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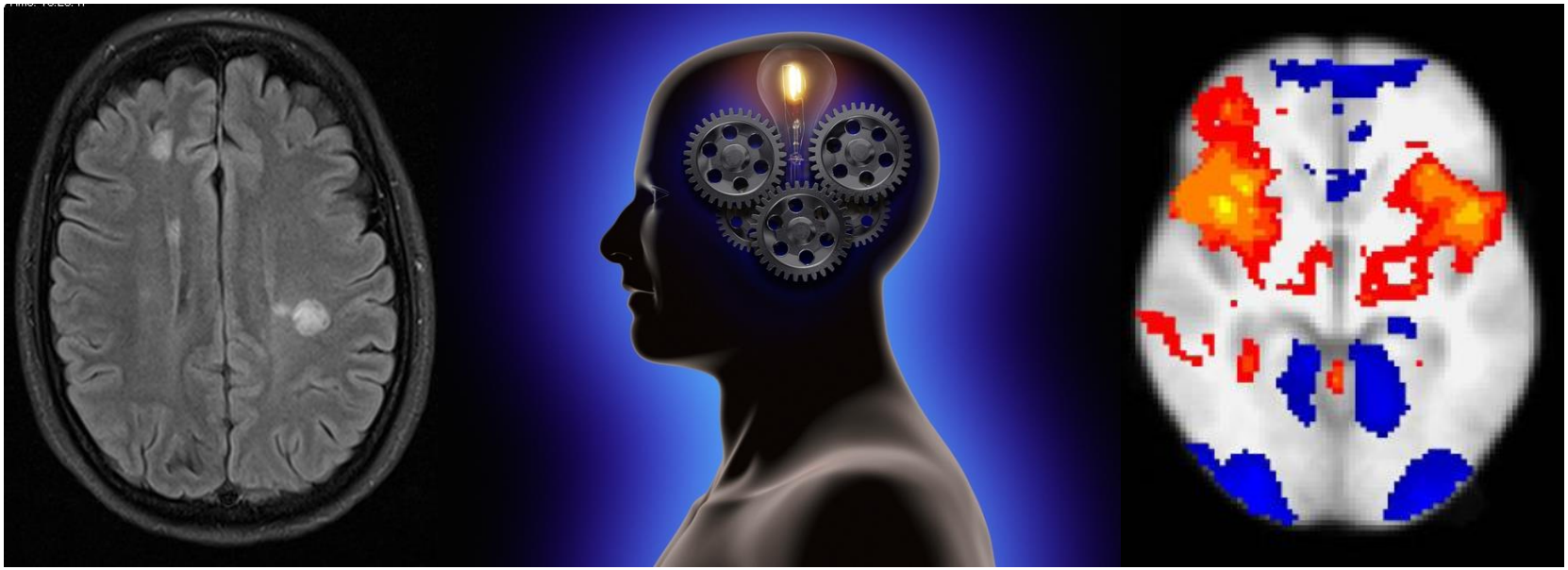
Lernen, Gedächtnis und Demenz

Reinhold Schmidt



Wie lernen wir

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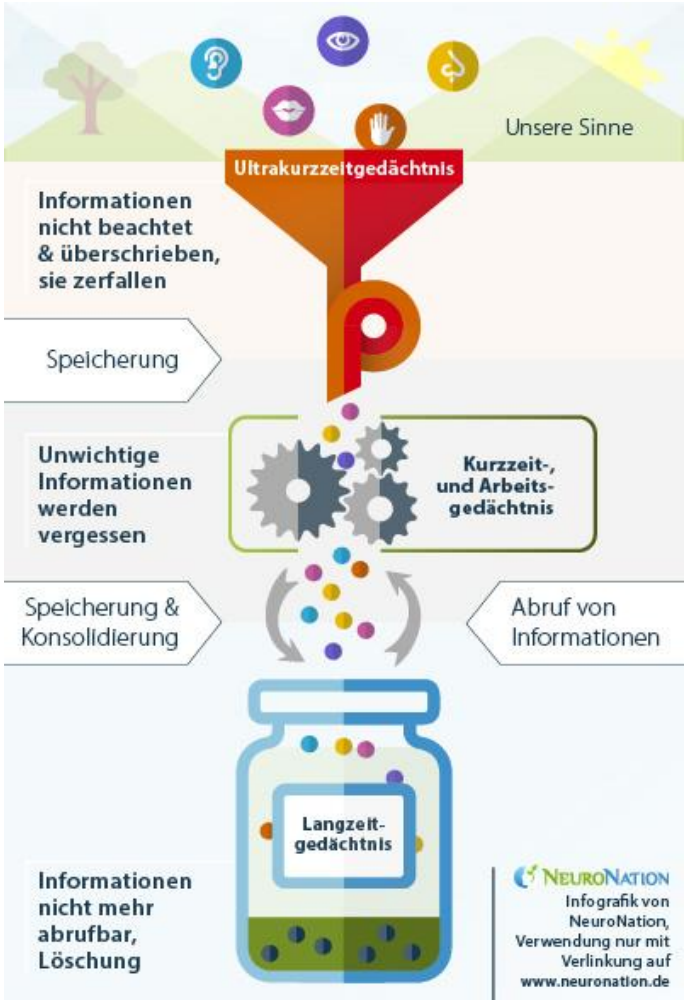
- Immer
- Aber nicht immer das, was andere wollen
- Oft lernen wir was wir später nicht brauchen
- Meist lernen wir ohne es zu wissen

Der Weg vom Sinneseindruck ins Langzeitgedächtnis



Weniger als eine Sekunde Mustererkennung/Aufmerksamkeitszuwendung-kein Computer-alle Informationen werden aufgenommen und bearbeitet

Sekunden bis Minuten-Löschen durch Überschreiben mit neuer Information

Diegedächtnisspannedeskurzzeitgedächtniss esbeträgtetwafünfbisneunchunks

Tage bis Jahrzehnte

DAS Gedächtnis gibt es nicht

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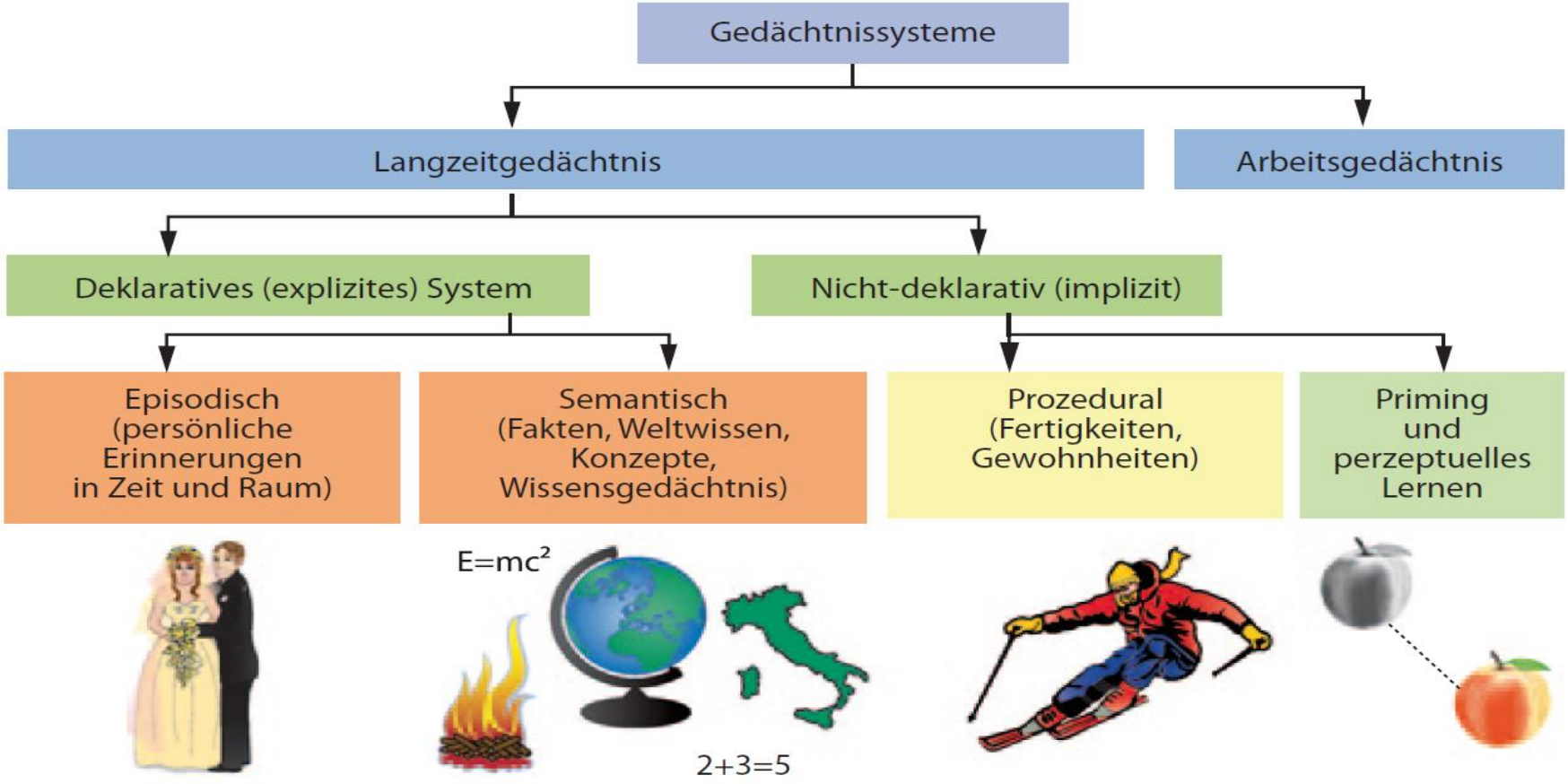
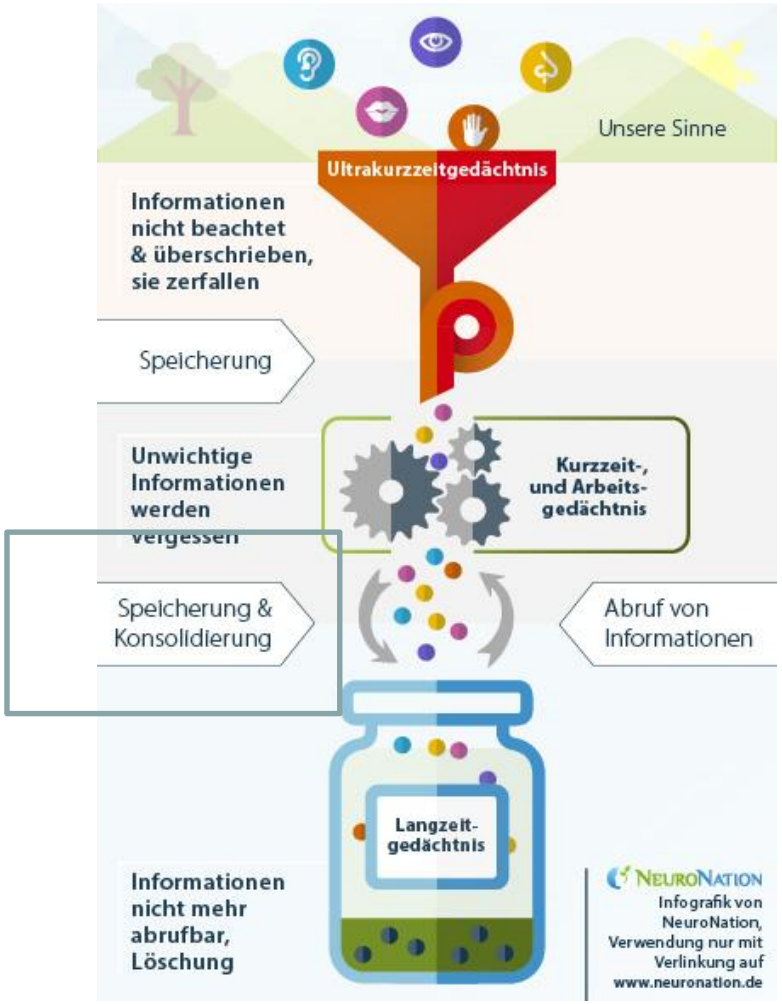


Inhalte werden also vom KZG in das vielfältige Langzeitgedächtnis gebracht….aber wie funktioniert das?



Was passiert im Gehirn wenn wir lernen

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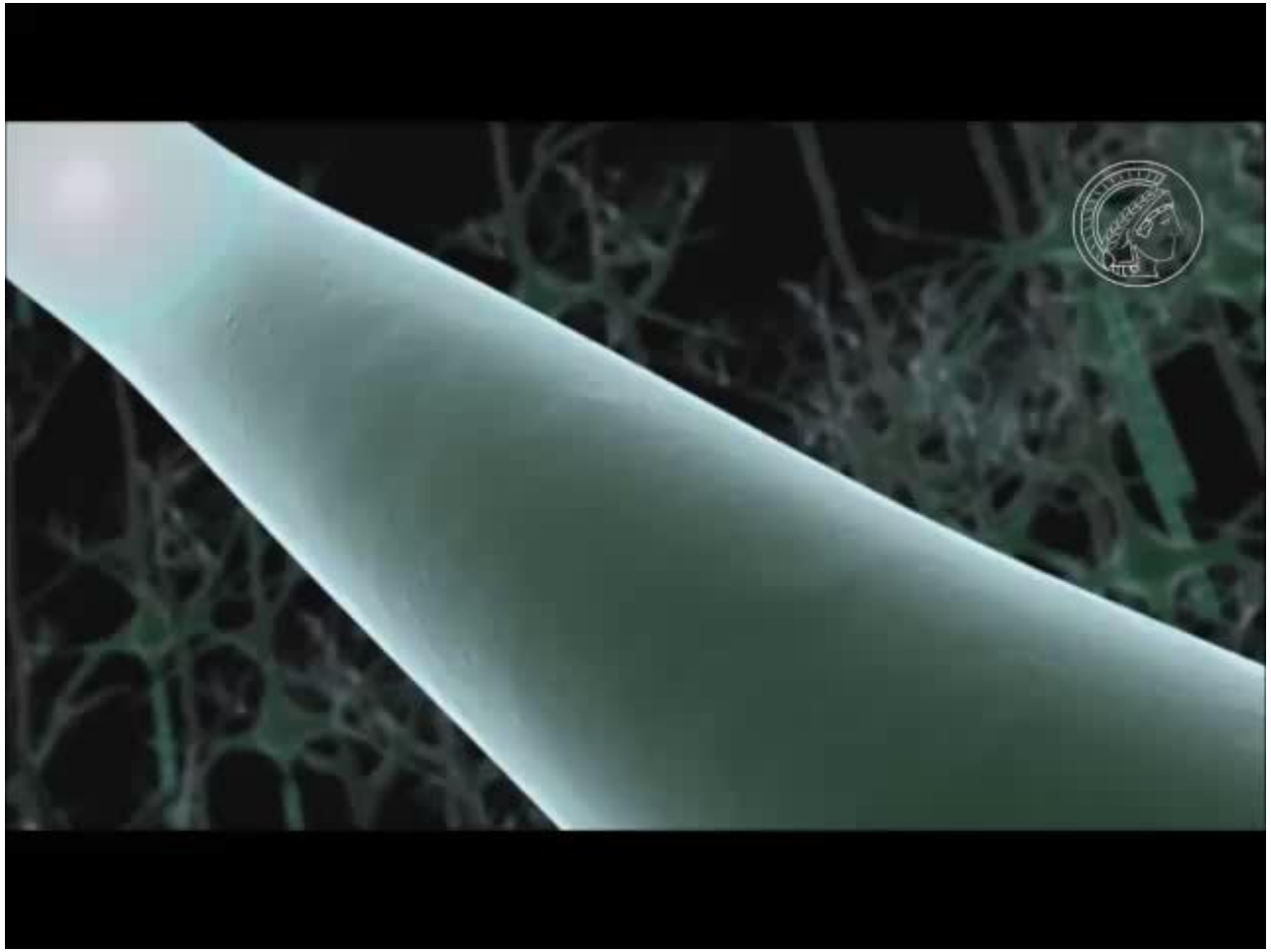

Lernstrategien

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Ergebnisse eines 10 minütigen Testes:

- 10% von dem, was wir lesen
- 20% von dem, was wir hören
- 30% von dem, was wir sehen
- 50% von dem, was wir hören + sehen
- 70% von dem, was wir selber sagen
- 90% von dem, was wir selber tun (!)
- Mischstrategien sind also das Beste
- und nichts ist besser als es selber zu tun

