Cognitive Trajectories Associated with Amyloid-β Deposition in Normal Aging and MCI

Presenter:
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12th Annual Mild Cognitive Impairment Symposium, Miami Beach, January 18, 2014

- I have nothing relevant to disclose.

Taking the long view: Cognitive-change correlates of amyloid-beta in non-demented older adults

- Outline
  - Study 1: Aβ & cognitive change in a non-demented oldest-old sample (85+)
  - Study 2: Aβ & cognitive change in a younger-old sample of normal aging (65+)
  - Study 3: Aβ & subjective ratings of memory change in normal aging

Background

VIEWS & REVIEWS

Meta-analysis of amyloid-cognition relations in cognitively normal older adults

Trey Hedden, PhD
Hwamee Oh, PhD
Alayna P. Younger, BA
Tanu A. Patel

ABSTRACT

Objective: We conducted a meta-analysis of relationships between amyloid burden and cognition in cognitively normal, older adult humans.

Methods: Methods of assessing amyloid burden included were CSF or plasma assays, histopa-

<u>Hedden et al. (2013) meta-analysis</u>

- Small associations between A-beta & cognition in CN older adults
- Episodic memory, *r* = .12 with PiB imaging (primary analysis)
- Executive fx & global cognition, only sig. in secondary analysis
  - (*r* = .08 & *r* =.09)
- Visuospatial function, semantic memory (language), processing speed, working memory NS
- *5 / 34 datasets were longitudinal*

Background

- Studies reporting *longitudinal cognition* & A-beta imaging in CN:
  - Storandt et al., 2009, *WU*
  - Resnick et al, 2010, *BLSA*
  - Ewers et al., 2012, *ADNI (PiB-PET)*
  - Landau et al., 2012, *ADNI (florbetapir)*
  - Lim et al., 2013, *AIBL*
  - Villemagne et al., 2013, *AIBL*
  - Wirth et al., 2013, *BAC*

Taking the long view:

Cognitive-change correlates of amyloid-beta in non-demented older adults

Study 1: A-beta in the oldest-old (85 +)

- GEMS Imaging Sub-Study (U01 AT000162, PI DeKosky)
- A-beta positivity *highly prevalent* (55 %)
- weakly associated with cognitive status concurrent with imaging
  - Matthis et al., Annal of Neurol, 73(6), 2012
- associated with retrospective cognitive decline?

The Ginkgo Evaluation of Memory Study (GEMS)

- 2000- 2008: Randomized, double-blind, placebo-controlled 4-site trial
- n= 3072
- 240 mg of Ginkgo biloba daily
- No drug effect observed on incident dementia (DeKosky et al., 2008) or cognitive decline (Snitz et al., 2009)
- Mortality 12.4%; lost 6.4%; dementia 17.0% (= endpoint)

The GEMS Imaging Sub-Study

- 2009: PiB-PET & MRI imaging
- n = 194 Pittsburgh participants, non-demented at GEMS close-out
- Mean age 85.5 (range 82-94); educ. 14.7 years (range 9-20); 59.3% ♂
- Neuropsychological assessment; consensus diagnosis
- Pittsburgh Compound B (PiB)-PET; SUVr summed 50-70 minutes, referenced to cerebellum
- Global cortical cutoff of 1.57 SUVr defined Aβ-negative vs. Aβ-positive groups

GEMS Neuropsychological Test Battery

Six evaluations over 8 years prior to PiB-PET imaging

Snitz et al., Neurology. 80(15):1378-1384, 2013

COGNITIVE DOMAIN	TESTS	
Memory	California Verbal Learning Test	Modified Rey-Osterrieth Figure recalls
Visuospatial Reasoning	Modified Block Design	Modified Rey-Osterrieth Figure copy
Attention/ psychomotor speed	Trail Making part A	Digit span forward
Executive function	Trail Making part B	Digit span backward; Stroop color-word interference test
Language	Modified Boston Naming	Verbal fluency (category and initial letter)

Analysis:

Linear mixed models, adjusting for age, sex, race & education

Aβ status x Time interaction term reflects group difference in cognitive performance slopes over time

Aβ-status group characteristics at time of PiB imaging

	Aβ –negative n = 87 **(44.9%)**	Aβ –positive n =107 **(55.1%)**	*p*
Age, mean (SD), y	85.2 (2.5)	85.7 (3.0)	.18
Male sex, n (%)	55 (63.2%)	59 (55.1%)	.26
Non-white race, n (%)	3 (3.4%)	4 (3.7%)	.91
Education, mean (SD), y	14.7 (2.8)	14.7 (2.5)	.97
APOE*4 allele carrier, n (%)	5/82 (6.1%)	32/98 (32.7%)	**<.01**
Estimated premorbid verbal IQ	118.3 (8.3)	119.3 (7.1)	.35

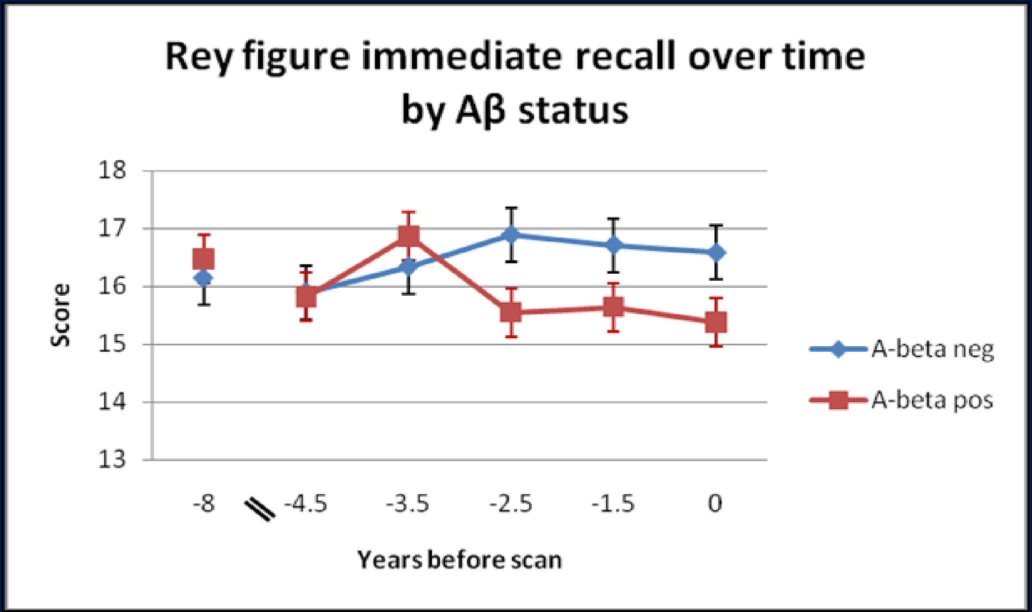
Neuropsychological test performance at imaging

	Aβ –negative n = 86	Aβ –positive n =104	*p*
CVLT sum learning trial	44.9 (11.6)	41.5 (12.1)	.07
CVLT delayed recall	8.5 (3.7)	8.0 (3.7)	.37
Rey figure immediate recall	16.7 (3.8)	15.6 (4.0)	.08
Rey figure delayed recall	16.2 (4.1)	15.8 (4.1)	.74
Rey figure copy	20.7 (2.4)	20.2 (2.2)	.13
Trails A	42.3 (15.0)	48.5 (17.8)	**.05**
Trails B	106.7 (45.4)	123.3 (51.9)	.06
Semantic fluency (animals)	15.8 (3.7)	14.4 (4.0)	**.05**
Letter fluency (F, S)	27.3 (8.6)	28.3 (8.0)	.34

