"Alzheimer's Disease and the need of New Technologies"

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Hellenic Alzheimer Foundation

Among the 10 more important medical topics on AGEING

The first is:

Dementia

J MORLEY J Gerontol A Biol Sci Med Sci 2004; 59: 24-33

Outline

- Epidemiology-Ageing: E-Education
- Diagnosis (MCI and AD)
- Prevention
- Current Management
  - Pharmacological
  - Non-Pharmacological
- Future Directions

Prevalence in Greece

- Municipality of Pylea
- Total 9,5% >70, (1992-94)

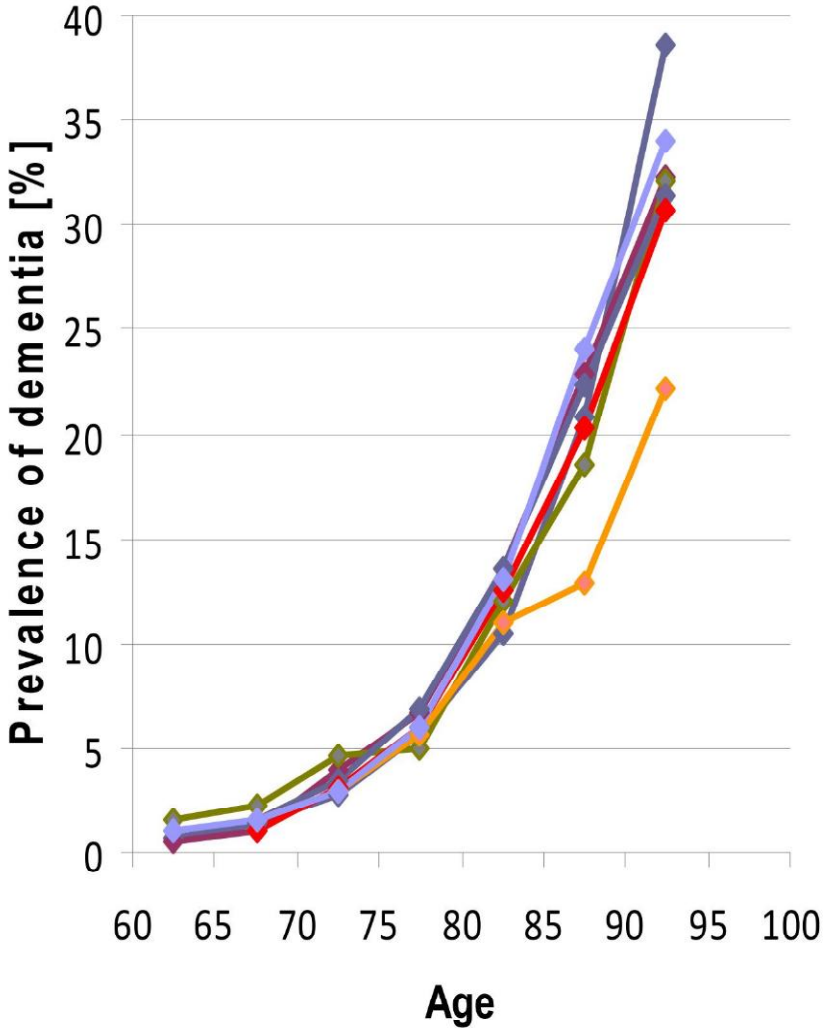
- Municipality of Alexander the Great
- Total 3,6% >65 (2009)

- Tsolaki M et al. 1999, 2010, 2013

Prevalence in Crete, 2012

- 8 villages
- Mountain area of Rethymnis
- 546 live in other towns
- 468 were absent
- 170 denied to respond
- 8 had dementia
- 534 responded

Prevalence of dementia according to the main published meta-analyses

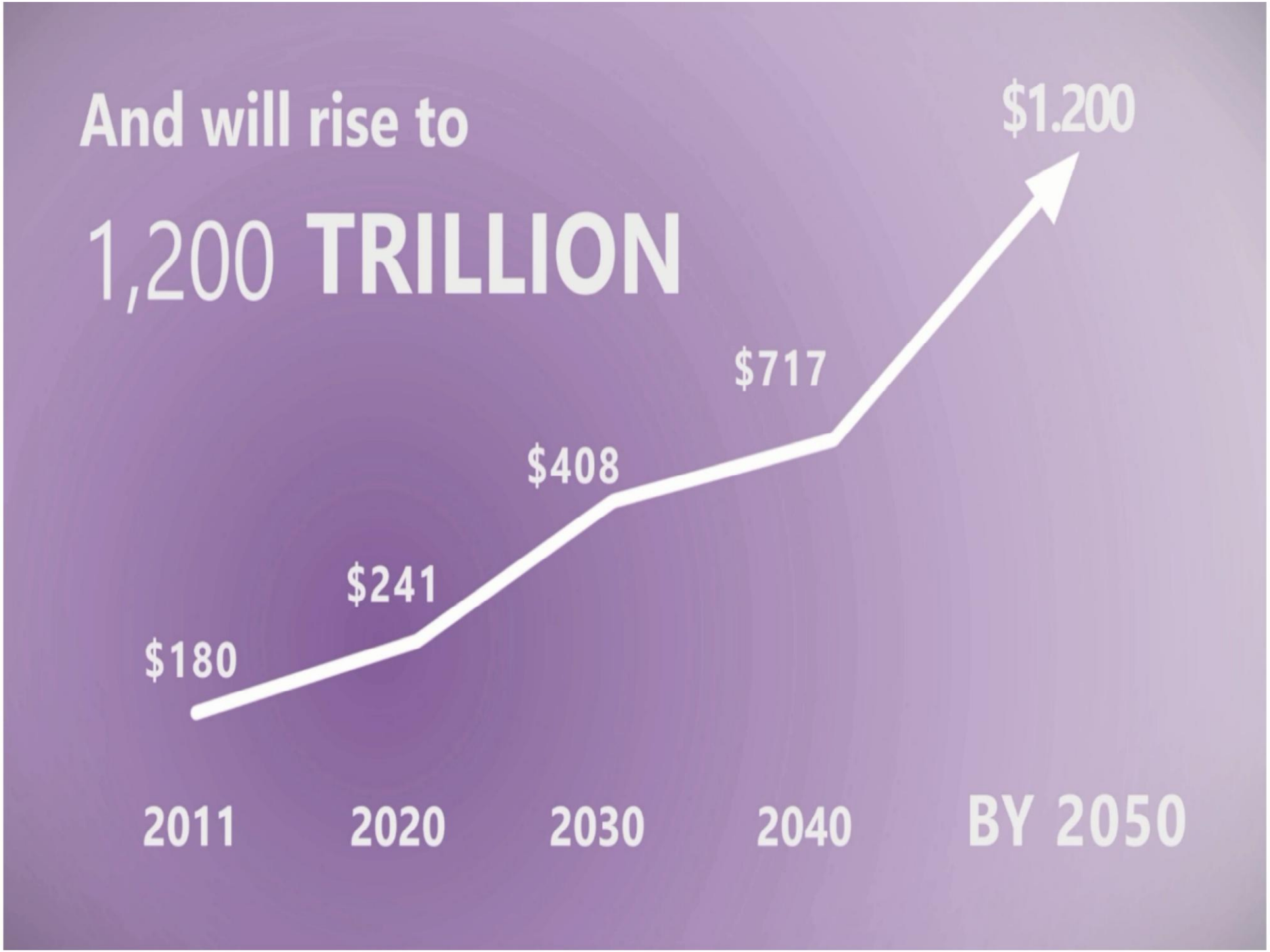


AGE
is the main risk factor of dementia

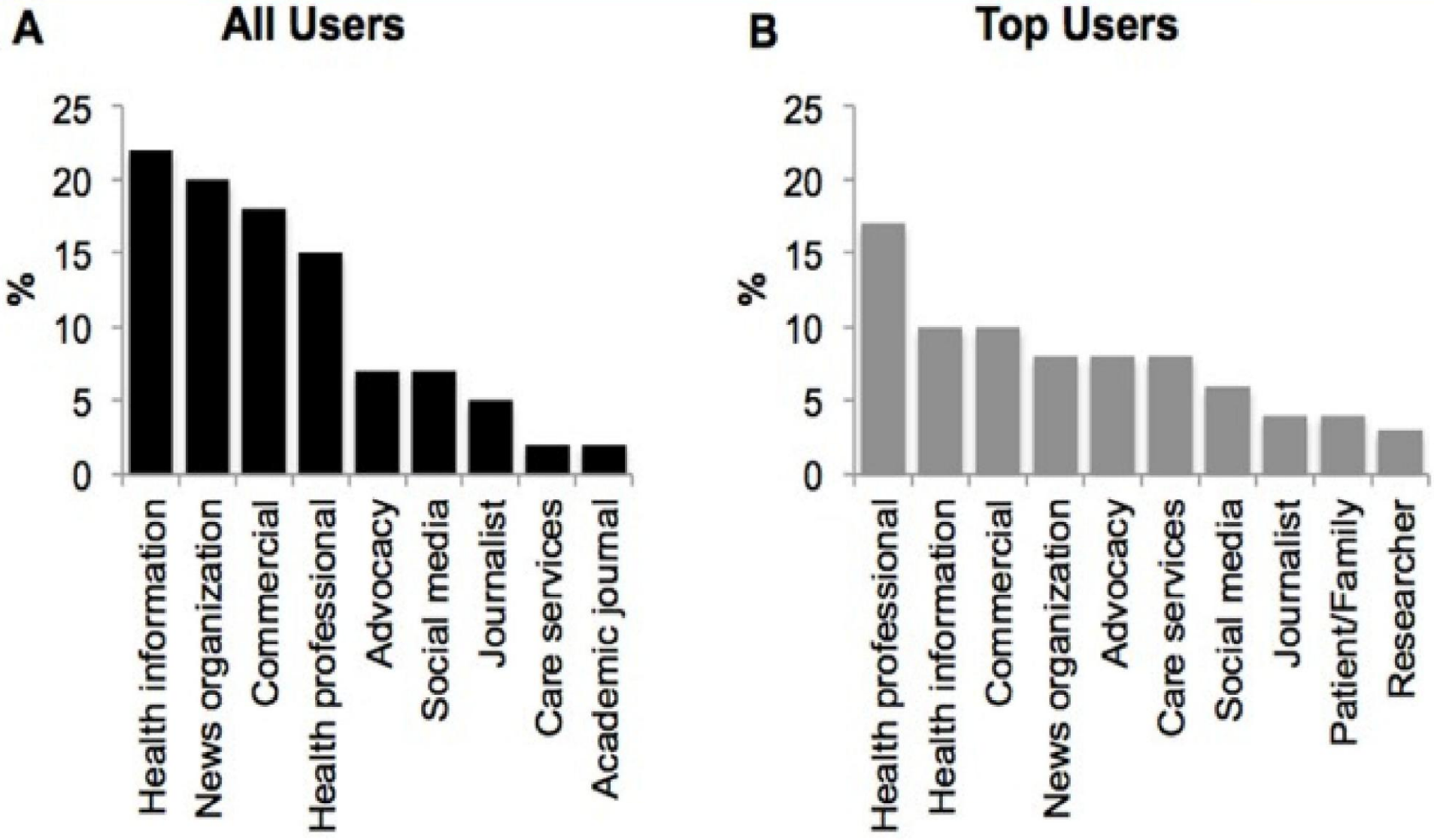
- Jorms et al (1987), Female + male
- Hofman et al (1991), Female
- Hofman et al (1991), Male
- Ritchie and Kildea (1995), Female + male
- Lobo et al (2000), Female
- Lobo et al (2000), Male
- Fratiglioni and Rocca (2001) Female + male

From FR HERRMANN, JP MICHEL and JM ROBINE Springfield/Hong Kong Congress 2008


Every 68:00”
One person is diagnosed with Alzheimer’s Disease


And will rise to
1,200 TRILLION
$1.200
$717
$408
$241
$180
2011
2020
2030
2040
BY 2050

Aging 2.0: Health Information about Dementia on Twitter.



Numbers in Greece (Our experience)

- Only 5% of elderly know to use PC
- Only 15% have used PC in Day Centers

- **But**
- 90% believe that the use of PC can help them
- 100% say that it is very easy
- 100% want to use it again

1st Question
New technology and

- **Privacy and security:** How can technology help people with dementia share health-related information while addressing privacy and security concerns that families have about home monitoring?

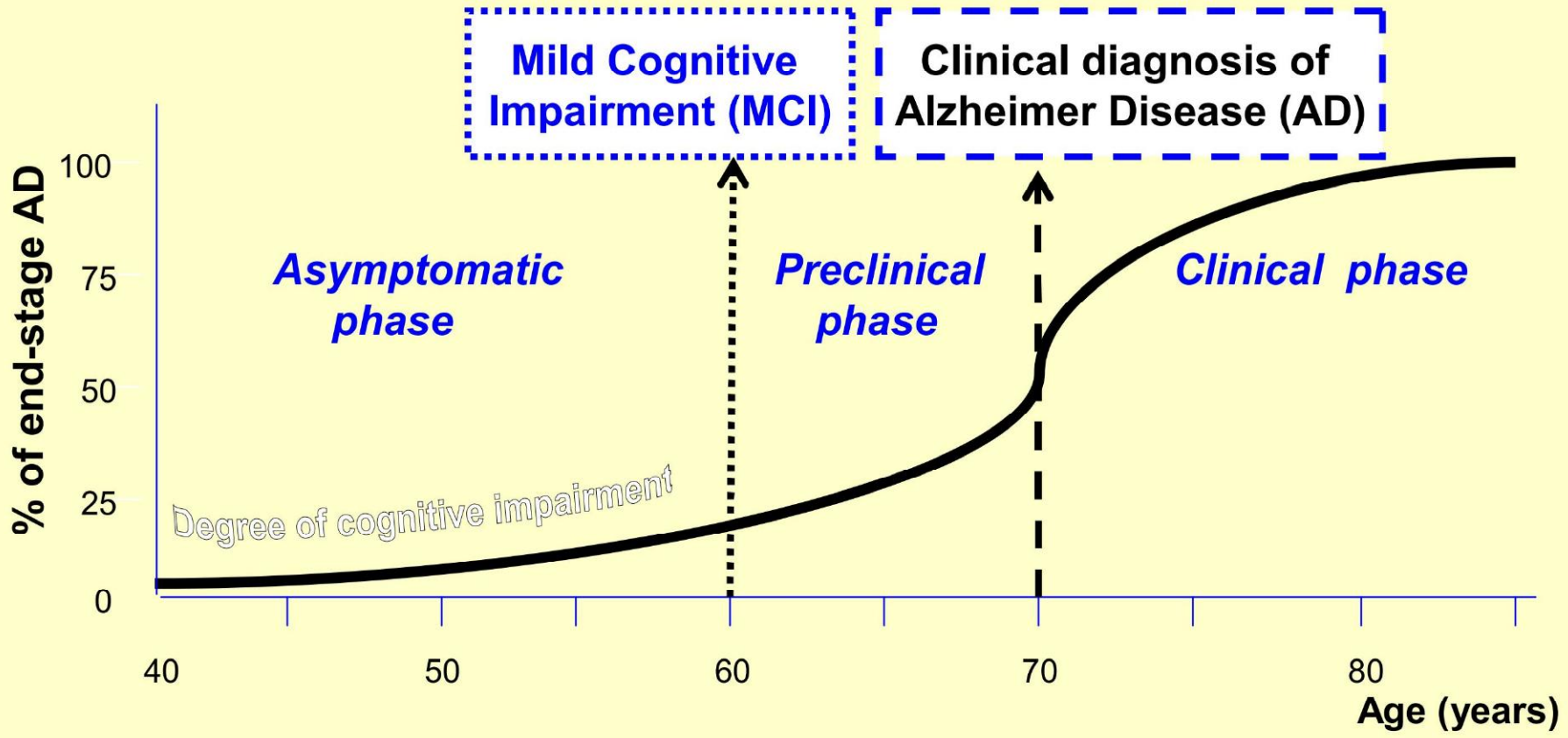
2nd Question

What happens with Aging?
Can we change it?
Can we do something more than education with new technologies?

Outline

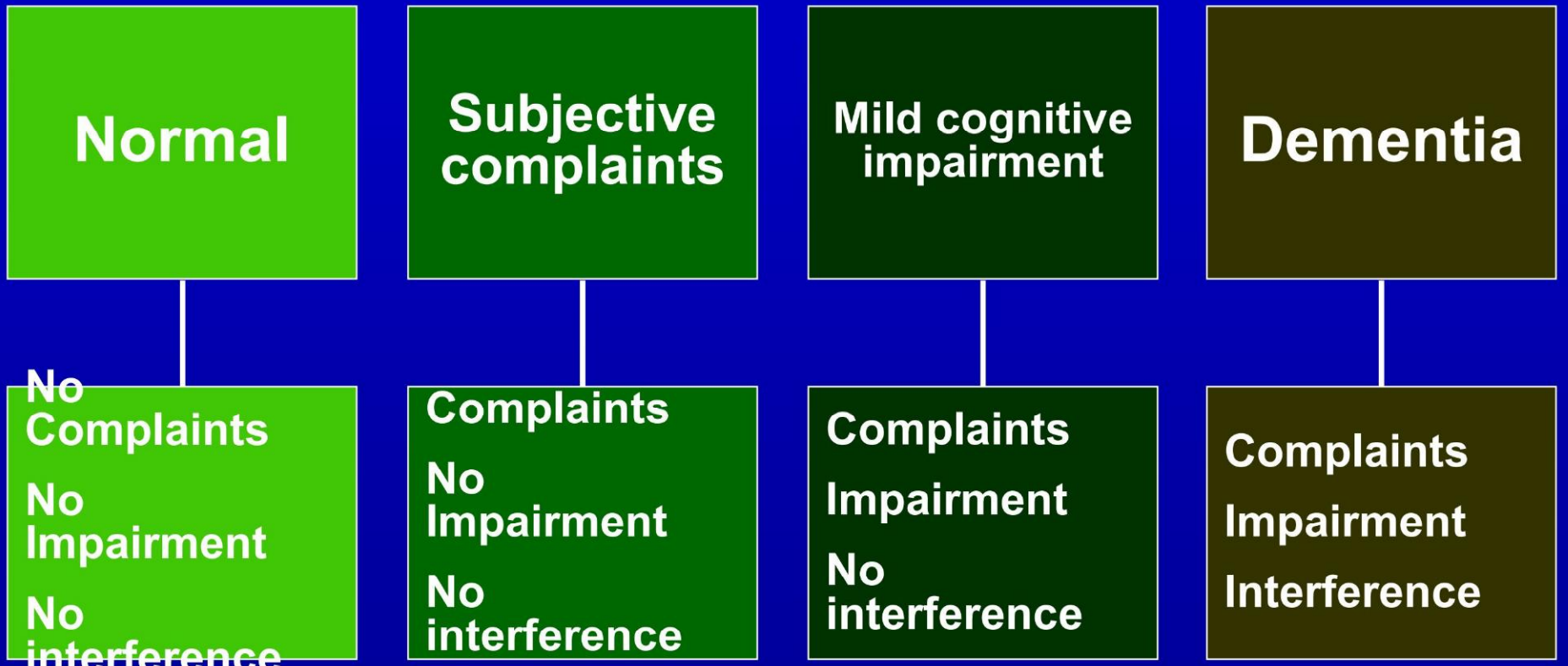
- Epidemiology-Age-**Education**
- Diagnosis (MCI and AD)
- Prevention
- Current Management
  - Pharmacological
  - Non-Pharmacological
- Future Directions

Alzheimer´s Disease
A Lifelong Commitment



Modified from PJ VISSER 2000 and M KIPIVELTO 2005

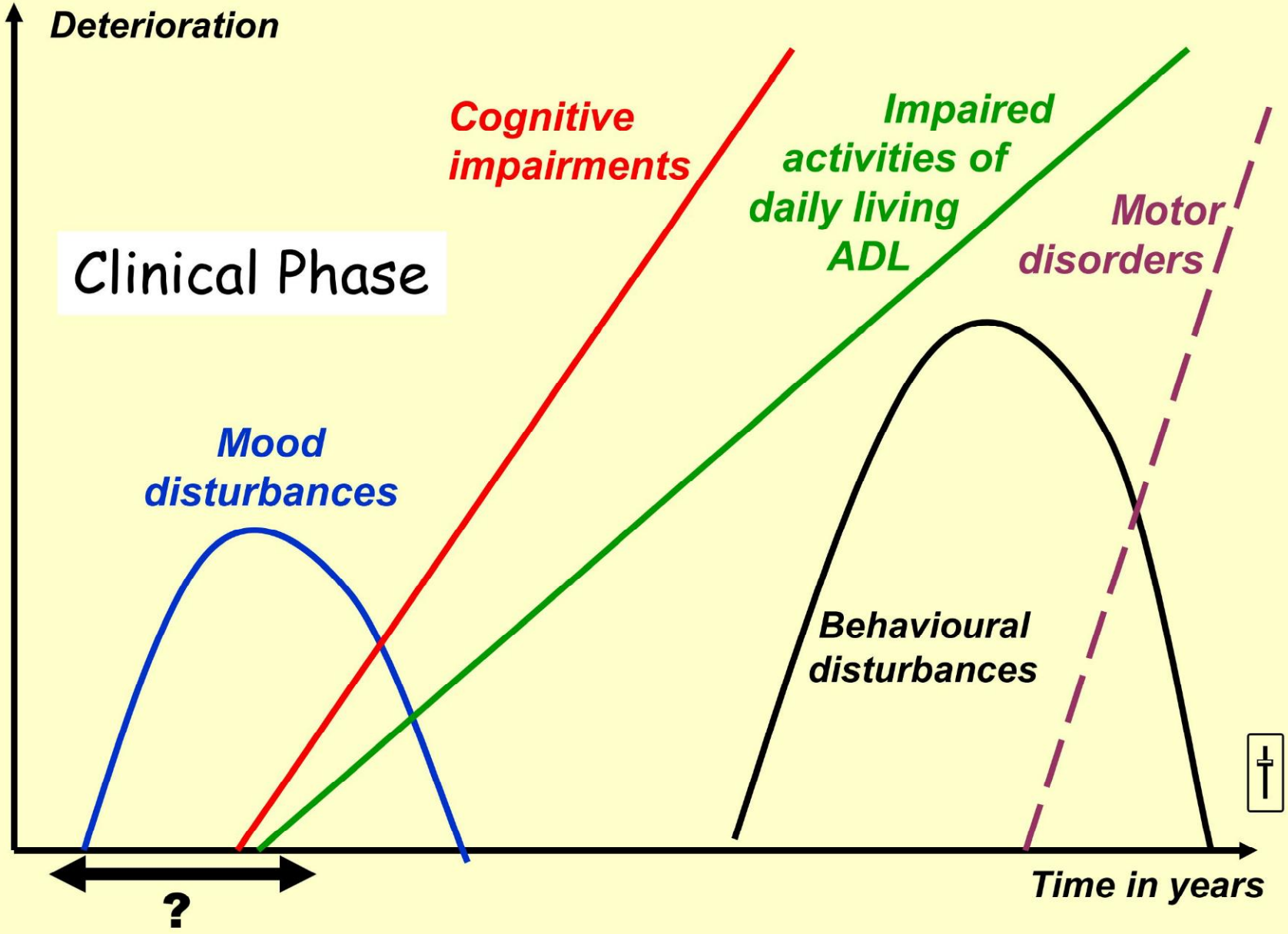
What is MCI? (P. Visser, 2010)



Outline

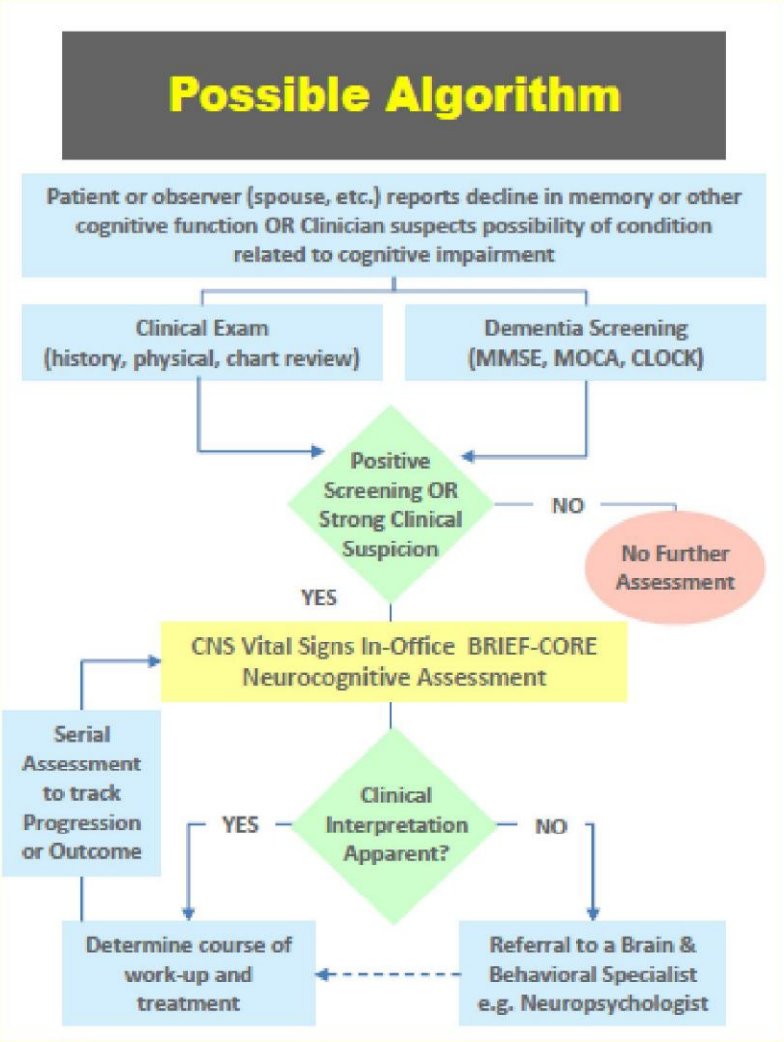
- Epidemiology-**Education**
- Diagnosis (MCI and AD), **Neuropsychology**, **Genetics, Neuroimaging**
- Prevention-
- Current Management
  - Pharmacological
  - Non-Pharmacological
- Future Directions

Alzheimer Disease Progression



From S GAUTHIER 1996

CNS Vital Signs



Mindstreams

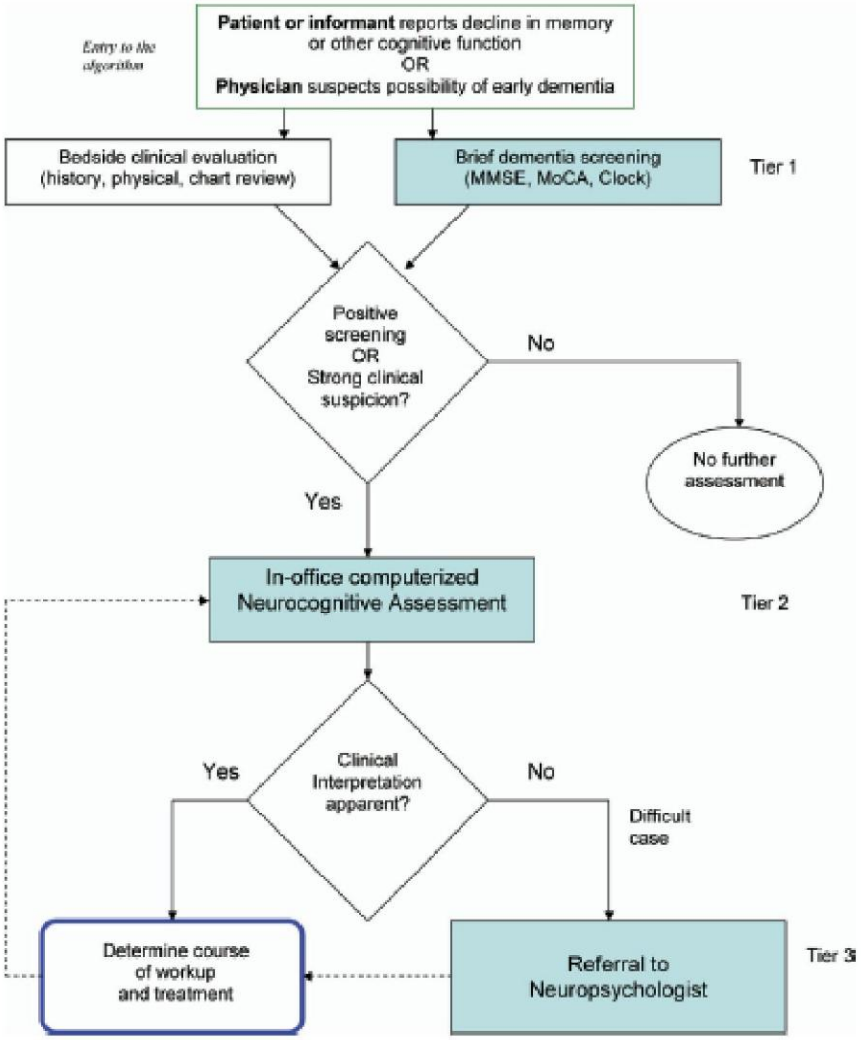


Fig. 4. Diagnostic algorithm. Three-tier clinical algorithm for evaluation of cognitive impairment in the elderly.

Cognitive Function Test

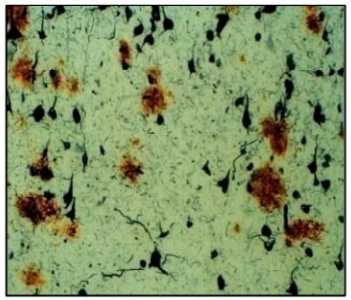
Our Experience (Collaboration program)

Cognitive Tests with PC	Our new efforts
CAMCOG-CAT ***ANAM*** ***CANTAB*** ***CNSVS*** ***CogniScreen*** ***CALLS*** ***COGDRAS*** ***CSI*** ***COGselftest*** ***CogState*** ***CNTB*** ***CANS-MCI*** ***CAMCI*** ***MCI Screen*** ***MicroCog*** ***Mindstreams*** ***TDAS*** CAT Cognitive Function test	Amsterdam for ADL Salonica Test for ABC

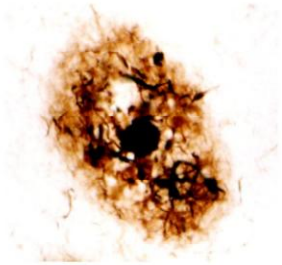
3rd Question

- **Early detection:** How can caregivers capture behavioral data from everyday devices like cell phones and home camera systems?

