Family History, Subjective Memory Complaints and Brain Amyloid Load in the ADNI Study

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MINISYMPOSIUM 2:
Subjective Cognitive Decline: Epidemiology, Biomarkers and Progression to MCI and Dementia

Miami, January 16, 2016

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ADNI

Disclosures & Acknowledgements

- **National Institute on Aging**
  - ADNI: U01 AG024904 & RC2 AG036535
  - Indiana: R01 AG19771 (AJS), P30 AG10133 (IADC), K01AG049050 (SLR)
  - U01 AG032984, U24 AG21886, P30 AG010129, K01 AG030514
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- Alzheimer's Association & Brin Wojcicki Foundation
  - Whole Genome Sequencing of ADNI-GO/2
- Disclosures:
  - Siemens Healthcare, Eli Lilly, Avid, Pfizer, Arkley BioTek

Rationale

- Pathophysiological processes associated with AD are detectable up to two decades prior to onset of dementia.
- Early detection during the long preclinical and prodromal stages of disease is critical to support therapeutic and preventative interventions that likely need to be instituted prior to significant neurodegenerative changes.
- The presence of self-perceived cognitive changes (variously described as subjective complaints, concerns, decline or impairment) and similar observations by knowledgeable informants may represent the earliest prodromal stage.
- Challenges include heterogeneity in symptom expression and variability in how these changes are defined and assessed. An international working group arrived at a consensus framework to describe this condition as *subjective cognitive decline (SCD)* and efforts are underway to operationalize research criteria.

Prediction of Dementia by Subjective Memory Impairment

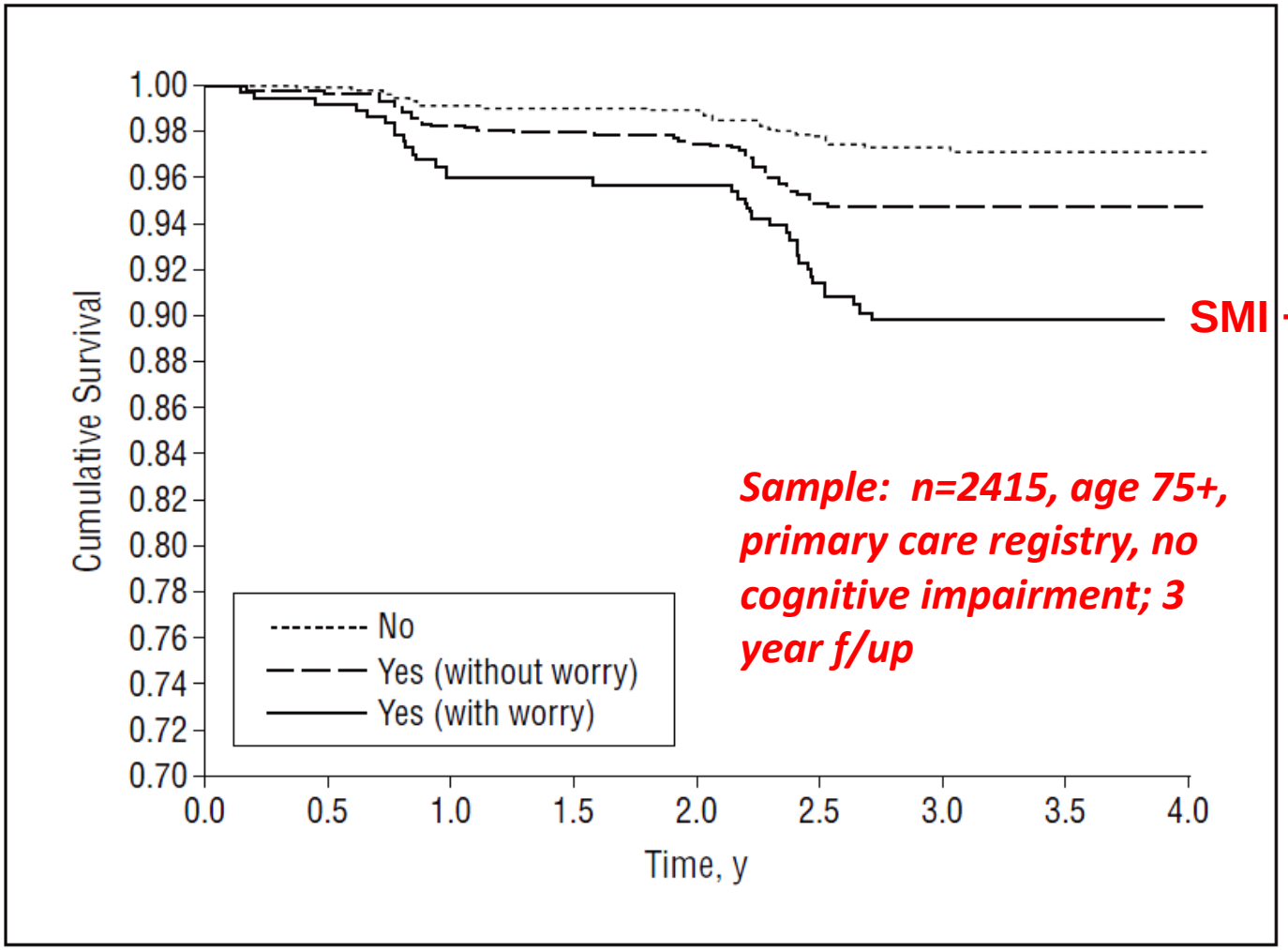

Figure. Kaplan-Meier survival curves showing the conversion to dementia in Alzheimer disease relative to the presence of subjective memory impairment with or without worry at baseline.

Jessen et al; Arch Gen Psychiatry; 2010, 67(4):414-422

Source of Cognitive Complaints: Self vs. Informant (NACC Data)

ELSEVIER

Gifford et al 2013

Alzheimer's & Dementia ■ (2013) 1–9

Research Article

The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults

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[f]*VA Boston Healthcare System, Boston, MA, USA*

Abstract

Objective: The objective of this study was to compare whether different sources of cognitive complaint (i.e., subjective and informant) predict diagnostic conversion in nondemented older adults.

Methods: Participants from the National Alzheimer's Coordinating Center had a baseline diagnosis of normal cognition (NC; n = 4414; mean age, 73 ± 8 years; 69% female) or mild cognitive impairment (MCI; n = 1843; mean age, 74 ± 8 years; 52% female). Multinomial logistic regression related baseline cognitive complaint (no complaint, self only, informant only, or both self and informant) to diagnostic outcome (reversion, stable, or conversion).

Results: At follow-up, 14% of NC participants converted to MCI/dementia (3.5 ± 1.8 years), and 41% of MCI participants converted to dementia (3.0 ± 1.6 years). Among NC participants, self complaint only (odds ratio [OR], 2.1; 99% confidence interval (CI),1.5–2.9; $P < .001$), informant complaint only (OR, 2.2; 99% CI, 1.2–3.9; $P < .001$), and both self and informant complaint (OR, 4.2; 99% CI, 2.9–6.0; $P < .001$) were associated with diagnostic conversion compared with no complaint. Among participants with MCI—compared with no complaint, informant complaint only (OR, 2.2; 99% CI, 1.2–4.3, $P = .002$), and both self and informant complaint (OR, 2.9; 99% CI, 1.8–4.8; $P < .001$)—were associated with conversion.

