WORLD WIDE ADNI BOSTON INTRODUCTION

Michael Weiner

Michael W. Weiner, M.D.
Disclosures

Scientific Advisory Boards
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BOLT Inter-national

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inThought
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Alzheimer's Drug Discovery Foundation

Funding for Travel

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Paul Sabatier University
Tohoku University
Novartis
Neuroscience School of Advanced Studies (NSAS)
Danone Trading, BV
MCI Group, France
University of California, San Diego; ADNI

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Pfizer
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Stock Options
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Synarc

ADNI Support

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Alzheimer's Drug Discovery Foundation
Anonymous Foundation
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Roche

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Cure Alzheimer's Fund
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Elan
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ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

FUNDED BY NATIONAL INSTITUTE ON AGING

NIBIB,NIMH,NINR,NINDS,NCRR,NIDA and CIHR

M. Weiner, P. Aisen, R. Petersen, C. Jack, W. Jagust, J. Trojanowski, L. Shaw, A. Toga, L. Beckett, D. Harvey, M. Donohue, R. Green, A. Saykin, J. Morris, N. Cairns, T. Sather, L. Thal (D)

John Hsiao, Neil Buckholz, Adam Schwartz

Private Partners Scientific Board (PPSB)

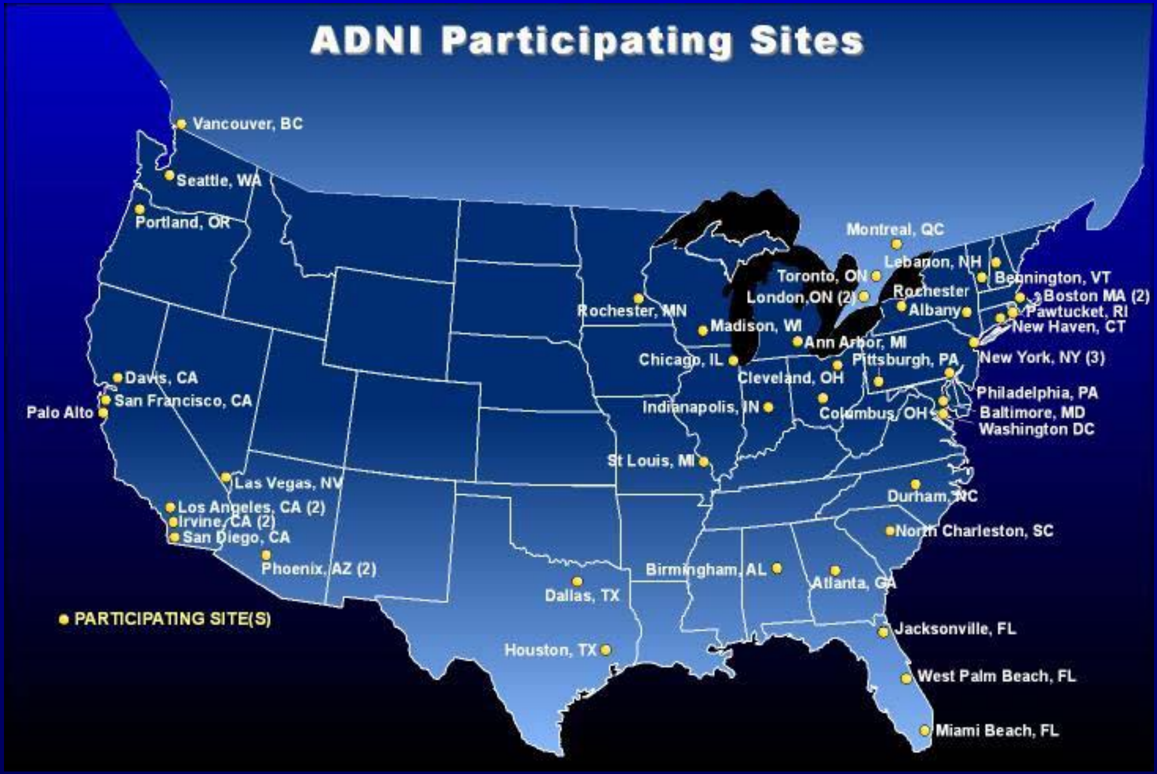
And Site PIs, Study Coordinators and over 1500 subjects enrolled in 58 Sites in US and Canada

