Correlating Cognition and Biomarkers in Preclinical APOE e4 and PS1 Mutation Carriers

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Funding: NIA P30AG19610, NIA R01AG031581, and the Arizona Alzheimer's Disease Consortium

Preclinical Alzheimer's disease is…

1. Biomarkers:
    1. Neuropathology
    2. Imaging
    3. CSF
2. Neuropsychology
    1. Memory
    2. Executive
    3. Other
3. Subjective: symptoms without "objective findings"

(Caveat: what threshold of neuropsychological decline, functional impairment, or subjective symptoms trips the MCI diagnosis?)

Assumptions: What is Preclinical?

- Neuropsychological decline: any amount that occurs prior to a) reaching MCI criteria or b) triggering a patient to seek clinical evaluation
- Functional decline: within a CDR score of zero, within generally accepted age appropriate behavior (e.g., a 40 yo professional basketball player)
- Subjective decline: any amount that falls short of seeking clinical evaluation
- The above do not reflect gross medical negligence

Cross Sectional and Longitudinal Studies of Presymptomatic APOE e4 Carriers

AD Pathology in Young APOE e4 Carriers

(Kok et al, Ann Neurol 2009)

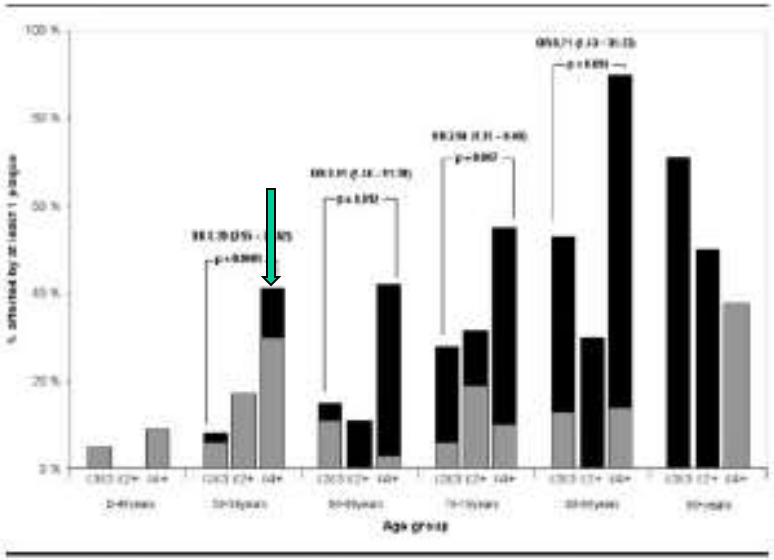


Fig 2. The prevalence of plaques (≥1 plaque) against apolipoprotein E genotype and age group, indicating neuritic plaques in the Tampere Autopsy Study series. Numbers in brackets are 95% confidence interval (CI). Grey Bars = *Non neuritic plaques;* Black Bars = *Neuritic plaques.*

40% of 50-59 yo e4's have AP's

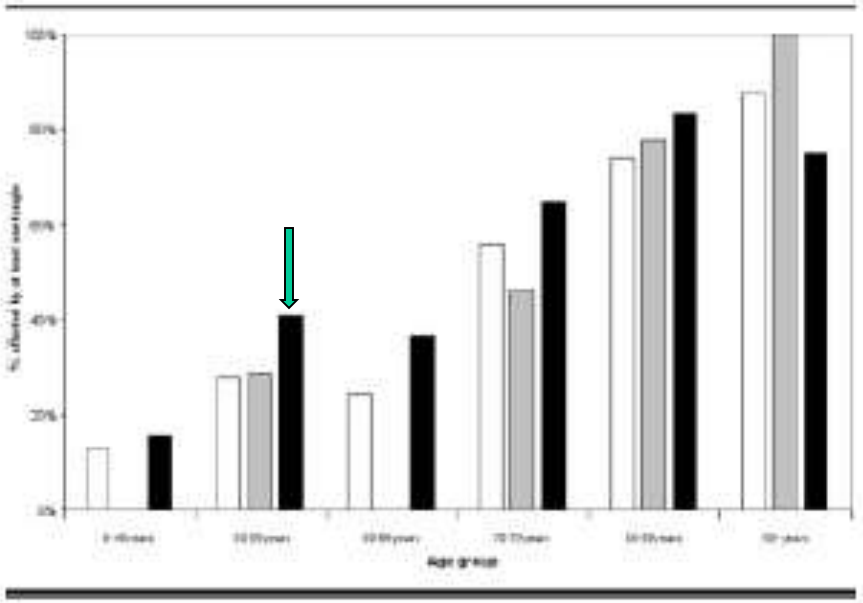


Fig 5. The prevalence of tangles (≥1 tangle) against apolipoprotein E (APOE) genotype and age group in the Tampere Autopsy Study series. White bars = *APOE ε3/ε3;* Grey bars = *APOE ε2+;* Black bars = *APOE ε4+.*

40% of 50-59 yo e4's have NFT's

Methods

- **Subject selection**
  - APOE Genotyping
  - Screening tests
  - APOE and ADC Cohorts
- **Screening tests**
  - Medical history
  - Neurologic Exam
  - Psychiatric Exam
  - Folstein MMSE
  - Hamilton Depression Scale
- **Test Procedures**
  - Neuropsychology
  - PET (FDG, Amyloid)
  - MRI
  - Other
- **Longitudinal Study**
  - Every 1-2 years
- **Statistical Model**
  - Isolate longitudinal change from entry performance
  - Linear vs quadratic