Conclusions: Cognitive complaints are related to conversion among nondemented older adults. Complaint from both (i.e. mutual complaint) sources was most predictive of diagnostic outcome, followed by informant complaint, highlighting the need for obtaining informant corroboration to enhance prognosis and distinguish underlying pathological processes from normal cognitive aging. Self complaint was related inconsistently to diagnostic outcome.

Keywords: Mild cognitive impairment; Alzheimer's disease; Cognitive complaints; Prognosis; Conversion

"Complaint source is important; the combination of self and informant complaint was most predictive of diagnostic outcome, followed by informant complaint only, highlighting the need for obtaining informant corroboration to distinguish underlying pathological processes from normal cognitive aging."

14% of 4414 NC participants converted to MCI/dementia.
Self complaint only (OR 2.1)
Informant only (OR 2.2)
Both self & informant (OR 4.2) - associated with conversion.

Neuroimaging and Genetics

- Early studies showed that older adults with cognitive complaints had changes on MRI similar to those seen in amnestic MCI and increasing data is now becoming available on changes in other AD biomarkers including PET and CSF in individuals with SCD.
- Given the heritability of AD (estimated up to 60-80%), cognitive concerns are often given more weight in the setting of a positive family history for AD or another dementia.
- In older adults with cognitive concerns, combining imaging and other AD biomarkers with genetic risk appears to be a promising approach to identify those at risk and for trial enrichment.

Selected Examples

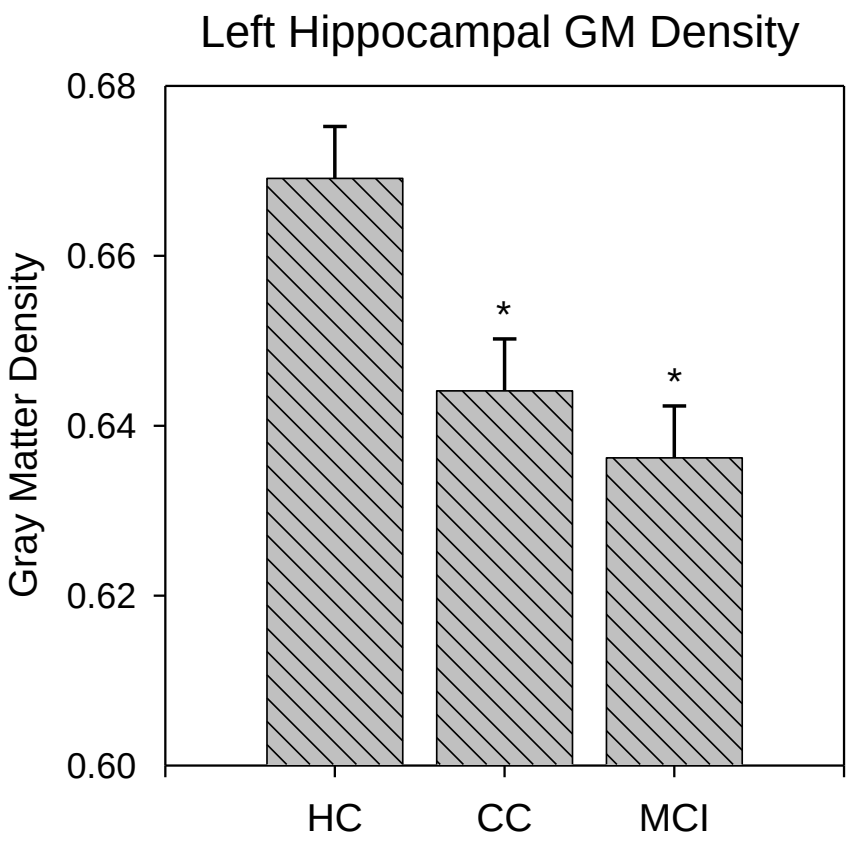
Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI

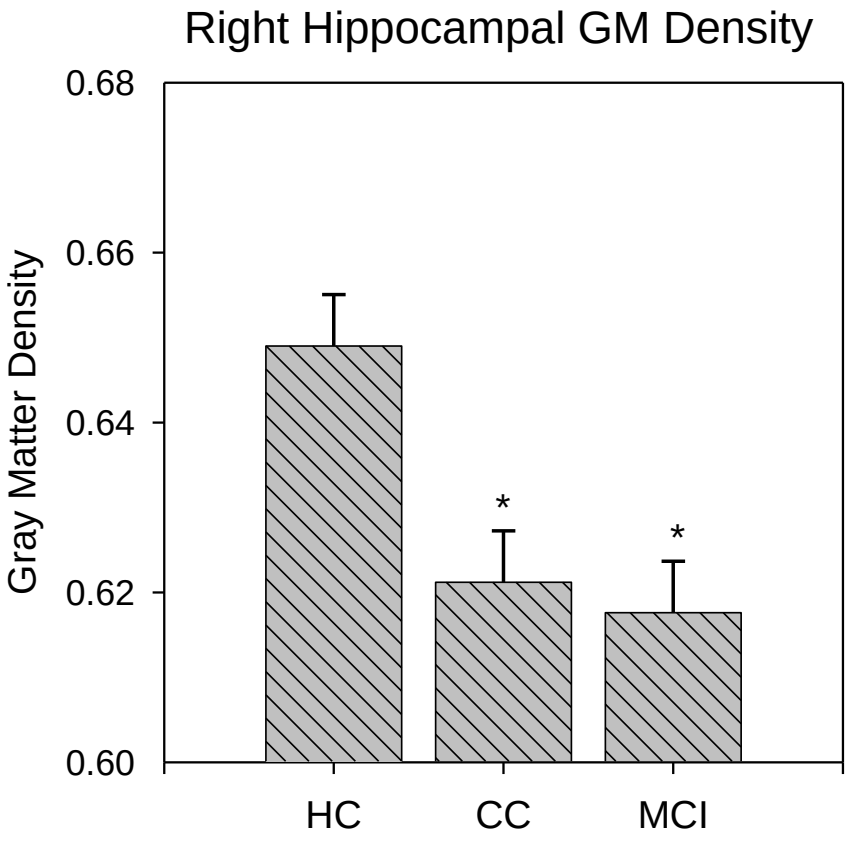
A.J. Saykin, PsyD; H.A. Wishart, PhD; L.A. Rabin, PhD; R.B. Santulli, MD; L.A. Flashman, PhD; J.D. West, MS; T.L. McHugh, MA; and A.C. Mamourian, MD

Abstract—*Objective:* To examine the neural basis of cognitive complaints in healthy older adults in the absence of memory impairment and to determine whether there are medial temporal lobe (MTL) gray matter (GM) changes as reported in Alzheimer disease (AD) and amnestic mild cognitive impairment (MCI). *Methods:* Participants were 40 euthymic individuals with cognitive complaints (CCs) who had normal neuropsychological test performance. The authors compared their structural brain MRI scans to those of 40 patients with amnestic MCI and 40 healthy controls (HCs) using voxel-based morphometry and hippocampal volume analysis. *Results:* The CC and MCI groups showed similar patterns of decreased GM relative to the HC group on whole brain analysis, with differences evident in the MTL, frontotemporal, and other neocortical regions. The degree of GM loss was associated with extent of both memory complaints and performance deficits. Manually segmented hippocampal volumes, adjusted for age and intracranial volume, were significantly reduced only in the MCI group, with the CC group showing an intermediate level. *Conclusions:* Cognitive complaints in older adults may indicate underlying neurodegenerative changes even when unaccompanied by deficits on formal testing. The cognitive complaint group may represent a pre–mild cognitive impairment stage and may provide an earlier therapeutic opportunity than mild cognitive impairment. MRI analysis approaches incorporating signal intensity may have greater sensitivity in early preclinical stages than volumetric methods.