Alzheimer ‘s disease



Beta-amyloid plaques



Neurofibrillary Tangles

Genetic Factors

Environmental Factors

Mutations

- APP (Chr. 21)
- Presenilin 1 (Chr. 14)
- Presenilin 2 (Chr. 1)

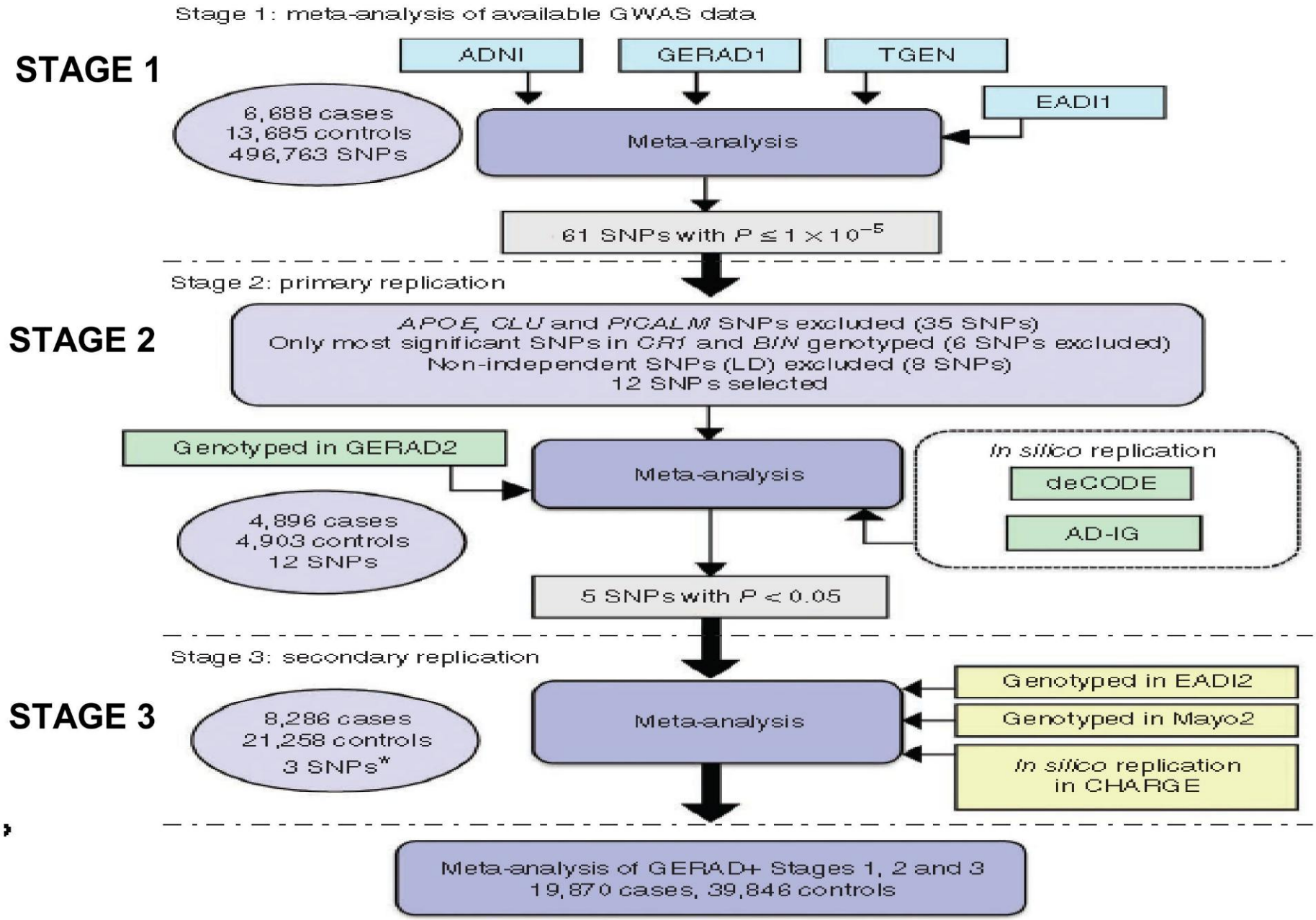
Genetic Risk Factors

- ApoE4 (Chr. 19)
- CR1, PICALM, CLU, Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP, TREM2

- High cholesterol
- High blood pressure
- Smoking
- Omocystinaemia
- Diabetes Mellitus
- Physical inactivity

Familial AD
1-5% of cases
- Early onset (35-65 y.)

Sporadic AD
- 95-99 % of cases
- Late onset (>65 y.)

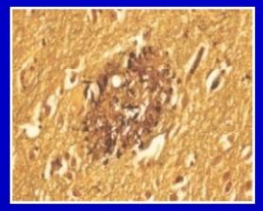

Stage 1: meta-analysis of available GWAS data
STAGE 1
ADNI
GERAD1
TGEN
EADI1
6,688 cases
13,685 controls
496,763 SNPs
Meta-analysis
61 SNPs with $P \leq 1 \times 10^{-5}$
Stage 2: primary replication
STAGE 2
APOE, CLU and PICALM SNPs excluded (35 SNPs)
Only most significant SNPs in CR1 and BIN genotyped (6 SNPs excluded)
Non-independent SNPs (LD) excluded (8 SNPs)
12 SNPs selected
Genotyped in GERAD2
Meta-analysis
In silico replication
deCODE
AD-IG
4,896 cases
4,903 controls
12 SNPs
5 SNPs with $P < 0.05$
Stage 3: secondary replication
STAGE 3
8,286 cases
21,258 controls
3 SNPs*
Meta-analysis
Genotyped in EADI2
Genotyped in Mayo2
In silico replication
in CHARGE
Meta-analysis of GERAD+ Stages 1, 2 and 3
19,870 cases, 39,846 controls

Alzheimer's disease

Genes

Environment

Abnormal beta amyloid processing

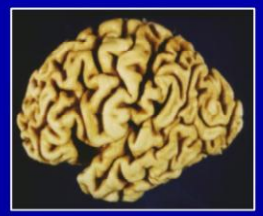


Plaques

Neuronal dysfunction

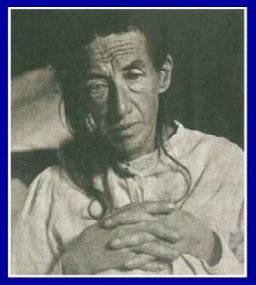
Tangles

Neuronal death



Atrophy

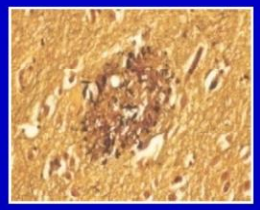
Impaired cognition



Memory loss

Alzheimer's disease

Abnormal beta amyloid processing



Plaques

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Neuronal dysfunction

Tangles

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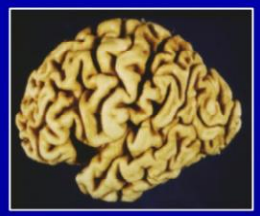
Neuronal death



Atrophy

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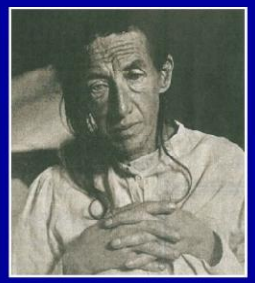
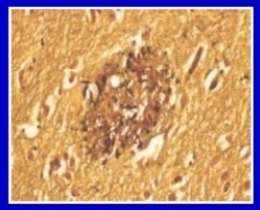
Impaired cognition



Memory loss

Alzheimer's disease

Abnormal beta amyloid processing



Plaques →

PET scanner

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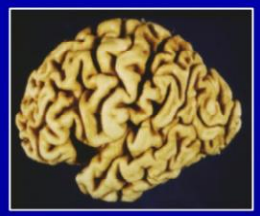
Neuronal dysfunction

Tangles

↓

Neuronal death



Atrophy

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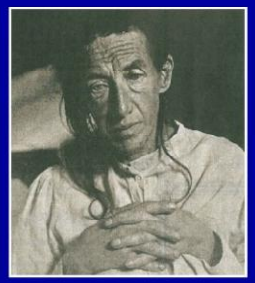
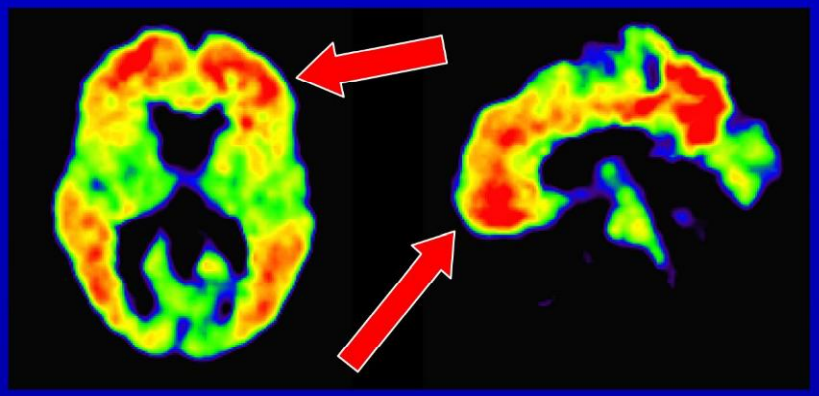
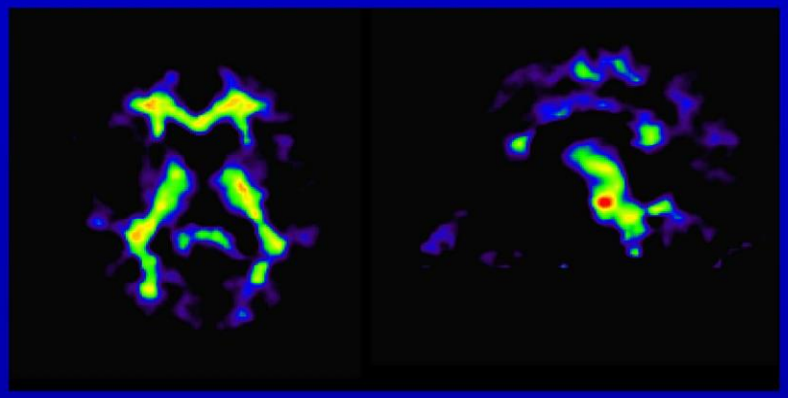
Impaired cognition



Memory loss

PET PiB scan



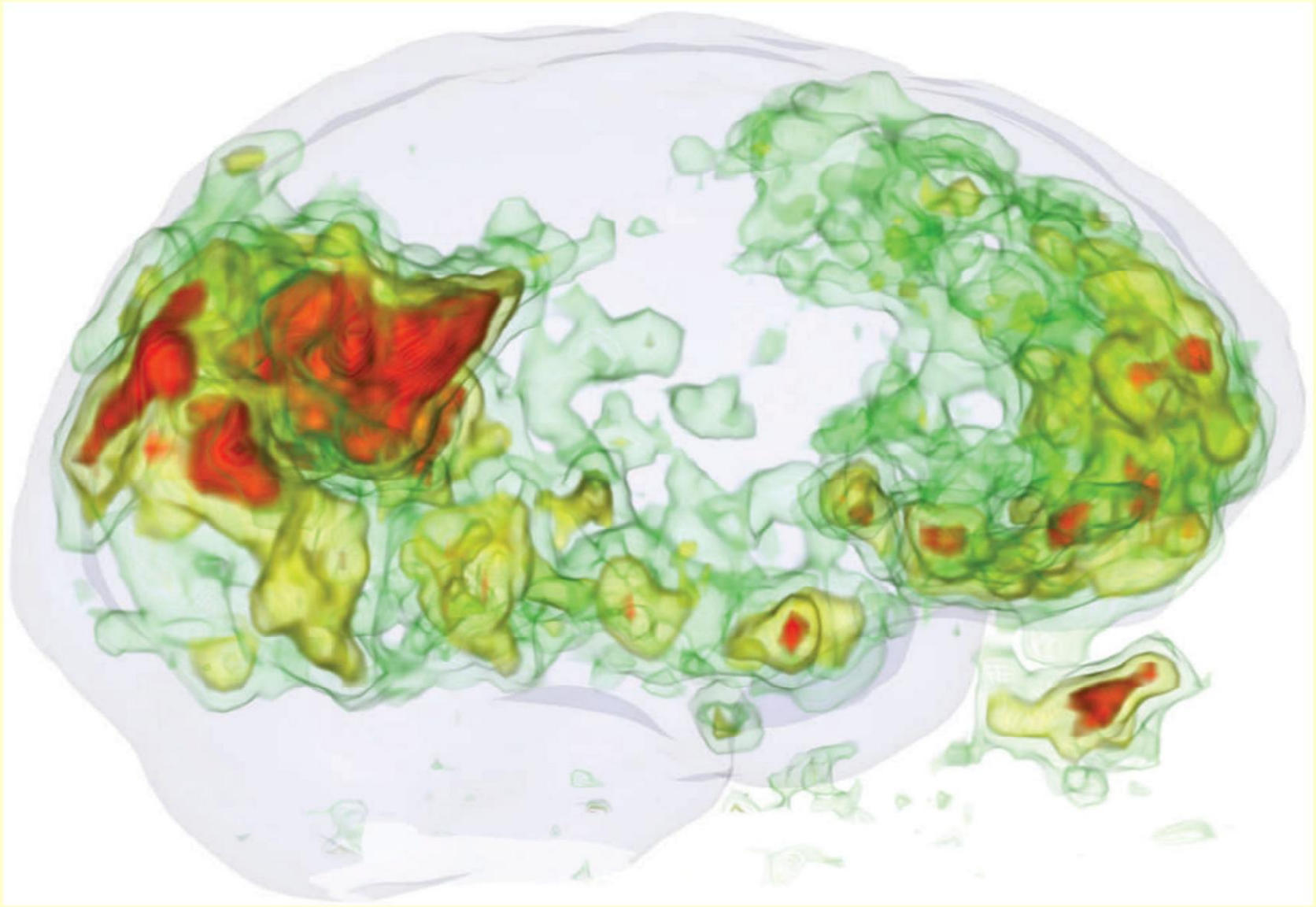


Alzheimer

Control

Plaques

PIB PET ⇨ Ligands bind to amyloid peptides



IKONOMOVIC MD et al Brain 2008; 131: 1630-45

Alzheimer's disease

Abnormal beta amyloid processing

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Neuronal dysfunction

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Neuronal death

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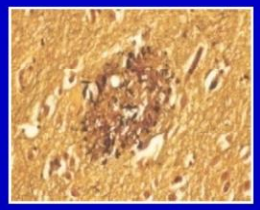
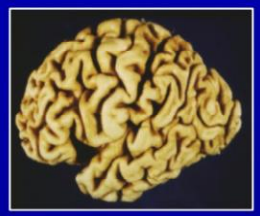
Impaired cognition

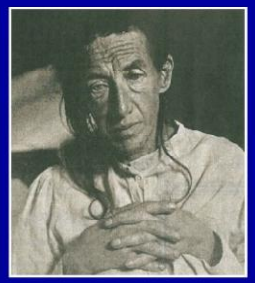


Plaques

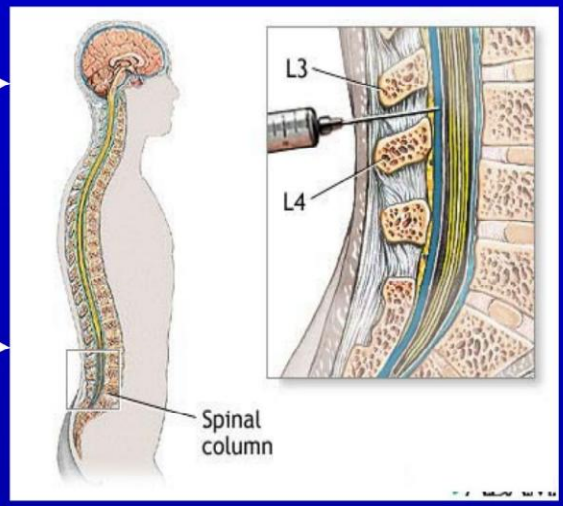
Tangles



Atrophy

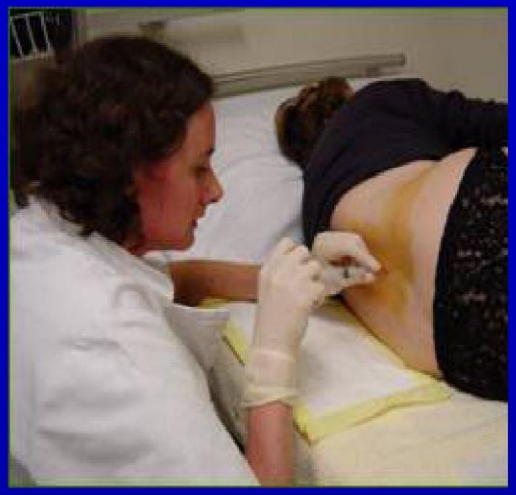


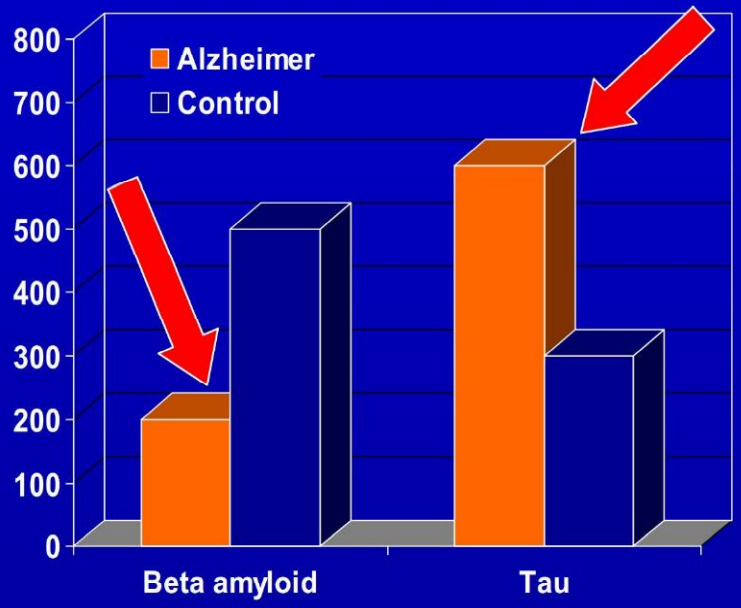
Memory loss



Lumbar puncture

Lumbar puncture

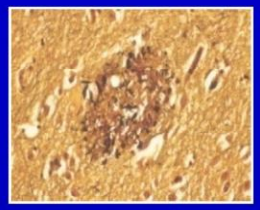




Markers in cerebrospinal fluid

Alzheimer's disease

Abnormal beta amyloid processing



Plaques

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Neuronal dysfunction

Tangles

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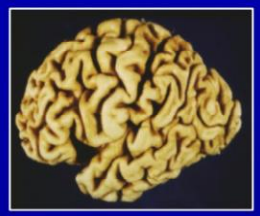
Neuronal death



Atrophy →

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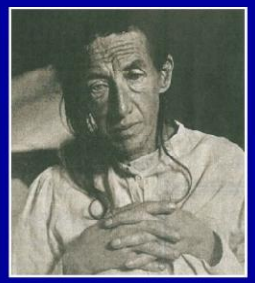
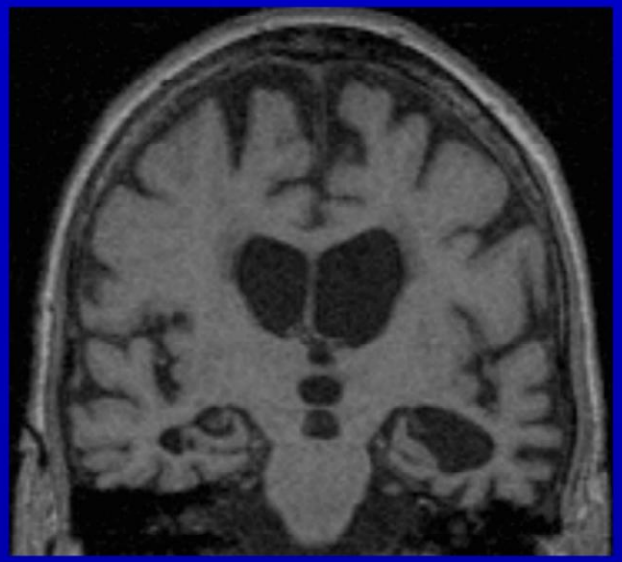
Impaired cognition



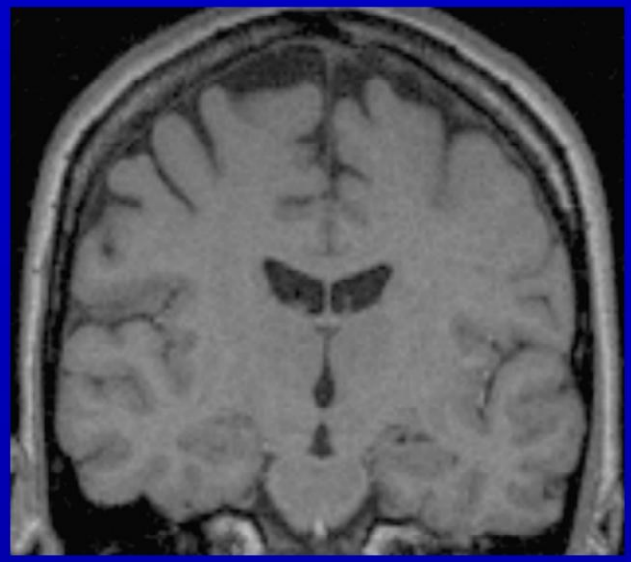
Memory loss

MRI scanner

MRI scan



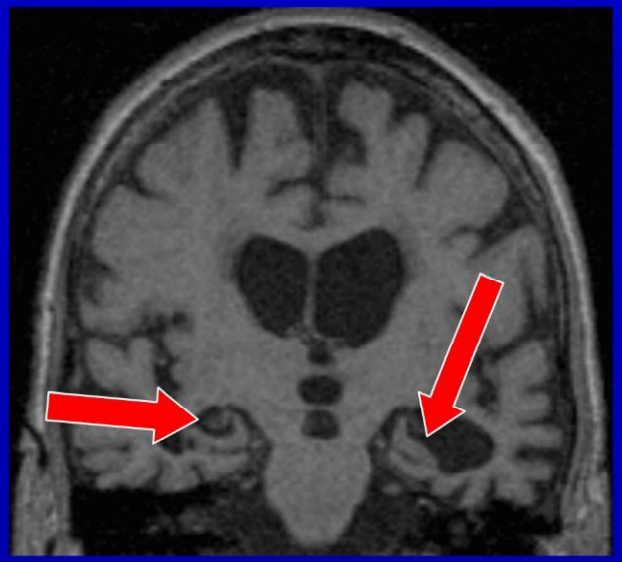
Alzheimer



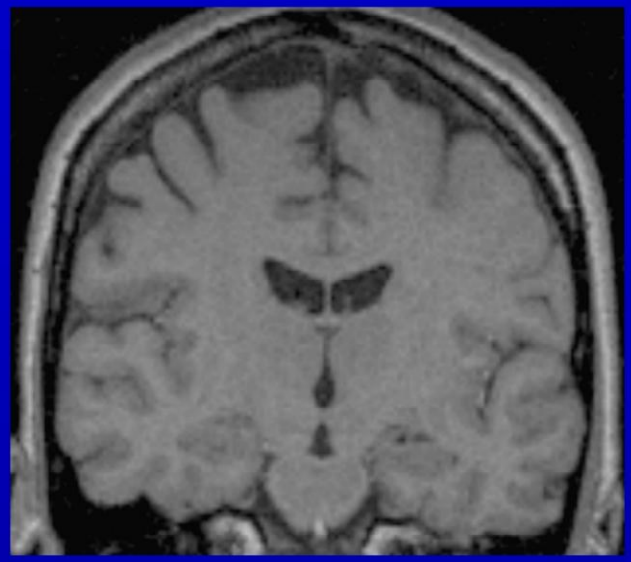
Control

Atrophy

MRI scan



Alzheimer



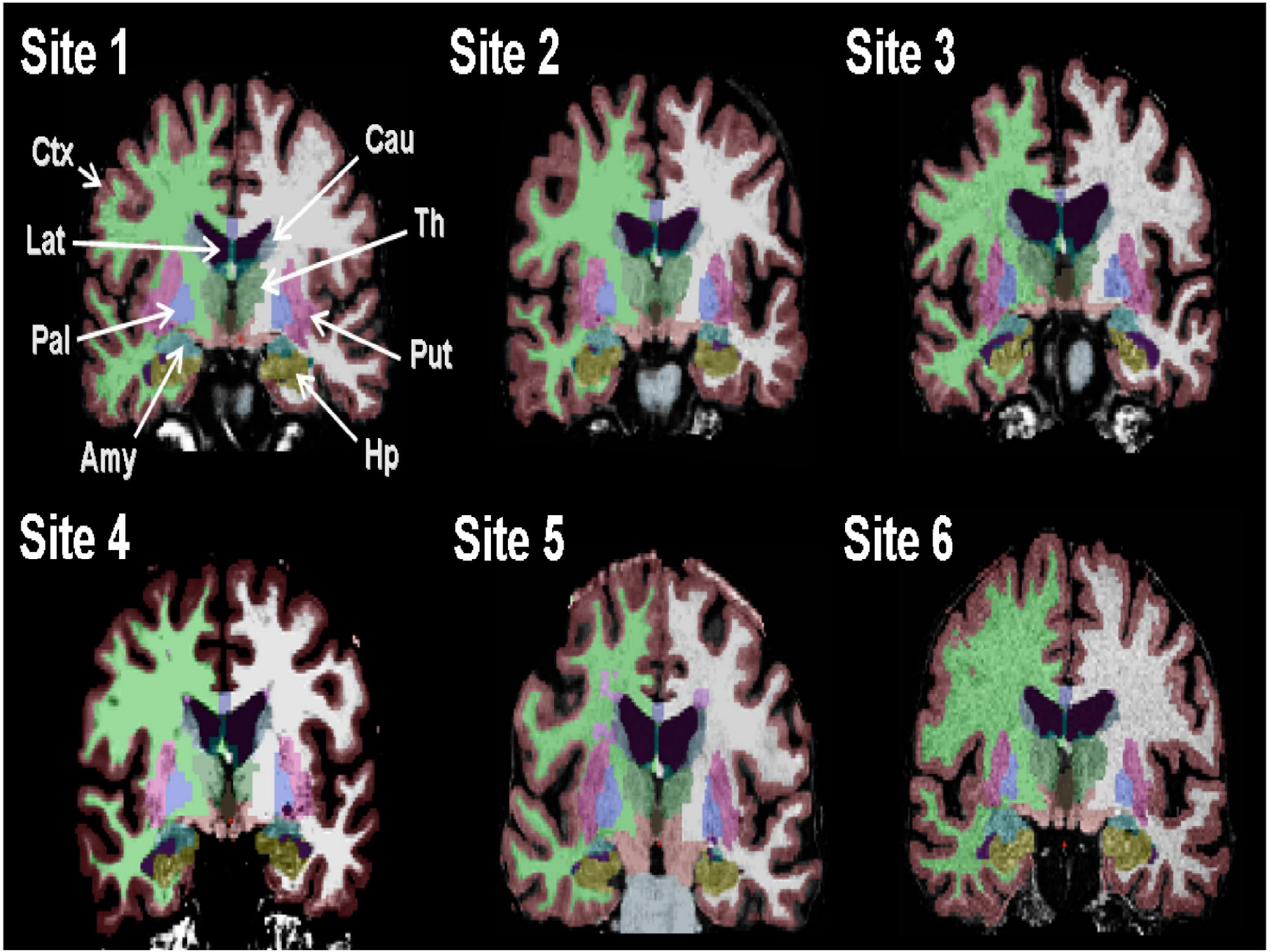
Control

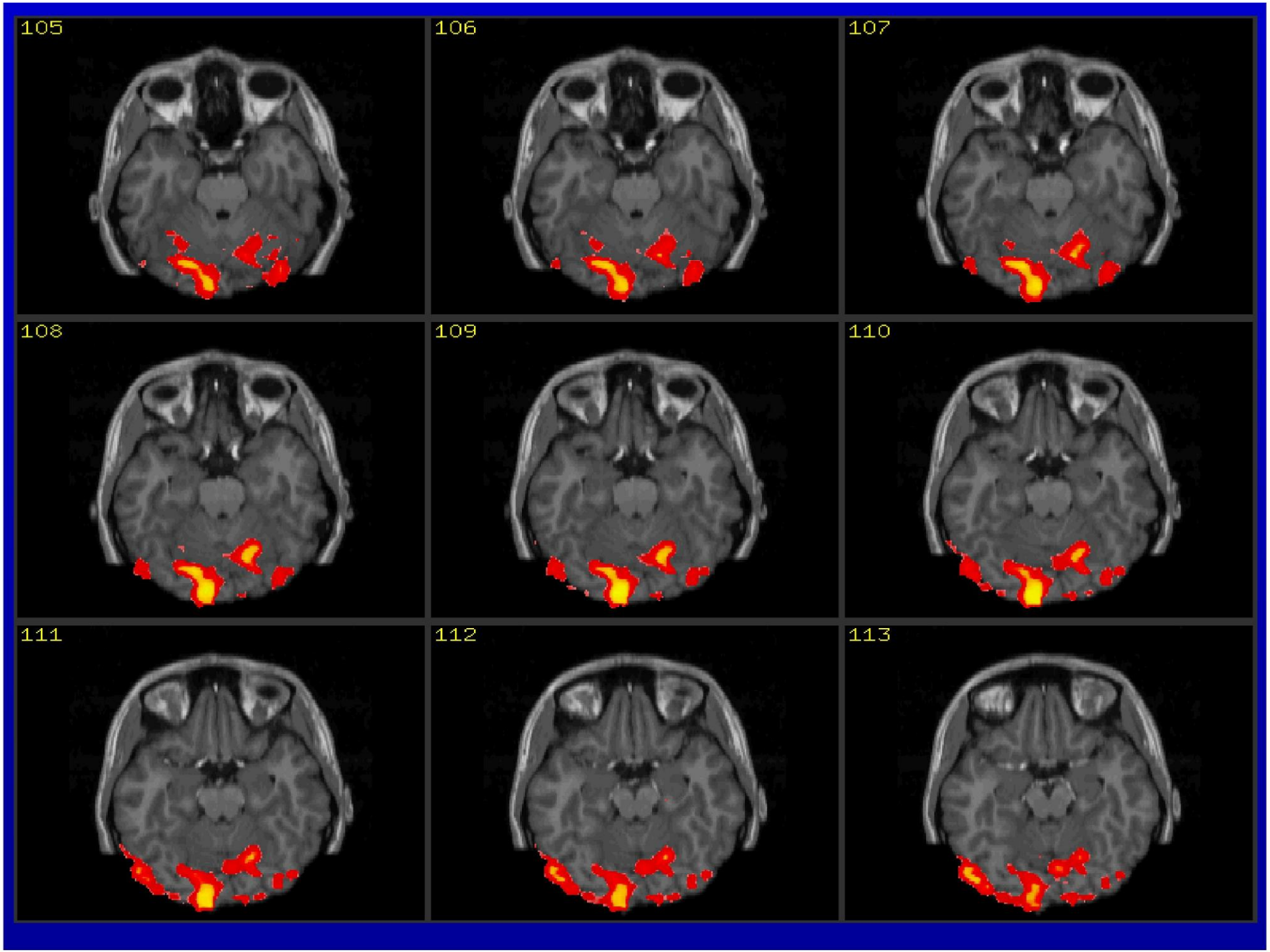
Medial temporal lobe atrophy

Medial Temporal Atrophy in Dementia

AD	28/28	(100%)
VaD	21/24	(87.5%)
DLB	16/26	(62%)
Controls	1/26	(4%)

Barber et al. Neurology 52:1153, 1999


Site 1
Site 2
Site 3
Site 4
Site 5
Site 6
Ctx
Cau
Th
Lat
Pal
Put
Amy
Hp


105
106
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113

4th Question

Can we find a better method for an earlier diagnosis and ability to do a better differentiation?