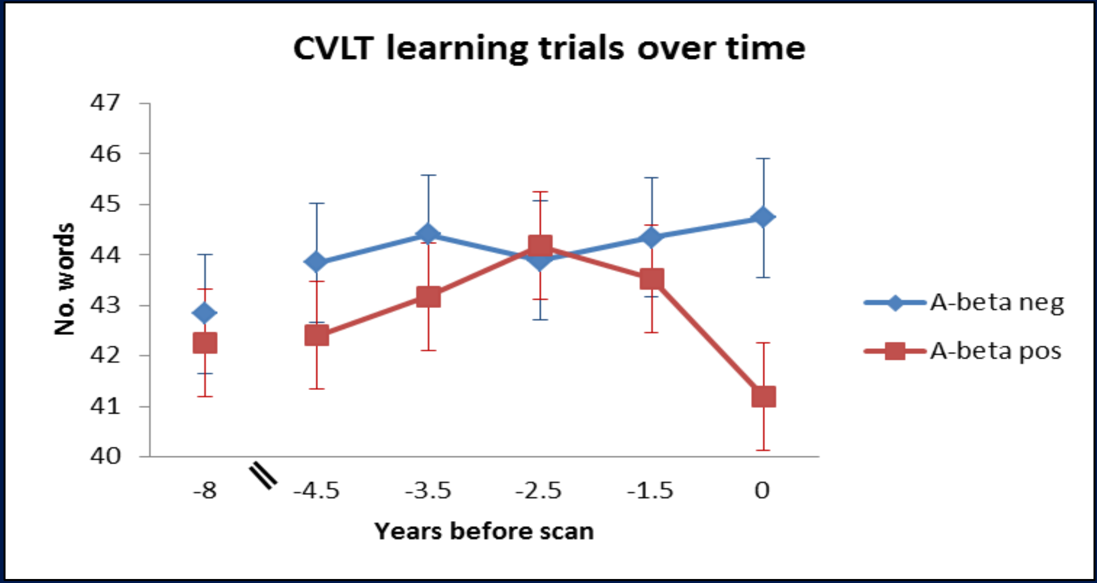
Annual rates of change on NP tests over previous 8 years

	Aβ –negative	Aβ –positive	Group X Time *p*
Memory			
CVLT delayed recall	-0.03	-0.09	.22
R-O figure delayed recall (range 0-24)	+0.10	-0.10	**.02**
Executive functions			
Trails B (sec.) **	+1.56	+3.33	**.01**
Stroop color-word interference (no.)	-2.28	-2.07	.65
Visuospatial construction			
Block design (range 0-24)	-0.13	-0.06	.32
R-O figure copy (range 0-24)	-0.14	-0.24	.06
Language			
Semantic fluency	-0.01	-0.18	**.01**
Phonemic fluency	+0.35	+0.36	.99
Boston Naming Test (range 0-30)	+0.07	+0.06	.91
Attention			
Trails A (sec.) **	+0.39	+1.02	**.02**
Digit Span forward	+0.03	-0.02	.24

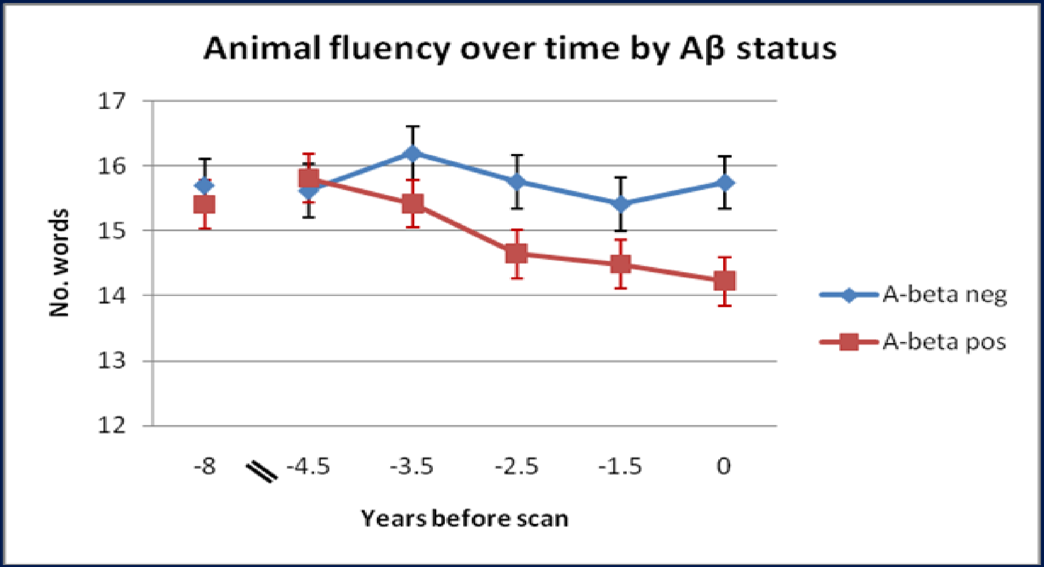
Shape of cognitive trajectories: mixed model estimates of each group at each assessment



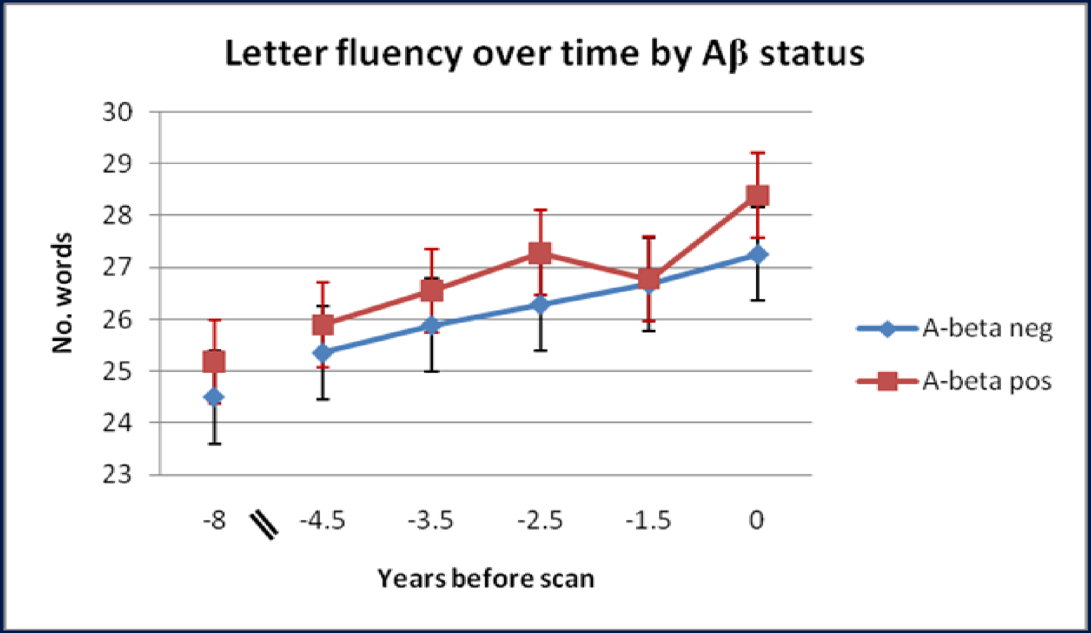
Learning & Recall



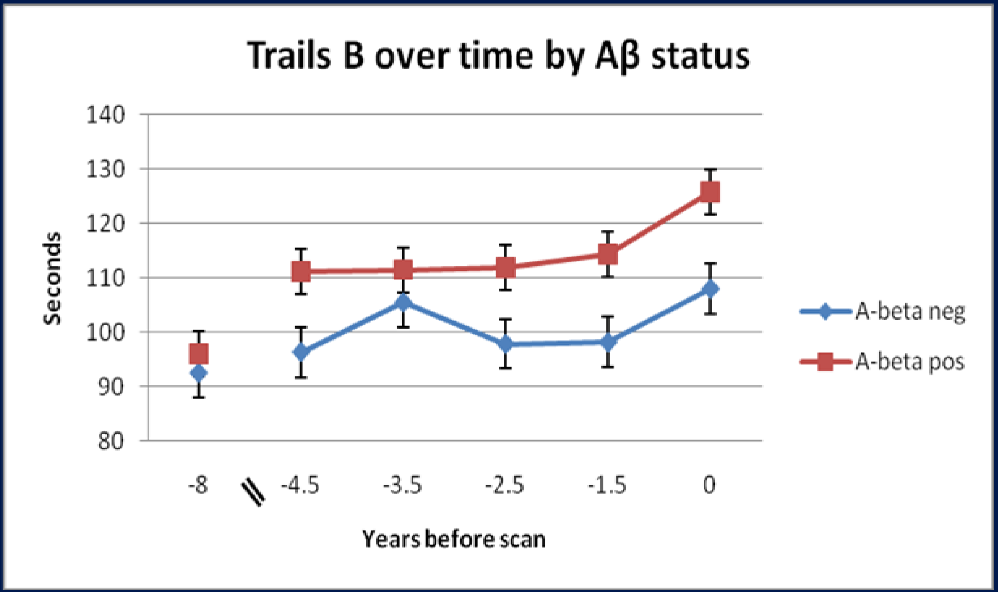
Shape of cognitive trajectories: mixed model estimates of each group at each assessment