NEUROLOGY 2006;67:834–842

Baseline Hippocampal Gray Matter Density in MCI & Cognitive Complaints





N=40,40,40

** MCI < HC, p <.001*

** CC < HC, p <.005*

Saykin et al, NEUROLOGY 2006;67:834-842

Altered Structural Connectivity (DTI)

Biochimica et Biophysica Acta 1822 (2012) 423–430

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Selective changes in white matter integrity in MCI and older adults with cognitive complaints ☆

Yang Wang [a], John D. West [a], Laura A. Flashman [b], Heather A. Wishart [b], Robert B. Santulli [b], Laura A. Rabin [c], Nadia Pare [d], Konstantinos Arfanakis [e], Andrew J. Saykin [a,b,*]

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[d] The Nebraska Medical Center, Omaha, NE, USA
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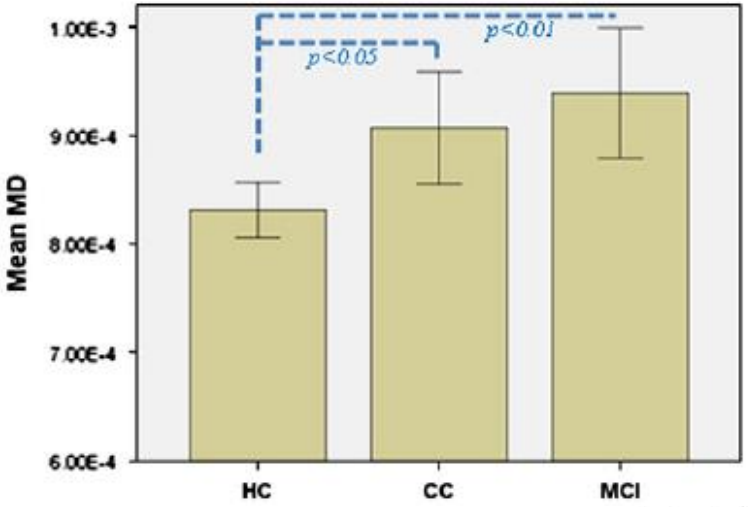

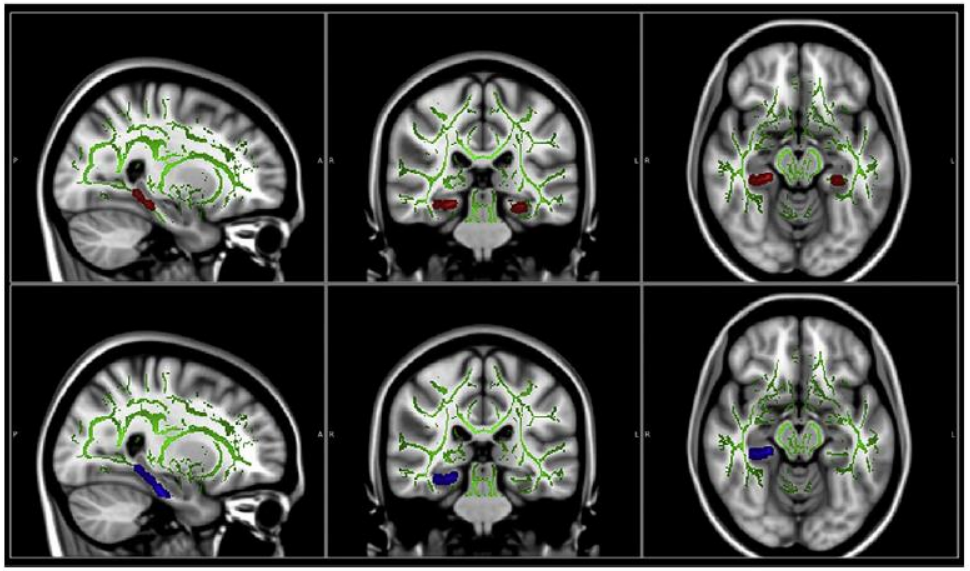

Fig. 1. Voxel-wise DTI comparison using tract-based spatial statistics analysis. The brain images showing underlying standard Montreal Neurological Institute (MNI) atlas MNI152 1-mm brain template and white matter skeleton derived from tract-based spatial statistics (TBSS) analysis (shown in green). Red color indicates tracts with reduced fractional anisotropy (FA) in bilateral parahippocampal white matter in patients with MCI vs. controls; Blue color indicates region with increased radial diffusivity (DR) in right parahippocampal white matter in MCI vs. controls. Only clusters surviving correction for multiple comparisons of voxel-wise whole brain analysis are shown on brain images ($p<0.01$). Statistical maps were dilated from the TBSS skeleton for visualization purposes.

Functional Connectivity (Resting State fMRI)

Journal of Alzheimer's Disease 35 (2013) 751–760
DOI 10.3233/JAD-130080
IOS Press

Altered Default Mode Network Connectivity in Older Adults with Cognitive Complaints and Amnestic Mild Cognitive Impairment

Yang Wang[a], Shannon L. Risacher[a], John D. West[a], Brenna C. McDonald[a,b], Tamiko R. MaGee[a], Martin R. Farlow[b], Sujuan Gao[c], Darren P. O'Neill[a] and Andrew J. Saykin[a,*]
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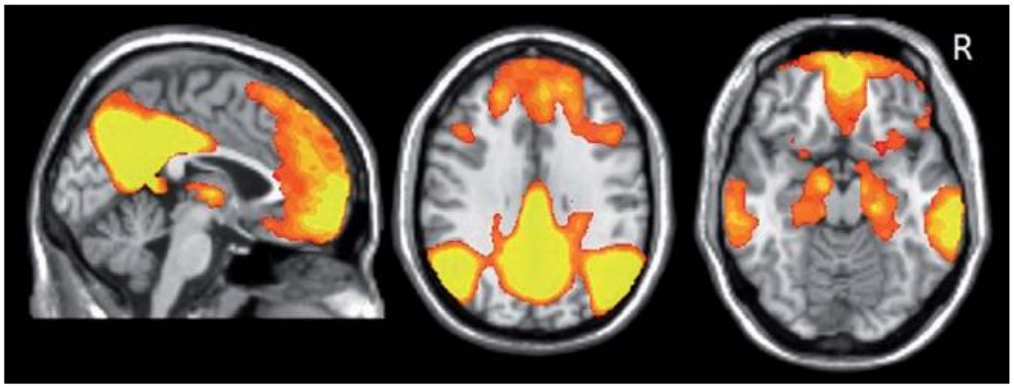

Fig. 1. Illustration of default model network (DMN) regions derived from group independent component analysis (ICA). The DMN component identified by meta-ICA analysis included the posterior cingulate cortex, precuneus, medial prefrontal cortex, lateral parietal regions, lateral temporal regions, and bilateral medial temporal regions ($p < 10^{-4}$).