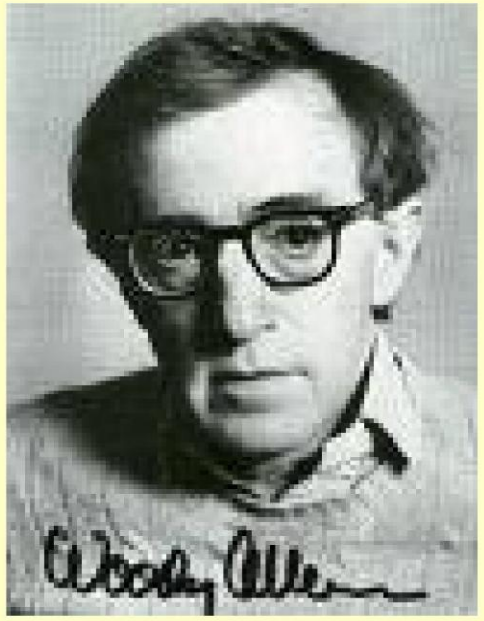
Can technology help us?

Outline

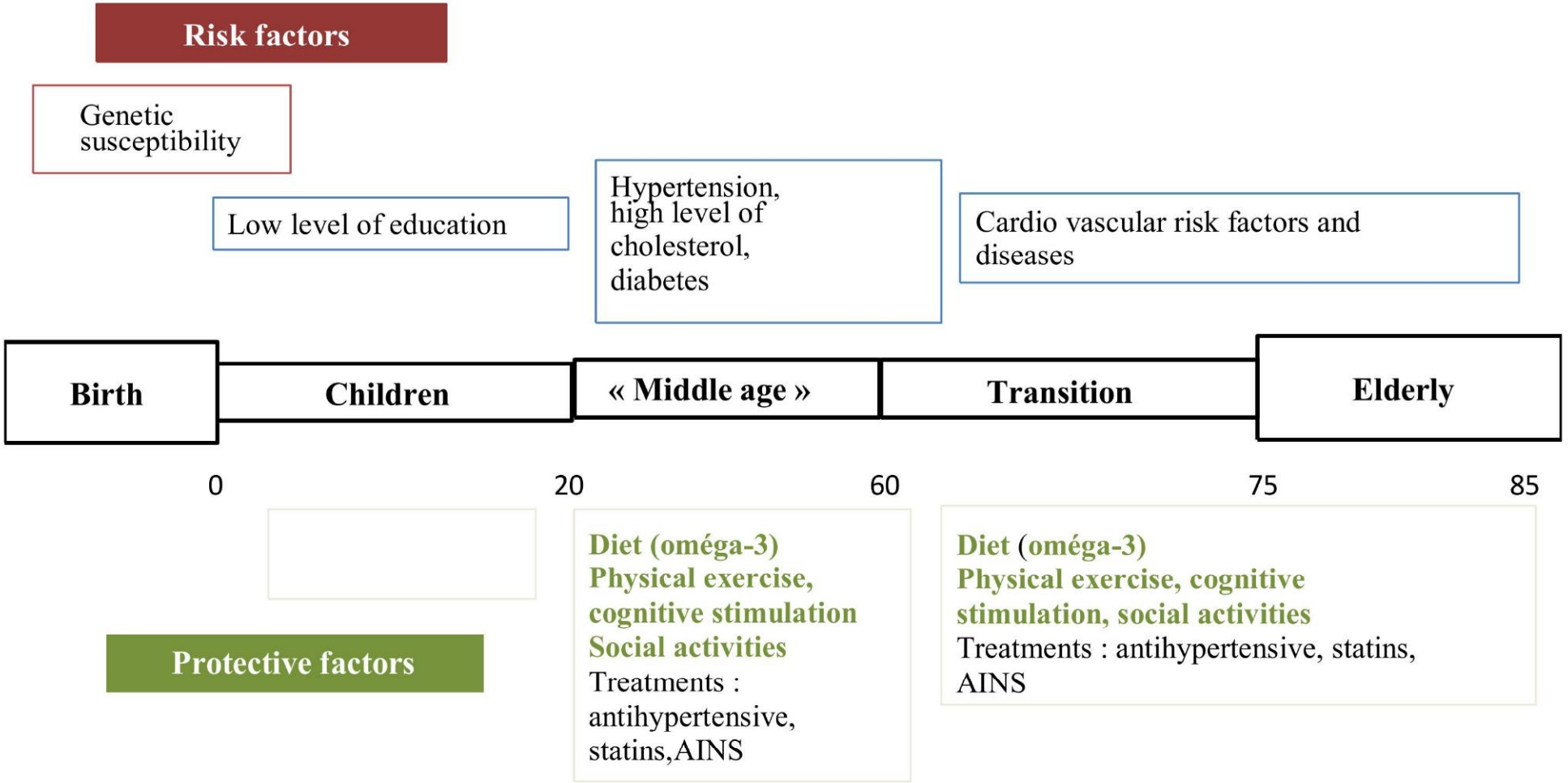
- Epidemiology-Age
- Diagnosis (MCI and AD)
- Prevention- **Education**
- Current Management
  - Pharmacological
  - Non-Pharmacological
- Future Directions

I'm interested in the future because that is where I plan to spend my next years.

Woody Allen

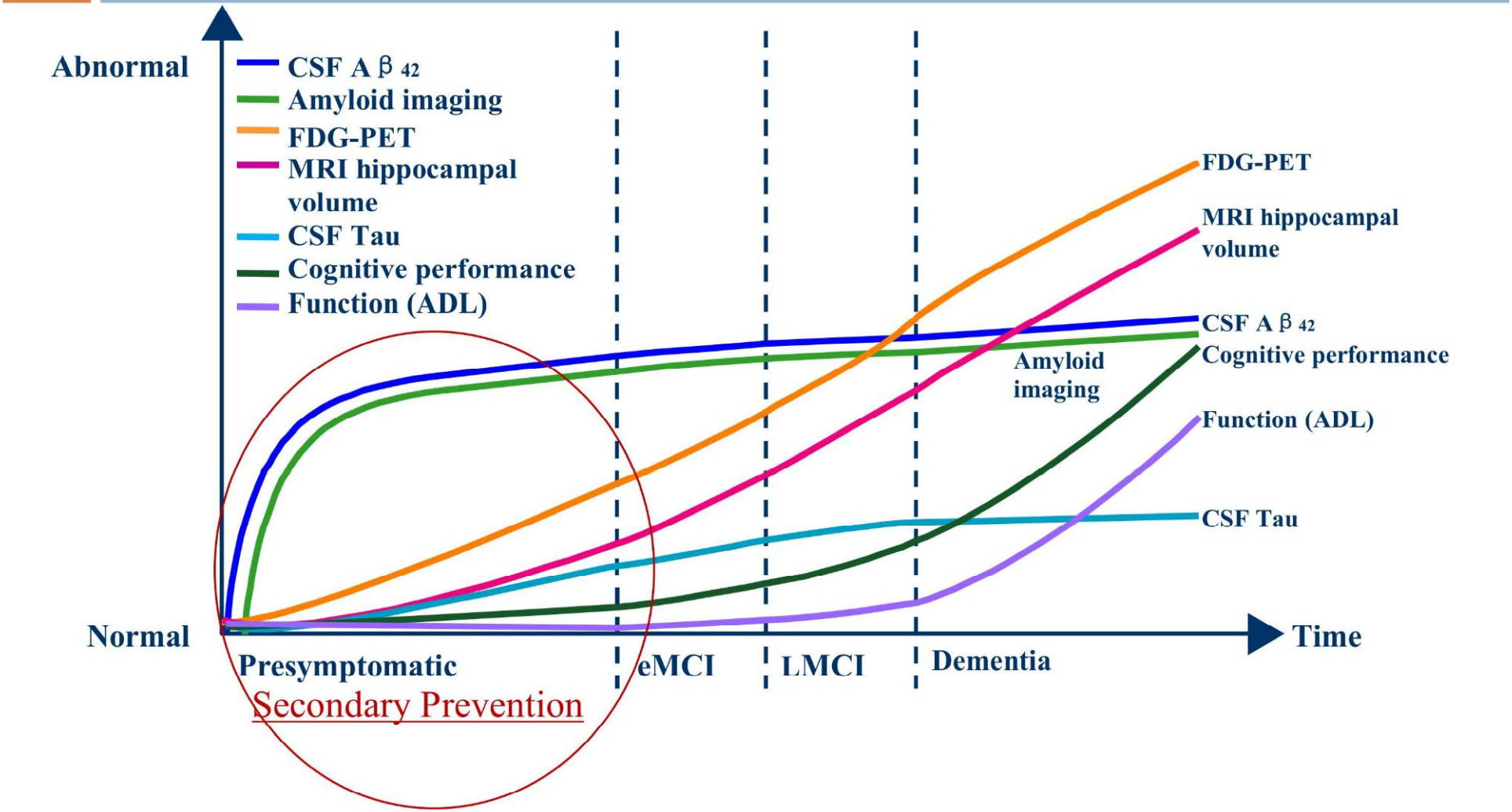


Late onset of AD is a multifactorial disease



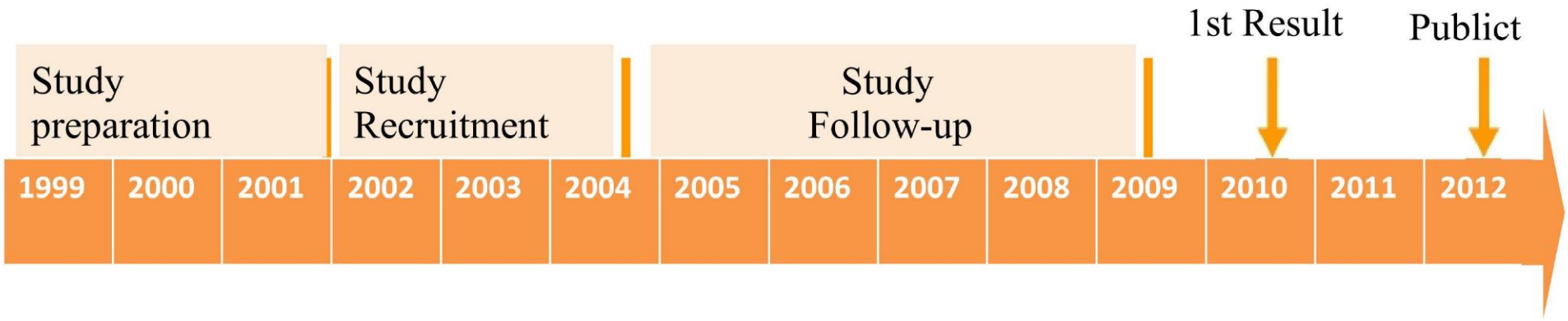
(FratiglioniL et al, 2004; FratiglioniL et al, 2007)

AD Progression

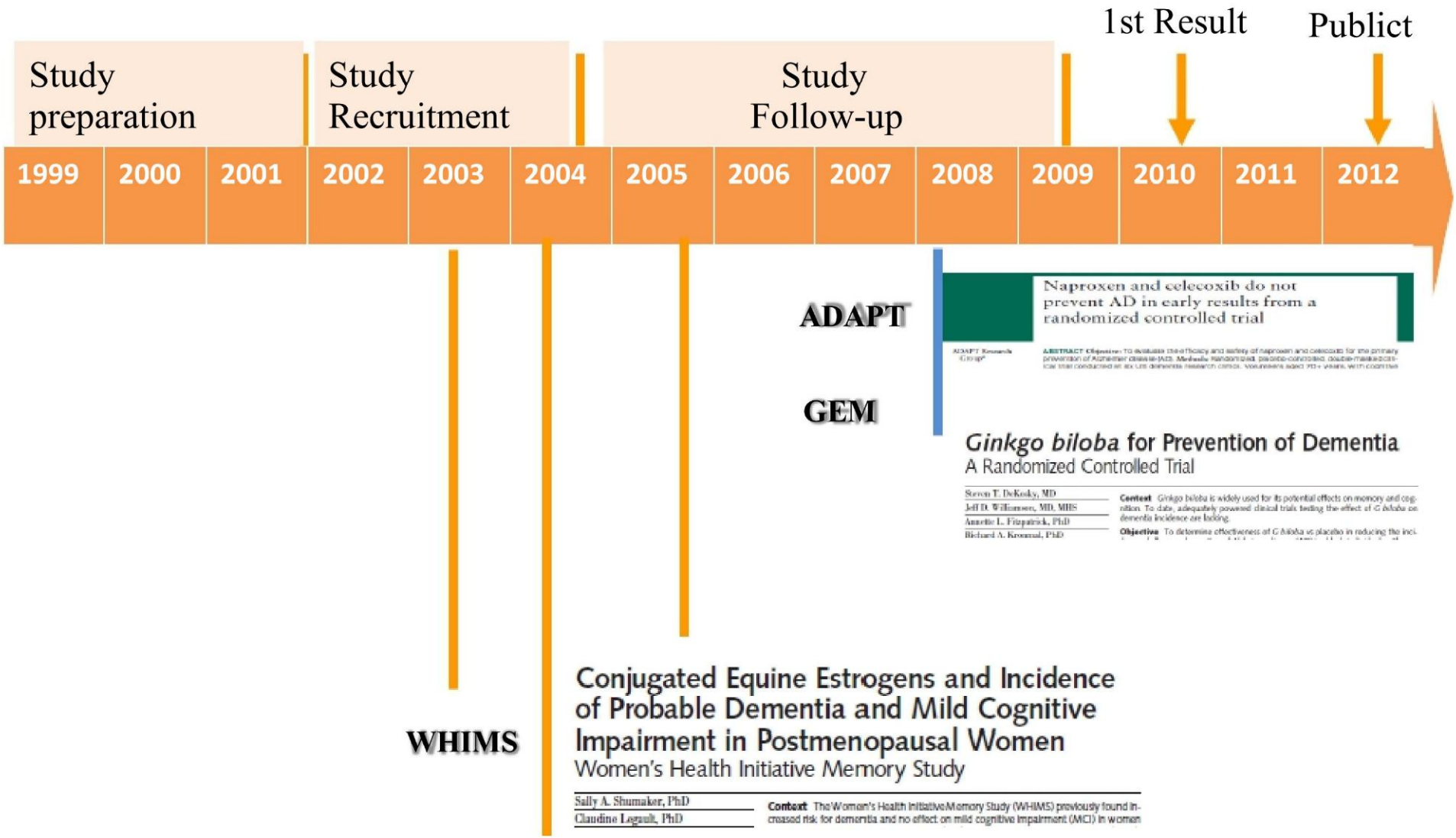


Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

Recent prevention trial, ex guidage timeline



Recent prevention trial, ex guidage timeline



Recent prevention trials

Recent trials

Ongoing trials

Future trials

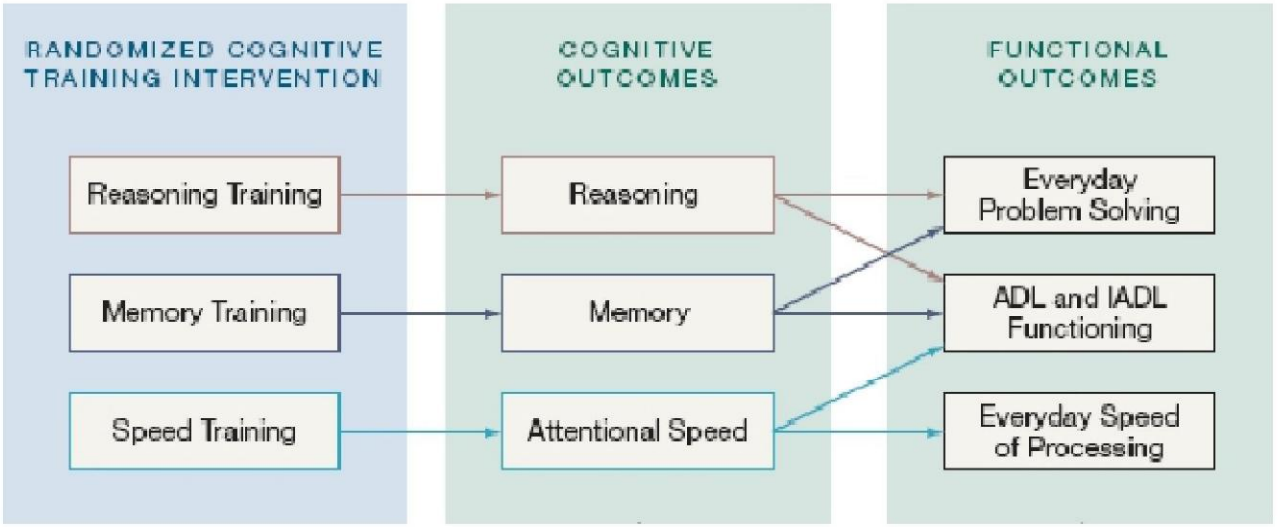
AD large preventive trials, outcome = incidence of AD

	drug	inclusion	enrichment	n	duration	status
PreADVISE >SELECT	Vitamin E Selenium Vitamin E + Se	> 55 y Men		10 800 (7500)	9-12 yr	Stopped AE
WHIMS > WHI	Estrogen Estrogen-Progesterone	> 65 y Women		4 532	6 yr	Negative /increase *the risk*
PREPARE	Estrogen-Progesteron Estrogen	> 65 y Women	Family history of memory problem		3 yr	Stopped /whims results
ADAPT	Naproxen Celecoxib	> 70	Family history of dementia (1st degree)	2 625	5 yr	Stopped AE
GEM > CHS	Ginkgo biloba	> 75		3 072	5-7 yr	Negative / power?
GuidAge	Ginkgo biloba	> 70	Memory complaint	2 854	5 yr	Negative / power?

Effect of cognitive stimulation (ACTIVE trial)

Method: 2832 persons (mean age, 73.6 years), living independently in 6 US cities, was recruited and randomized in 4 groups (3 active and 1 control)

Figure 1. Conceptual Model of ACTIVE Trial

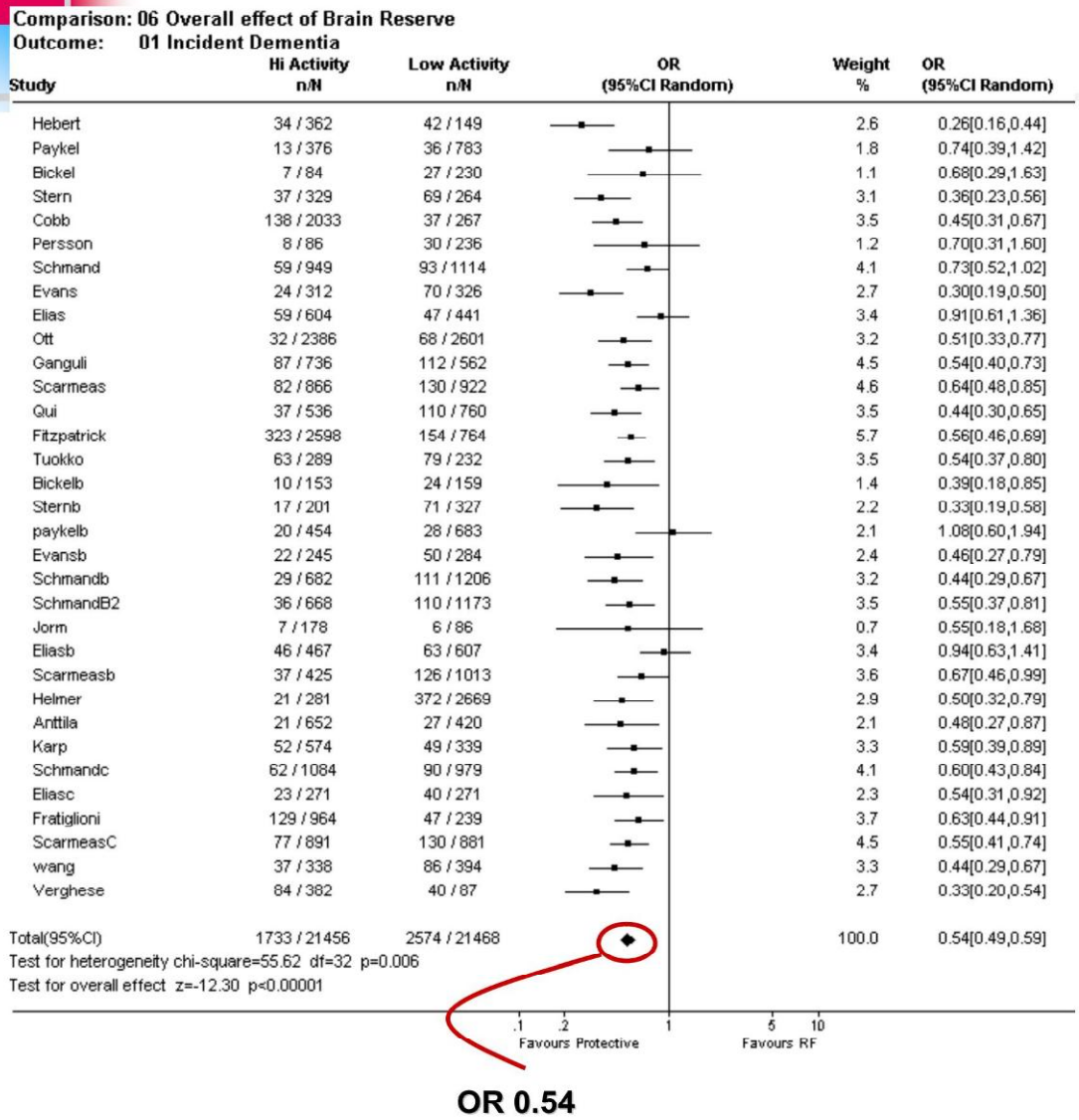


Results:

- The reasoning group reported significantly less difficulty in the instrumental activities of daily living (IADL) (effect size, 0.29; 99% [CI], 0.03-0.55).
- Each intervention maintained effects on its specific targeted cognitive ability through 5 years.

Willis S, JAMA, 2006

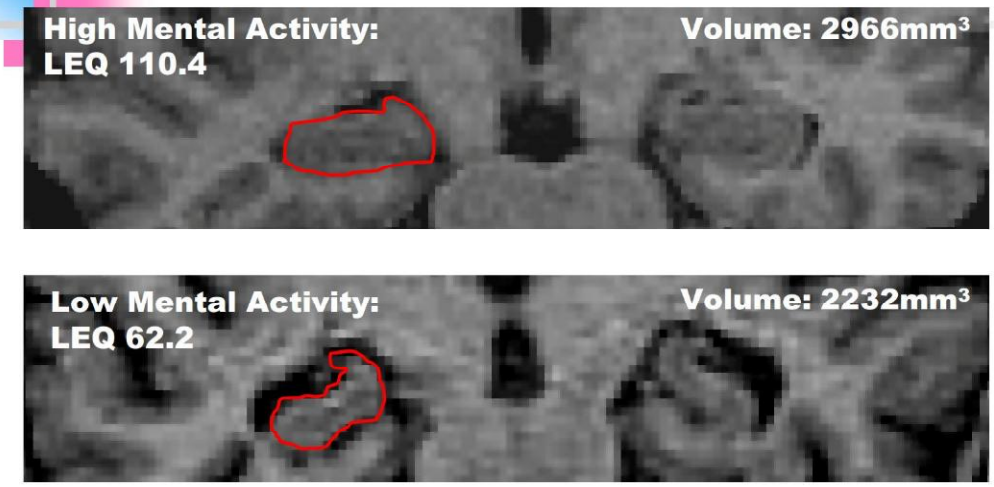
Cognitive Lifestyle



Valenzuela & Sachdev. *Psychological Medicine* (2006)

Cognitive Lifestyle is Neuroprotective

Hippocampal Volume



Four Nations Collaboration

CFAS Study, UK

Washington Heights/North Manhattan Ageing Study, NYC USA

ESPIRIT Study, Montpellier, France

Memory & Ageing Study, Sydney Australia

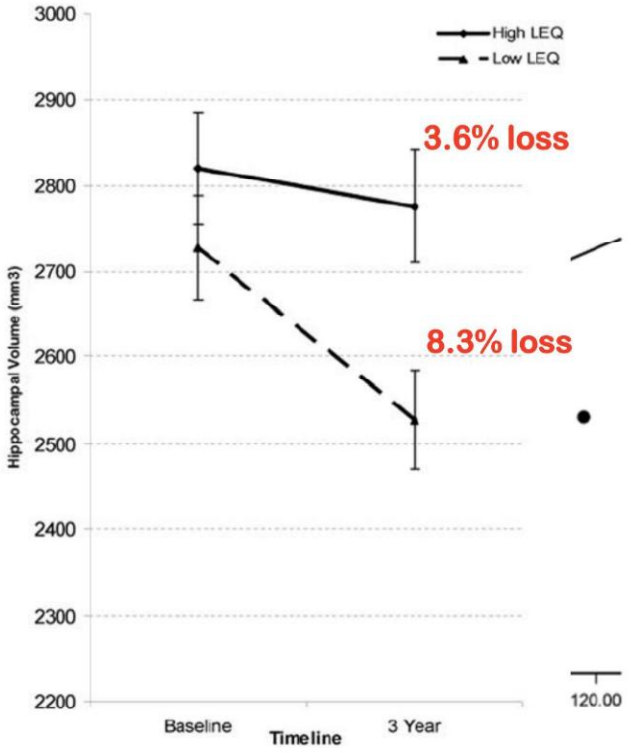


Figure 1. Average hippocampal volume (across right and left sides) in high (solid) and low (dashed) LEQ groups at baseline and 3 year follow-up. Error bars represent standard error of mean. *p-value after covariate control for age, gender, hypertension, baseline volume and total intracranial volume.
doi:10.1371/journal.pone.0002598.g001

Valenzuela et al. *PloS One 2008*

Effect of physical exercise (FABS trial)

- **Methods:**
  - 170 volunteers who reported memory problems (mean age, 68.6 years), were randomized in 2 groups (6 months home-based program of physical activity, versus education and usual care).

- **Results:**
  - At 18 months, participants in the intervention group improved 0.73 points (95% CI, -1.27 to 0.03) on the ADAS-Cog,and versus 0.04 points (95% CI, -0.46 to 0.88) in the usual care group.

  - The average improvement of 0.69 points on the ADAS-Cog score compared with the usual care control group is small (but modest amount of physical activity).

Lautenschlager NT, JAMA, 2008

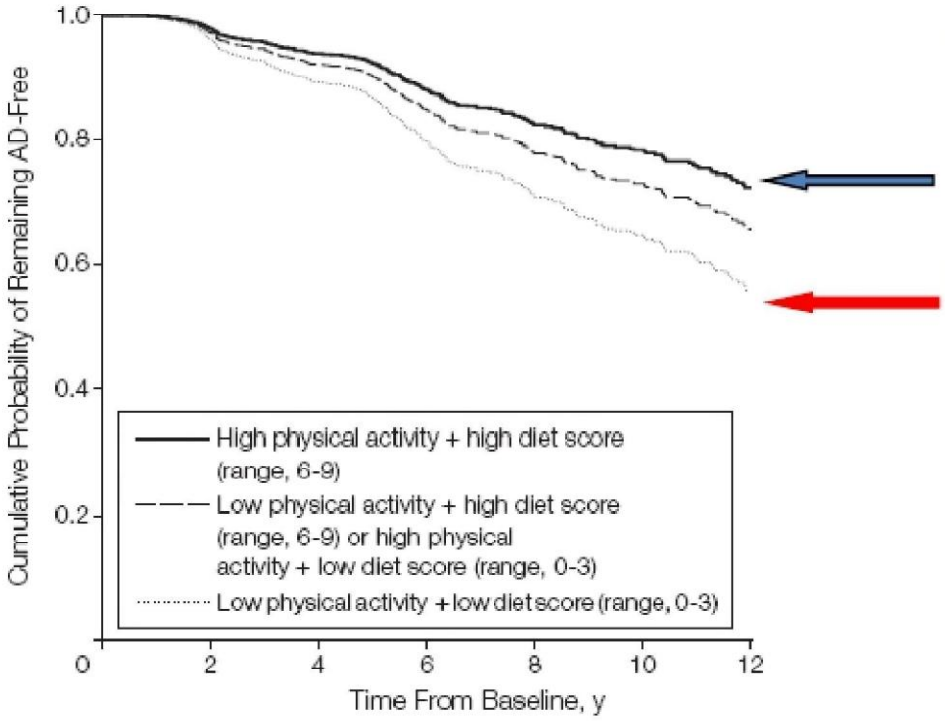
Effect of nutrition (ancill. Facit trial)

- **Methods:**
  - 818 participants (mean age, 60 years) were randomized (800 µg daily oral folic acid or placebo) for 3 years, in the Netherlands.
  - The effect on cognitive performance was measured as the difference between the two groups in the 3-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency.
- **Results**:
  - The 3-year change in memory (difference in Z scores 0·132, 95% CI 0·032 to 0·233), information processing speed (0·087, 0·016 to 0·158) and sensorimotor speed (0·064, –0·001 to 0·129) were significantly better in the folic acid group than in the placebo group.

Durga, Lancet, 2007

Synergic effect of diet and physical exercise **suggested in cohort studies**

Figure 2. Alzheimer Disease (AD) Incidence by High or Low Physical Activity Levels and Mediterranean-Type Diet Adherence Scores



No. at risk							
High + high	490	462	330	129	95	71	40
Low + high or high + low	903	834	578	243	178	124	56
Low + low	487	434	283	129	95	61	31

Survival curves are based on Cox analysis. Low physical activity was defined as a median of 0 hours per week of activity; high physical activity, a median of 1.3 hours per week of vigorous, 2.4 hours per week of moderate, or 3.8 hours per week of light activity, or a combination thereof.