ADNI: over 1500 subjects

2004-2017

Naturalistic study of AD progression

- **413 NORMAL**
- **49 SMC+ 40?**
- **565 L MCI**
- **301 E MCI**
- **323 AD**
- **longitudinal**
- **57 sites**
- **Clinical, blood, LP**
- **Cognitive Tests**
- **MRI: multimodal**
- **FDG PET**
- **PIB PET**
- **Florbetapir PET**
- **Genetics, genomics**



All data in public database: UCLA/LONI/ADNI: No embargo of data

EFFECTS OF APOE 4 ON AMYLOID POSITIVITY

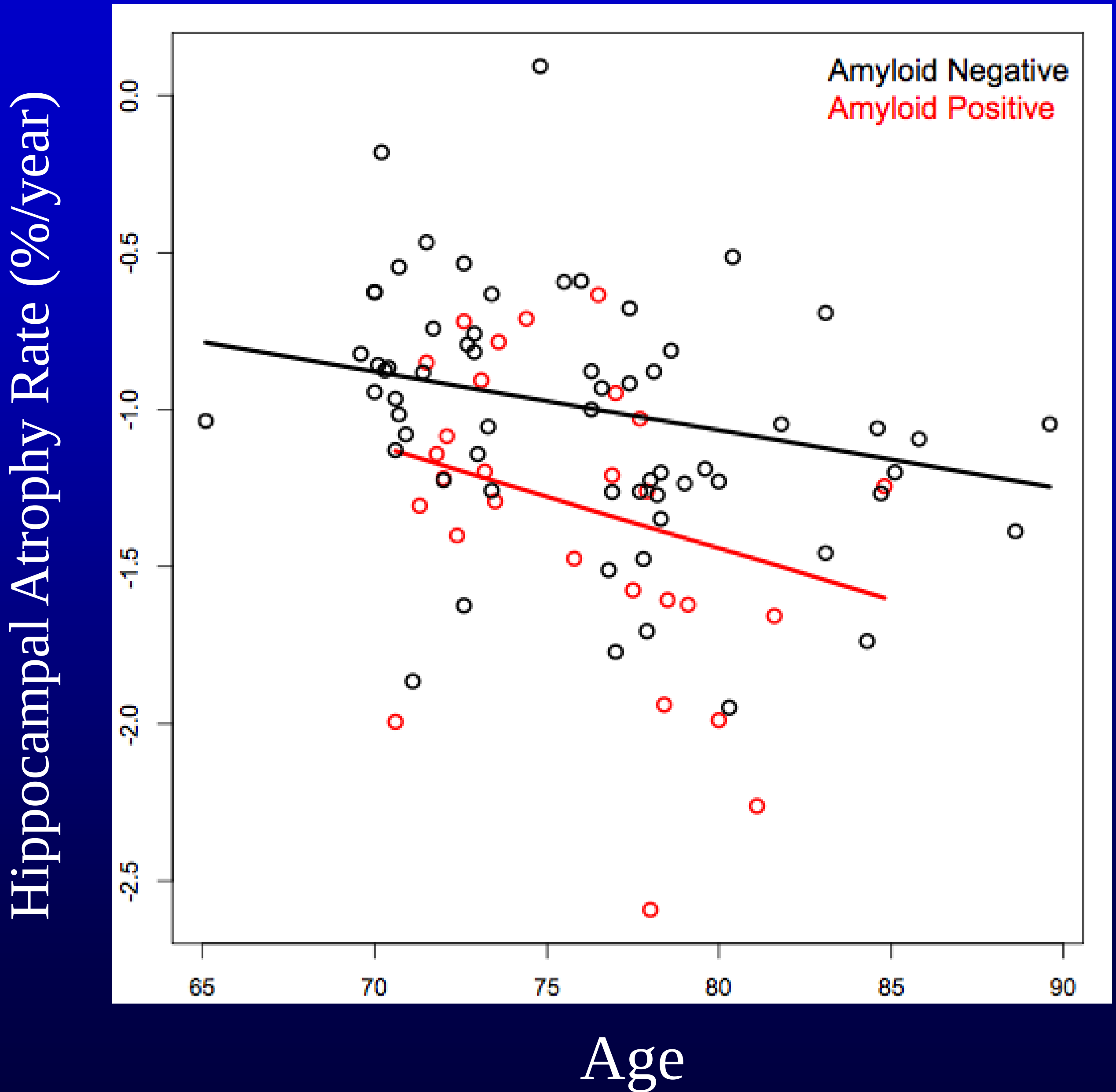
- AD patients with APOE4 are 99% likely to be amyloid positive
- AD patients without APOE4 are much less like to be amyloid positive
  - Perhaps only 55-75% of APOE4 negative AD subjects are amyloid positive