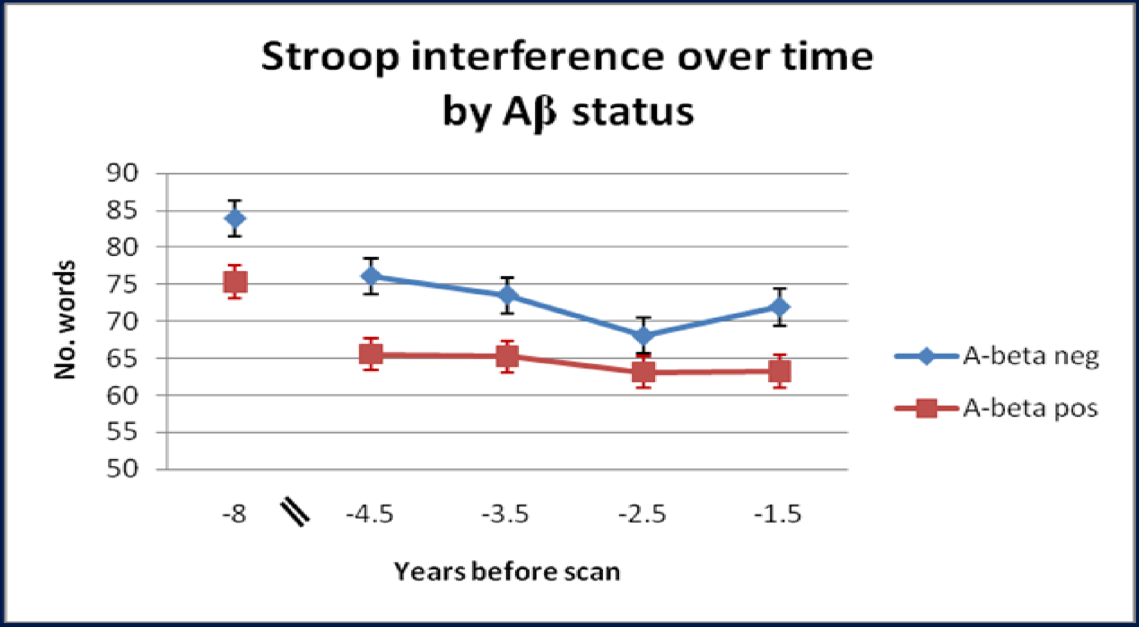
Verbal fluency



Shape of cognitive trajectories: mixed model estimates of each group at each assessment



Executive control



Baseline neuropsychological testing 8 years before PiB imaging

	Aβ –negative	Aβ –positive	*p*
Memory			
CVLT delayed recall	8.9 (3.3)	9.0 (3.1)	.90
R-O figure delayed recall (range 0-24)	15.6 (5.2)	16.2 (5.0)	.43
Executive functions			
Trails B (sec.) **	92.6 (37.2)	96.0 (38.8)	.54
Stroop color-word interference (no. in 120 sec.)	84.3 (20.5)	76.1 (21.5)	**< .01**
Ravens Progressive Matrices	29.7 (3.9)	28.5 (4.6)	.07
Visuospatial construction			
Block design (range 0-24)	13.6 (4.4)	12.4 (4.3)	**.05**
R-O figure copy (range 0-24)	21.6 (2.5)	21.6 (3.3)	.99
Language			
Semantic fluency	15.7 (4.2)	15.4 (3.9)	.62
Phonemic fluency	24.5 (8.6)	25.2 (7.4)	.56
Boston Naming Test (range 0-30)	26.8 (2.6)	26.3 (2.6)	.16
Attention			
Trails A (sec.) **	39.1 (11.1)	40.4 (14.1)	.48
Digit Span forward	8.1 (2.2)	8.1 (2.2)	.98

** higher = worse

Conclusions from GEMS Imaging Sub-Study

- Highly prevalent Aβ in oldest-old associated with steeper cognitive decline, retrospectively
- But small effect sizes of change
  - implications for prevention trials
- 8 years before imaging: Aβ-status group differences on tests reflecting executive functions
  - unlikely due to age, education, premorbid IQ

Taking the long view:

Cognitive-change correlates of Aβ in non-demented older adults

Study 2: Aβ in a younger sample

- Normal Aging Study (R37 AG025516; PI Klunk)
- *n* = 80
- mean age 74 (SD 5.9) years
- *prospective* study design
- carefully screened, cognitively normal at baseline
  - *MCI excluded*
- Aβ positivity 29 % at baseline
  - *regional definition; 5 cortical regions & ventral striatum*
- associated with cognitive change over time ?

Group characteristics at baseline

Aizenstein et al., *Arch Neurol* 2008; Nebes et al., *Neuropsychologia*, 2013

	A-beta negative (n=57)	**A-beta positive** (n=23)	*p*
Age, y	73.3 (5.4)	76.2 (6.4)	**.04**
Sex, female	42 (72 %)	11 (48 %)	**.04**
Education	14.9 (2.5)	14.9 (2.8)	.80
Estimated IQ	109.7 (12.1)	109.2 (13.2)	.92
Race (white)	51 (8 %)	19 (83 %)	.13
APOE*4	5 (9.4 %)	9 (45.0 %)	**.002**
MMSE	28.5 (1.5)	28.7 (1.7)	.71
GDS	2.0 (2.1)	1.7 (1.9)	.75
Follow-up time, y	2.9 (1.9) (range 0 – 7.4)	2.9 (2.0) (range 0 – 5.5)	.97

