Advanced Psychometrics Methods in Cognitive Aging Research

Psychometric and statistical methods for cognitive aging science

August 19-24 2018

Granlibakken Conference Center at Lake Tahoe in California

Impact of Cognitive Reserve in Preclinical Alzheimer's Disease

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Acknowledgements

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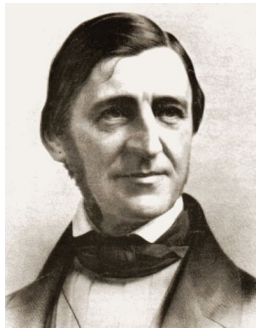
- The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Disclosures

- Consulting / Scientific Advisory Boards
  - Eli Lilly Pharmaceutical Company
  - Neurotrack
  - Biogen Idec
  - Janssen Pharmaceuticals

These disclosures are not relevant to the work presented today

Famous People with Alzheimer's Disease



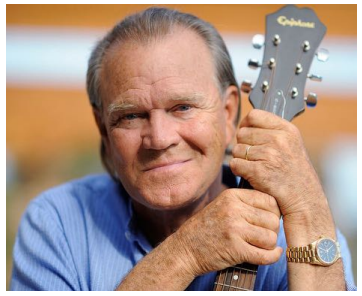
Ralph Waldo Emerson

B. Smith

Burgess Meredith

Winston Churchill

Sugar Ray Robinson



Glen Campbell

Peter Falk

Ronald Reagan

Rosa Parks

Norman Rockwell

Carl Weathers

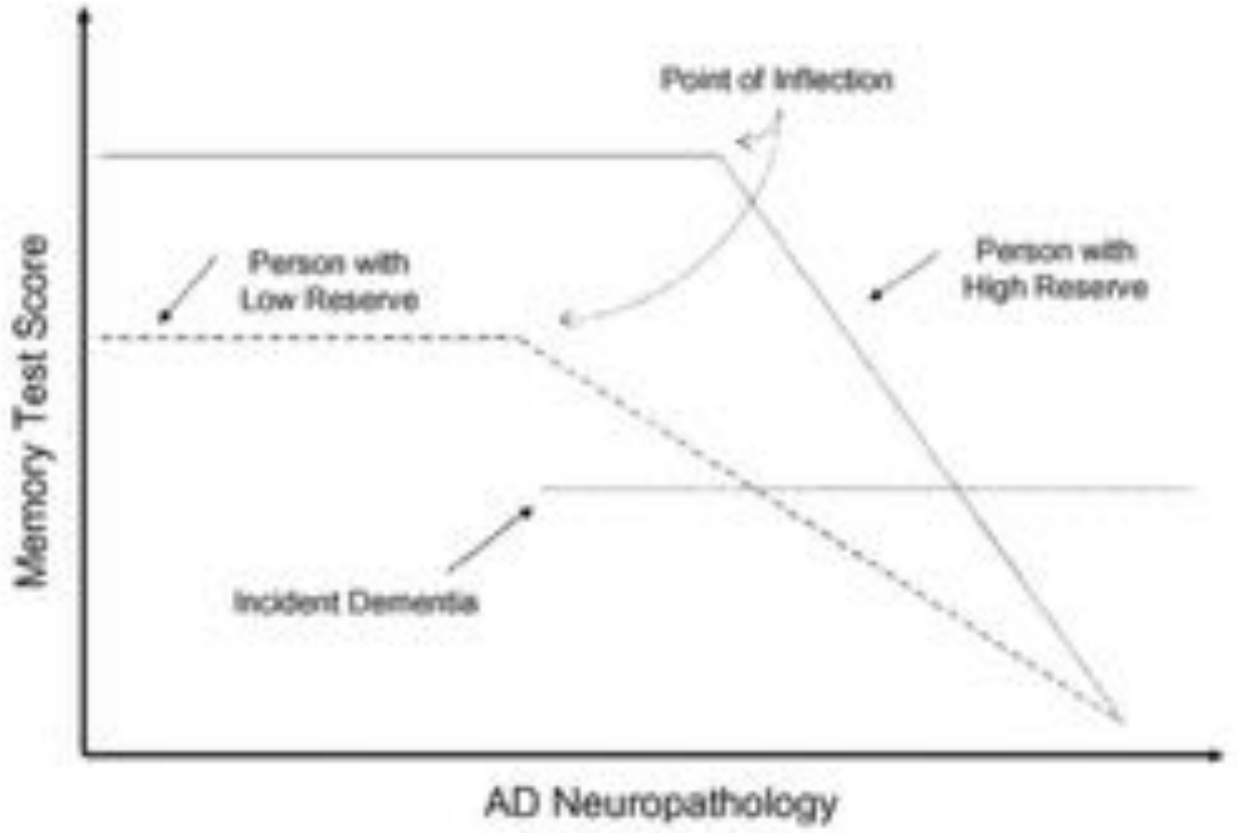
Pat Summit

Erik Erikson

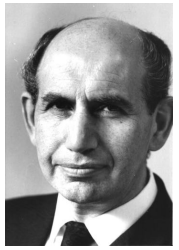
Abigail Van Buren "Dear Abby"

Henry Ford

How Cognitive Reserve May Mediate Between AD Pathology and Clinical Expression



Stern Y, *Neuropsychologia.* 2009:47; 2015-2028


Sir Martin Roth


Sir Bernard Tomlinson

Brit. J. Psychiat. (1968), 114, 797–811

The Association Between Quantitative Measures of Dementia and of Senile Change in the Cerebral Grey Matter of Elderly Subjects

By G. BLESSED, B. E. TOMLINSON and MARTIN ROTH

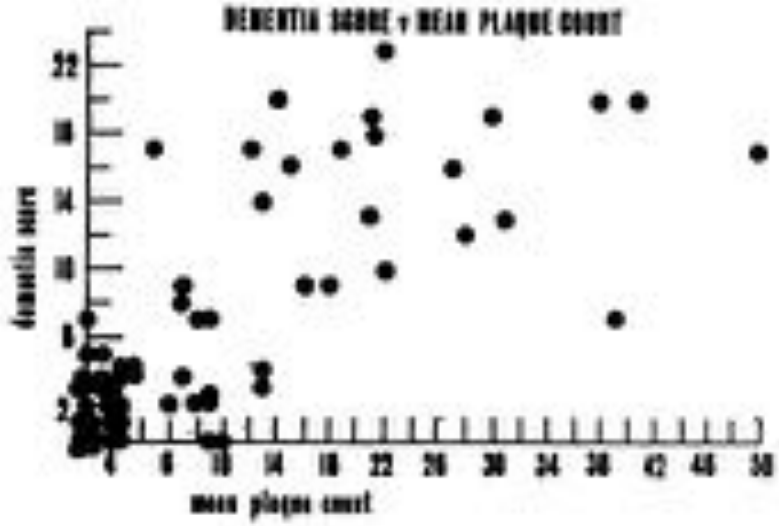
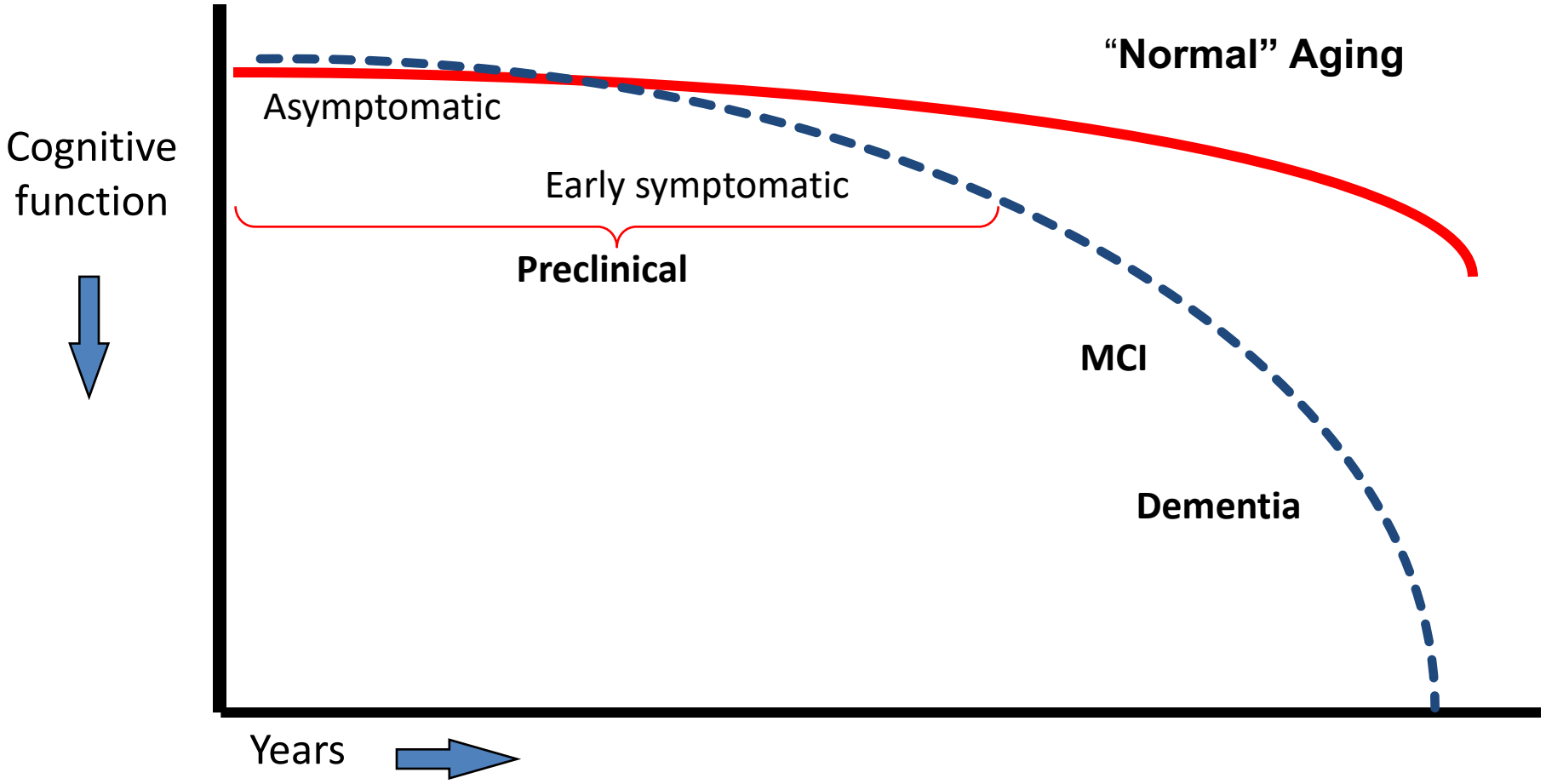


FIG. 3.—Relationship of dementia score to mean plaque count in 60 aged subjects.