Neuropsychology Battery

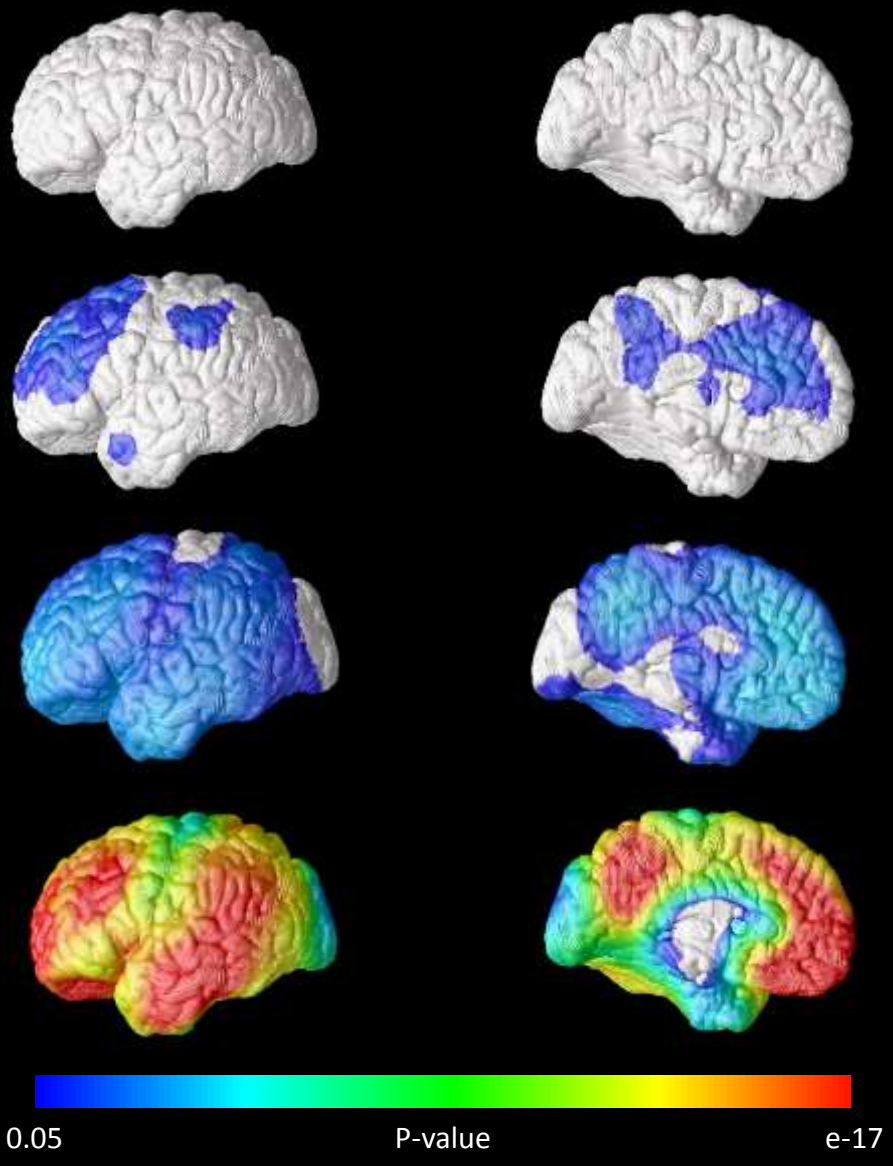
- Intellectual Domains
  - Memory
  - Executive
  - Language
  - Spatial
  - “General”
- Subjective
  - Observer
  - Self
- Behavioral
  - Depression
  - Anxiety
  - Paranoia
  - Somatization
  - Aggression

Cross Sectional Amyloid Imaging Subset

	NC	HTZ	HMZ	p
N	12	8	8	
Age	64(5)	67(4)	63(4)	.14
Female/Male	9/3	7/1	5/3	.51
Education	15(2)	17(2)	15(2)	.02
MMSE	29.7(.7)	29.6(1.1)	29.6(.7)	.99
AVLT-LTM	8.5(3.3)	10.6(3.8)	8.5(4.0)	.40
CFT-copy	34.5(2.0)	32.5(3.9)	35.4(.9)	.08
CFT-recall	19.4(7.3)	21.2(9.3)	19.8(6.5)	.88
COWAT	47.5(11.8)	53.6(10.6)	49.8(2.5)	.40

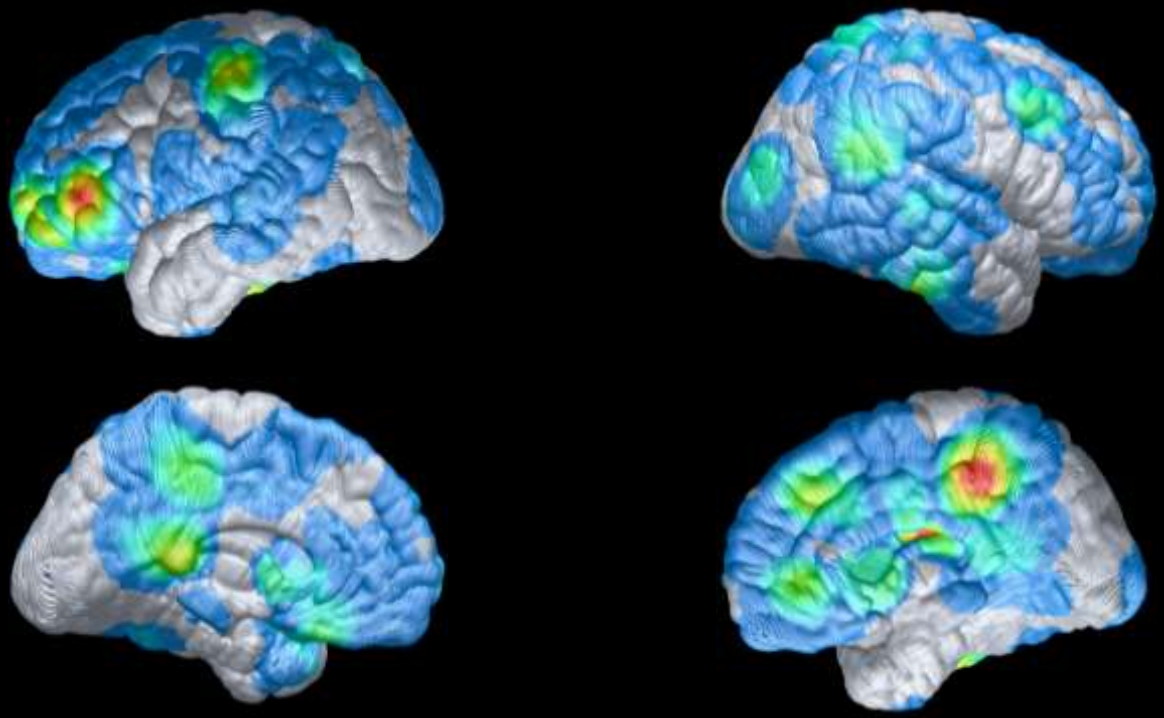
Reiman et al, *PNAS* 2009

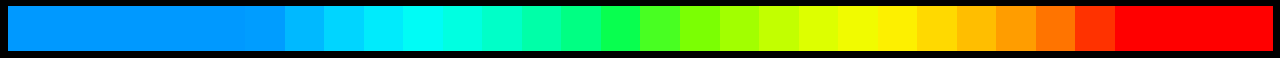
PiB PET Measurements of Fibrillar Aβ Burden in Cognitively Normal Older People (mean age 64) at Three Levels of Alzheimer's Disease Risk