Decreased Right Hippocampal Connectivity in Cognitive Complaint Group

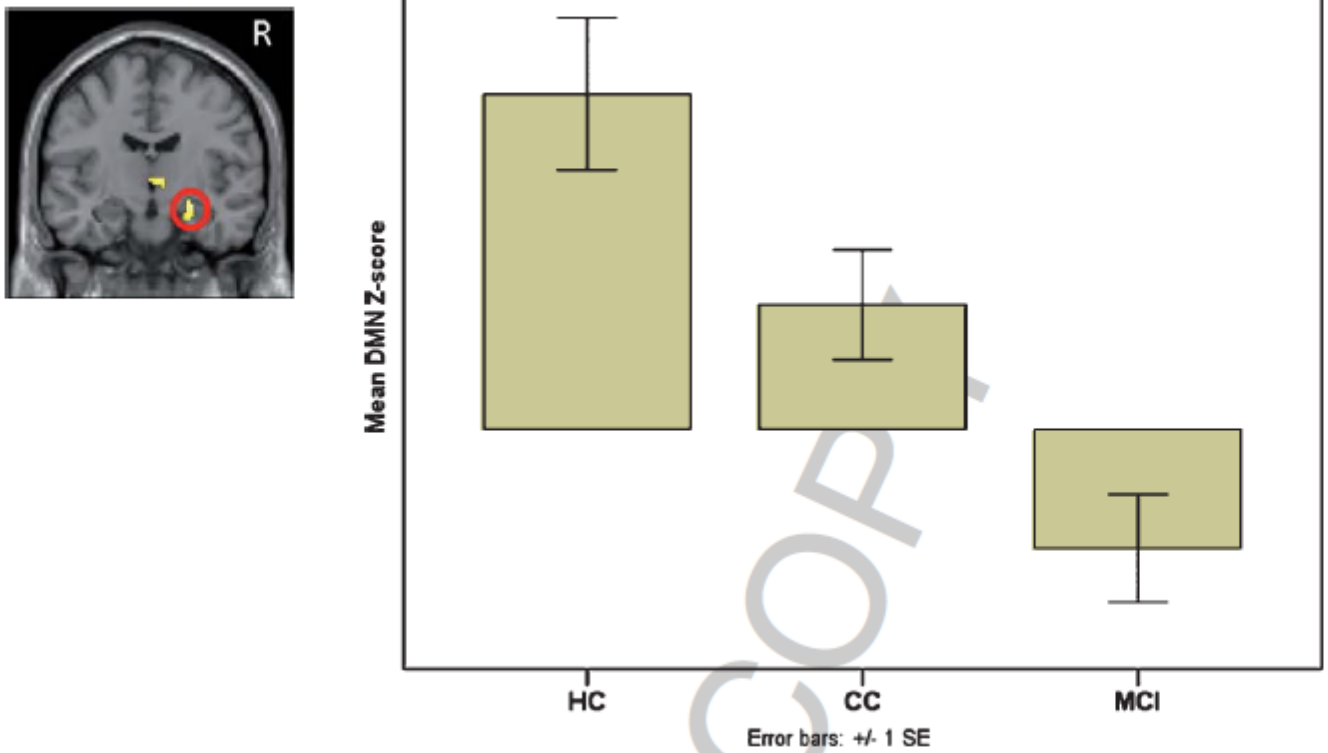

Fig. 3. Region of interest analysis of default mode network (DMN) connectivity in the right hippocampus showed significant differences in DMN Z-scores (±SE) between groups (HC > CC > MCI; $p < 0.02$), covaried for age, years of education, and gender.

Wang et al JAD 2013

ADNI SMC Group

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) has focused on multimodal longitudinal biomarker studies of early and late stage MCI and clinical AD, as well as cognitively normal older adult controls.
- Late in ADNI-2 a new group with significant memory concerns (SMC), essentially equivalent to SCD, was added.
- Efforts to standardize SCD/SMC within ADNI included a psychometrically-defined score on episodic memory items (n=12) from the 20 item Cognitive Change Index (CCI) in the context of CDR=0 and normal performance.
- Genetic factors play a significant role in SMC, particularly the strong influence of *APOE* ε4 carrier status on measures of amyloid burden (Risacher et al 2015).

ADNI Significant Memory Concern Group

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ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-13

Alzheimer's & Dementia

APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern

Shannon L. Risacher[a,b], Sungeun Kim[a,b,c], Kwangsik Nho[a,b,c], Tatiana Foroud[b,d], Li Shen[a,b,c], Ronald C. Petersen[e], Clifford R. Jack, Jr.,[f], Laurel A. Beckett[g], Paul S. Aisen[h], Robert A. Koeppe[i], William J. Jagust[j], Leslie M. Shaw[k], John Q. Trojanowski[k], Michael W. Weiner[l,m], Andrew J. Saykin[a,b,c,d,*], for the Alzheimer's Disease Neuroimaging Initiative (ADNI)[1]

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Participant Characteristics

Demographics

	HC		SMC		EMCI		DX	*APOE*	DX by *APOE*
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**			
n	132	53	71	33	174	131	n/a		
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.6)	70.3 (5.2)	71.7 (7.3)	70.5 (7.0)	0.016	0.004	NS
Gender (M, F)	68, 64	21, 32	31, 40	14, 19	88, 86	82, 49	0.020	NS	*0.050*
Education (years)	16.7 (2.5)	16.2 (2.6)	16.6 (2.7)	17.2 (2.0)	16.1 (2.6)	16.1 (2.6)	<0.001	NS	NS
Parental History of Dementia (% +)[1]	41.7%	66.0%	55.7%	65.6%	54.4%	69.2%	<0.001	0.012	<0.001
Parental History of AD (% +)[2]	33.1%	58.0%	36.1%	43.8%	31.2%	54.1%	<0.001	NS	<0.001

[1] 8 participants missing data (1 SMC ε4-, 1 SMC ε4+, 5 SMC ε4-, 1 EMCI ε4+)
[1] 11 participants missing data (2 HC, 3 EMCI, 3 LMCI, 3 AD)

Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Family History of Dementia

APOE status by group: ε4+

	HC		SMC		EMCI		DX	*APOE*	DX by *APOE*
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**			
n	132	53	71	33	174	131	n/a		
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.6)	70.3 (5.2)	71.7 (7.3)	70.5 (7.0)	0.016	0.004	NS
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Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Family History of Dementia

APOE status by group: ε4-

	HC		SMC		EMCI		DX	*APOE*	DX by *APOE*
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**			
n	132	53	71	33	174	131	n/a		
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.6)	70.3 (5.2)	71.7 (7.3)	70.5 (7.0)	0.016	0.004	NS
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Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Family History of AD

APOE status by group: ε4+

	HC		SMC		EMCI		DX	*APOE*	DX by *APOE*
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**			
n	132	53	71	33	174	131	n/a		
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.6)	70.3 (5.2)	71.7 (7.3)	70.5 (7.0)	0.016	0.004	NS
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[1] 11 participants missing data (2 HC, 3 EMCI, 3 LMCI, 3 AD)

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Family History of AD

APOE status by group: ε4-

	HC		SMC		EMCI		DX	*APOE*	DX by *APOE*
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**			
n	132	53	71	33	174	131	n/a		
Age (years)	73.7 (6.1)	71.8 (6.4)	72.5 (5.6)	70.3 (5.2)	71.7 (7.3)	70.5 (7.0)	0.016	0.004	NS
Gender (M, F)	68, 64	21, 32	31, 40	14, 19	88, 86	82, 49	0.020	NS	*0.050*
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[1] 11 participants missing data (2 HC, 3 EMCI, 3 LMCI, 3 AD)

Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Psychometric Performance and Self and Informant Cognitive Concerns