"It would appear that a certain amount of the change estimated by plaque count may be accommodated within the reserve capacity of the cerebrum without causing manifest intellectual impairment" **(page 807).**

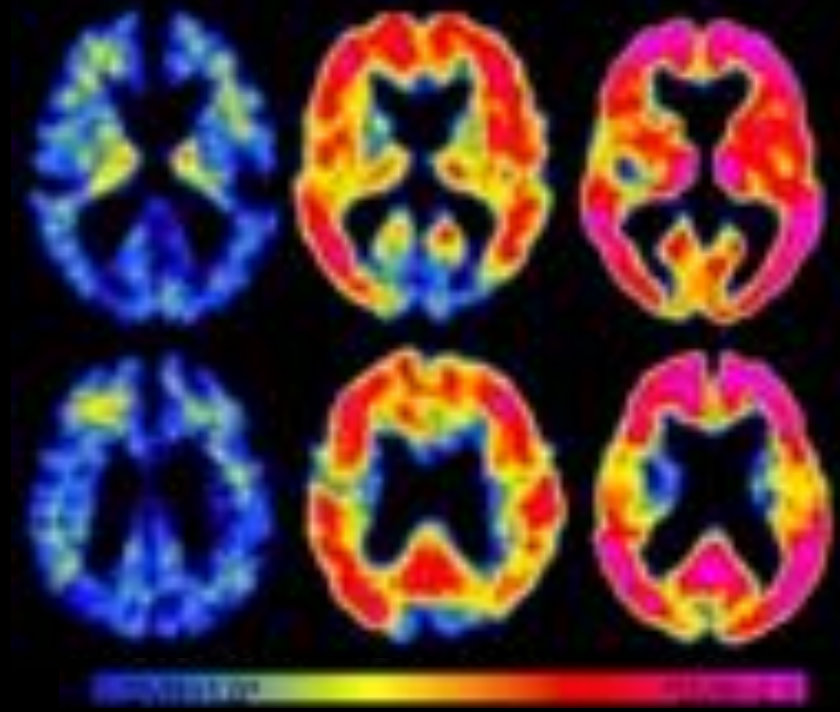
The continuum of Alzheimer's disease



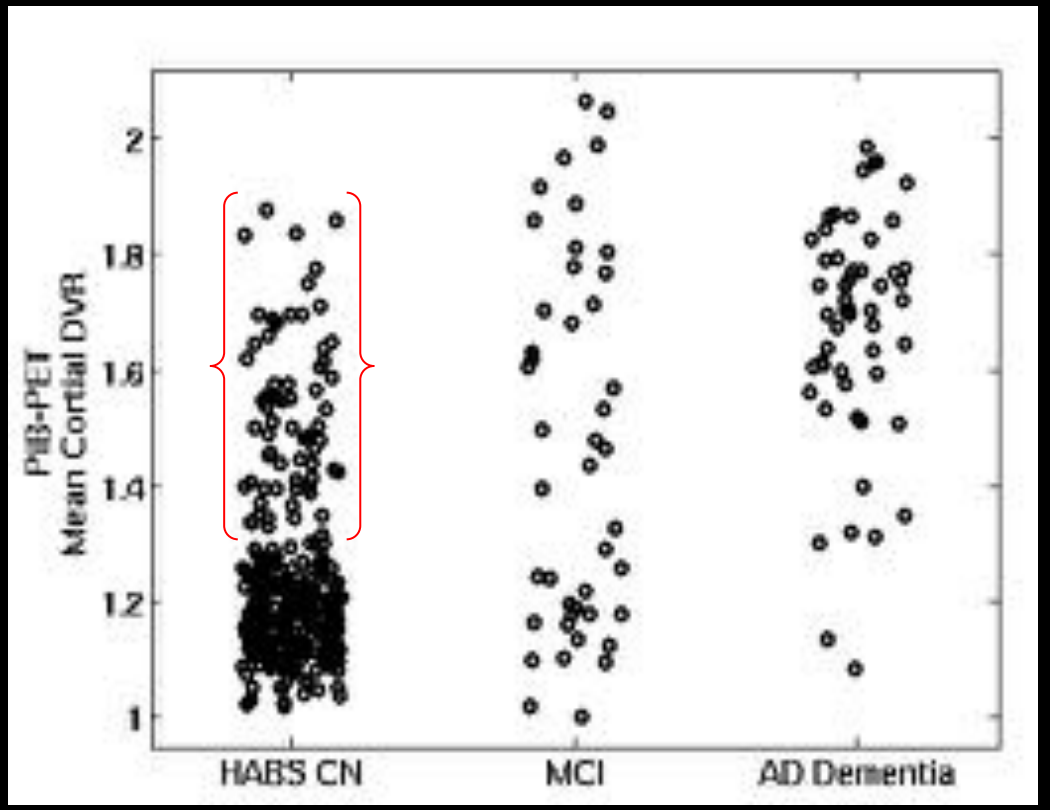
Sperling R et al *Alzheimer & Dementia* 2011,
Jack CR et al Alzheimer & Dementia, 2018

Keith Johnson, MD

PET Amyloid Imaging in Clinically Normal Older Individuals



CN Aβ– CN Aβ+ AD Aβ+



Harvard Aging Brain Sudy

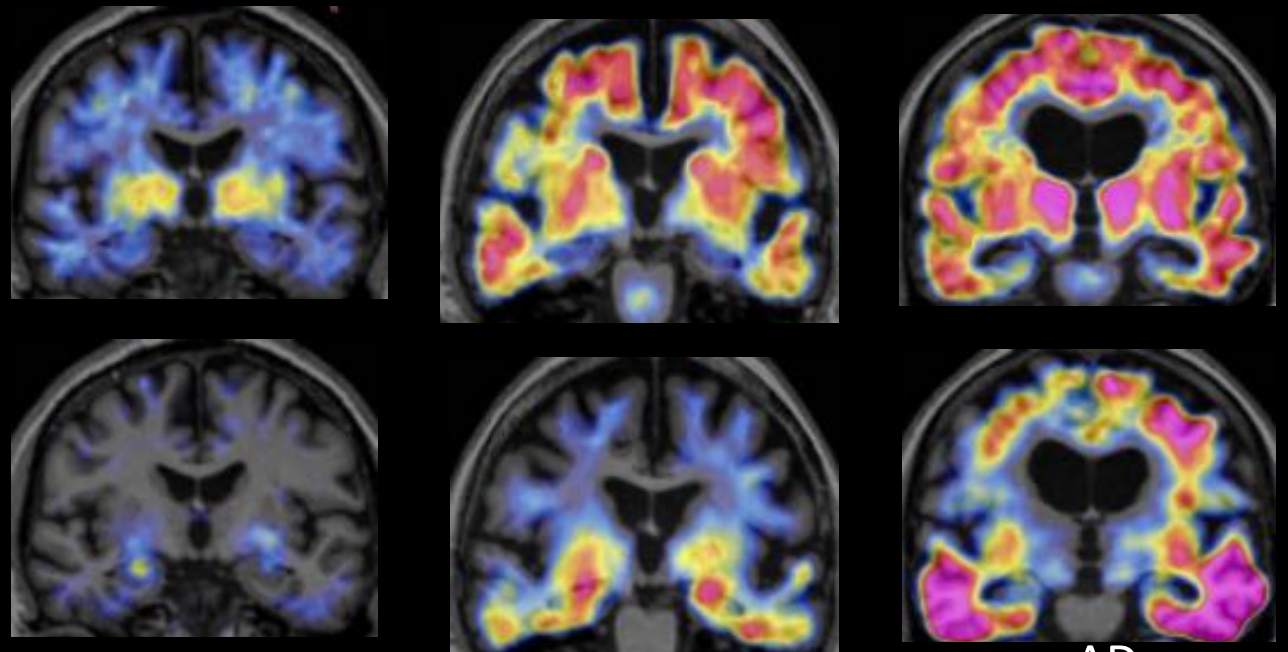
Sperling, Mormino, Johnson *Neuron* 2014

Keith Johnson, MD

PET Amyloid and Tau Imaging

Aβ (PiB)

Tau (T807)



CN CN AD Dementia

Sperling, Mormino, Johnson *Neuron* 2014

ELSEVIER

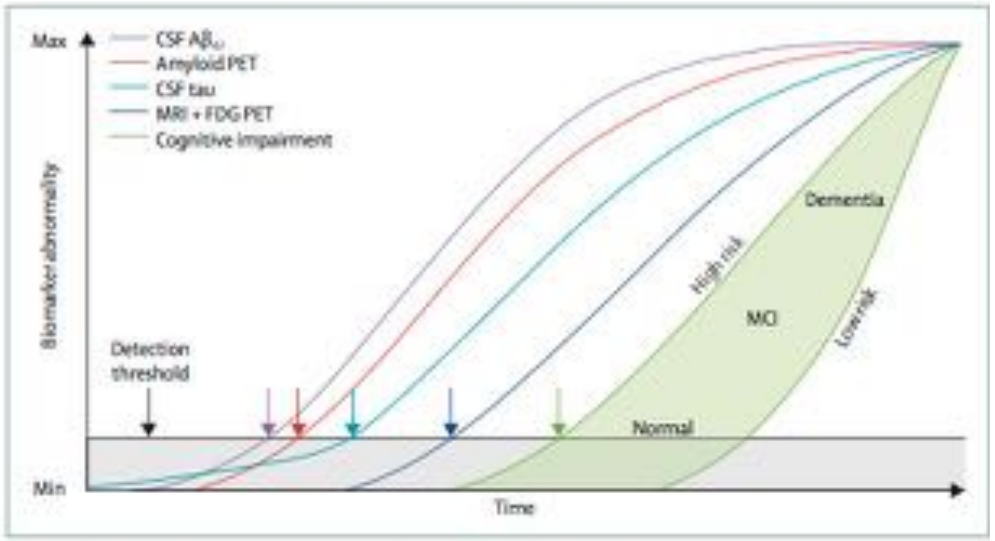
Alzheimer's & Dementia ■ (2011) 1–13

Alzheimer's & Dementia

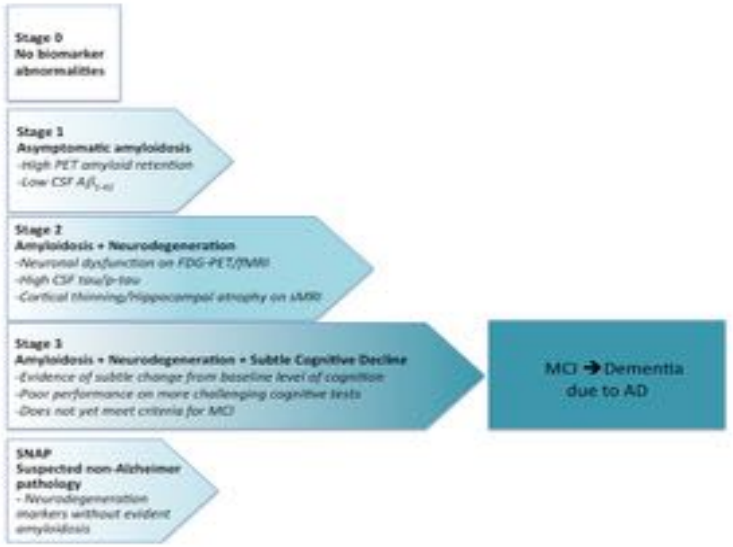
Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

Jack et al, *Lancet* 2013



Sperling R et al, *Neuron,* 2014



Original Investigation

Synergistic Effect of β-Amyloid and Neurodegeneration on Cognitive Decline in Clinically Normal Individuals

Elizabeth C. Mormino, PhD; Rebecca A. Betensky, PhD; Trey Hedden, PhD; Aaron P. Schultz, PhD; Rebecca E. Amariglio, PhD; Dorene M. Rentz, PsyD; Keith A. Johnson, MD; Reisa A. Sperling, MD

JAMA Neurol. doi:10.1001/jamaneurol.2014.2031
Published online September 15, 2014.

Table 1. Clinically Normal Individuals Classified Into Preclinical Stages

Variable	Stage 0 (n = 81)	Stage 1 (n = 19)	Stage 2 (n = 28)	SNAP (n = 38)
Age, median (IQR), y	70 (67-76)	73 (69-77)	77 (73-82)	79 (75-82)
Educational level, median (IQR), y	17 (14-18)	16 (14-18)	16 (15-18)	16 (14-18)
Female sex, %	59.3	52.6	71.4	36.8
APOE4^{+}, %	18.7	58.8	57.7	18.9

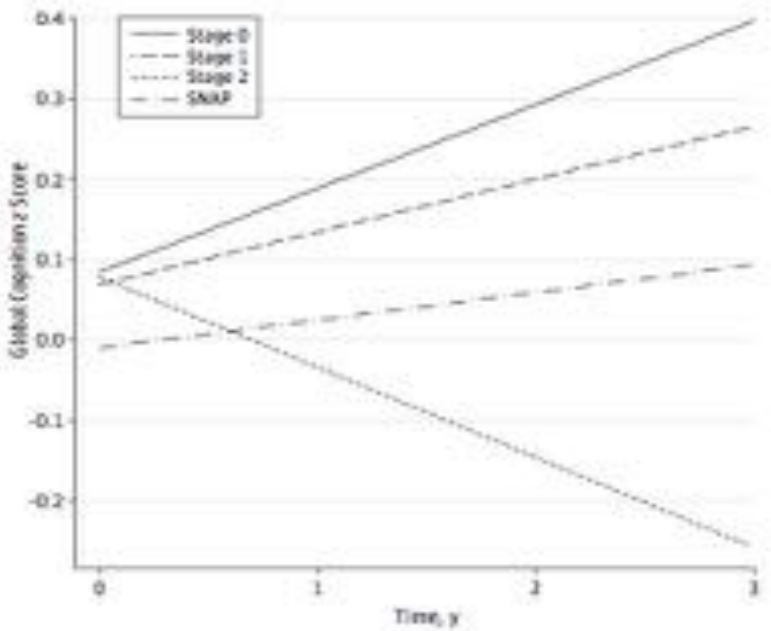
Abbreviations: IQR, interquartile range; SNAP, suspected non-Alzheimer disease pathology.