Lernatmosphäre nüchtern betrachtet

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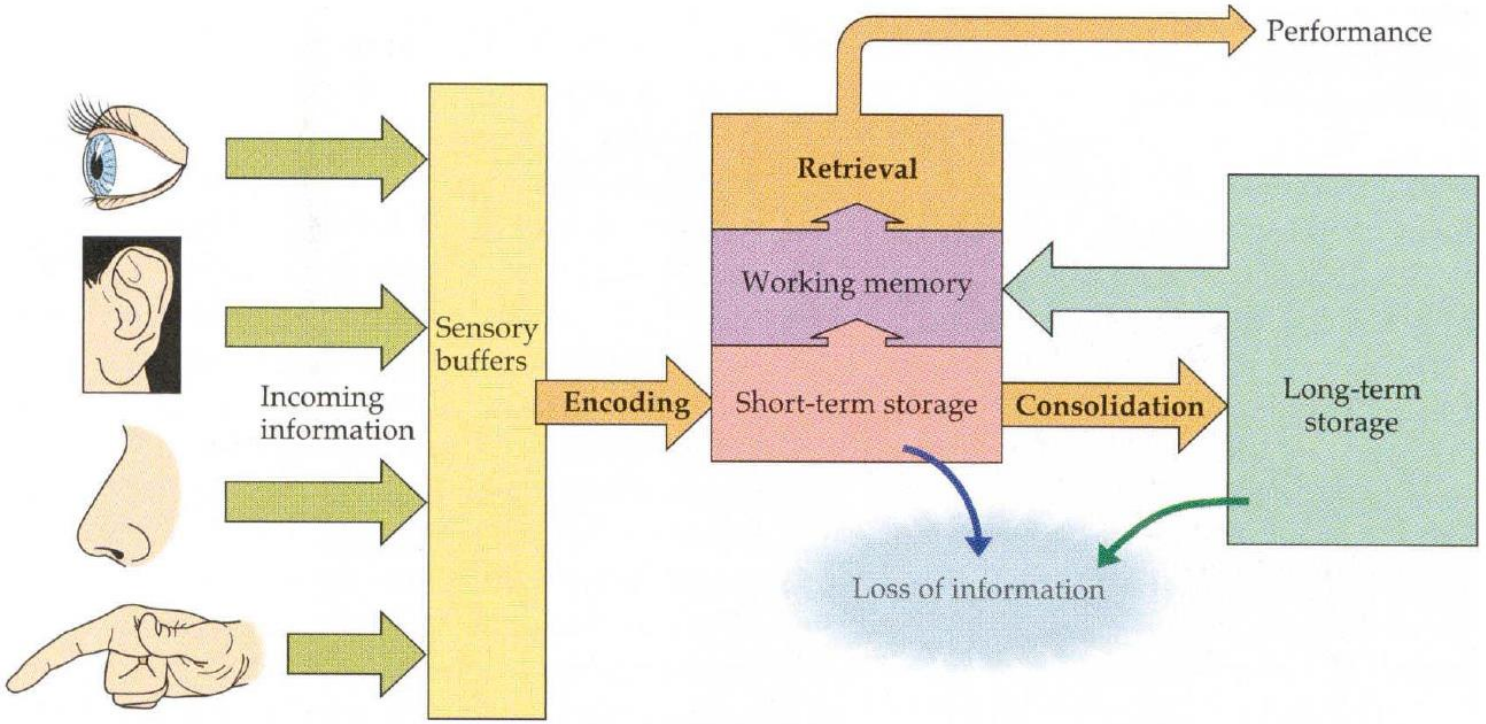
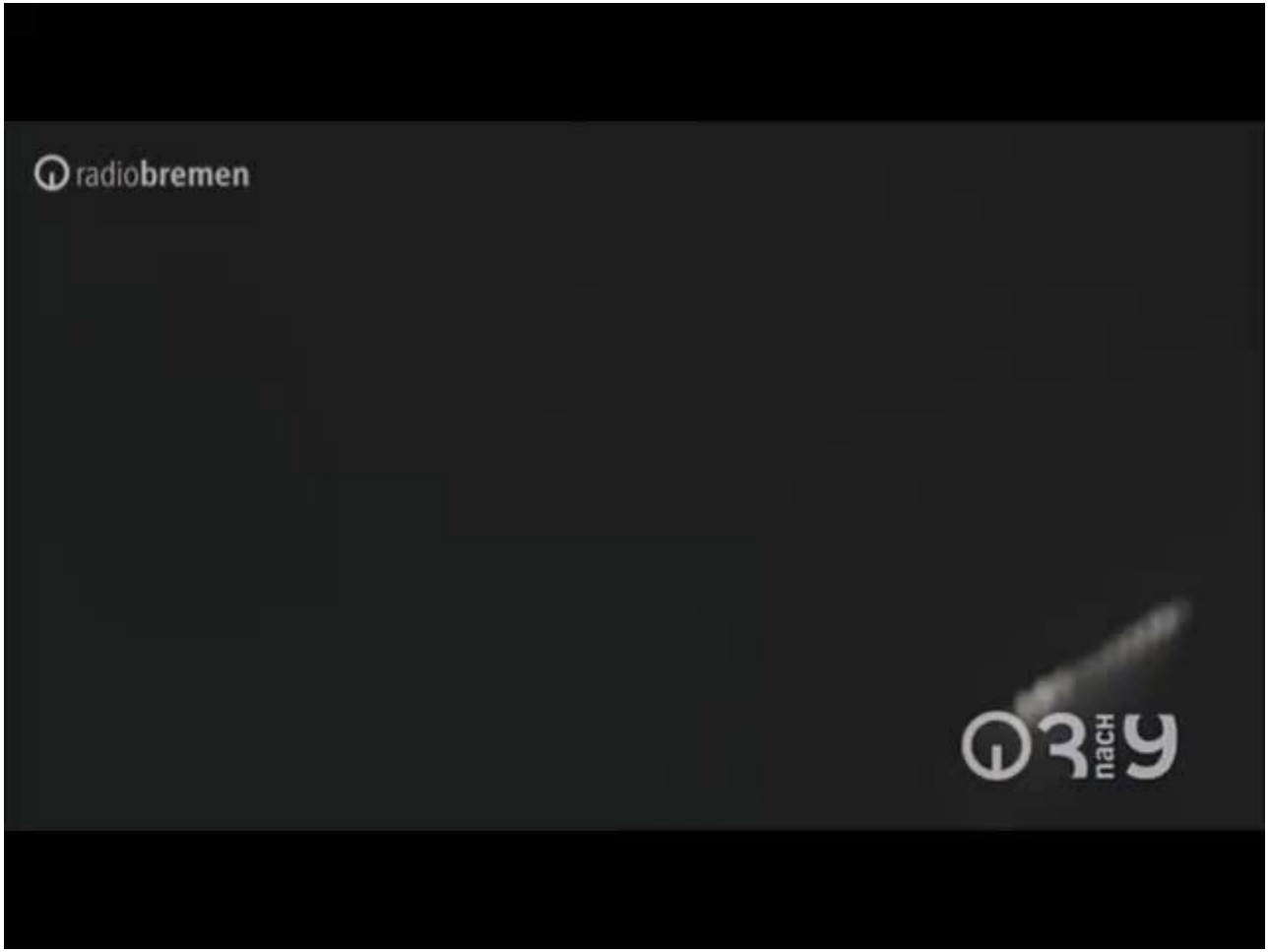
- Dopamin: Leistung, Aufmerksamkeit, Arbeitsgedächtnis
- Opioide: Belohnung
- Oxytocin: soziale Bindung, persönlicher Einsatz für bestimmte Menschen

- Interesse/Aufmerksamkeit
- Soziale Anerkennung
- Persönliche Wertschätzung
- Gute Vorbilder
- Chance auf Erfolg
- Fairness

Das getäuschte Gedächtnis




radiobremen
3 nach 9

Agenda

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- Aufbau und Funktionen des Gehirns
- Wodurch gelingen uns heute neue Einblicke in das Gehirn ?
- Denken und Lernen – wesentliche Funktionen des Gehirns
- Was macht das Internet mit unseren Gehirnen-Digitale Immigranten und Eingeborene

Internet Gebrauch ändert unsere Gehirn in kurzer Zeit

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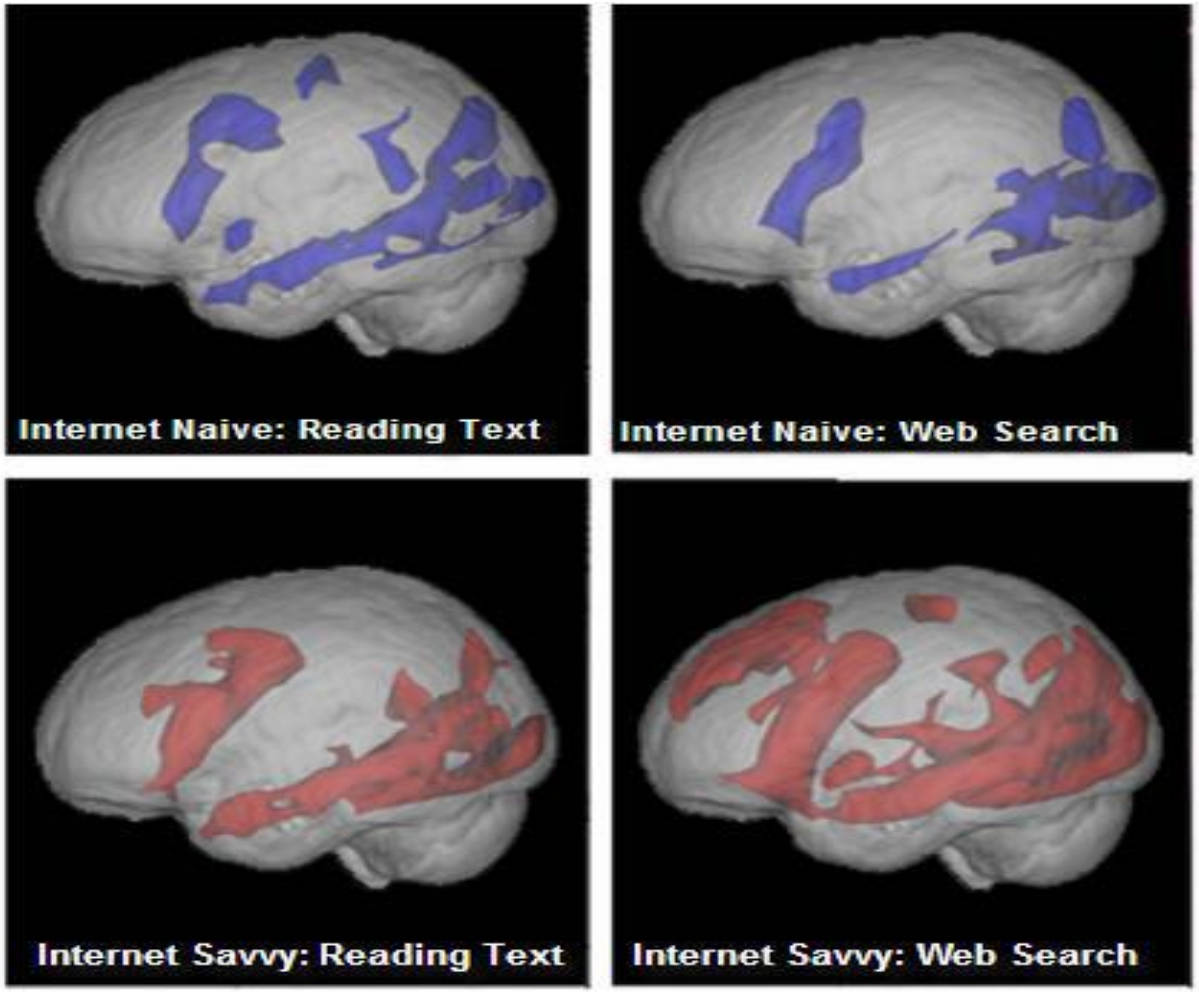

Das Ausjäten der Synapsenverbindungen

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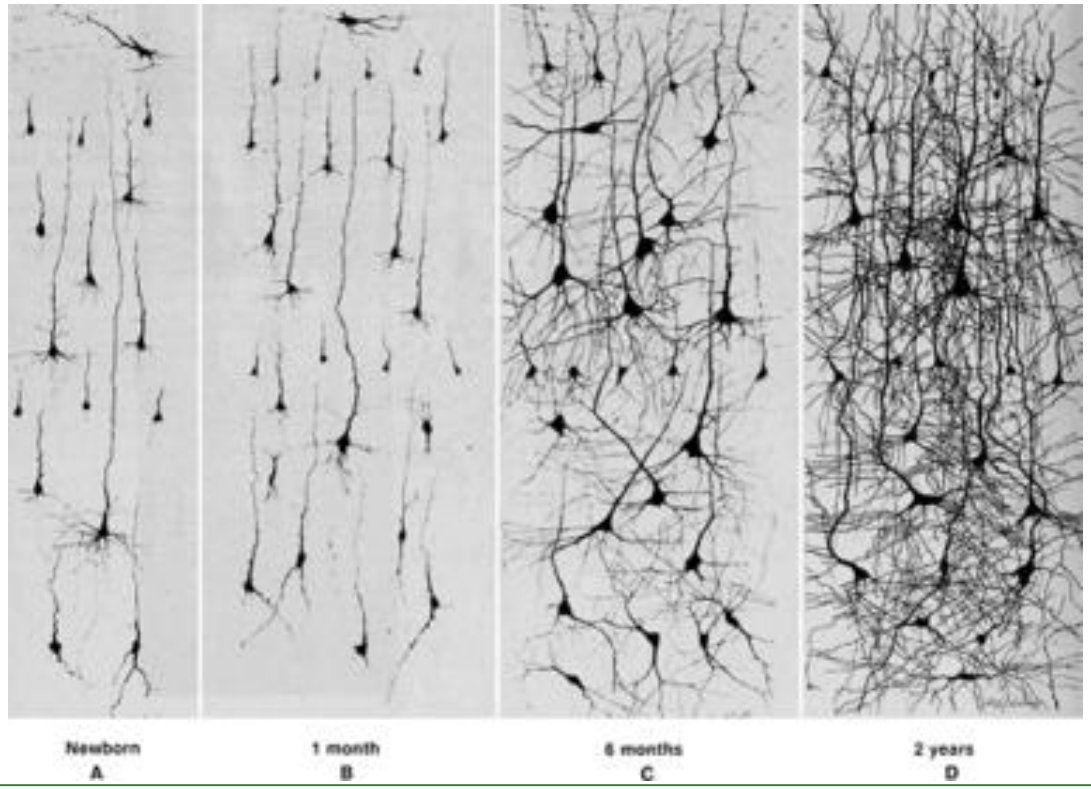
‚Mittels Erfahrung arbeitet das Gehirn daran, aus der Masse möglicher Schaltkreise eine sehr kleine Auswahl zu treffen. Jeff Lichtmann, 2012



Die nächste Generationen werden andere Gehirne haben

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Das Hirn der Digitalen Natives (Gary Small)

Verringerte Regelkreise	Verstärkte Regelkreise
Zwischenmenschlicher Kontakt	Reaktion auf visuelle Stimuli
Körpersprachliche Signale	Verabeitung großer Informationsmengen
Aufmerksamkeitsspanne	Schnelle Entscheidungen was wichtig ist
Stimulus Junkies um Langeweile auszugleichen	Gehirnprozesse werden effizienterdas wird unsere Vorstellung davon prägen, was "Intelligenz" ist
Es fällt schwer Belohnungen aufzuschieben	
Vorauschauend Denken	

Was passiert im Gehirn bei Alzheimer Kranken ?

