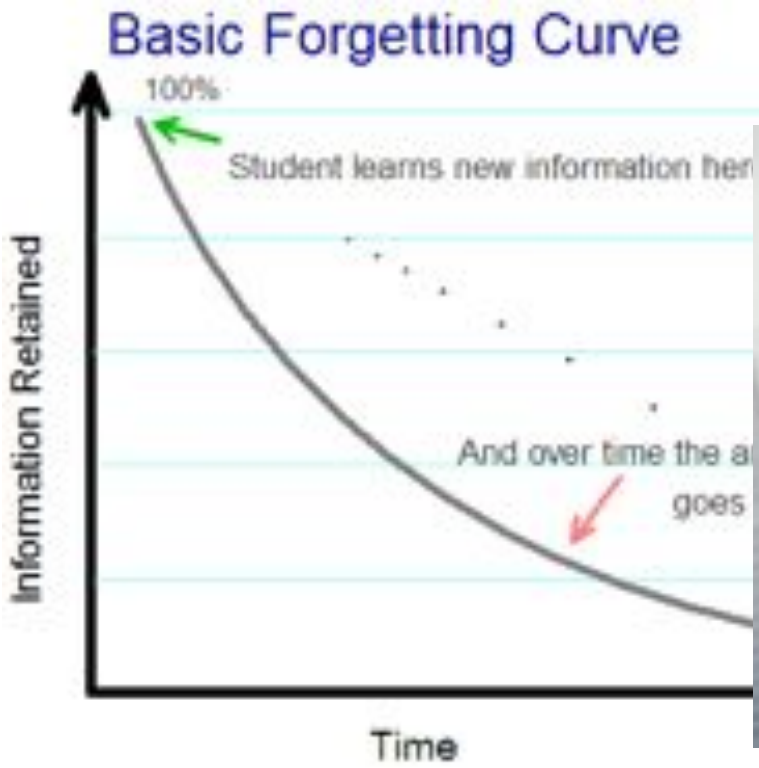
Luis Buñuel – Gedächtnis
(1900 – 1983)

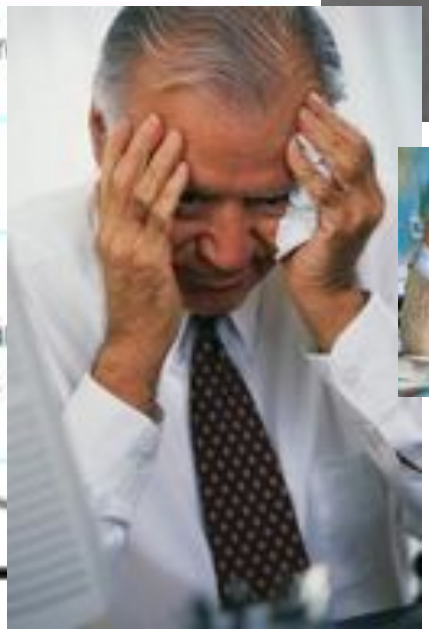
„Man muß erst beginnen, sein Gedächtnis zu verlieren, und sei's nur stückweise, um sich darüber klarzuwerden, daß das Gedächtnis unser ganzes Leben ist. Ein Leben ohne Gedächtnis wäre kein Leben... Unser Gedächtnis ist unser Zusammenhalt, unser Grund, unser Handeln, unser Gefühl. Ohne Gedächtnis sind wir nichts..."

(Luis Bunuel)

Was ist normal??

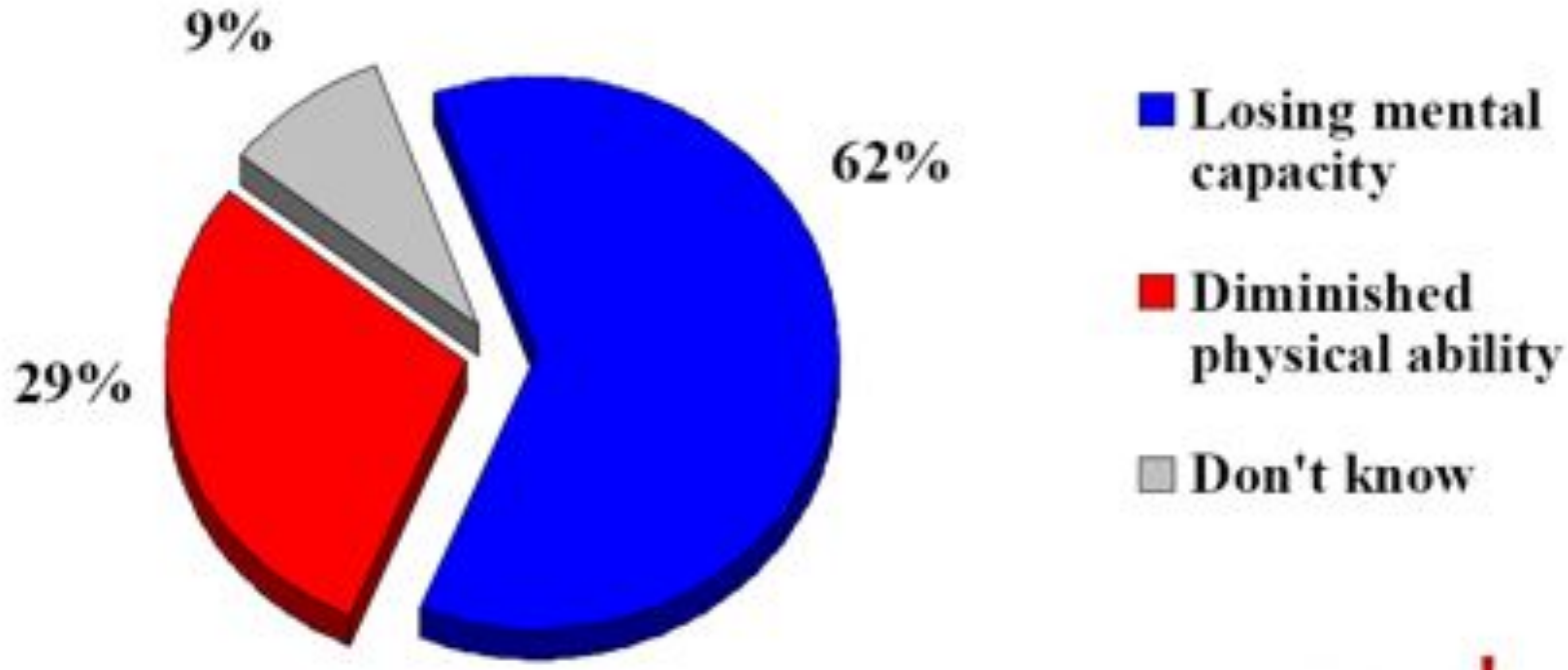






Losing Mental Capacity is Greatest Fear

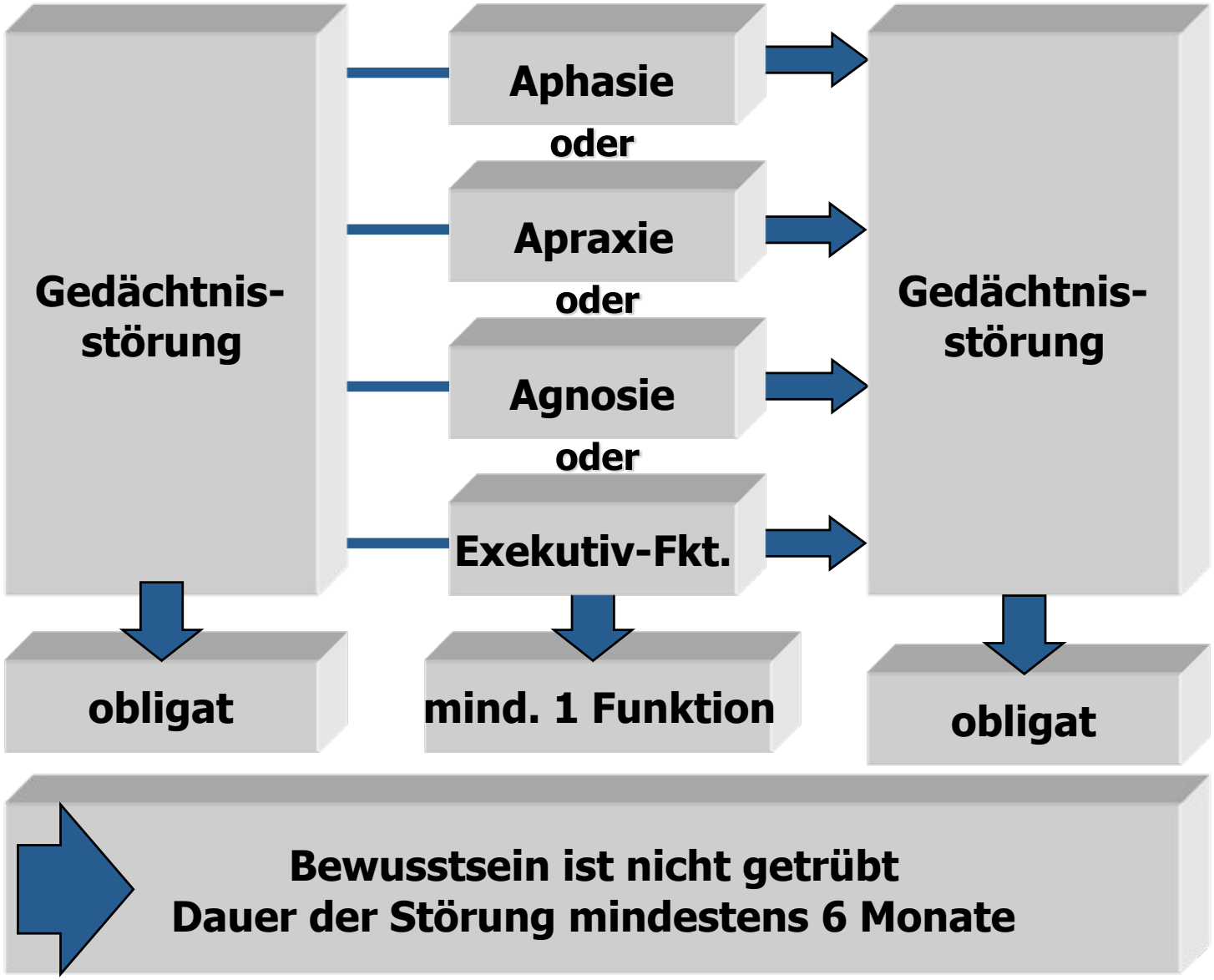
When you think about aging, what do you fear more: diminished physical ability or losing mental capacity?



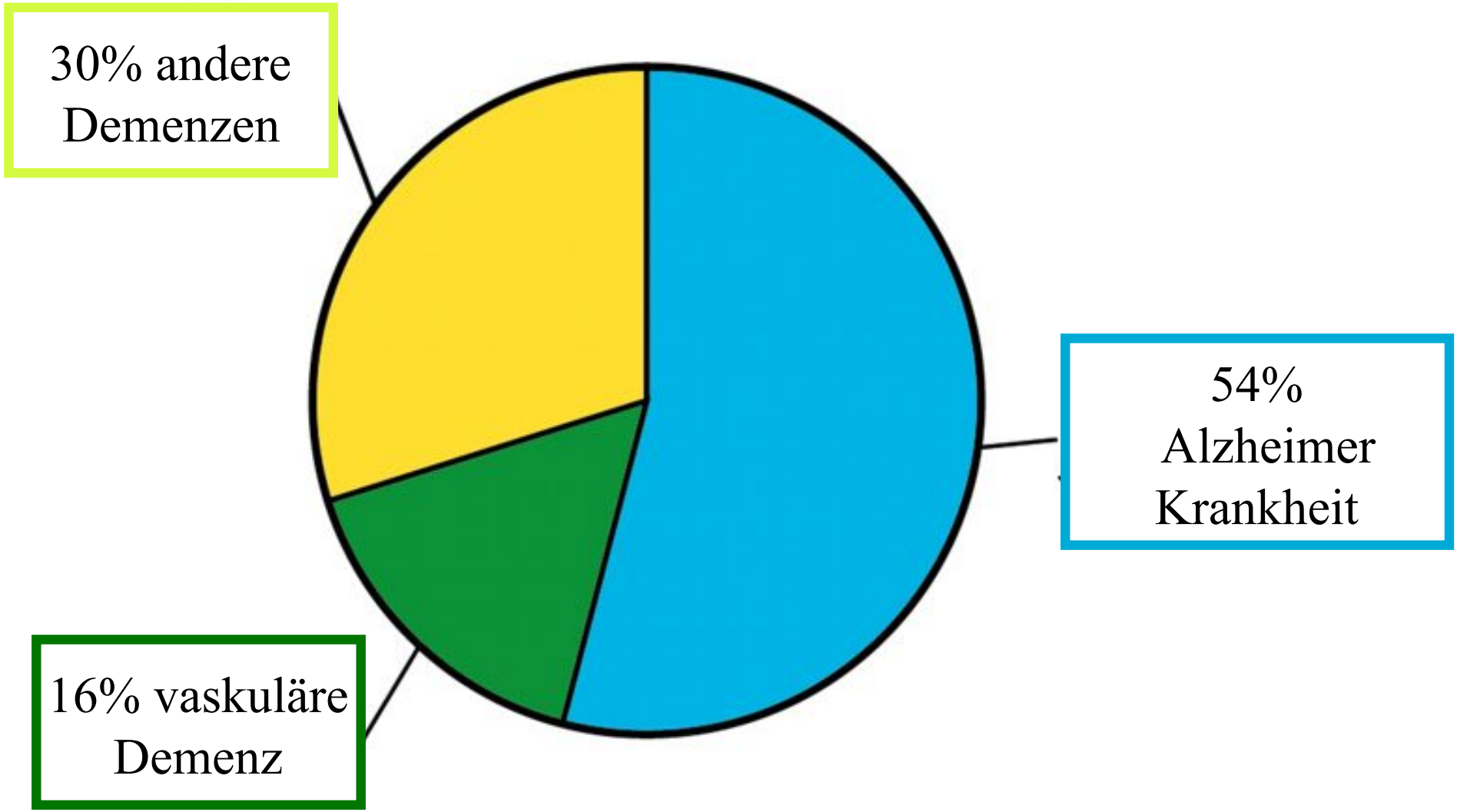
Taking Our Pulse: The PARADE/Research!America Health Poll
Charlton Research Company, 2005

Research!America
AN ALLIANCE FOR DISCOVERIES IN HEALTH

Demenz

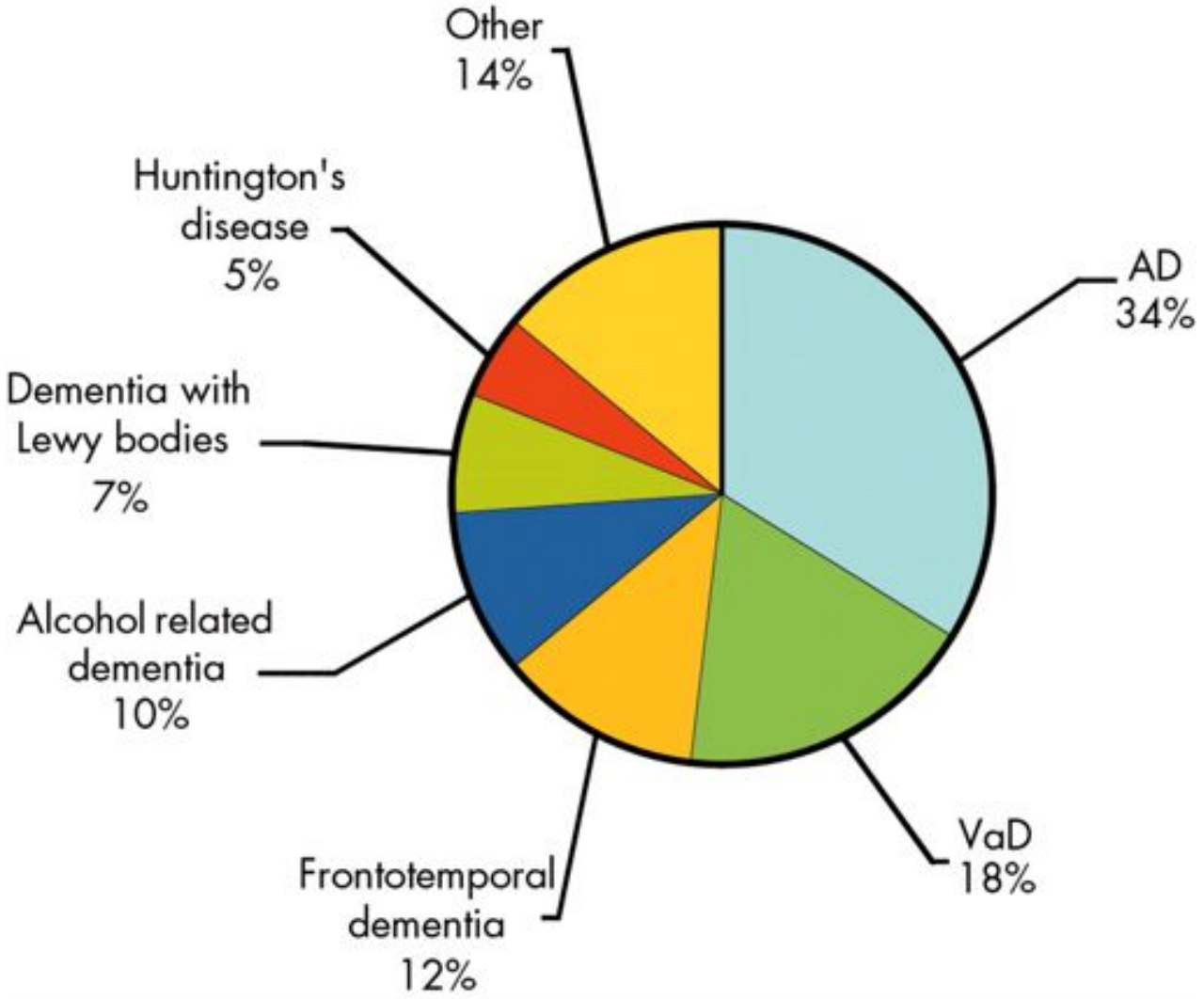

Gedächtnis-
störung
Aphasie
oder
Apraxie
oder
Agnosie
oder
Exekutiv-Fkt.
Gedächtnis-
störung
obligat
mind. 1 Funktion
obligat
Bewusstsein ist nicht getrübt
Dauer der Störung mindestens 6 Monate

Demenzprävalenz mit spätem Beginn (≥ 65 Jahre)

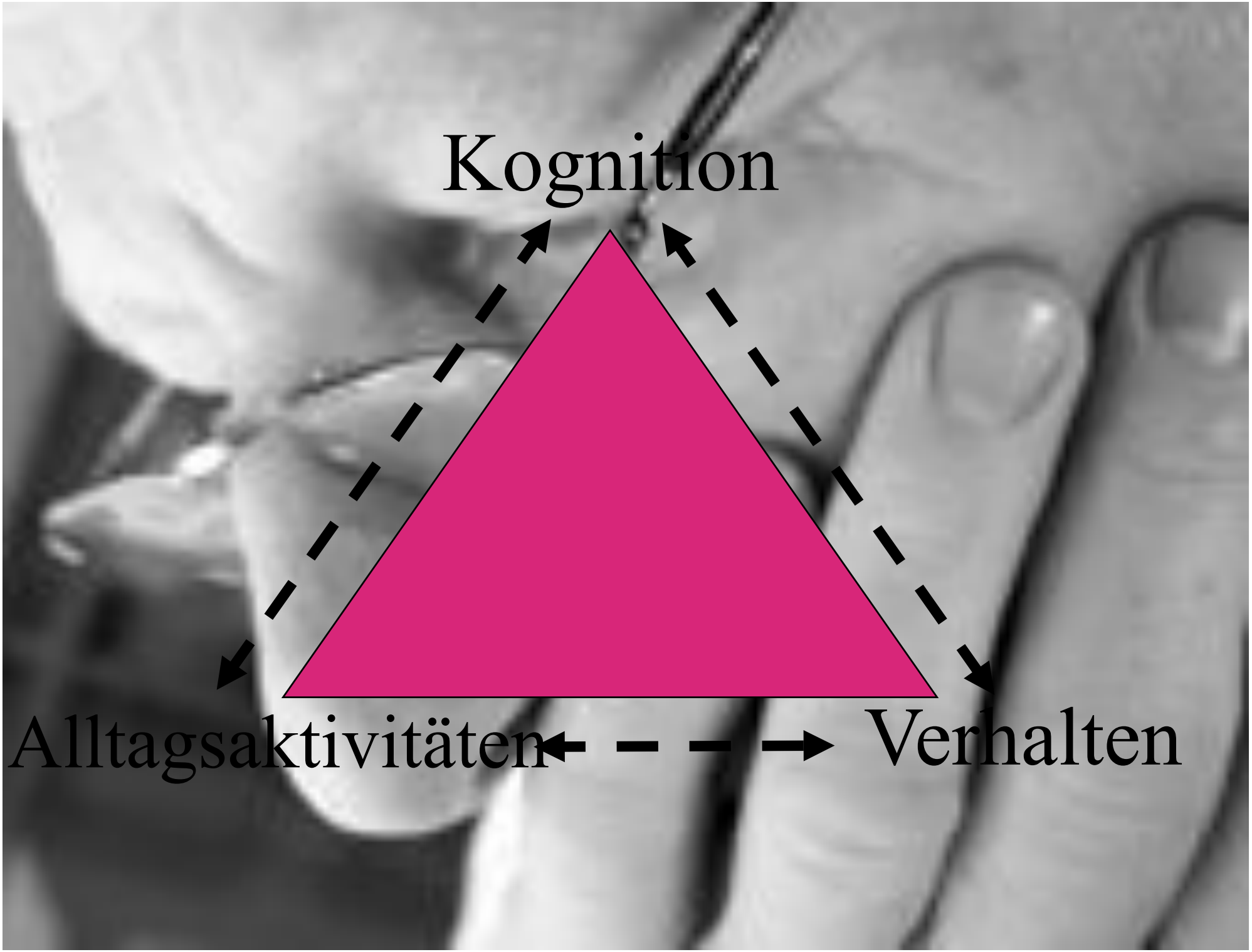


•**Lobo A**, Launer LJ, Fratiglioni L, *et al.* Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic diseases in the elderly research group. *Neurology* 2000;**54** (11 suppl 5) :S4–9.