Table 2. Decline Across Preclinical Groups

Contrast	Estimate (SE)	*P* Value
SNAP vs stage 0	-0.069 (0.032)	.03
SNAP vs stage 1	-0.031 (0.041)	.44
Stage 1 vs stage 0	-0.038 (0.038)	.32
Stage 2 vs stage 0	-0.215 (0.032)	<.001
Stage 2 vs stage 1	-0.177 (0.042)	<.001
Stage 2 vs SNAP	0.146 (0.035)	<.001
Trend test stage 0-2	-0.106 (0.015)	<.001

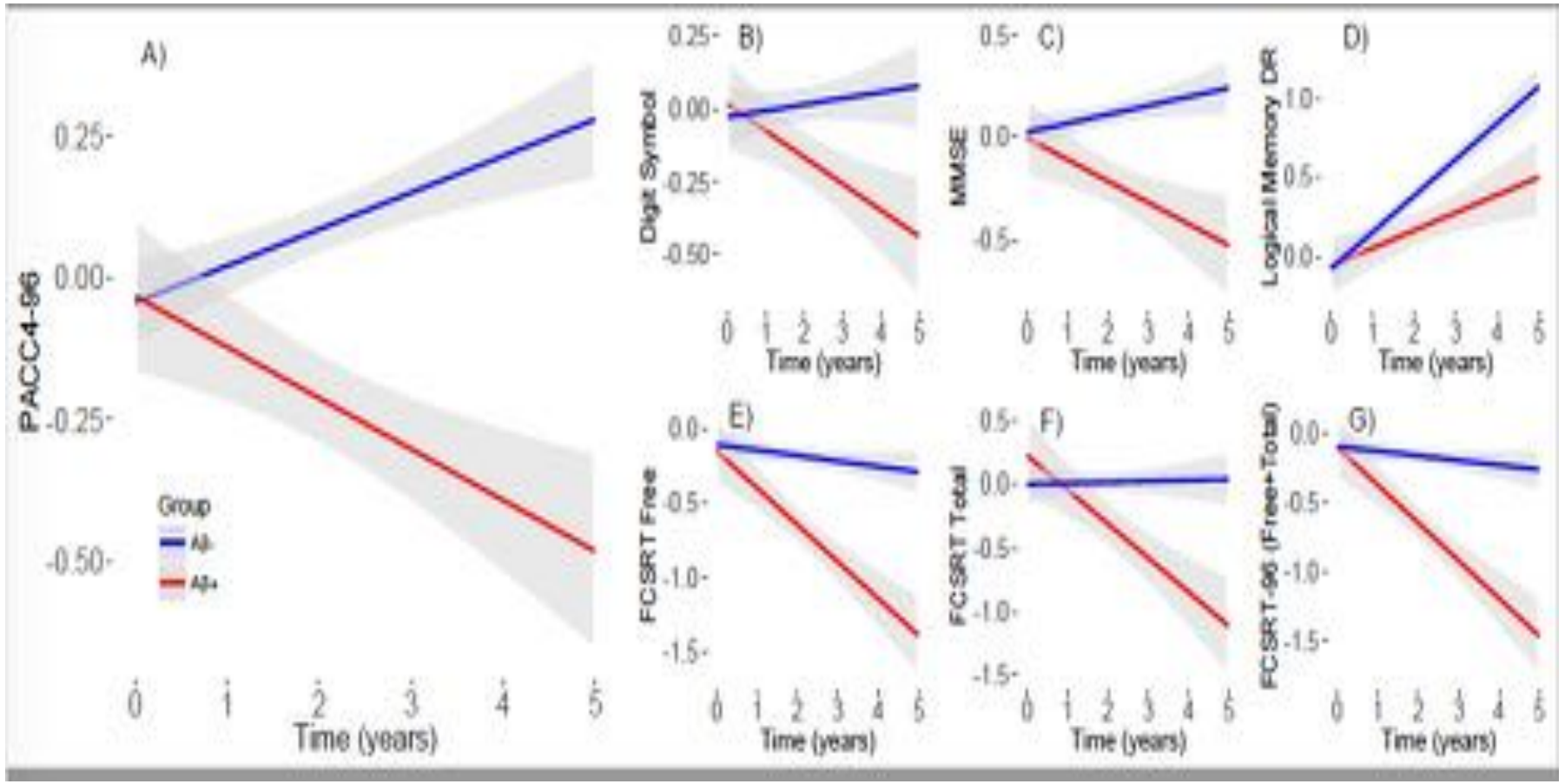
Abbreviation: SNAP, suspected non-Alzheimer disease pathology.

Figure. Cognitive Decline Across Preclinical Stages



Decline on Cognitive Composite in Amyloid Positive Normal Elderly

Alzheimer's & Dementia, 2017



What confers reserve or resilience?

Articles that came from Friday Harbor 2009

Journal of the International Neuropsychological Society (2011), **17**, 615–624.

doi:10.1017/S1355617711000014

SPECIAL SERIES

Cognitive Activities During Adulthood Are More Important than Education in Building Reserve

Bruce R. Reed,[1,2] Maritza Dowling,[3] Sarah Tomaszewski Farias,[1] Joshua Sonnen,[4] Milton Strauss,[5] Julie A. Schneider,[6] David A. Bennett,[6] AND Dan Mungas[1]

Journal of the International Neuropsychological Society (2011), **17**, 593–601.

doi:10.1017/S1355617710001748

SPECIAL SERIES

Conceptual and Measurement Challenges in Research on Cognitive Reserve

Richard N. Jones,[1,2] Jennifer Manly,[3] M. Maria Glymour,[4] Dorene M. Rentz,[5] Angela L. Jefferson,[6] AND Yaakov Stern[3,7]

Journal of the International Neuropsychological Society (2011), **17**, 625–638.

doi:10.1017/S1355617711000476

SPECIAL SERIES

Explaining Differences in Episodic Memory Performance among Older African Americans and Whites: The Roles of Factors Related to Cognitive Reserve and Test Bias

Denise C. Fyffe,[1] Shubhabrata Mukherjee,[2] Lisa L. Barnes,[3] Jennifer J. Manly,[4] David A. Bennett,[3] AND Paul K. Crane[2]

Journal of the International Neuropsychological Society (2011), **17**, 639–642.

doi:10.1017/S1355617711000579

SPECIAL SERIES—COMMENTARY

Elaborating a Hypothetical Concept: Comments on the Special Series on Cognitive Reserve

Yaakov Stern, PhD
Cognitive Neuroscience Division, Taub Institute, Columbia University College of Physicians and Surgeons, New York, New York

Articles that came from Friday Harbor 2009

doi:10.1093/brain/awq154 Brain 2010: 133; 2196–2209 | 2196

BRAIN
A JOURNAL OF NEUROLOGY

Measuring cognitive reserve based on the decomposition of episodic memory variance

Bruce R. Reed,[1,2] Dan Mungas,[1] Sarah Tomaszewski Farias,[1] Danielle Harvey,[3] Laurel Beckett,[3] Keith Widaman,[4] Ladson Hinton[1] and Charles DeCarli[1]

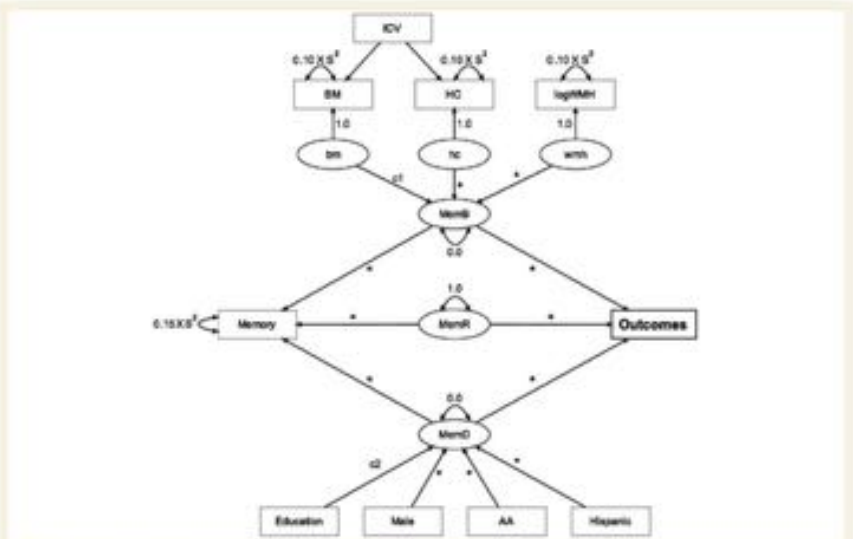
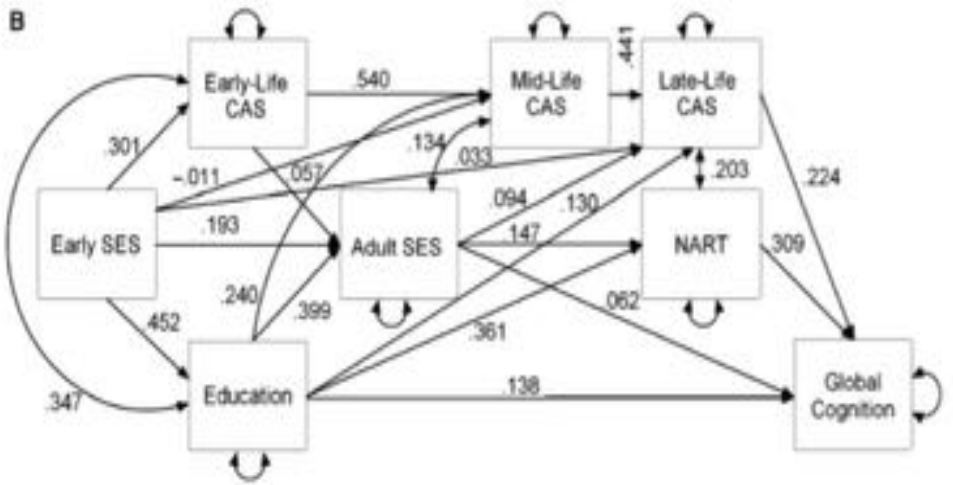


Figure 1 Analytic model for decomposing episodic memory into independent components and relating these components to external variables. Rectangles represent observed variables and ovals represent latent variables. Observed demographic and MRI variables were allowed to correlate freely (paths not shown). Freely estimated parameters are indicated by 'asterisk'. S^2 refers to sample variance. c1 and c2 are scaling constants selected to set variances at 1.0 for the MemB and MemD latent variables.

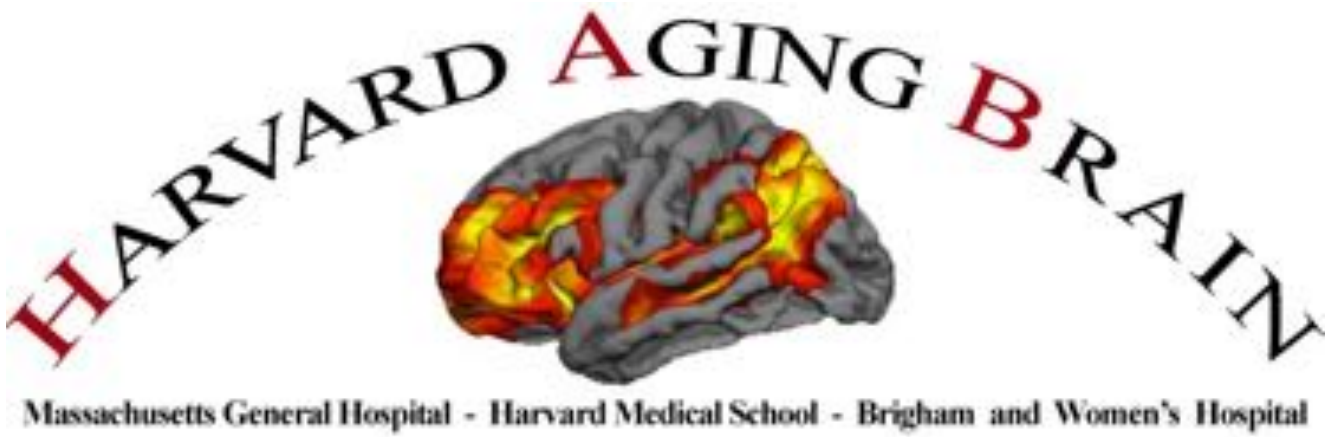
CLINICAL INVESTIGATIONS

A Life Course Model of Cognitive Activities, Socioeconomic Status, Education, Reading Ability, and Cognition