Physical exercise+++ (1,3 h/week) And mediterranean diet

Low physical activity And no mediterranean diet

SCARMEAS, JAMA 2009

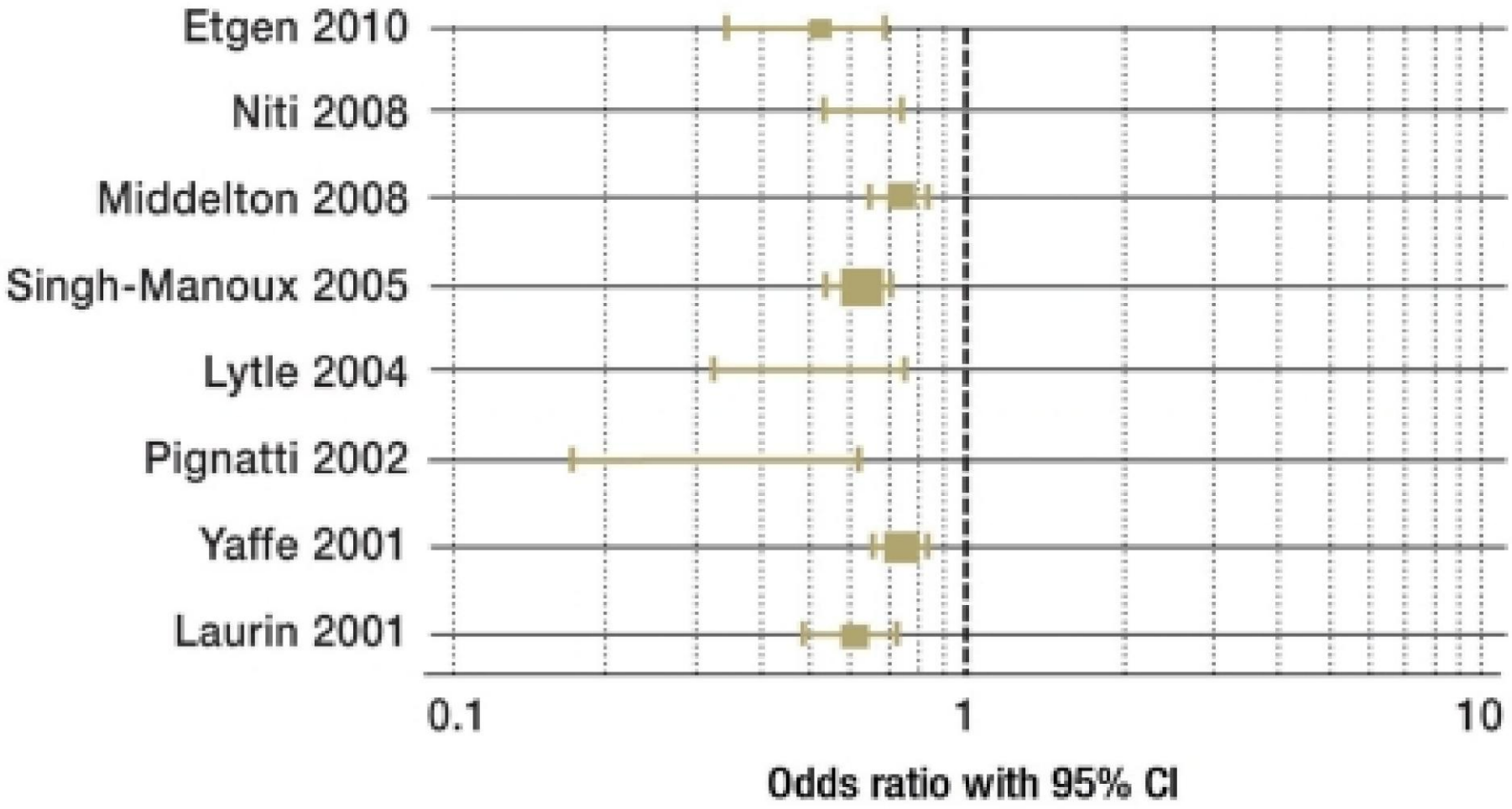

Can Mental & Physical Exercise Prevent Cognitive Decline?

MENTAL AND PHYSICAL ACTIVITY over time

- Cross sectional and prospective cohort studies consistently identify both
  - reduced risk of dementia and
  - reduced rate of cognitive decline
- ...in individuals who have engaged in
  - mentally and physically active pursuits
    - over their lifetime, or
    - even in late life

(Valenzuela & Sachdev, 2006a,b,c)

PHYSICAL AND COGNITIVE EXERCISE (> 1000 PARTICIPANTS).



Ongoing prevention trials

Multidomain Ongoing trials

	Intervention	Target	Measures	Subjects	Int/FU
MAPT	1.Multidomain (cognitive training + physical exercise+ nutrition) 2. Omega3 3. Association Multidomain+Omega3 Versus : PBO	> 70 y Frail Subjective memory complaint Slow walking speed Difficulties in IADL	Cognitive decline (FCSRT) IRM PET-FDG PET-AV45 Biobanque	1680	3y/5y
FINGER	1.Multidomain (nutritional guidance + increased physical activity + cognitive training, + increased social activity) + intensive monitoring of vascular and metabolic risk factors. Versus Standard health counseling at baseline	aged 60-77 dementia Risk Score 6 points or more at least one of the CERAD criteria: i) MMSE: 20-26 points ii) word list memory task (3x10 words): 19 words or less iii) delayed recall: 75% or less	Cognitive impairment ; Neuropsychological Test Battery, and Stroop and Trail Making tests. Neuro-imaging	1200	2/7 y

Multidomain Intervention - ongoing

	Intervention	Target	Assessment	n	FU
PREDIVA	1.Multidomain Intensive vascular care for elderly people by nurse practitioners in general practice 2. Versus : regular care	Age: 70-78 years	Incidence of dementia	3534	6y

Example of sharing data

EDPI

European Dementia Prevention Initiative

www.edpi.org

- **FINGER** Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- **preDIVA** Prevention of Dementia by Intensive Vascular Care
- **MAPT** Multidomain Alzheimer Preventive Trial

UNIVERSITY OF EASTERN FINLAND

UNIVERSITY OF CAMBRIDGE

Karolinska Institutet

amc

Université de Toulouse

Université Paul Sabatier TOULOUSE III

Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

- HATICE Project (Edo Richard, Miia Kivipelto, Sandrine Andrieu)
  - Healthy Aging Through Internet Counselling of the Elderly

SEVENTH FRAMEWORK PROGRAMME

Future prevention trials

Recent trials → Ongoing trials → Future trials

Target: Younger ?

Duration: Longer ?

Sample Size: Larger ?

Non pharmacological OUR EXPERIENCE

- MCI 5 month intervention
  - Improvement in general cognitive performance, attention, language, verbal memory, executive function, visual perception and ADL

(*Tsolaki et al, 2011. Neurodegenerative diseases*)

Participants

1255 patients

547 were excluded

517 living in rural areas

30 no available caregiver

708 were included, but

22 died

60 institutionalized

52 serious medical problem

574 patients were included in 5 months follow – up

253 MCI

122 nPhTh

13 PhTh

39 combined

79 no therapy

321 MD

77 nPhTh

41 PhTh

114 combined

89 no therapy

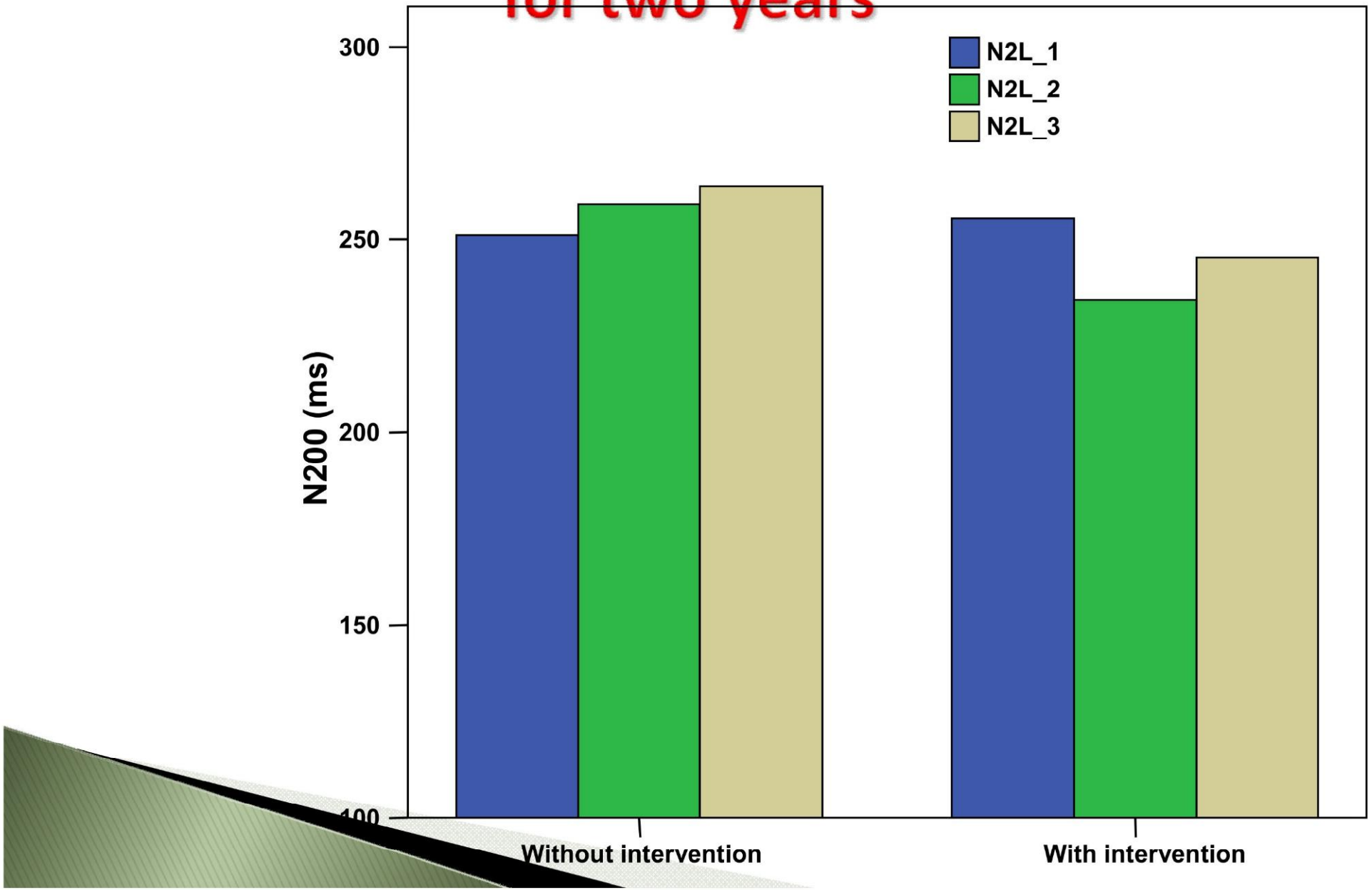
Neuropsychological assessment

- **CAMCOG** (Roth, Huppert, Tum, & Mouthjoy, 1988)
- **MMSE** (Folstein et al., 1975)
- **ROCF** (Rey, 1941)
- **RBMT** (Wilson, Cockburn, Baddeley, & Hiorns, 1989)
- **RAVLT** (Rey, 1958)
- **MoCA** (Z. Nazreddine, MD. 2004)
- **Verbal Fluency**
- **Alternating hand movement** (Luria, 1966)
- **Luria 3 step** (Luria, 1966)
- **WCST** (Berg, 1948)
- **TEA** (Robertson, Ward, Ridgeway, Nimmo-Smith, 1996)
- **WAIS – R** (Wechsler, 1981)
- **STROOP** (Stroop, 1935)
- **BNT** (Kaplan, Goodglass, & Weintraub, 1983)
- **PPT** (Howard, Patterson, 1992)
- **BDAE** (Goodglass & Kaplan, 1983)
- **TRAIL MAKING A, B** (Armitage, 1946)
- **GDS** (Sheikh, & Yesavage, 1986)
- **FUCAS** (Kounti, Efklides, Kazis, Tsolaki, & Kiosseoglou, 2002)
- **FRSSD** (Hutton, 1990)
- **NPI** (Cummings, 1997

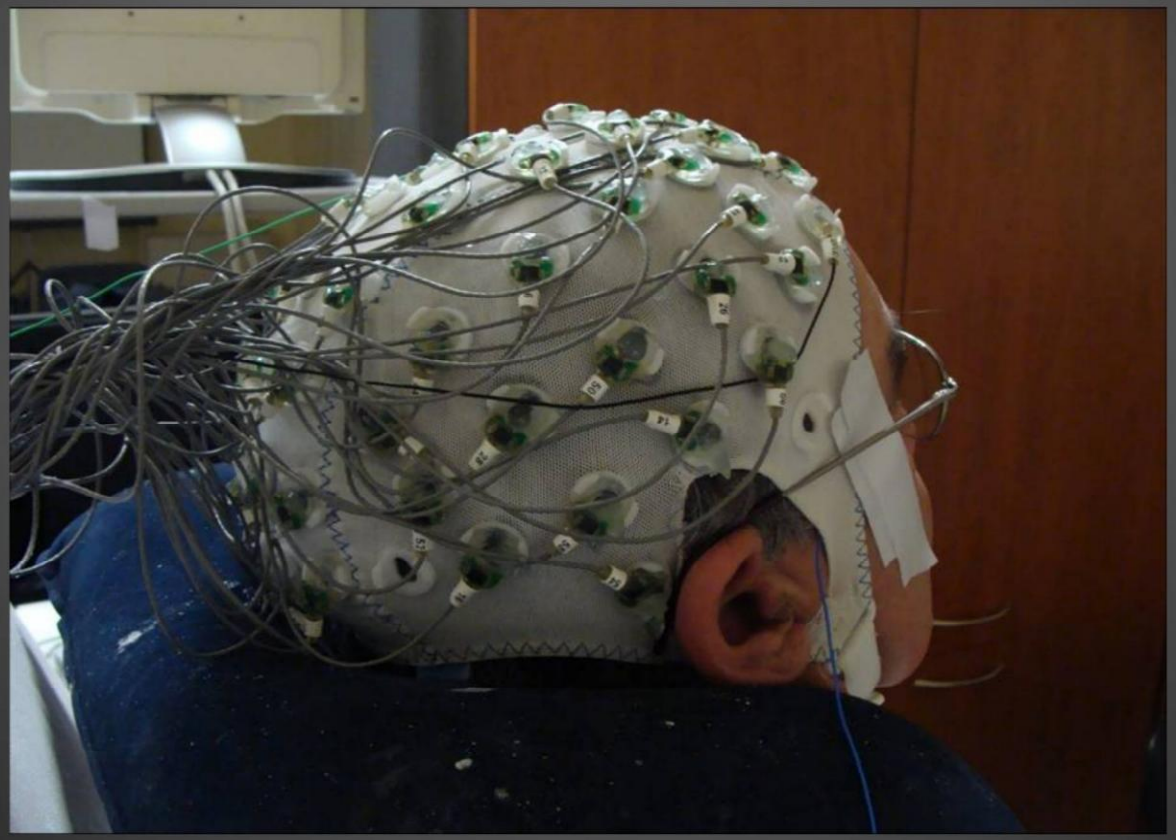
PUBLICATION

- **Effectiveness of Nonpharmacological Approaches in Patients with Mild Cognitive Impairment.**
- Tsolaki M, Kounti F, Agogiatou C, Poptsi E, Bakoglidou E, Zafeiropoulou M, Soumbourou A, Nikolaidou E, Batsila G, Siambani A, Nakou S, Mouzakidis C, Tsiakiri A, Zafeiropoulos S, Karagiozi K, Messini C, Diamantidou A, Vasiloglou M.
- **Neurodegener Dis. 2011; 8(3):138-45.**

Patients with MCI are stable for two years



Neurophysiological Assessment- EEG



EFNS recommendations for Prevention, Sorbi et al. 2012

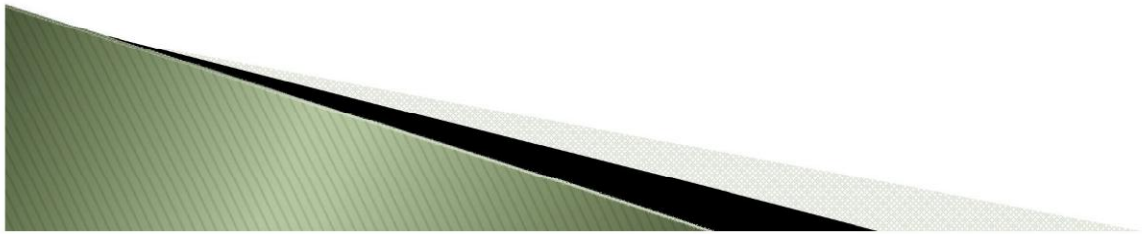
Guidelines for primary and secondary prevention

There is no treatment, no lifestyle, which could have an effect in prevention or delay of onset of different forms of dementia until today.

Finally we wait results from 36 studies

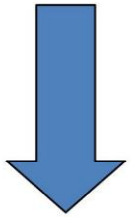
5th Question
Prevention and new Technologies

How can technology provide the kind of engagement that could prevent or delay Alzheimer's?

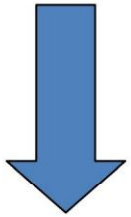


Possible Neuroprotective Mechanisms

Complex Mental Activities



1. **Disease modification**
2. **Resistance to toxicity**
3. **Neurogenesis, synaptogenesis, angiogenesis**



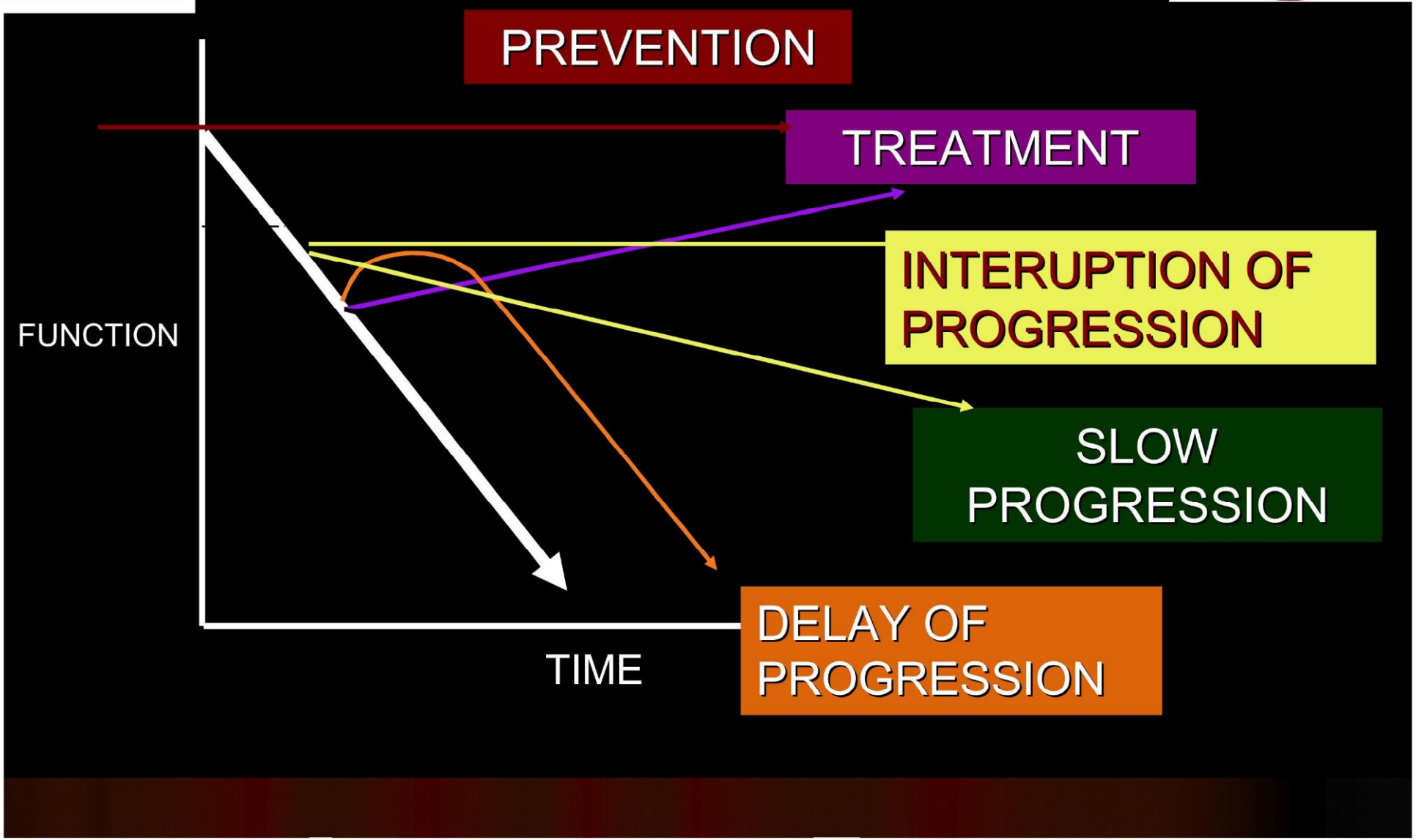
Volumetric differences in hippocampus

Functional Effects

OUTLINE

- : MANAGEMENT
- HISTORY
- CURRENT TREATMENT
  - Pharmacological
  - Non-Pharmacological
    - Education-Awareness
    - Interventions for patients-Biomarkers
    - Care for caregivers
- FUTURE DIRECTIONS

Management of AD- 21ος CENTURY



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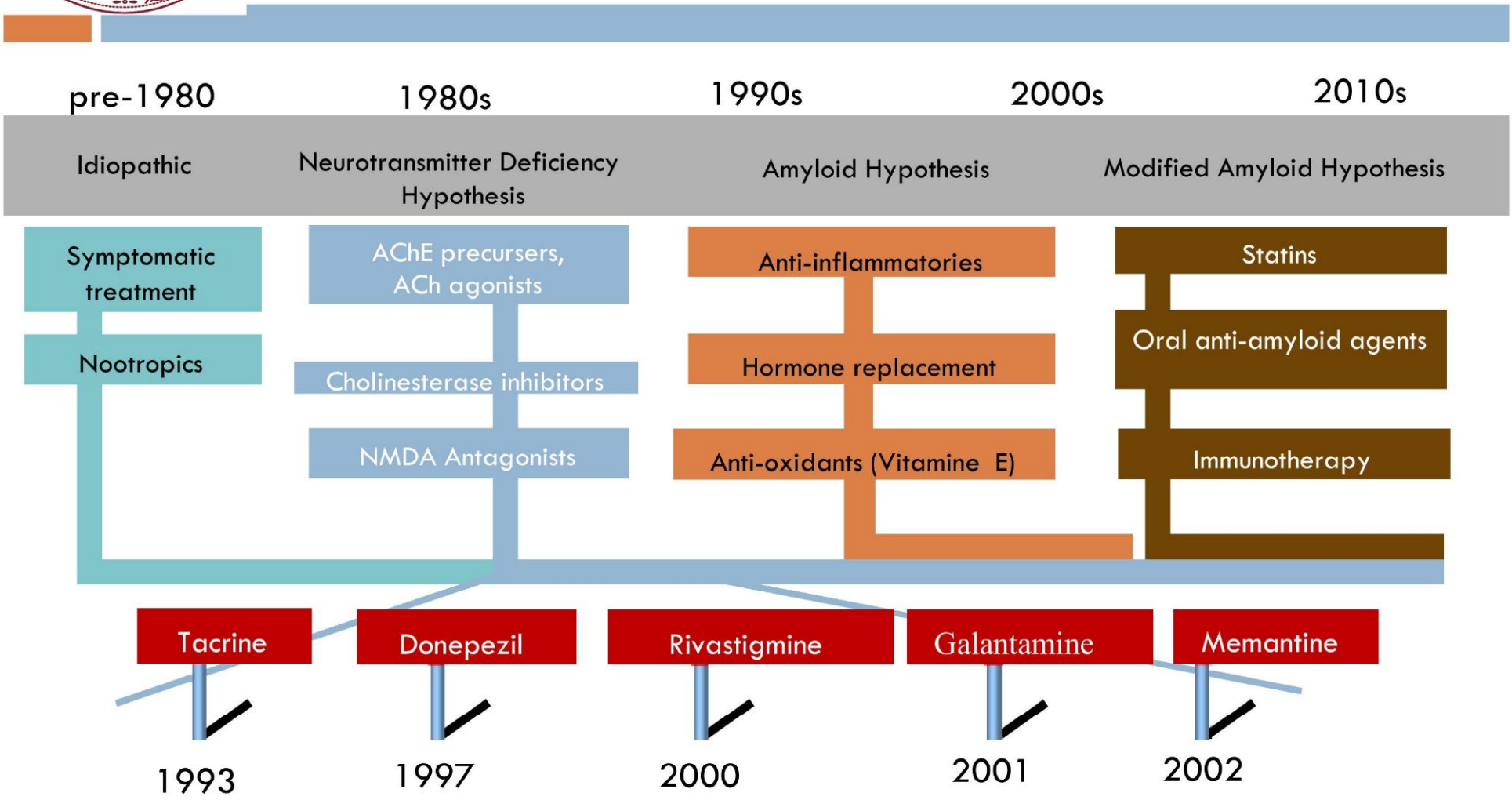
Brief History of AD Therapeutics

- 1906: Dr. Alois Alzheimer describes AD
- 1906-1970's: General assumption that this is an unusual and untreatable degenerative disease of middle age
- 1970's: Cholinergic hypothesis suggests treatment strategy
- 1976: Dr. Robert Katzman editorial: The Prevalence and Malignancy of Alzheimer's Disease
- 1986: First positive (?) treatment study (Dr. William Summers)
- 1993: Tacrine is approved; 3 other similar drugs follow
- 2003: Memantine is approved, representing a second therapeutic class for AD
- 2003 to 2011: Nothing
- 2012: Immunotherapy phase III?