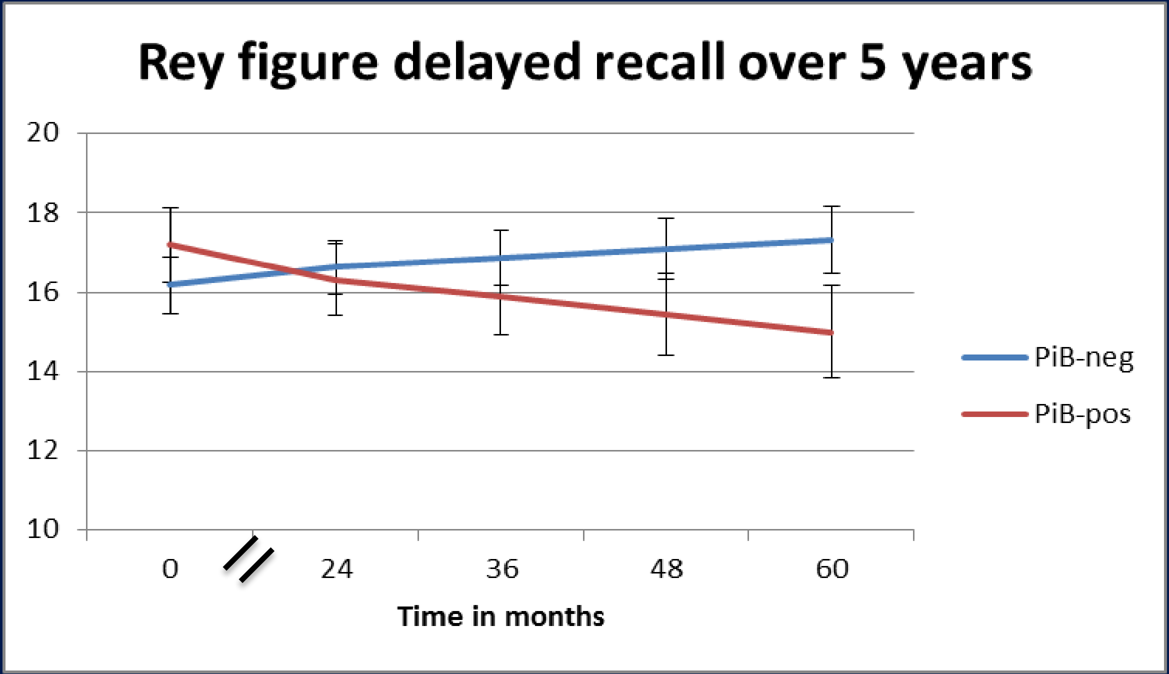
Cognitive test performance at baseline

	A-beta negative (n=57)	A-beta positive (n=23)	*P* *(adjusted)*
Episodic Memory			
CERAD WLL delayed recall	6.90 (1.73)	7.35 (1.54)	*ns*
Rey figure delayed recall	15.74 (3.49)	16.75 (3.56)	*ns*
Language			
30-item Boston Naming Test	28.25 (2.16)	28.17 (2.21)	*ns*
Verbal fluency – animals	19.96 (4.79)	19.43 (4.73)	*ns*
Verbal fluency – initial letter	41.44 (14.28)	39.96 (12.78)	*ns*
Visuospatial Construction			
Rey figure copy	20.38 (1.71)	20.39 (2.63)	*ns*
Block design	11.92 (4.08)	11.82 (5.49)	*ns*
Attention / Broad Executive Functions			
Trail Making Test Part A	30.13 (11.21)	30.31(9.90)	*ns*
Trail Making Test Part B	71.46 (31.26)	89.05 (38.23)	*ns*
Digit Symbol	53.04 (10.86)	47.50 (10.68)	*ns*

Cognitive test performance at baseline

	A-beta negative (n=57)	A-beta positive (n=23)	*P* (adjusted)
Information Processing speed			
Simple RT, ms	266.59 (45.15)	267.96 (49.09)	*ns*
Choice RT – perceptual, ms	745.40 (168.70)	786.06 (177.36)	*ns*
Choice RT – conceptual, ms	759.68 (160.71)	802.79 (163.02)	*ns*
Working Memory			*ns*
N-back	32.86 (11.80)	33.87 (13.91)	*ns*
Letter-number sequencing	9.98 (2.88)	9.13 (2.91)	*ns*
Inhibitory Control			*ns*
Stroop RT – incongruent, ms	830.95 (138.43)	943.15 (195.57)	**.03**
Hayling, RT – incongruent, ms	2288.11 (1658.55)	2321.04 (1414.61)	*ns*

Longitudinal cognitive slopes

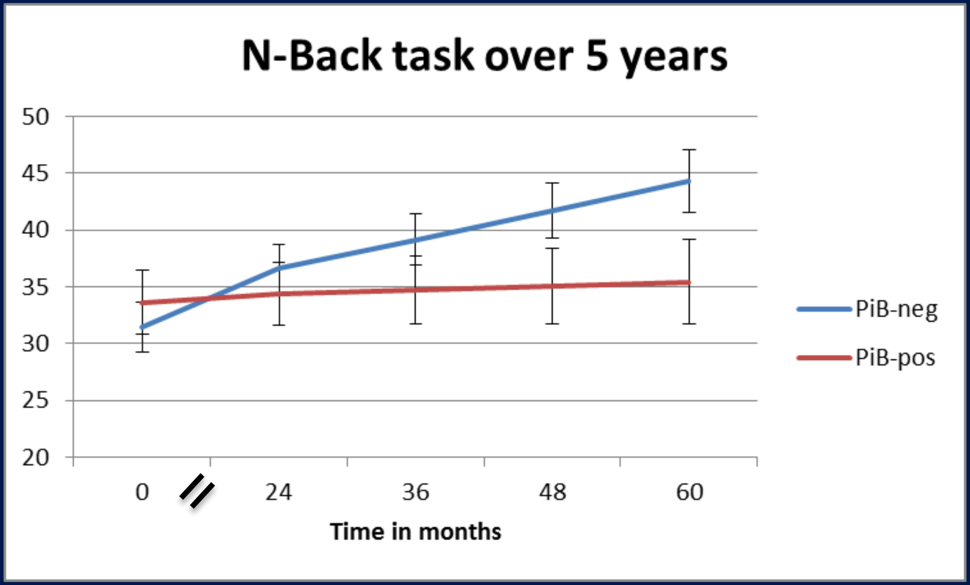


Analysis:

Linear mixed models, adjusting for age, sex, race & education

Aβ status x Time interaction term reflects group difference in cognitive performance slopes over time

Longitudinal cognitive slopes



Analysis:

Linear mixed models, adjusting for age, sex, race & education

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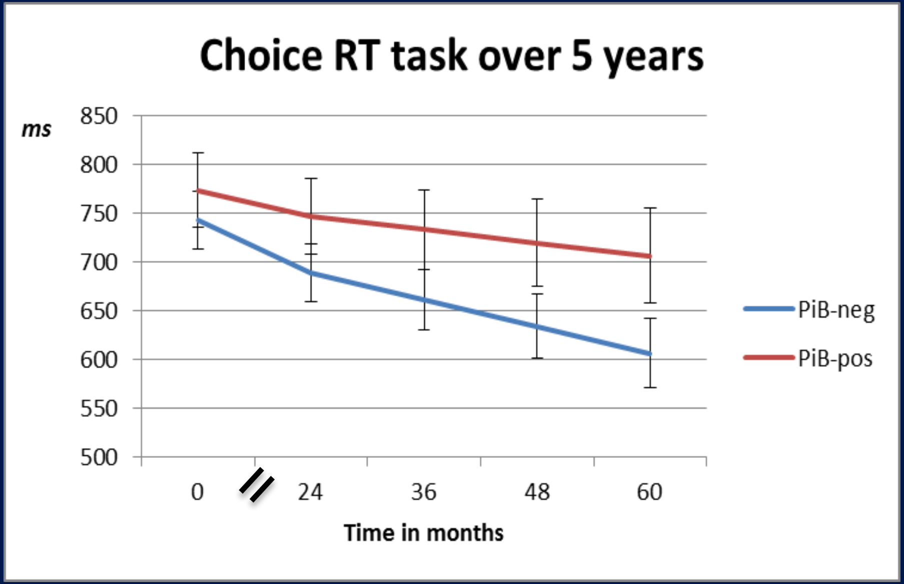
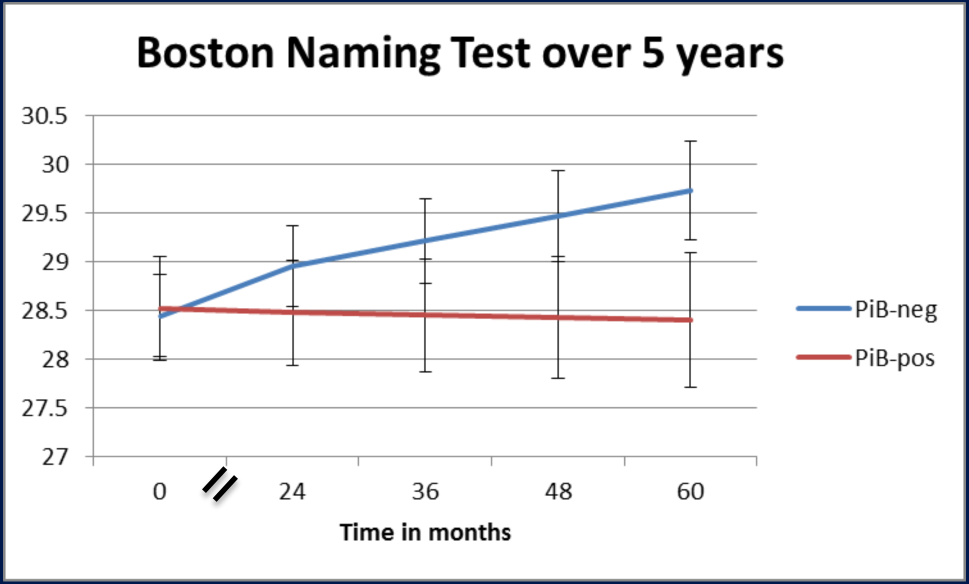




Conclusions from the Normal Aging study

- Aβ in younger-old carefully screened, cognitively normal (baseline) associated with *very little cognitive decline*
  - memory
- Significant slope differences between Aβ-groups reflect *lack of improvement* in Aβ (+) vs. Aβ (-)
  - processing speed task
  - working memory task
  - confrontation naming task

Practice (re-test) effects

- Learning of test content
  - *episodic memory*
- Familiarization with task procedures
  - *procedural (non-declarative) learning*
- Anxiety reduction
  - *affective processes (desensitization)*

Cognitive aging research: "nuisance" effect ?