Angela L. Jefferson, PhD,[*†] *Laura E. Gibbons, PhD,*[‡] *Dorene M. Rentz, PsyD,*[§] *Janessa O. Carvalho, PhD,*[‖] *Jennifer Manly, PhD,*[#] *David A. Bennett, MD,*[**] *and Richard N. Jones, ScD*[††]



Results from the Harvard Aging Brain Study

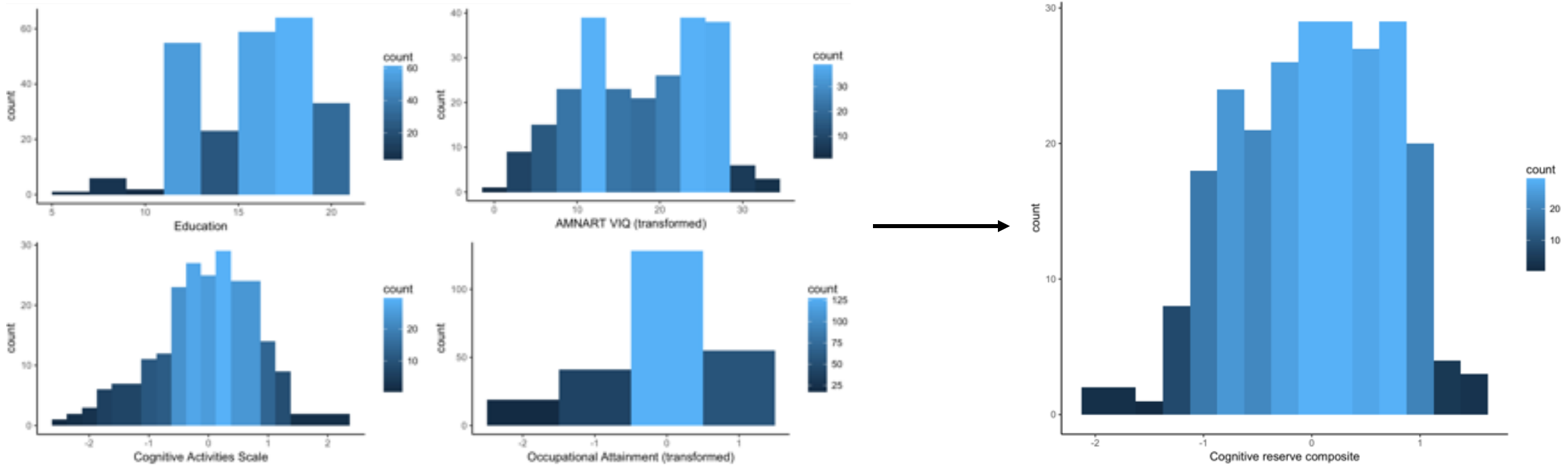


Measuring proxies of cognitive reserve

presented at AAIC 2017

	Occupational Attainment (Hollingshead)	Cognitive Activities Scale (40yr to now)	Education	AMNART Verbal IQ
Occupational Attainment (Hollingshead)				
Cognitive Activities Scale (40yr to now)	0.25***			
Education	0.73***	0.32***		
AMNART Verbal IQ	0.34***	0.28***	0.41***	

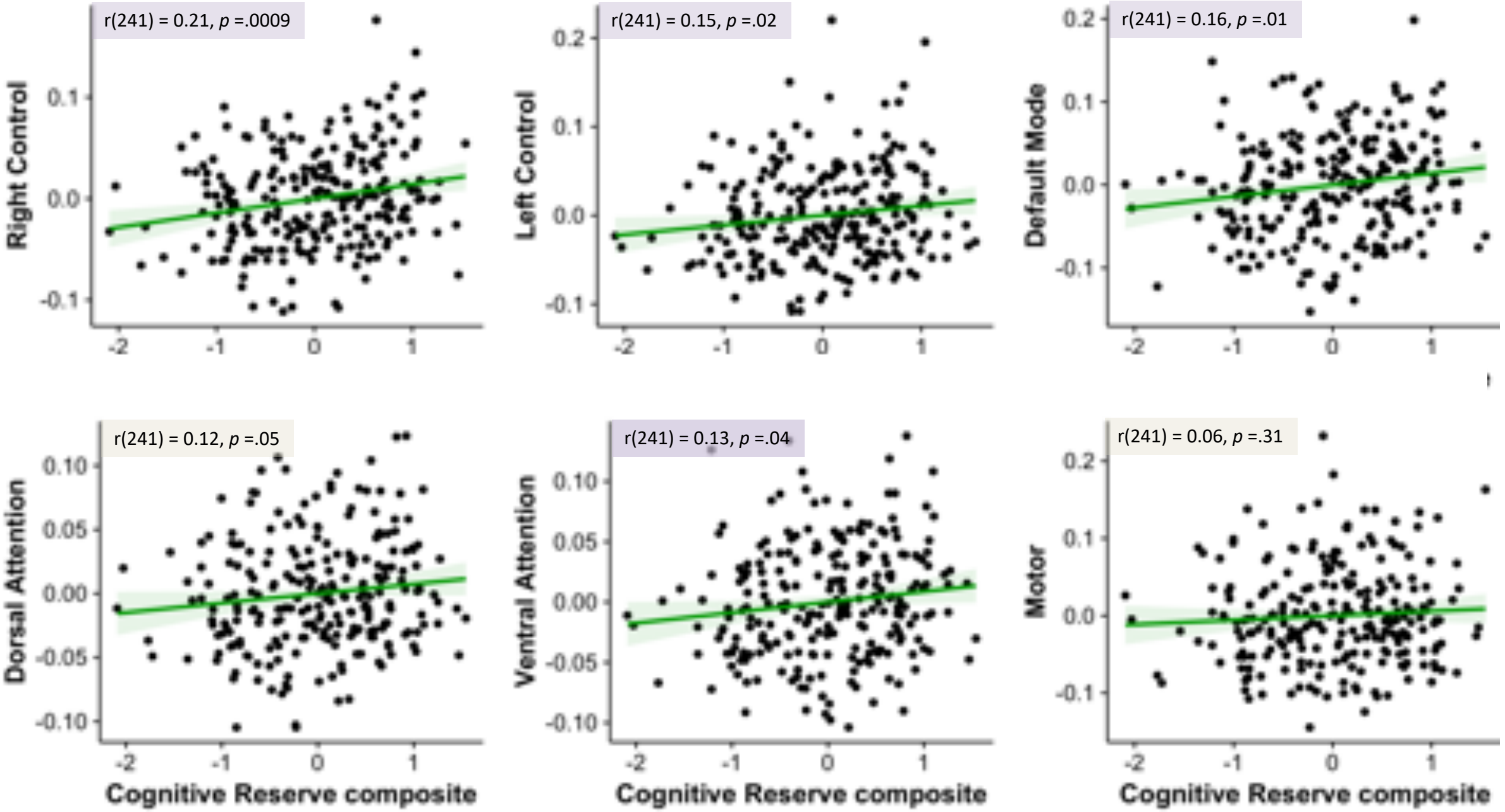
Computed correlation used spearman-method with listwise-deletion.



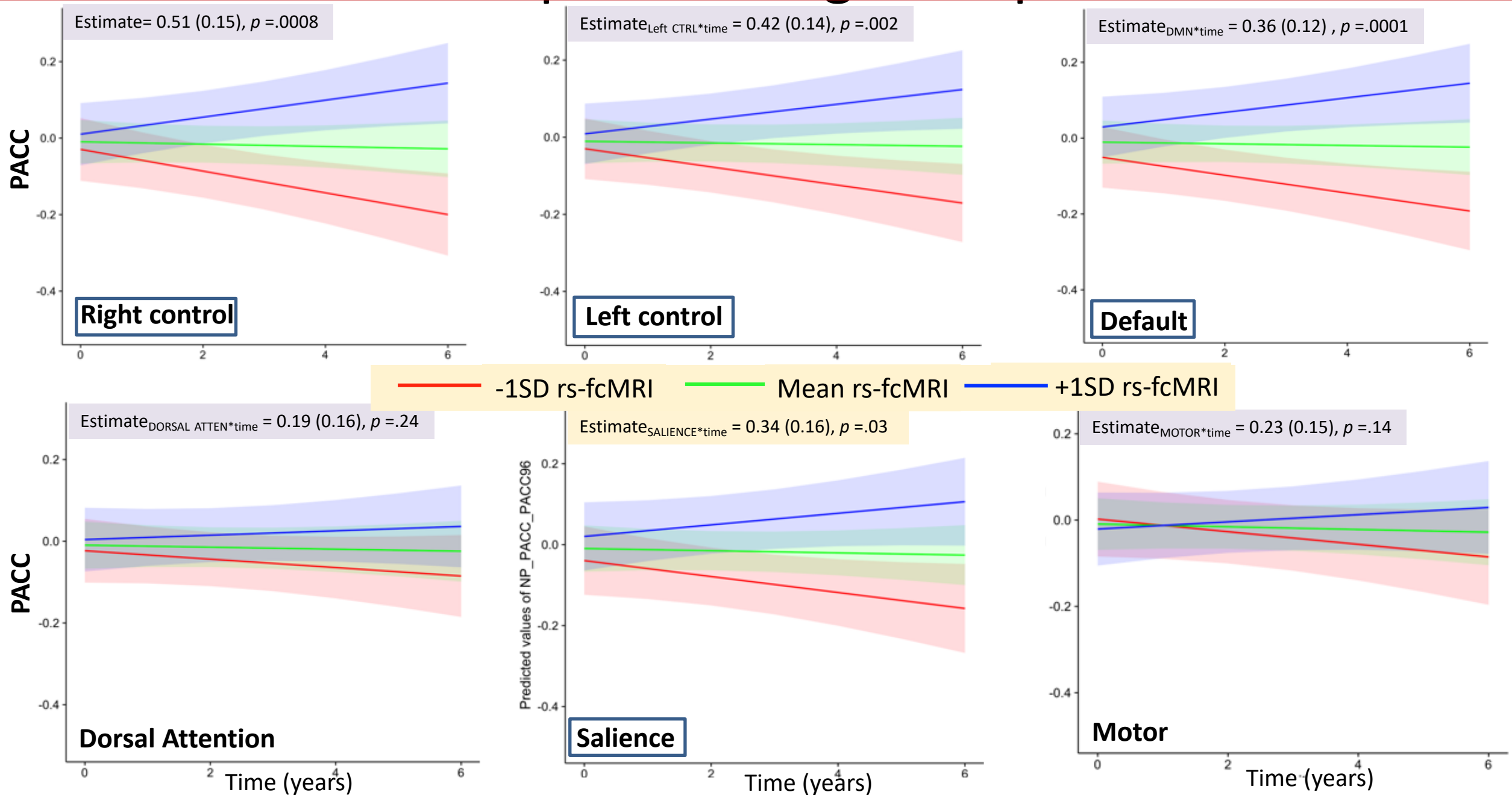
Demographics

	Overall (n=243)	Aβ- (n=182)	Aβ+ (n=61)	
	Mean (SD)	Mean (SD)	Mean (SD)	*p* value
Demographics				
Age (years)	73.5 (6.3)	72.8 (5.9)	75.6 (5.5)	.001
Gender (% Female)	60%	59%	61%	.67
CDR = 0	100%	100%	100%	-
PiB FLR DVR	1.16 (0.2)	1.06 (0.1)	1.45 (0.1)	<.001
Aβ (% high burden)	25%	-	-	-
APOEε4 (% carrier) (n=235)	42%	18%	61%	<.001
Cognitive reserve				
Education (years) [6-20]	15.7 (3.1)	15.6 (3.1)	16.0 (2.6)	.28
Occupational attainment [7-49]	19.1 (11.1)	18.7 (11.1)	20.06 (11.5)	.42
Cognitive Activities [-2.2-2.6]	0.01 (3.2)	0.04 (0.9)	-0.05 (0.9)	.48
AMNART Verbal IQ [78-132]	120.6 (9.1)	120.2 (9.4)	121.8 (8.9)	.23