Development of Alzheimer Pharmacotherapy



Relkin, ADAD 2006

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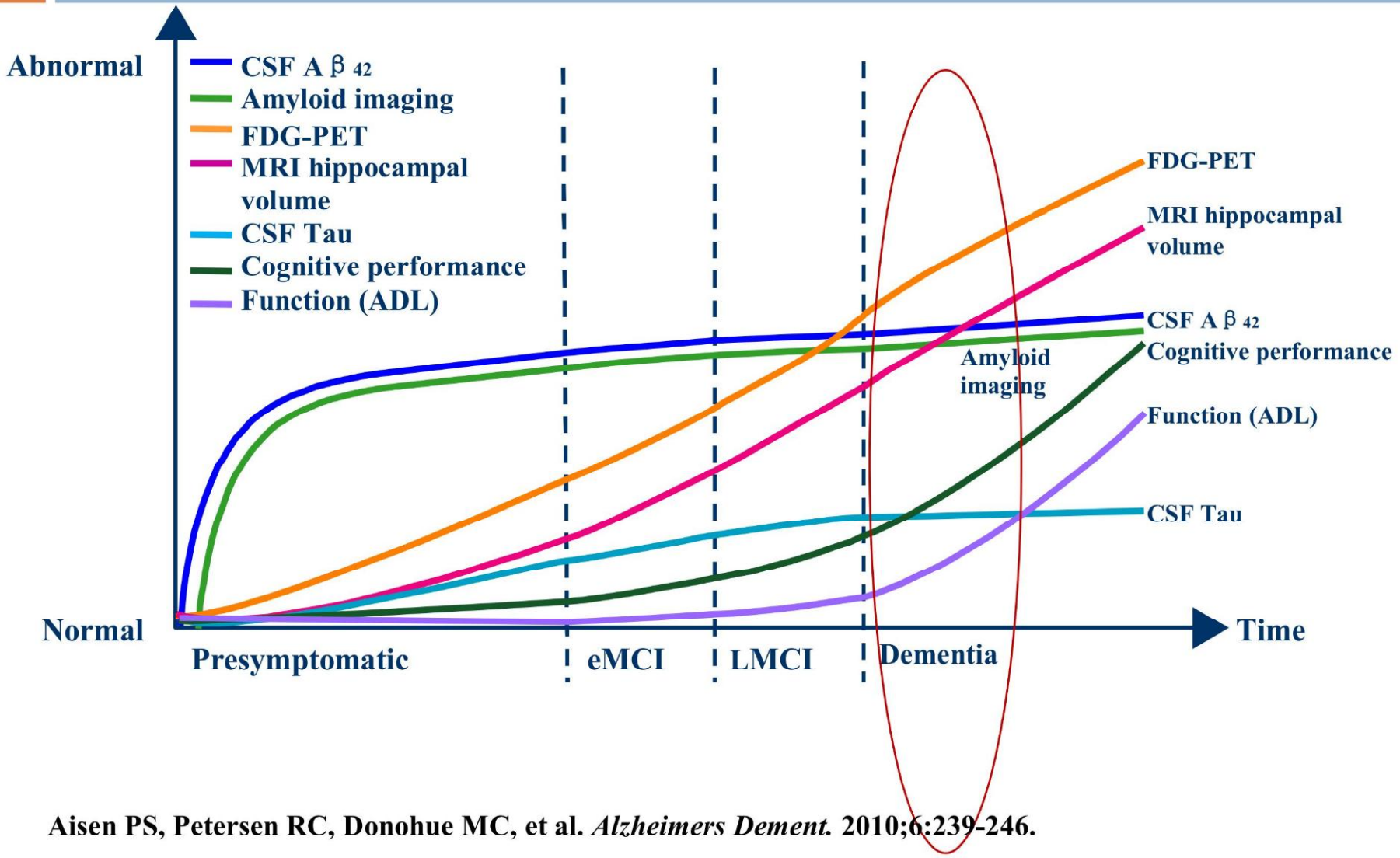
AD Progression



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

Cholinergic changes in Alzheimer's disease

- In the cerebral cortex and hippocampus of patients with AD
  - Decline in ChAT activity[1]
  - Decreased levels of AChE[1]
  - *Increased* levels of BuChE[1]
- Depletion of ACh-positive neurons in the basal forebrain: especially in moderate to severe disease stages[2]

1. Perry EK, et al. *Neuropathol Appl Neurobiol* 1978;4:273–7
2. Whitehouse PJ, et al. *Science* 1982;215:1237–9

EFNS recommendations for the treatment of dementia (2007)

Alzheimer's disease

ChEIs (rivastigmine, donepezil, galantamine, tacrine) at diagnosis

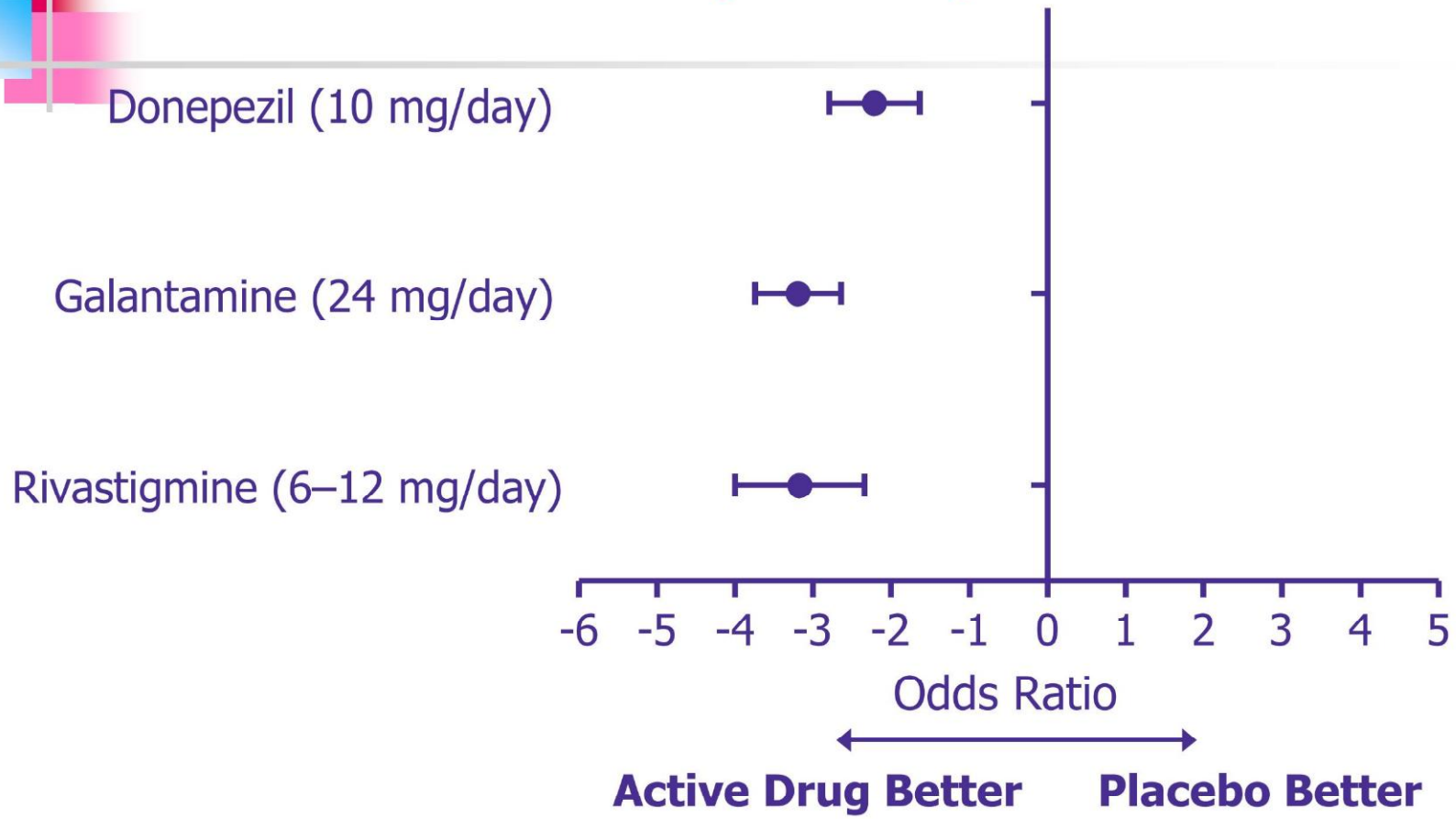
Memantine alone, or in combination with a ChEI, in patients with moderate to severe Alzheimer's disease

Insufficient evidence for the use of ginkgo biloba, anti-inflammatory drugs, nootropics, selegiline, oestrogens, vitamin E or statins

Parkinson's disease dementia

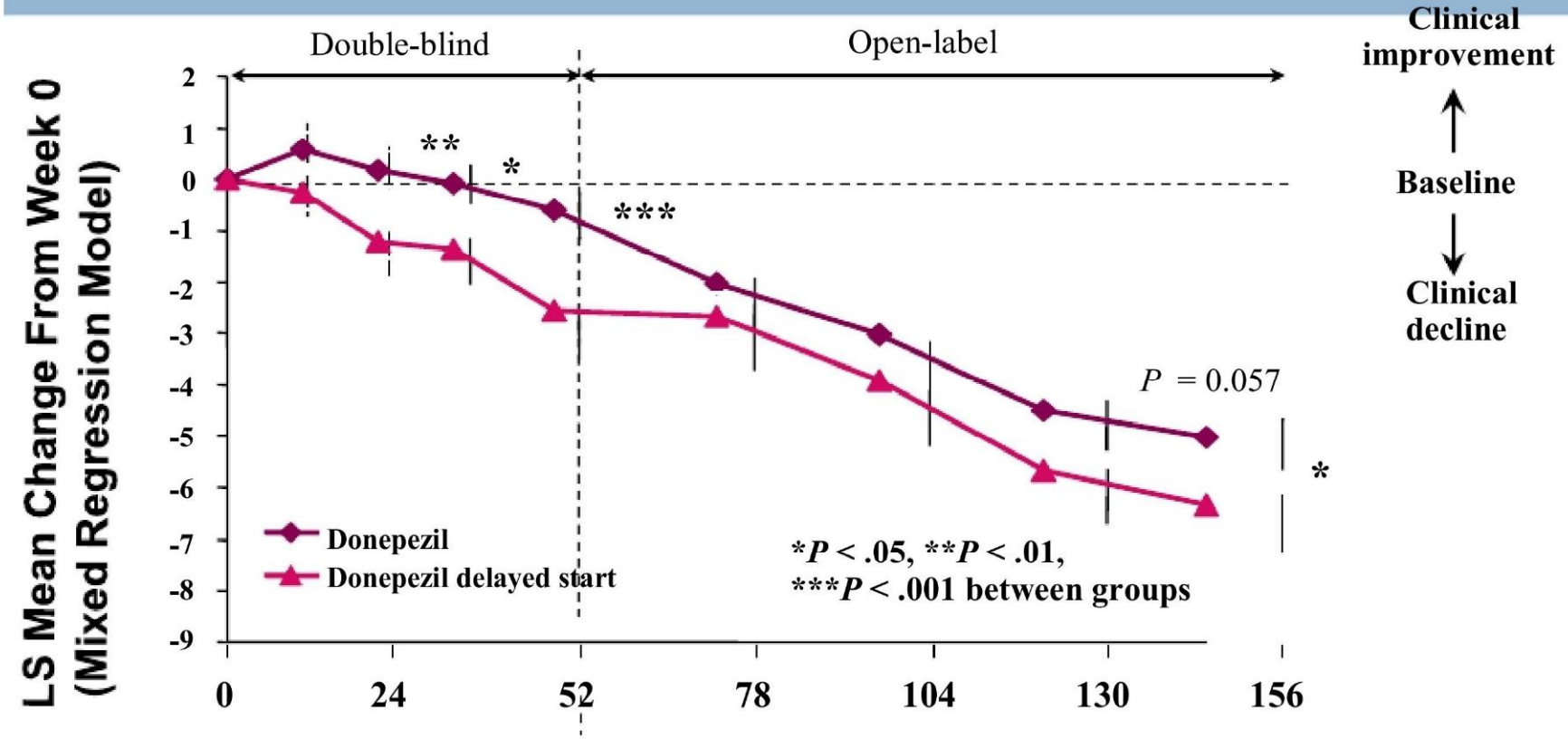
- ChEIs (rivastigmine is the only ChEI approved for PDD)
- Insufficient evidence for the use of memantine

Effects of oral ChEIs on cognition: Meta-analysis of pivotal trials



Ritchie CW, et al. *Am J Geriatr Psychiatry* 2004:12:358–69

Donepezil in Mild and Moderate AD - a longterm study (MMSE score)



Donepezil	n =135	121	91	76	69	63	54
Delayed start	n =137	120	98	68	64	60	52

Winblad et al, Dementia and Ger Cogn Dis 2006

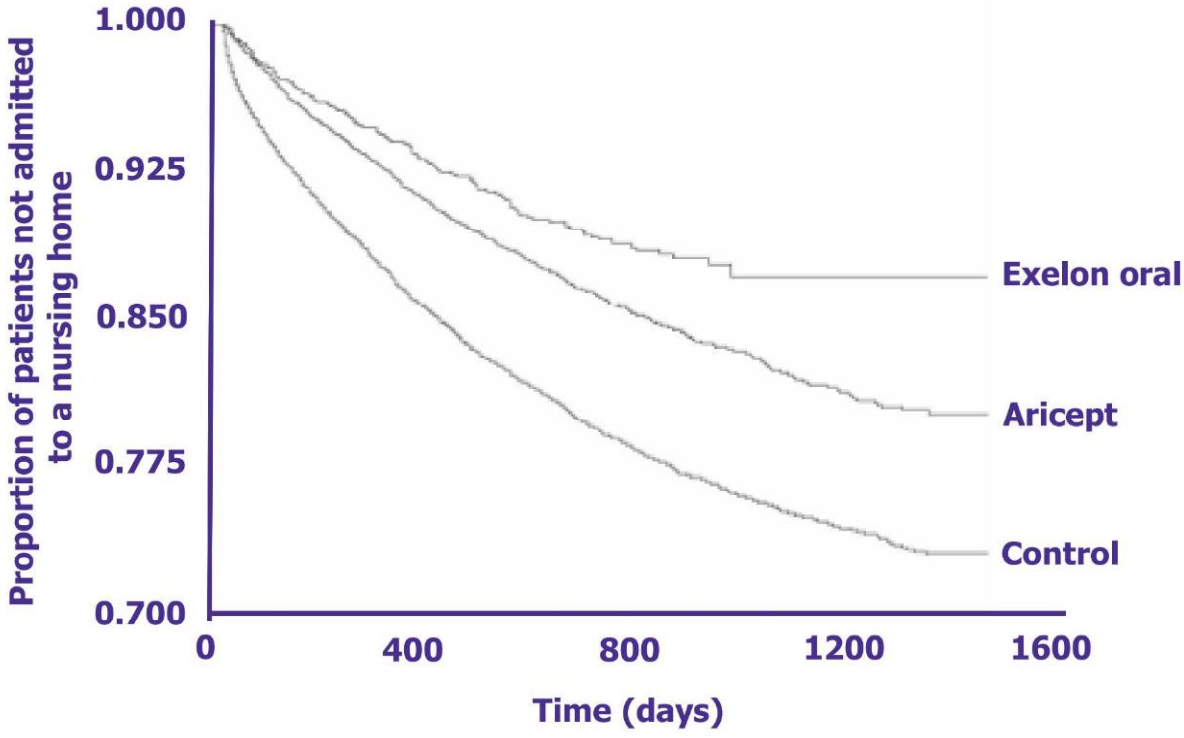
RIVASTIGMINE FOR ALZHEIMER'S DISEASE

- Nine trials involving 4775 patients support that rivastigmine appears to be beneficial for people with mild to moderate AD. In comparisons with placebo improvements were seen in the rate of decline of cognitive function, activities of daily living and severity of dementia with daily doses 6-12 mg
- There is evidence that the lower dose smaller patch is associated with fewer side effects than the capsules or the higher dose larger patch and has comparable efficacy to both.

- **Birks J., Grimley E.J., Iakovidou V., Tsolaki M., Holt FE.**
- Cochrane Database 2009 Apr. 15 2009

ChEIs may reduce nursing home placement (and associated costs)

Kaplan-Meier plot of time to nursing home placement in patients on oral rivastigmine or donepezil compared with no ChEI therapy (control)



Retrospective observational evidence from California Medicaid data
Singh G, et al. *J Am Geriatr Soc* 2005;53:1269–70

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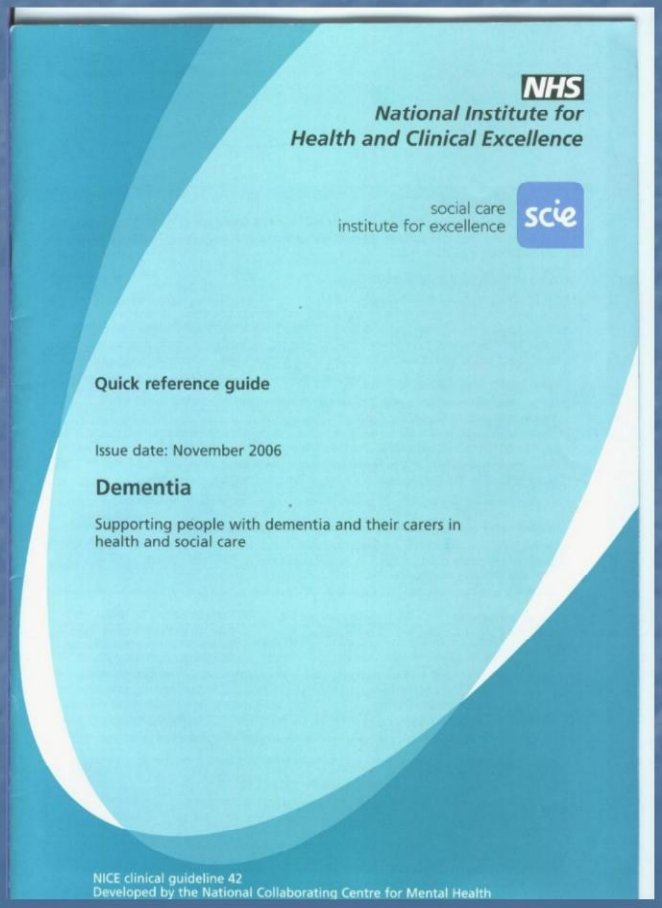
NICE-SCIE guidance on the management of the dementias (UK) (2006) www.nice.org.uk



- *People with mild/moderate dementia of all types should be given the opportunity to participate in a structured group cognitive stimulation programme … provided by workers with training and supervision … irrespective of any anti-dementia drug received …'*

7TH PANHELLENIC CONFERENCE OPENING CEREMONY

OUTLINE

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Non-pharmacological intervention to Alzheimer patients

Takeda et al., 2012

Therapy	*Cognitive*	*ADL*	*BPSD*
ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia			
Snoezelen/multisensory stimulation	+	+	+
Reality orientation	+	+	+
Reminiscence therapy	+	–	+
Physical activity	+	+	+
Light therapy	+	–	+
Aromatherapy	–	–	+
Animal-assisted therapy	–	–	+
Music therapy	+	–	+

DAY CENTERS

- 4 Day Centers in Thessaloniki
- 1 for patients with moderate – severe dementia
- 2 funded from Ministry of Health and European Union



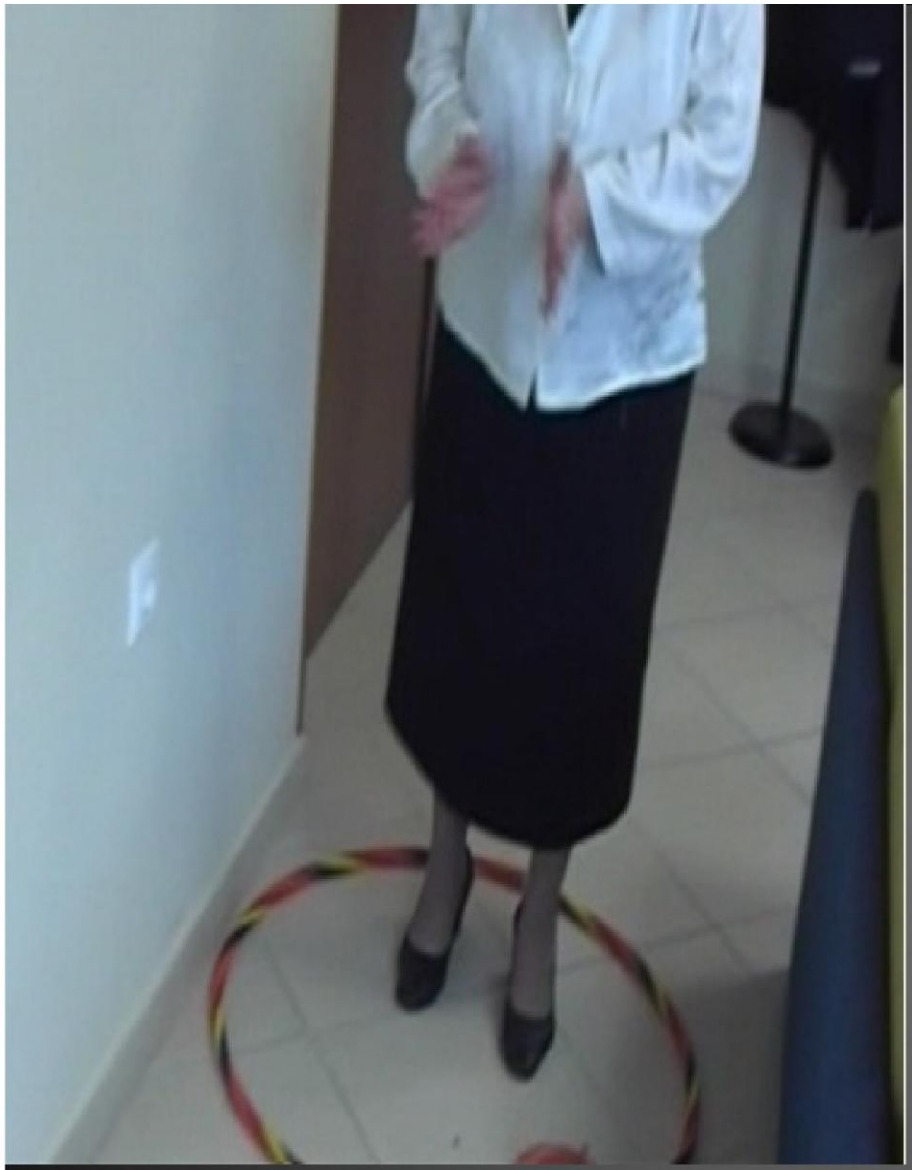


CASIO
24/01/2008 10:02

Group games

Group games


Reality Orientation in Current events

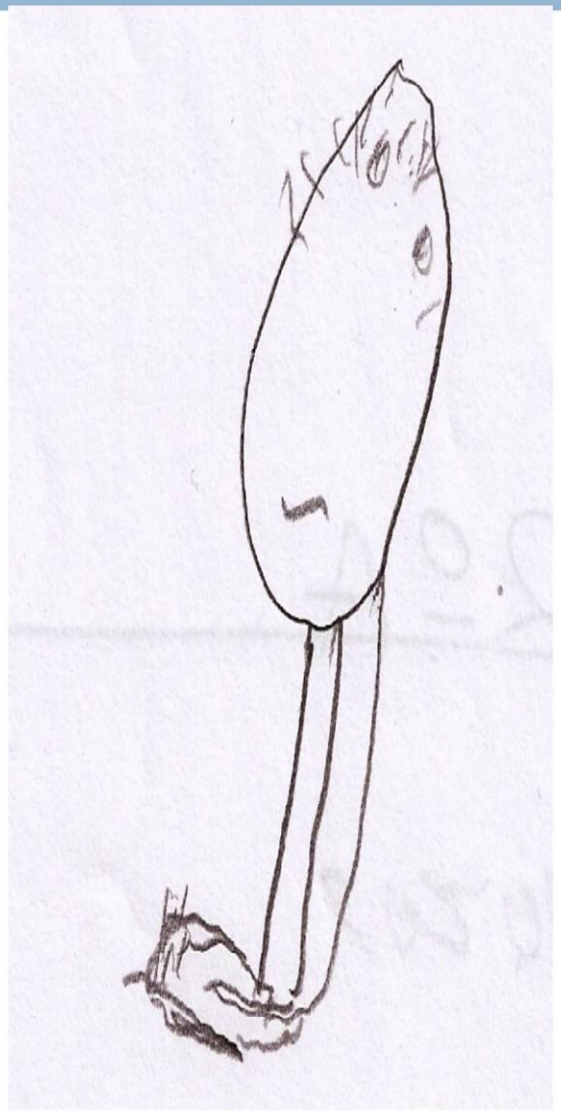


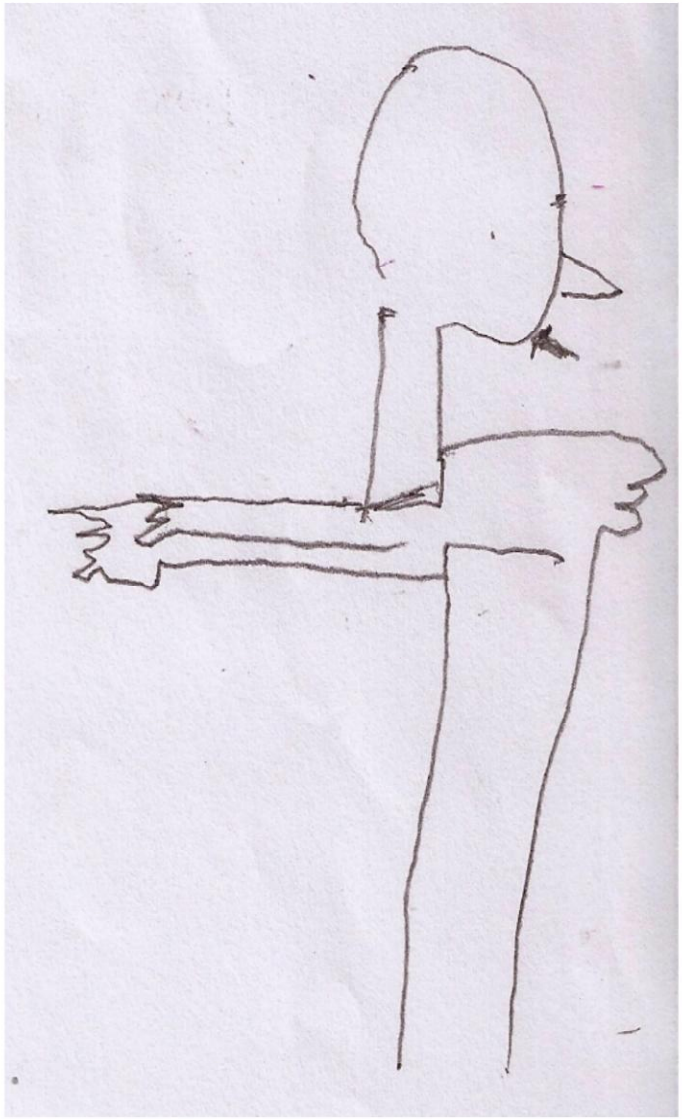

4
3


7

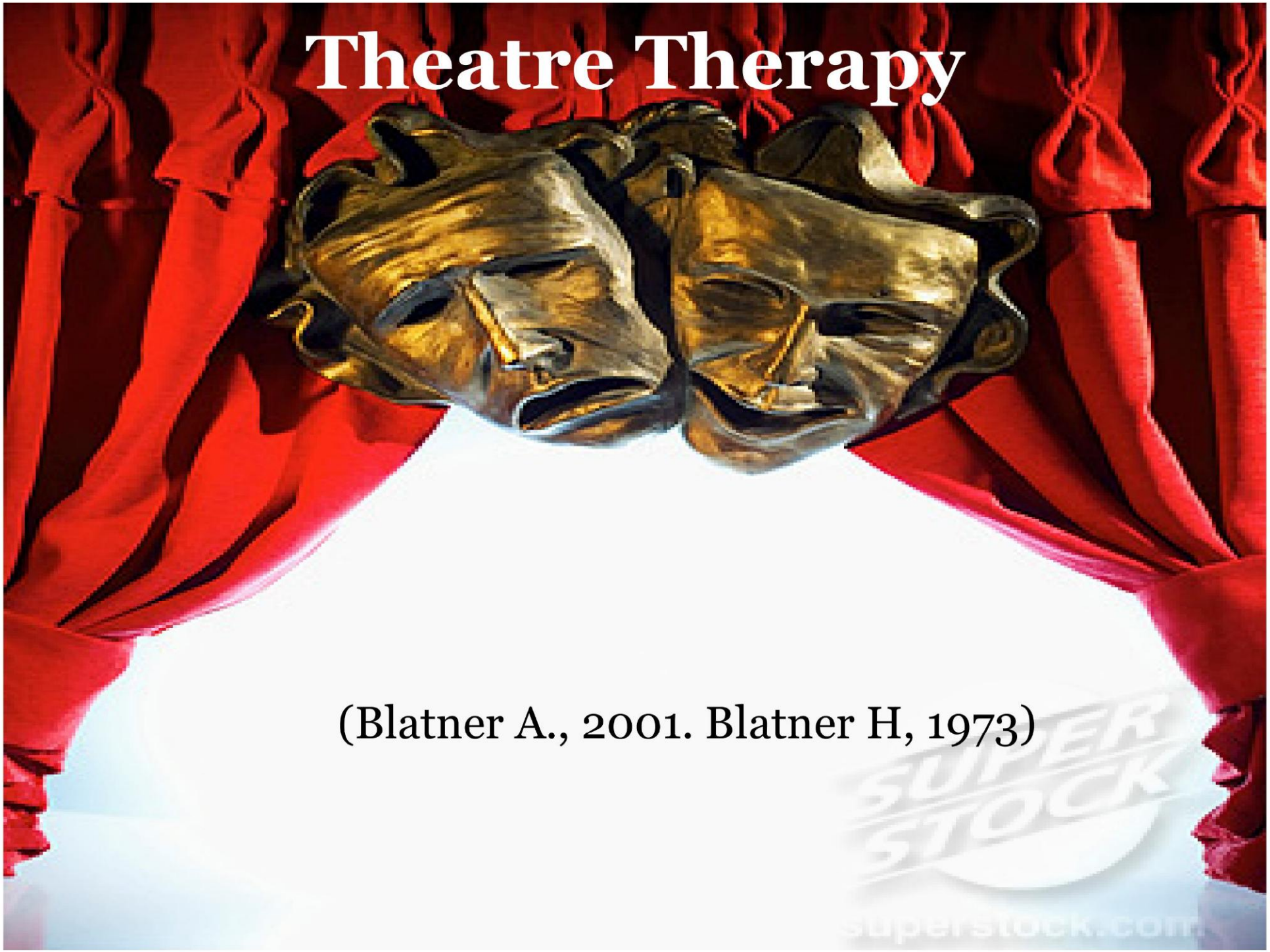
Painting Myself

Painting Myself





Theatre Therapy



(Blatner A., 2001. Blatner H, 1973)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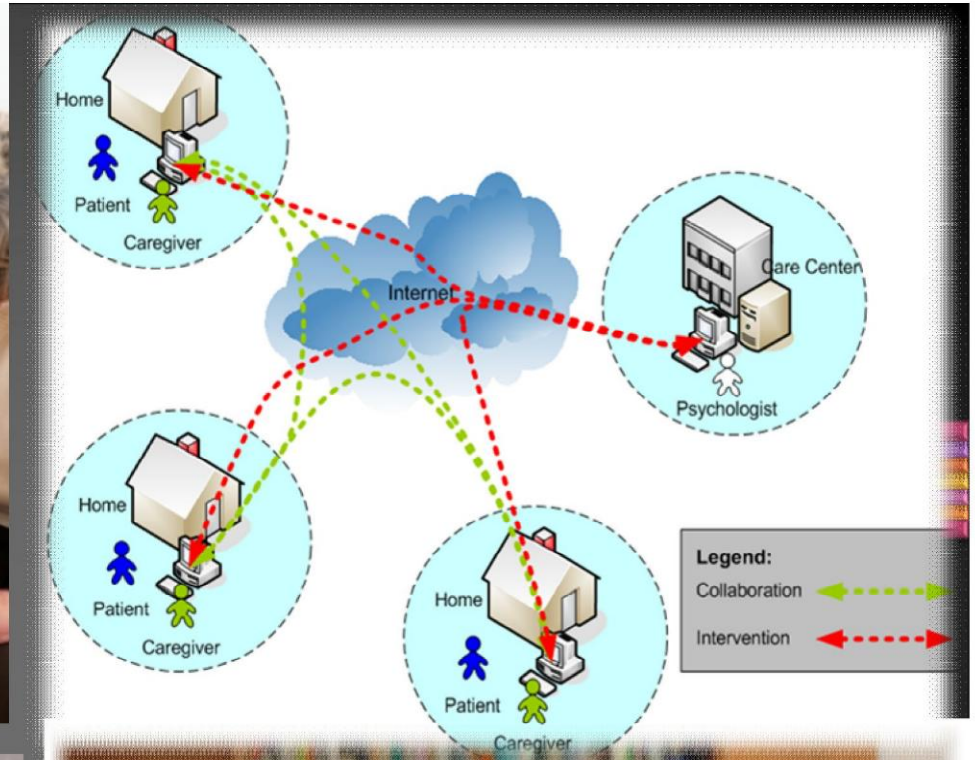
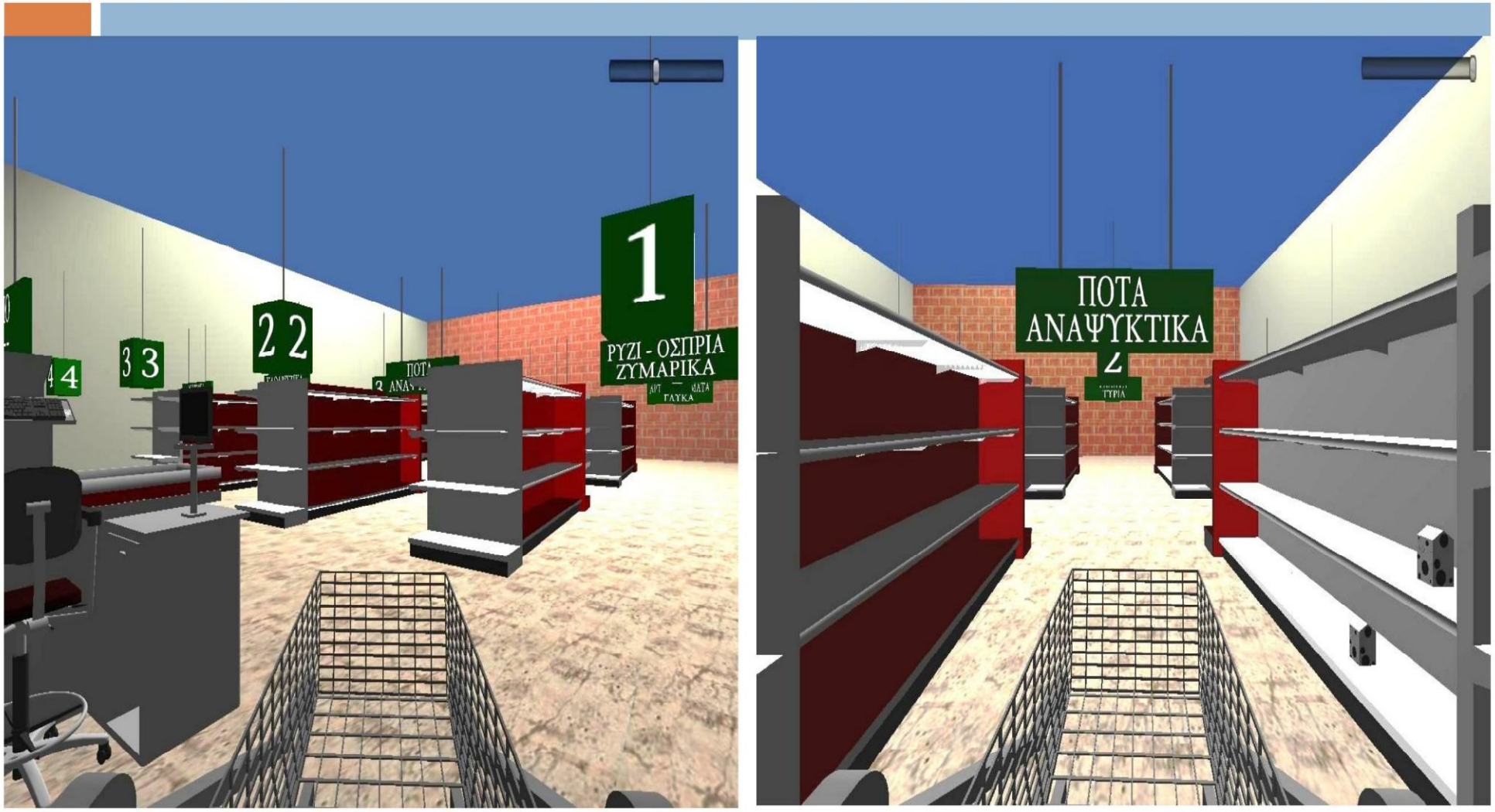

Home
Patient
Caregiver
Internet
Care Center
Psychologist
Home
Patient
Caregiver
Home
Patient
Caregiver
Legend:
Collaboration
Intervention

LLM Design Idea

6th Question
New technology and

- **Patterns of lucidity:** How can technology help identify the optimal times for an individual with Alzheimer's to conduct complex household tasks or interact with others?