	HC		SMC		EMCI		DX*	*APOE**	DX by *APOE**
	ε4-	ε4+	ε4-	ε4+	ε4-	ε4+			
CDR-SB	0.03 (0.12)	0.04 (0.17)	0.09 (0.19)	0.06 (0.17)	1.22 (0.68)	1.39 (0.94)	<0.001	NS	NS
MMSE Total Score	29.1 (1.3)	28.9 (1.2)	28.9 (1.2)	29.0 (1.2)	28.5 (1.4)	28.1 (1.6)	<0.001	NS	NS
MoCA Total Score[1]	25.8 (2.3)	25.6 (2.4)	25.5 (2.8)	25.4 (2.5)	24.1 (2.9)	23.5 (3.1)	<0.001	NS	NS
Memory Composite	0.94 (0.52)	0.86 (0.56)	0.92 (0.45)	0.87 (0.50)	0.59 (0.50)	0.45 (0.55)	<0.001	0.013	NS
Executive Function Composite	0.88 (0.74)	0.82 (0.75)	0.72 (0.75)	0.64 (0.82)	0.56 (0.72)	0.28 (0.81)	<0.001	0.022	NS
Self E-Cog: Memory[3]	1.5 (0.4)	1.5 (0.4)	1.9 (0.6)	2.0 (0.6)	2.2 (0.7)	2.3 (0.7)	<0.001	NS	NS
Self E-Cog: Global[3]	1.3 (0.3)	1.3 (0.3)	1.5 (0.3)	1.6 (0.4)	1.8 (0.5)	1.8 (0.5)	<0.001	NS	NS
Informant E-Cog: Memory[4]	1.2 (0.4)	1.3 (0.3)	1.6 (0.6)	1.5 (0.4)	2.0 (0.7)	2.1 (0.7)	<0.001	NS	NS
Informant E-Cog: Global[4]	1.1 (0.2)	1.2 (0.3)	1.3 (0.4)	1.3 (0.3)	1.6 (0.5)	1.7 (0.6)	<0.001	NS	NS

[3] 5 participants missing data (2 HC ε4-, 1 SMC ε4-, 1 EMCI ε4-, 1 EMCI ε4+)
[4] 3 participants missing data (1 SMC ε4-, 2 SMC ε4+)
[3] 12 participants missing data (1 HC ε4-, 2 HC ε4+, 3 SMC ε4-, 2 SMC ε4+, 3 EMCI ε4-, 1 EMCI ε4+)
[4] 26 participants missing data (3 HC ε4-, 1 HC ε4+, 2 SMC ε4-, 4 SMC ε4+, 8 EMCI ε4-, 8 EMCI ε4+)
* Adjusted means and SD are shown (adjusted for age, gender, and years of education where appropriate)

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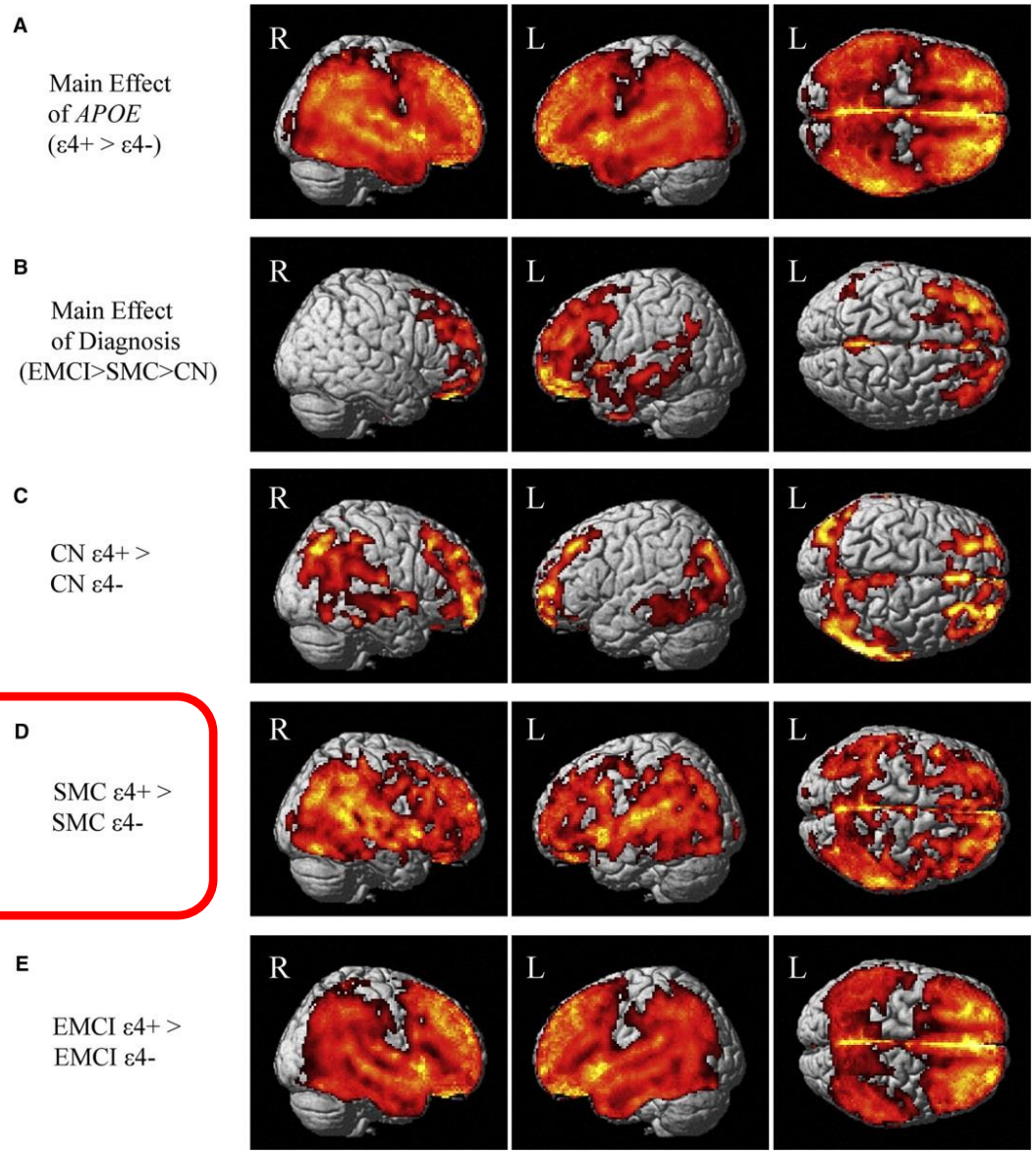
Amyloid PET by Dx & *APOE* ε4 Status