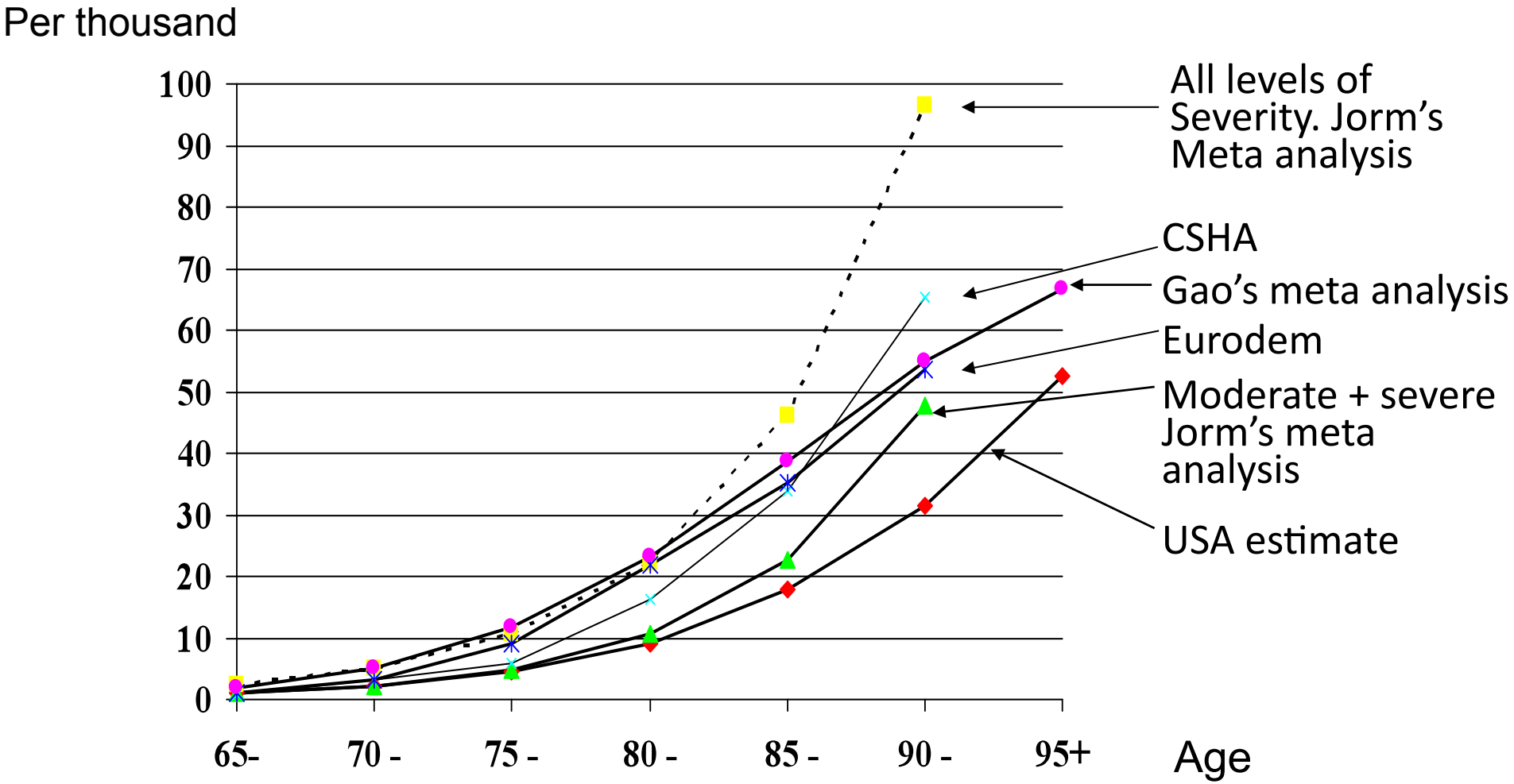
Demenz mit frühem Beginn (< 65 Jahre)



Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry* 2003;**74**:1206–9.

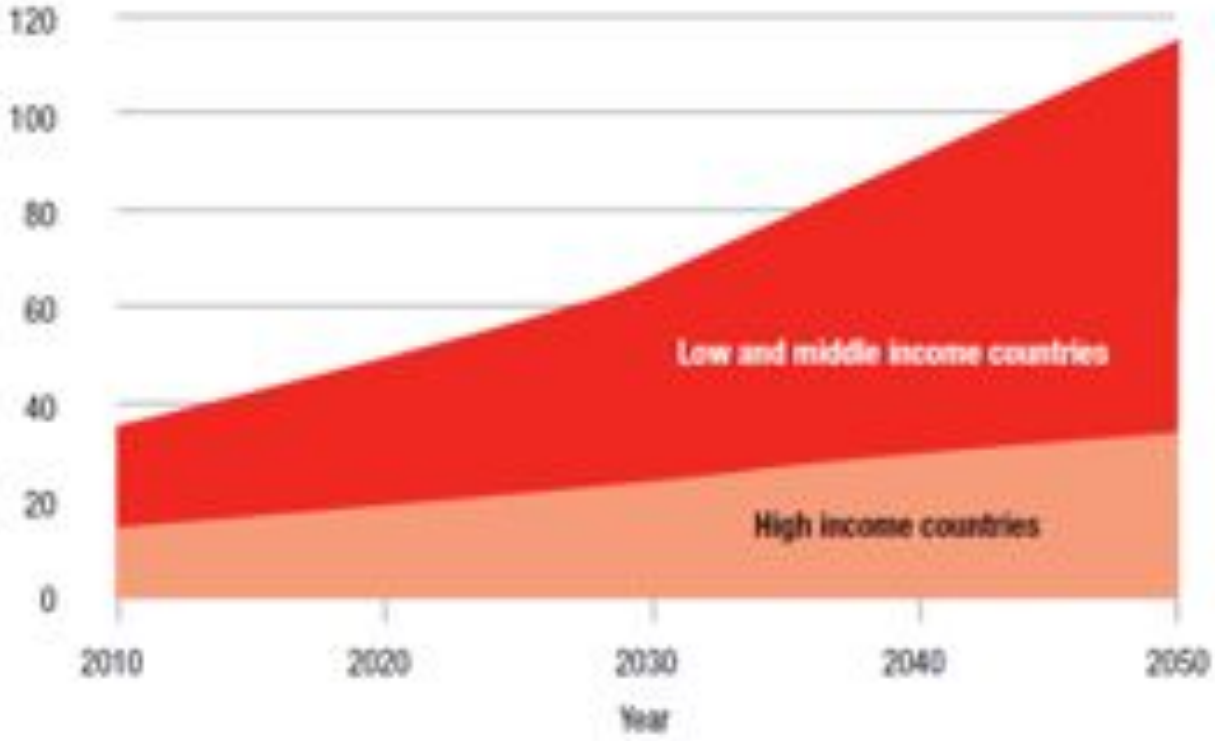

Kognition
Alltagsaktivitäten
Verhalten

Estimates of the incidence of Alzheimer's disease

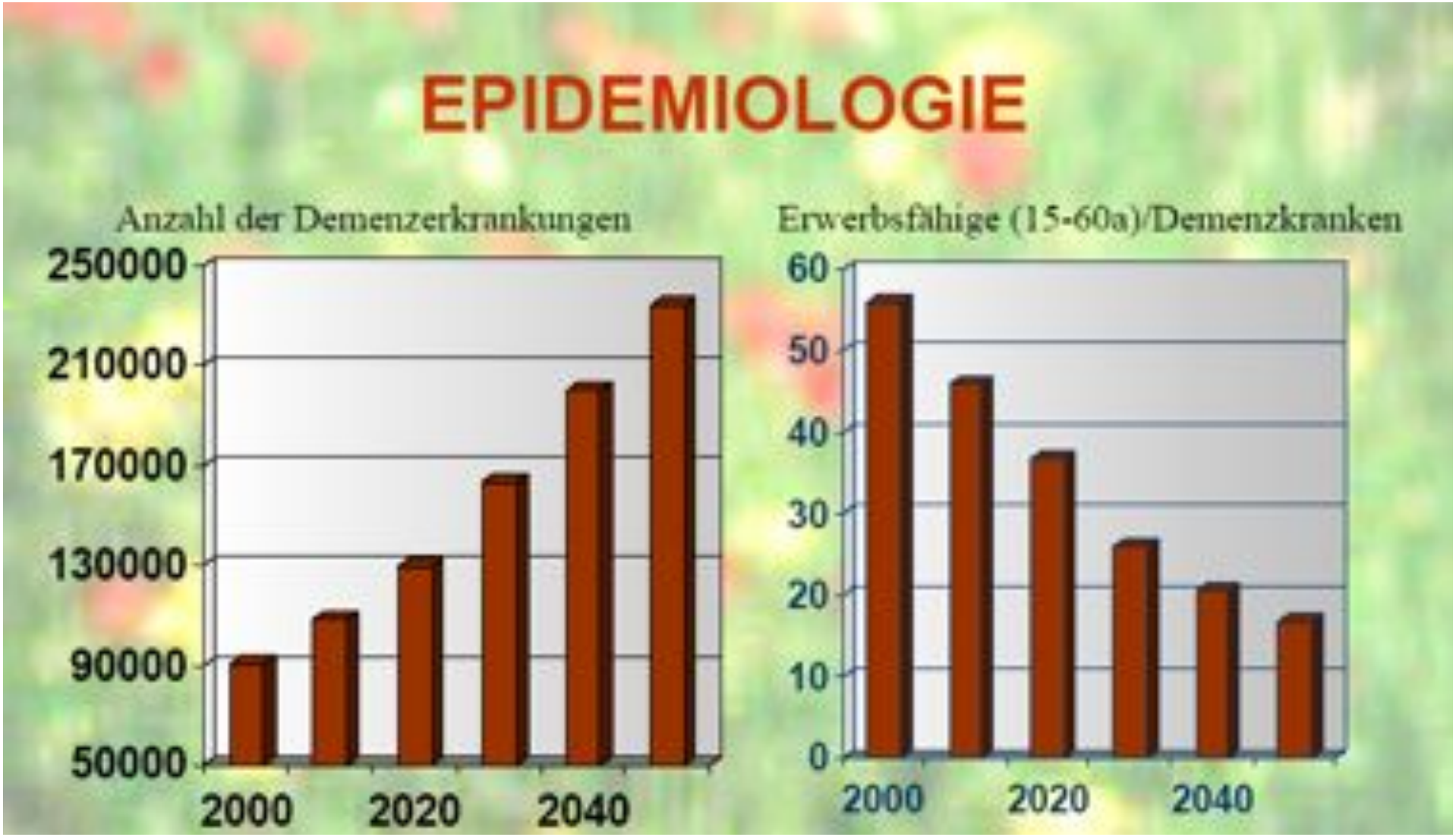


Die Weltbevölkerung wird älter – Anstieg von dementiellen Erkrankungen

Figure 1 **The growth in numbers of people with dementia (in millions) in high income countries, and low and middle income countries**



Österreich



Wancata et al., 2002

Diskussionspunkte

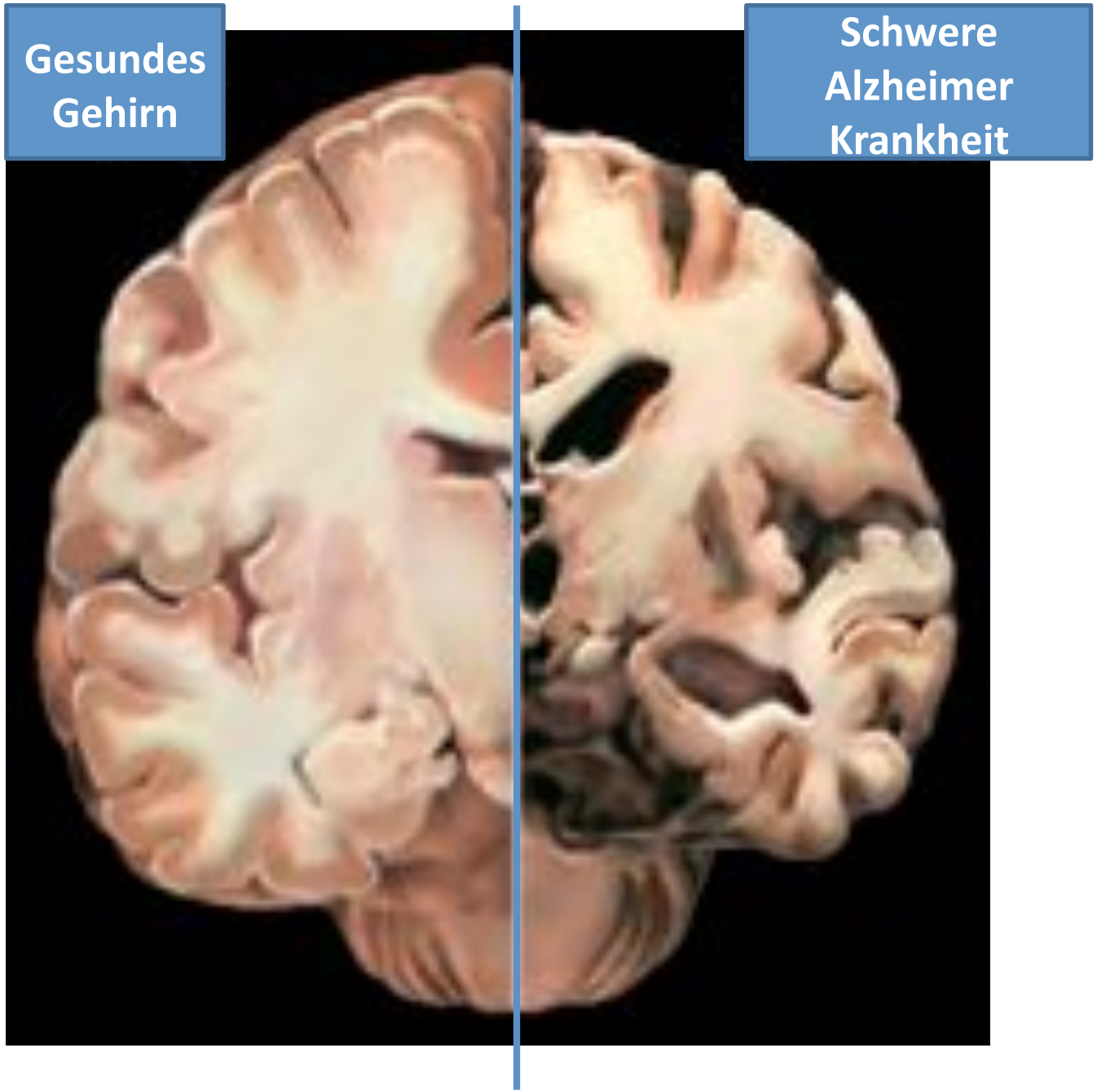
- Epidemiologie
- Pathologie
- Krankheitsverlauf
- Therapie
- Erfolgreiches Altern

100 Jahre Alzheimer Forschung

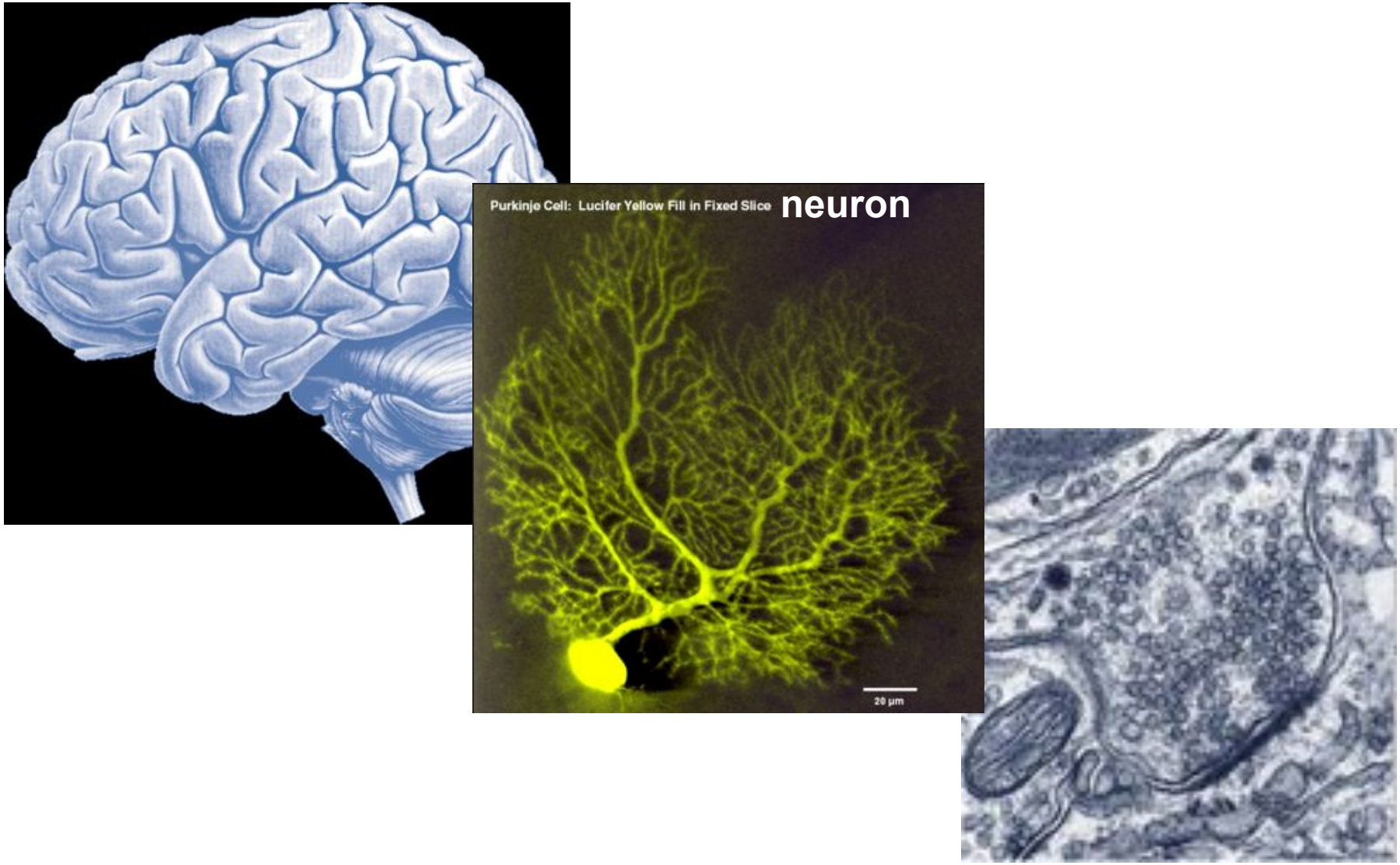
Alzheimers „erste" Patientin Auguste D. starb nach 4,5 Jahren Krankenhausaufenthalt am 28. August 1906 in der Frankfurter Irrenanstalt.

Am 3. November 1906, anlässlich der 37. Wanderversammlung der Südwestdeutschen Irrenärzte in Tübingen präsentierte Alois Alzheimer die Veränderungen im Gehirn von Auguste D.

Es gab keine Diskussion!

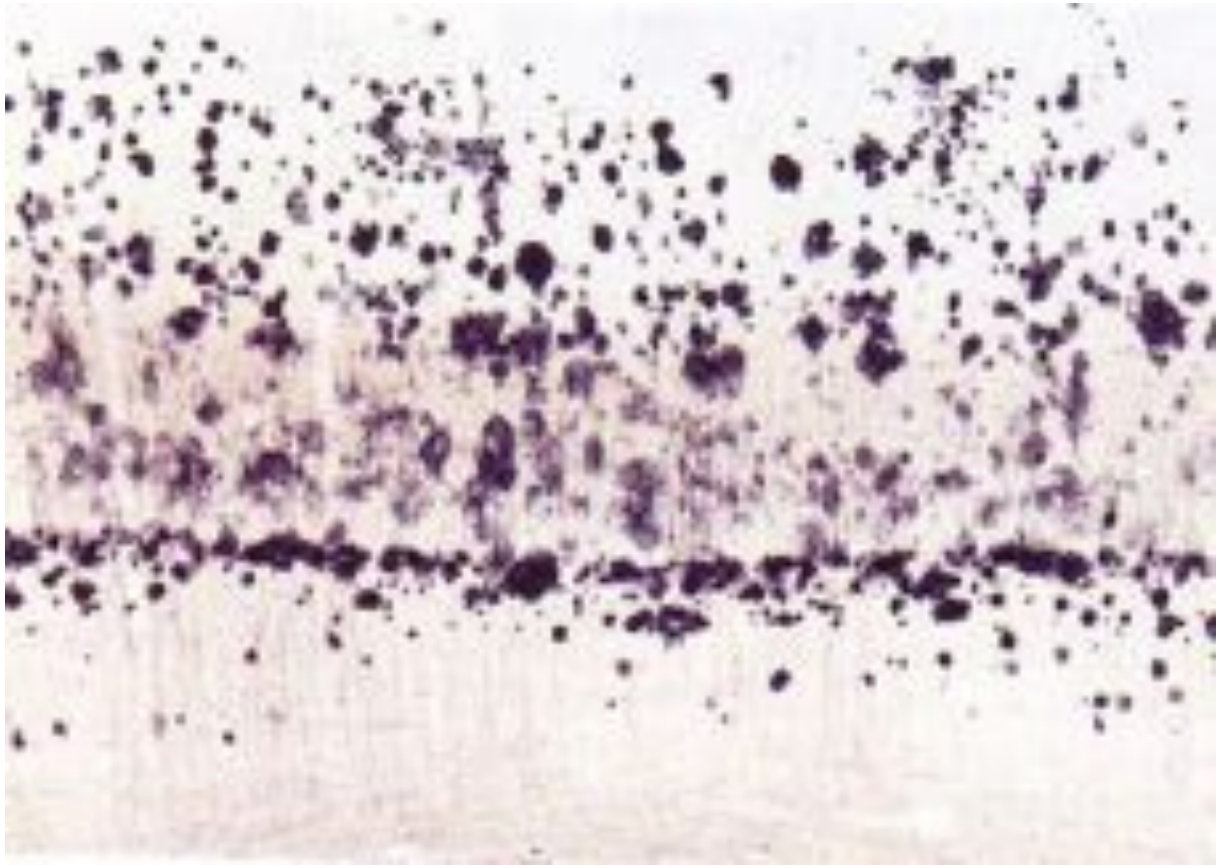

Gesundes Gehirn
Schwere Alzheimer Krankheit


Amyloid - Pathologie
Tau - Pathologie
Synaptische Veränderungen

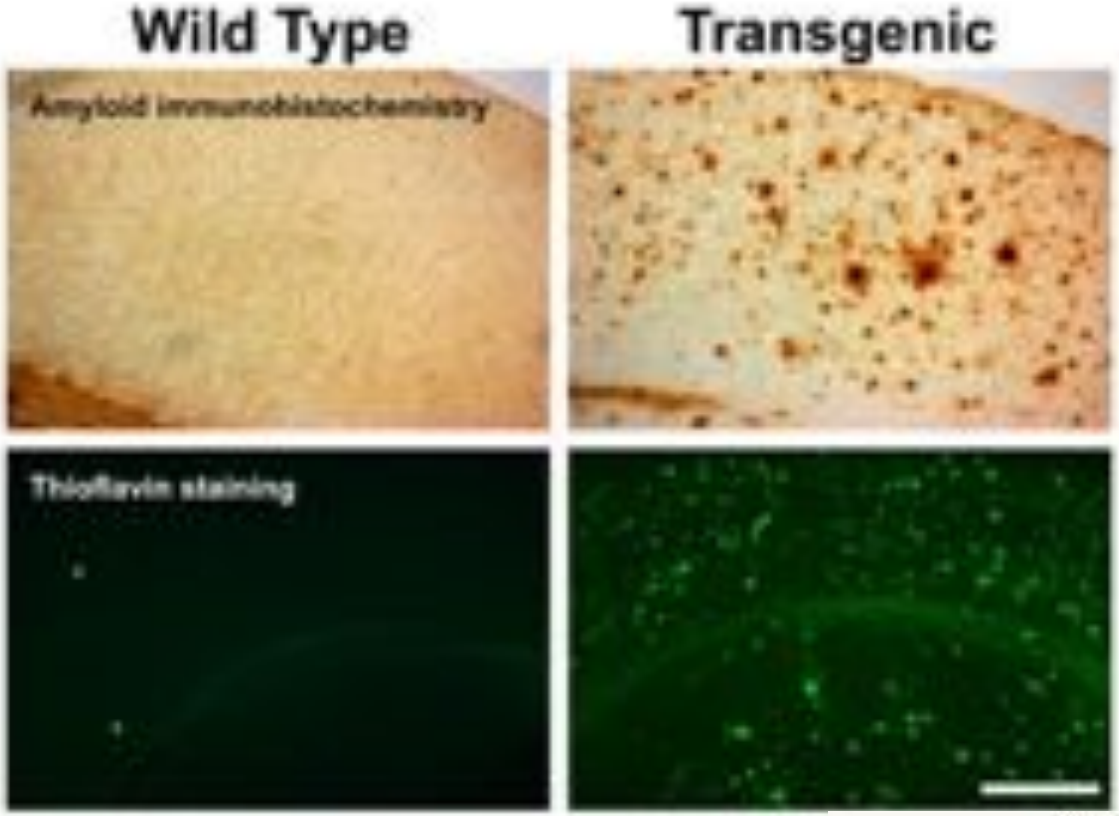

Purkinje Cell: Lucifer Yellow Fill in Fixed Slice
neuron
20 µm

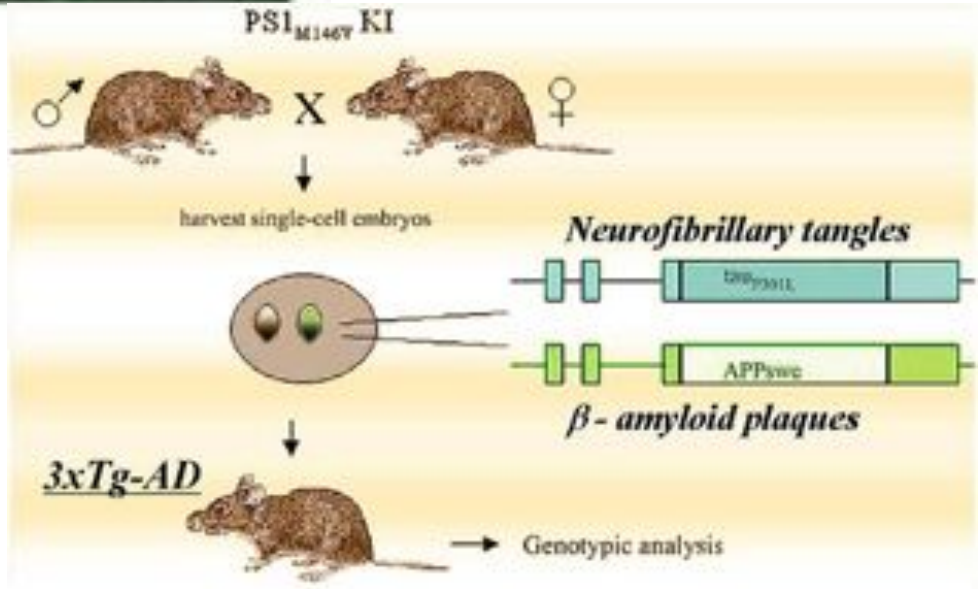
Beta-Amyloid Plaques (neocortex)