Hippocampal atrophy rate in Controls multivariate regression model

	Estimate	Std. Error	P value
Age	-8.962×10^{-1}	9.612×10^{-1}	0.3534
Female	-3.732	11.22	0.7400
ICV	2.135×10^{-5}	3.590×10^{-5}	0.5534
ApoE4+	-2.643	12.41	0.8317
WM Hypo	-3.535×10^{-4}	8.696×10^{-4}	0.6852
Amyloid	-23.84	10.75	0.0289*

$R^2=0.0372$

Effect of Age on Rate of Hippocampal Atrophy in Controls by Amyloid Positivity

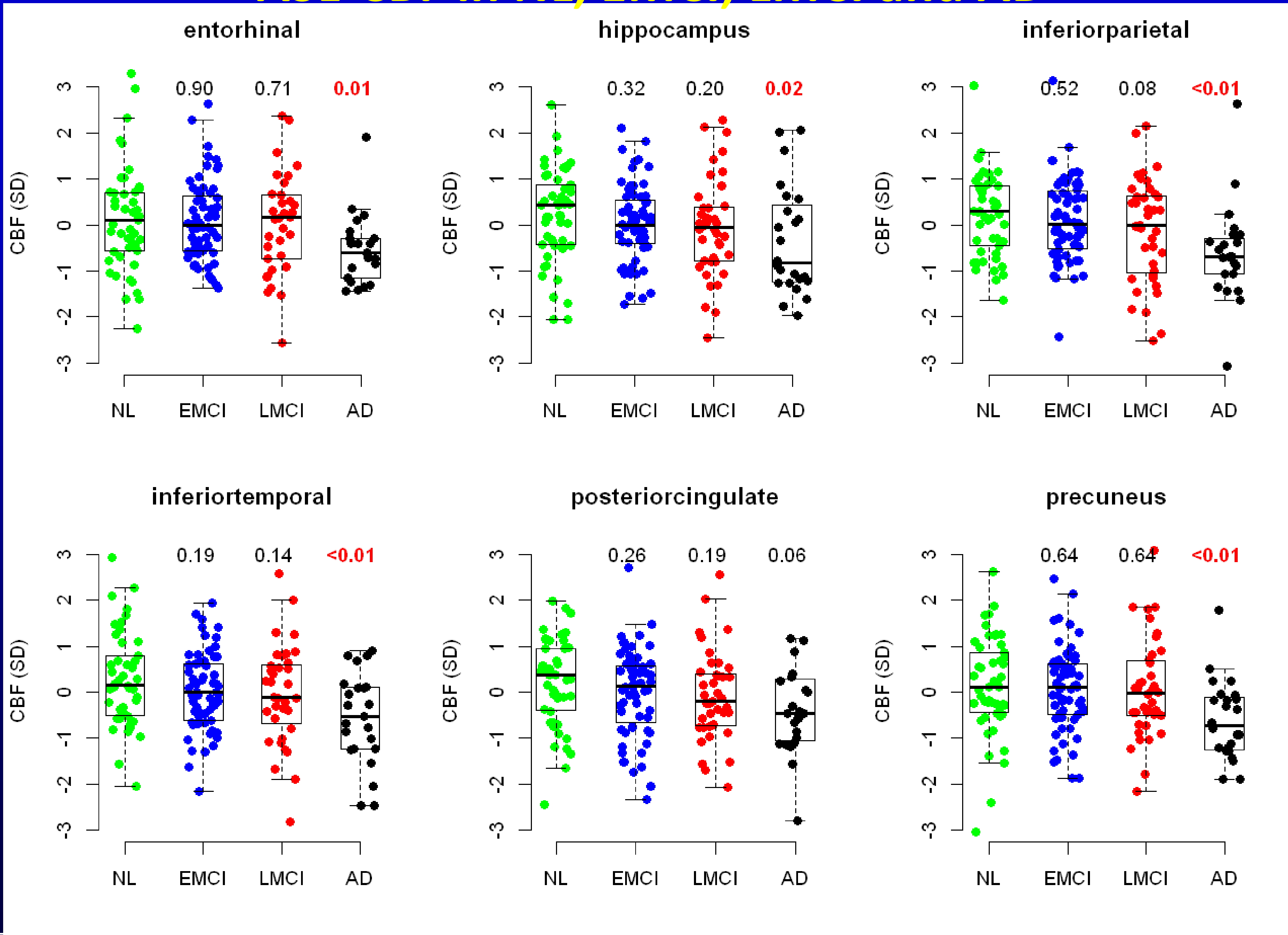


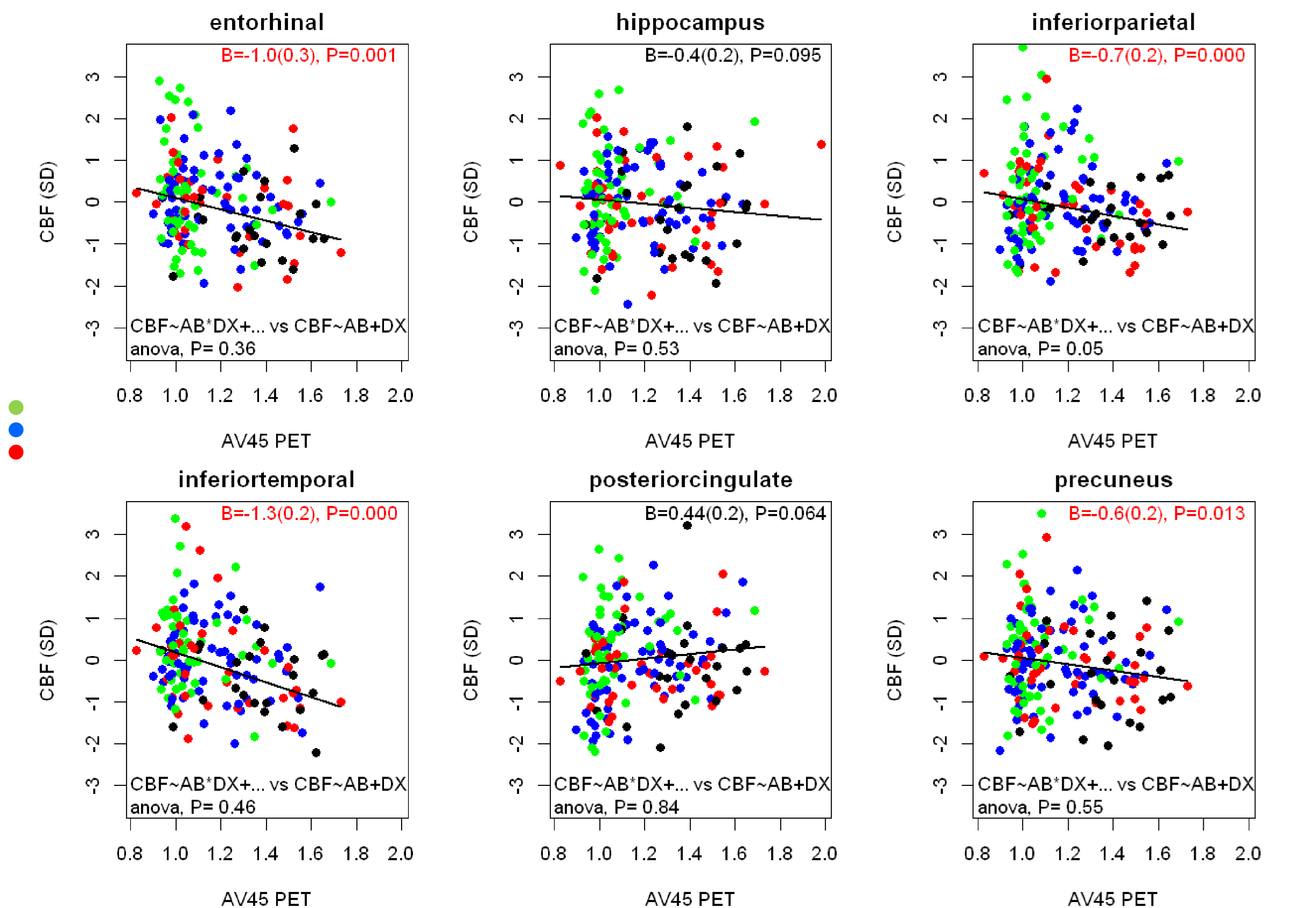
Rates of regional atrophy in subjects classified as β-amyloid (+) or (-)