Adapted from Reiman et al, *PNAS* 2009

relation between 24-mo PiB DVR increases & *APOE ε4* gene dose in cognitively normal older adults





0.05 P-value 0.001

Reiman et al, unpublished data

Neuropsychological Correlates

Memory

Cross sectional and Longitudinal Modeling of Age-Related Memory Decline and APOE e4

	NC (n=498)	e3/4 (n=238)	e4/4 (n=79)	p
Age (yr)	61.4	58.4	56.8	<.001
Ed (yr)	15.4	15.4	15.4	.98
% Female	69.1	68.9	68.4	.99
% FDR	52.8	68.8	87.2	<.001
% >1 Epoch	73.1	73.1	84.8	.08
Duration (yrs)	4.7	5.1	5.7	.01

Auditory Verbal Learning Test

REY AUDITORY VERBAL LEARNING TEST (RAVLT) ***Phase I***

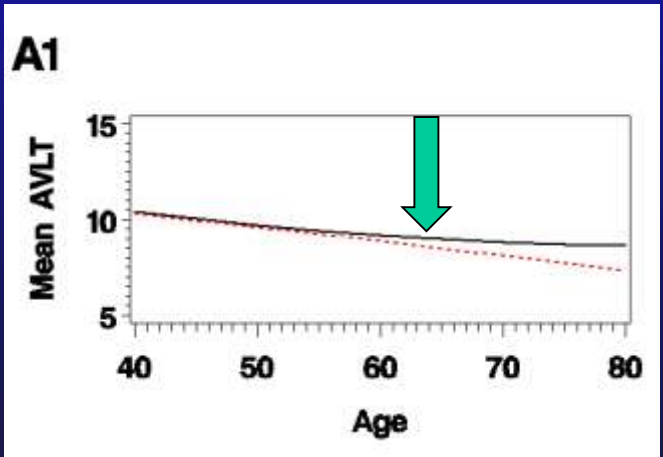
Patient: _____

Age: _____

LIST A	1	2	3	4	5	LIST B	1	LIST A	6	7
DRUM						DESK		DRUM		
CURTAIN						RANGER		CURTAIN		
BELL						BIRD		BELL		
COFFEE						SHOE		COFFEE		
SCHOOL						STOVE		SCHOOL		
PARENT						MOUNTAIN		PARENT		
MOON						GLASSES		MOON		
GARDEN						TOWEL		GARDEN		
HAT						CLOUD		HAT		
FARMER						BOAT		FARMER		
NOSE						LAMB		NOSE		
TURKEY						GUN		TURKEY		
COLOR						PENCIL		COLOR		
HOUSE						CHURCH		HOUSE		
RIVER						FISH		RIVER		
SCORE										

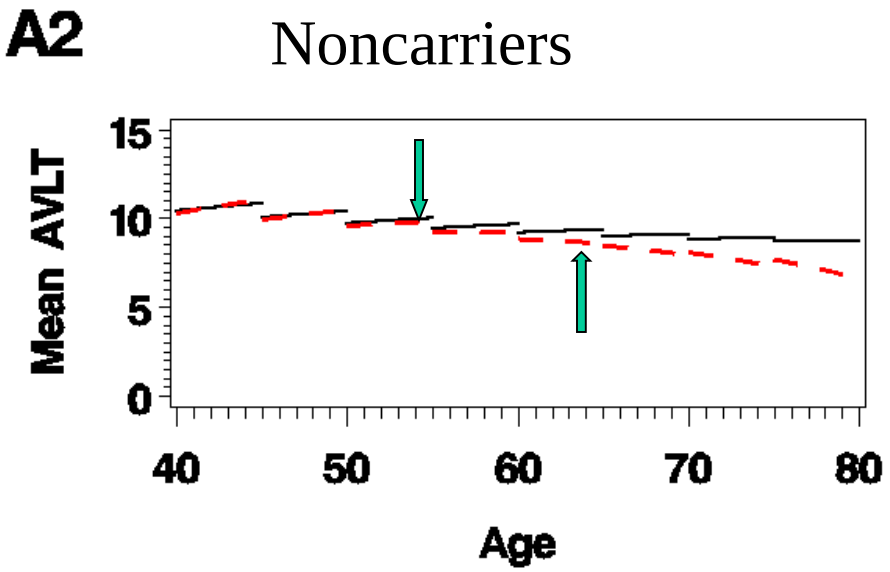
AVLT LTM By Age Decile At Entry

	E4 Noncarriers			E4 Carriers		
	N	Observed	Model	N	Observed	Model
20-29	9	12.44(2.07)	12.26	6	11.00(2.97)	11.03
30-39	22	10.64(2.63)	10.27	24	10.13(2.85)	10.24
40-49	27	10.48(2.42)	10.44	36	10.00(3.57)	9.83
50-59	169	9.63(3.10)	9.50	114	9.92(3.10)	9.55
60-69	148	8.89(2.91)	8.84	78	8.10(3.51)	8.21
70-79	83	8.70(3.53)	8.73	40	8.18(2.77)	7.94
80-89	29	9.38(2.97)	8.81	14	6.43(3.52)	6.48