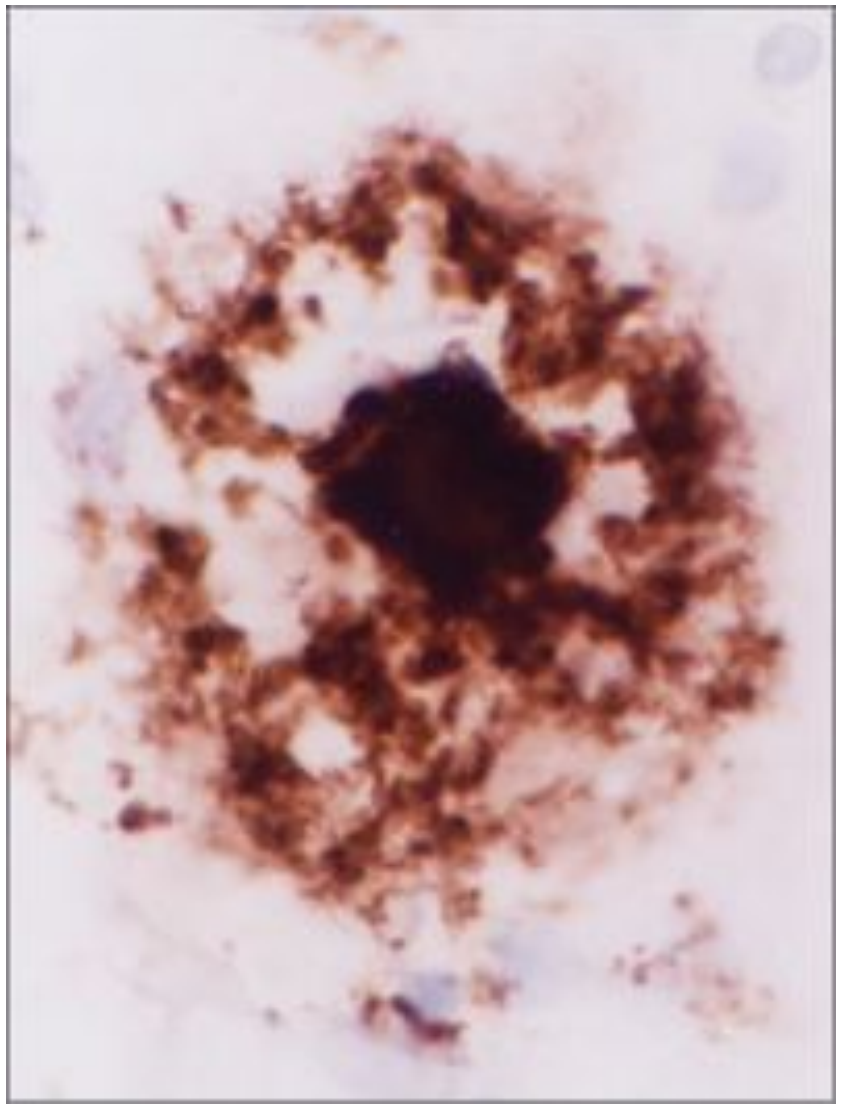
Stadium A

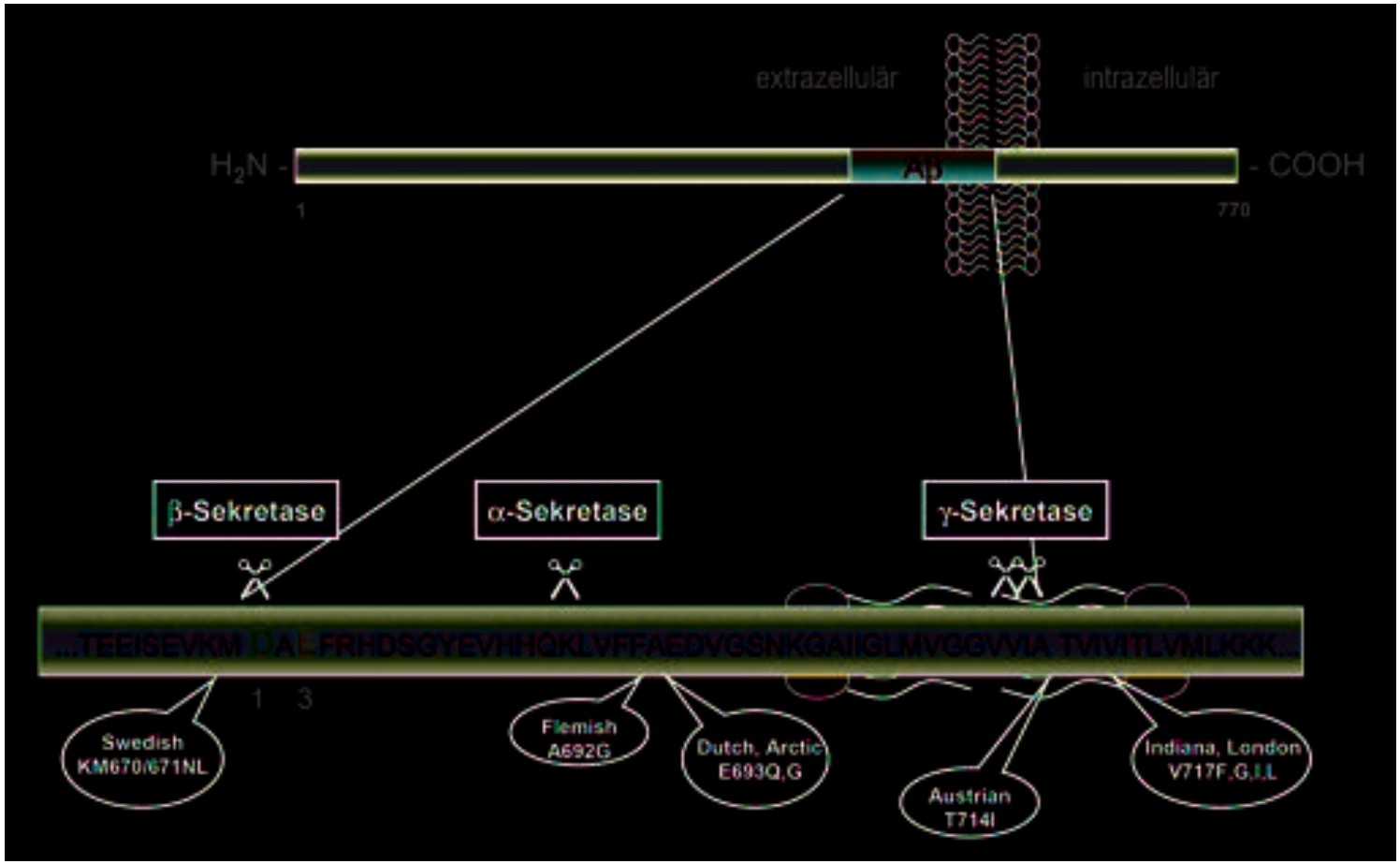


Stadium C

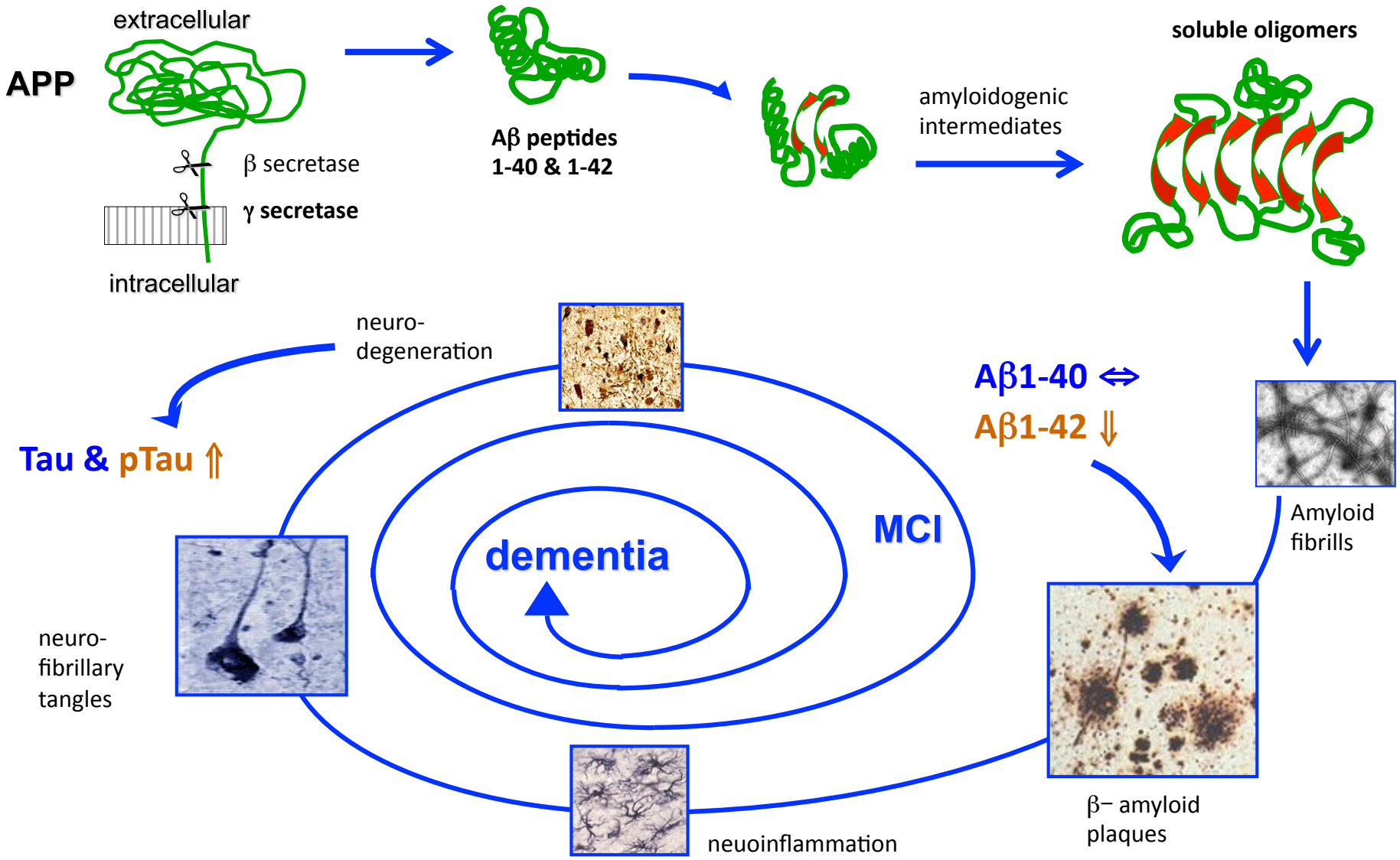

Wild Type
Transgenic
Amyloid immunohistochemistry
Thioflavin staining


PS1M146V KI
X
harvest single-cell embryos
Neurofibrillary tangles
APPswe
β - amyloid plaques
3xTg-AD
Genotypic analysis

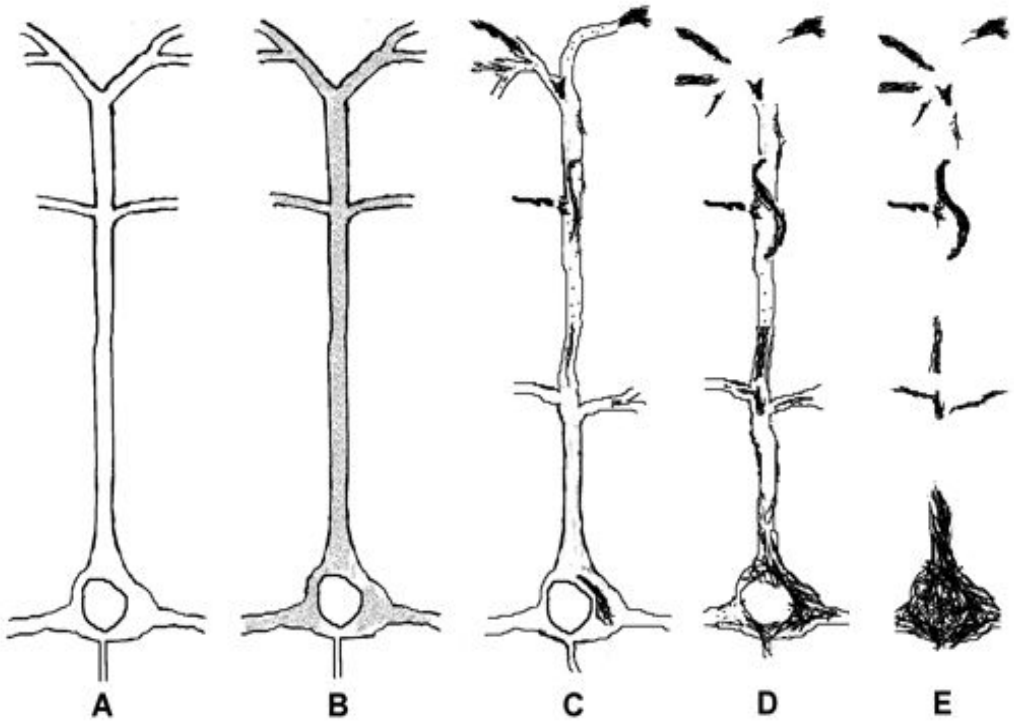


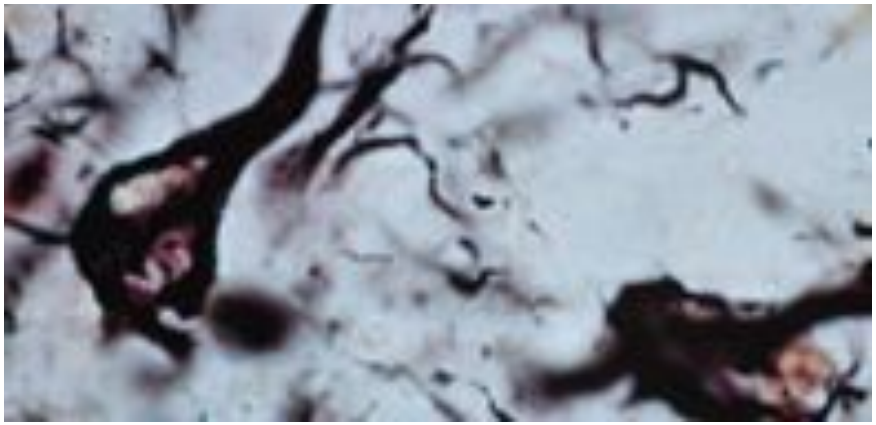

extrazellulär
intrazellulär
H2N -
Aβ
- COOH
1
770
β-Sekretase
α-Sekretase
γ-Sekretase
1 3
Swedish
KM670/671NL
Flemish
A692G
Dutch, Arctic
E693Q,G
Austrian
T714I
Indiana, London
V717F,G,I,L