	Amyloid Positive				Amyloid Negative			
	Region	Rate	fx	p	Region	Rate	fx	p
1	LateralVentricle	1837	0.369	0	InferiorTemporal	−221	−0.409	0
2	Hippocampus	−101	−0.334	0	MiddleTemporal	−216	−0.365	0
3	SuperiorTemporal	−276	−0.331	0	LateralVentricle	1264	0.336	0
4	MiddleTemporal	−311	−0.282	0	Fusiform	−161	−0.317	0
5	SuperiorFrontal	−402	−0.264	0	LateralOccipital	−170	−0.295	0
6	InferiorParietal	−337	−0.263	0	ParsOrbitalis	−41	−0.294	0
7	InferiorTemporal	−281	−0.258	0	Hippocampus	−64	−0.285	0
8	Parahippocampal	−66	−0.256	0	IsthmusCingulate	−37	−0.274	0
9	Insula	−114	−0.246	0	SuperiorTemporal	−167	−0.273	0
10	Precentral	−321	−0.245	0	InferiorLateralVentricle	83	0.264	0

Philip Insel

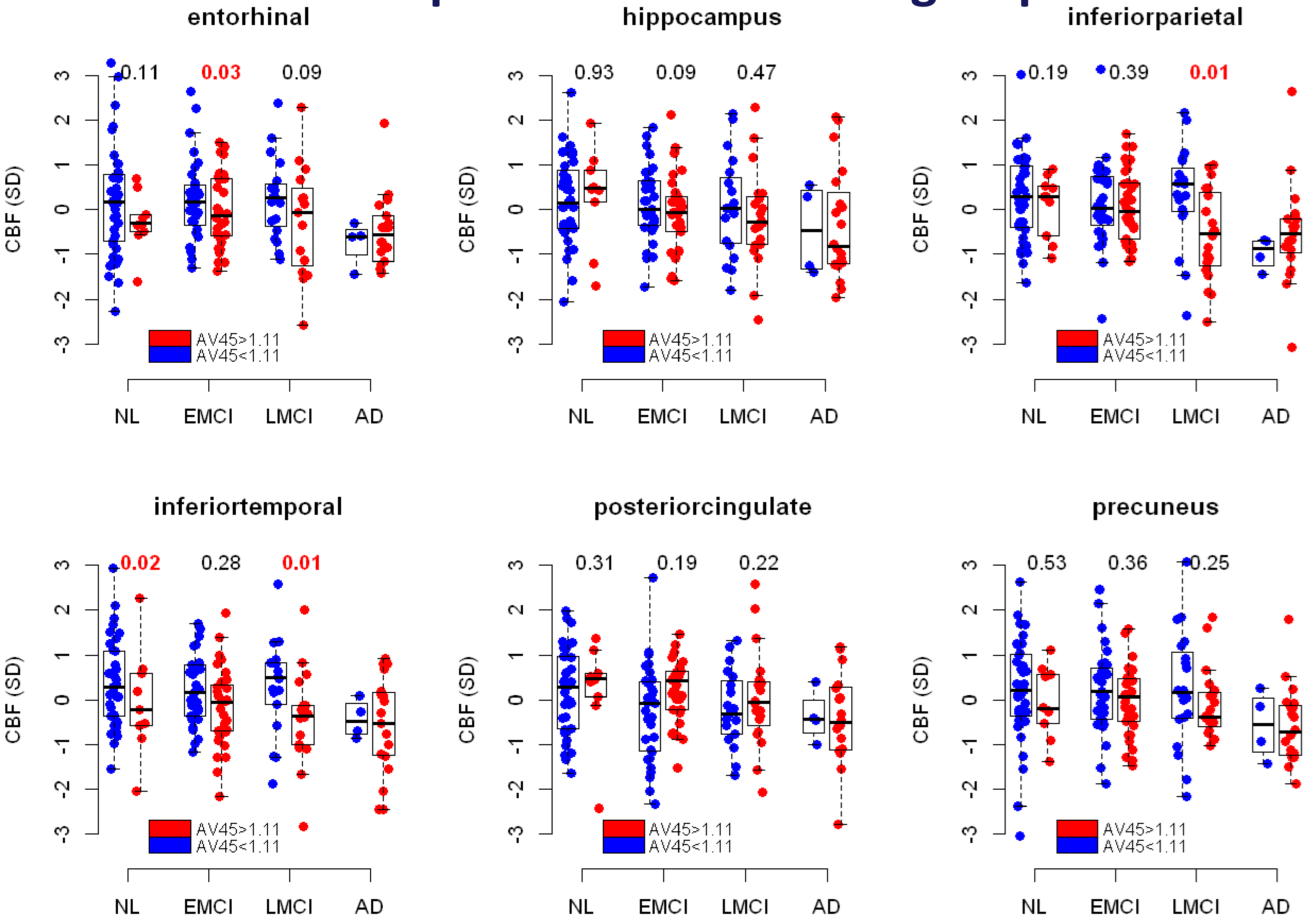
ASL-CBF in NL, EMCI, LMCI and AD





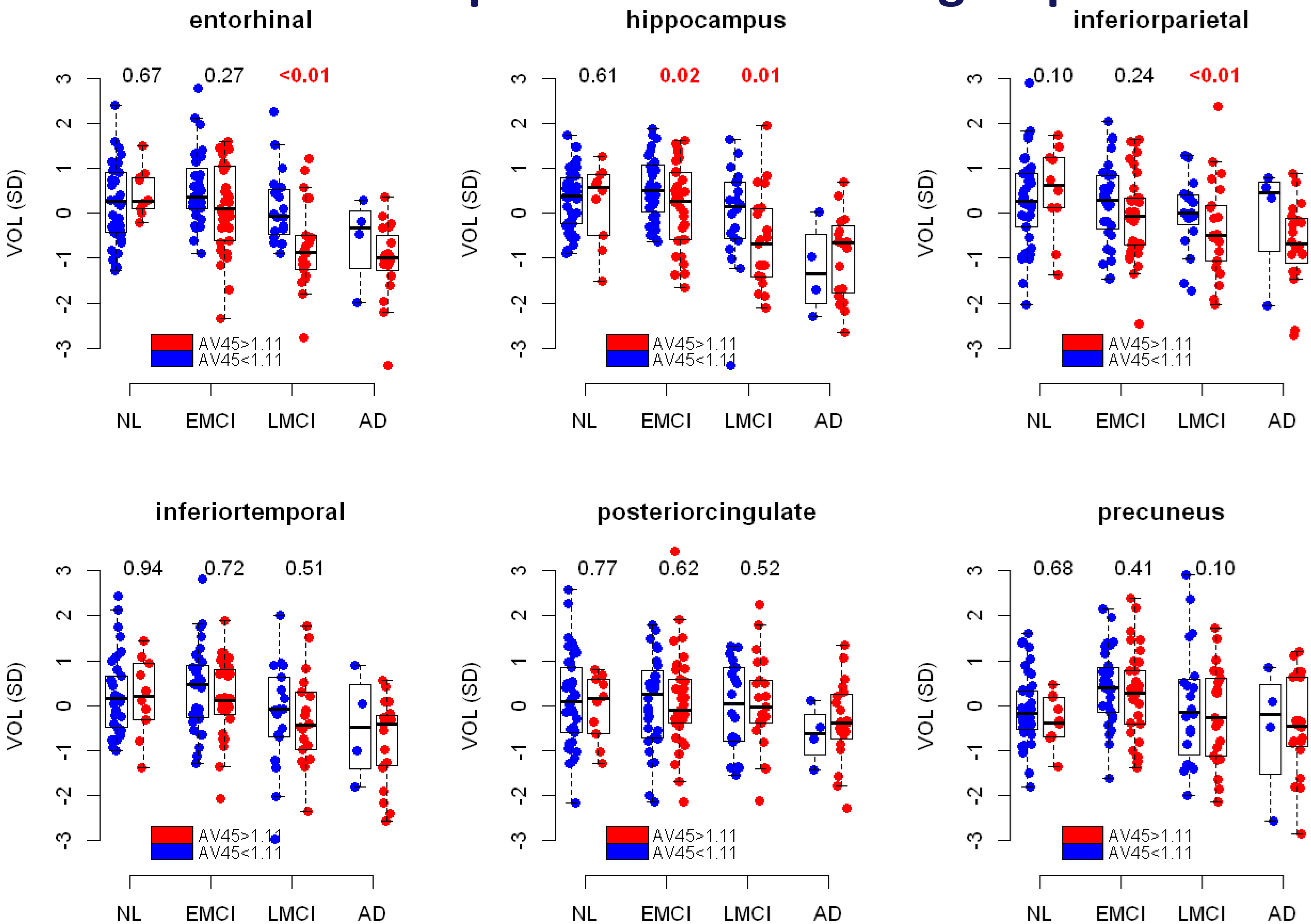
entorhinal
B=-1.0(0.3), P=0.001
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.36
hippocampus
B=-0.4(0.2), P=0.095
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.53
inferiorparietal
B=-0.7(0.2), P=0.000
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.05
inferiortemporal
B=-1.3(0.2), P=0.000
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.46
posteriorcingulate
B=0.44(0.2), P=0.064
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.84
precuneus
B=-0.6(0.2), P=0.013
CBF~AB*DX+... vs CBF~AB+DX
anova, P= 0.55
CBF (SD)
AV45 PET
-3
-2
-1
0
1
2
3
0.8
1.0
1.2
1.4
1.6
1.8
2.0