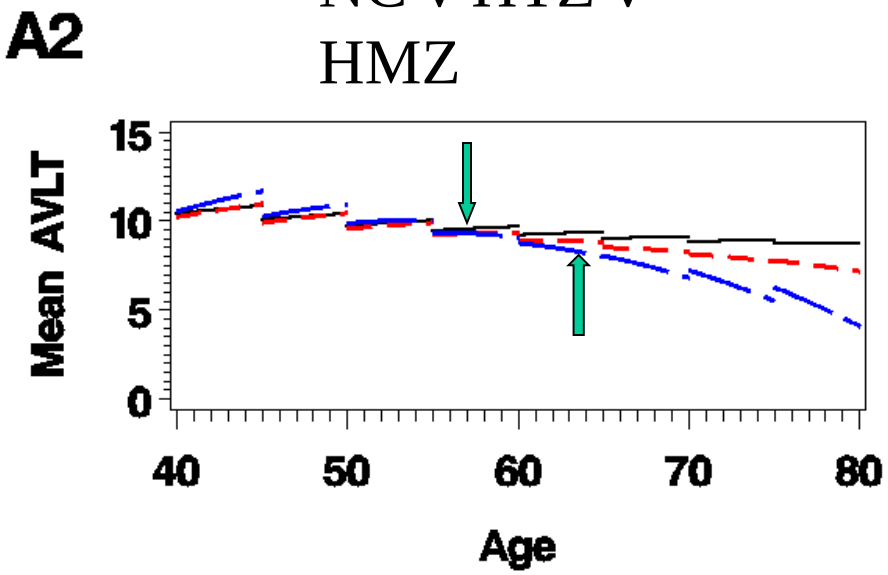


Longitudinal Trajectories of Change in AVLT-LTM Score

Carriers v Noncarriers



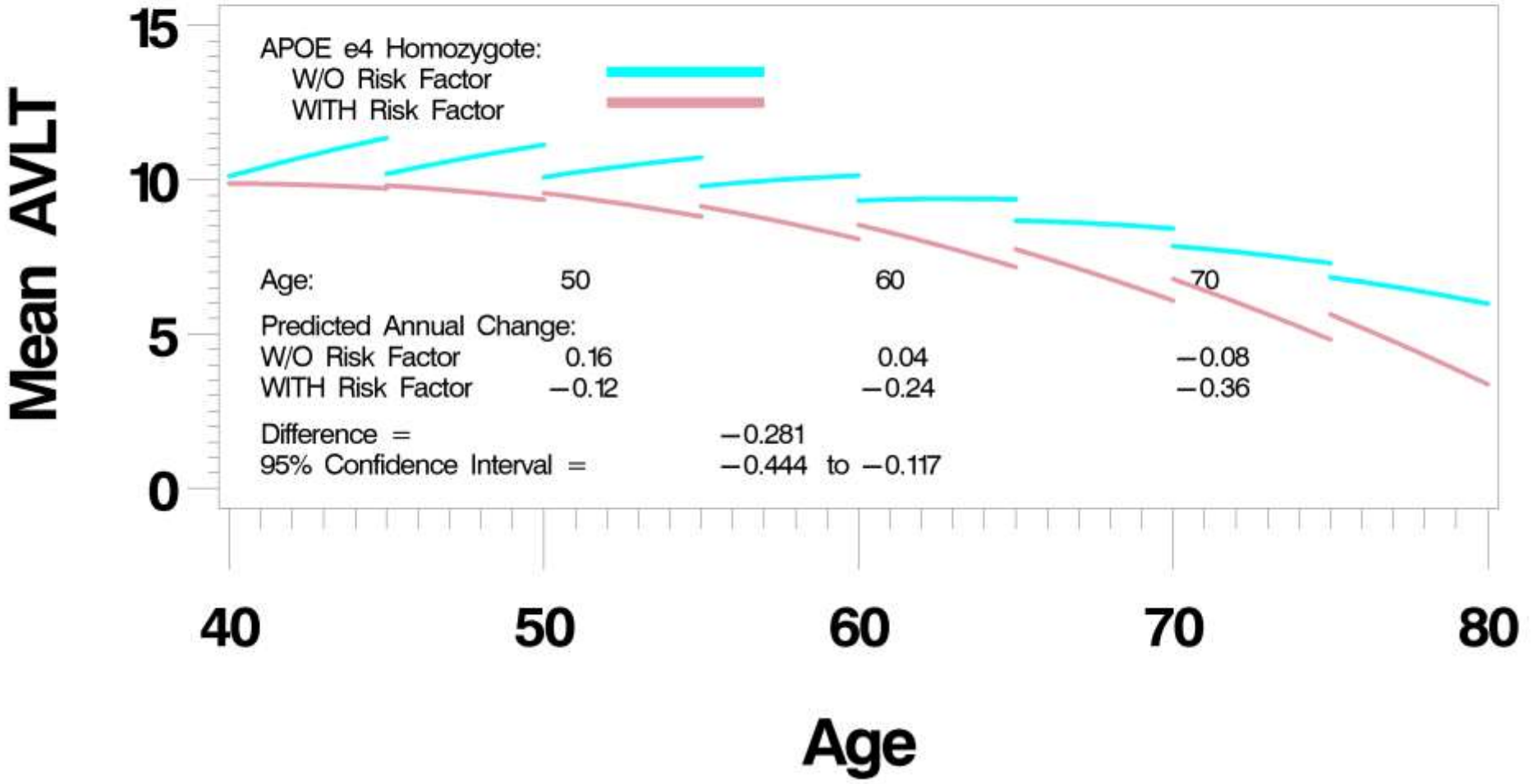
NC v HTZ v HMZ



Caselli RJ et al, NEJM 2009

AVLT Longitudinal

Risk Factor: CV Risk (HT,DB,Smk,Chol; Any Epoch)