Amyloid cascade hypothesis of Alzheimer´s Dementia

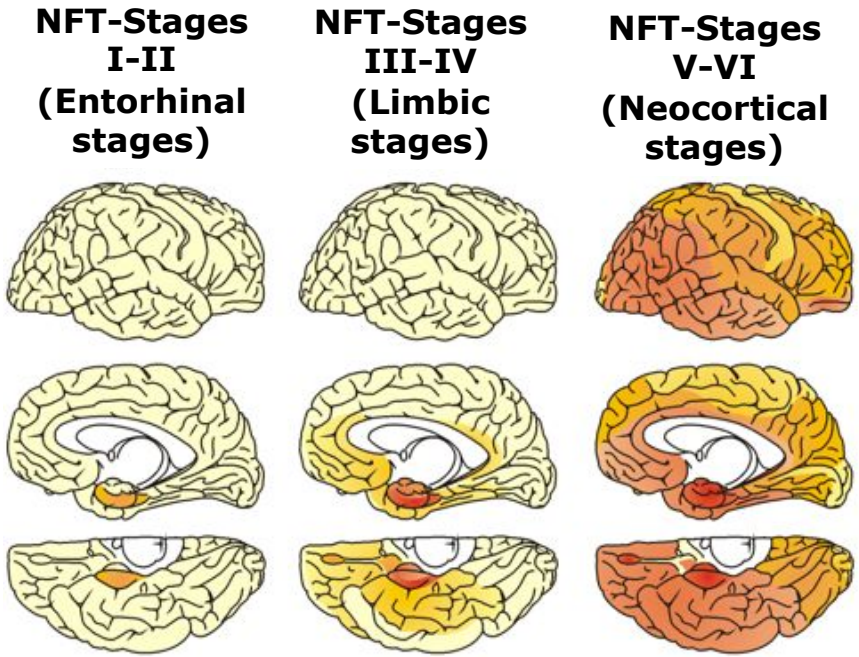


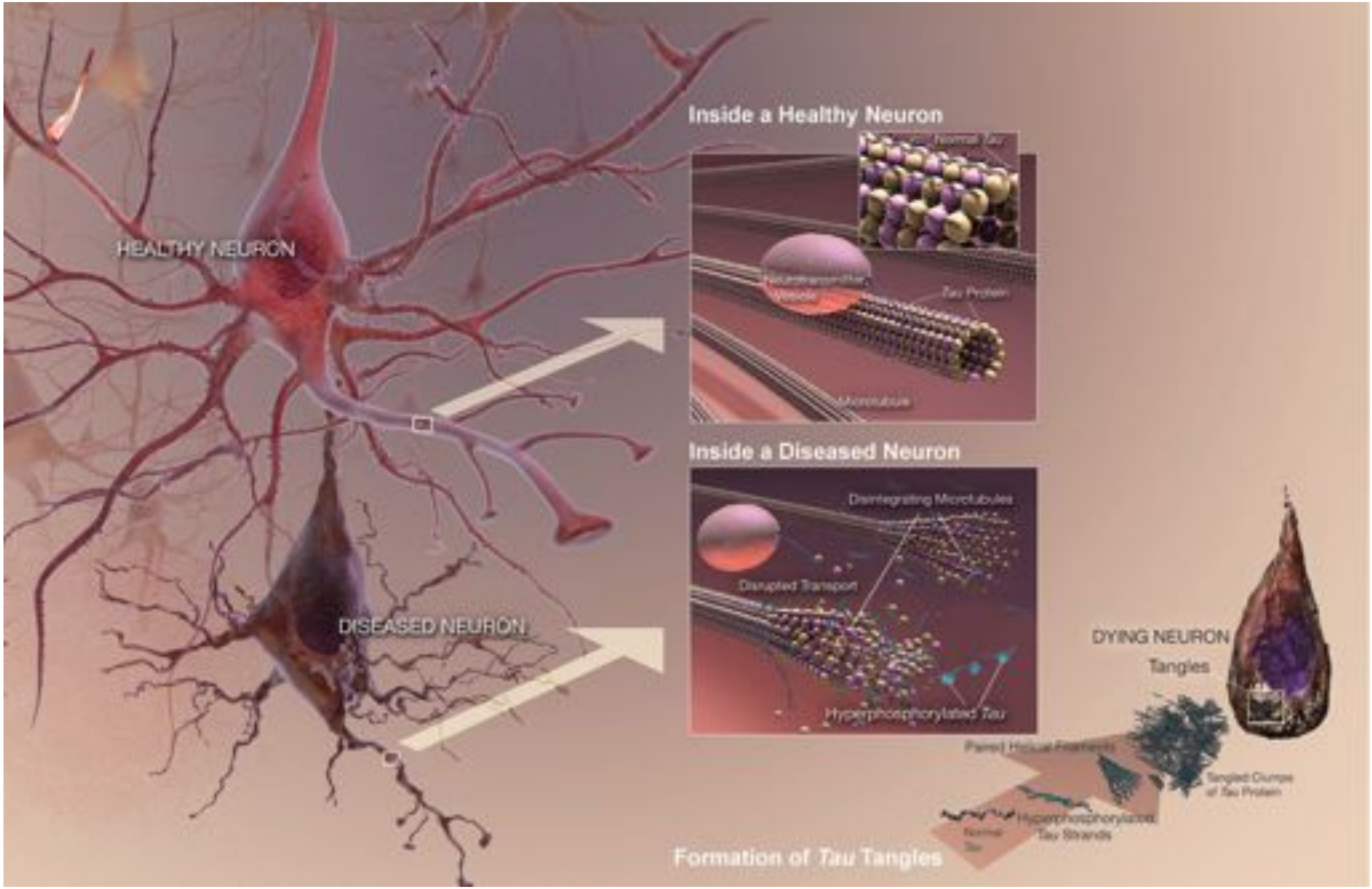
Tauprotein - Pathology





Duration:
years to decades

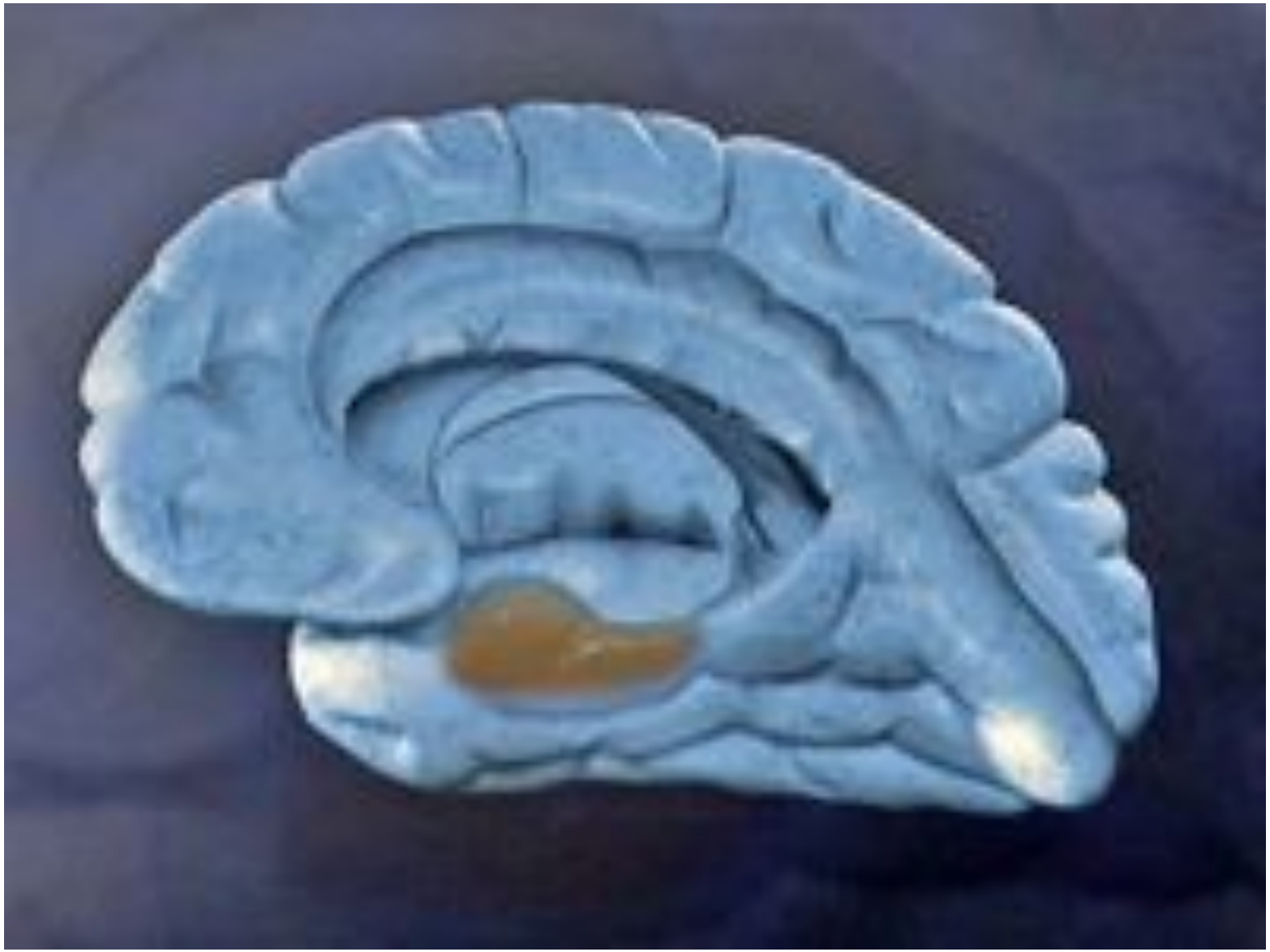


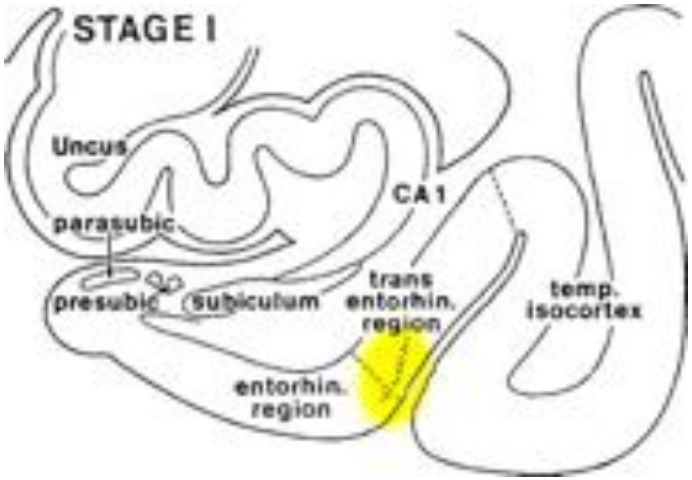

HEALTHY NEURON
DISEASED NEURON
Inside a Healthy Neuron
Tau Protein
Inside a Diseased Neuron
Disintegrating Microtubules
Disrupted Transport
Hyperphosphorylated Tau
DYING NEURON
Tangles
Tangled Clumps of Tau Protein
Hyperphosphorylated Tau Strands
Formation of Tau Tangles

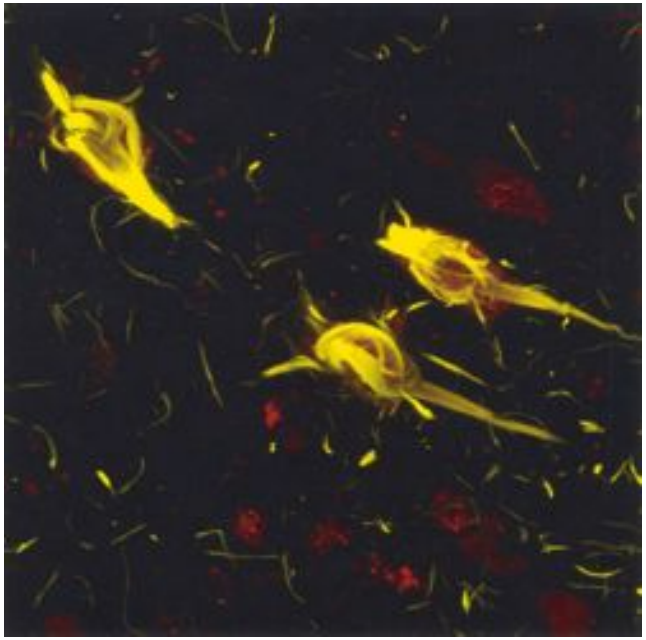
Diskussionspunkte

- Epidemiologie
- Pathologie
- Krankheitsverlauf
- Therapie
- Erfolgreiches Altern

Bei Alzheimer beginnt in und um den Hippocampus (dunkel eingefärbt) das Zellsterben

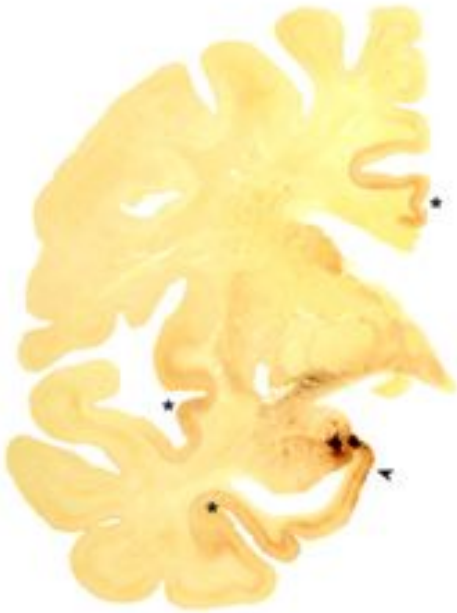






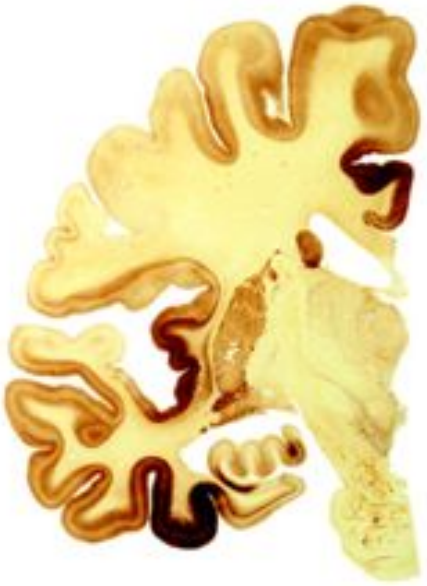
A Stage 3

B Stage 4



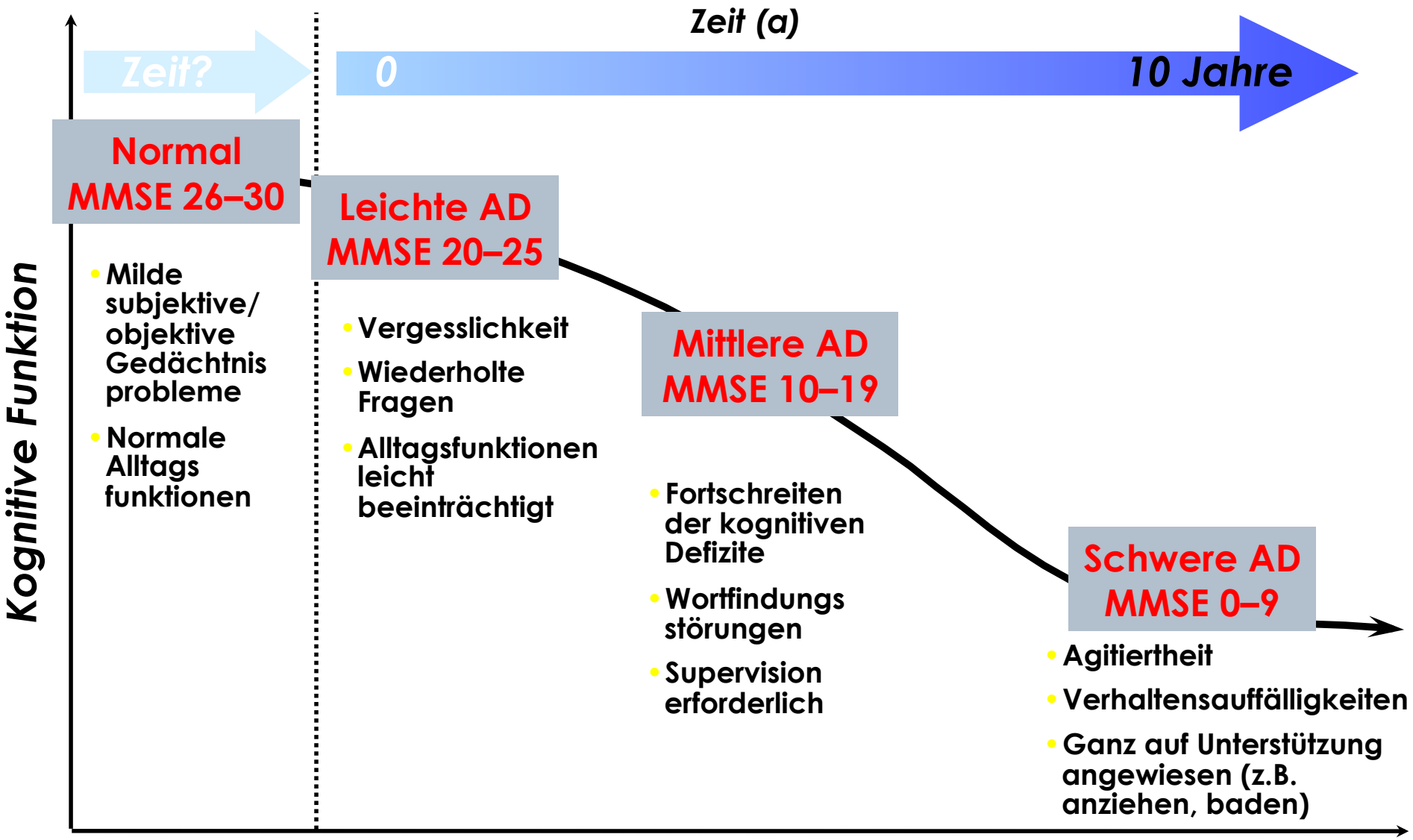
C Stage 5

D Stage 6

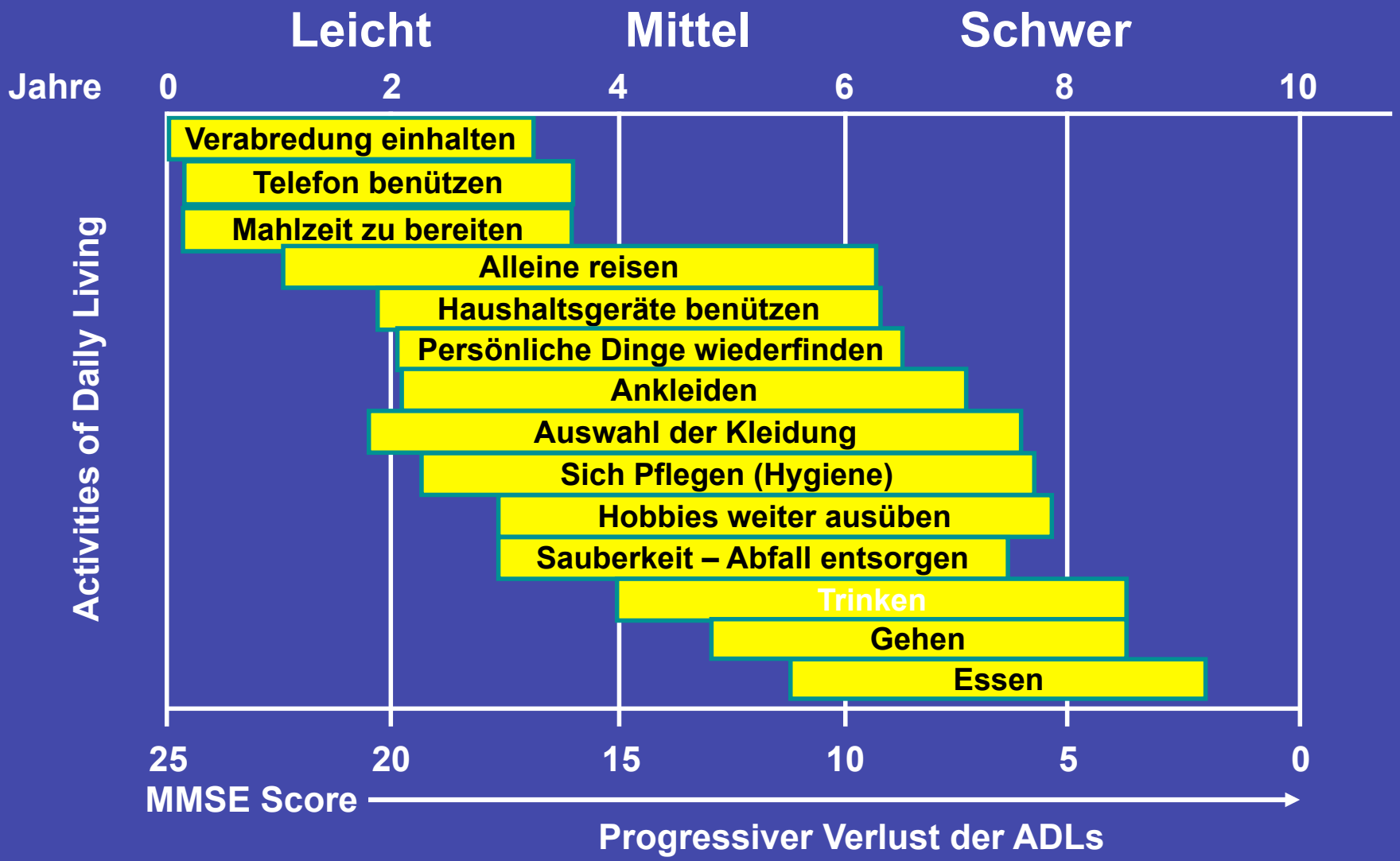


Alzheimer zu Beginn und im Endstadium: Das Zellsterben hat sich über die ganze Großhirnrinde ausgebreitet

Klinischer Verlauf der Alzheimer Krankheit (AD)



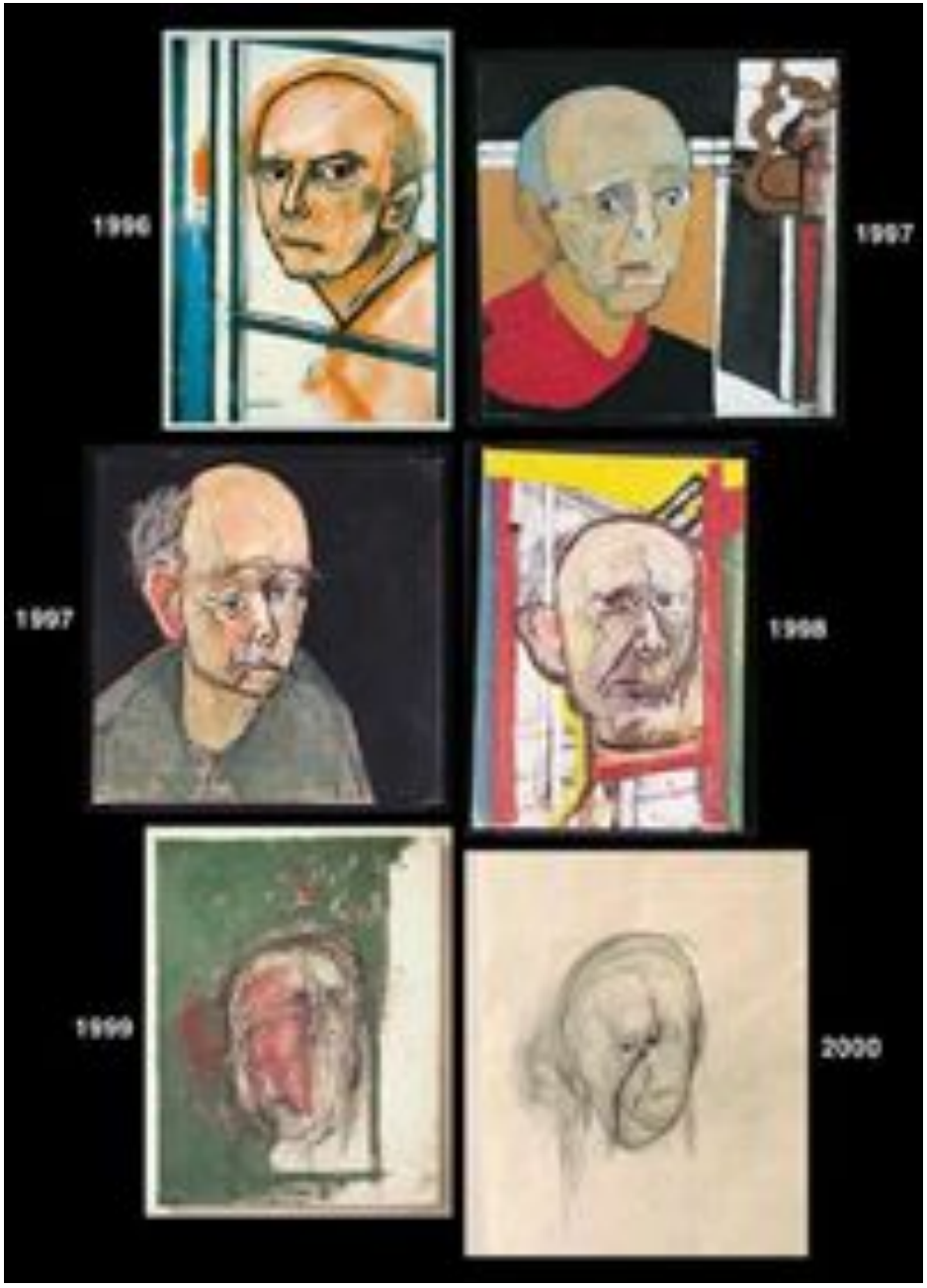
Fortschreitende Beeinträchtigung der Alltagsaktiviäten



Adapted from Galasko D, et al. *Eur J Neurol*. 1998;5(suppl 4):S9-S17.