Activities of Daily Living



5 groups of 8 excercises

Language exercises

symbiosis
Alzheimer's Support

SymbioMusic


ΠΑΙΓΝΙΔΙΑ
ΠΑΙΔΑΚΙΑ
ΑΛΦΑΒΗΤΑΡΙΟ

7th and 8th Questions
Late stages and technology

- **Safety:** How can new technologies add to or improve on existing safety monitoring systems?
- **Independence:** How can wireless sensor technologies support activities of daily living? How can current technologies be improved?

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Neurophysiological Assessment-EEG

Group therapy

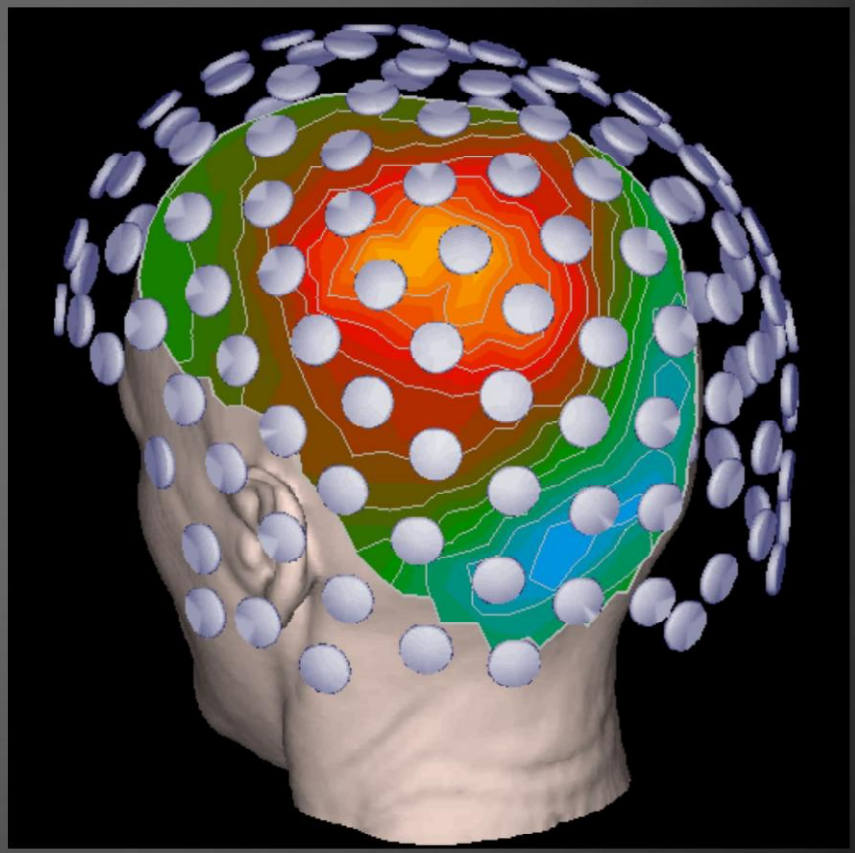
41 participants

MMSE>20

Once a week

1 ½ hour

24 therapies

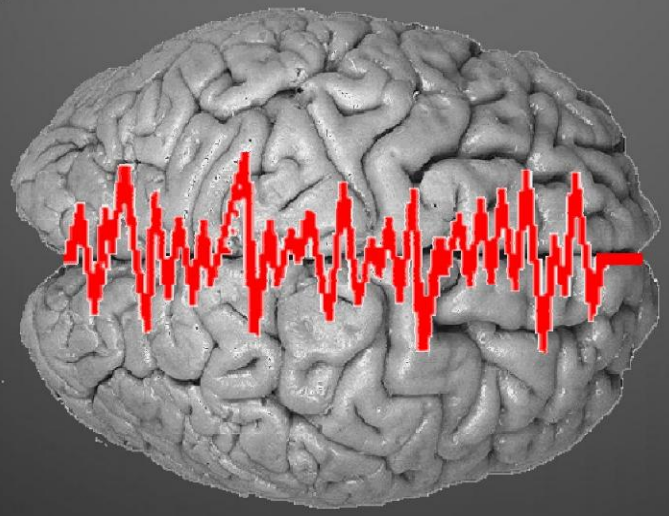


Participants

	Experimental group N=41	Control group N=26	p
Gender M/F	Α7/Γ34	Α4/Γ22	0.560
Age (years)	68.78 (7.66)	67.23 (8.20)	0.150
Education (years)	11.41 (4.85)	11.30 (4.13)	0.430
MMSE	28.34 (1.52)	28.03 (1.21)	0.100

Results

- Significant improvement mainly in right hemisphere nets (p=0.002)



Right parietal-occipital and right parietal and right frontotemporal-frontal

	before	after	p
FT8-F8	0.469	0.344	0.002
PO4-P8	0.456	0.319	0.002

Left parietal-occipital and right frontal and parietal area

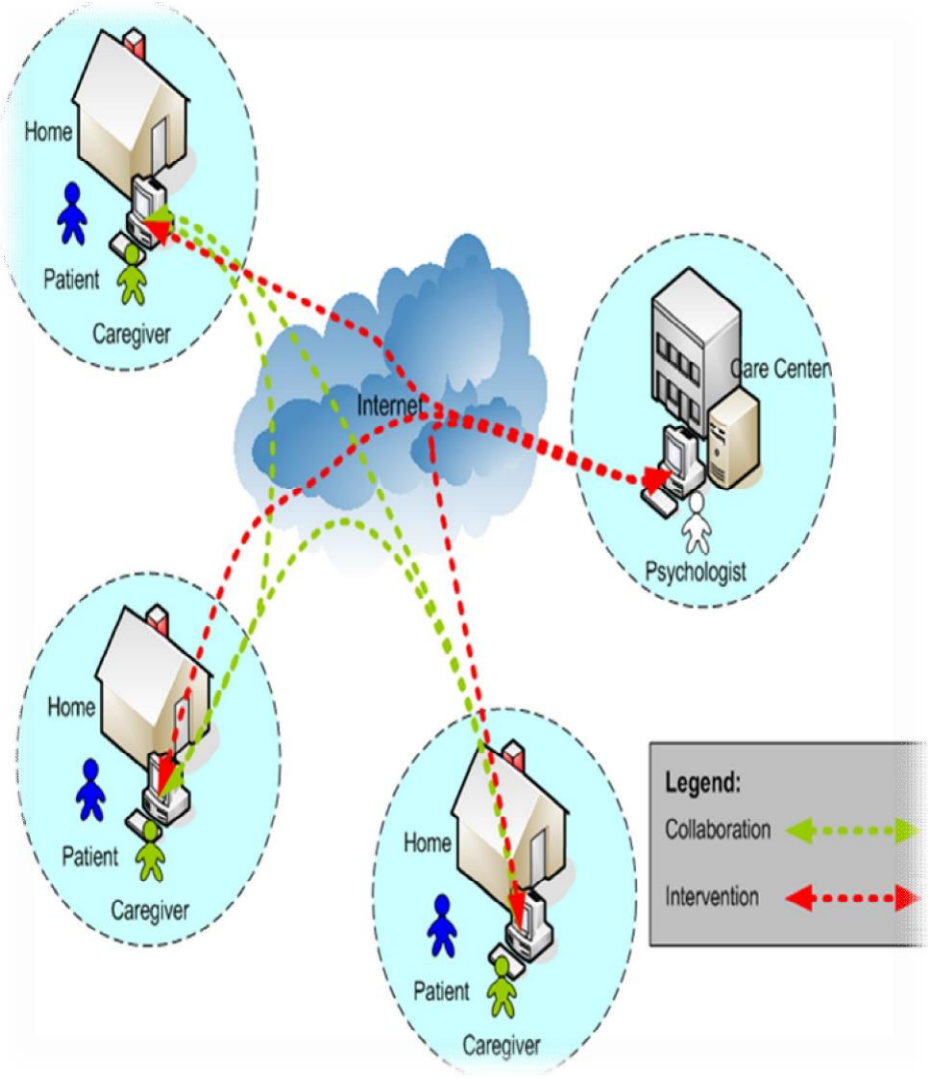
	before	after	.p
PO3-FC6	0.462	0.324	0.001
P6-P8	0.444	0.317	0.001

OUTLINE

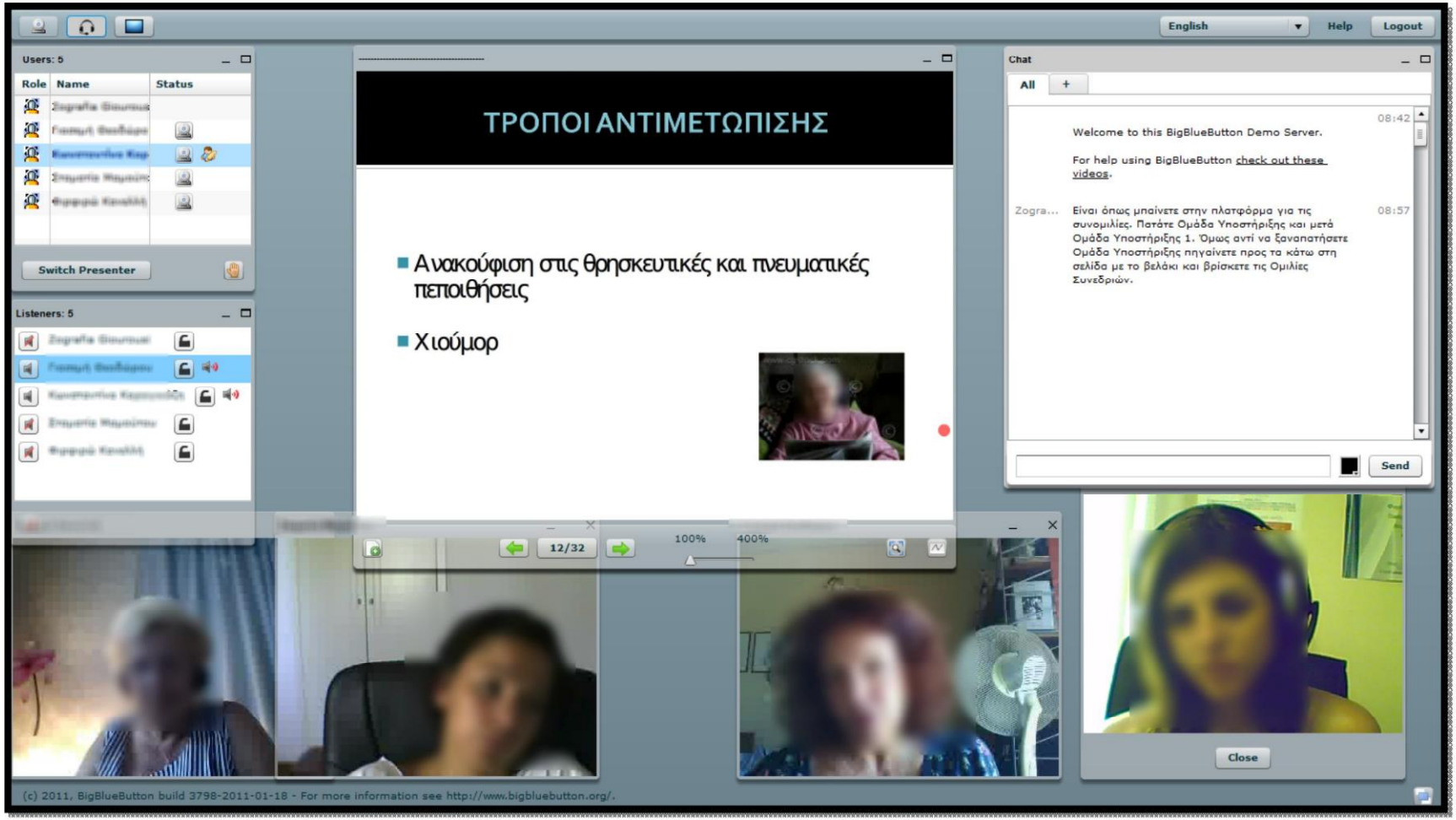
- MANAGEMENT
  - HISTORY
  - PREVENTION
  - CURRENT TREATMENT
    - Pharmacological
    - **Non-Pharmacological**
      - Education-Awareness
      - Interventions for patients
      - **Care for caregivers**
  - FUTURE DIRECTIONS

Caregivers

- Psycho-education
- Support group (CBT)
- Family therapy
- Relaxation techniques
- On line support groups



Support group on line



9th Question
New Technology and

- **Social support:** How can face or audio recognition technology provide real-time feedback reminders and support for social interactions?

World Alzheimer' s Day

ZUMBATHON

Theatre for our Caregivers

Theatre by children for caregivers

Music Evening for Caregivers

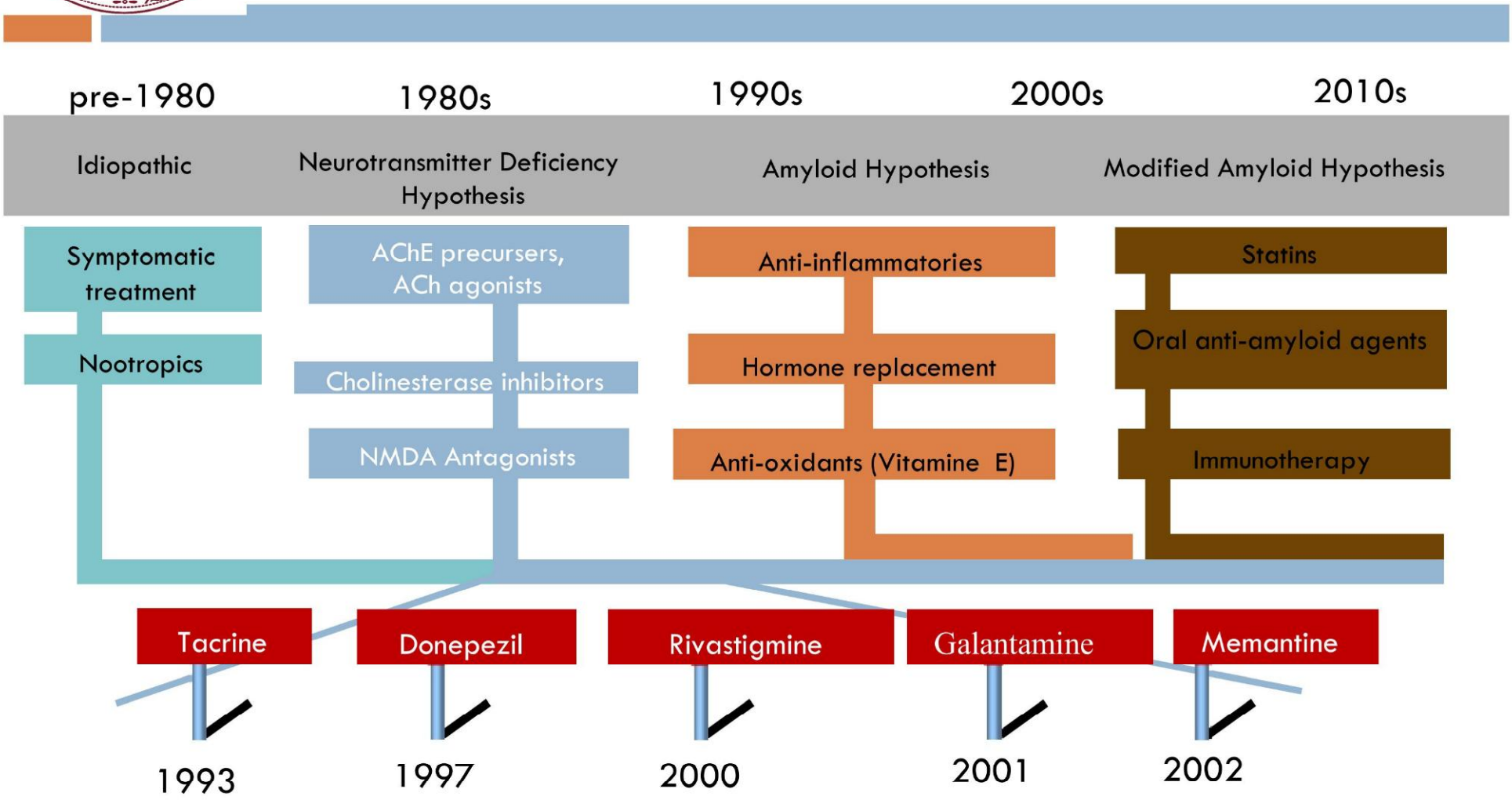
Music Evening for Caregivers

Tango night with Staff dancing

OUTLINE

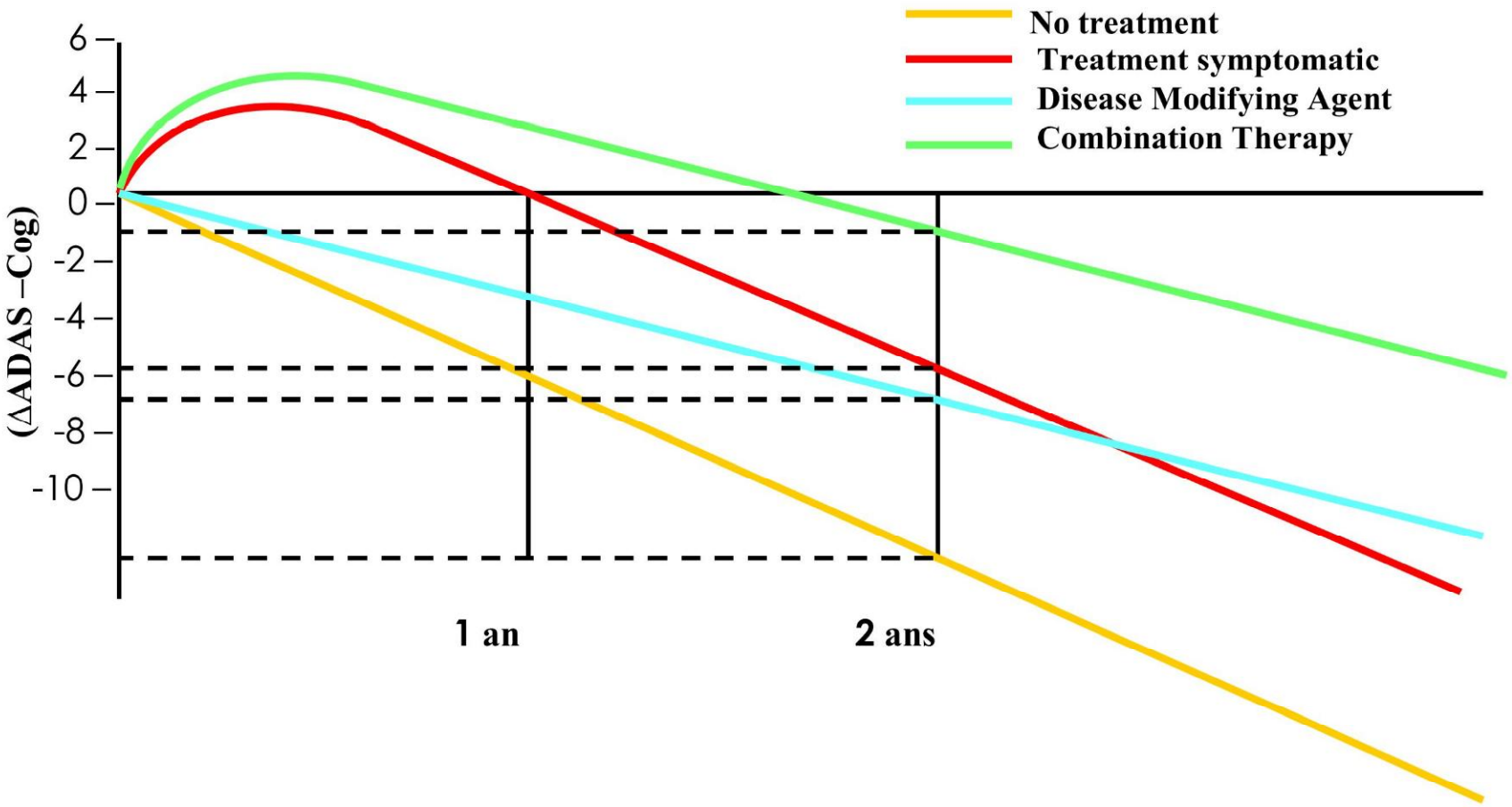
- MANAGEMENT:
  - HISTORY
  - CURRENT TREATMENT
    - Pharmacological
    - Non-Pharmacological
      - Education-Awareness
      - Interventions for patients
      - Care for caregivers
  - FUTURE DIRECTIONS

Development of Alzheimer Pharmacotherapy



Relkin, ADAD 2006

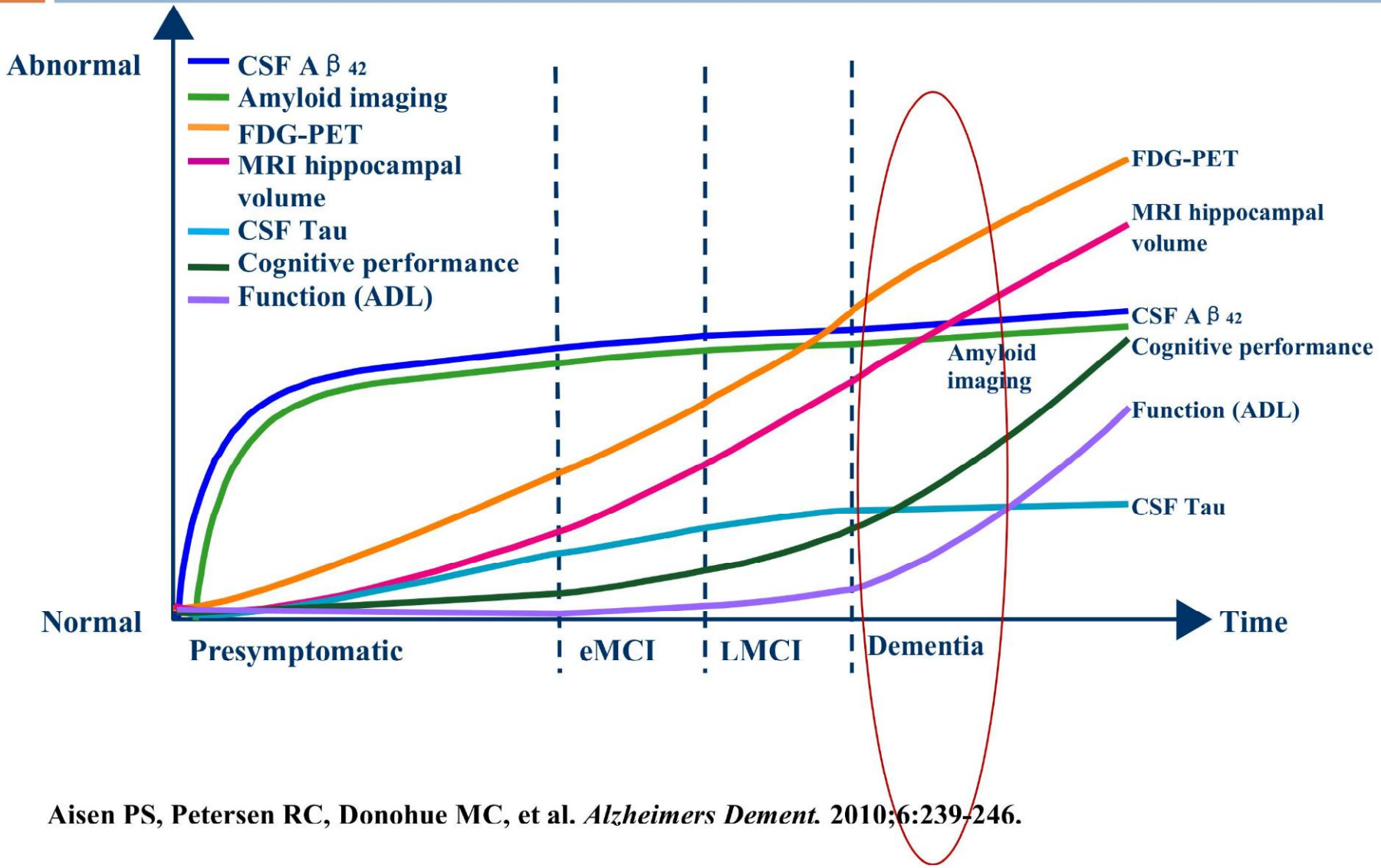
Disease Modifying drugs



The Concept of disease Modifying treatment

- **Difficult to define and subject of much debate**
- **Able to reduce the progression rate**
- **Effect on the physiopathological mechanism of the disease**
- **Able to have a long-lasting effect on disability**

AD Progression



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

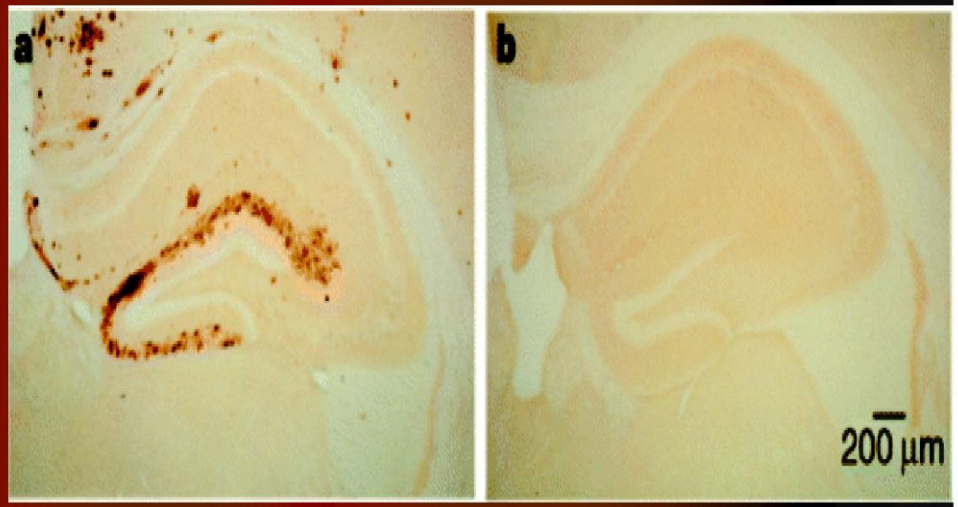
Recent AD Trials: promising targets, mostly negative trials