Die pathologischen Veränderungen der Alzheimer Erkrankung

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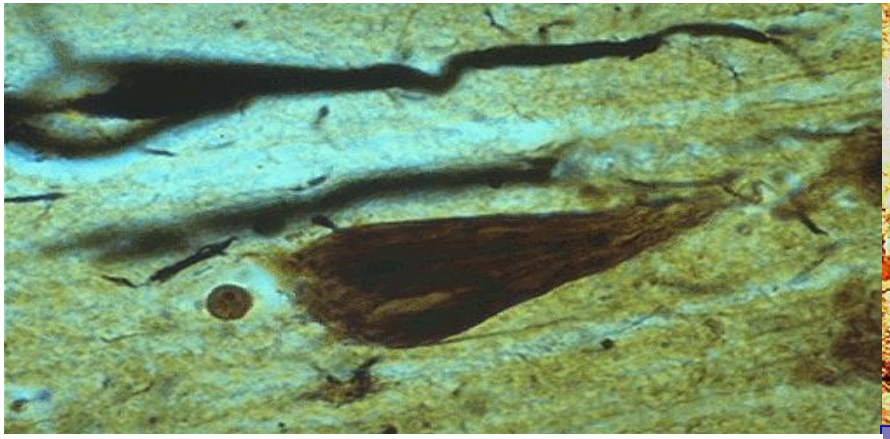
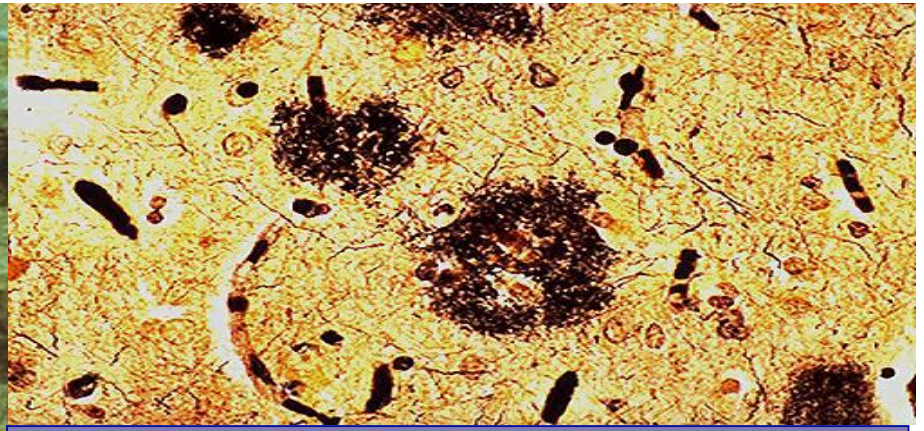
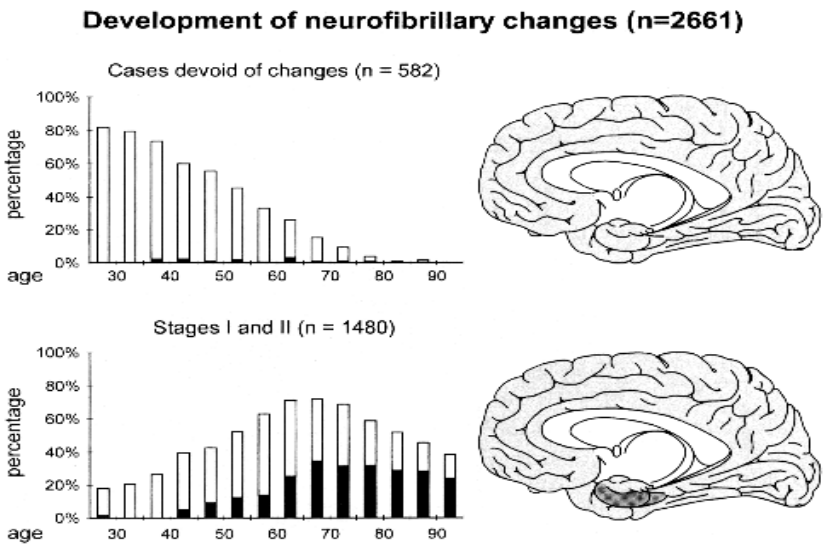
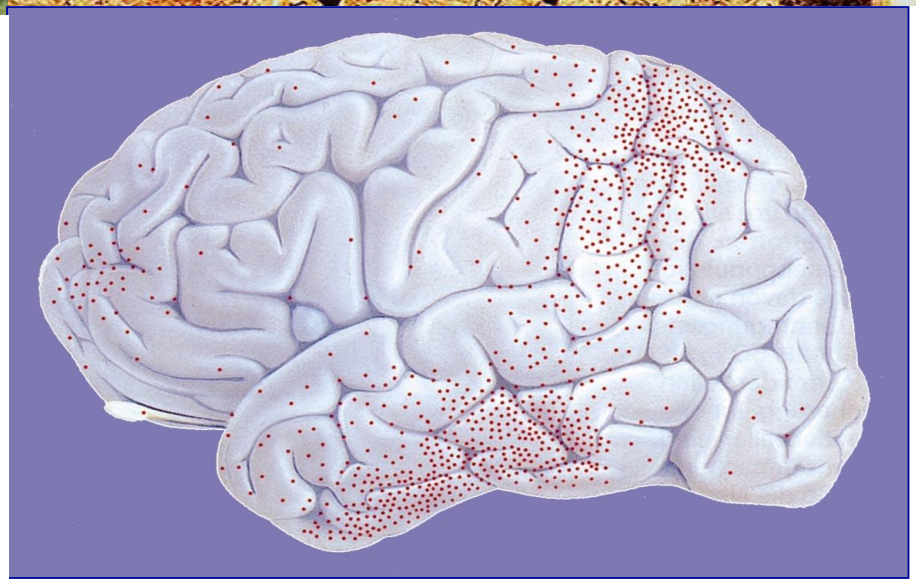
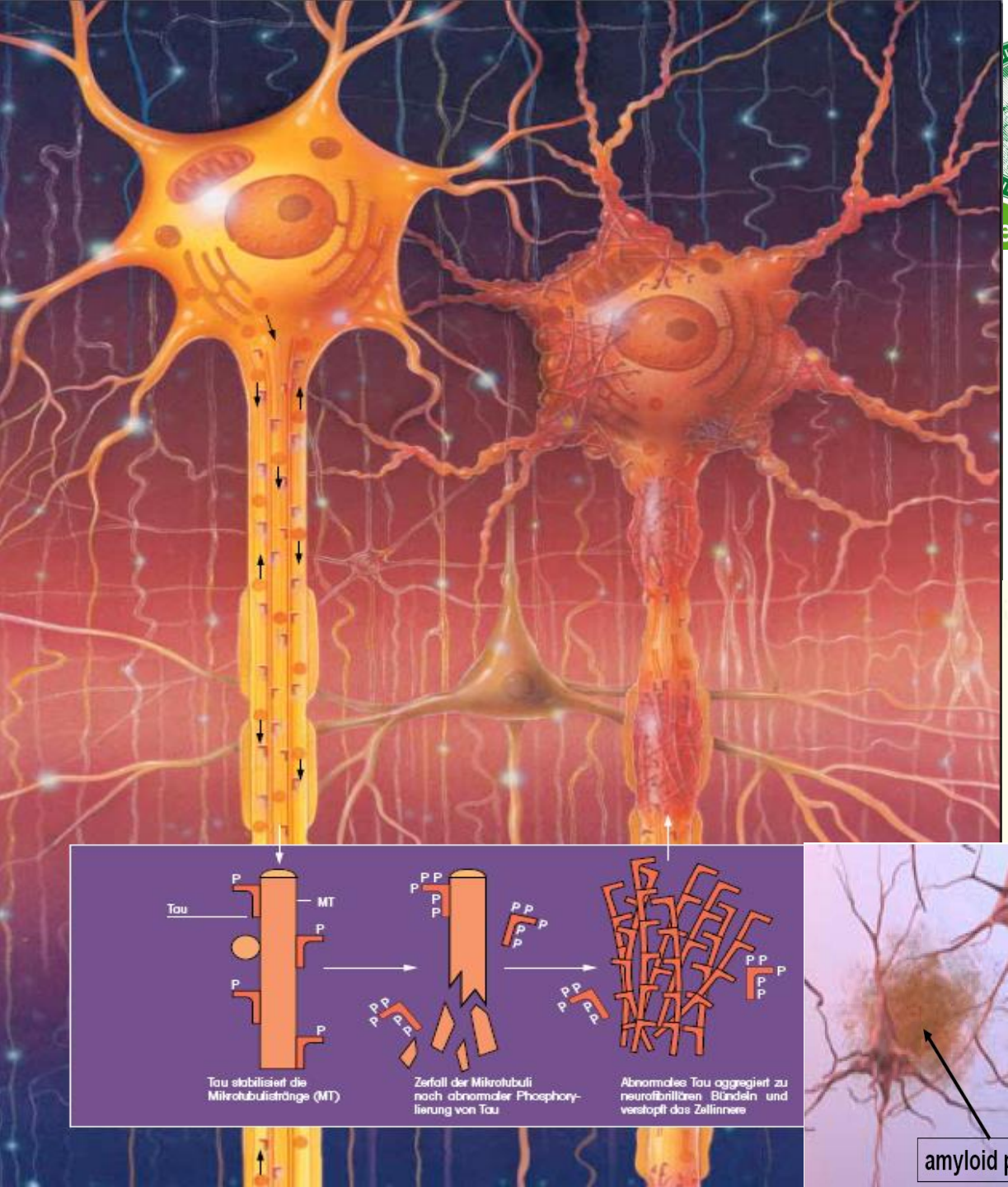




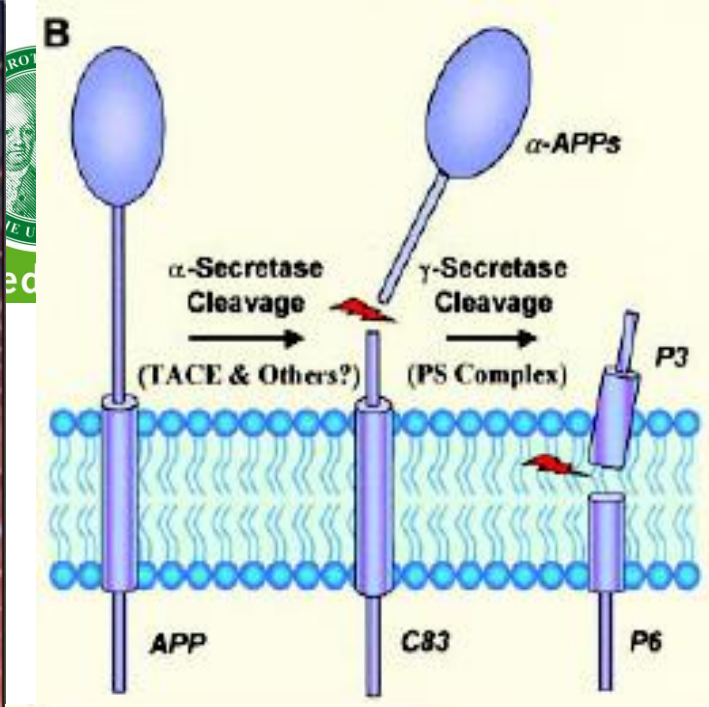


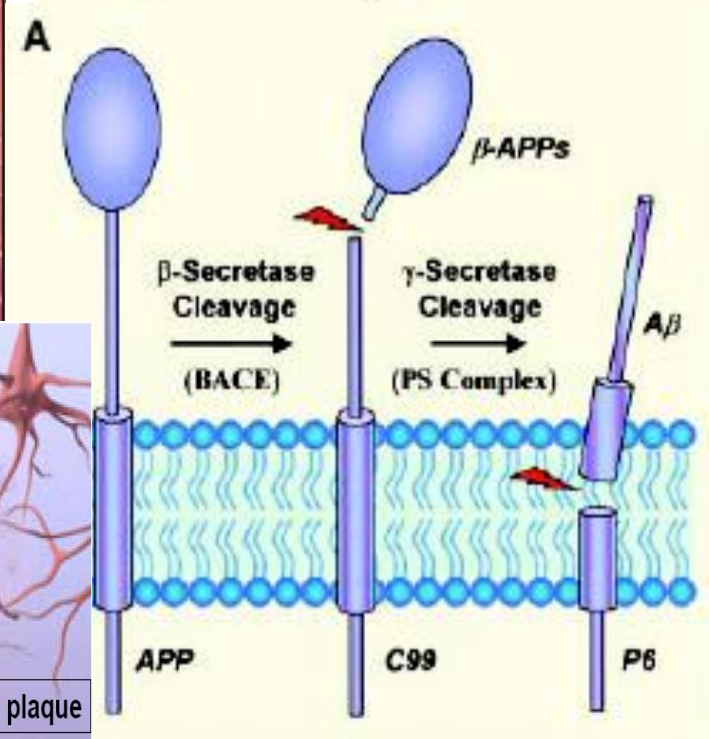


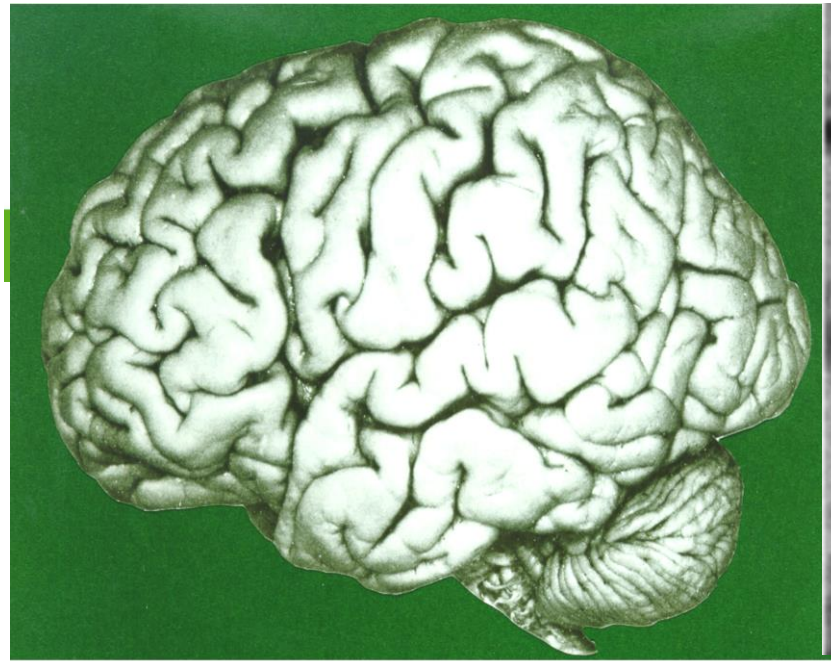


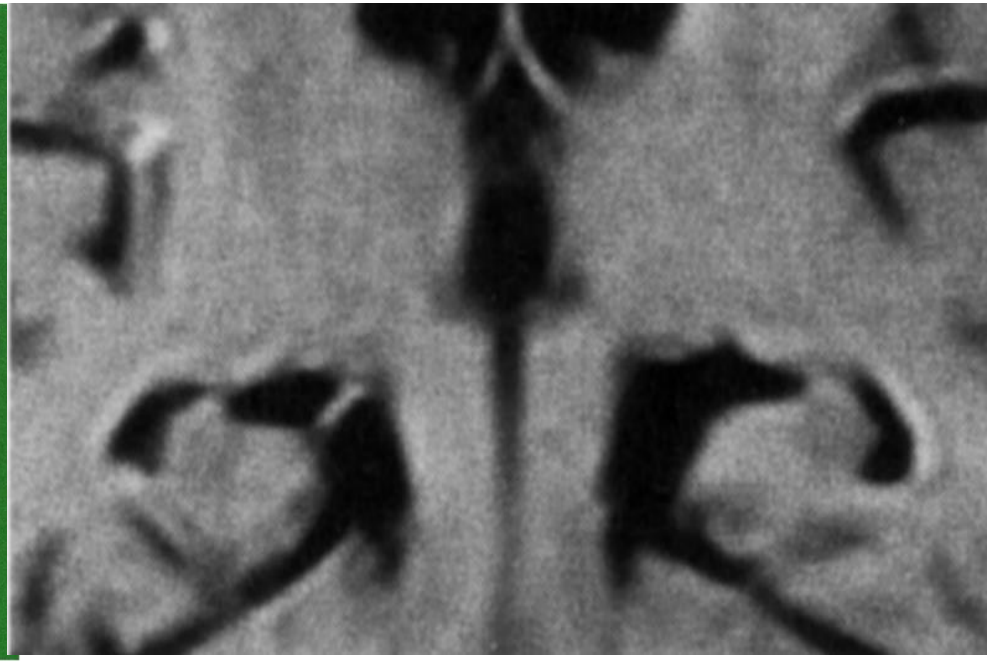
Tau
MT
P
Tau stabilisiert die Mikrotubulistränge (MT)
Zerfall der Mikrotubuli nach abnormaler Phosphorylierung von Tau
Abnormales Tau aggregiert zu neurofibrillären Bündeln und verstopft das Zellinnere