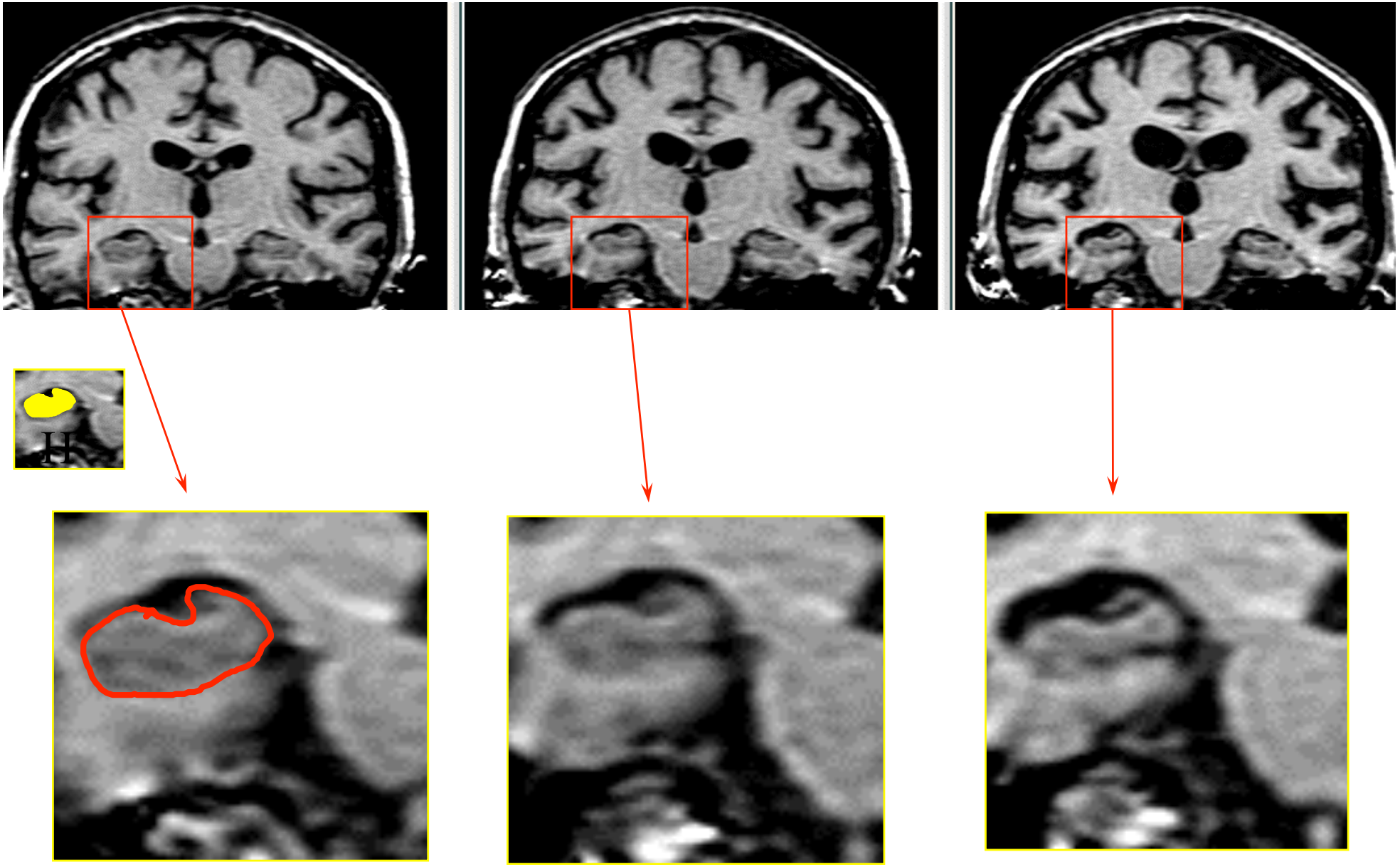
A self-portrait of William Utermohlen

1995



2000

1967



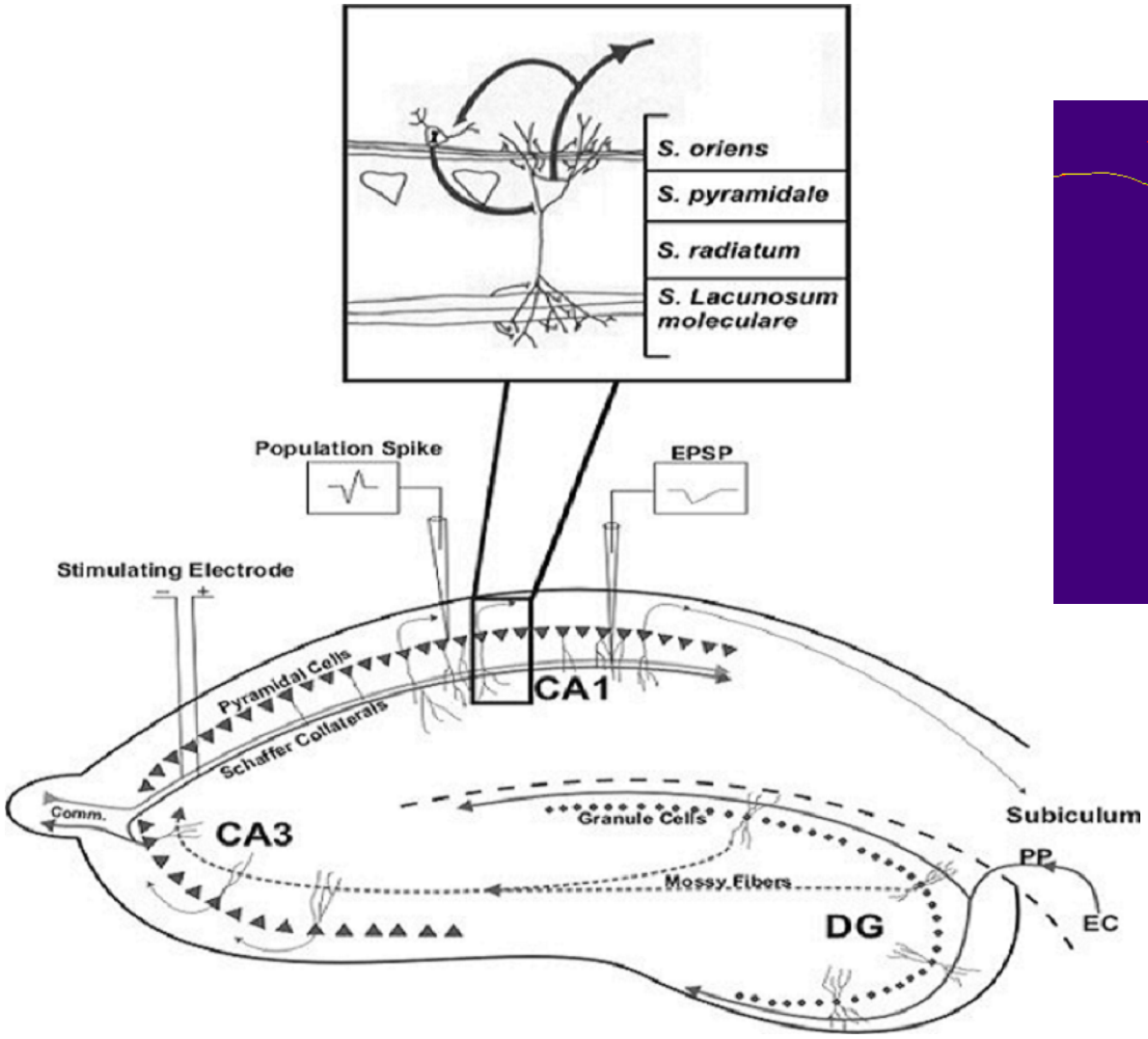
Koronare Schnitte von einem Patienten
mit beginnender Alzheimer Krankheit

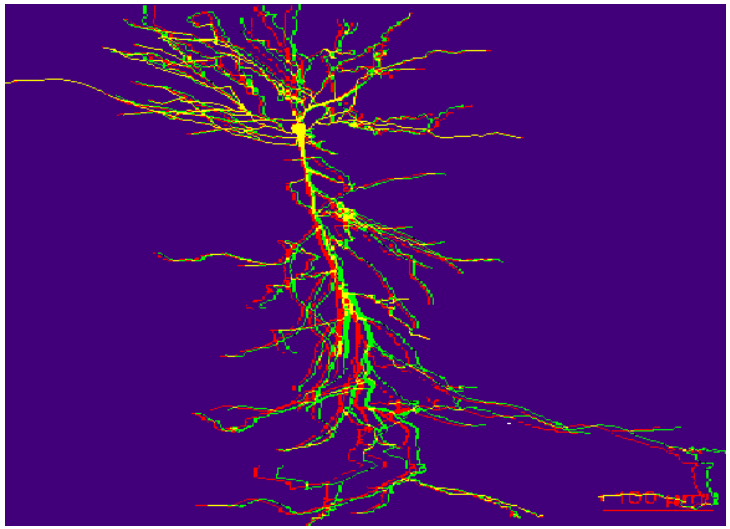
Hippocampus

"Explizites Gedächtnis".

- Essentielle Bedeutung für neue Gedächtnisinhalte (episodisch/ autobiographisch/explizit)
- Notwendig für einfache räumliche Aufgaben.

CA1 pyramidal neuron

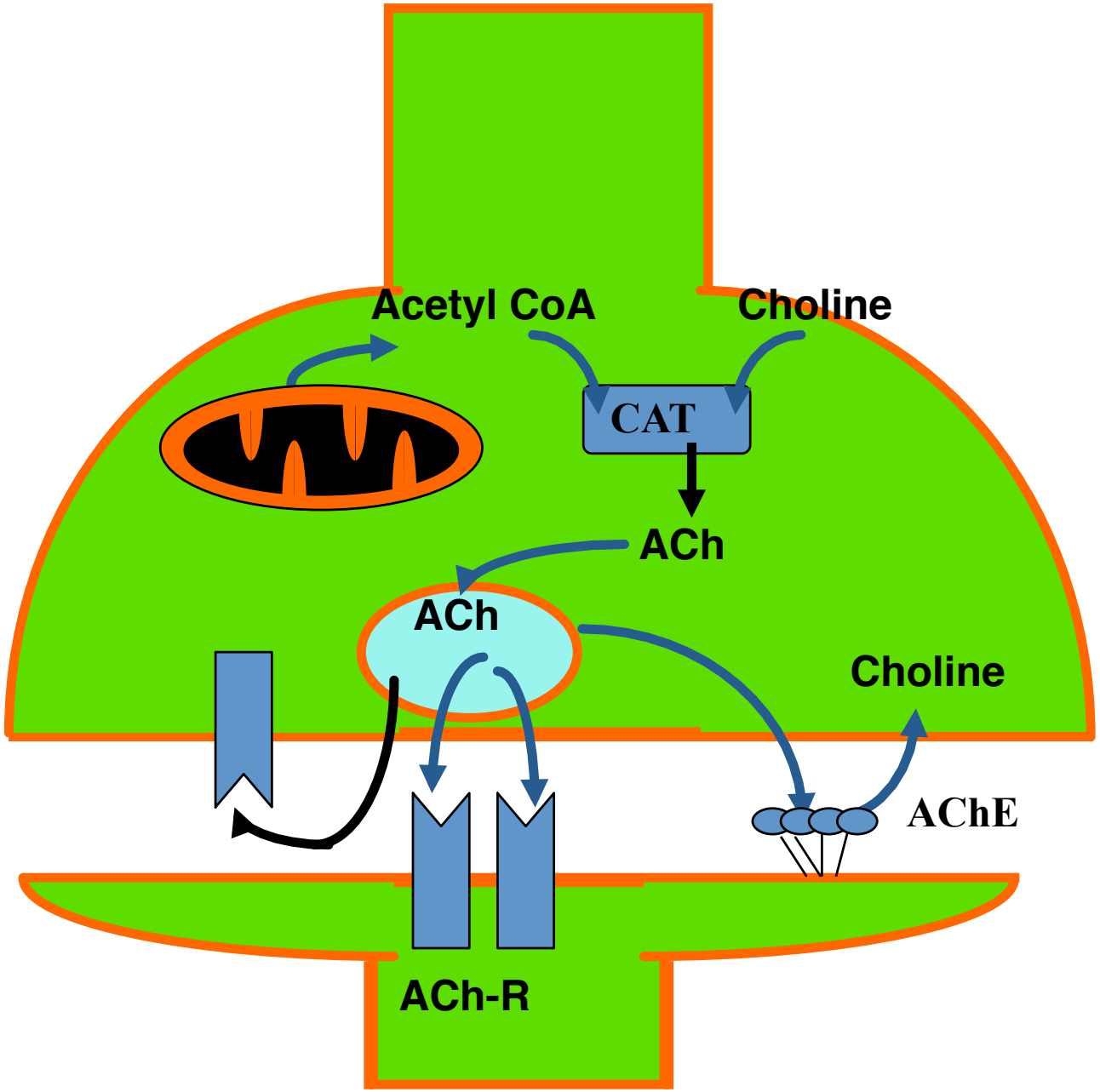


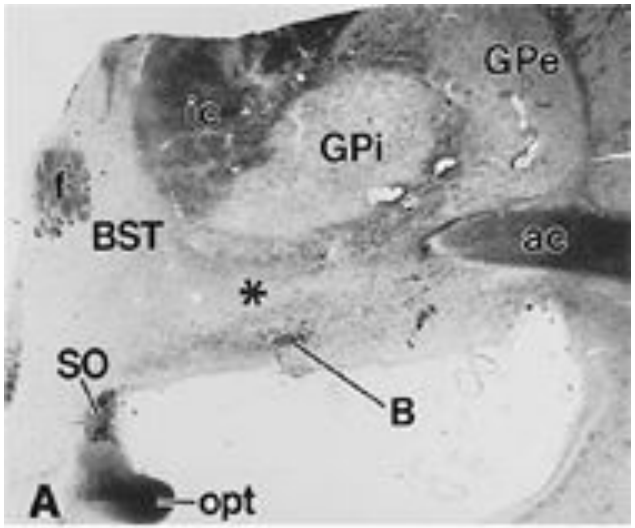


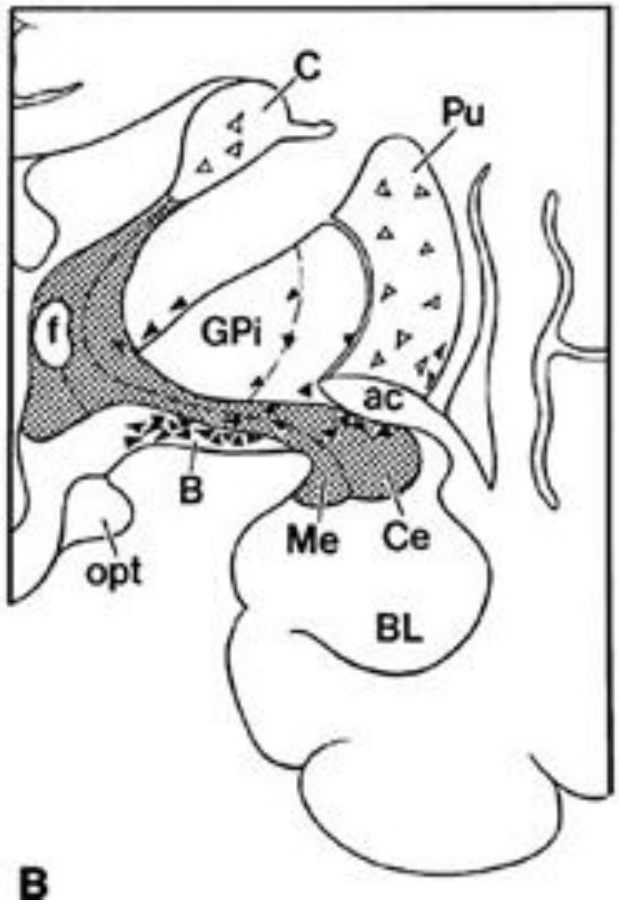
Diskussionspunkte

- Epidemiologie
- Pathologie
- Krankheitsverlauf
- Therapie
  - Symptomatisch
  - Neue Entwicklungen
- Erfolgreiches Altern

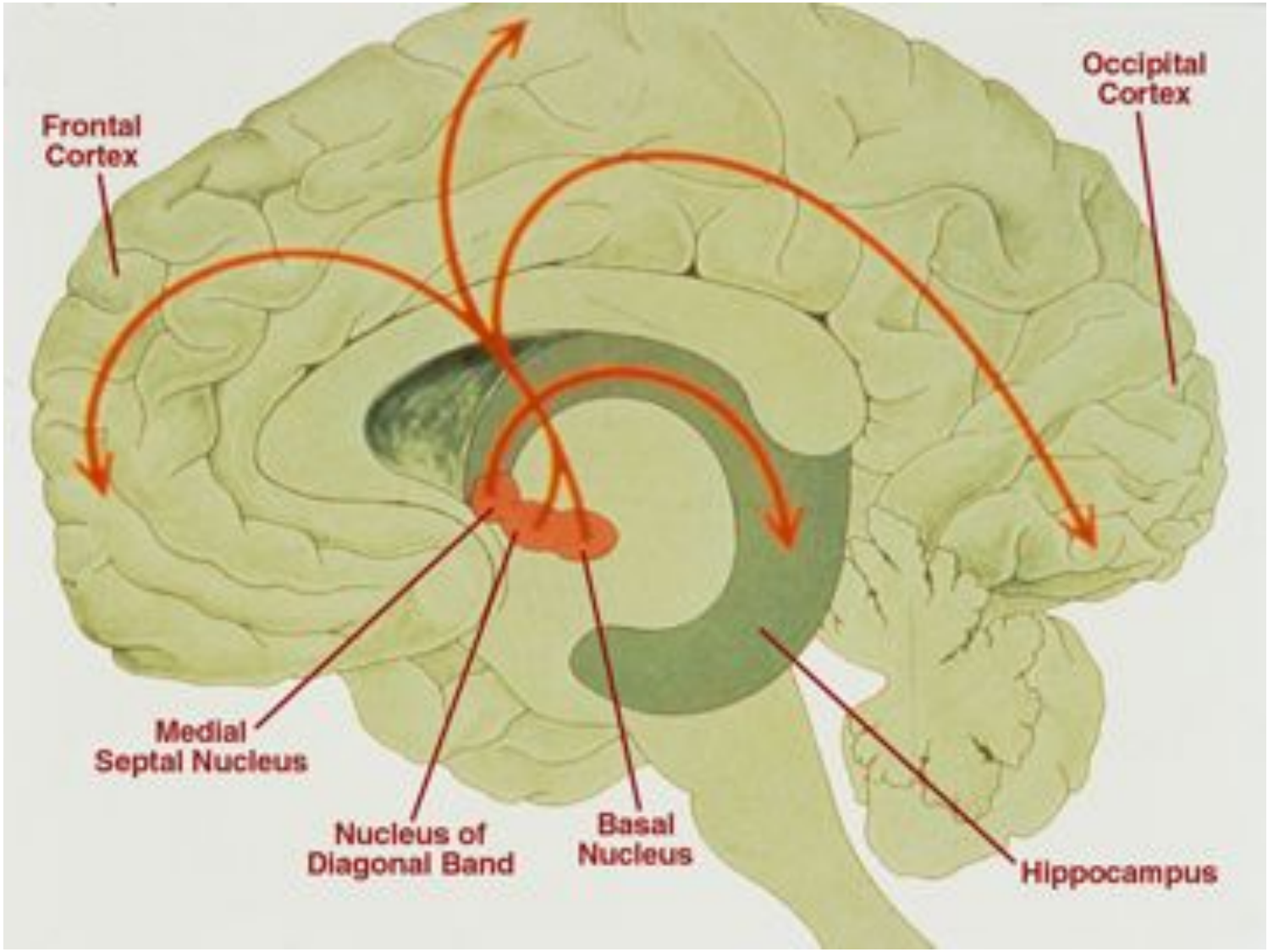
Cholinergic terminal



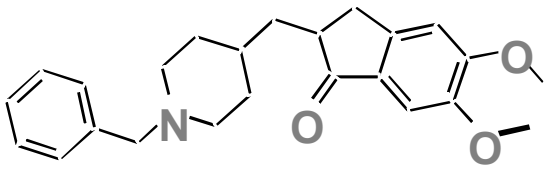




Nucleus Basalis – cholinergic System



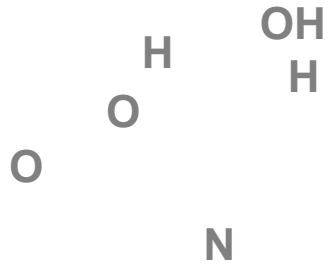
Cholinesterase Hemmer



Donepezil

Mechanism: AChE-I

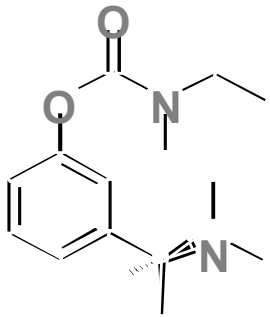
Inhibition: reversible



Galantamin

Mechanism: AChE-I

Inhibition: reversible



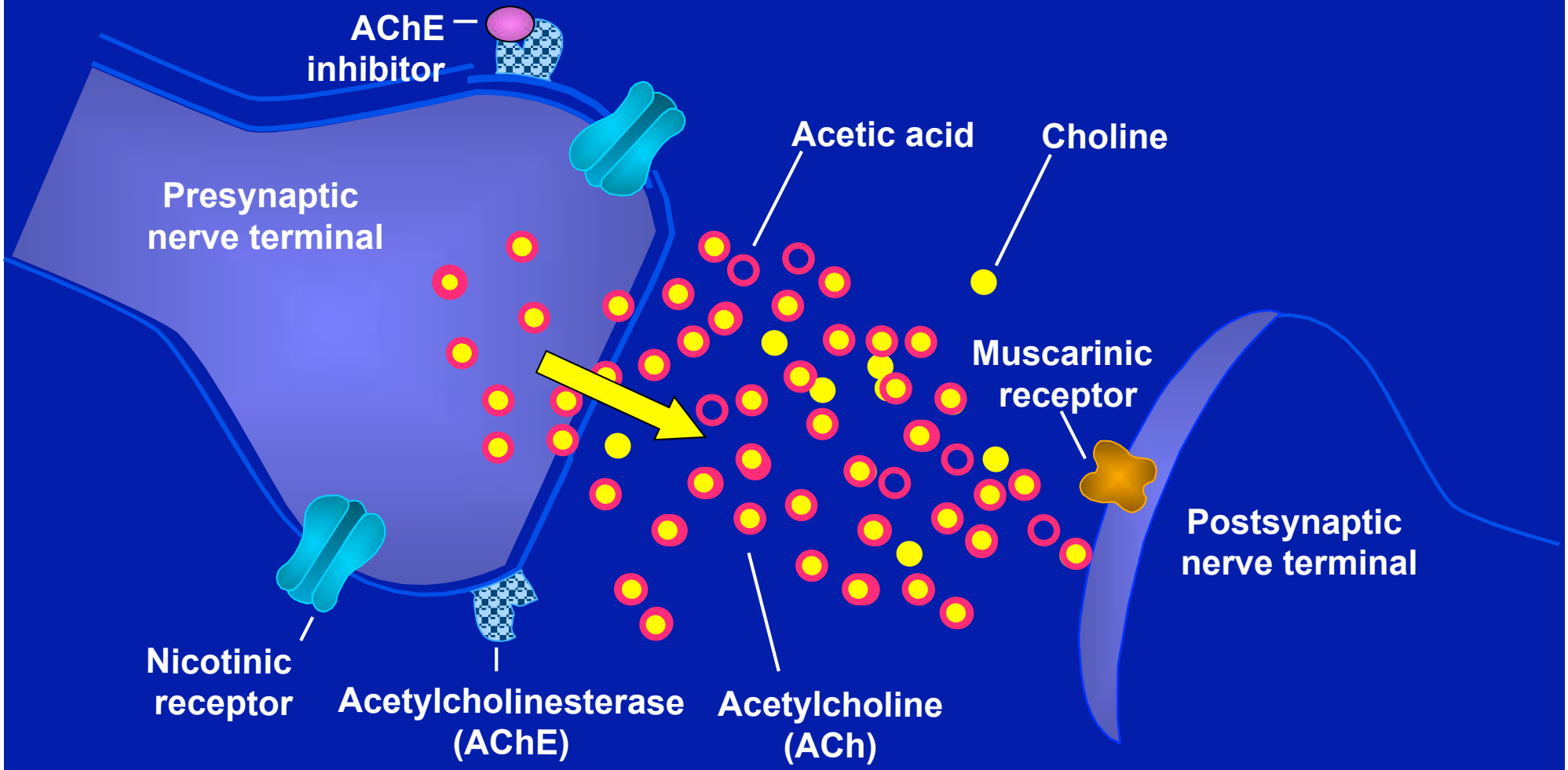
Rivastigmin

Mechanism: AChE/BuChE-I

Inhibition: pseudo-irreversible

Weinstock, 1999

Nervenzelle und Acetylcholin



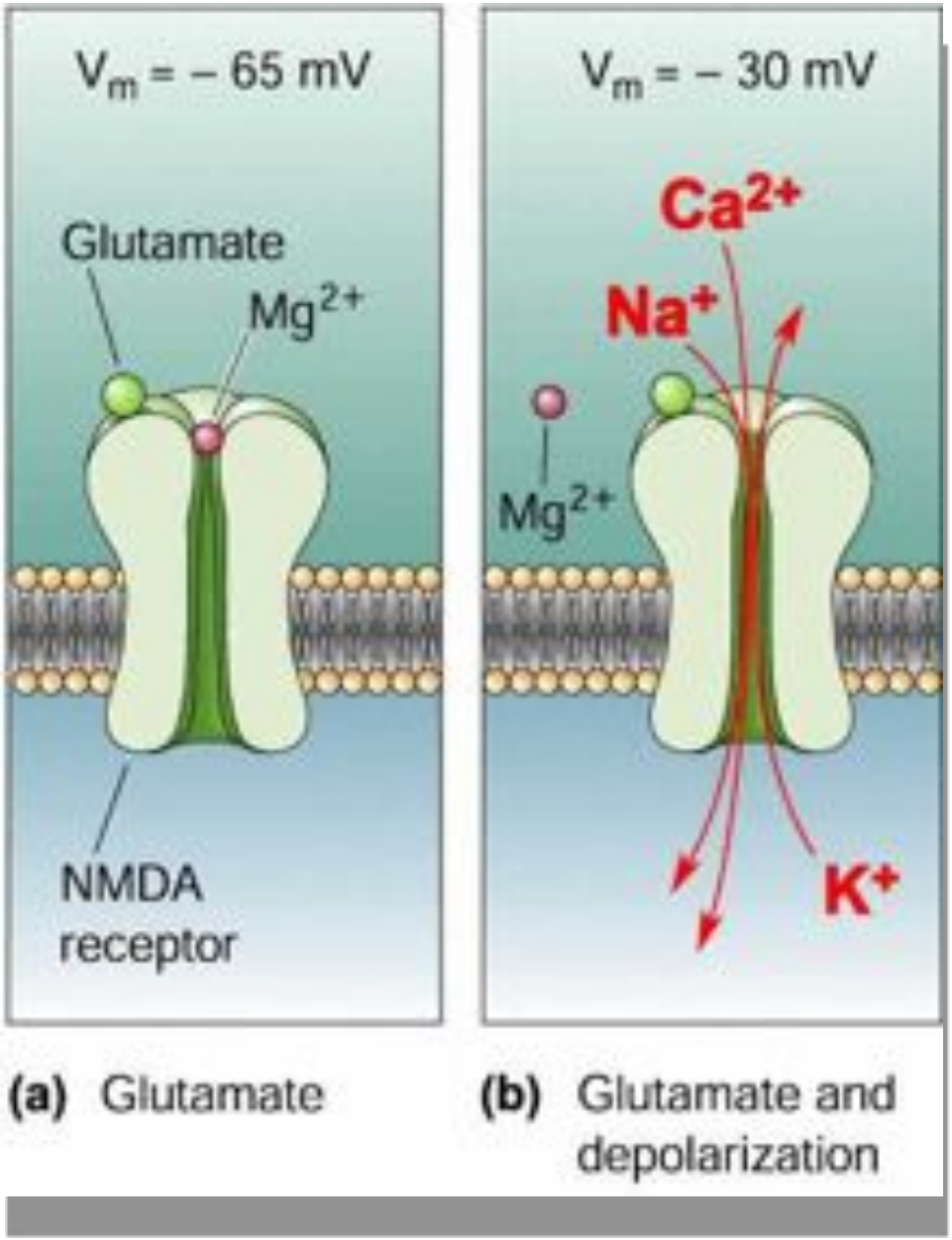
Nordberg A, Svensson A-L. *Drug Safety*. 1998;19:465-480.