Greater CR is related to greater functional connectivity



rs-fcMRI predicts cogntiive performance

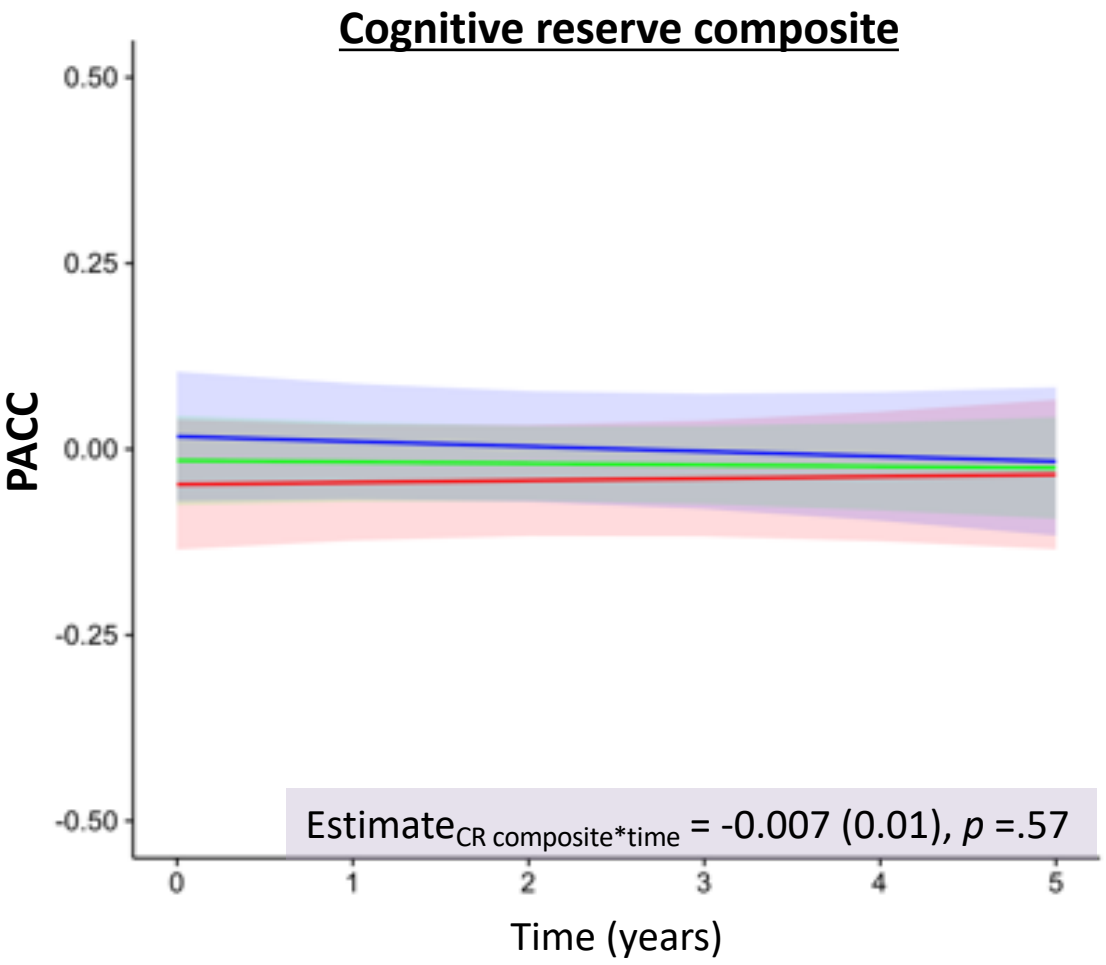


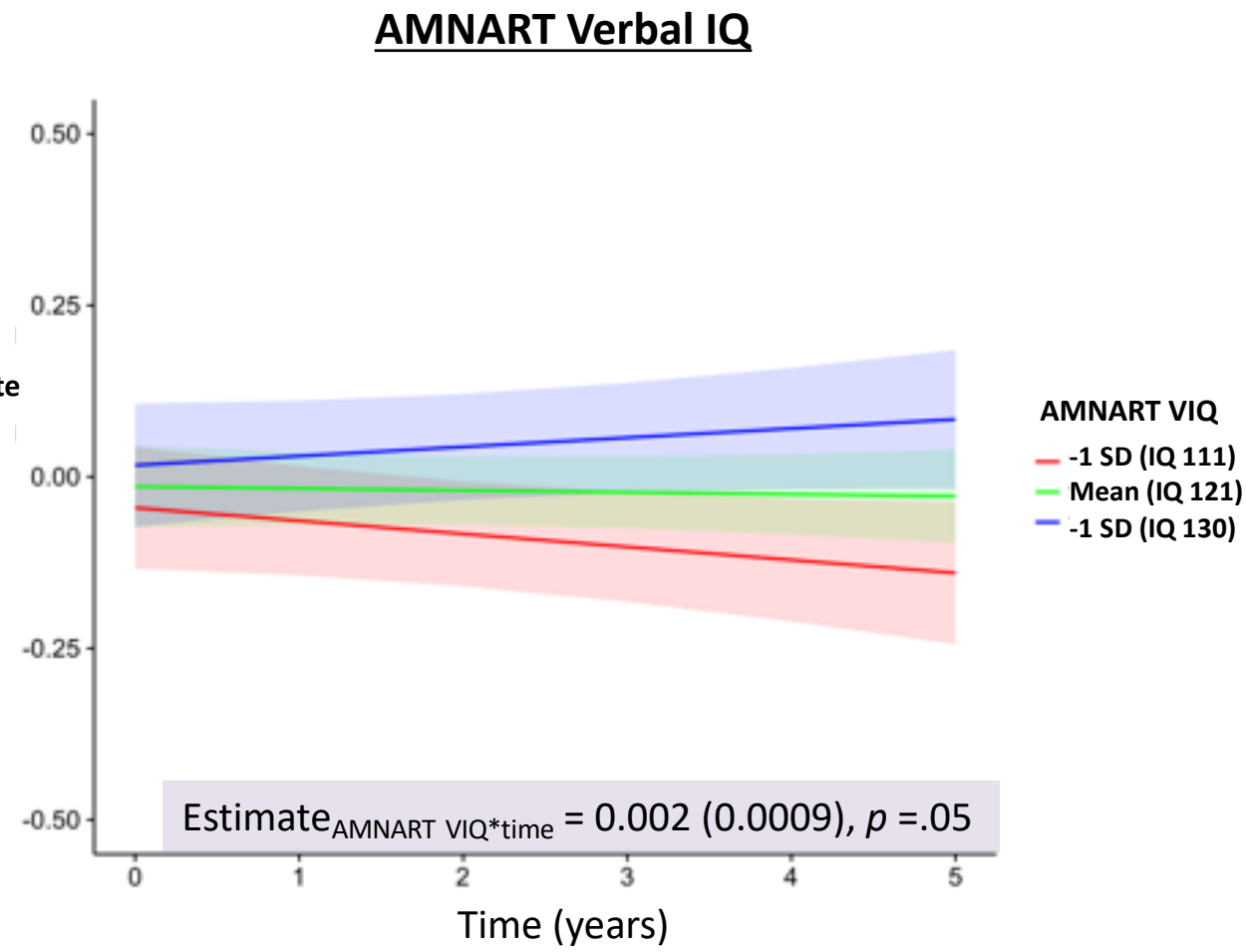
AMNART VIQ: strongest relationships with cognitive networks

	Education	*AMNART Verbal IQ*	*Cognitive Activities Scale*	*Occupational Attainment*
Right Control	0.19**	0.22***	0.05	0.10
Left Control	0.11	0.19**	0.11	0.00
Default Mode	0.12	0.20**	0.14*	0.08
Dorsal Attention	0.17*	0.15*	-0.05	0.10
Salience	0.09	0.17**	0.13*	0.06
Motor	0.12	0.10	-0.02	0.03

Computed correlation used spearman-method with listwise-deletion

AMNART VIQ, not composite, subtly related to cognitive change





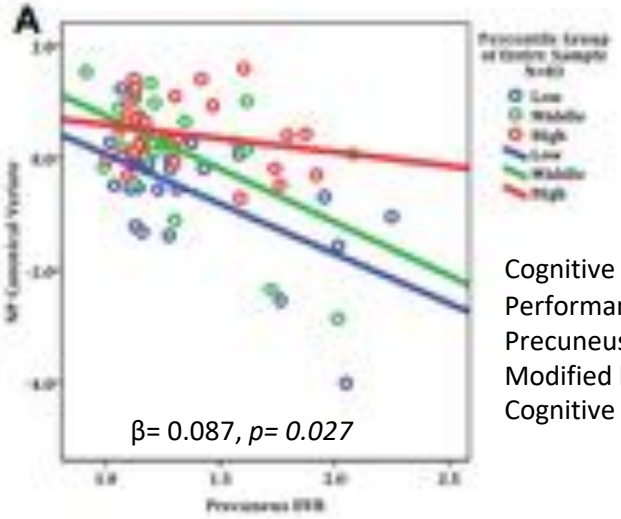
Relationship of CR to Performance in Preclinical AD

Cognition, Reserve, and Amyloid Deposition in Normal Aging

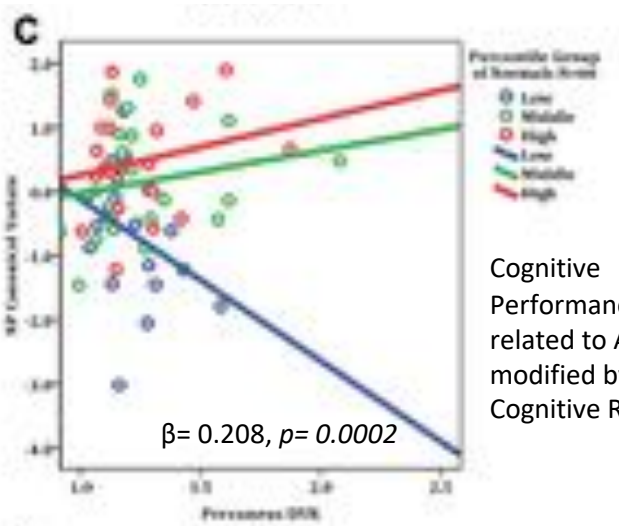
Dorene M. Rentz, PsyD,[1,2] Joseph J. Locascio, PhD,[2,3] John A. Becker, PhD,[4] Erin K. Moran, BA,[4] Elisha Eng, BA,[1] Randy L. Buckner, PhD,[4,5,6,7,8] Reisa A. Sperling, MD,[1,2] and Keith A. Johnson, MD[1,2,4]

DM Rentz, et al. *Ann Neurol* 2010; 67:353-364.

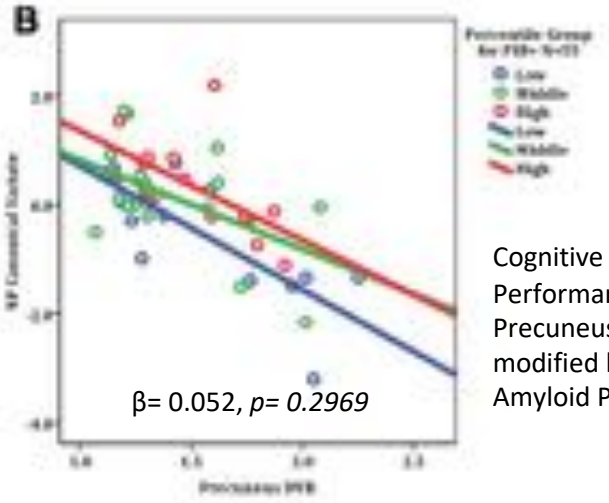
NC=66, AD= 17



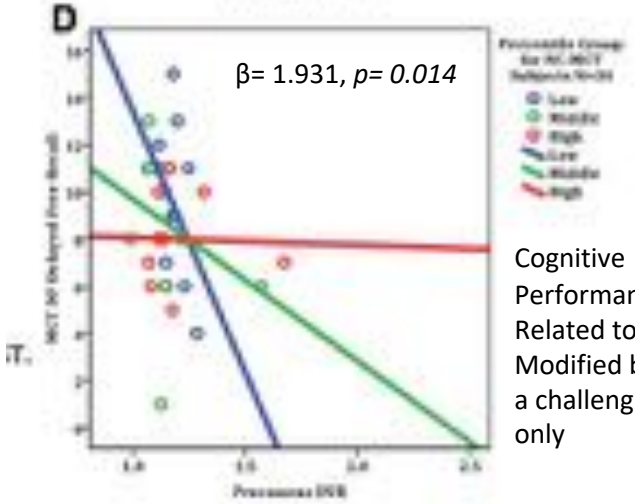
Cognitive Performance vs. Precuneus Aβ Is Modified by Cognitive Reserve



Cognitive Performance is not related to Aβ but Is modified by Cognitive Reserve



Cognitive Performance vs. Precuneus Aβ is not modified by CR in Amyloid Positive



Cognitive Performance is Related to Aβ and Modified by CR on a challenging test only