Practice (re-test) effects:
Perspectives from the literature

- Biologic relevance

Terminal decline and practice effects in older adults without dementia

The MoVIES project

Hiroko H. Dodge, PhD
Chia-Ning Wang, MS
Chung-Chou H. Chang, PhD
Mary Ganguli, MD, MPH

ABSTRACT

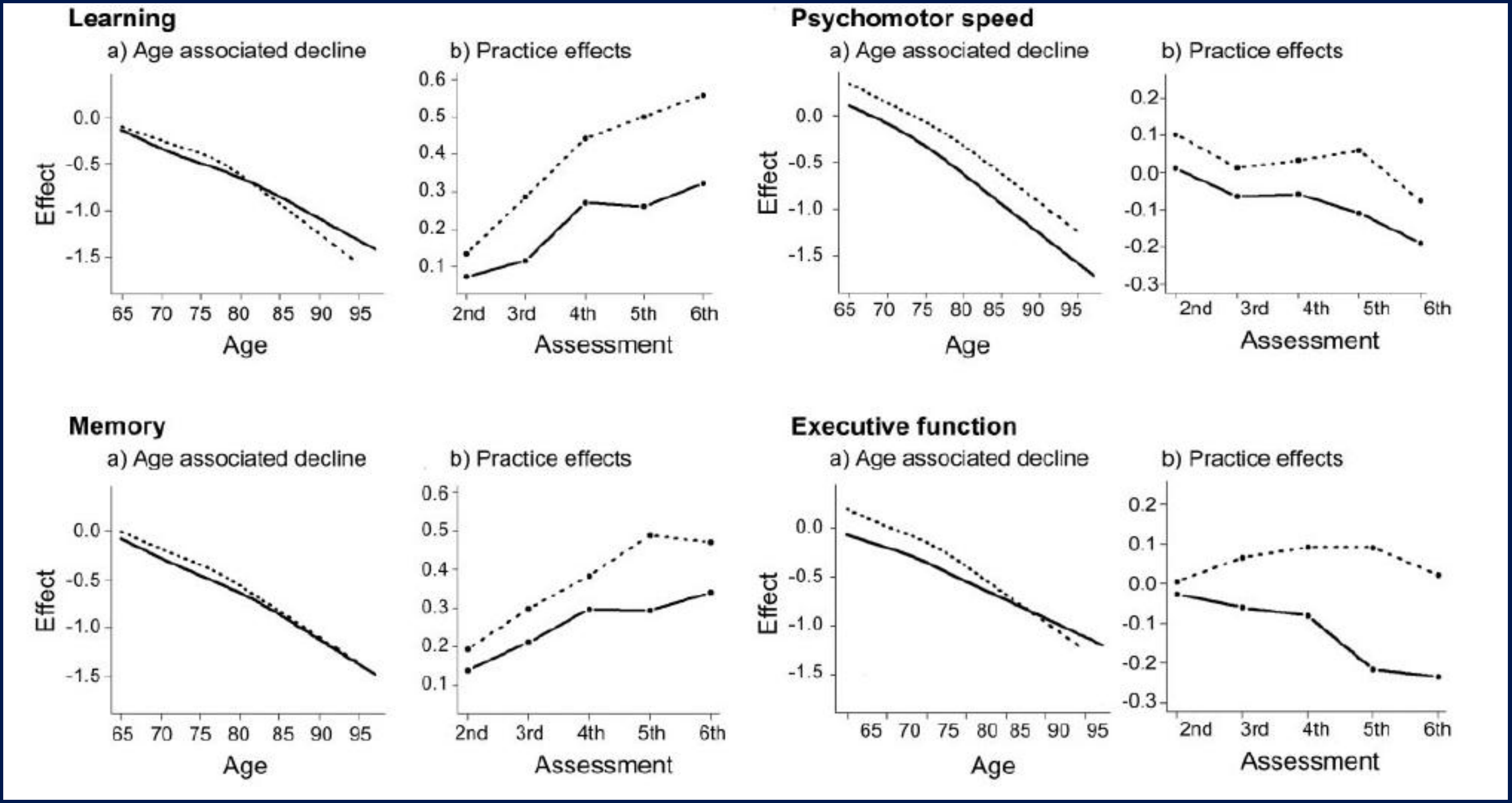
Objective: To track cognitive change over time in dementia-free older adults and to examine terminal cognitive decline.

Methods: A total of 1,230 subjects who remained free from dementia over 14 years of follow-up were included in a population-based epidemiologic cohort study. First, we compared survivors and decedents on their trajectories of 5 cognitive functions (learning, memory, language, psy-

Dodge et al., Neurology, 2011

Practice (re-test) effects:
Perspectives from the literature

- Biologic relevance: decedents vs. survivors



Dodge et al., Neurology, 2011

Practice (re-test) effects:
Perspectives from the literature

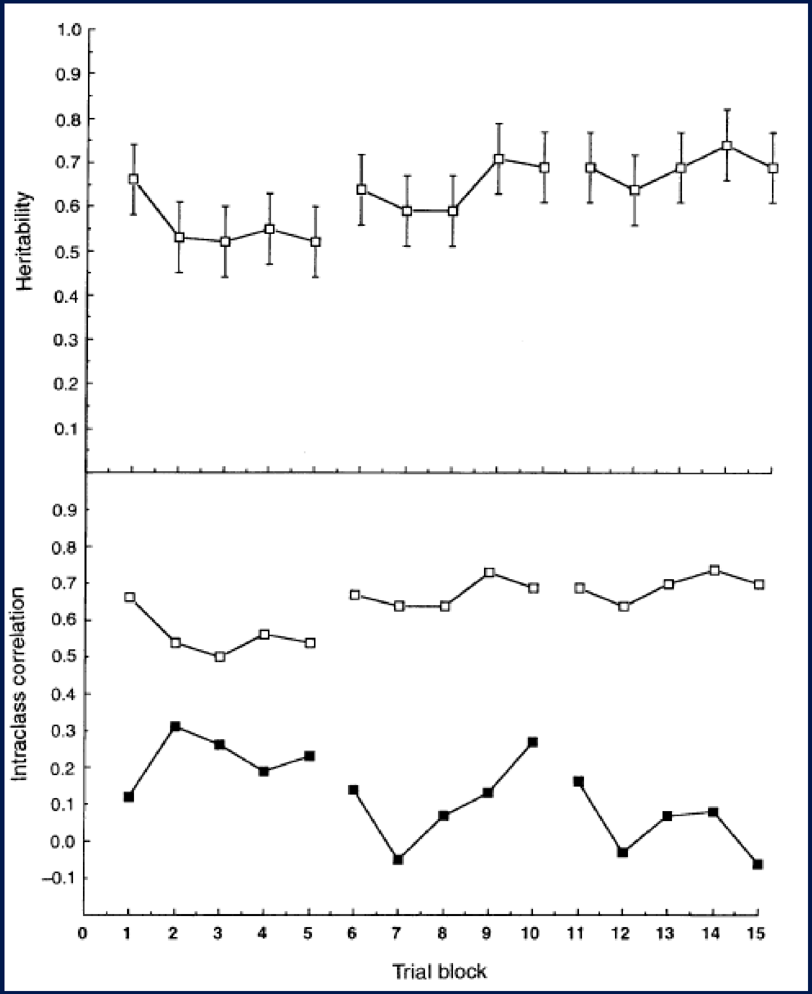
- Biologic relevance

LETTERS TO NATURE

Genetic and environmental contributions to the acquisition of a motor skill

Paul W. Fox*, Scott L. Hershberger† & Thomas J. Bouchard Jr*‡

Nature, 384(6607), 1996



- Twin study: MZ vs. DZ
- Rotary pursuit task
  - 3 consecutive days, 25 trials per session