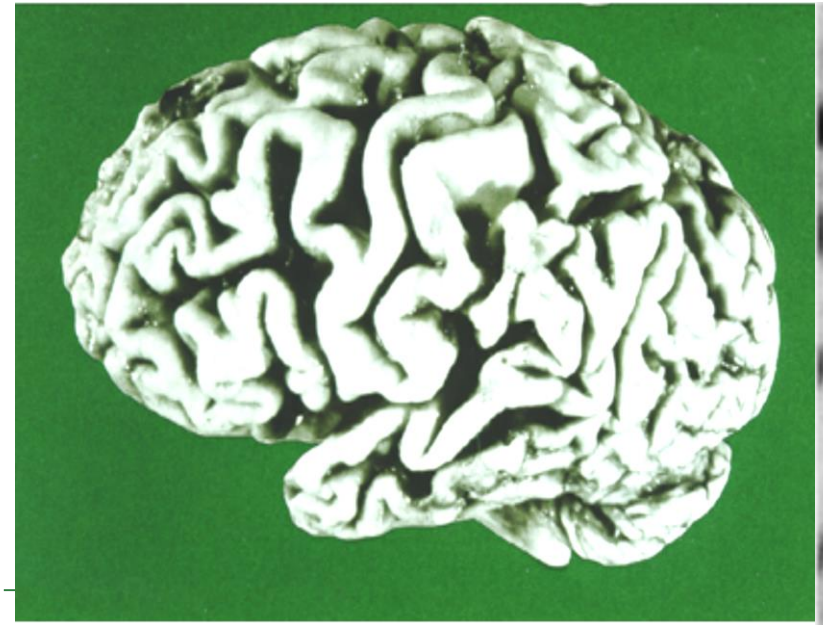
amyloid plaque

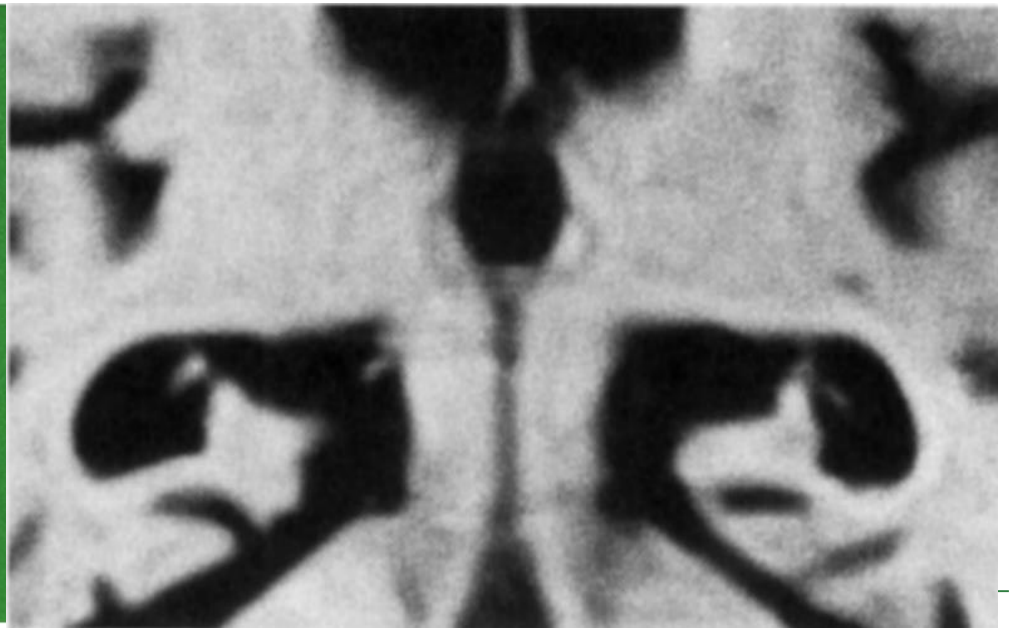

B
α-APPs
α-Secretase Cleavage
(TACE & Others?)
γ-Secretase Cleavage
(PS Complex)
P3
APP
C83
P6


A
β-APPs
β-Secretase Cleavage
(BACE)
γ-Secretase Cleavage
(PS Complex)
Aβ
APP
C99
P6









Was sind die Symptome der Alzheimer Krankheit ?

Symptome der Demenz

- **Gedächtnis**
  - Wiederholte Fragen oder Konversationen
  - Verlegen persönlicher Gegenstände
  - Vergessen von Ereignissen oder Terminen
  - Verlorengehen auf bekannten Wegen
- **Logisches Denken, Urteilsvermögen**
  - Schwierigkeiten beim Verstehen von Sicherheitsrisiken
  - Unfähigkeit Finanzen zu managen
  - Schwierigkeiten beim Treffen von Entscheidungen
  - Unfähigkeit komplexe Aktivitäten zu planen
- **Beeinträchtigung visuell-räumlicher Fähigkeiten**
  - Unfähigkeit Gesichter oder bekannte Objekte zu erkennen oder Gegenstände im direkten Gesichtsfeld zu finden trotz guter Sehfähigkeit
  - Unfähigkeit einfache Werkzeuge oder Geräte zu bedienen
  - Schwierigkeiten beim Ankleiden
- **Sprache**
  - Schwierigkeiten in der Wortfindung
  - Beeinträchtigung der Sprachflüssigkeit
  - Sprach-, Buchstabier-Schreibfehler
- **Persönlichkeits-und Verhaltensauffälligkeiten**

Wann beginnt die Alzheimer Krankheit?

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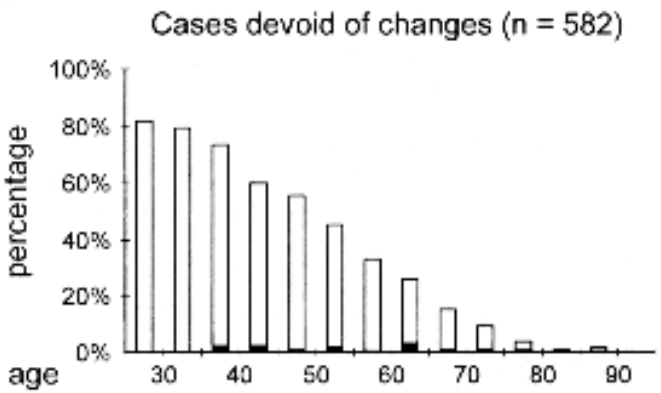
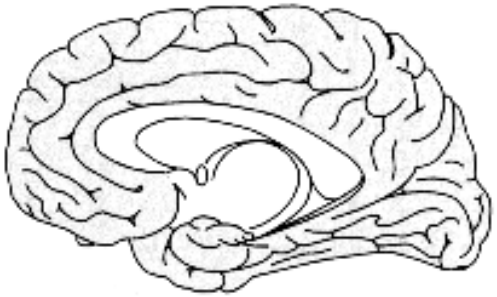
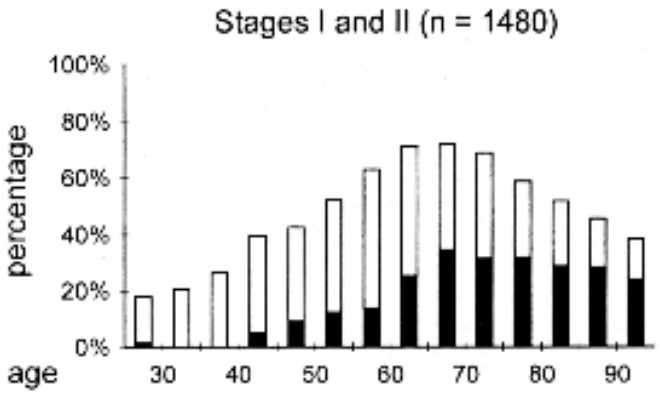
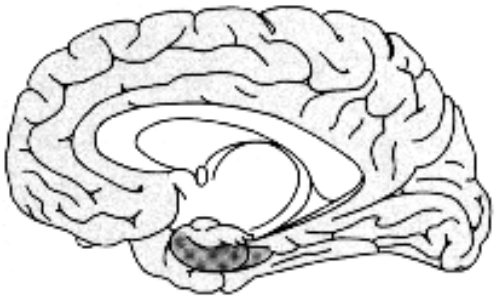
Alzheimer Pathologie und Lebensalter

Development of neurofibrillary changes (n=2661)



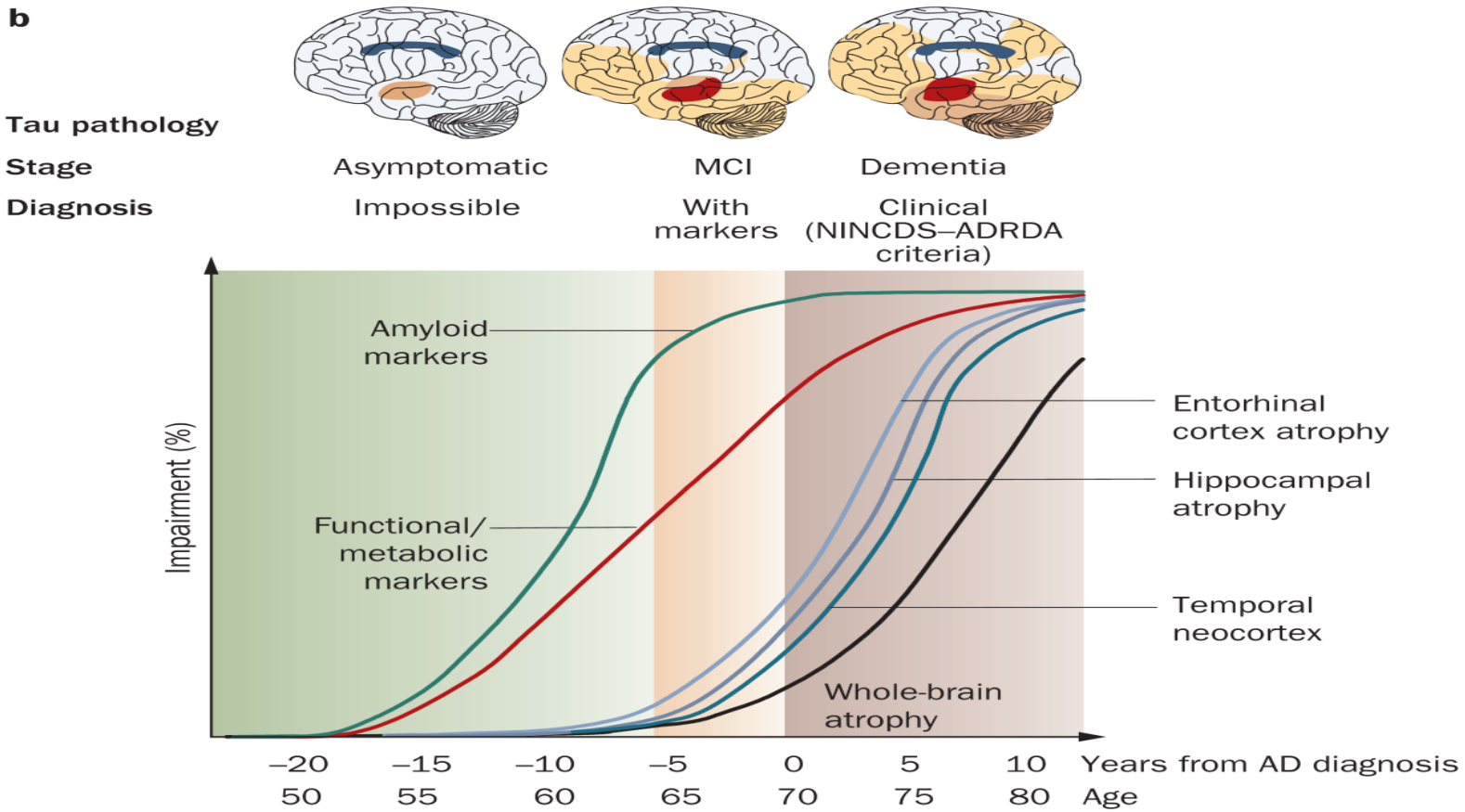






WIE FRÜH KANN MAN DIAGNOSTIZIEREN ?

Das Kontinuum der Alzheimer Krankheit



Amyloid Pathologie und frühe neuronale Degeneration

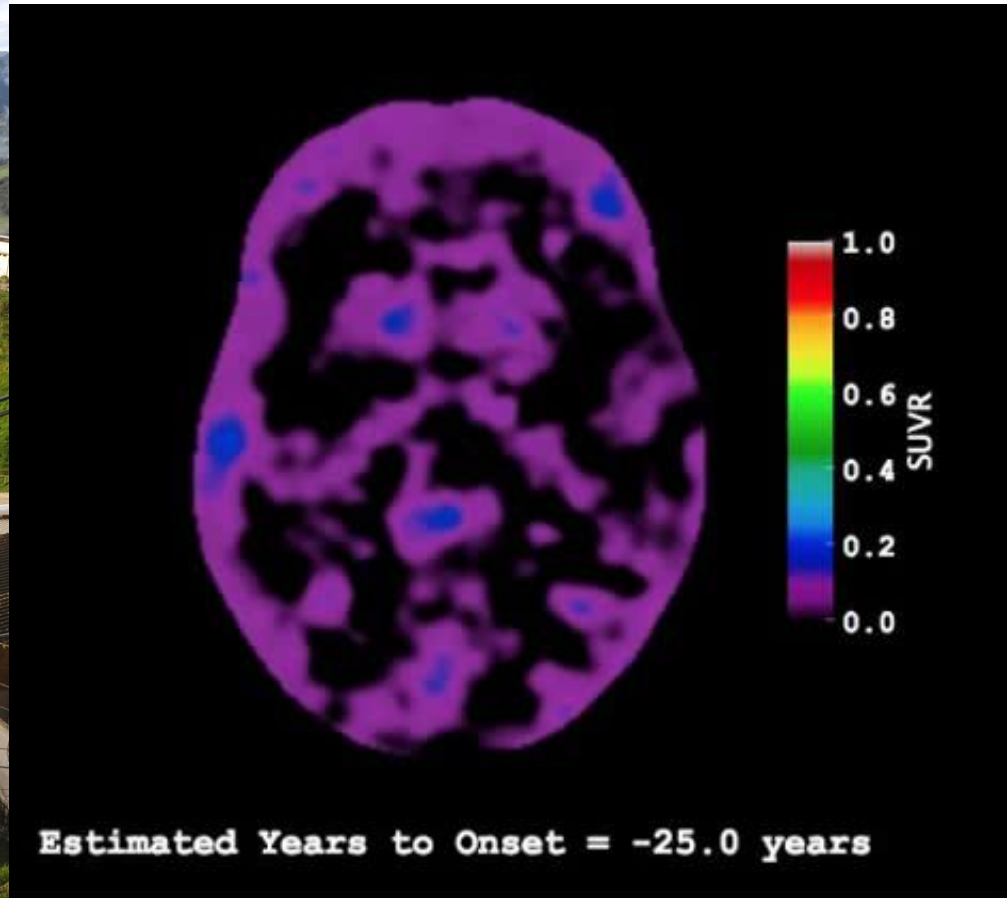
Ausgedehnte Neurodegeneration und irreversibler Neuronenverlust mit progressivem kognitivem und funktionellem Abbau

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network



Was kann man tun um Alzheimer zu verhindern?