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

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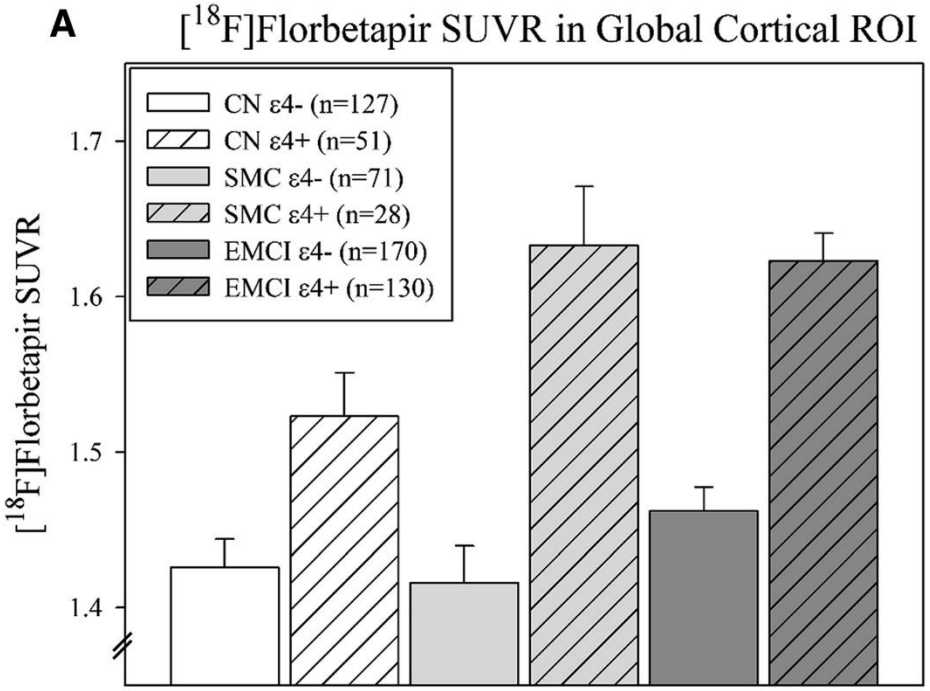
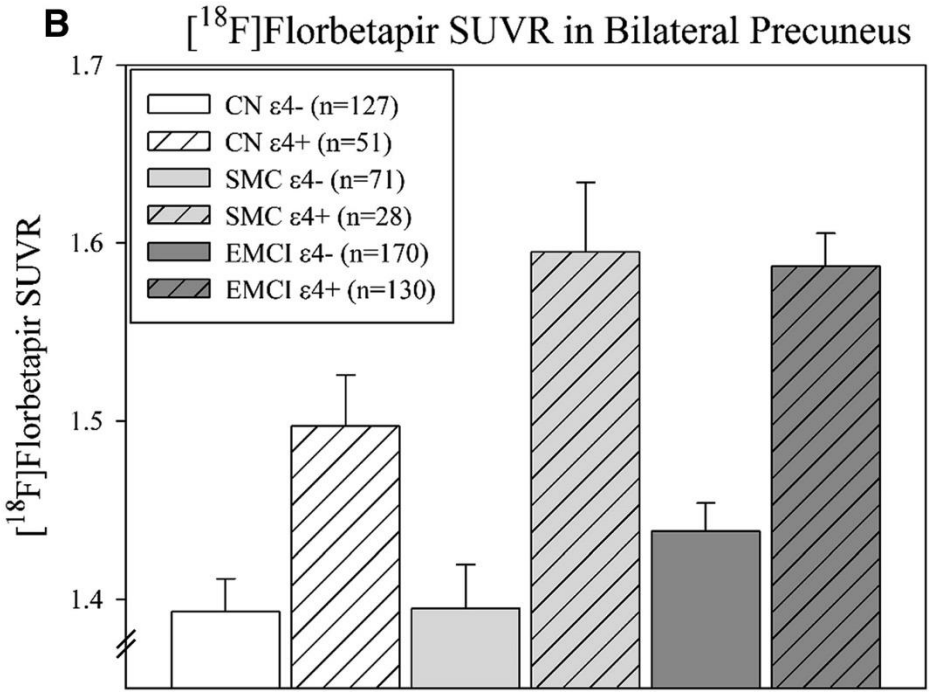
Effect of *APOE* ε4 Carrier Status on Amyloid Deposition ([^{18}F]Florbetapir PET) within DX Group





Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

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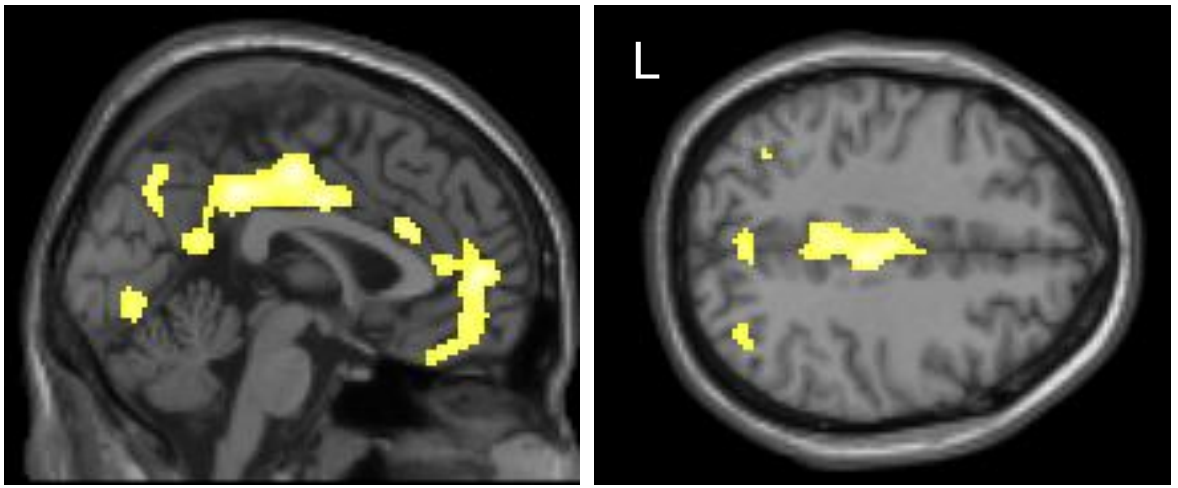
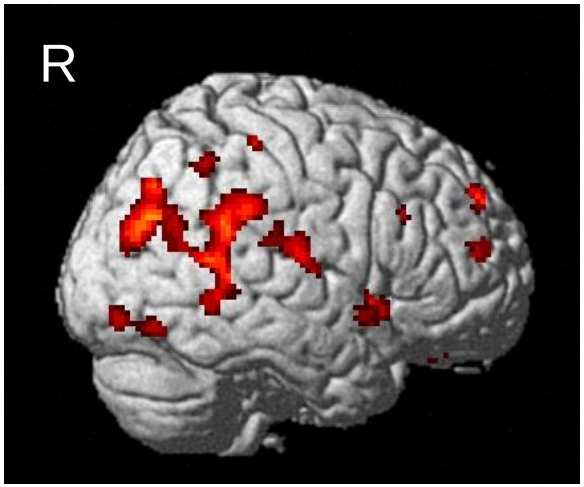
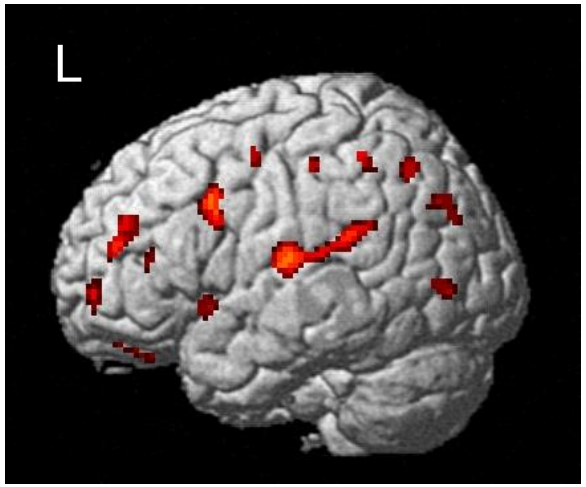
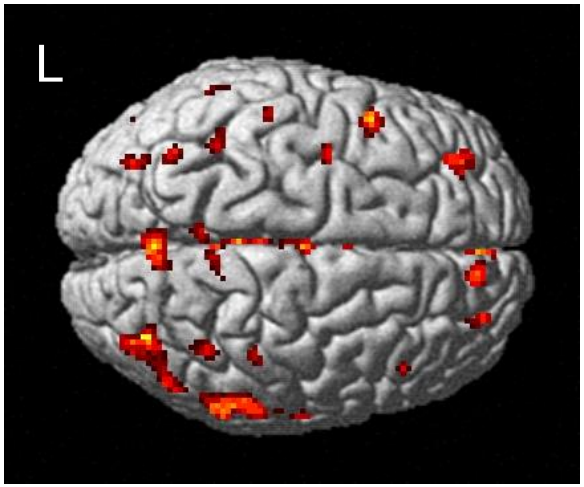
Results: Effect of *APOE* ε4 Carrier Status on Amyloid Deposition in SMC