Practice (re-test) effects:
Perspectives from the literature

- Relevance to MCI / AD risk:

Predictors of Preclinical Alzheimer Disease and Dementia

A Clinicopathologic Study

James E. Galvin, MD, MPH; Kimberly K. Powlishta, PhD; Kenneth Wilkins, MD; Daniel W. McKeel, Jr, MD; Chengjie Xiong, PhD; Elizabeth Grant, PhD; Martha Storandt, PhD; John C. Morris, MD

Arch Neurol, 62(5), 2005

- Neuropathologic preclinical AD (CDR 0 at time of death) vs. controls
  - Less improvement over 6 years on:
    - *memory test (WMS Associate Memory)*
    - *Boston Naming Test*

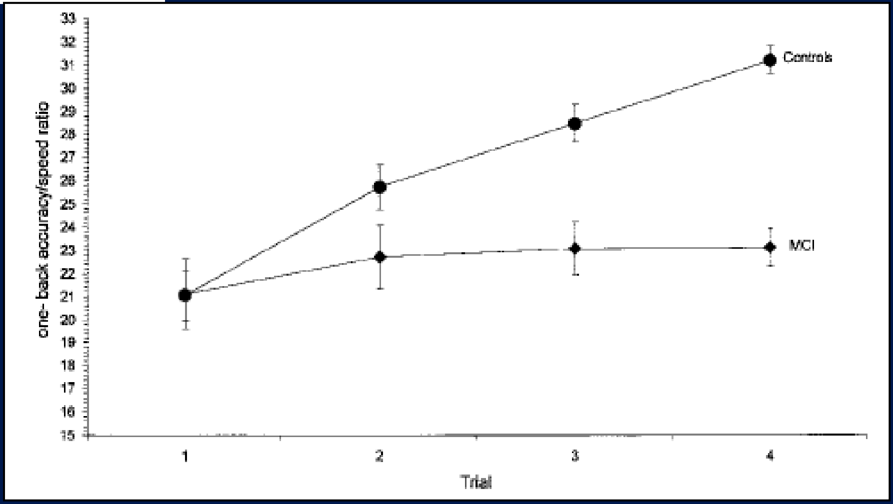
Practice (re-test) effects:
Perspectives from the literature

- Relevance to MCI / AD risk:

Mild cognitive impairment can be detected by multiple assessments in a single day

D. Darby, MD, PhD; P. Maruff, PhD; A. Collie, PhD; and M. McStephen, BSc

NEUROLOGY 2002;59:1042–1046



- CogState RT tasks
  - Repeated 4 x in a day
  - MCI attenuated benefit

Neurobiology of Aging 28 (2007) 885–893

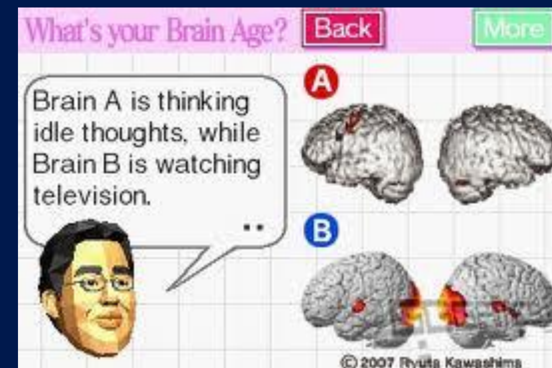
Effects of ApoE genotype and mild cognitive impairment on implicit learning

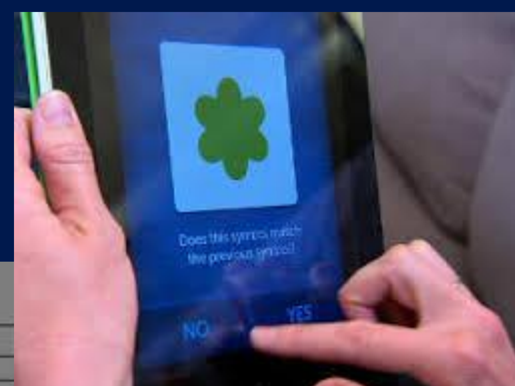
Selam Negash[a,*], Lindsay E. Petersen[a], Yonas E. Geda[b], David S. Knopman[a], Bradley F. Boeve[a], Glenn E. Smith[a], Robert J. Ivnik[a], Darlene V. Howard[c], James H. Howard Jr.[c,d], Ronald C. Petersen[a]

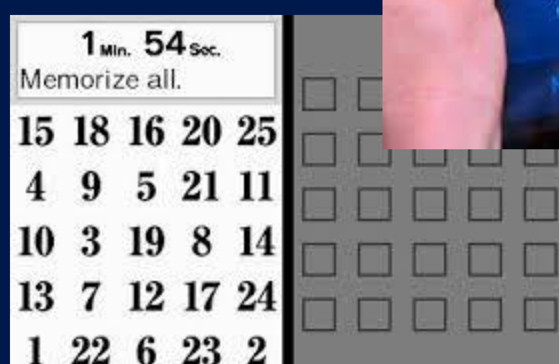
- Implicit learning tasks
  - APOE4 carriers: deficits on visual contextual cueing task