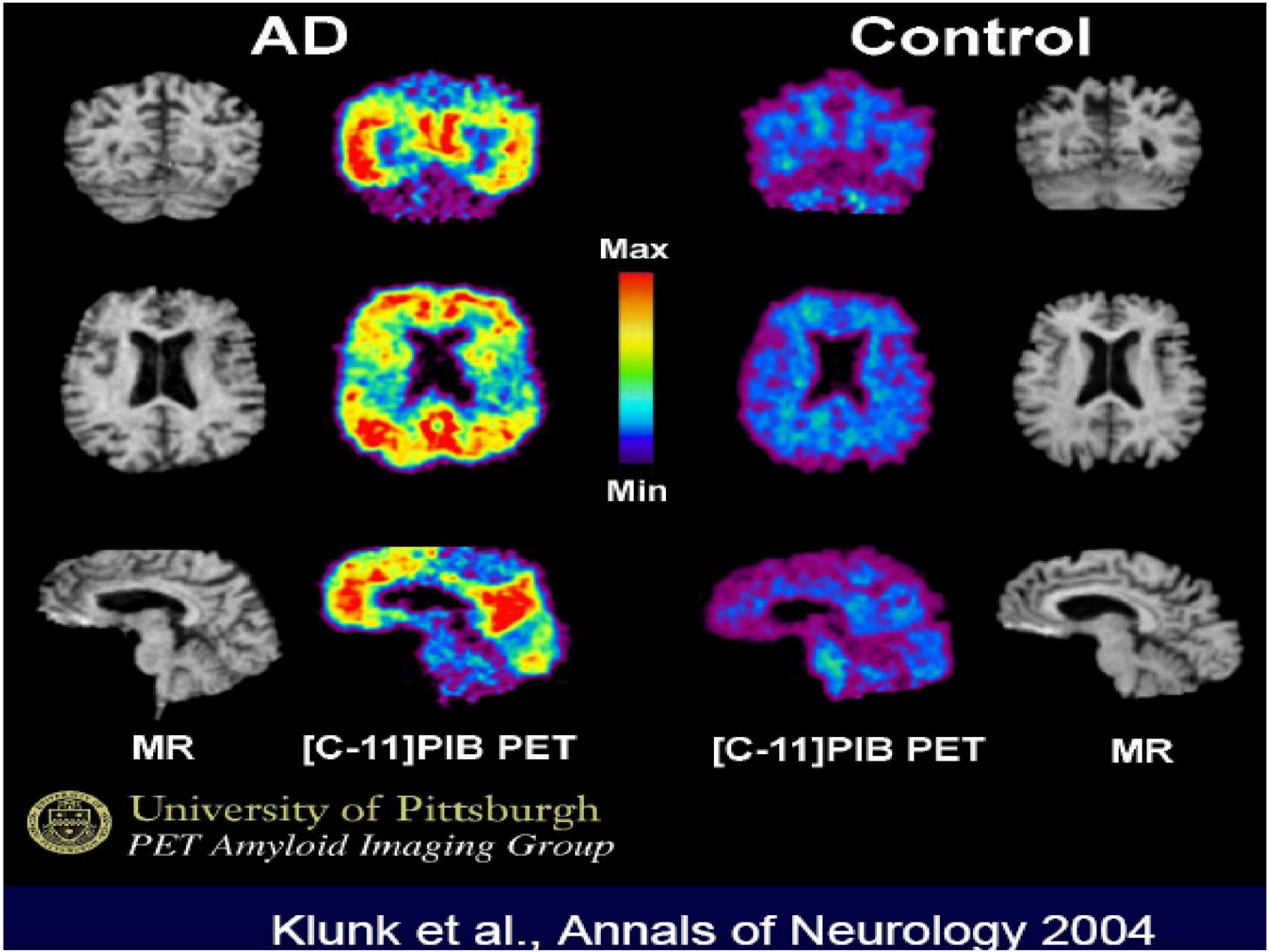
Negative Phase III:

- Xaliproden (neuroprotection)
- Tramiprosate (amyloid anti-aggregation)
- Tarenflurbil (gamma secretase inhibitor)
- Rosiglitazone (metabolic, anti-inflammatory)
- Leuprolide (endocrine)
- Dimebon (mitchondrial?)
- Semagacestat (gamma secretase inhibitor)
- Dimebon (add-on)

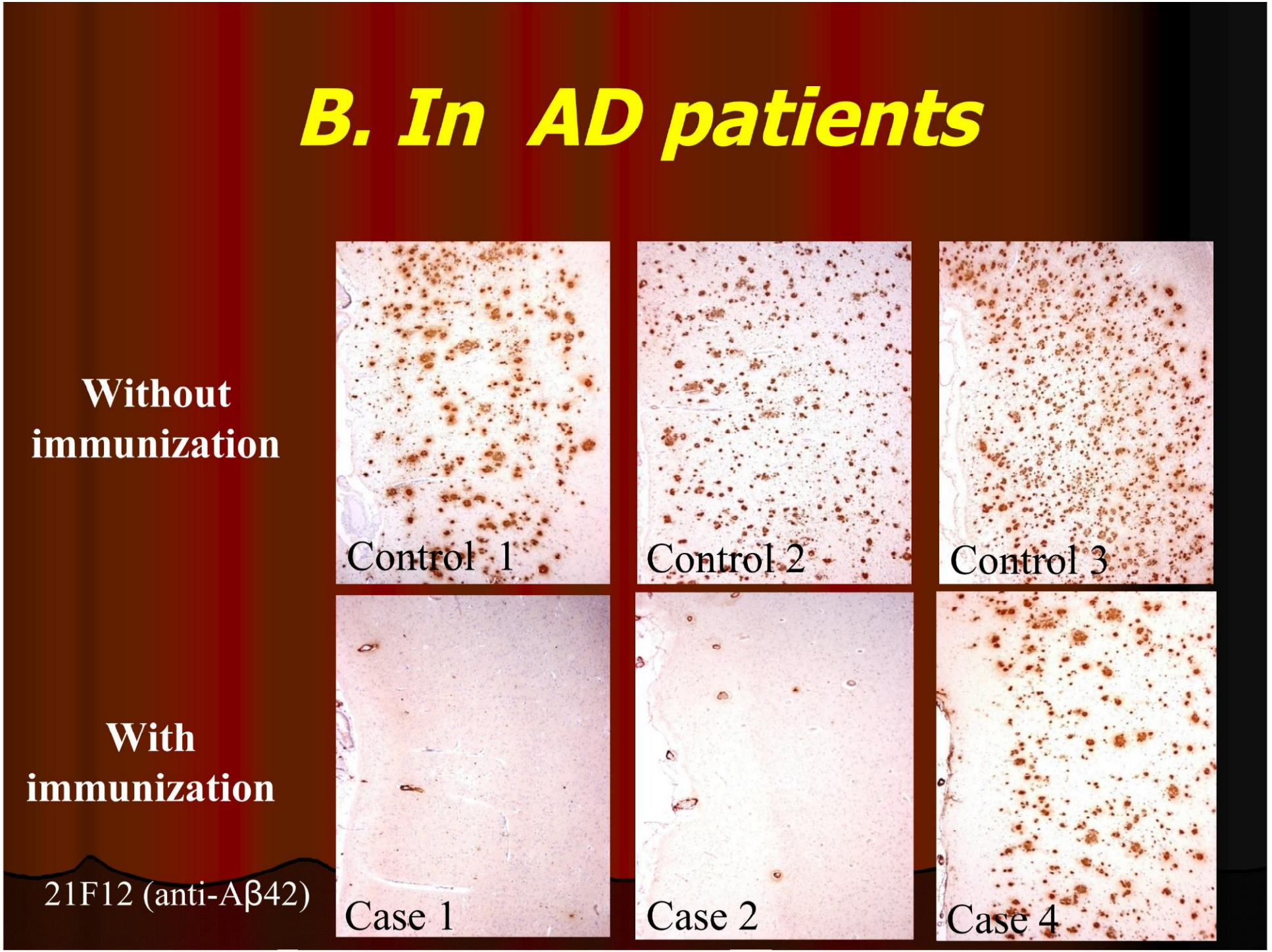
History of immunization A. In animals with AD

- Schenk D. Decrease of Amyloid beta with active immunization
- Nature 1999; 400: 173-177




AD
Control
Max
Min
MR
[C-11]PIB PET
[C-11]PIB PET
MR
University of Pittsburgh
PET Amyloid Imaging Group
Klunk et al., Annals of Neurology 2004

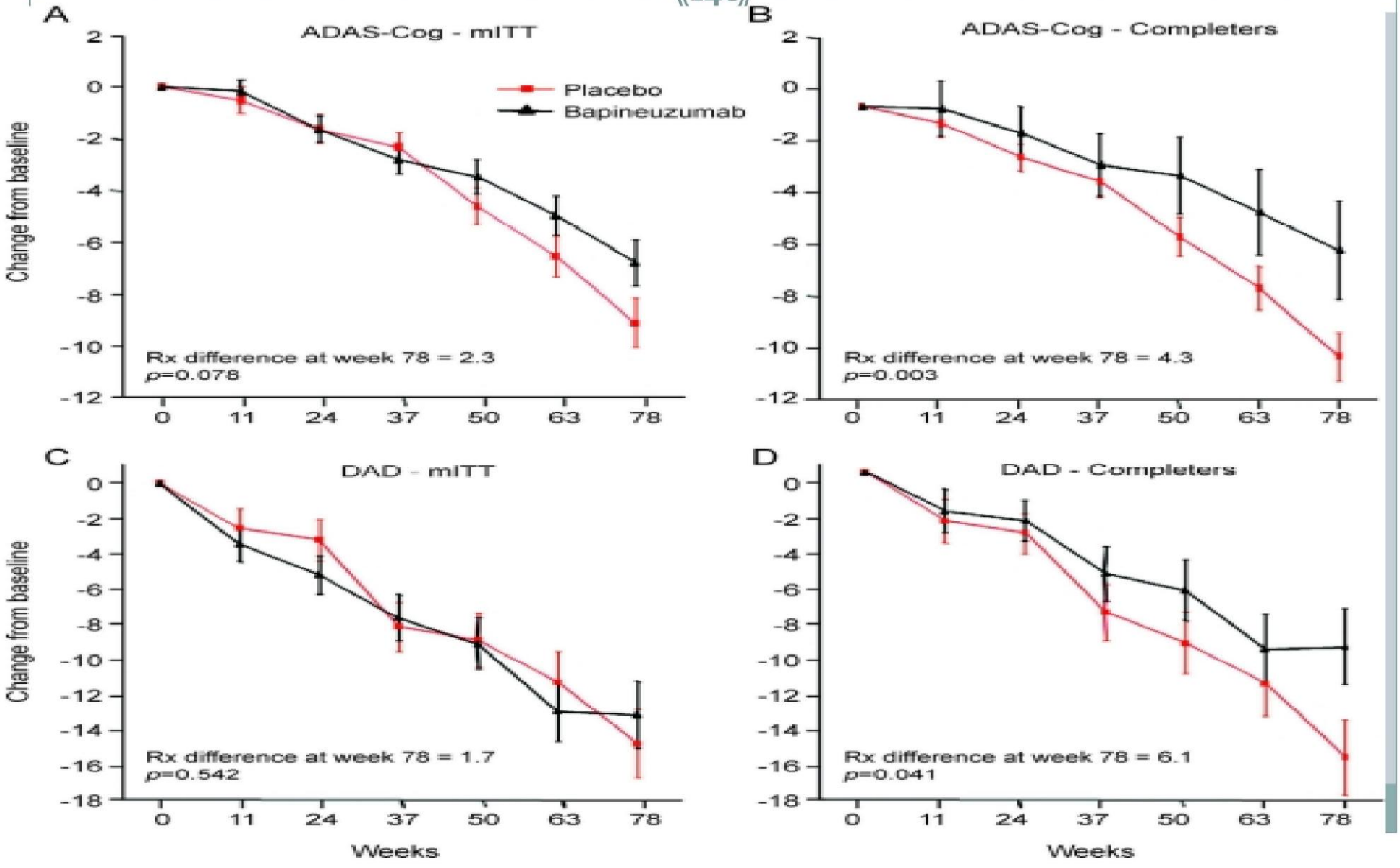
B. In AD patients



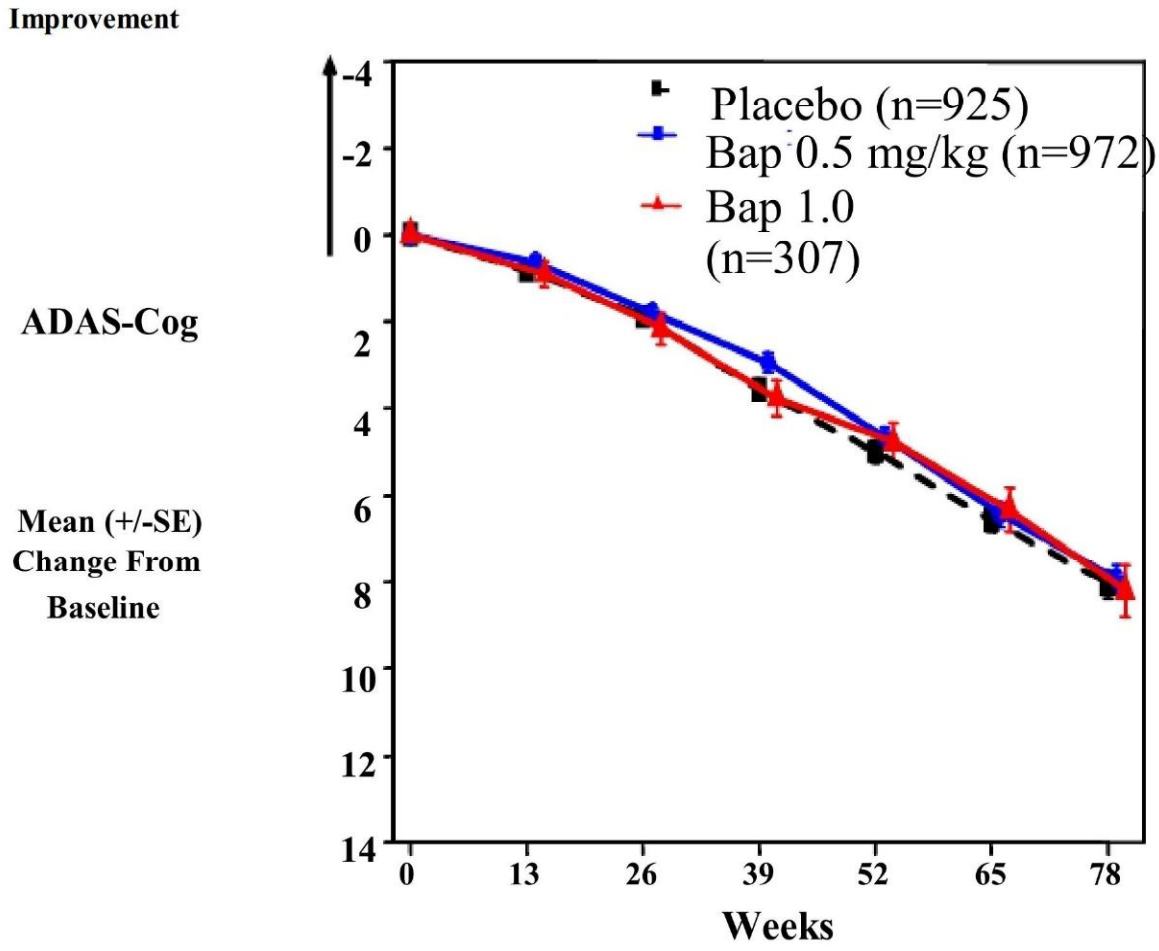
Aβ Immunotherapies in development.

Drug Name	Sponsor	Characteristics		Phase	References
Monoclonal Antibodies		*Epitope*[*]	*Isotype*		
Bapineuzumab (AAB-001)	Janssen/Elan/Pfizer	1–5 (free N- terminus)	IgG1	III	[1,53]; NCT00575055 and NCT00574132
Solanezumab (LY2062430)	Eli Lilly	13–28	IgG1	III	[37–40]; NCT00905372
PF-04360365	Pfizer	33–40 (free C- terminus)	IgG2	II	[42,62]; NCT00722046
MABT5102A	Genentech	NP	NP	I	[43,63]; NCT00736775
GSK933776A	GlaxoSmithKline	NP	NP	I	NCT00459550
Gantenerumab (R1450/RO4909832)	Hoffmann-La Roche	NP	IgG1	I	NCT00531804
Intravenous Immunoglobulin					
Gammagard	Baxter; NIH Alzheimer's Disease Cooperative Study			III	[46]; NCT00818662
Octagam	Octapharma			II	NCT00812565
Active Vaccines		*Fragment*[*]			
CAD106	Novartis	1–6		II	[64]; NCT00795418
ACC001	Pfizer	1–7		II	NCT00498602
UB311	United Biochemical	1–14		I	NCT00965588
V950	Merck	NP		I	NCT00464334
AD01/AD02	Affiris	[**]		I	[47]; NCT00711139/NCT00711321

Phase II: Neurology. 2009 December 15; 73(24): 2061–2070



Phase 3: Bapineuzumap Pooled 302/301 ADAS-Cog Change from Baseline



Pla vs Bap 0.5 mg/kg **p=0.793**
Pla vs Bap 1.0 mg/kg **p=0.842**

No Results

Johnson & Johnson, Pfizer and Eli Lilly studies of 5 years with 2 medications and 2400 patients.

The disapearence of β-amyloid (20 molecules)

With a cost of 270.000.000 $

NO RESULTS

Nature 04-09-12 *(Callaway E., Alzheimer's drugs take a new tack. 489:13–14 doi:10.1038/489013a)*

- 9 of 9 studies phase III with no results

BAXTER ANNOUNCES TOPLINE RESULTS OF PHASE III STUDY OF IMMUNOGLOBULIN FOR ALZHEIMER'S DISEASE

DEERFIELD, Ill., May 7, 2013 – Baxter International Inc. (NYSE:BAX) today announced that its Phase III clinical study of immunoglobulin (IG) did not meet its co-primary endpoints of reducing cognitive decline and preserving functional abilities in patients with mild to moderate Alzheimer's disease. The Gammaglobulin Alzheimer's Partnership (GAP) study was conducted by Baxter in collaboration with the Alzheimer's Disease Cooperative Study (ADCS), a clinical trial consortium supported by the United States National Institute on Aging in the National Institutes of Health.

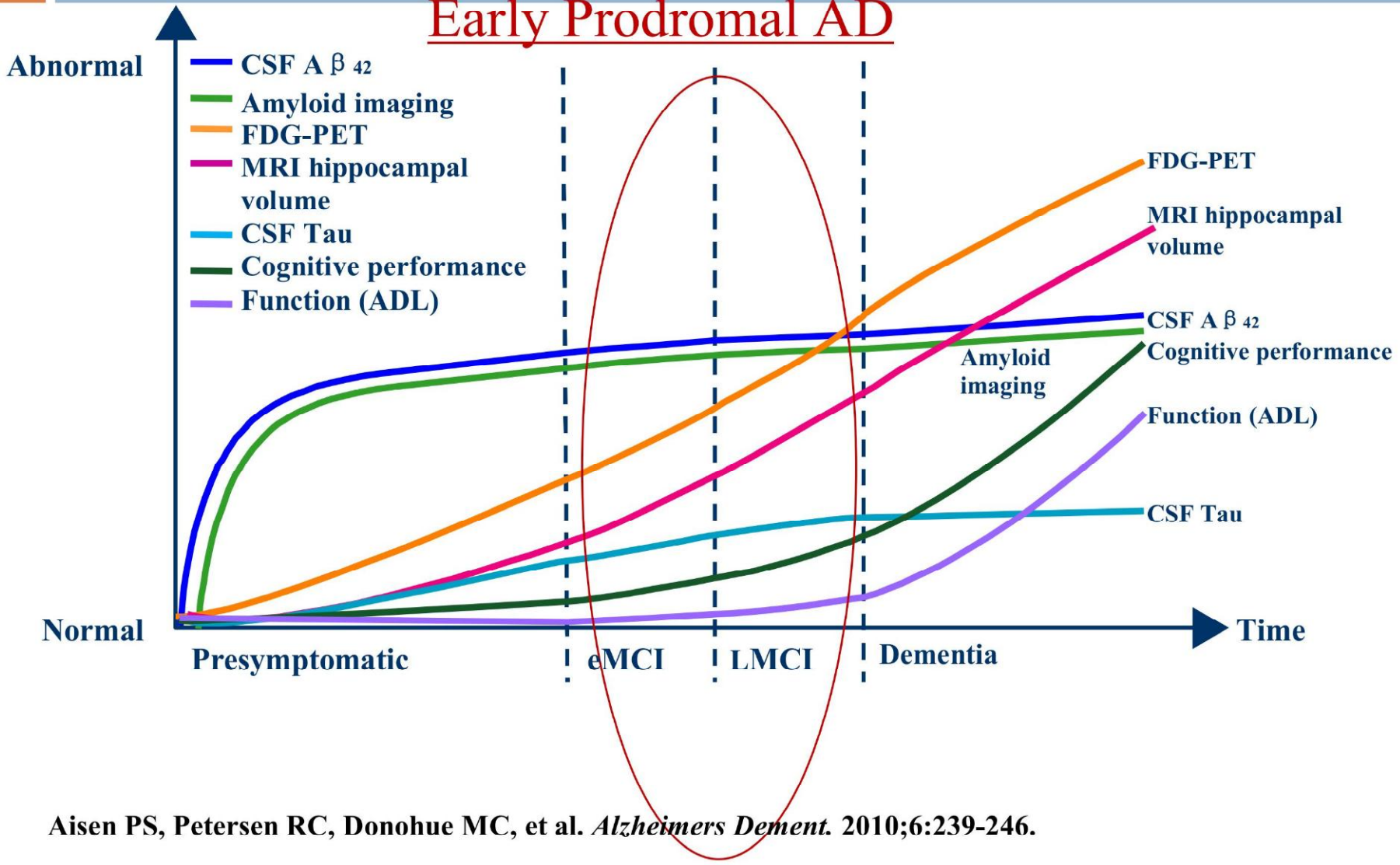
Is dementia too late to treat?

- Neuropathology of AD in the dementia stage is characterized by widespread neurodegeneration and irreversible neuronal loss
- This stage may be too advanced in order to demonstrate clinically relevant benefit with disease-modifying therapies that do not also show symptomatic effects.
- Non-clinical studies suggest immunotherapy with anti-amyloid mAbs produces greater benefit with earlier intervention.

OUTLINE

- MANAGEMENT
  - HISTORY
  - PREVENTION
  - CURRENT TREATMENT
    - Pharmacological
    - Non-Pharmacological
      - Education
      - Interventions for patients
      - Care for caregivers
  - **FUTURE DIRECTIONS-EARLY and LATE future**

AD Progression



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

Current Phase II Predementia AD Trials

Experimental agent	BMS-708163	ACC-001	NewGam 10% IVIG	Gantenerumab
Sponsor	Bristol-Myers Squibb	Pfizer, JANSSEN	Sutter Health	Hoffmann-La Roche
AD stage	Prodementia AD	Early AD	Amnestic MCI	Prodromal AD
Sample size	270	108	50	360
Clinical criteria	Memory complaint MMSE 24-30 WMS Logical Memory or FCSRT Not AD dementia	Reported change in cognition MMSE ⩾25 Global CDR=0.5 Not AD dementia	Petersen criteria of aMCI (⩾domain) CDR=0.5 MMSE 24-30	Caregiver reported decrease in memory over 12 months MMSE ⩾24
Biomarker criteria	CSF – A β 42 <200pg/mL – or t-tau/A β 42 ⩾0.39 CT or MRI scan consistent with AD	Positive AD amyloid-PET scan	No moderate or severe cortical or hippocampal atrophy	Amyloid PET

WHAT COULD HELP US;

CSF FINDINGS have 50-70% of patients with MCI

PET Fibrillar beta amyloid 40-70%

Both examinations suggest the MCI patients who will progress to AD De Mayer G 2010

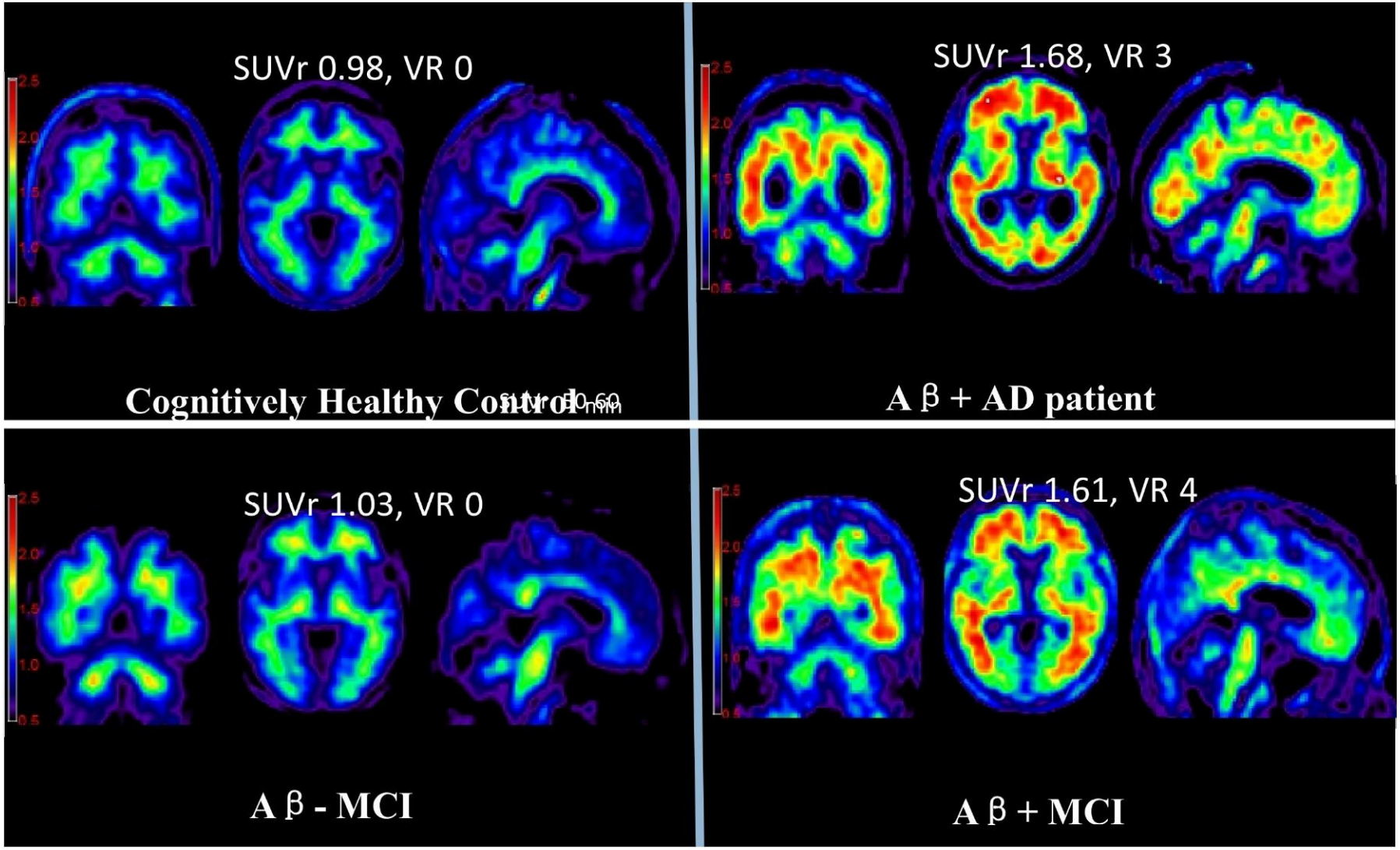
Biological markers of beta Amyloid: **Aβ CSF**, **Aβ PET**

Biological markers of brain injury: **Tau CSF**, **atrophy in hippocampus , FDG PET**

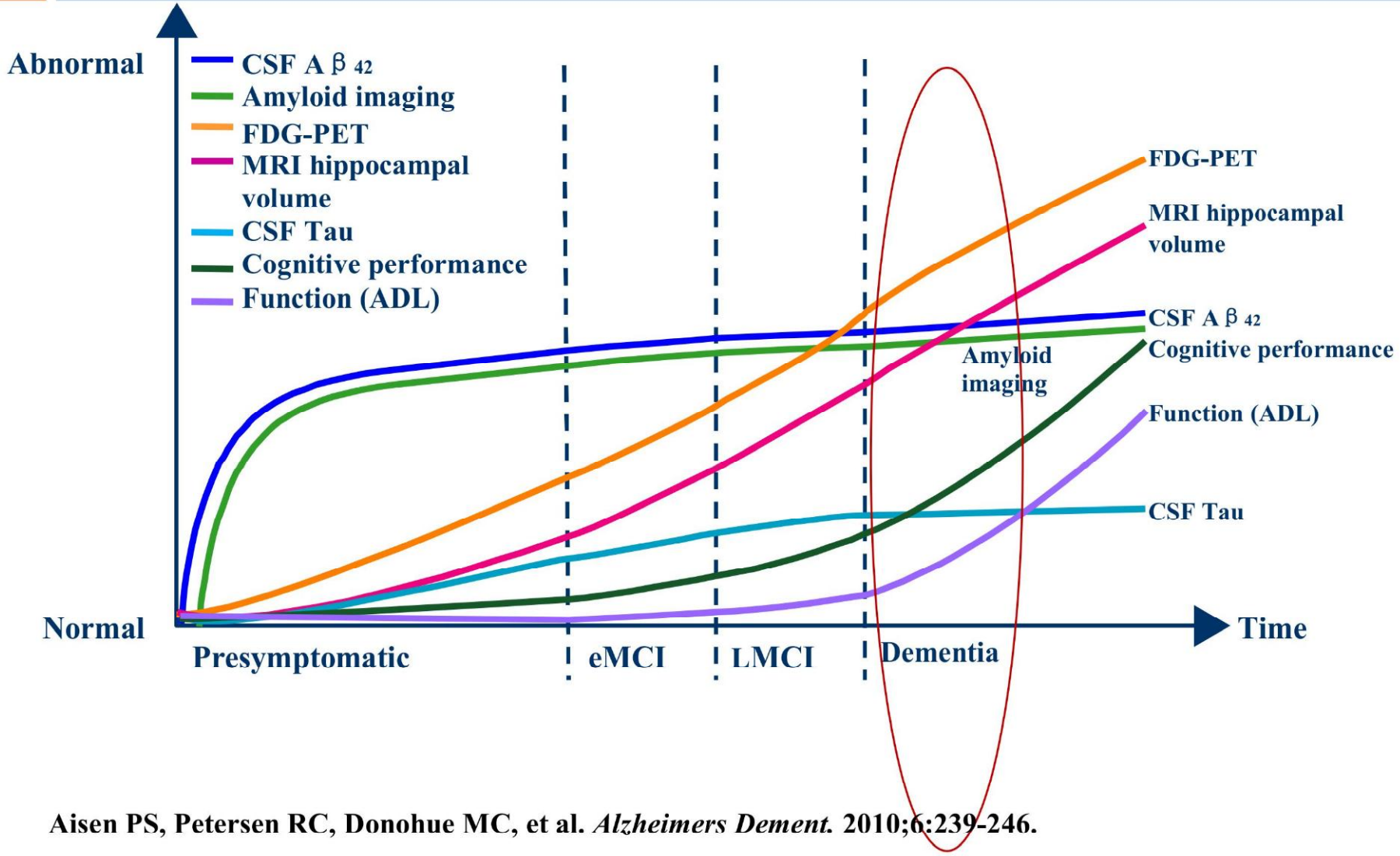
There is a big need for early diagnosis

MRI 3T
Neuropsychological Battery (Three hours)
EEG, ERPs
CSF
Blood

Amyloid Imaging with Florbetapir F 18



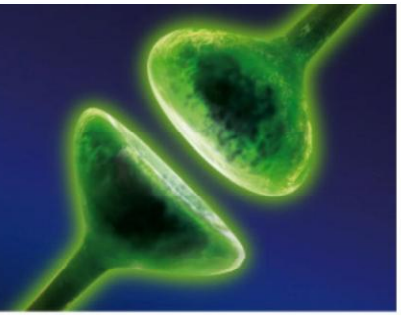
What about new medications for AD?