ε4+ > ε4-





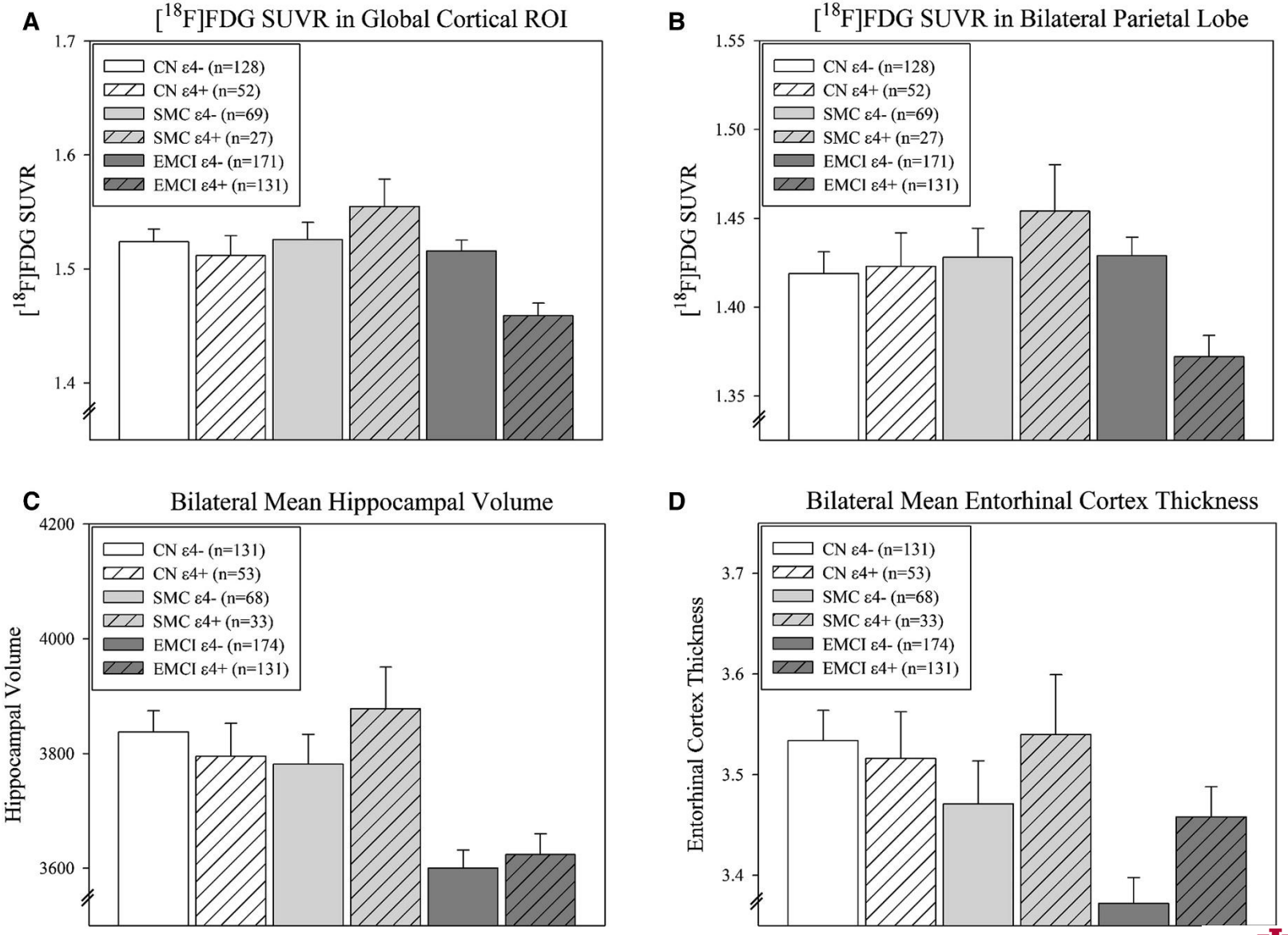




Covaried for age and gender

Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Effect of *APOE* ε4 status on FDG PET & MRI