“Practice effects” are now ubiquitous

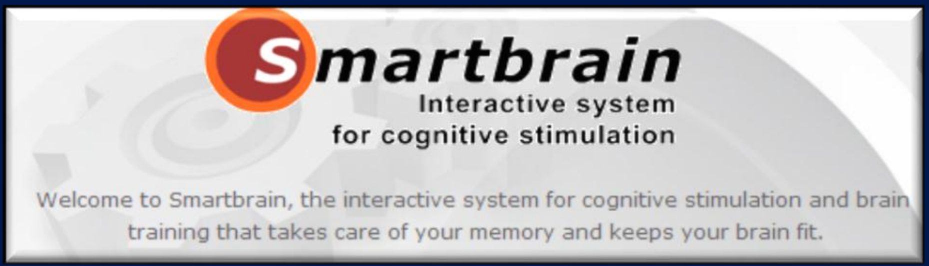
lumosity



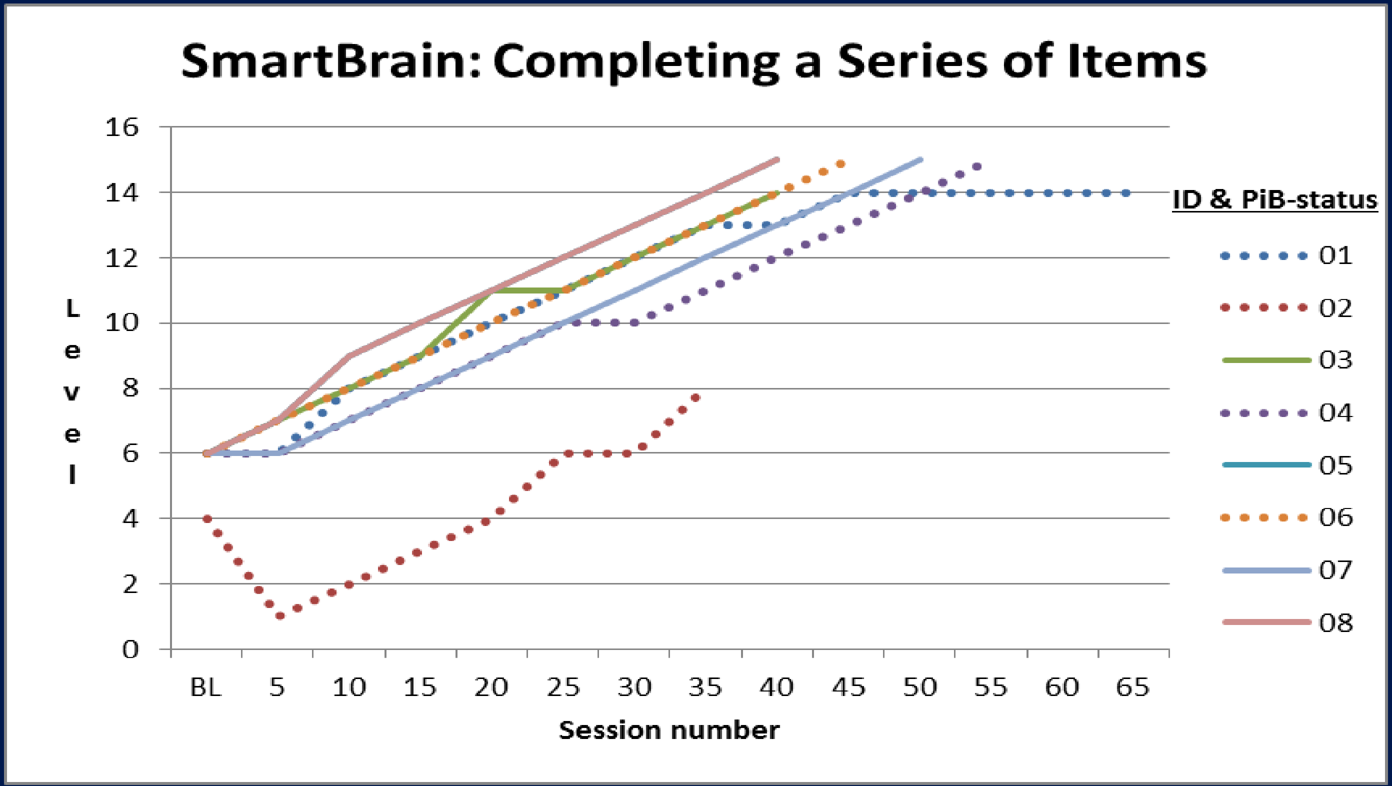




Practice (re-test) effects:
‘Brain-training’ paradigms



- n = 8 MCI patients, all with **PiB-PET** imaging close to time of SmartBrain use



Taking the long view:
Cognitive-change correlates of Aβ in non-demented older adults

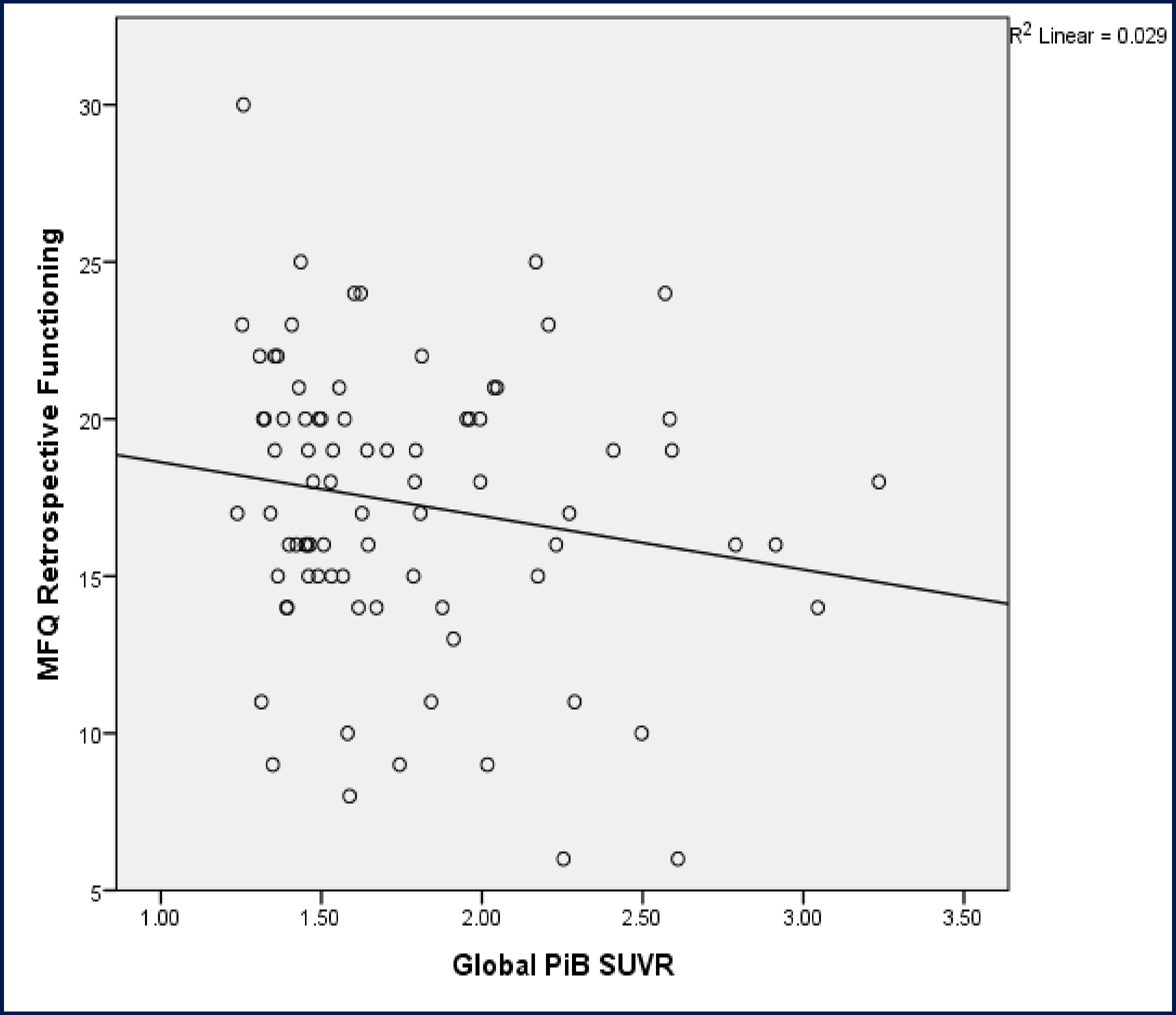
Study 3: Subjective cognitive change over time

– associated with Aβ in normal aging?

Subjective Cognitive Complaint (SCC) questionnaire study

- Add-on to two ongoing PiB-imaging studies
  - (Klunk, PI; P01 AG025204; Klunk R37 AG025516)
- Sample description
  - **n = 89** cognitively normal (CN) participants
  - mean age 80.8 (SD 8.4) years; IQR = 74 to 86 years
  - mean educ. 16.6 (SD 9.6) years
  - 48% female; 90% white
- Memory Functioning Questionnaire *(Gilewksi et al., 1990*; 64 items)
  - General Frequency of Forgetting (33 items)
  - Serious of Forgetting (18 items)
  - Retrospective Functioning (5 items)
  - Mnemonics Usage (8 items)