Demenzprävention ist möglich

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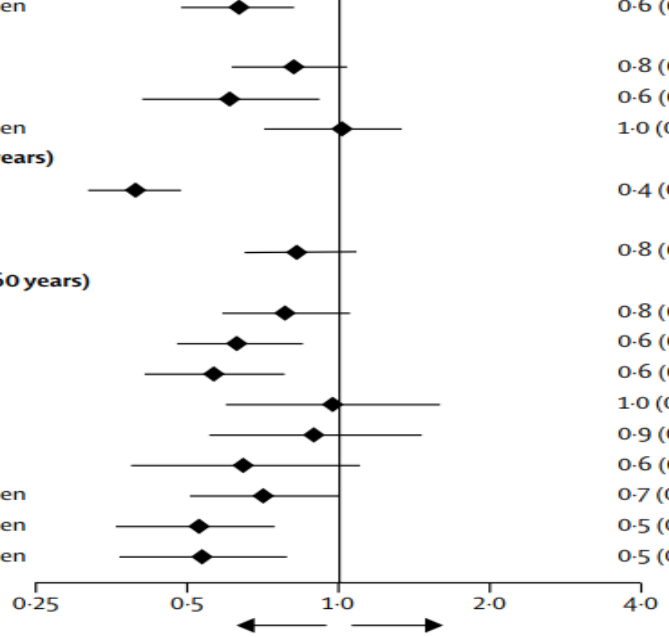
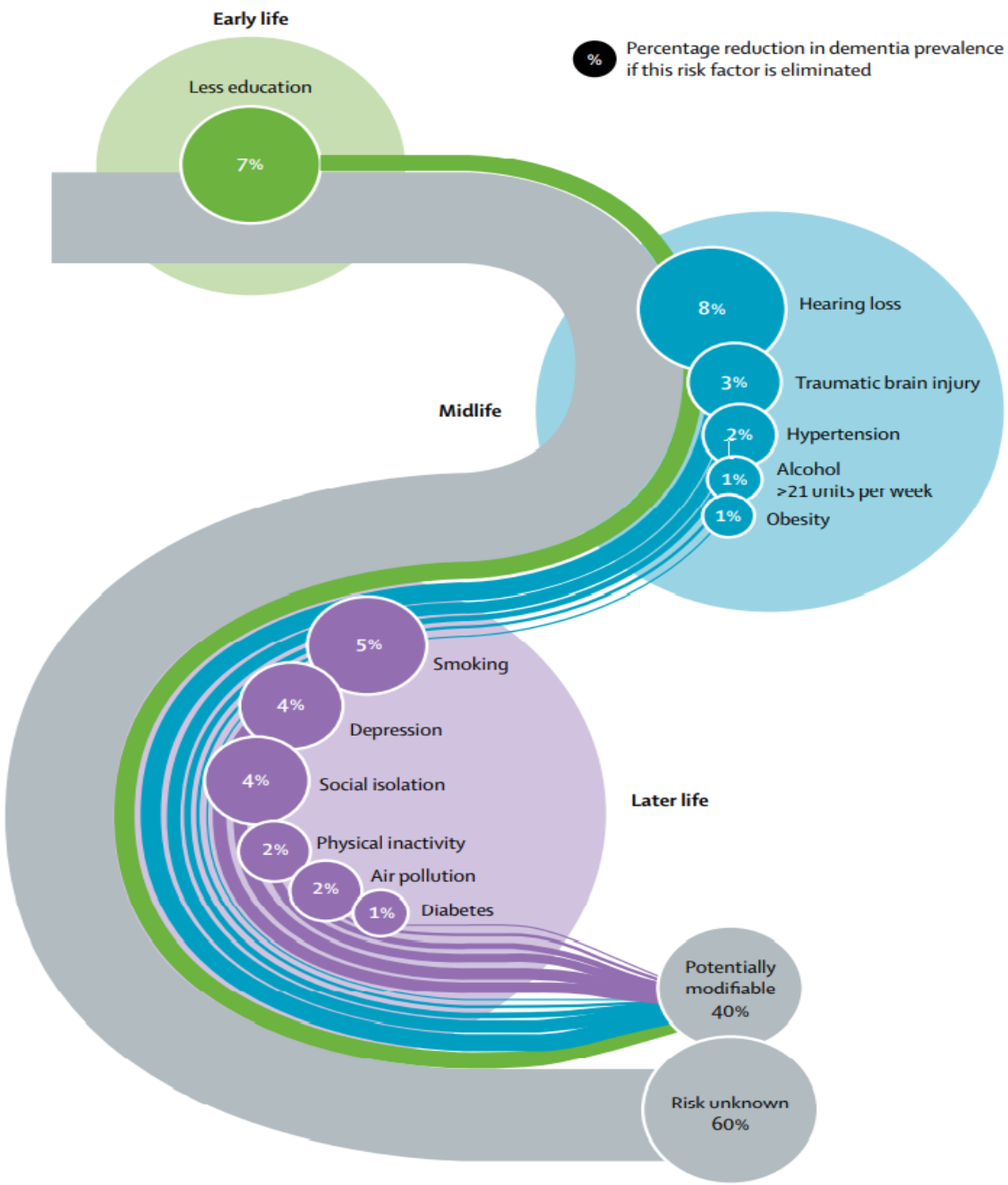
Population		Hazard ratio incidence ratio (95%CI)
Rotterdam (age 60–90 years)		
2000 *vs* 1990	Total	0·8 (0·6–1·0)
2000 *vs* 1990	Men	0·7 (0·4–1·2)
2000 *vs* 1990	Women	0·8 (0·5–1·1)
Bordeaux (clinical diagnosis, age ≥65 years)		
1999 *vs* 1988	Total	0·9 (0·7–1·1)
1999 *vs* 1988	Men	1·2 (0·8–1·9)
1999 *vs* 1988	Women	0·9 (0·7–1·2)
Bordeaux (algorithmic diagnosis, age ≥65 years)		
1999 *vs* 1988	Total	0·6 (0·5–0·8)
1999 *vs* 1988	Men	1·1 (0·7–1·8)
1999 *vs* 1988	Women	0·6 (0·5–0·8)
CFAS (age ≥65 years)		
2008 *vs* 1991	Total	0·8 (0·6–1·0)
2008 *vs* 1991	Men	0·6 (0·4–0·9)
2008 *vs* 1991	Women	1·0 (0·7–1·3)
IIDP (African American age ≥70 years)		
2001 *vs* 1992	Total	0·4 (0·3–0·5)
IIDP (Yoruba age ≥70 years)		
2001 *vs* 1992	Total	0·8 (0·6–1·1)
Framingham heart study (age ≥60 years)		
1986–91 *vs* 1977–83	Total	0·8 (0·6–1·0)
1992–98 *vs* 1977–83	Total	0·6 (0·5–0·8)
2004–08 *vs* 1977–83	Total	0·6 (0·4–0·8)
1986–91 *vs* 1977–83	Men	1·0 (0·6–1·6)
1992–98 *vs* 1977–83	Men	0·9 (0·6–1·4)
2004–08 *vs* 1977–83	Men	0·6 (0·4–1·1)
1986–91 *vs* 1977–83	Women	0·7 (0·5–1·0)
1992–98 *vs* 1977–83	Women	0·5 (0·4–0·7)
2004–08 *vs* 1977–83	Women	0·5 (0·4–0·8)



Viele Risikofaktoren-nicht alle bieten Möglichkeit für Prävention

z.B.Kopfgröße

weibliches Geschlecht



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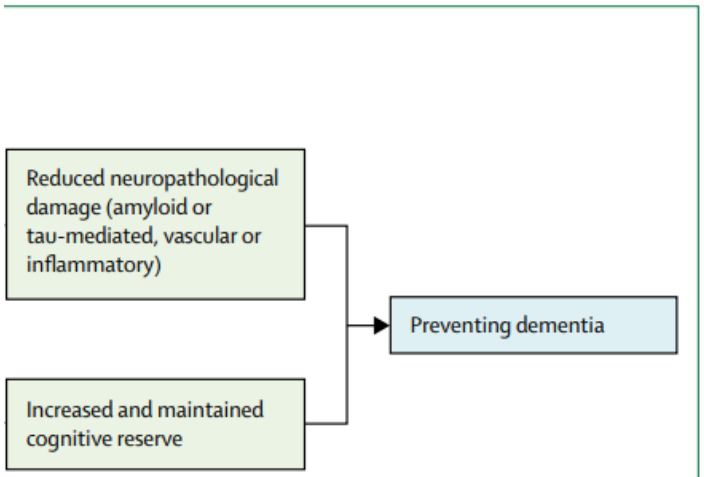

Kognitive Reserve: Definition

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Kapazität des Gehirnes,

Schädigungen zu kompensieren und

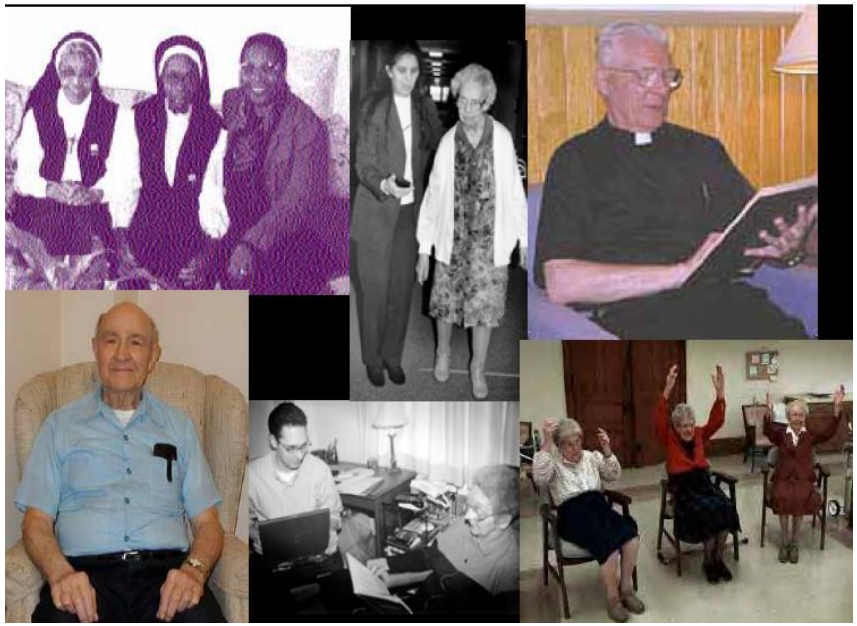
die klinische Manifestationen von Erkrankung zu

minimieren

The Rush Memory and Aging Project

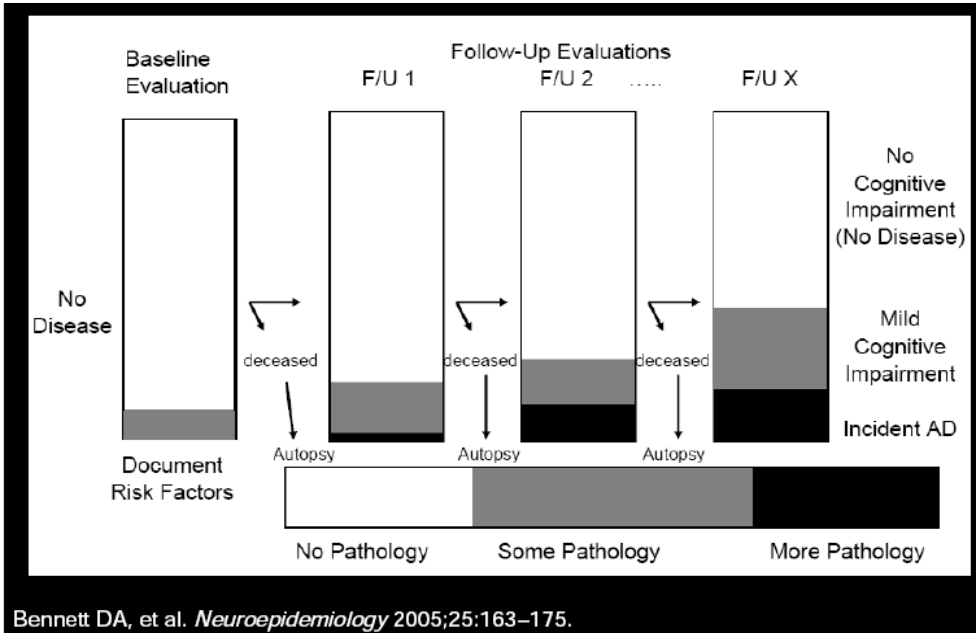
… because memories should last a lifetime

- Began enrollment in 1997
- > 1,200 residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive and motor testing, and blood draw.
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
- > 95% follow-up of survivors
- > 250 incident MCI and > 175 incident AD cases
- ~ 85% autopsy rate with > 250 autopsies to date



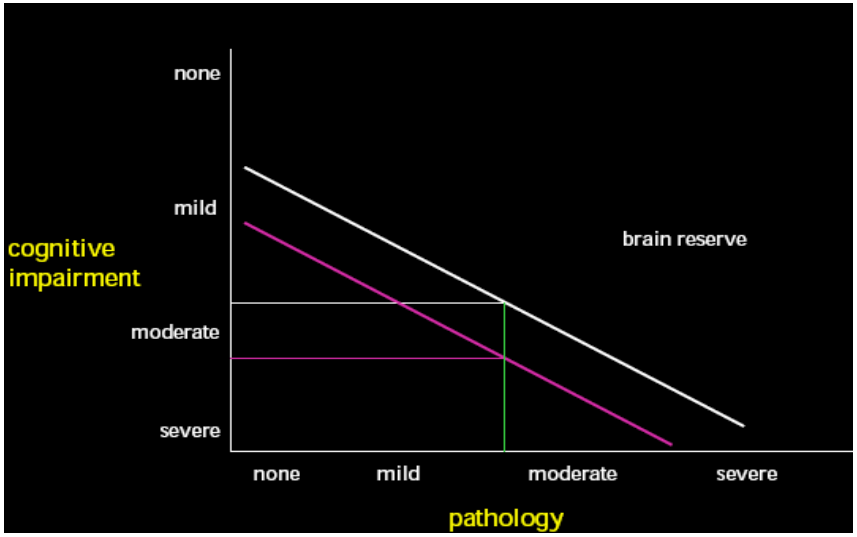
The Religious Orders Study

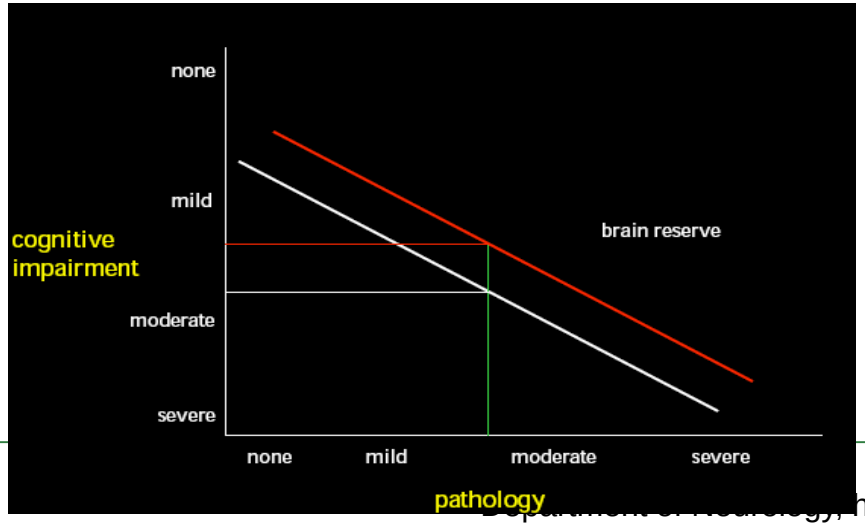
- Began enrollment in 1994
- > 1,100 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing
- All agreed to brain donation at the time of death
- > 95% follow-up of survivors
- > 350 incident MCI and > 250 incident AD cases
- ~ 95% autopsy rate with > 425 brain autopsies



Bennett DA, et al. *Neuroepidemiology* 2005;25:163–175.