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

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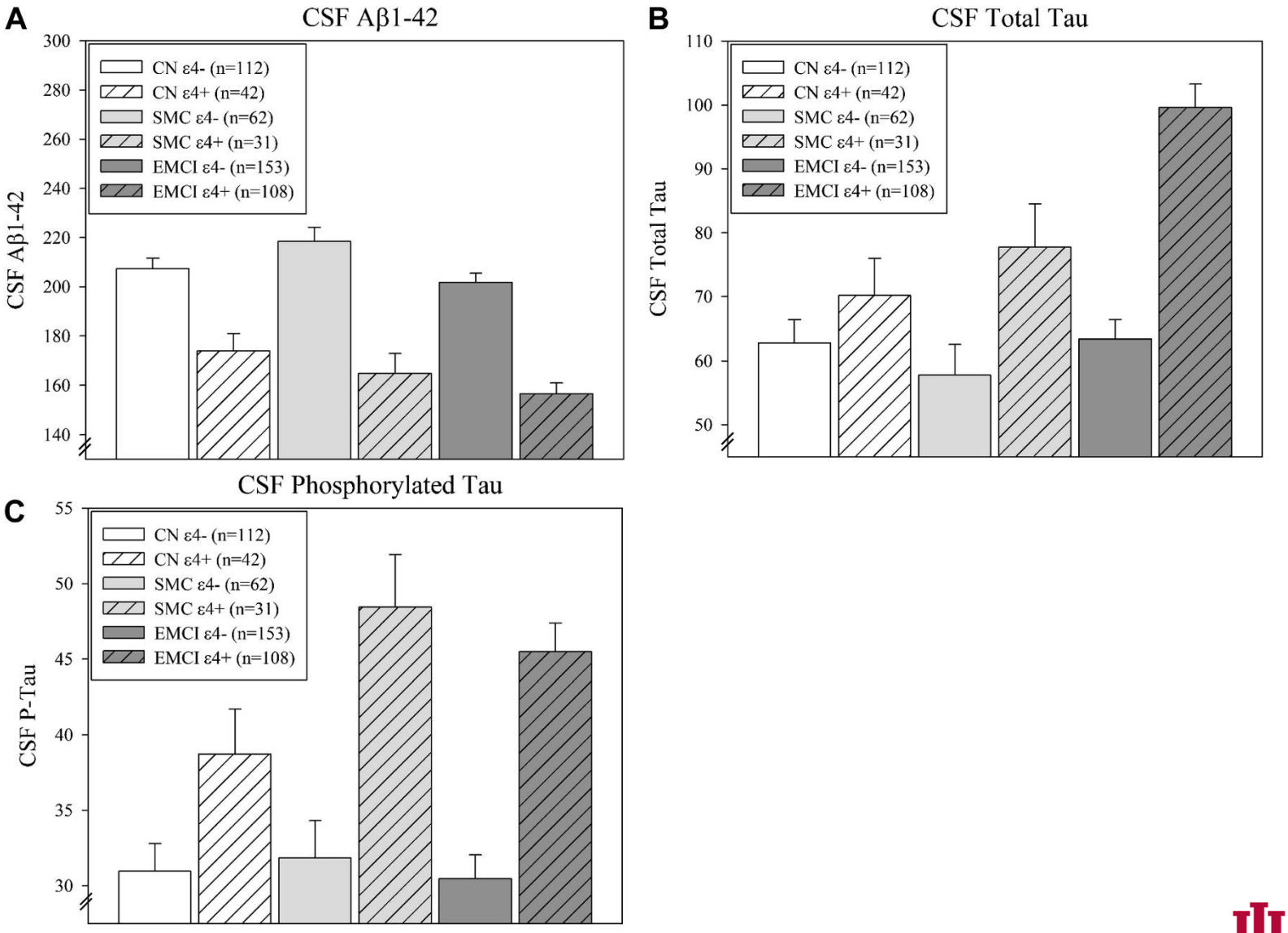
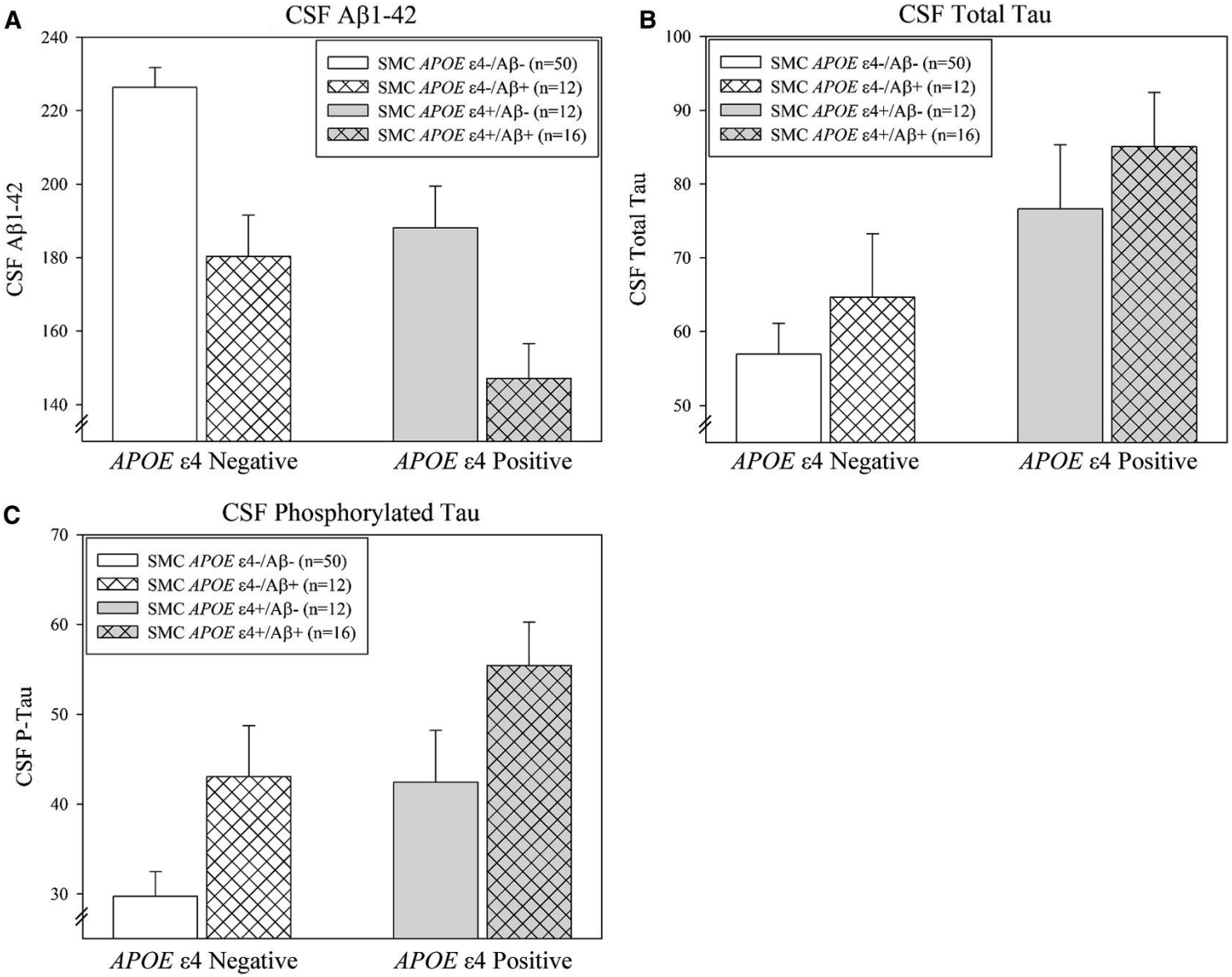
Effect of *APOE* ε4 Status on CSF Biomarkers



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

SMC: Effect of *APOE* ε4 and Amyloid PET on CSF Aβ1-42 and tau AD Biomarkers



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

Implications & Future Directions

- Contrasting the SMC group to controls and those with early MCI across key AD biomarkers available in ADNI it is clear that genetics plays a selective role depending on the specific biomarker modality.
- Screening for SCD in primary care settings is feasible enabling individuals to be referred to memory centers for more detailed assessment and treatment or participation in intervention trials, as appropriate. Comparative effectiveness needs to be evaluated.
- Advances in assessment and operationalization of SCD are underway to support comparable future studies & meta-analyses.
- What is the epidemiology and heritability of SCD in older adults? Larger international cohort studies are underway.
- What is the long-term outcome of SMC/SCD and do biomarker and genetic data modify prognosis? Role of environment and lifestyle?
- Can selection for SCD meaningfully enrich clinical trials?
- Beyond *APOE,* do other genes and pathways modify outcomes?

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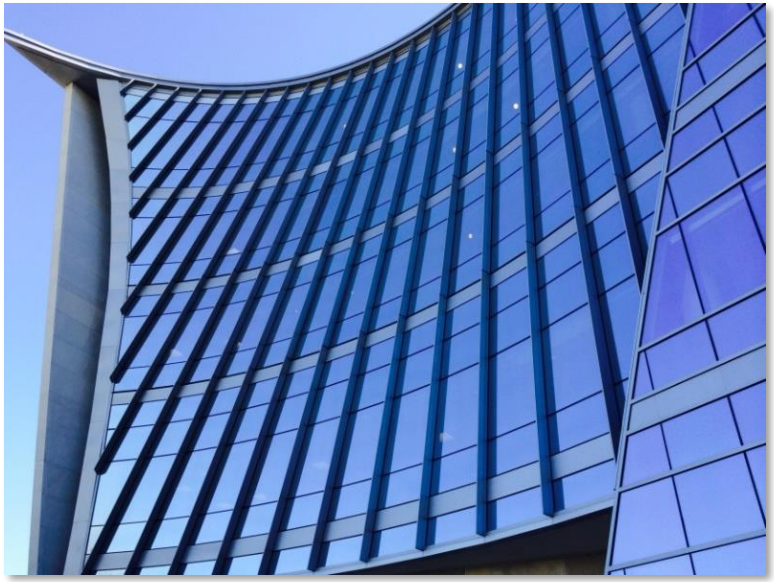

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