Pfizer
Aricept
10mg DONEPEZILHYDROKLORID
28 tabletter
Pfizer
Aricept
5mg
28 tabletter


Reminyl 8 mg
56 comprimidos con cubierta pelicular
JANSSEN-CILAG


Exelon 6 mg
Exelon 4,5 mg
Exelon 3 mg
Exelon 1,5 mg

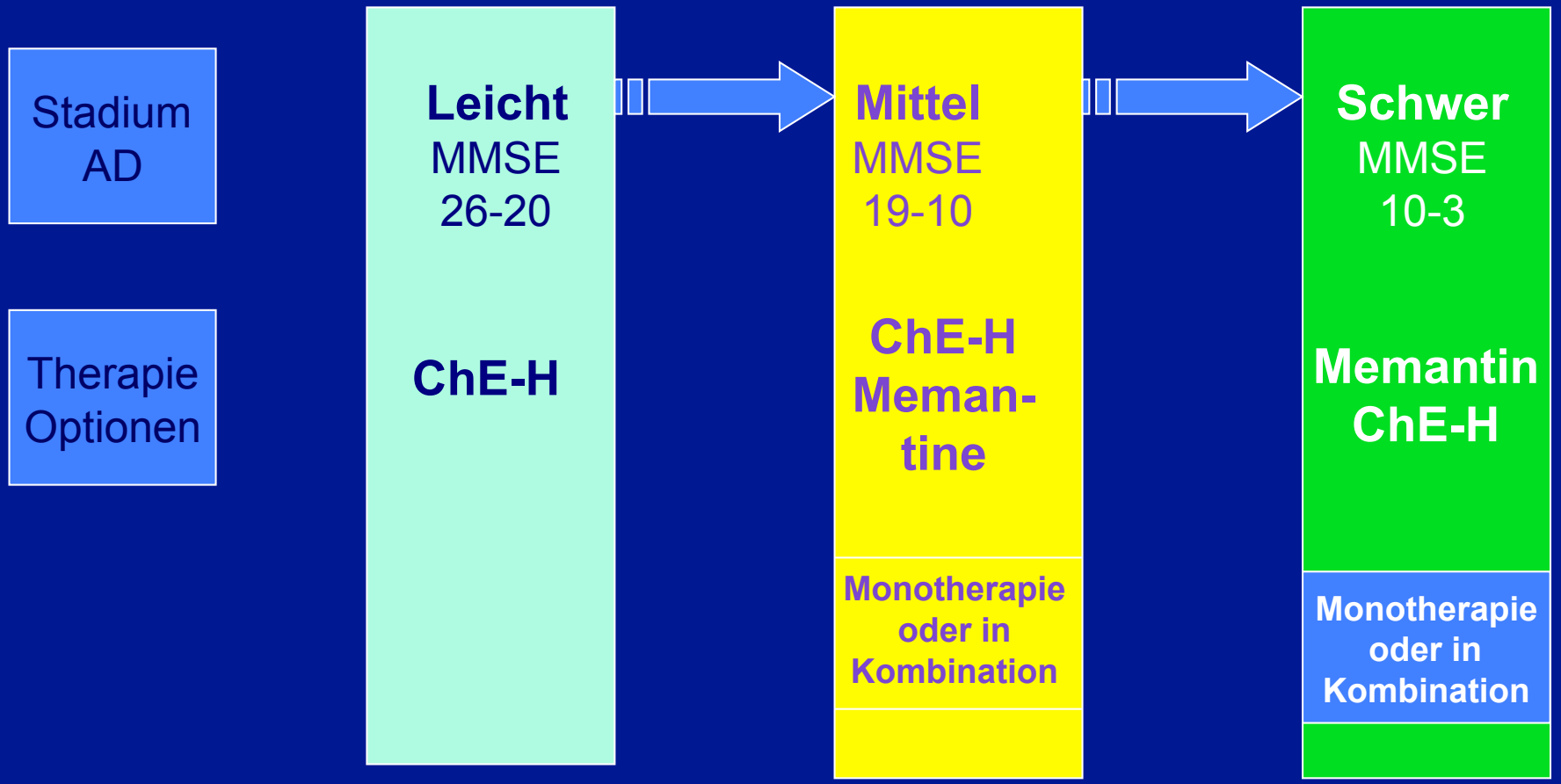
Glutamat - NMDA receptor




Ebixa
10 mg
Ebixa
10 mg

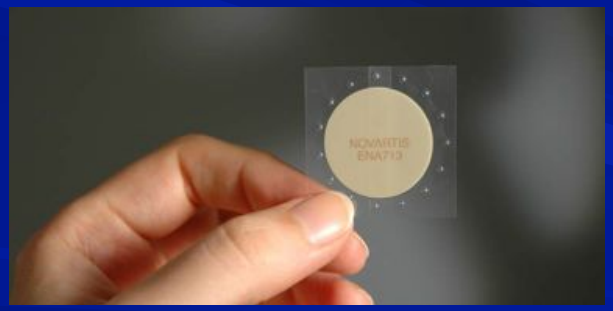

AXURA
100
AXURA
AXURA
AXURA

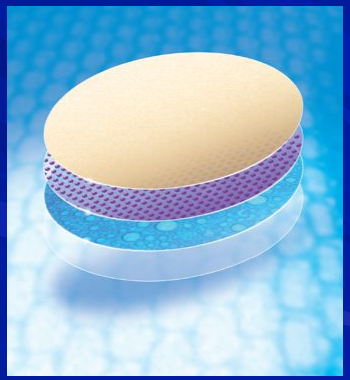
Therapie Algorithmus Alzheimer Demenz



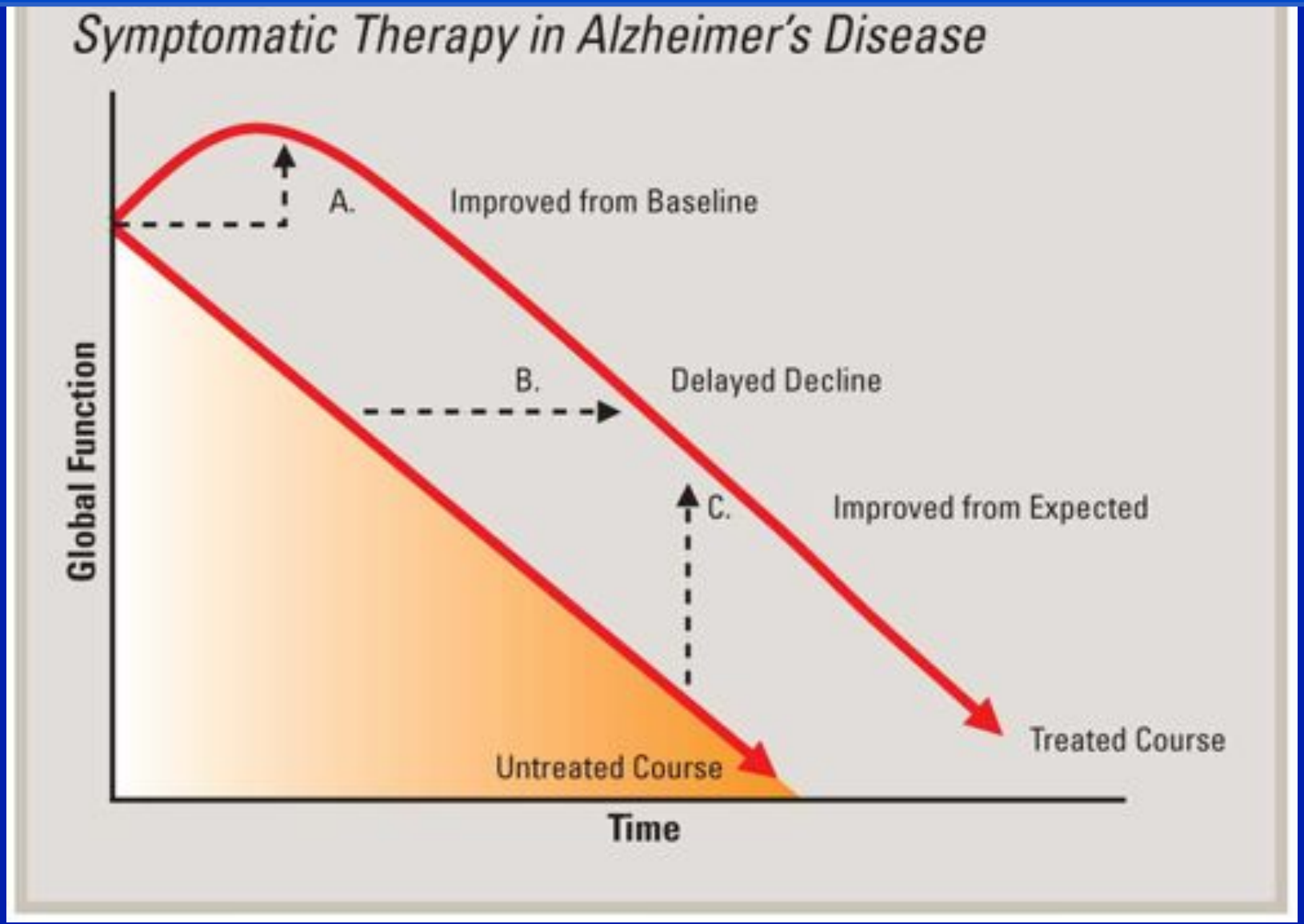
Neue Darreichungsformen als Möglichkeit zur Compliance-Verbesserung

- Anforderungen:
  - 1x täglich
  - Einfache Anwendung
  - Kein zusätzlicher Aufwand
  - Erwiesene Wirksamkeit und Verträglichkeit

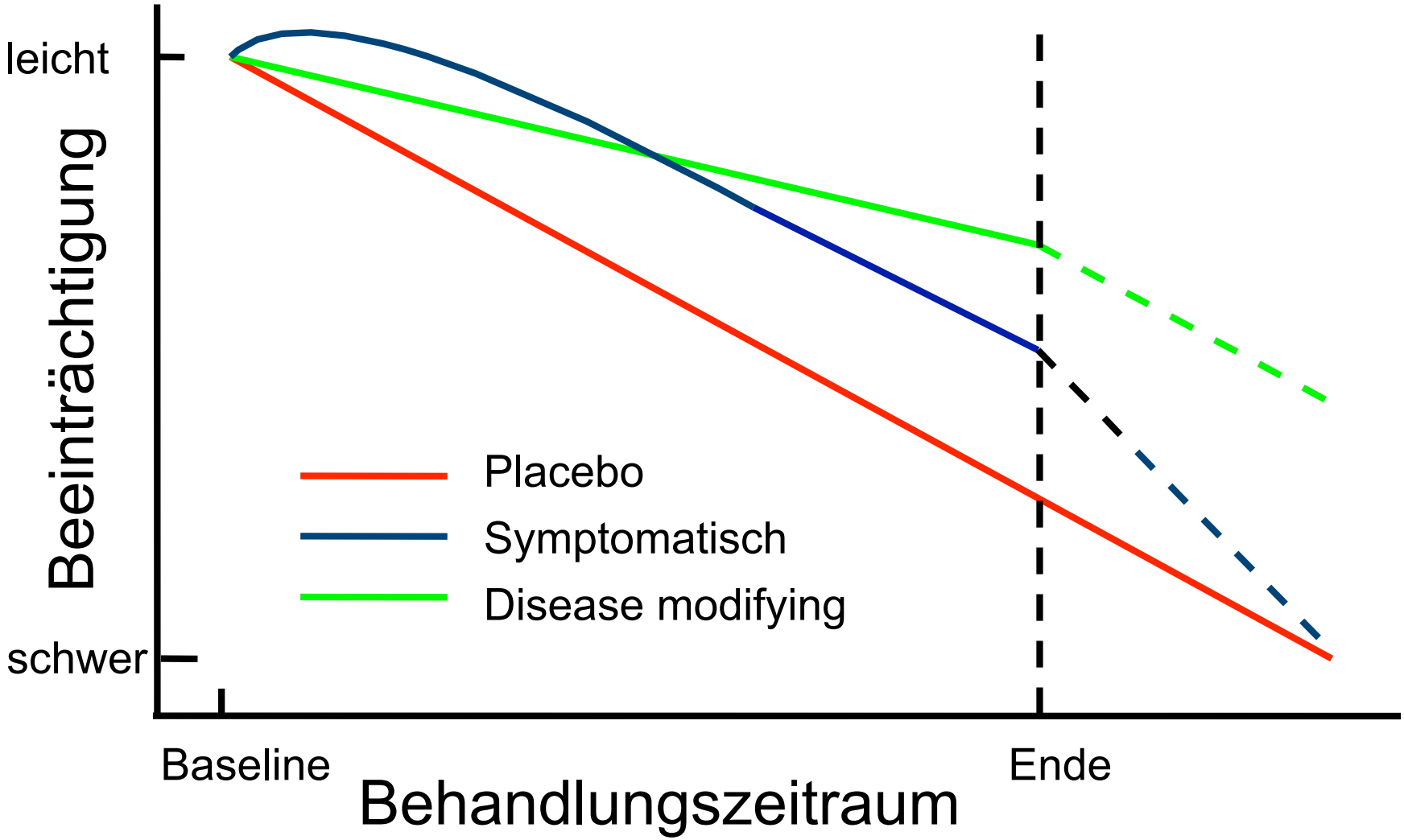


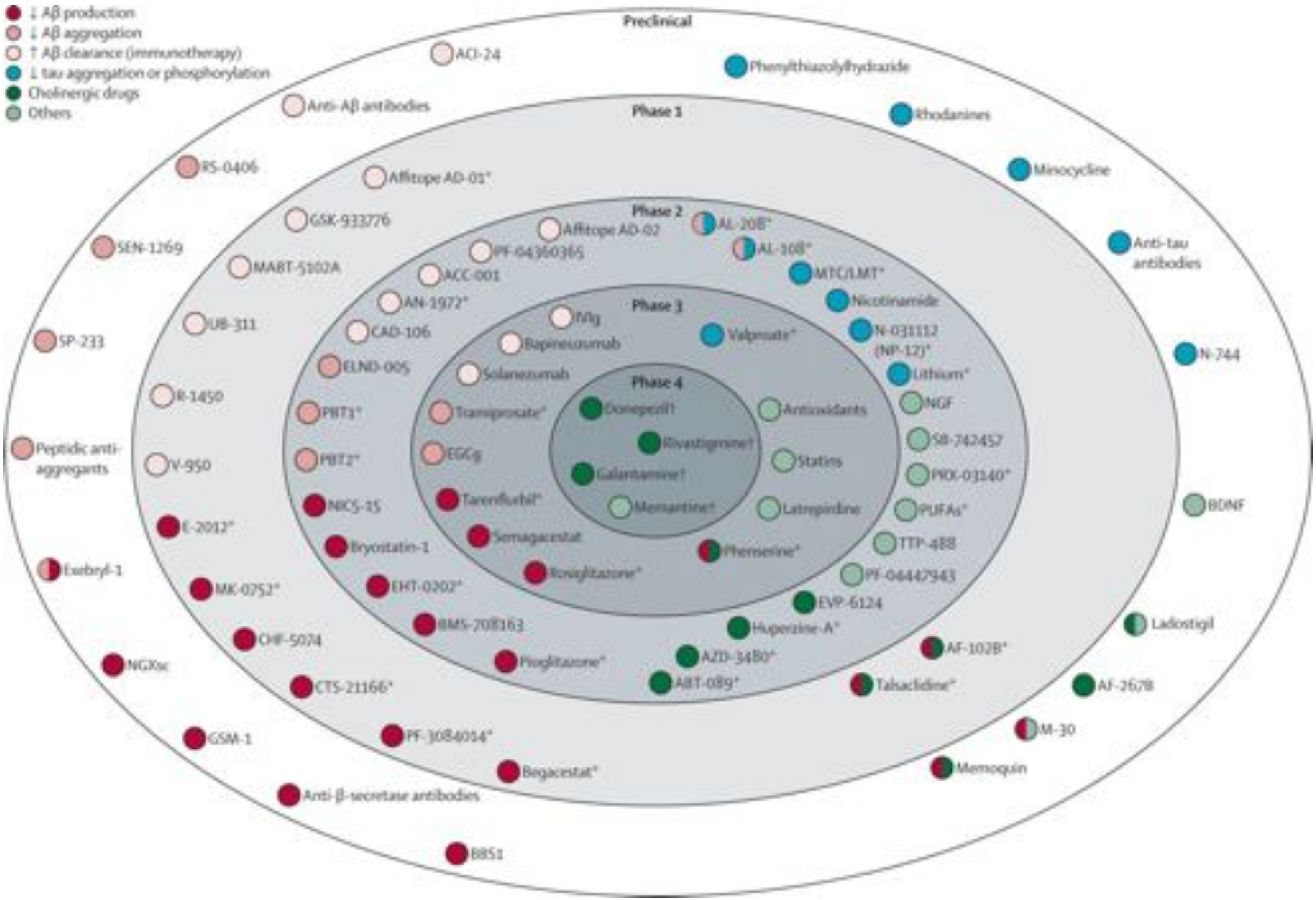


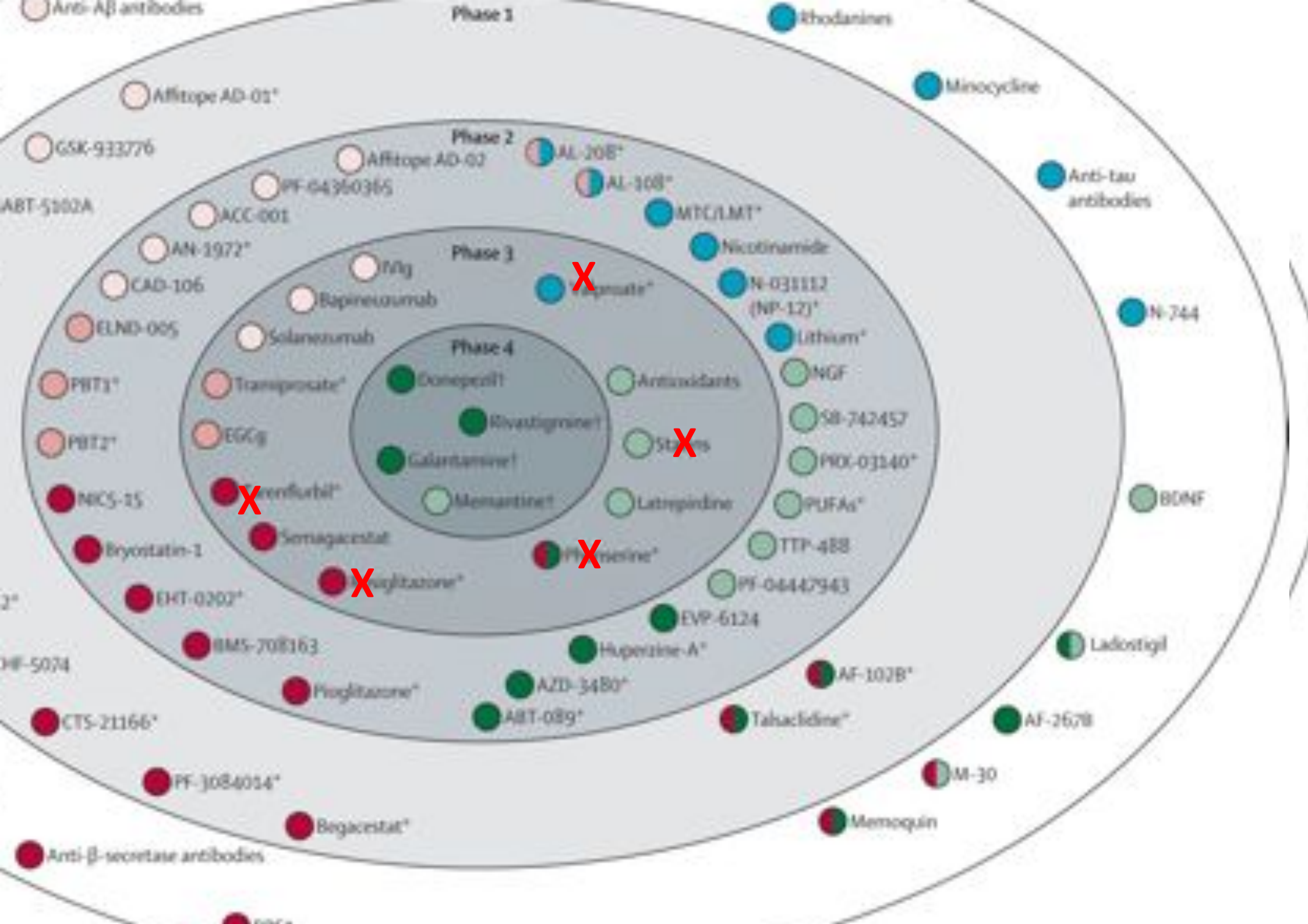
- Neue Formen:
  - Pflaster
  - Schmelztablette