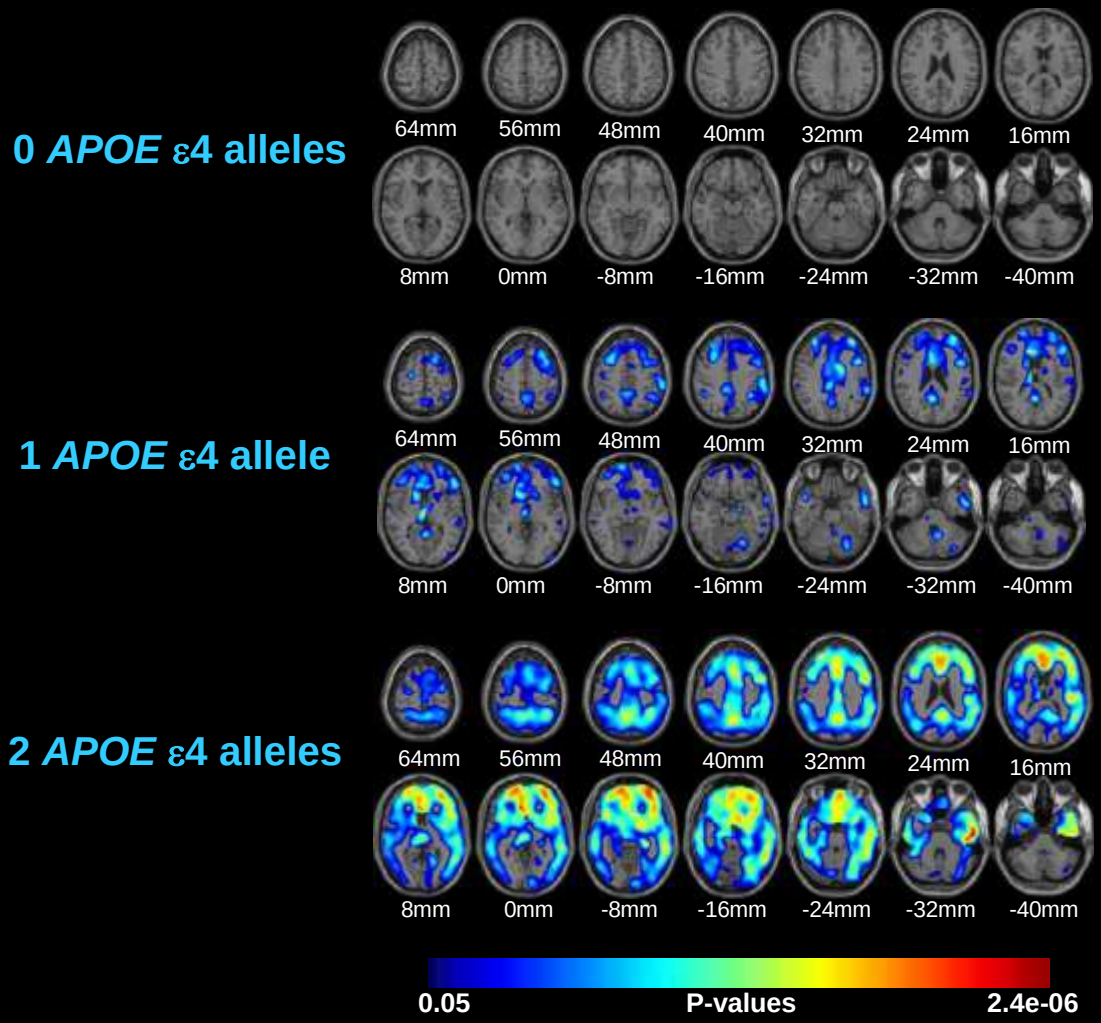


Caselli et al, Neurology 2011

Neuropsychological Correlates

Executive

Presymptomatic AD is Characterized By FRONTAL, not medial temporal fibrillar amyloid…does this frontal amyloid accelerate frontal decline?



Adapted from Reiman et al, *PNAS* 2009

Frontal Lobe Battery

(APOE Cohort alone)

- Psychomotor Speed
  - Controlled Oral Word Association Test
  - WAIS-R Digit Symbol Substitution
- Working Memory
  - PASAT 2 and 3 second versions
  - WAIS-R Mental Arithmetic
  - WAIS-R Digit Span
- Problem Solving
  - Wisconsin Card Sorting Test

Entry Demographics

	NC (n=356)	e3/4 (n=194)	e4/4 (n=71)	p
Age (yr)	57.2	56.0	55.6	.37
Ed (yr)	15.5	15.7	15.5	.57
% Female	69.4	70.6	85.9	<.001
% FDR	56.1	72	87.2	<.001
% >1 Epoch	74.7	77.8	87.3	.07
Duration (yrs)	6.2	6.3	6.6	.72

Caselli RJ et al, Neurology 2011

Quadratic Models of Aging

		e4 Noncarrier		e4 Carrier
Memory	AVLT-LTM*	<.001		<.001
	SRT-total free*	<.001		<.001
	CFT recall	<.001		<.001
	VRT correct*	.02		<.001
Executive Function	WCST-Cat	.01		<.001
	PASAT-3 sec	<.001		<.001
	COWAT	.01		<.001
	TMT-A	.86		.99
Language	BNT	<.001		<.001
	Token	.02		.82
	WAIS-Similar	.69		.02
	WAIS-Vocab	<.001		.42
Visuo-spatial	JLO	.34		.02
	Faces	.18		.02
	CFT-copy	.004		.27
	WAIS-Blocks	<.001		<.001

Quadratic Models of APOE e4 Effects

		E4 Carrier v Noncarrier		Gene Dose
Memory	AVLT-LTM*	**.009**		**.005**
	SRT-total free*	**<.001**		**<.001**
	CFT recall	.42		.44
	VRT correct*	**.004**		**<.001**
Executive Function	WCST-Cat	.16		.09
	PASAT-3 sec	.16		.10
	COWAT	.38		.27
	TMT-A	.72		.68
Language	BNT	.25		.88
	Token	.70		.60
	WAIS-Similar	.13		.14
	WAIS-Vocab	.57		.72
Visuo-spatial	JLO	.56		.11
	Faces	.19		.25
	CFT-copy	.19		.97
	WAIS-Blocks	.45		.28

Neuropsychological Correlates

Subjective Cognition

Multidimensional Assessment of Neurodegenerative Symptoms

- Paired self and observer questionnaires
- 87 questions
- 0-4 scale (never-daily)
- Cognition, behavior, motor categories