Subjective memory *change* & PiB retention



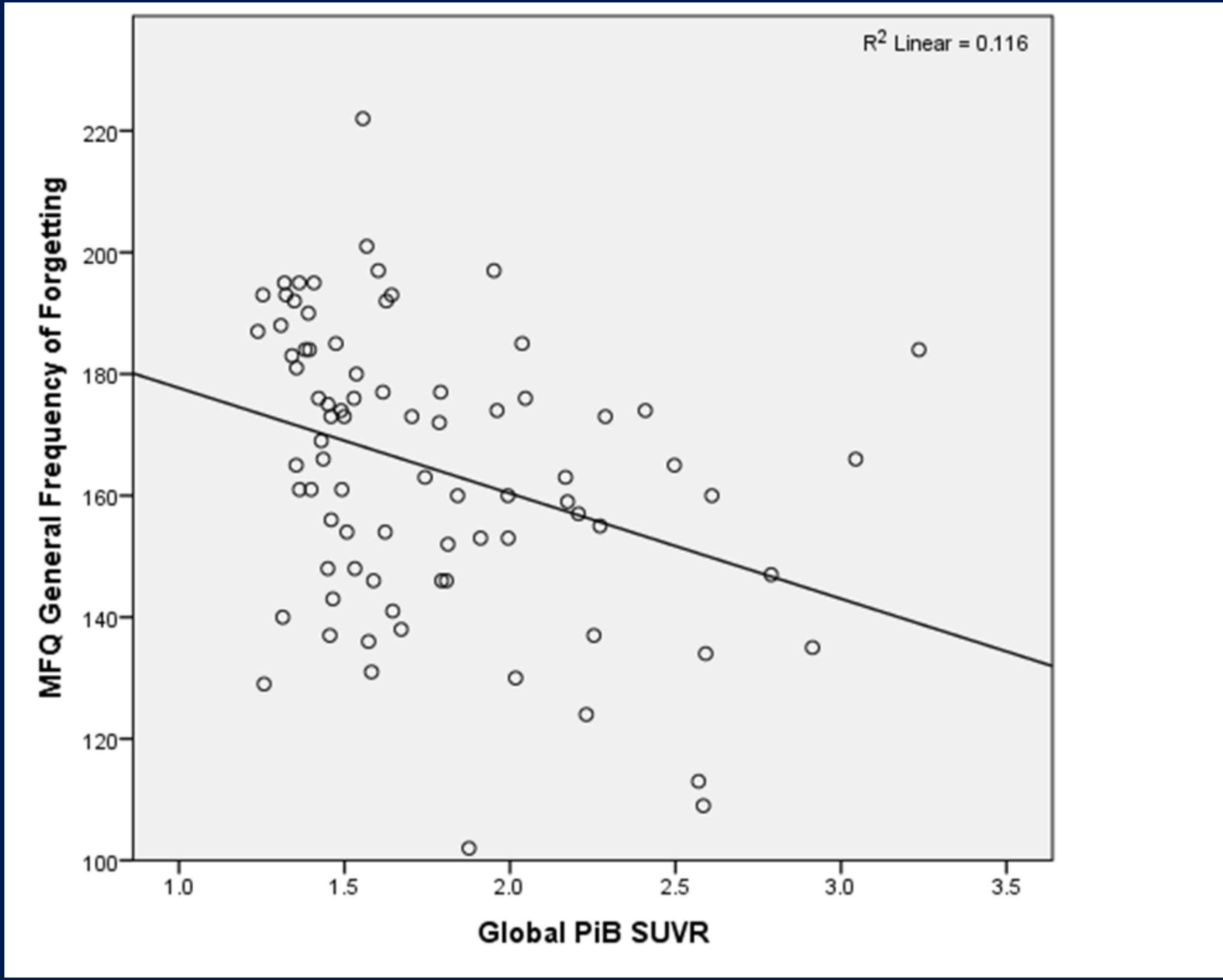
"*How is your memory compared to the way it was …*"

- *1 year ago*
- *5 years ago*
- *10 years ago*
- *20 years ago*
- *when you were 18*

Response scale: 1 – 7 "*much worse*" to "*same*" to "*better*")

- 5 items
- higher = better functioning

Subjective memory *failures* & PiB retention



"*How often do these present a problem for you*…"

- -names
- -faces
- -appts.
- -where put things
- -words
- -dates
- -phone numbers
- -etc.

(1 – 7, "*always*" to "*never*")

- 33 items
- higher = better functioning

r = .34, $p < .05$

Replication of MFQ-factor pattern – amyloid findings from Amariglio et al. 2012 , and Merrill et al., 2012 (FDDNP)

Conclusions:

- Aβ in oldest-old: associated with steeper cognitive decline
  - Longitudinal associations stronger than cross-sectional
- Aβ in younger-old: associated with attenuated improvement in test performance
  - Implications for different study designs / cognitive outcomes ?
- Aβ in normal aging (broad age range) <u>not</u> associated with subjective ratings of memory decline

Acknowledgments

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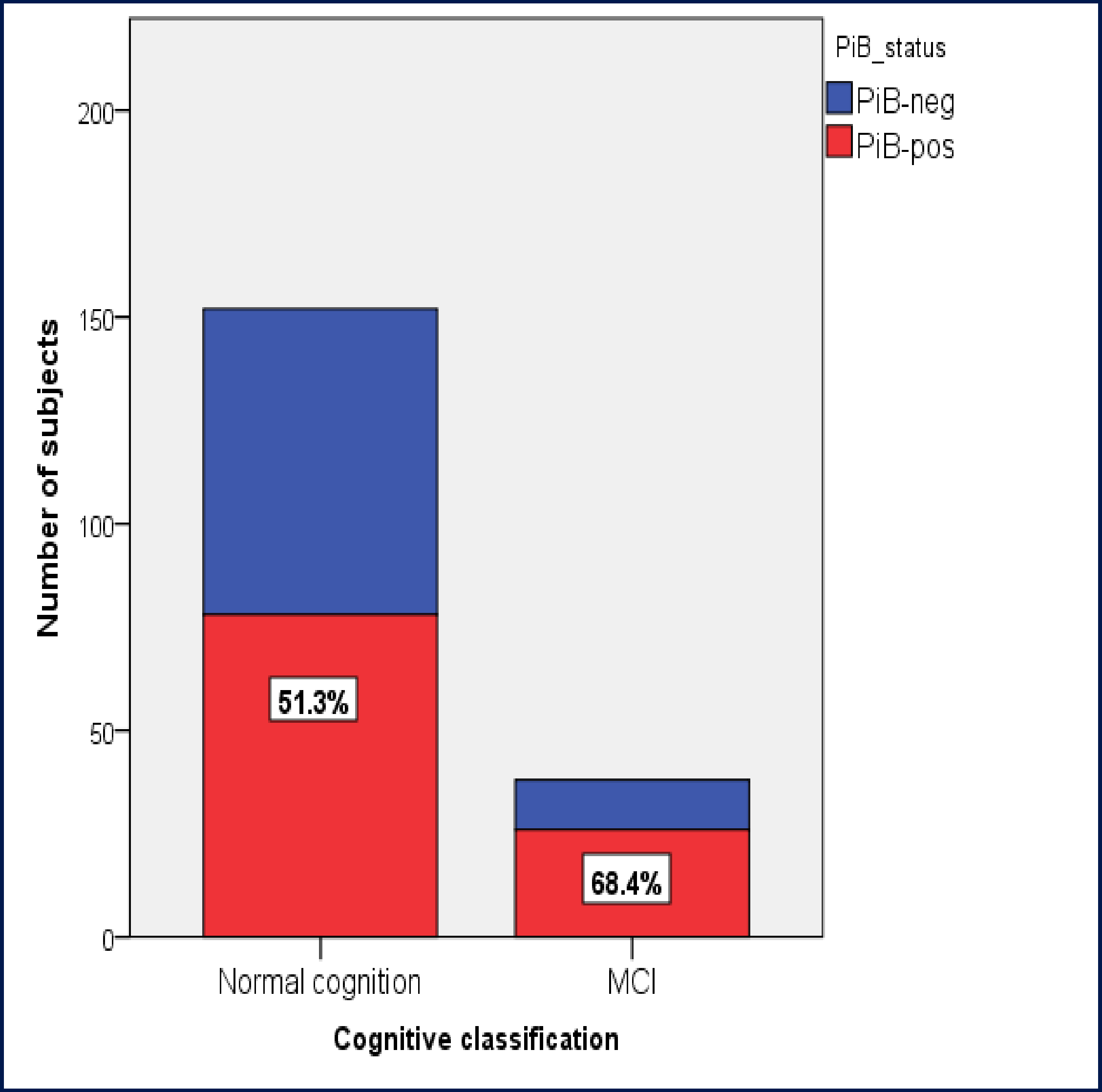
  - K23 AG038479; P01 AG025204; R37 AG025516
  - U01 AT000162 from the National Center for Complementary and Alternative Medicine, Office of Dietary Supplements; National Institute on Aging; National Heart, Lung and Blood Institute
- Amyloid Imaging Group and PET Research Center, University of Pittsburgh
- Ginkgo Evaluation of Memory Study investigators, staff, study participants and their study proxies
- Amyloid Pathology and Cognition in Normal Elderly Study (Klunk PI) investigators, staff and study participants
- PiB Program Project Grant (Klunk PI) investigators, staff and study participants
- Univ. Pittsburgh ADRC
- Mary Ganguli, Bill Klunk, Judy Saxton, Bob Nebes, Jim Becker

Extra slides

The Ginkgo Evaluation of Memory (GEM) Imaging Sub-Study



- Diagnostic breakdown (n=194 usable scans):
  - Normal cognition, n=152
  - Amnestic MCI, n=27
  - Non-amnestic MCI, n=11
  - Dementia, n=3; Unclassifiable, n=1

Total sample: 55.2% PiB-pos

In vivo assessment of amyloid-β deposition in nondemented very elderly subjects

Matthis et al., Annals of Neurology, 2012; 73 (6)