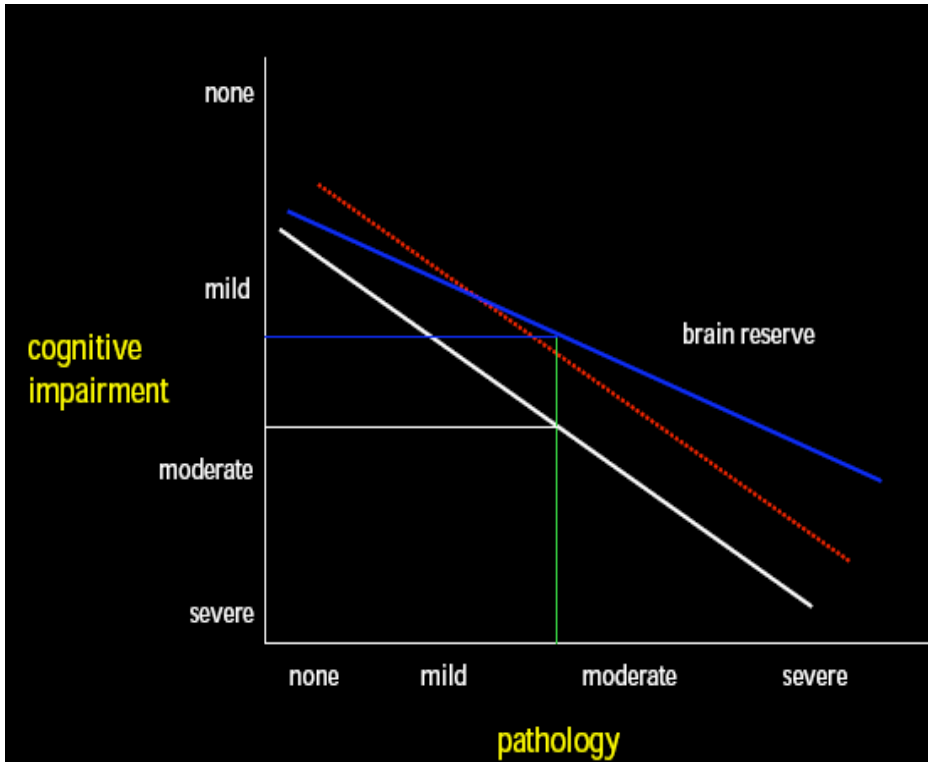
Additiv wirkende Faktoren





- Neigung zu Dystress
- Einsamkeit
- Depression
- Risikofaktoren
- Kognitive Aktivitäten

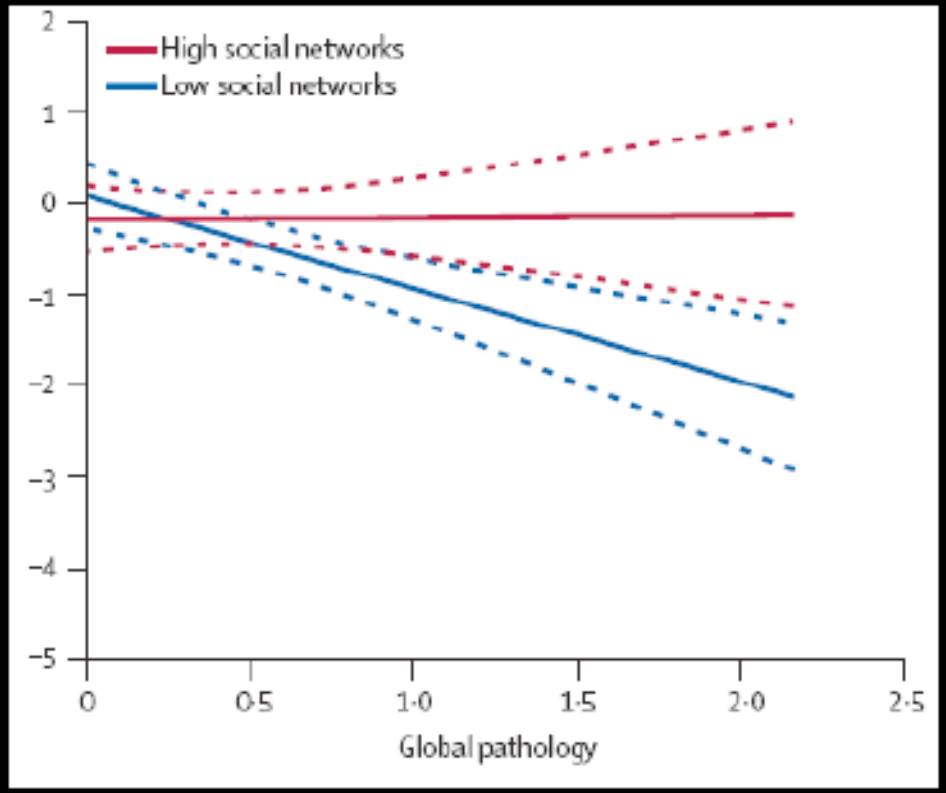
Interaktive Effekte

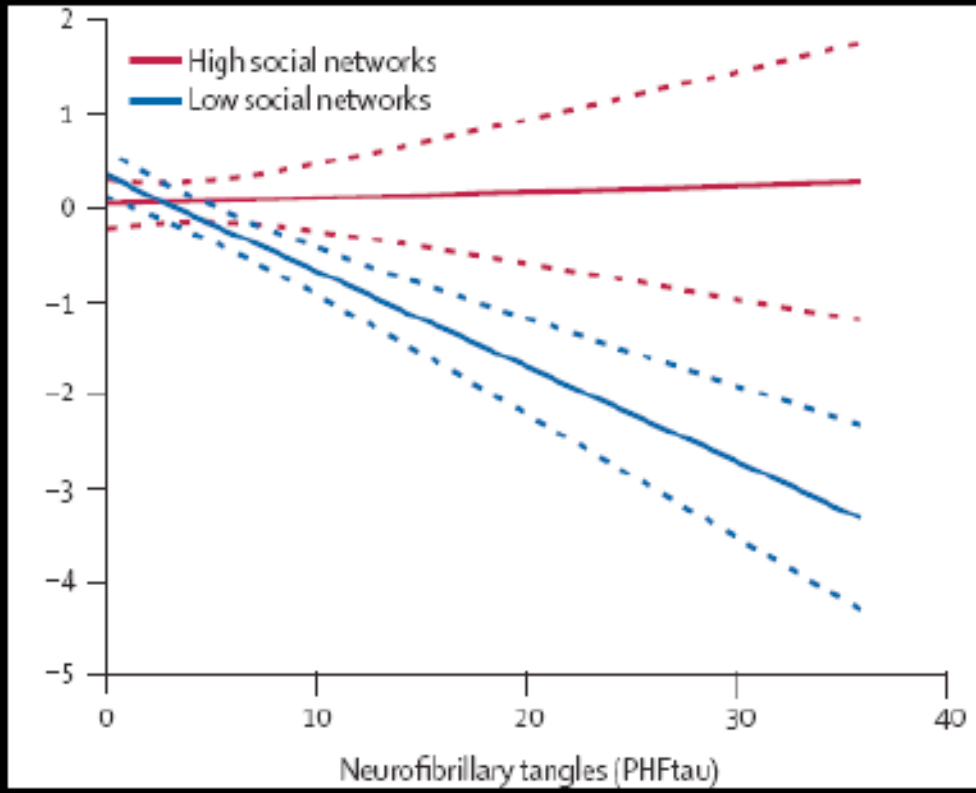


- Zielstrebigkeit
- Ausbildungsjahre
- Soziale Netzwerke

The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

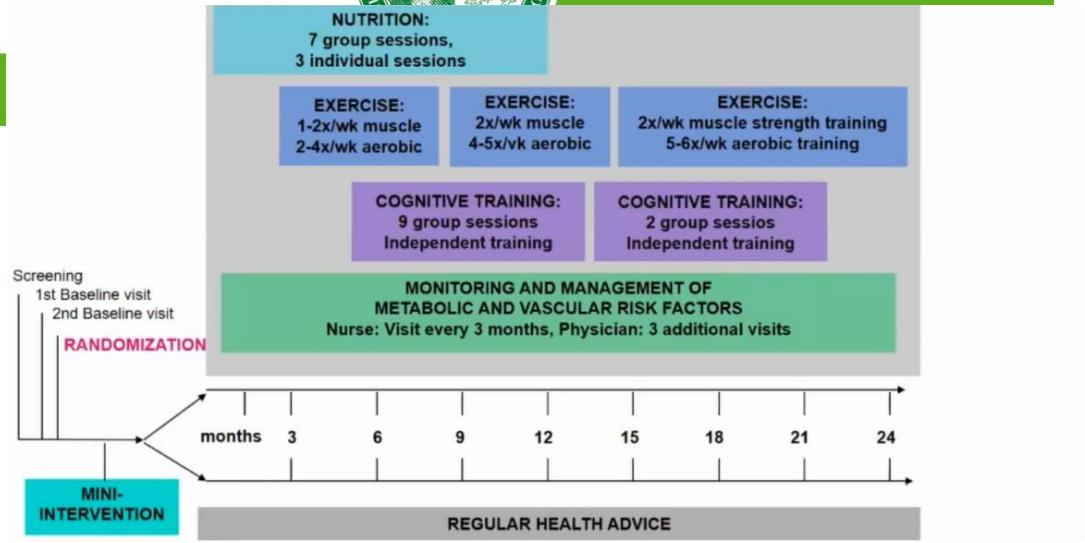
Number of children, relatives (besides spouse and children) and other friends that they saw each month that they felt close to and at ease with and could talk to about private matters and could call upon for help.

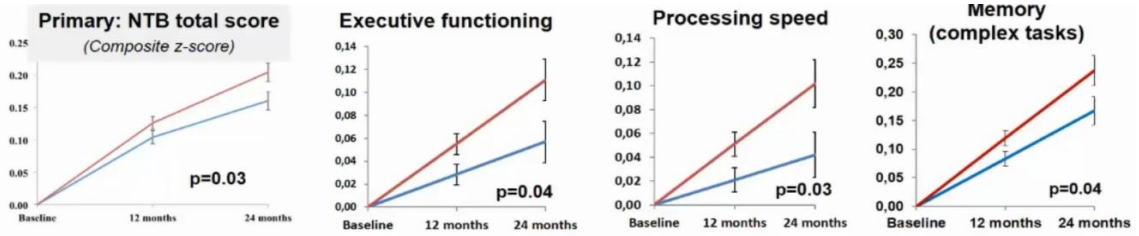




Bennett DA, et al. *Lancet Neurology* 2006;5:406-412.

FINGER APPROACH





Improvement **+ 25%** **+ 83%** **+ 150%** **+ 40%**

Ngandu, Kivipelto et al. Lancet 2015

- **Lower risk for cognitive decline**
- **30% lower risk for functional decline (IADL)** (*Kulmala et al., manuscript*)
- **Better health related quality of life** (*Strandberg et al, Eur Ger Med 2017*)

Ongoing Digital Studies

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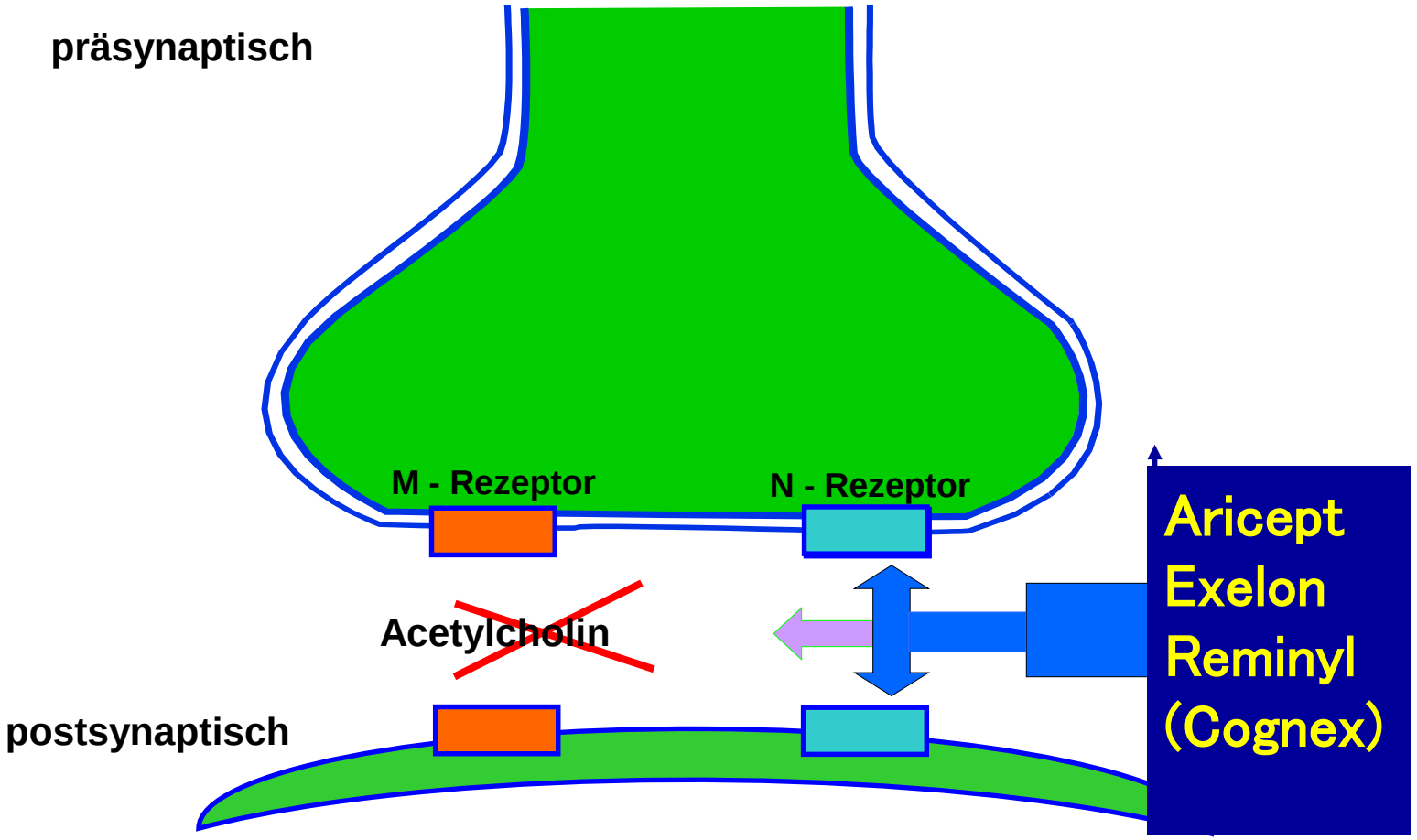
Title	Sample/Sampling Method	Interventions	Availability	Study Length	Primary Outcomes	Issues Addressed
MYB	• n = 2143 (planned) • Australian adults aged 53 + • Recruitment from longitudinal health study (45 and Up)	• Exercise • Diet • Cognition • Depressive/Anxiety symptoms • Lifestyle risk factors (e.g., smoking/heavy drinking)	• 3 years • 2–4 modules assigned in 1 year (risk factor dependent) • Motivational session every 3 months • Annual follow-up	• Improvement/lack of decline in composite cognitive score • Decreased incidence of dementia • Impact on module-focused risk factors • Assessing efficacy of an online approach	• Fully remote intervention • Personally tailored interventions	• Web-based intervention • Fully digital intervention • Personalized risk-factor intervention
DC-MARVEL	• n = 200 (planned) • Aged 45–64 years • At risk for dementia	• Diet • Exercise • Cognitive training • Sleep • Stress • Social engagement • Health coaching	• Online • Not publicly available	• 2 years	• Lifestyle risk and protective factor score • Cognitive assessment score • Clinical biomarkers	• Cross-platform, app-based intervention • Fully digital intervention • Personalized intervention plans
BBL-CD	• Australian adults aged 65 + years • SCD or previously diagnosed MCI	• Diet • Exercise • Cognitive activity	• Online • Not publicly available	• 6 Months • 1 module/ 2 week (one week in between) • Assessed at 9 weeks, 3 and 6 months	• Cognition, Executive Function and IADLs (ADAS-Cog-Plus) • AD risk/protective lifestyle factors • Motivation, health-related quality of life, adherence	• Personalized intervention plans • Participants experiencing cognitive impairment
HATICE	• n = 2725 • Finnish, Dutch, French adults age 65 + • Two or more cardiovascular risk factors • History of diabetes or cardiovascular disease	• Diet • Exercise • Cardiovascular risk factor management	• Online, not publicly available	• 18 months • FTF interview and biometrics at baseline and 18 months. • Online questionnaires at baseline, 3, 12 and 18 months. • Phone call for medication use at 12 months	• Increase in composite z-scores of biometrics from baseline • Intervention unaffected by cultural differences (when adjusted to that culture)	• Culture-specific guidelines on CVRF/weight can affect implementation • Coaches serve mostly as motivational support for change

The gray background is just to the table to be clearer. ADRD = Alzheimer's disease and related dementias; BBL-CD = Body, Brain, Life for Cognitive Decline; DC-MARVEL = Digital Cognitive Multi-domain Alzheimer's Risk Velocity study; FTF = Face-to-face; HATICE = Healthy Aging Through Internet Counselling in the Elderly; IADL = Instrumental Activity of Daily Living; MCI = Mild Cognitive Impairment; SCD = Subjective Cognitive Decline.