Locke et al, Dem Ger Cog Dis 2009

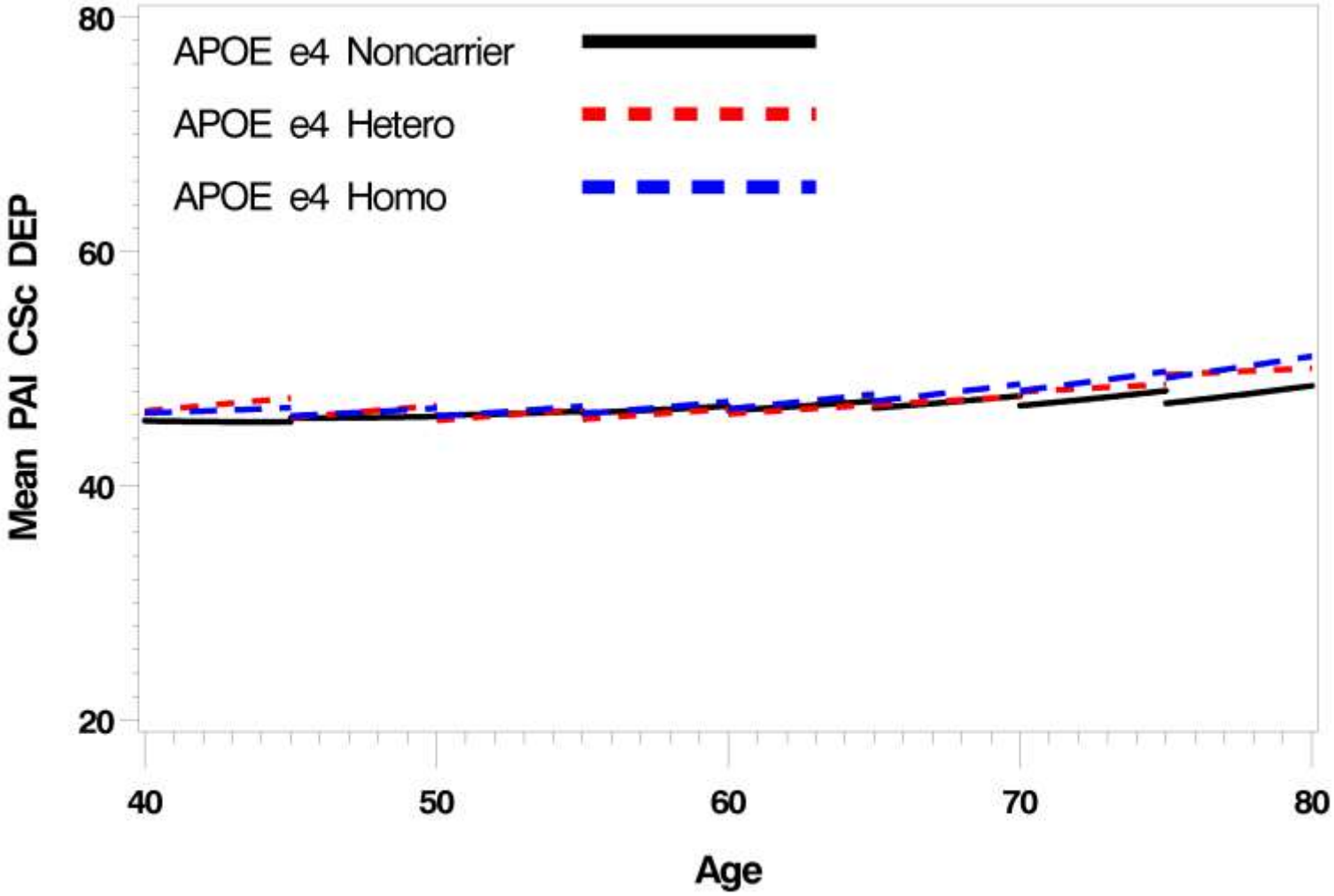
Demographics

	Self = 0	Self > 0	p*	Informant = 0	Informant > 0	p
N	310	137		330	117	
Age	58.7 (6.9)	59.8 (8.3)	0.15	58.6 (7.0)	60.3 (8.3)	0.031
Education	15.7 (2.4)	15.5 (2.6)	0.6	15.7 (2.4)	15.4 (2.5)	0.16
Female (%)	219 (70.8%)	93 (68.1%)	0.58	242 (73.3%)	66 (56.4%)	0.0011
APOE e4+ (%)	136 (43.8%)	53 (38.4%)	0.3	123 (37.3%)	56 (47.9%)	0.049
MMSE	29.7 (.6)	29.4 (.8)	<.0001	29.6 (.7)	29.6 (.7)	0.24
MANS-Self	0	36.1 (32.4)	<.0001	6.3 (17.1)	24.6 (35.0)	<.0001
MANS-Informant	4.7 (13.0)	15.0 (28.0)	<.0001	0	30.0 (28.1)	<.0001

Cognitive and Behavioral Scores

	Self = 0	Self > 0	p*	Informant = 0	Informant > 0	p
AVLT-LTM	9.2 (3.4)	9.2 (3.0)	0.97	9.4 (3.4)	8.7 (3.0)	0.063
VRT	6.9 (1.9)	6.5 (1.9)	0.03	6.9 (1.9)	6.5 (2.0)	0.1
PASAT-3 s	45.8 (11.9)	42.9 (13.8)	0.054	45.6 (12.2)	43.0 (13.2)	0.059
WAIS-arith	11.9 (2.5)	10.9 (2.7)	0.0002	11.7 (2.6)	11.3 (2.7)	0.09
WCST-error	29.3 (19.5)	33.2 (19.6)	0.015	29.4 (19.1)	33.6 (20.7)	0.045
TMT-A sec	28.0 (9.0)	29.2 (10.6)	0.54	27.9 (9.5)	29.6 (9.5)	0.051
CFT-copy	34.4 (2.4)	34.1 (2.5)	0.026	34.5 (2.3)	33.8 (2.7)	0.008
Ham-D	1.9 (2.6)	3.4 (3.7)	<.0001	2.1 (2.8)	2.9 (3.5)	0.007
Beck Depr	3.1 (3.3)	6.3 (5.1)	<.0001	3.7 (4.0)	5.2 (4.6)	0.0004
GDS	2.1 (2.6)	4.4 (4.7)	<.0001	2.3 (3.0)	4.0 (4.5)	<.0001
PAI-Somat	45.8 (5.7)	49.7 (9.6)	<.0001	46.5 (6.7)	48.4 (8.6)	0.04
PAI-Anxiety	44.5 (5.7)	47.2 (7.4)	.0002	44.8 (6.0)	46.7 (7.1)	0.008
PAI-Depr	45.0 (6.7)	48.6 (8.7)	<.0001	45.4 (7.4)	48.4 (7.7)	<.0001

But…Unlike Memory Decline, Depression Scores Do Not Differentially Accelerate Preclinically In APOE e4 Carriers