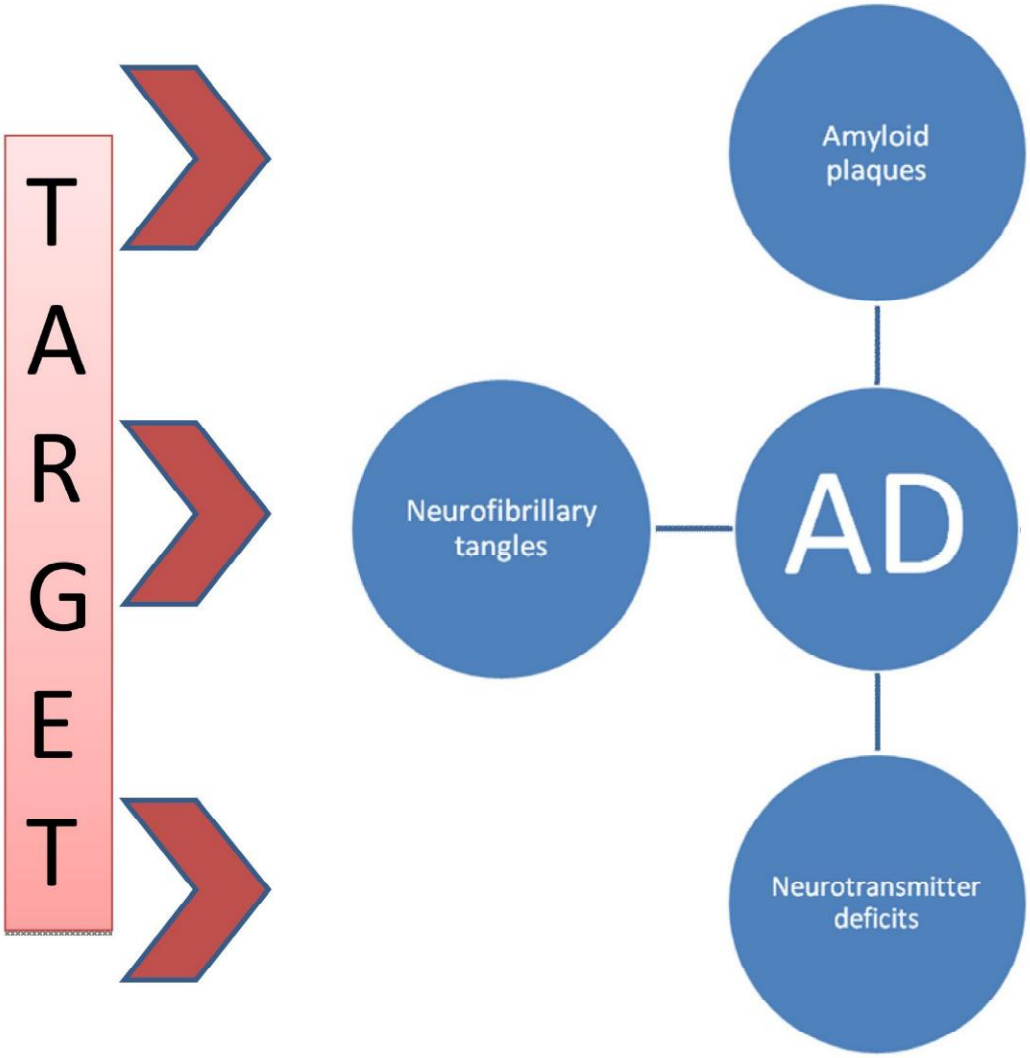


Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

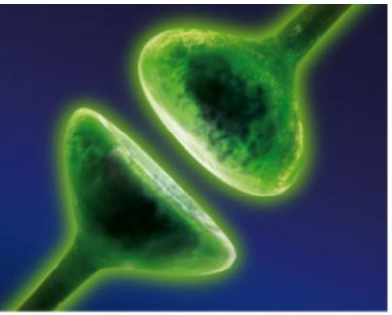

A new nutritional approach targeting Synapse loss
NUTRICIA
Souvenaid®

AD Management: Approaches





Souvenaid – designed to support synapse formation



- Souvenaid, a multi-nutrient drink, hypothesis driven
- Based on 10 years' pre-clinical work

Fortasyn™ Connect

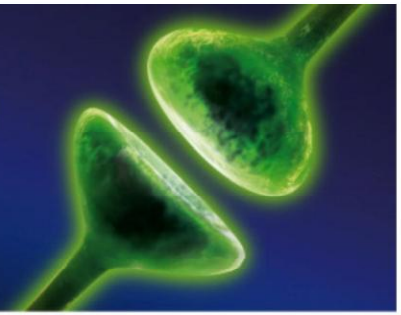
- Uridine (UMP)
- Omega-3 fatty acids
- Choline
- Phospholipids
- B vitamins
- Antioxidants

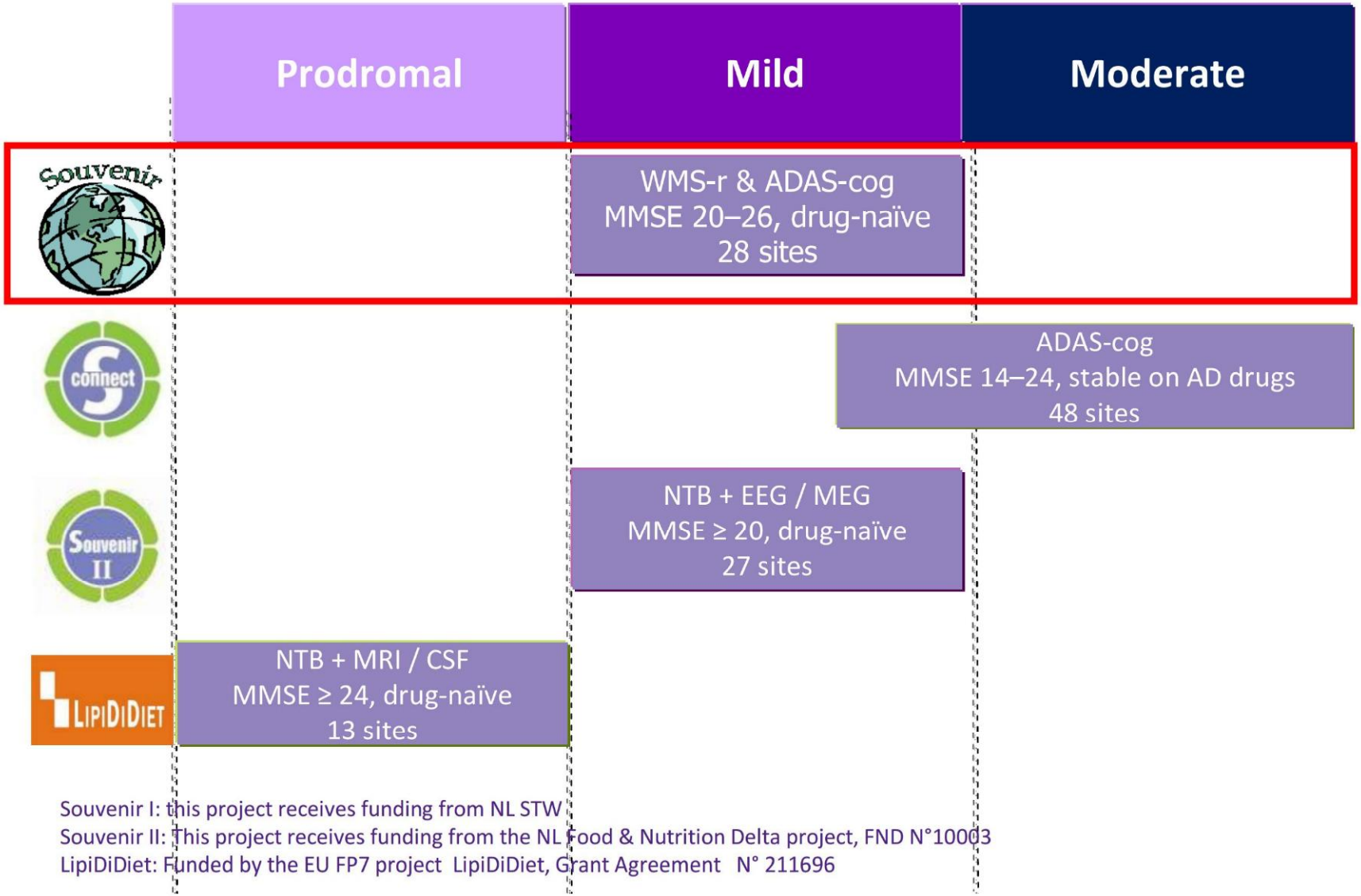
Targeted to

Support formation of synapses

Various international pre-clinical research consortia
Including Lipidiet, LipiDiDiet, Dementia, Neuronutrients
Dr Kiliaan, Professor Soininen, Professor Hartmann

Full clinical trial programme across the AD spectrum





Souvenir I: this project receives funding from NL STW
Souvenir II: This project receives funding from the NL Food & Nutrition Delta project, FND N°10003
LipiDiDiet: Funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696

ELSEVIER

Alzheimer's & Dementia 6 (2010) 1–10

Alzheimer's & Dementia

Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial

Philip Scheltens[a,*], Patrick J. G. H. Kamphuis[b], Frans R. J. Verhey[c], Marcel G. M. Olde Rikkert[d], Richard J. Wurtman[e], David Wilkinson[f], Jos W. R. Twisk[g], Alexander Kurz[h]

1. Very good safety and tolerability profile:
   - No differences in AEs
   - Very high compliance (94%)
2. Expected nutritional and biochemical changes
3. Significant effect on end point 1 Memory (WMS-r)
4. No effect on end point 2 Cognition (ADAS-cog)
   - Baseline as predictor
5. Additional analysis on subgroups and behaviour:

= Paper # 1 – *Published*

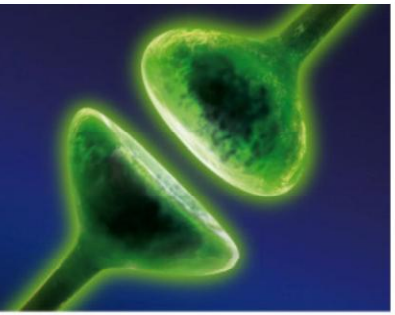
- Cognition in subgroup of moderate AD = Paper # 2 - *published*
- Effect on BMI = Paper # 3 - *published*
- ADL in low BMI subgroup = Paper # 3 - *published*
- Memory effect in very mild AD = Paper # 4 - *published*

Souvenir II: Effect of Souvenaid on memory in patients with mild AD

Significant effect on NTB memory domain score during 24 weeks (p=0.023)

Souvenir II: Statistical analysis re-run by Rush Alzheimer's Disease Center
ITT, Mixed Model for Repeated Measures, 2 df contrast (trajectory of change, mean ± SE)

Souvenir II: Summary



- Souvenaid improves memory during 24 weeks in mild AD patients
- Very positive safety profile
- Very high adherence

LipiDiDiet: EU funded running long-term trial

Principal investigator: Professor Hilkka Soininen, University of Eastern Finland, Kuopio, Finland

Multi-country, multi-centre study (13 sites in The Netherlands, Germany, Sweden and Finland)

24-Months randomised, controlled trial in 300 people with prodromal AD

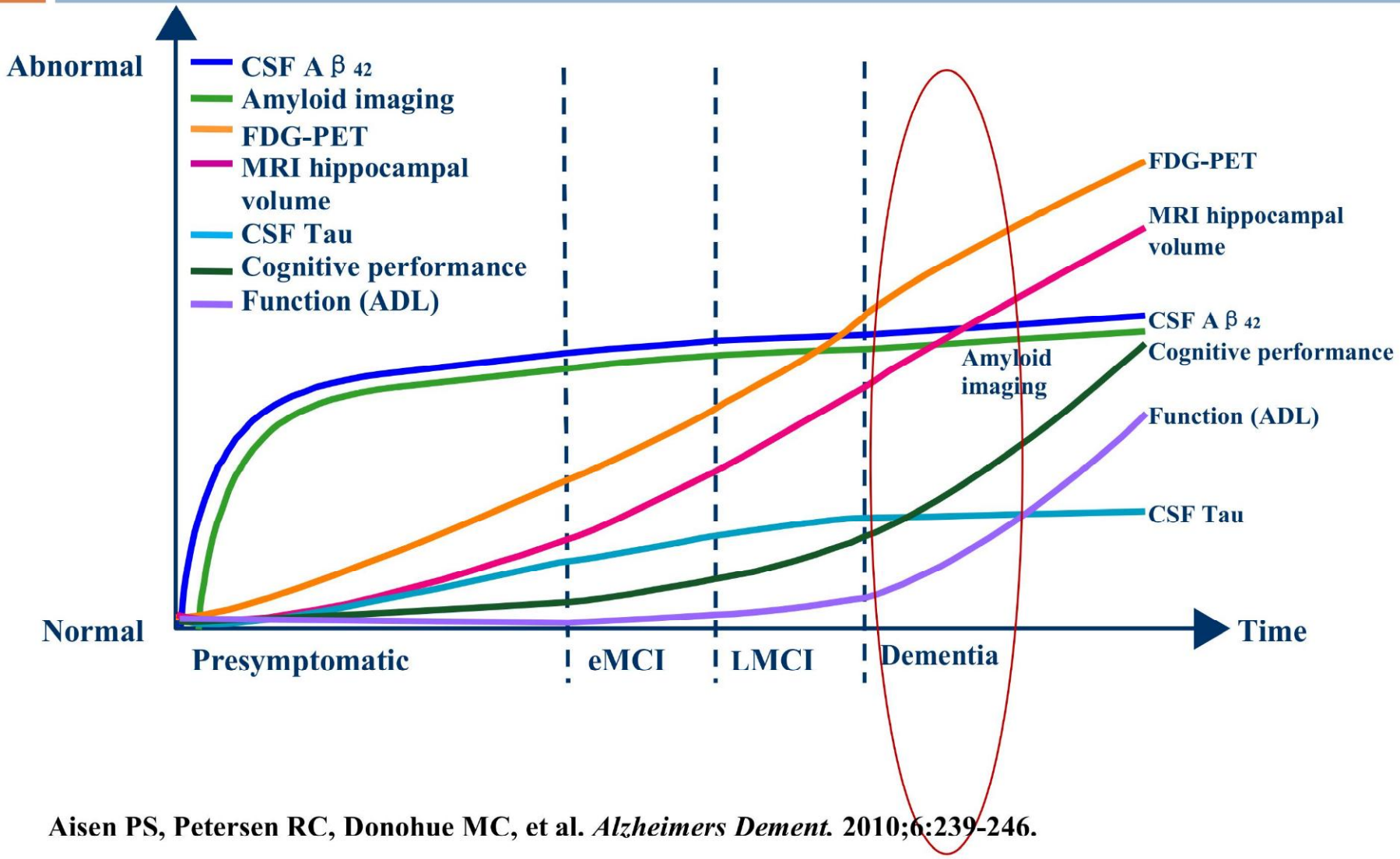
Eligibility:

- Prodromal Alzheimer diagnosis (Dubois et al, 2007)
- MMSE ≥ 24

Outcome measures:

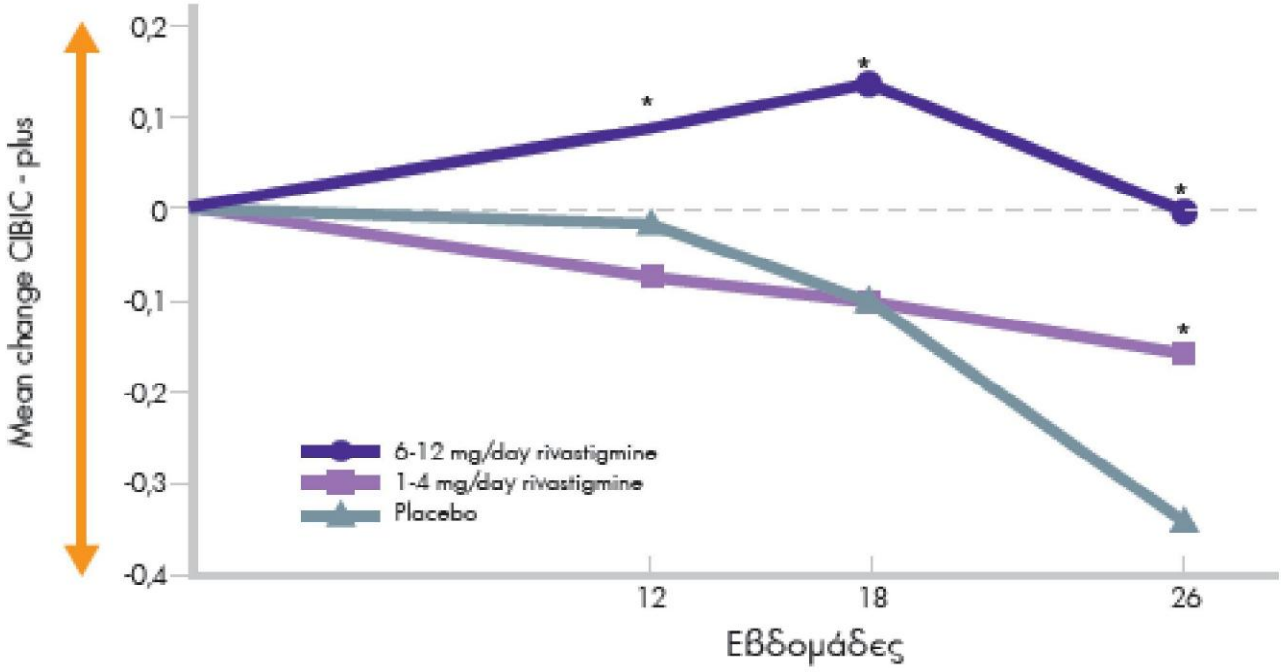
- **Primary:** z-score of a Neuropsychological Test Battery
- **Secondary:** Progression to AD, functional (ADCS-ADL) nutritional biomarkers, safety and adherence
- **Biomarkers:** CSF and MRI

What about AD?



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

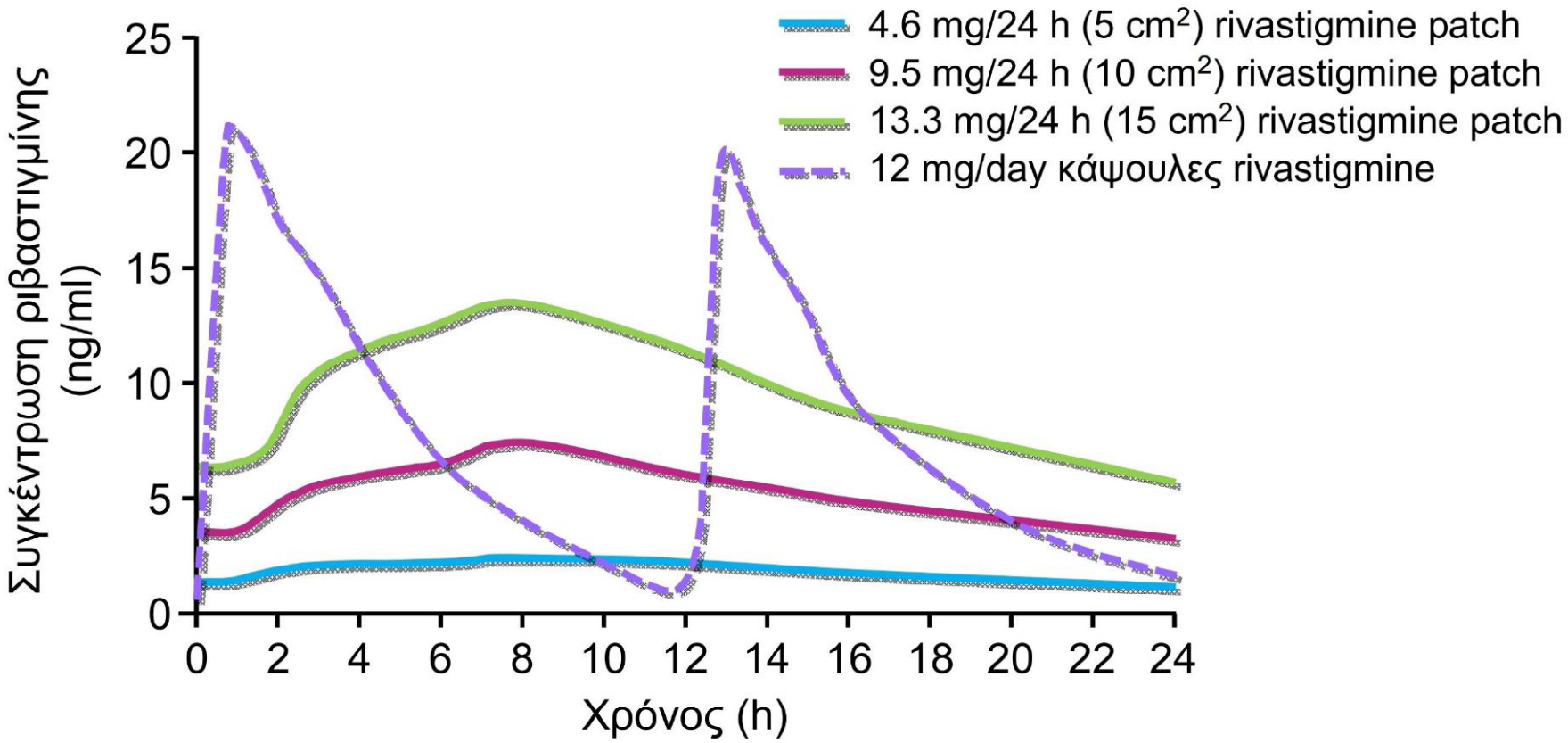
Rivastigmine and dose-depended results



Αποτελέσματα από τυχαιοποιημένη μελέτη ριβαστιγμίνης (Exelon) έναντι placebo διάρκειας 26 εβδομάδων

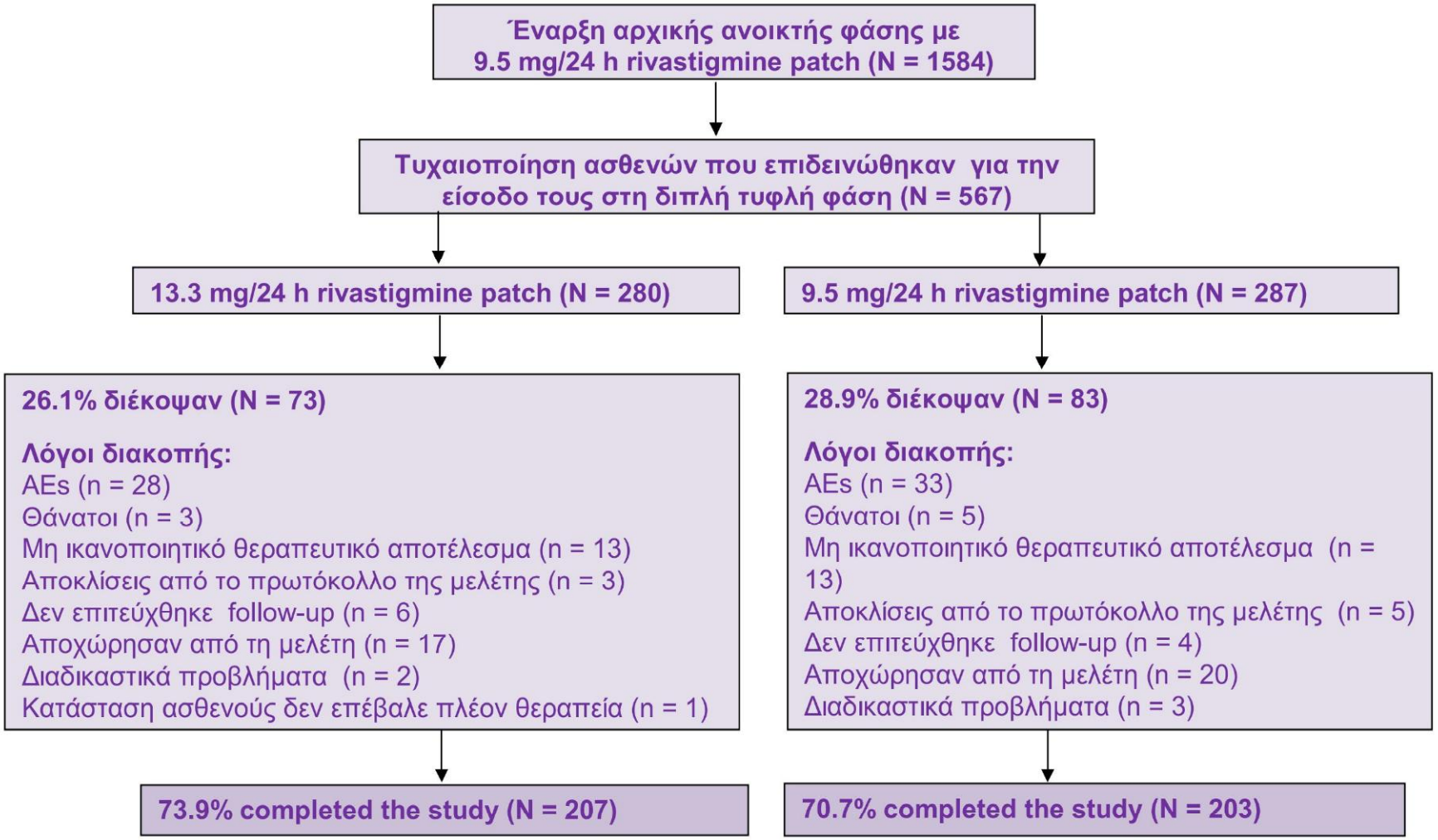
Προσαρμογή από Schneider et al.[4]

The best pharmacokinetic profil with rivastigmine patch

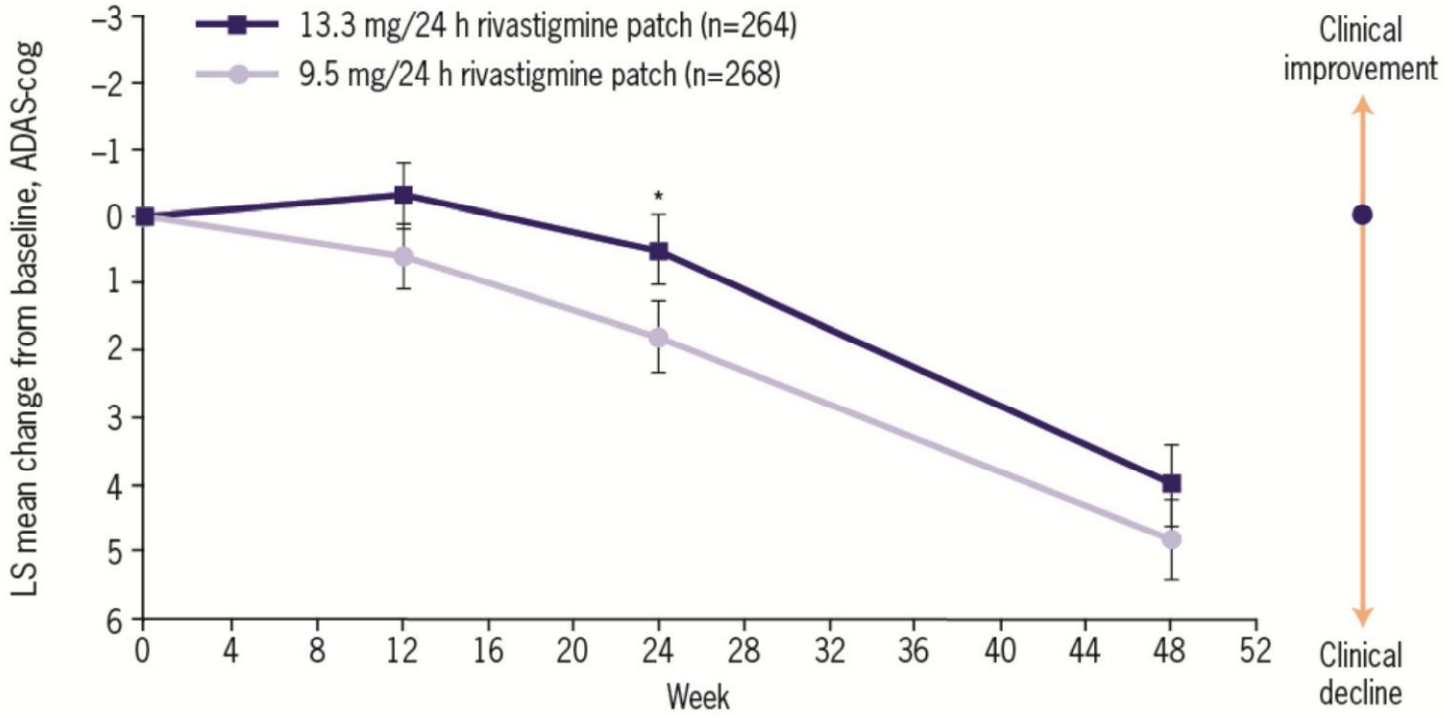


[1]Mercier F *et al. Curr Med Res Opin* 2007;23(12):3199–204. [2]Novartis, data on file.

Participants



More delay in deterioration of cognitive function with Exelon Patch 13,3 mg



ITT-DB, Intention-To-Treat double-blind; LOCF, Last Observation Carried Forward; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; LS, least-squares; error bars represent the standard error of the mean; *p = 0.027 13.3 mg/24 h *versus* 9.5 mg/24 h patch. P-value based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-cog score.

Summary drug treatment

- AD is a multifactorial disease
- There is a need for

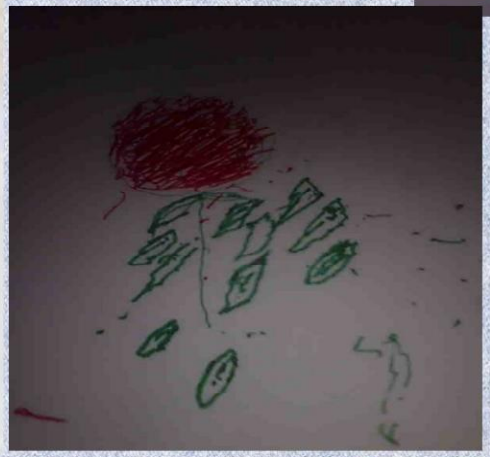
DISEASE MODIFYING DRUGS

  - With different modes of action and perhaps also individualized regimens

Aβ	Tau	ApoE	Chol	Inflam	OS

- In parallel, there is a need for **EARLY DIAGNOSTIC TOOLS / BIOMARKERS**

This disease touch the button “delete” of the computer of our life



We have something to do. We are all candidates…

Dwayne J. Clark, Αύγουστος, 2012


The patient with dementia suffers.
We have to do something for him today

- Considering the increased knowledge on AD causes and treatment possibilities during the last 30 years - even though many trials lately have been negative - there are all reasons to be optimistic about the future!

  but…..

- MORE RESEARCH IS NEEDED!

Thank you for your attention