Brain Imaging and Behavior (2017) 11:383–390
DOI 10.1007/s11682-016-9640-4

SI: RESILIENCE/RESERVE IN AD

Cognitive resilience in clinical and preclinical Alzheimer's disease: the Association of Amyloid and Tau Burden on cognitive performance

Dorene M. Rentz[1,2] · Elizabeth C. Mormino[1] · Kathryn V. Papp[1,2] · Rebecca A. Betensky[3] · Reisa A. Sperling[1,2,4] · Keith A. Johnson[1,2,4,5]

	CN Mean (SD) or count (n)	*MCI/AD* Mean (SD) or count (n)	*Mean Difference*	*p*
n	133	17/6		
Age	76.17 (6.23)	69.41 (9.97)	6.76	0.001
Sex (M/F)	59/74	19/4		0.001
Education (years)	15.91 (2.96)	16.29 (3.38)	0.38	0.597
Inferior Temporal T807	1.20 (0.09)	1.61 (0.44)	0.40	0.001
PiB	1.21 (0.21)	1.50 (0.26)	0.28	0.001
MMSE	29.18 (1.02)	26.61(3.06)	2.57	0.001
AMNART	121.59 (8.75)	121.22 (8.01)	0.37	0.850
Global CDR (1/0.5/0)	0.03 (0.13)	0.41 (0.05)	0.38	0.001

MMSE Mini Mental Status Exam, *CDR* Clinical Dementia Rating, *MCI* Mild Cognitive Impairment, *AD* Alzheimer's disease, *AMNART*- American National Adult Reading Test

Methods: Statistical Analysis

Demographics: Independent Sample T-Tests, Fisher's Exact Tests explored differences between diagnostic groups

Multiple linear regression analyses: Across CN, MCI and AD subjects

Dependent Variable: MMSE
Predictors: Age, Education, AMNART IQ, PIB DVR with cerebellar reference, T807 with cerebellar gray pons reference, Interaction of AMNART and PIB; Interaction of AMNART and T807 using 5 models:

Model 1	Model 2	Model 3	Model 4	Model 5
PIB-PET		PiB-PET	PiB-PET	T807-PET
	T807-PET	T807-PET	PIB*VIQ	T807 * VIQ

All models controlled for age, education, AMNART IQ and clinical status: NC/MCI/AD

Cross-sectional Relationships with Amyloid, Tau and MMSE

	t	*B(SE)*	*p*	*F*	*df*	*p*	*Adj. R^2*
Overall Model 1				21.66	5148	0.000	0.40
Age	-0.81	-0.01 (0.02)	0.422				
Education	2.30	0.09 (0.04)	0.023				
VIQ	2.23	0.03 (0.01)	0.027				
Clinical Status	-7.05	-2.55 (0.36)	0.000				
PiB	-3.27	-1.70 (0.52)	0.001				
Overall Model 2				28.82	5148	0.000	0.48
Age	-1.72	-0.03 (0.02)	0.088				
Education	2.02	0.08 (0.04)	0.045				
VIQ	2.24	0.03 (0.01)	0.027				
Clinical Status	-4.97	-1.85 (0.37)	0.000				
T807	-5.73	-3.47 (0.61)	0.000				
Overall Model 3				24.09	6147	0.000	0.48
Age	-1.61	-0.03 (0.02)	0.109				
Education	2.04	0.08 (0.04)	0.044				
VIQ	2.29	0.03 (0.01)	0.024				
Clinical Status	-4.86	-1.82 (0.38)	0.000				
PiB	-0.84	-0.47 (0.56)	0.401				
T807	-4.62	-3.20 (0.69)	0.000				

Rentz, et al; *Brain Imaging and Behavior* (2017) 11:383-390

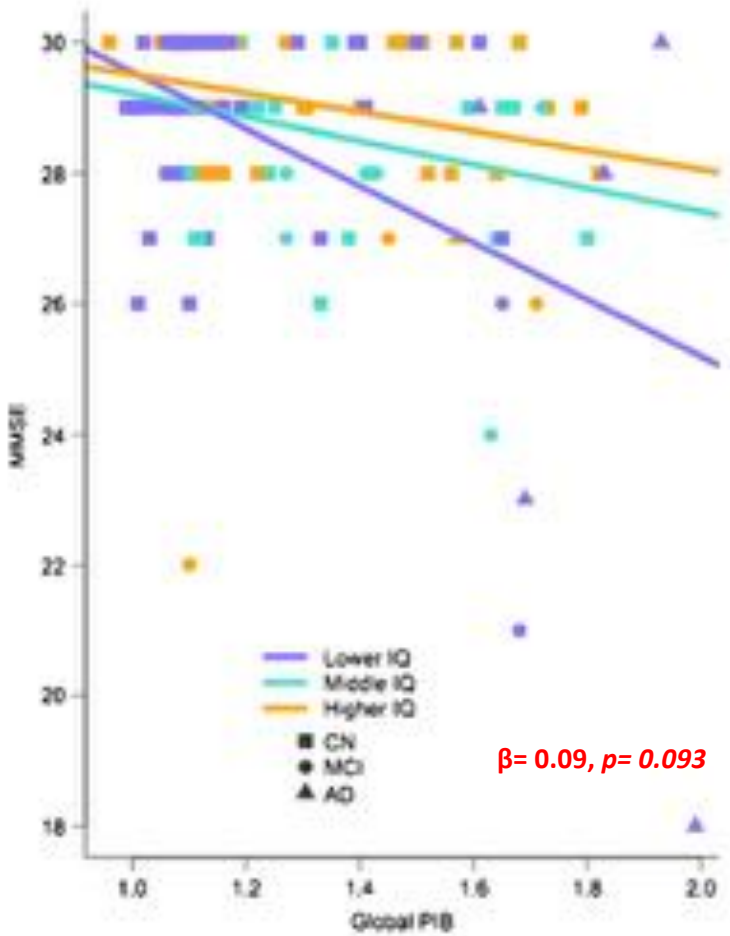
Cognitive Reserve Modifies Relationship with MMSE and Tau but not MMSE and Amyloid

Overall Model 4				18.76	6147	0.000	0.41
Age	-0.71	-0.01(0.02)	0.477				
Education	2473	0.10 (0.04)	0.015				
VIQ	-1.18	-0.08 (0.07)	0.239				
Clinical Status	-6.81	-2.47 (0.36)	0.000				
PiB	-1.95	-12.55 (6.44)	0.053				
PiB × VIQ	1.69	0.09 (0.05)	0.093	←			
Overall Model 5				26.77	6147	0.000	0.50
Age	-1.64	-0.03(0.02)	0.103				
Education	2.14	0.08 (0.04)	0.034				
VIQ	-2.43	-0.15 (0.06)	0.016				
Clinical Status	-5.21	-1.89 (0.36)	0.000				
T807	-3.58	-20.07 (5.61)	0.000				
T807 × VIQ	2.97	0.14 (0.05)	0.003	←			

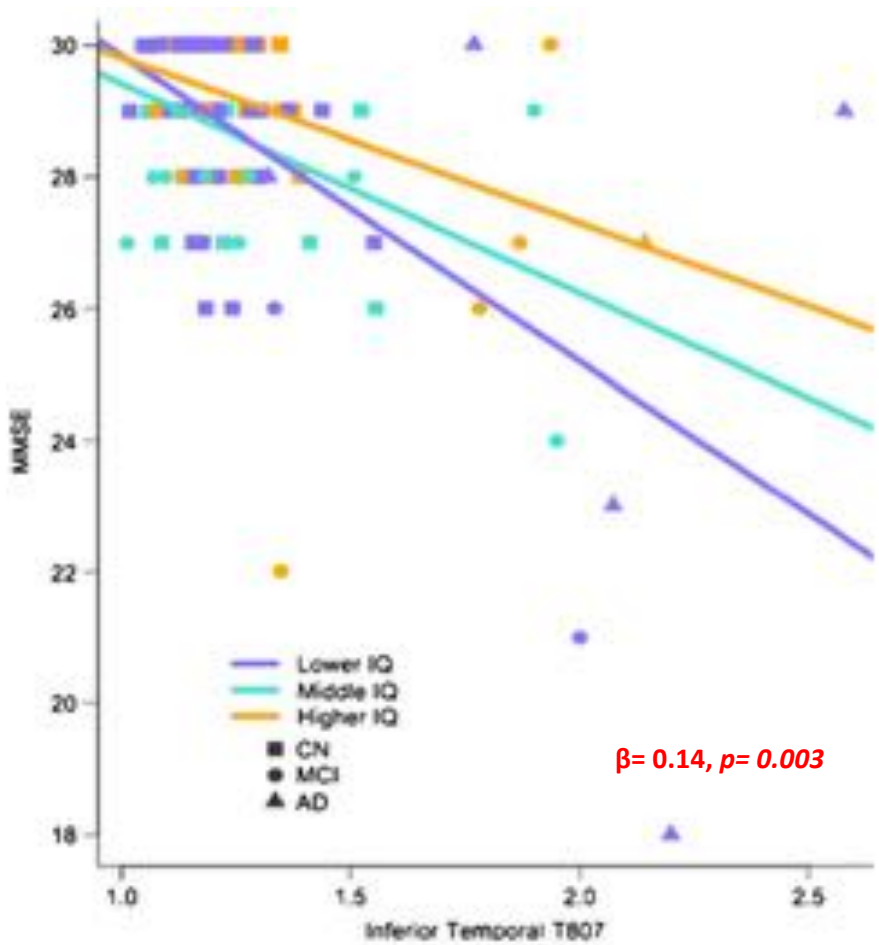
Rentz, et al; *Brain Imaging and Behavior* (2017) 11:383-390

Rentz, et al; *Brain Imaging and Behavior*
(2017) 11:383-390

Model 4: CR modifies relation of Aβ and Performance on MMSE



Model 5: CR modifies relation of Tau and Performance on MMSE



Methods: Statistical Analysis

Demographics: Independent Sample T-Tests, Fisher's Exact Tests explored differences between diagnostic groups

Multiple linear regression analyses: Across CN subjects only

Dependent Variable: MMSE
Predictors: Age, Education, AMNART IQ, PIB DVR with cerebellar reference, T807 with cerebellar gray pons reference, Interaction of AMNART and PIB; Interaction of AMNART and T807 using 5 models:

Model 6	Model 7	Model 8	Model 9
PIB-PET		PiB-PET	T807-PET
	T807-PET	PIB*VIQ	T807*VIQ

All models controlled for age, education, AMNART IQ

Cross-sectional Relationships with Amyloid, Tau and MMSE and Interaction with Cognitive Reserve in Cognitively Normal Only

	t	*B(SE)*	*p*	*F*	*df*	*p*	*Adj. R^2*
Overall Model 6				5.16	3124	0.001	0.11
Age	-1.48	-0.02 (0.01)	0.141				
Education	1.26	0.04 (0.03)	0.209				
VIQ	2.74	0.03 (0.01)	0.007				
PiB	-2.21	-0.93 (0.42)	0.029				
Overall Model 7				6.66	3124	0.000	0.15
Age	-0.76	-0.01(0.01)	0.451				
Education	1.74	0.06(0.03)	0.084				
VIQ	2.35	0.02(0.01)	0.020				
T807	-3.01	-2.88(0.96)	0.003				
Overall Model 8				4.34	4124	0.001	0.11
Age	-1.50	-0.02 (0.01)	0.135				
Education	1.09	0.04 (0.03)	0.277				
VIQ	1.51	0.09 (0.06)	0.134				
PiB	0.85	4.93 (5.79)	0.396				
PiB × VIQ	-1.01	-0.05 (0.05)	0.312				
Overall Model 9				5.53	4.124	0.000	0.15
Age	-0.95	-0.01(0.01)	0.343				
Education	1.74	0.06 (0.03)	0.085				
VIQ	-0.09	-0.09 (0.16)	0.457				
T807	-2.64	-2.62 (0.99)	0.009				
T807 × VIQ	0.97	0.09 (0.09)	0.335				