Locke et al, J Clin Psychiat 2014

Incident MCI

	Incident MCI (Entry)	Nonconverters (Entry)	p
N	20	427	
Age	63.8 (7.0)	58.8 (7.3)	0.003
Education years	15.4 (1.7)	15.6 (2.4)	0.67
Female (%)	9 (45%)	299 (70%)	0.03
APOE e4 carriers (%)	17 (85%)	163 (38.2%)	<0.0001
Duration followup	117.9 (49.7)	79.1 (57.2)	.003
MANS-Self	21.8 (34.9)	10.7 (24.0)	0.034
MANS-Informant	15.9 (33.1)	7.5 (18.8)	0.39
Hamilton Depression Scale	3.0 (3.4)	2.3 (3.0)	0.36
Beck Depression Inventory	3.8 (3.5)	4.1 (4.2)	0.95

Incident MCI

	Incident MCI (Entry)	Nonconverters (Entry)	p
N	20	427	
MMSE	29.4 (.8)	29.6 (.7)	0.14
AVLT-LTM	6.8 (2.6)	9.3 (3.3)	0.0007
SRT-total free	77.7 (12.6)	87.7 (11.3)	0.0005
Visual Retention Test	5.5 (1.9)	6.9 (1.9)	0.002
WMS logical memory delay	8.2 (5.0)	12.7 (3.8)	.0003
Categories-vegetables	10.8 (3.4)	15.5 (4.2)	<.0001
TMT-A seconds	34.3 (10.5)	28.1 (9.4)	0.012
TMT-B seconds	107.4 (47.8)	71.2 (28.9)	.0013
Facial Recognition Test	44.6 (3.5)	46.6 (3.8)	0.017

	Self +	Informant +
% developing MCI	6.9 (vs 2.6)%	9.4 (vs 2.2)%
Months to dx	58.9+/-39.2	28.0+/-40.4

MCI Patients Who Seek Evaluation are More Impaired

Test	Incident MCI	Prevalent MCI	p
N	39	39	
Age	72.8	75.5	.16
Education	16.1	15.0	.09
Sex (% women)	51%	43%	.57
AVLT Total Learn	32.5	28.8	.07
ST Delayed Recall	4.4	3.4	.07
LT Delayed Recall	2.5	2.0	.31
WAIS Digit Span*	11.3	8.7	.0006
WAIS Similarities*	12.0	9.7	.0002
WAIS Vocabulary*	11.8	10.2	.01
WCST-errors	25.8	42.3	.006
TMT-B (seconds)	105.9	168.7	.001
Token Test	42.2	39.4	.004
* Age scaled score, R v III			

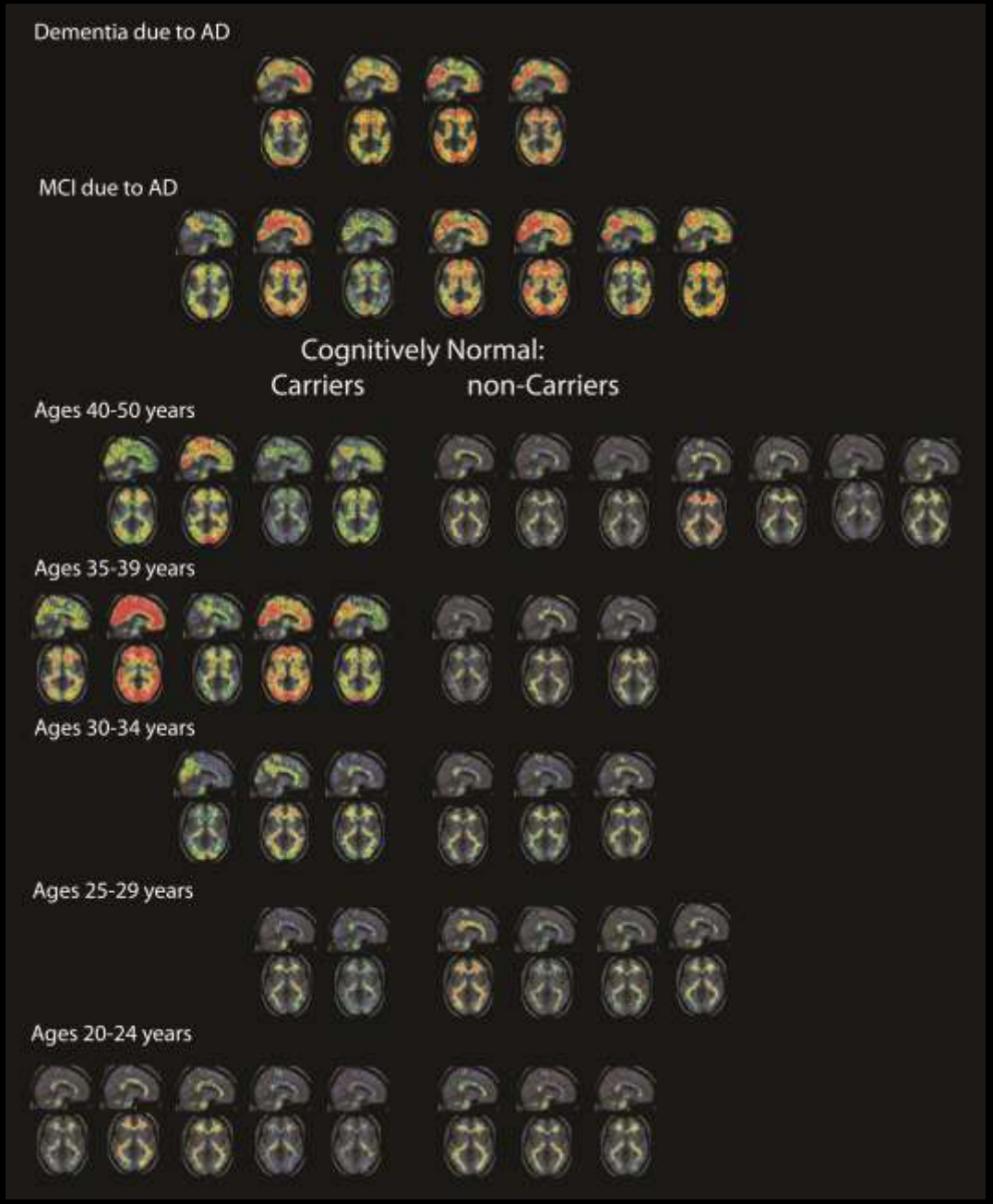
ALZHEIMER'S PREVENTION INITIATIVE

PSEN1 E280A Mutation Carriers & Non-Carriers in the API ADAD Registry

almost 3,700 kindred members

almost 900 mutation carriers (20%)

florbetapir PET in *PSEN1 E280A* 30 mutation carriers & 20 non-carriers (age 20-56)