Acetylcholinesterase Hemmer



The NMDA Receptor

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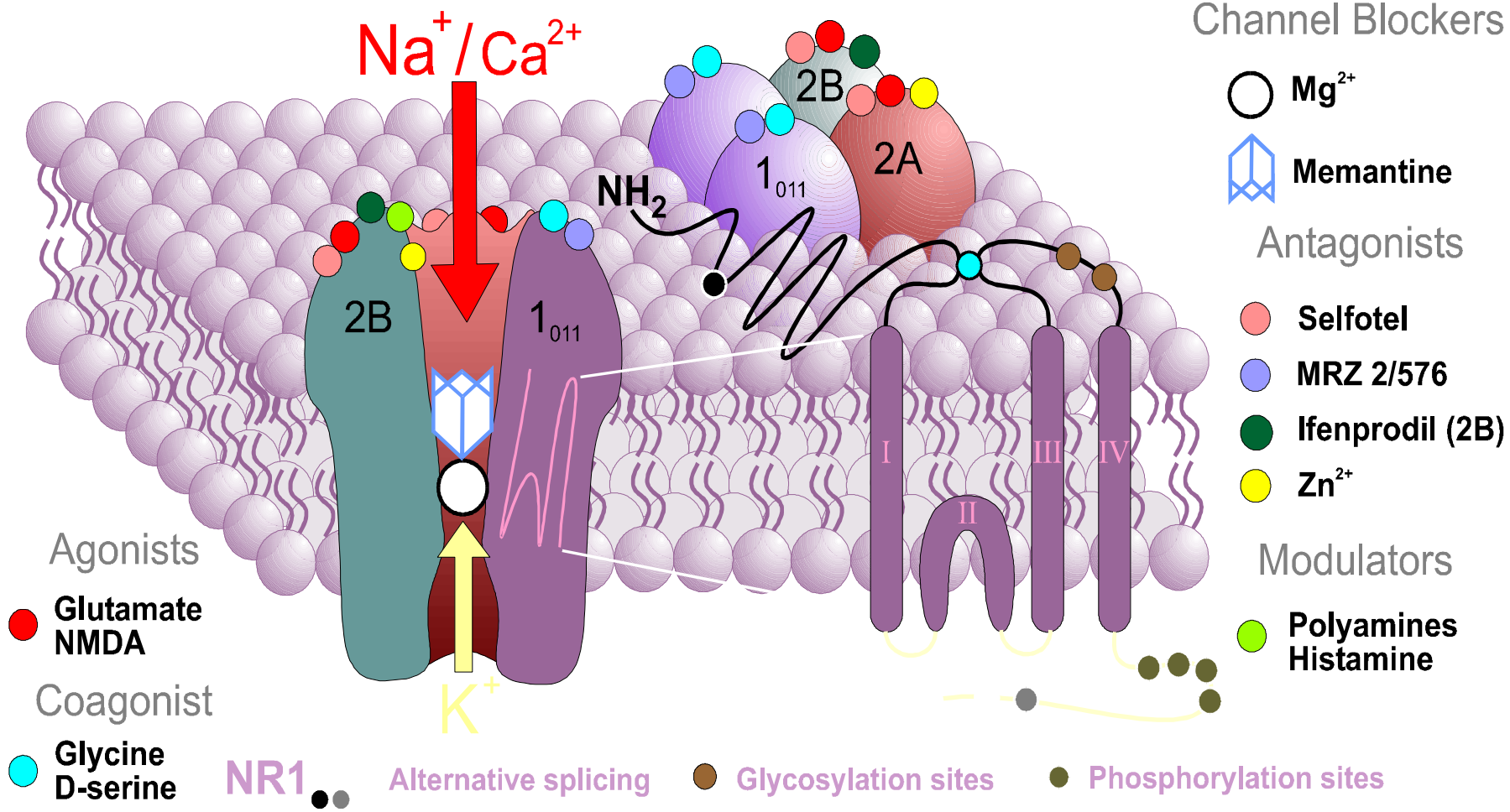
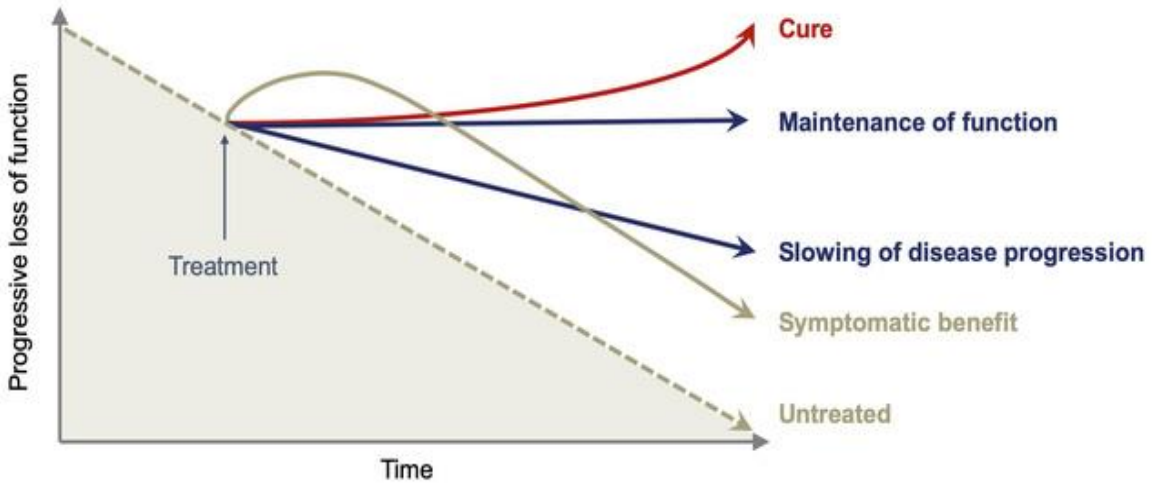


*Parsons, Danysz & Quack (1998) Drug News & Perspectives **11:** 523-569*

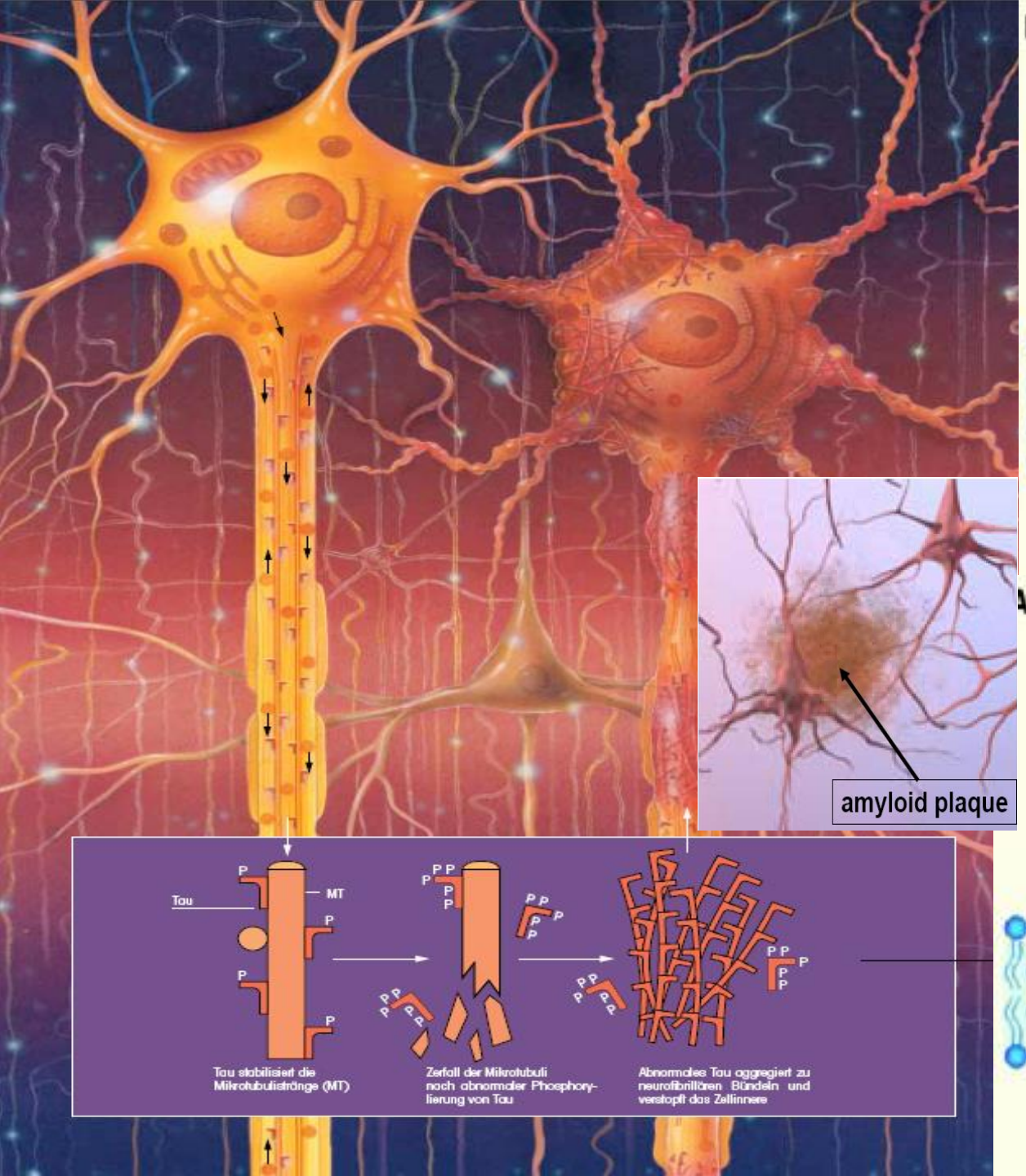
Wird die Zukunft Therapien bringen die die Ursache und nicht nur das Symptom behandeln?

The 'holy grail' – a disease-modifying drug



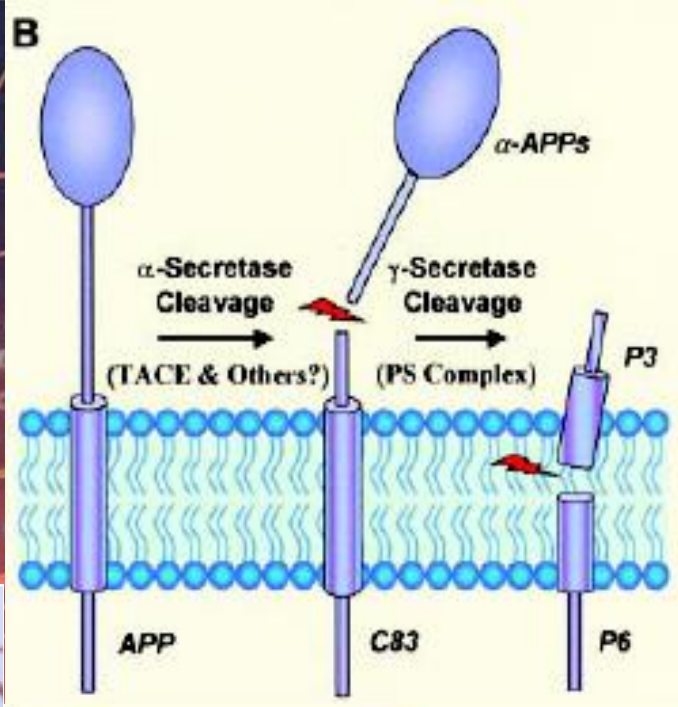
1. Kalia et al. Mov Disord 2015;30(11):1442–1450; 2. Lang & Espay. Mov Disord 2018;33(5) 660–677;
2. Adapted from: Lang. Nat Med 2010;16(11):1223–1226; 3. Adapted from: Van Dam & De Deyn. Nat Rev Drug Discov 2006;5(11):956–970

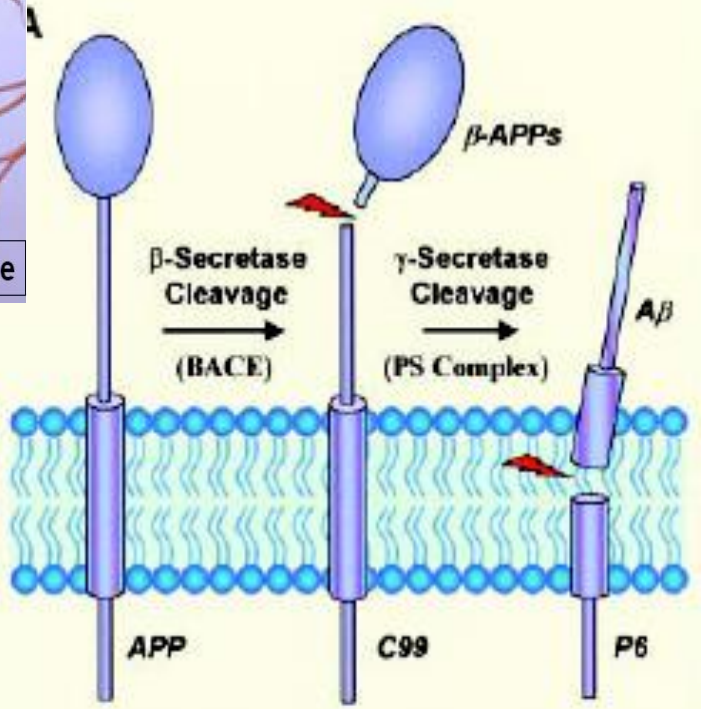
Lundbeck Institute Campus



amyloid plaque

Tau
MT
P
Tau stabilisiert die Mikrotubulistränge (MT)
Zerfall der Mikrotubuli nach abnormaler Phosphorylierung von Tau
Abnormales Tau aggregiert zu neurofibrillären Bündeln und verstopft das Zellinnere


B
α-APPs
α-Secretase Cleavage
(TACE & Others?)
γ-Secretase Cleavage
(PS Complex)
P3
APP
C83
P6


A
β-APPs
β-Secretase Cleavage
(BACE)
γ-Secretase Cleavage
(PS Complex)
Aβ
APP
C99
P6

Aß-directed Therapy 2012-2019

2012[115]	Bapineuzumab	Anti-Aβ MAb	Mild-to-moderate AD	Phase III	2,452	78	LOE	
2012[38]	Avagacestat	γ-Secretase inhibitor	Mild-to-moderate AD	Phase II	209	24	TOX and LOE	Worsens cognition
2012[37]	Avagacestat	γ-Secretase inhibitor	Prodromal AD	Phase II	263	104	TOX and LOE	Worsens cognition
2013[57]	Solanezumab	Anti-Aβ IgG1 MAb	Mild-to-moderate AD	Phase II	2,052	78	LOE	
2013[116]	Vanutide	Aβ antigen	Mild-to-moderate AD	Phase II	245	52	LOE	
2013[117]	Immunoglobulin	Anti-Aβ PAb	Mild-to-moderate AD	Phase III	390	78	LOE	
2013[118]	LY2886721	β-Secretase inhibitor	Mild-to-moderate AD	Phase II	70	26	TOX	
2013[119]	AZD3839	β-Secretase inhibitor	Healthy volunteers	Phase I	54	1	TOX	
2014[41]	Affitope AD02	Aβ antigen	Early AD	Phase II	332	78	LOE	Worsens cognition
2014[120]	CAD-106	Aβ antigen	Mild AD	Phase II	121	90	LOE	Worsens cognition
2014[121]	PBT2	Aβ aggregation inhibitor	Prodromal AD	Phase II	42	52	LOE	
2014[61]	Crenezumab	Anti-Aβ MAb	Mild-to-moderate AD	Phase II	433	73	LOE	Binds oligomeric Aβ
2014[58]	Gantenerumab	Anti-Aβ IgG1 MAb	Prodromal AD	Phase II	797	104	LOE	Binds oligomeric Aβ
2014[59]	Gantenerumab	Anti-Aβ IgG1 MAb	Mild AD	Phase II	387	104	LOE	Binds oligomeric Aβ
2016[5]	Solanezumab	Anti-Aβ IgG1 MAb	Mild AD	Phase III	2,129	80	LOE	
2017[122]	Solanezumab	Anti-Aβ IgG1 MAb	Prodromal AD	Phase III	2,450	104	LOE	
2017[123]	Verubecestat	β-Secretase inhibitor	Mild-to-moderate AD	Phase III	1,958	78	LOE	Worsens cognition
2018[34]	Verubecestat	β-Secretase inhibitor	Prodromal AD	Phase III	1,454	104	LOE	Worsens cognition and behavior
2018[124]	Atabecestat	β-Secretase inhibitor	Cognitively healthy subjects at risk of developing AD	Phase III	600	231	TOX and LOE	Worsens cognition
2018[125]	Lanabecestat	β-Secretase inhibitor	MCI and mild AD	Phase III	2,202	104	LOE	Worsens cognition
2018[125]	Lanabecestat	β-Secretase inhibitor	Mild AD	Phase III	1,899	104	LOE	Worsens cognition

The list is ordered by the year of publication of the main results of the studies.
Aβ = amyloid-β; AD = Alzheimer disease; LOE = lack of efficacy; MAb = monoclonal antibody; MCI = mild cognitive impairment; PAb = polyclonal antibody; TOX = toxicity.