Rentz, et al; *Brain Imaging and Behavior* (2017) 11:383-390

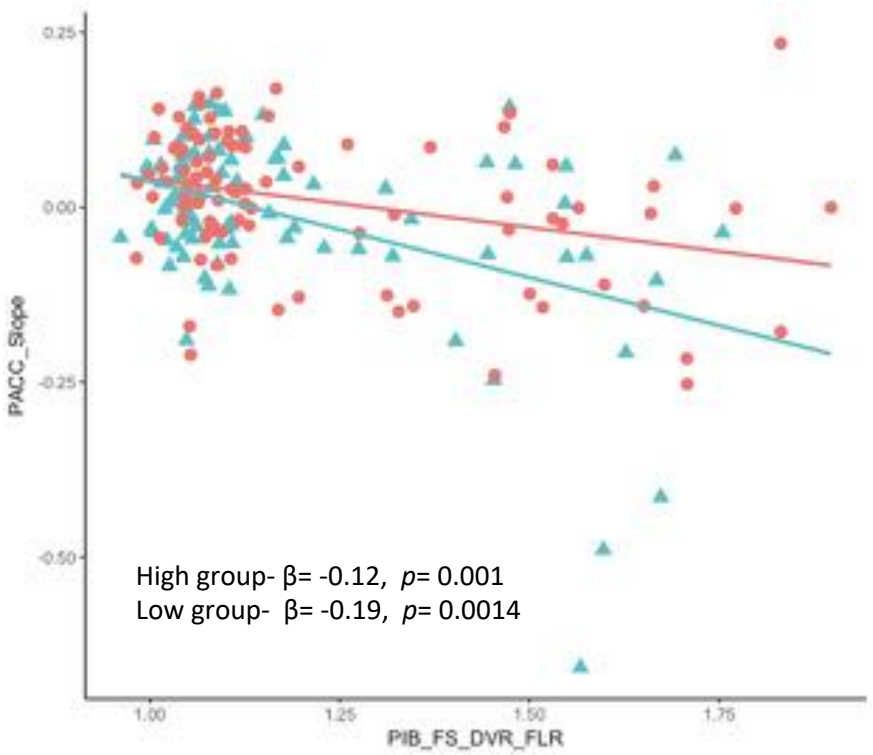
Sample Characteristics

- Analyses were completed on only those with T807 Tau Scans N=186
- Longitudinal Follow-up was restricted to year prior to the T807 Tau Scan
- Mean follow-up = 2.72 years
- Mean age= 75 (range 61 to 91 years)
- Aβ positive = 49; Aβ negative = 135
- CDR = 0; n= 167; CDR = 0.5; n= 18 at their tau baseline
- Mean MMSE = 29.15; range = 24-30

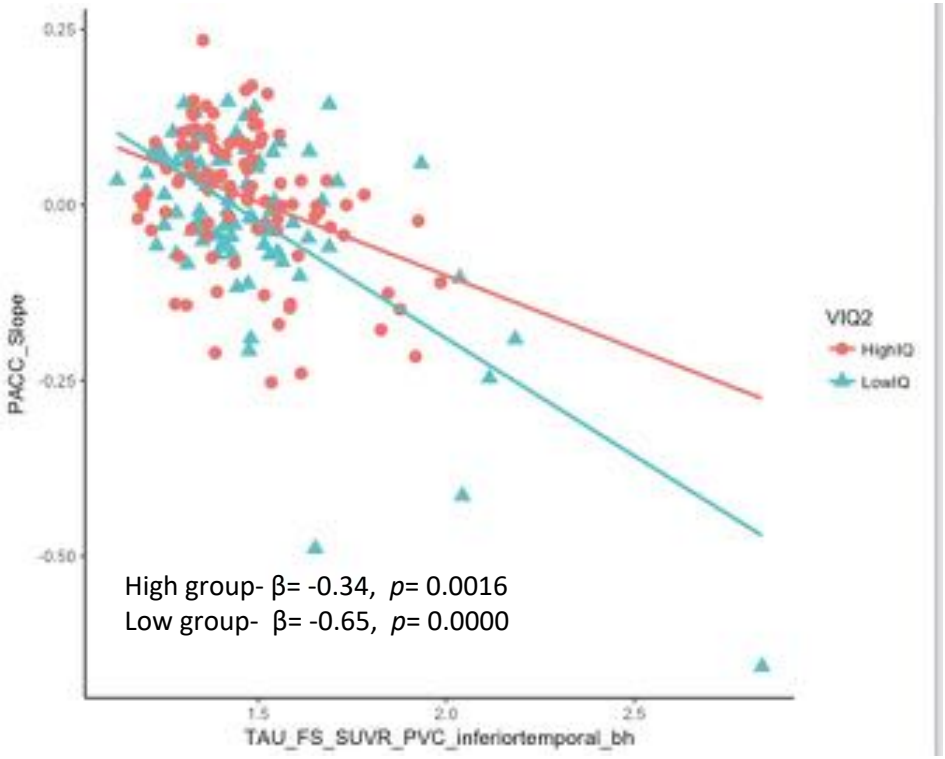
Unpublished data

CR modifies Aβ & Tau burden on PACC over time

PIB*VIQ*Time β= 0.007 *p*= 0.09

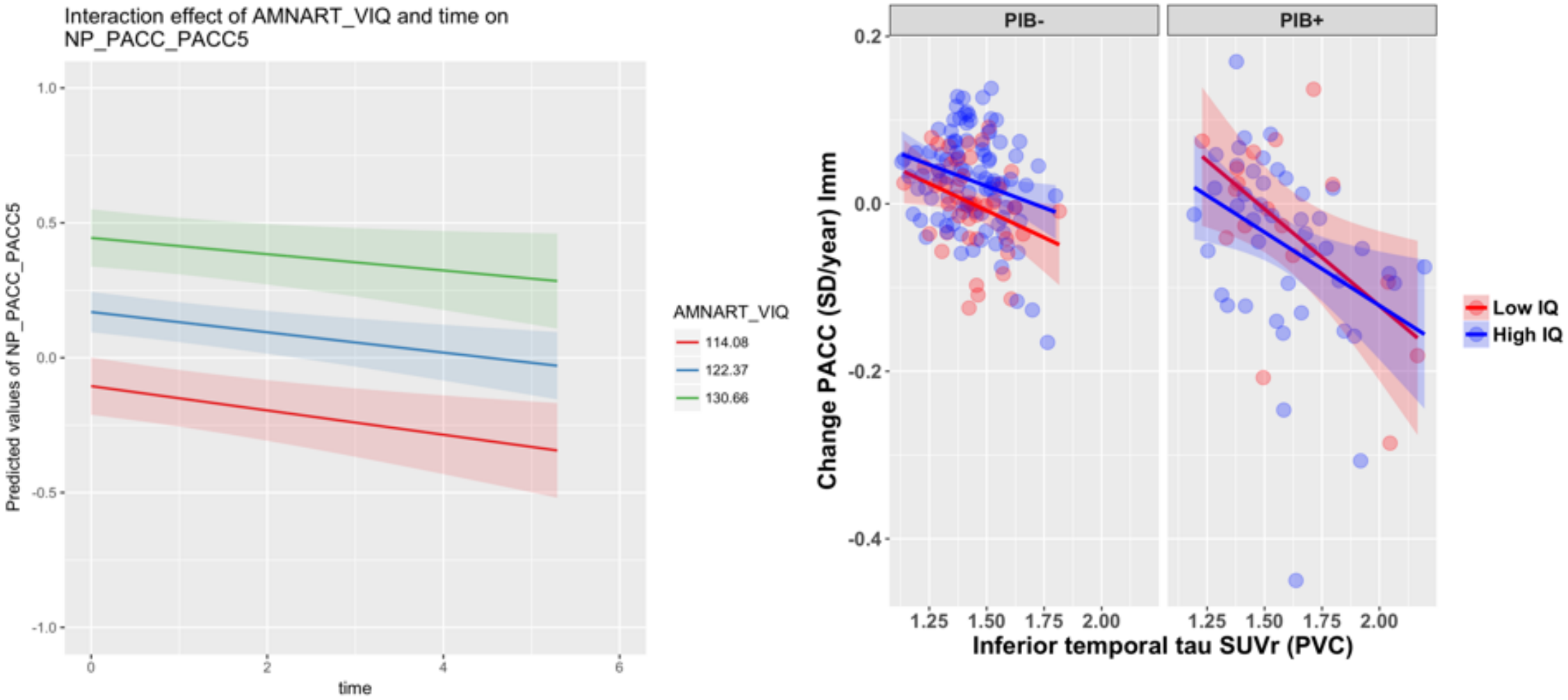


T807*VIQ*Time β= 0.24 *p*= 0.010



Unpublished data

Longitudinal effect of CR



Summary

- The longitudinal analyses show that greater Aβ and IFT tau deposition is associated with worse cognitive performance over time but CR tends to modify that relationship.
- Again, higher IFT tau had a stronger and more direct association with poorer cognitive performance over time than Aβ burden.
- CR may exert an initial beneficial effect by reducing the detrimental consequences of Aβ and tau burden but loses its protective effect over time.

Case Presentation of High CR

Neuropsychology
2004, Vol. 18, No. 1, 38–49

0894-4105/04/$12.00 DOI: 10.1037/0894-4105.18.1.38

Use of IQ-Adjusted Norms to Predict Progressive Cognitive Decline in Highly Intelligent Older Individuals