Symptomatic Therapy in Alzheimer's Disease
A.
Improved from Baseline
B.
Delayed Decline
C.
Improved from Expected
Treated Course
Untreated Course
Global Function
Time

Symptomatischer Effekt versus Krankheitsmodifikation




↓ Aβ production
↓ Aβ aggregation
↑ Aβ clearance (immunotherapy)
↓ tau aggregation or phosphorylation
Cholinergic drugs
Others
Preclinical
Phase 1
Phase 2
Phase 3
Phase 4
ACI-24
Phenylthiazolylhydrazide
Anti-Aβ antibodies
Rhodanines
RS-0406
Minocycline
Affitope AD-01*
GSK-933776
Affitope AD-02
AL-208*
SEN-1269
PF-04360365
AL-108*
Anti-tau antibodies
MABT-5102A
ACC-001
MTC/LMT*
AN-1972*
Nicotinamide
IVIg
UB-311
CAD-106
Valproate*
N-031112 (NP-12)*
SP-233
Bapineuzumab
N-744
ELND-005
Lithium*
Solanezumab
R-1450
NGF
PBT1*
Tramiprosate*
Donepezil†
Antioxidants
SB-742457
Peptidic anti-aggregants
PBT2*
EGCg
Rivastigmine†
Statins
PNX-03140*
V-950
Galantamine†
Tarenflurbil*
Memantine†
Latrepirdine
PUFAs*
BDNF
NIC5-15
E-2012*
Semagacestat
Pheserine*
TTP-488
Bryostatin-1
Ibuprofen*
PF-04447943
Esebryl-1
Rosiglitazone*
MK-0752*
EHT-0202*
EVP-6124
BMS-708163
Huperzine-A*
Ladostigil
CHF-5074
AF-102B*
NGXsc
Pioglitazone*
AZD-3480*
CTS-21166*
ABT-089*
Talsaclidine*
AF-267B
GSM-1
PF-3084014*
M-30
Begacestat*
Memoquin
Anti-β-secretase antibodies
BB51


Phase 1
Phase 2
Phase 3
Phase 4
Anti-Aβ antibodies
Rhodanines
Affitope AD-01*
Minocycline
GSK-933776
Affitope AD-02
AL-208*
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Anti-tau antibodies
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CTS-21166*
ABT-089*
Tahaclidine*
AF-267B
PF-3084014*
M-30
Begacestat*
Memoquin
Anti-β-secretase antibodies

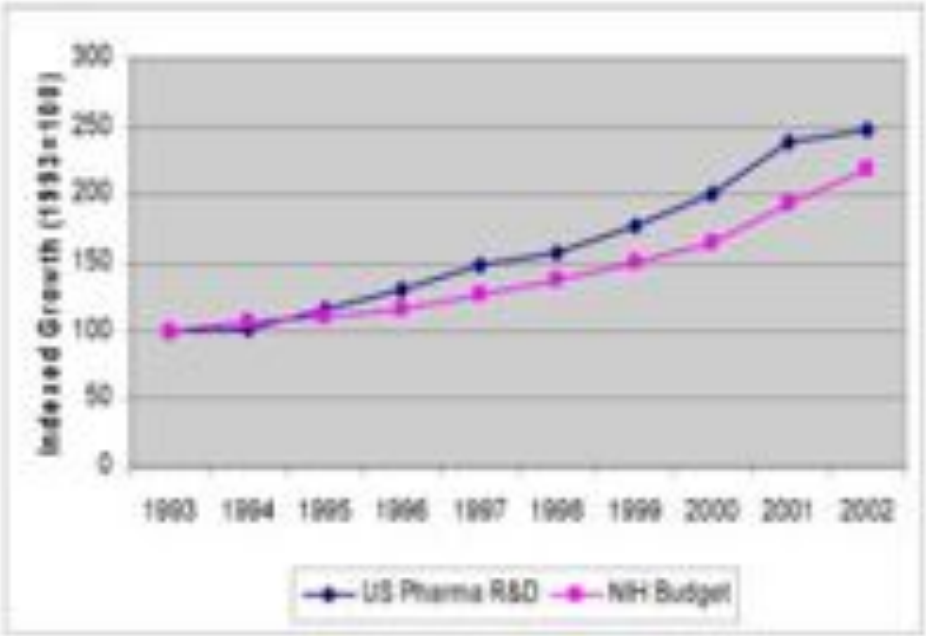
Sabbagh, 2009,
The American Journal of Geriatric Pharmacotherapy

Table I. Phase III randomized, placebo-controlled, double-blind, parallel-group clinical trials.

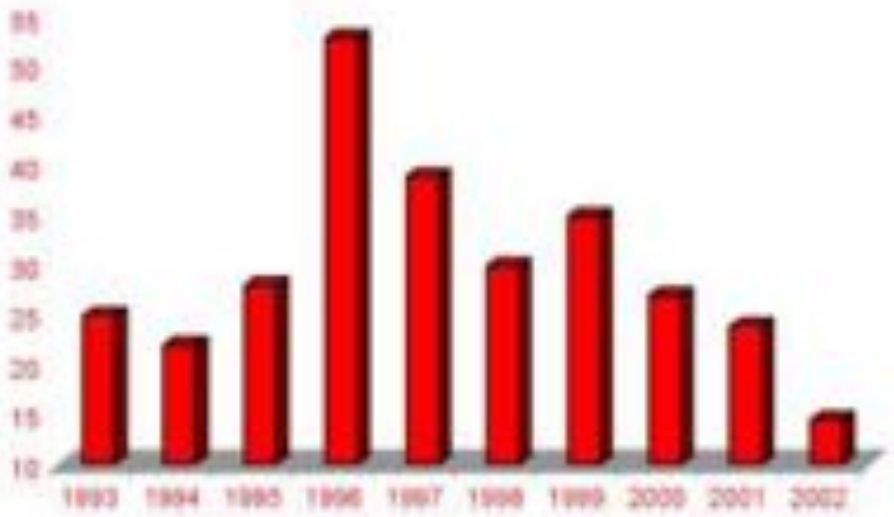
Agent	No. of Patients*	Mechanism of Action	Status†
Atorvastatin[29]	600	HMG CoA–reductase inhibitor	Unsuccessful
Bapineuzumab (AAB-001)[54–57]	3850	Passive Aβ immunization	Ongoing
Dimebon[61–64]	2825	Stabilizes mitochondrial function	Ongoing
Ginkgo biloba[3]	3069‡	Unknown	Unsuccessful
LY450139[69,70]	2600	γ-Secretase inhibition	Ongoing
LY2062430 (solanezumab)[128,129]	2000	Passive Aβ immunization	Ongoing
NSAIDs[14–19]	>2500	Anti-inflammatory	Unsuccessful
Phenserine[71]	384	ChEI, inhibits Aβ formation	Unsuccessful
Rosiglitazone[76–78]	3713	Peroxisome proliferator–activated receptor γ agonist	Ongoing
Simvastatin[30]	400	HMG CoA–reductase inhibitor	Unsuccessful
Tarenflurbil[36]	1600	SALA	Unsuccessful
Tramiprosate[39]	1052	Antifibrillar	Unsuccessful
Xaliproden[46,47]	2761	Serotonin antagonist with nerve growth factor effects	Unsuccessful

HMG CoA = hydroxymethylglutaryl coenzyme A; Aβ = amyloid-β; ChEI = cholinesterase inhibitor; SALA = selective Aβ42-lowering agent.
*All Phase III trials for each compound combined.
†*Ongoing* indicates that the trial was in progress as of June 2009. *Unsuccessful* indicates that the trial was completed, the primary efficacy end points were not met, and further development of the compound is not anticipated, at least for the treatment of Alzheimer's disease.
‡Patients had amnestic mild cognitive impairment or normal cognition.

Medical investment

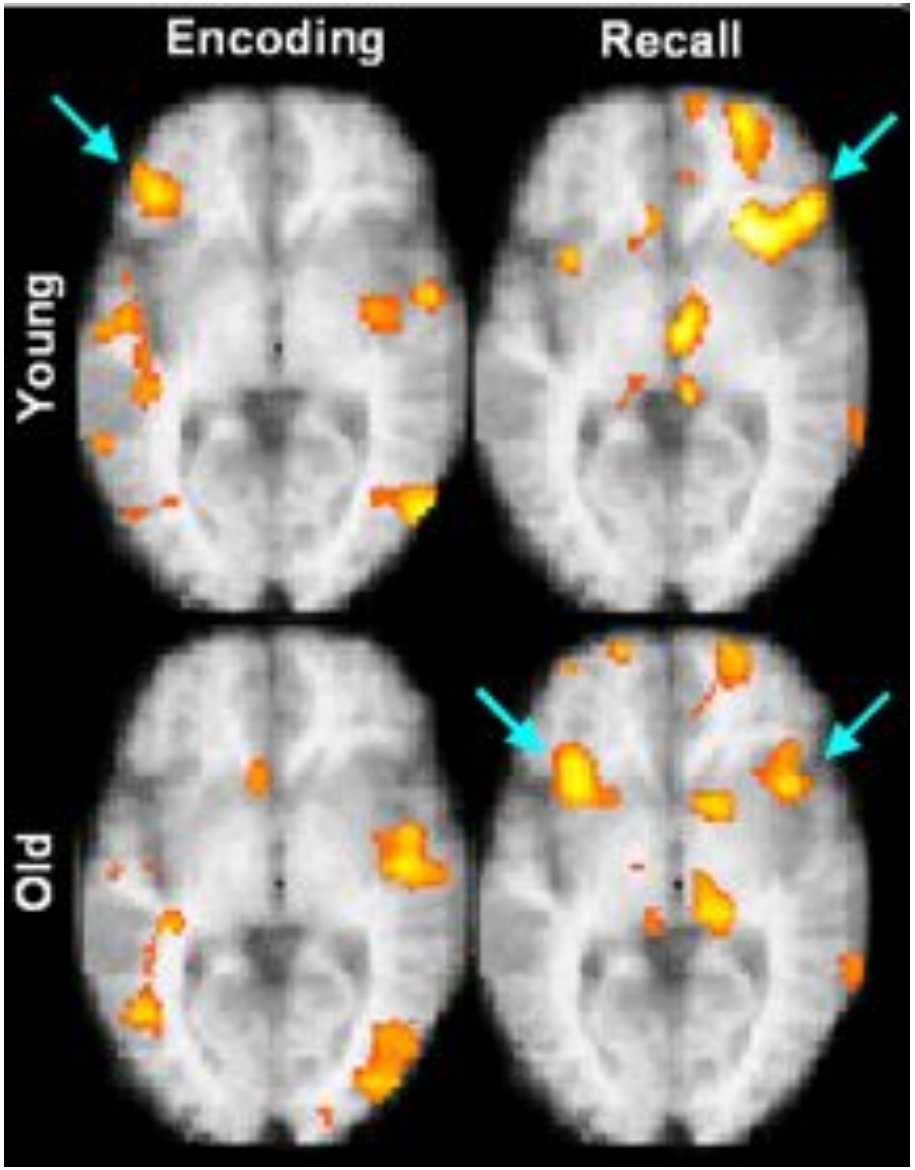


New medical treatments

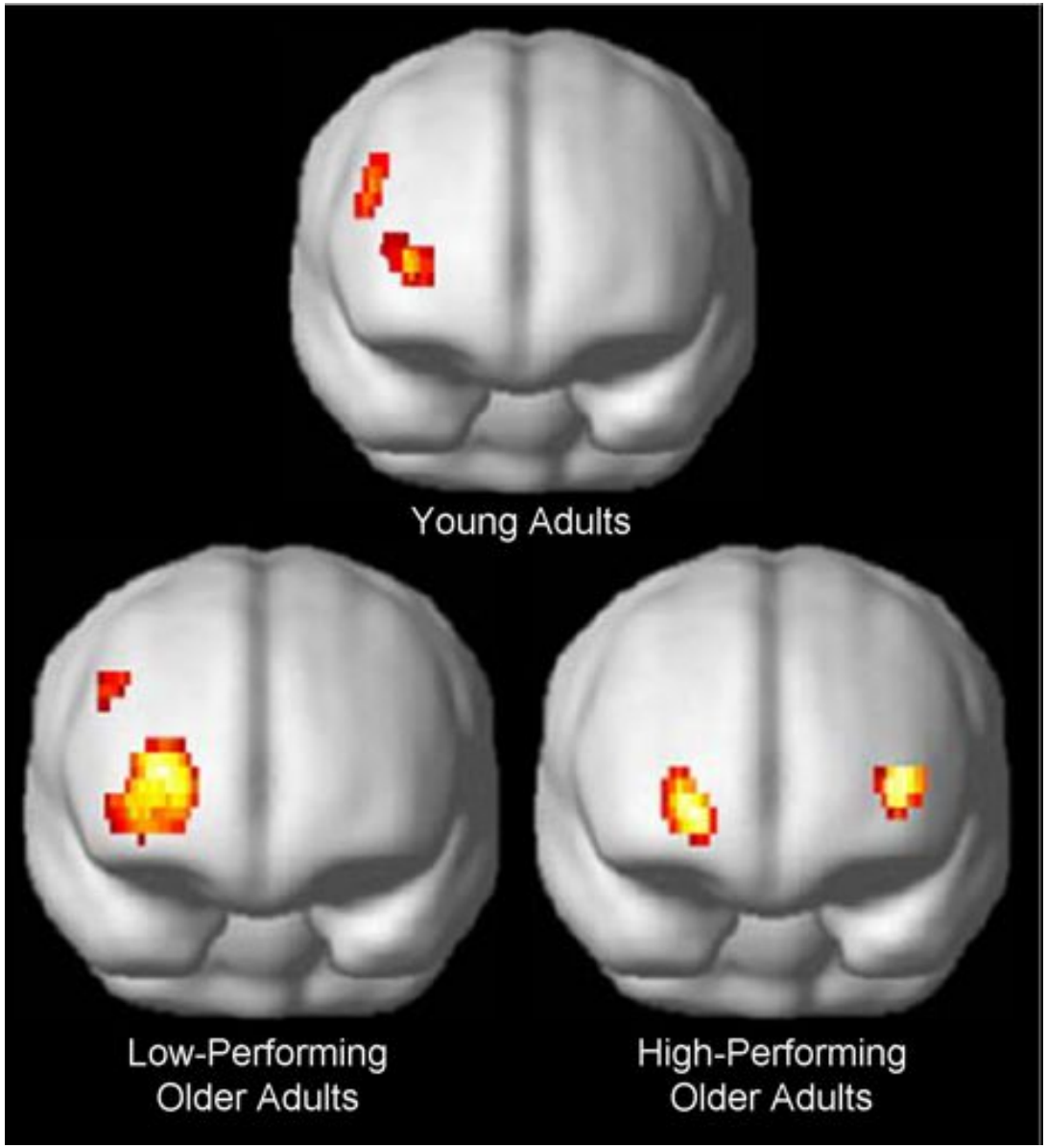


Diskussionspunkte

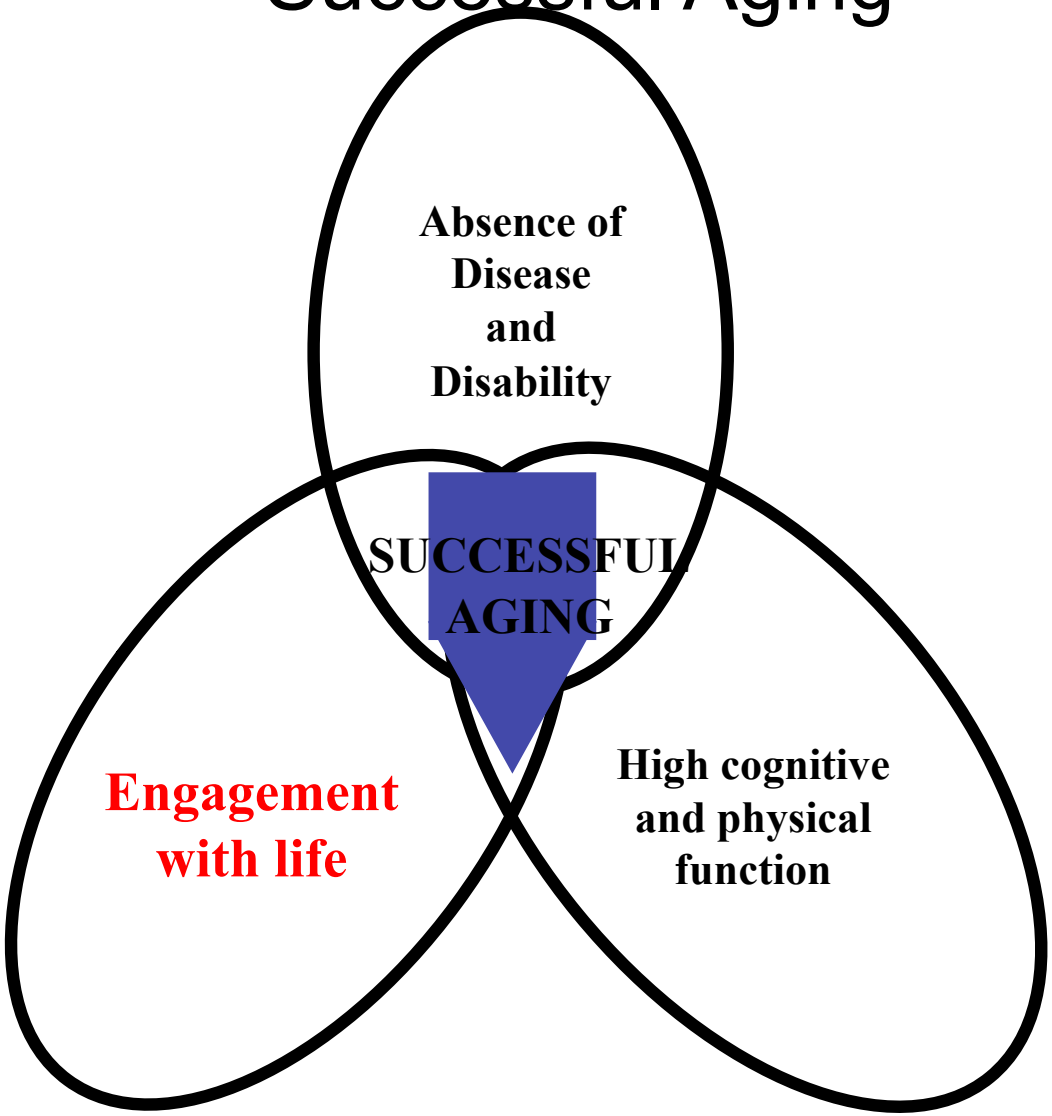
- Epidemiologie
- Pathologie
- Krankheitsverlauf
- Therapie
- Erfolgreiches Altern



Cabeza et al., 2002


Young Adults
Low-Performing
Older Adults
High-Performing
Older Adults

Example of Quantitative Research: Successful Aging



1987

1998

(Rowe and Kahn, 1998)

Erfolgreiches Altern

- Optimismus
- Positive Einstellung gegenüber dem Altern
- Resilienz
- Gefühl der persönlichen Befähigung
- Geringes Stressniveau (< life events)
- Aktiver Modus auf jeder Ebene

Raffaello Sanzio, 1509
Plato
Aristoteles

Thomas W. Meeks; Dilip V. Jeste.
Neurobiology of Wisdom: A Literature Overview.
Archives of General Psychiatry, 2009; 66 (4): 355

Wisdom is viewed as a complex human trait with 6 subcomponents:

1) prosocial behavior
2) social decision making/pragmatic knowledge of life
3) emotional regulation
4) self-reflection
5) tolerance of diverse values,
6) and effective dealing with uncertainty.

What is the impact of lifestyle factors on the risk of dementia?