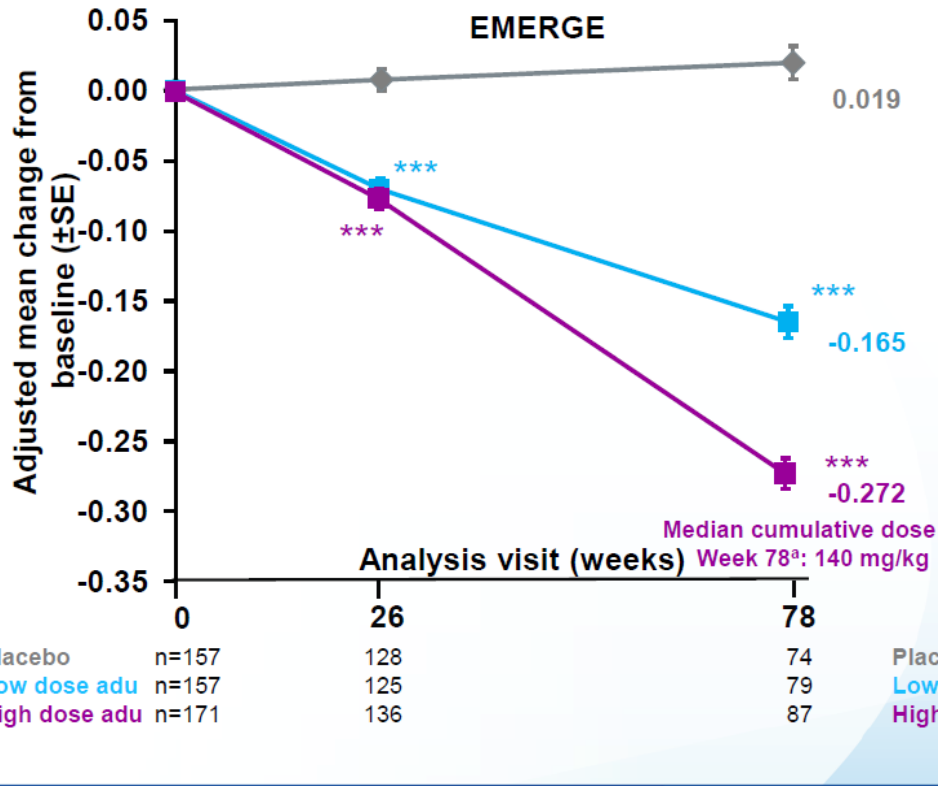
Aducanumab Phase 3 studies EMERGE and ENGAGE

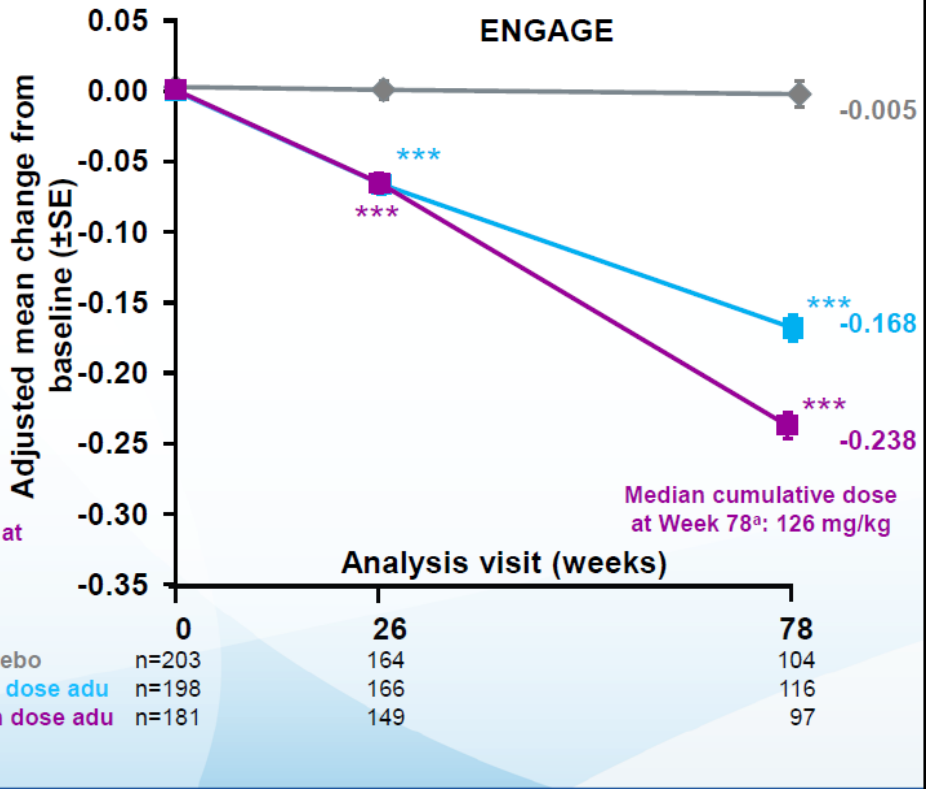
Studies	Two identical,18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	▪ CDR-SB at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers

Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

ADUCANUMAB

Longitudinal change from baseline in amyloid PET SUVR

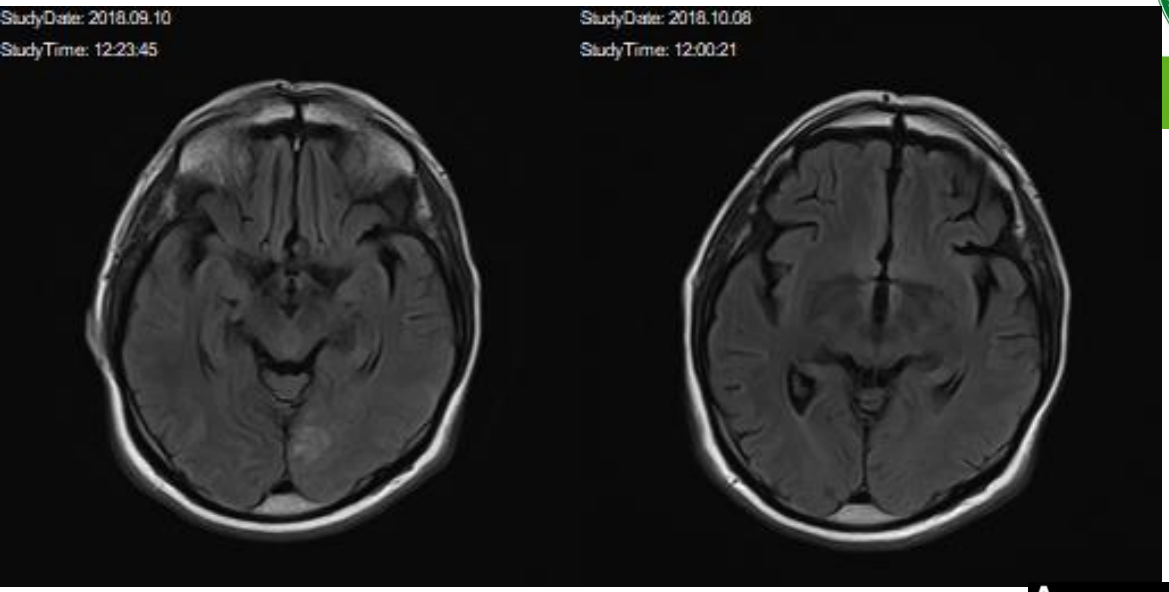




Following study termination based on futility, analysis of a larger dataset showed:

Prespecified primary and secondary endpoints at Week 78

	EMERGE			ENGAGE		
	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value		Placebo decline (n=545)	Difference vs. placebo (%)[a] p-value[b]	
		Low dose (n=543)	High dose (n=547)		Low dose (n=547)	High dose (n=555)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120	1.56	**-0.18** (-12%) 0.2250	**0.03** (2%) 0.8330
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493	-3.5	**0.2** (-6%) 0.4795	**-0.1** (3%) 0.8106
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097	5.140	**-0.583** (-11%) 0.2536	**-0.588** (-11%) 0.2578
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006	-3.8	**0.7** (-18%) 0.1225	**0.7** (-18%) 0.1506



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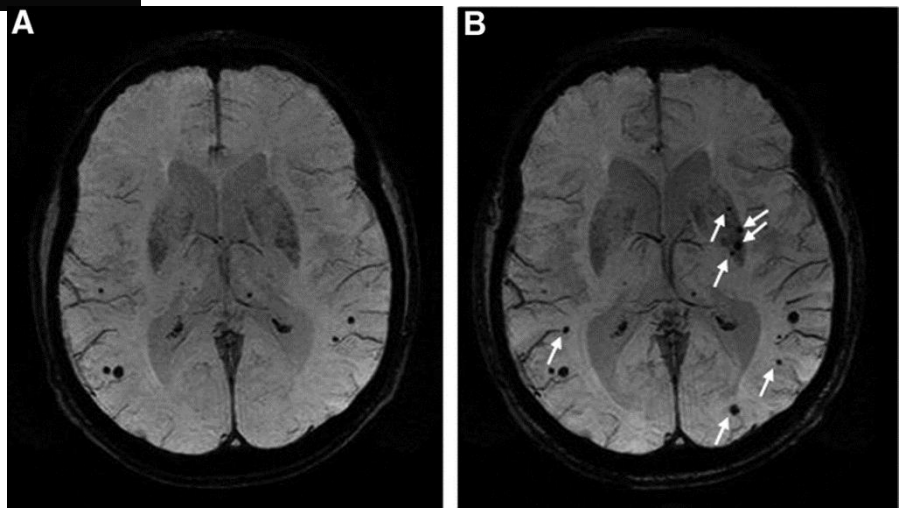
Progression von zerebralen Mikrobltungen

ARIA-E bei einem Patienten unseres Zentrums 6 Monate nach Aducanumabinitiierung und Normalisierung innerhalb eines Monats nach Absetzen.



FDA NEWS RELEASE

FDA Grants Accelerated Approval for Alzheimer's Drug

June 7, 2021

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Today, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. Aduhelm was approved using the accelerated approval pathway, which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit.

The accelerated approval of Aduhelm is based on the surrogate endpoint of reduction of amyloid beta plaque in the brain—a hallmark of Alzheimer's disease.

Under the accelerated approval provisions, which provide patients suffering from the disease earlier access to the treatment, the FDA is requiring the company, Biogen, to conduct a new randomized, controlled clinical trial to verify the drug's clinical benefit. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

LANDMARK ALZHEIMER'S DRUG APPROVAL CONFOUNDS RESEARCH COMMUNITY

Many scientists say there is not enough evidence that Biogen's aducanumab is an effective therapy for the disease.

Desperate need

'Problematic data set'

Post-approval trial

US$56,000 | year per person for the drug. If 5% of 6 million people with Alzheimer's in the United States received the treatment, the drug's revenue would reach nearly $17 billion per year. This would make it the second top-selling drug, by current revenues.

Ripple effects

With a pathway to approval established, drug developers are likely to double down on anti-amyloid drugs. Drug companies Eli Lilly, Roche and Eisai already have anti-amyloid antibodies in phase III trials. They, too, might now be able to secure approvals with evidence of amyloid-lowering activity, regardless of the compounds' effects on cognition.

News & Analysis

Medical News & Perspectives

Recently Approved Alzheimer Drug Raises Questions That Might Never Be Answered

Rita Rubin, MA

JAMA August 10, 2021 Volume 326, Number 6 469

In its approval letter to Biogen, the FDA said the postmarket trial must be completed by August 2029 with the final report of its findings due in February 2030—more than 8½ years after approval. In a June 23 statement, Biogen and Eisai said they were "working with urgency" toward completing the confirmatory trial ahead of the 2029 deadline.

A month after the FDA approved aducanumab, though, the agency changed the indications section on the drug's label. Instead of anyone with Alzheimer disease, treatment should be initiated only in patients with mild cognitive impairment (MCI) due to Alzheimer disease or mild Alzheimer disease—the populations studied in the clinical trials.

"I understand the critics, and I love them. They're my friends and my colleagues," Salloway said in an interview.

"I don't happen to agree with their interpretation of the same data set."

Of 17 patients he's observed receiving long-term aducanumab therapy—first in the phase 1 trial and then in the open-label extension—10 have been more stable than expected, Salloway said, adding that he doesn't have data about whether the more stable patients had better amyloid clearance than those whose disease advanced more.

"Progress is often controversial," he said. "The data have issues, no doubt about it."

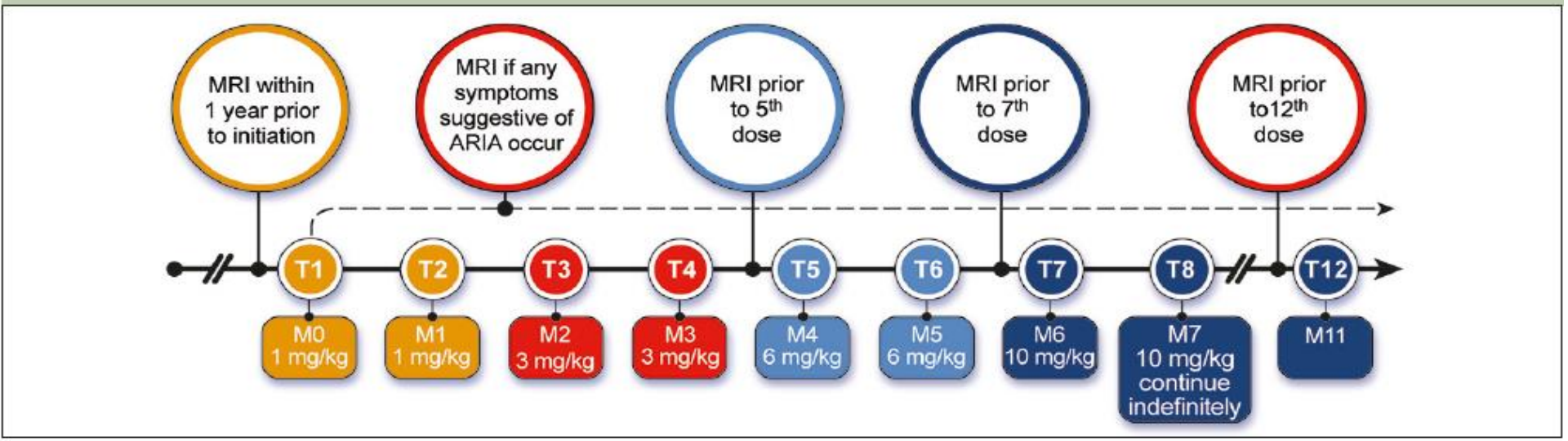
Define "Benefit"

However, Biogen presented no convincing evidence that correlated biomarker changes to cognitive benefits, noted a perspective article published online last November and coauthored by Mayo Clinic neurologist David Knopman, MD, 1 of the 3 members who resigned from the advisory committee after the FDA approved aducanumab. Knopman was recused from the meeting at which the drug was reviewed because he served as a site investigator for 1 of its phase 3 trials.

Table 2. Criteria for a positive amyloid PET for the three approved amyloid PET tracers (from drugs@FDA: FDA-Approved Drugs)

PET Tracer	Criteria for Interpreting as a Positive Scan
Florbetapir (Amyvid™)	A positive scan will have either: Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent gray-white contrast; OR, one or more areas in which gray matter radioactivity is intense and clearly exceeds radioactivity in adjacent white matter.
Florbetaben (Neuraceq™)	β-amyloid positive - smaller area(s) of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin involving the majority of the slices within at least one of the four brain regions ("moderate" β-amyloid deposition), or a large confluent area of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin and involving the entire region including the majority of slices within at least one of the four brain regions.
Flutemetamol (Vizamyl™)	Positive scans show at least one cortical region with reduction or loss of the normally distinct grey-white matter contrast. These scans have one or more regions with increased cortical grey matter signal (above 50-60% peak intensity) and/or reduced (or absent) grey- white matter contrast (white matter sulcal pattern is less distinct). A positive scan may have one or more regions in which grey matter radioactivity is as intense or exceeds the intensity in adjacent white matter.

Figure 1. Aducanumab dosing and MRI monitoring schedule (Prescribing Information (1) and Expert Panel recommendation; © J Cummings; illustrator M de la Flor, PhD)



Perspektiven

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- Hoher Trainings und Ausbildungsstand der Behandelnden erforderlich um nachteilige Konsequenzen zu verhindern
- Wachsender Bedarf für Alzheimer-Spezialist* innen aller Professionen und von Equipment.
- Effekte auf klinisches Trial Designs und Zulassungsverfahren
  - 2 Wochen nach der Zulassung von Aducanumab designierte die FDA bereits 2 andere Amyloid-Antiköper als “Fast-Track Breakthrough Therapies” (Lecanemab und Lilly´s Donanemab)