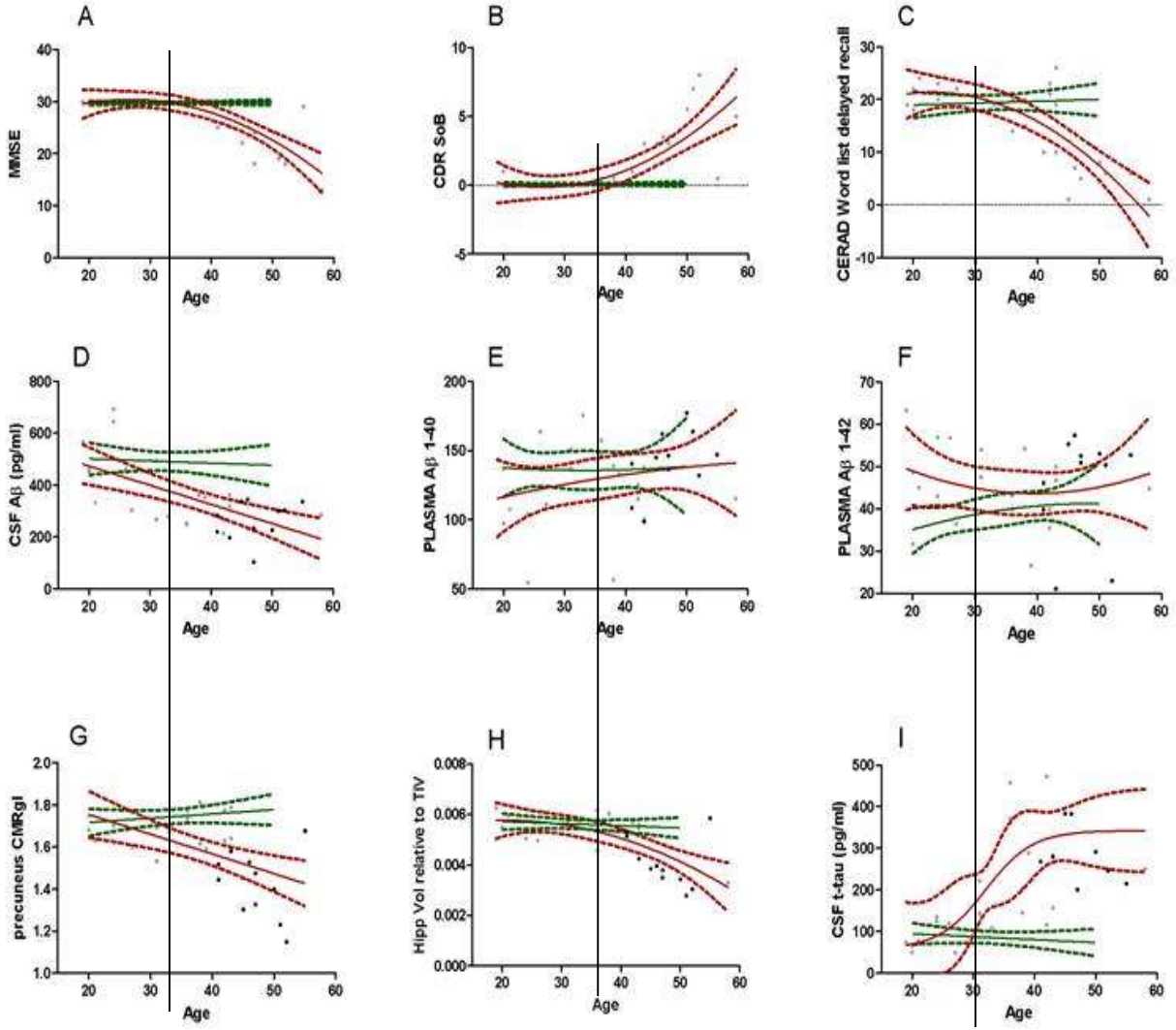
Fleisher et al, *Lancet Neurol* 2012

Florbetapir-PET Summary

- Predicted mean age (years) of clinical onset
  - MCI: 44
  - Dementia 49

- Mean age fibrillar Abeta
  - onset: 28.2 (evident in all carriers over age 30)
  - plateau: 37.6

relationships between cognitive / biomarker measurements & age
in PSEN1 E280A mutation carriers & non-carriers



Fleisher et al, *JAMA Neurol* (in press)

PS1 Cognitive Summary

- Memory precedes MMSE which precedes CDR change
- Memory decline begins very soon after CSF biomarker changes (abeta, tau) and amyloid PET positivity and many years before clinical diagnosis of MCI
- Memory decline and hippocampal atrophy occur nearly simultaneously

Summary

- Memory decline begins soon after imaging biomarker positivity in both APOE e4 and PS1 carriers
- In APOE e4 carriers, memory decline is the predominant neuropsychological characteristic of preclinical AD, not executive decline, but executive decline is a prominent feature of cognitive aging in general and is evident in clinical (vs incident) MCI patients
- Presymptomatic APOE e4 carriers and particularly homozygotes are more susceptible to additional stressors such as CV risk factors and medications
- Subjective cognitive impairment groups (self and informant) are at increased risk for clinical conversion despite higher levels of psychological distress but the predictive value for individual patients is poor (and definitions of SCI should be clarified: questionnaire vs seeking clinical evaluation)

Alzheimer's Disease Consortium

- Arizona State University (Graciela Gonzalez)
- Banner Alzheimer Institute (Eric Reiman, Jessica Langbaum)
- Barrow Neurological Institute (Leslie Baxter)
- Mayo Clinic Arizona (Richard Caselli, Dona Locke)
- Sun Health Research Institute (Tom Beach, Marwan Sabbagh)
- Translational Genomics Research Institute (Matt Huentelman)
- University of Arizona (Steve Rapscak, Geoff Ahern)