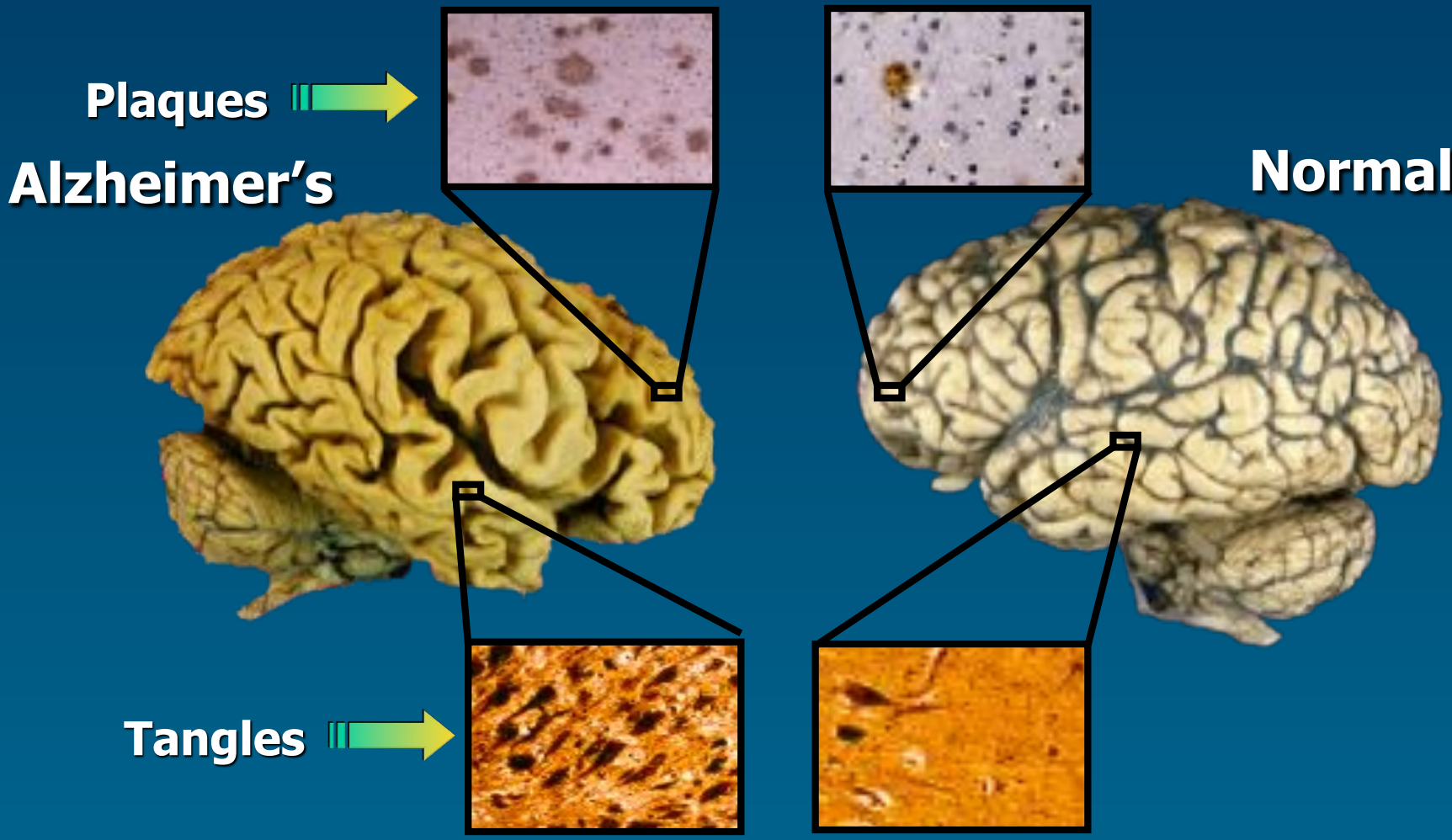
Neuropathology Group of the Medical Research Council/ Cognitive Function and Ageing Study (MRC CFAS)

„Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales“

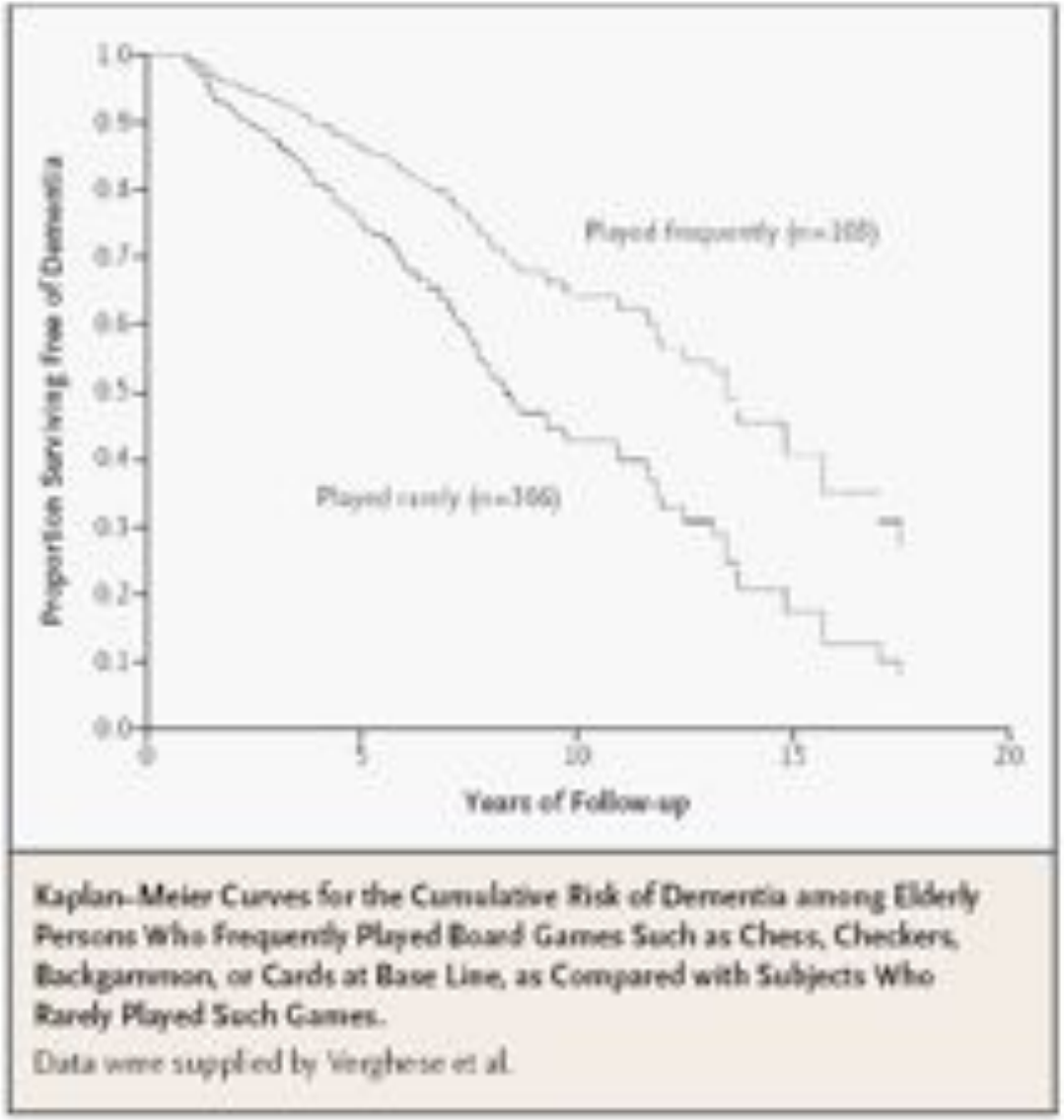
Lancet 2001;357: 169-75

histopathologisch	n = 100 dement	n = 109 nicht-dement
unauffällig	2%	13%
Amyloidplaques	81%	69%
Neurofibrillen	98%	82%
vaskuläre Veränd.	81%	76%
Lewy-Körperchen	12%	9%

Amyloid Plaques and Neurofibrillary Tangles in Alzheimer's Disease and Normal Aging



Courtesy of Harry Vinters, MD.



Kaplan–Meier Curves for the Cumulative Risk of Dementia among Elderly Persons Who Frequently Played Board Games Such as Chess, Checkers, Backgammon, or Cards at Base Line, as Compared with Subjects Who Rarely Played Such Games.

Data were supplied by Verghese et al.

Effortful mental activity and risk of dementia

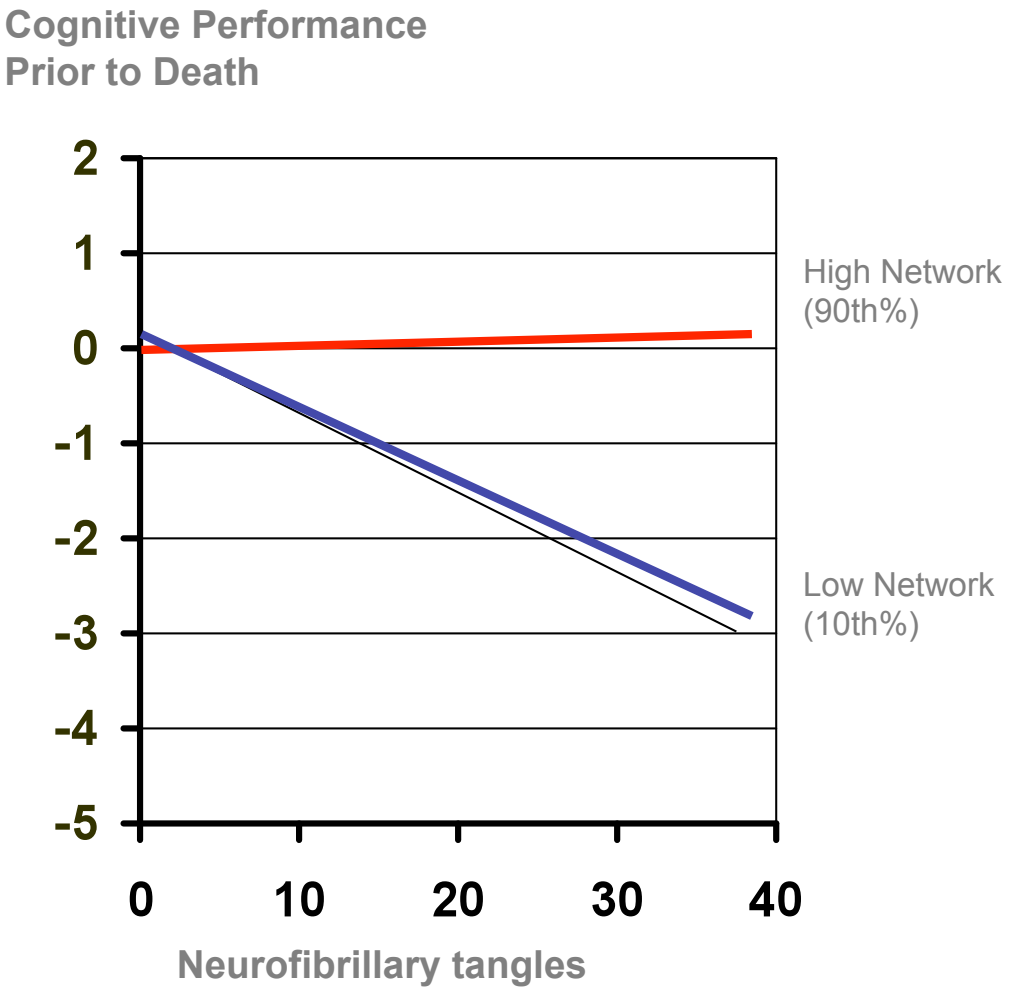
N = 459; mean age 79 years; median follow up 5.1 years;

124 developed dementia; 61 AD

Coyle (2003) *N Engl J Med* 348:2489-2490

Verghese et al. (2003) *N Engl J Med* 348:2508-2516

Social Networks & Alzheimer's Disease Pathology



N = 89

Mean age at enrolment 84.3 years

Mean age at proximate assessment prior to death 87.2 years

Female 55.1%

Education 14.4 years

Social networks 6.9

90^{th} % = 13 people; 10^{th} % = 2 people

Bennett et al. (2006) *Lancet Neurology* 5: 406-412

Purpose in Life

Characteristic[a]	Did Not Develop MCI	Developed MCI	*P* Value
Age, mean (SD), y	78.1 (7.3)	81.6 (6.5)	<.001
Female sex, %	76.8	75.4	.69
Race, white, non-Hispanic, %	89.4	92.6	.14
Education, mean (SD), y	14.5 (3.0)	14.7 (3.2)	.38
Purpose in life score, mean (SD)	3.7 (0.5)	3.6 (0.4)	.002
Depressive symptoms score, mean (SD)	1.1 (1.7)	1.4 (1.9)	.04
Neuroticism score, mean (SD)	14.3 (7.2)	15.1 (6.4)	.12
Social network size, mean (SD)	7.0 (6.3)	6.6 (6.1)	.25
No. of medical conditions, mean (SD)	1.4 (1.1)	1.2 (1.0)	.10
MMSE score, mean (SD)	28.7 (1.4)	28.2 (1.8)	<.001

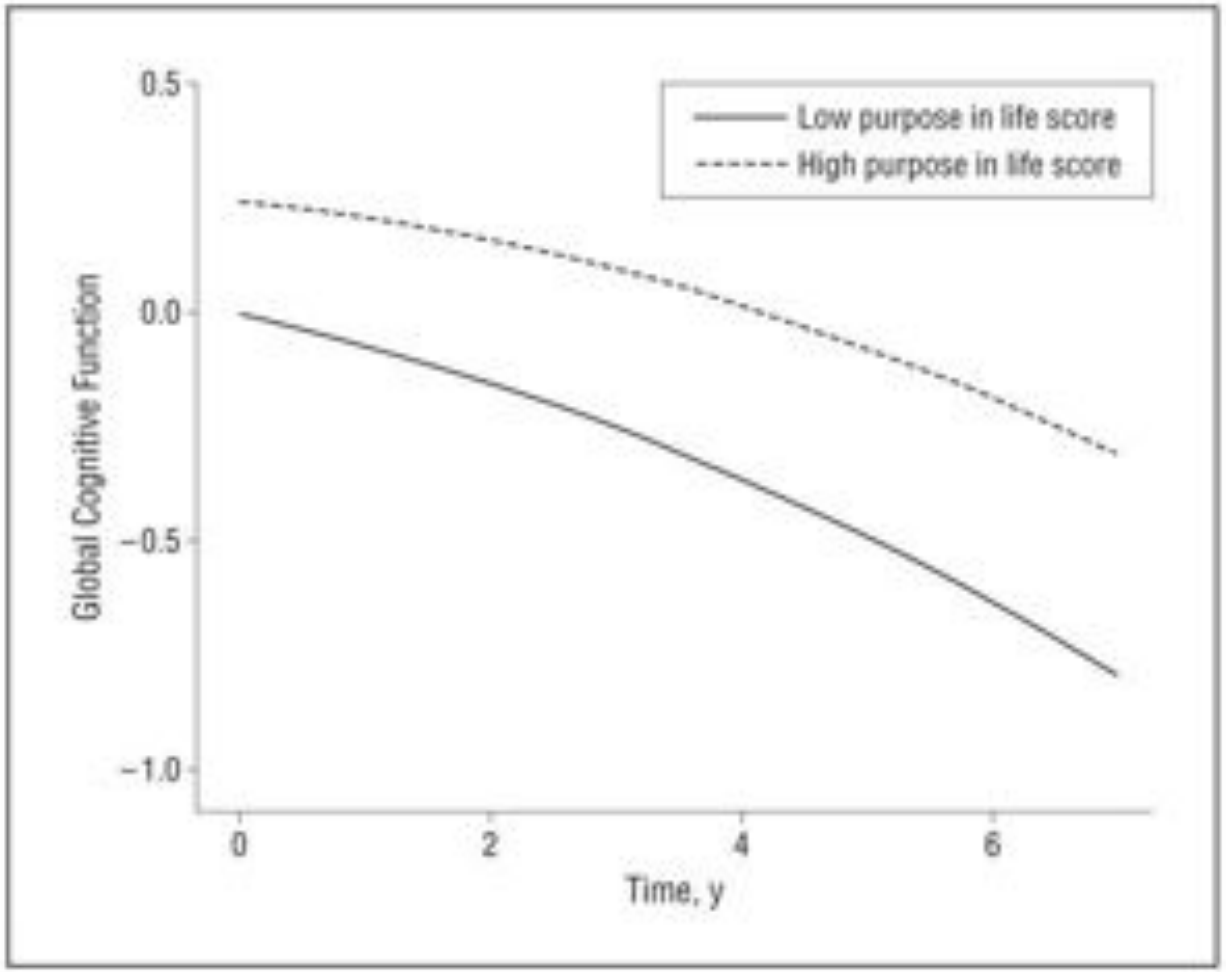
Baseline Characteristics of Participants Who Developed MCI vs Those Who Did Not
Abbreviations: MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
[a]Statistical significance is based on *t* tests, Wilcoxon rank sum tests or χ^2 tests, as appropriate.
Arch Gen Psychiatry. 2010 March; 67(3): 304–310.

Purpose in Life

	Statement
1	I feel good when I think of what I have done in the past and what I hope to do in the future.
2	I live life 1 day at a time and do not really think about the future.
3	I tend to focus on the present because the future nearly always brings me problems.
4	I have a sense of direction and purpose in life.
5	My daily activities often seem trivial and unimportant to me.
6	I used to set goals for myself, but that now seems like a waste of time.
7	I enjoy making plans for the future and working them to a reality.
8	I am an active person in carrying out the plans I set for myself.
9	Some people wander aimlessly through life, but I am not one of them.
10	I sometimes feel as if I have done all there is to do in life.

10-Item Measure of Purpose in Life
Arch Gen Psychiatry. 2010 March; 67(3): 304–310.

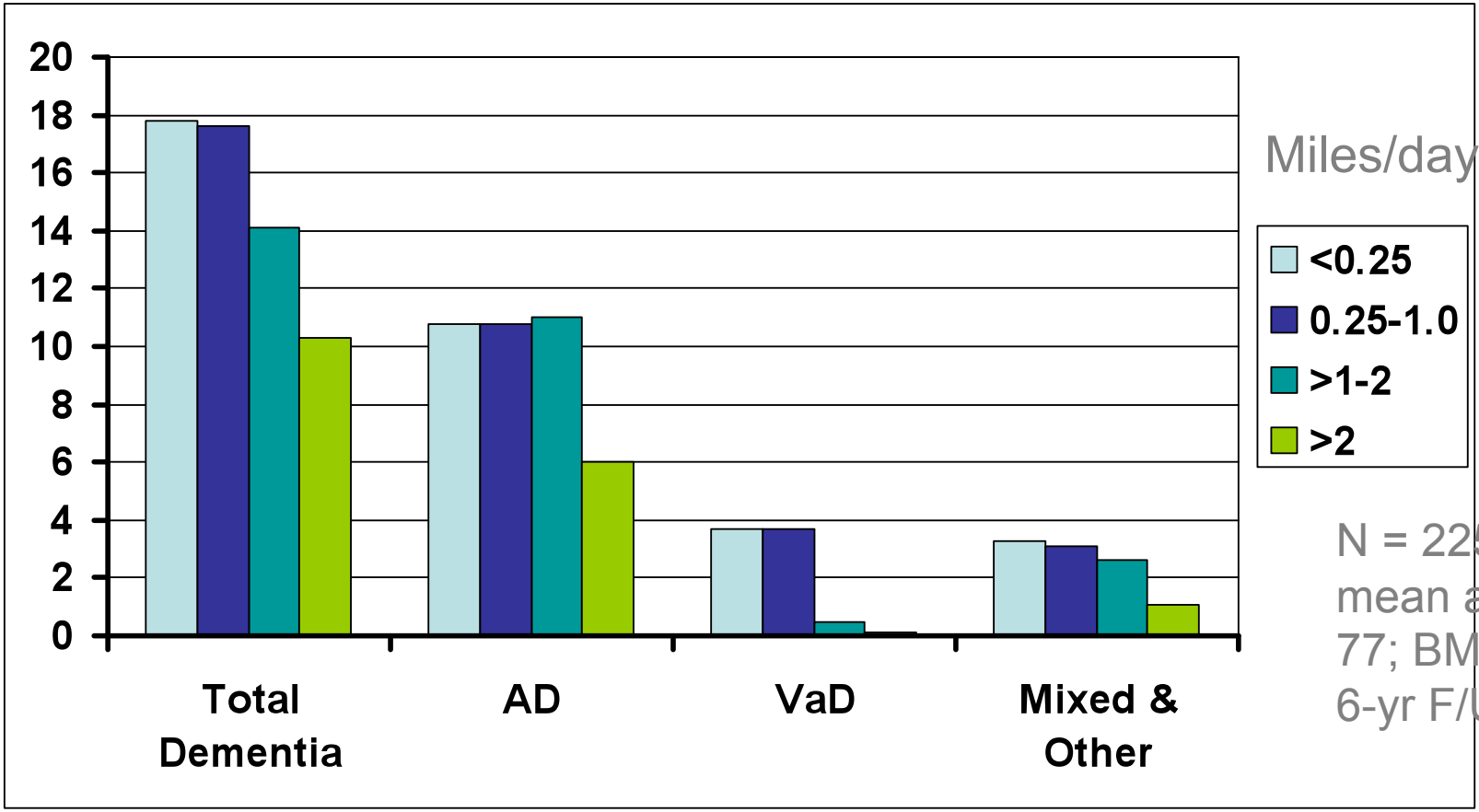
Decline in global cognition for participants with high vs low scores on the purpose in life measure.




Kognitive beeinträchtige Menschen: acht Kilometer pro Woche spazieren gehen, um die Abnahme ihrer Gehirnleistung möglichst lange hinauszuzögern. Gesunde Menschen benötigen 9,7 Kilometer

Walking & Dementia in Older Men

Cases per 1000 person-years



Abbott et al (2004) *JAMA* 292:1447-1453 [Honolulu-Asia Aging Study]

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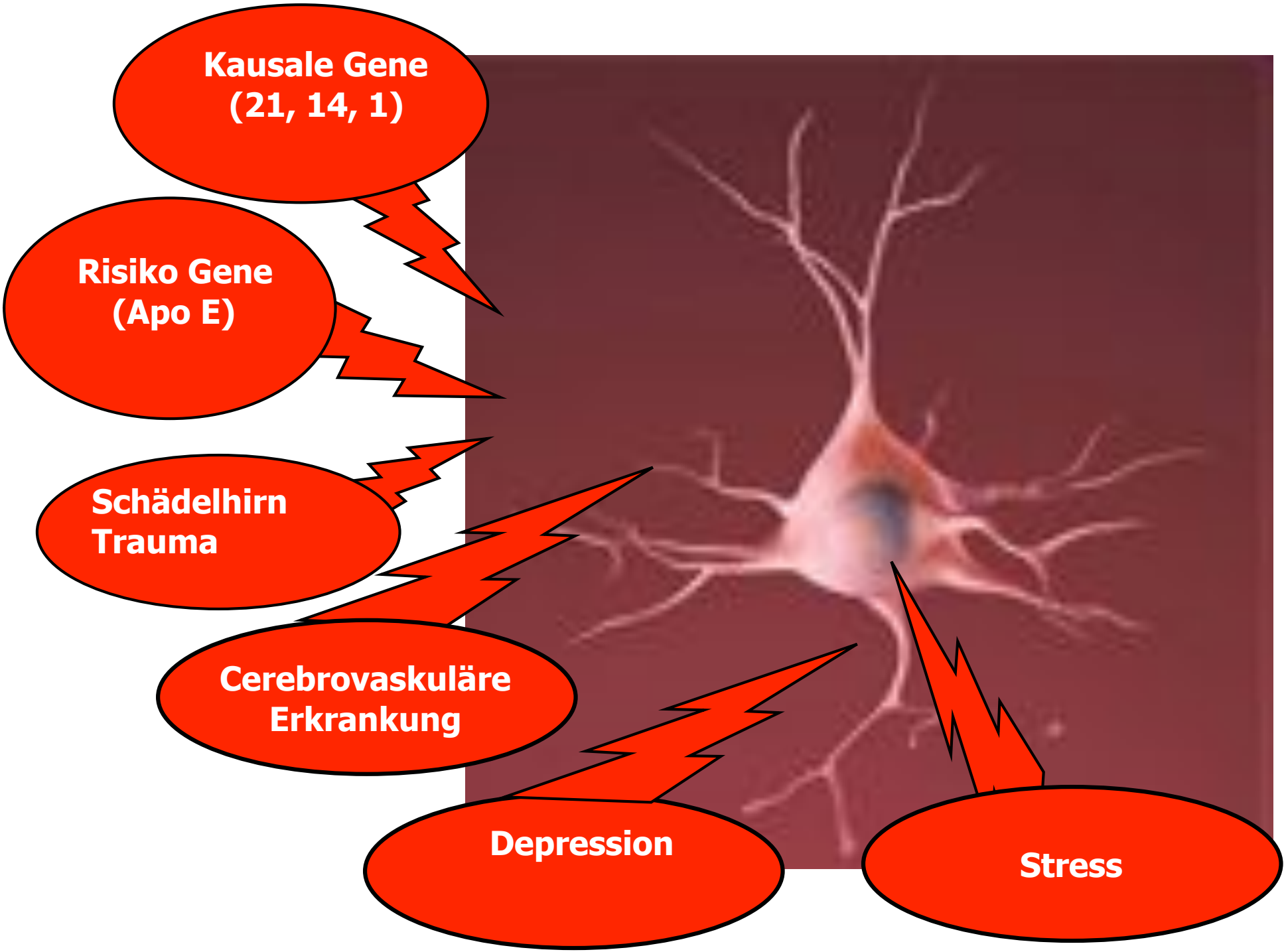
Kausale Gene
(21, 14, 1)
Risiko Gene
(Apo E)
Schädelhirn
Trauma
Cerebrovaskuläre
Erkrankung
Depression
Stress

Herzlichen Dank