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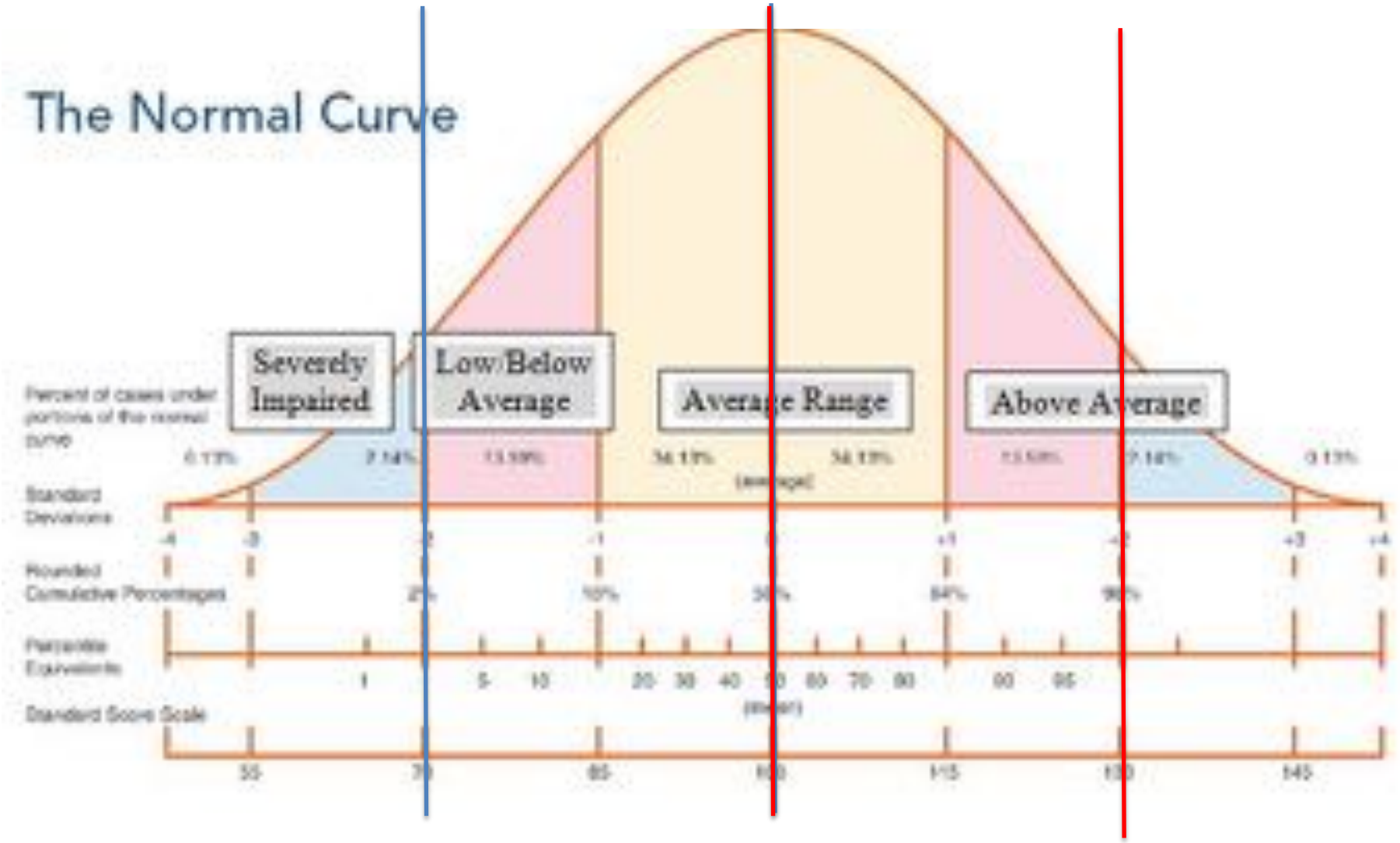
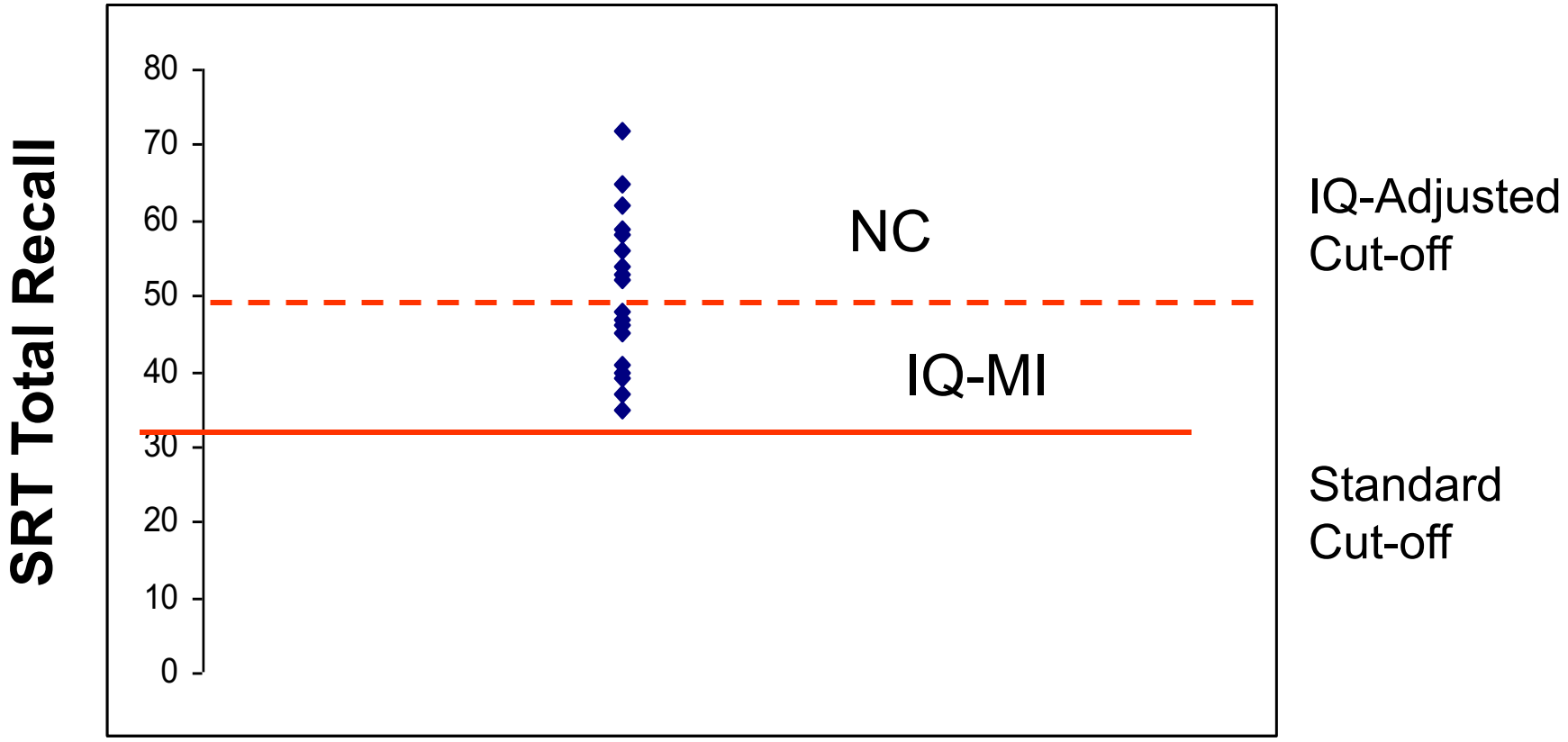
Identifying high-functioning older individuals in preclinical phases of Alzheimer's disease (AD) may require more sensitive methods than the standard approach. The authors explored the utility of adjusting for premorbid intelligence to predict progressive cognitive decline or Mild Cognitive Impairment (MCI) in 42 highly intelligent older individuals. When scores were adjusted for baseline IQ, 9 participants had executive impairments, 11 had memory impairments, and 22 scored in the normal range. None were impaired according to standard age norms. Three and a half years later, 9 participants with IQ-adjusted memory impairment declined in naming, visuospatial functioning, and memory; 6 converted to MCI. Three participants with normal memory declined. Implications for using IQ-adjusted norms to predict preclinical AD are discussed.

The Method: IQ-Adjustments

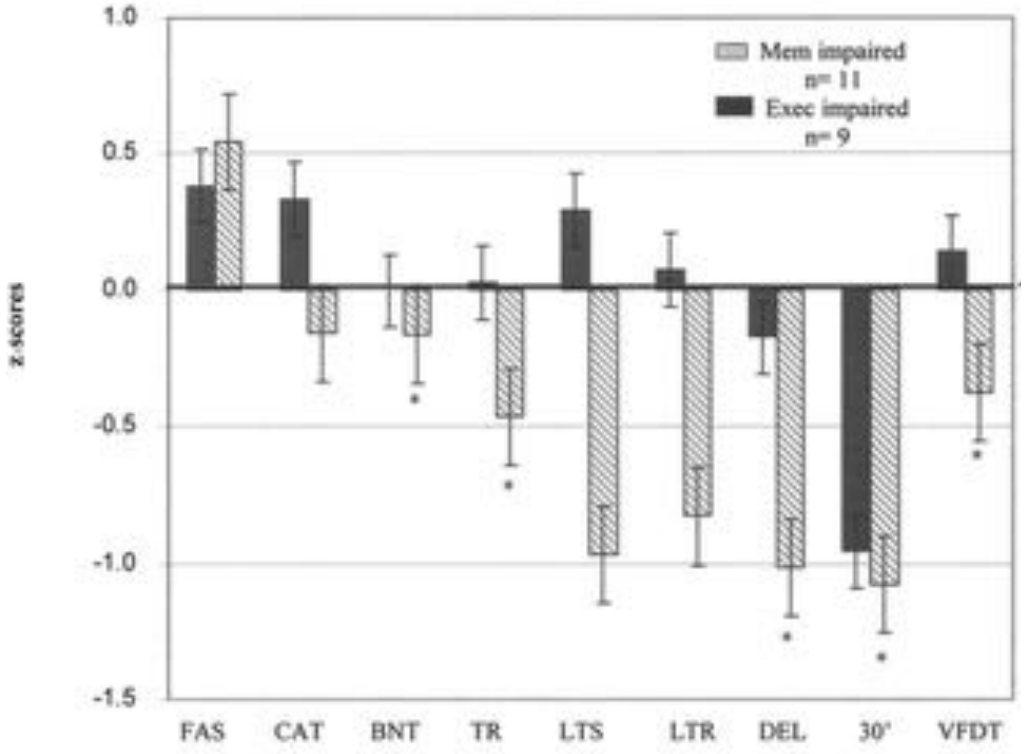
2SD below IQ of 130= 50th percentile



Standard Norms vs. IQ Adjusted



IQ-Adjusted Method Over Time



Chi-Square Analysis:

- Fifty-five percent of those predicted to decline subsequently met criteria for MCI, whereas only ten percent of those not predicted to decline went on to meet MCI criteria **($\chi^2 = 9.7$, p - 0.002).**

Odds Ratio

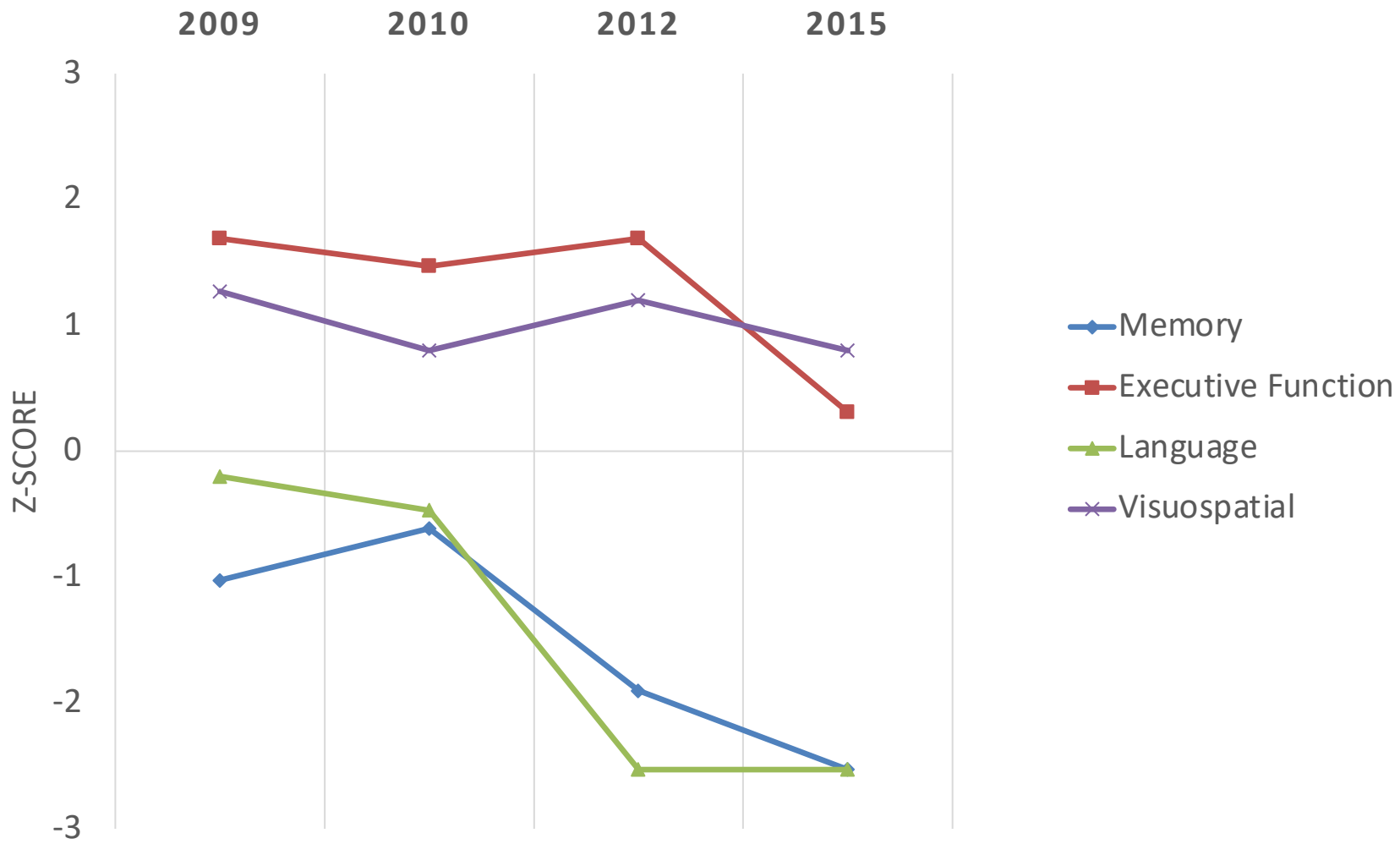
- The odds of developing MCI in highly intelligent elders predicted to decline are **11.2 times** greater than the odds of developing MCI in those not predicted to decline.

72-year old physician and Entrepreneur- EIQ= 130

Impairment Range for ability is <50th percentile

	2009	%ile	2010	%ile	2012	%ile	2015	%ile
MMSE	29	66th	27	5th	27	5th	25	1st
Reasoning			12	75th	14	91st	10	50th
FAS	67	99th	62	99th	77	99th	31	37th
CAT	36	16th	32	16th	35	25th	21	1st
CERAD Learning	22	58th	23	70th	22	58th	11	<1st
Delayed Recall	6	23rd	9	82nd	0	<1st	0	<1st
Multiple Choice	9	21st	10	70th	8	2nd	7	<1st
FCSRT FR	24	<24	17	<24	13	<24	2	<24
FCSRT CR	45	<44	41	<44	39	<44	5	<44
NAMING BNT	54	42nd	53	32nd	46	1st	30	<1st
VFDT	32	88th	31	79th	32	88th	31	79th

Cognitive Performance of 72 y/o Physician



HARVARD MEDICAL SCHOOL

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