Effects of Aβ on ASL-CBF within groups



AV45 used as continuous predictor

Effects of Aβ on volume within groups

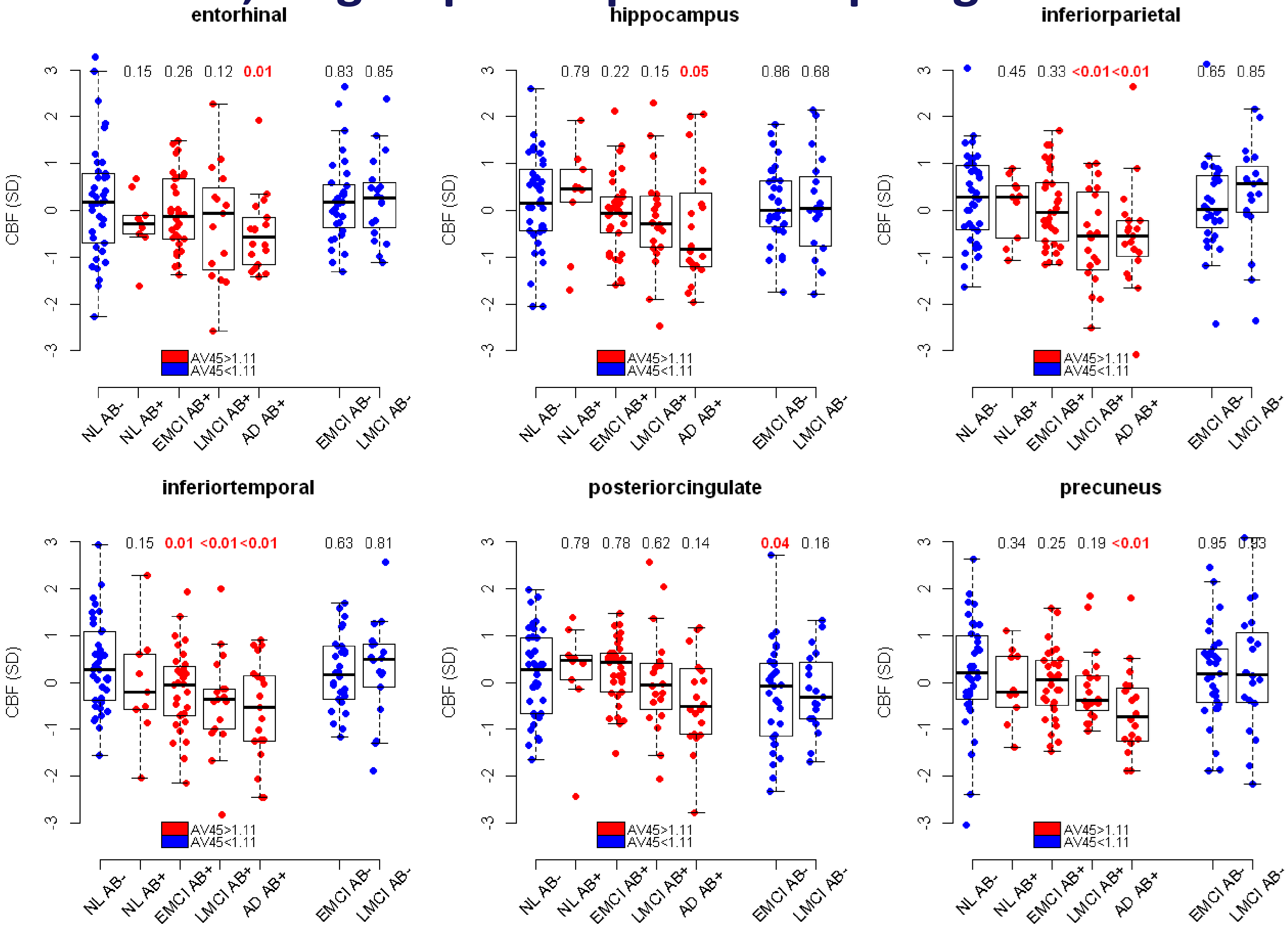


Comparing effects of Aβ pathology on ASL-CBF and volume

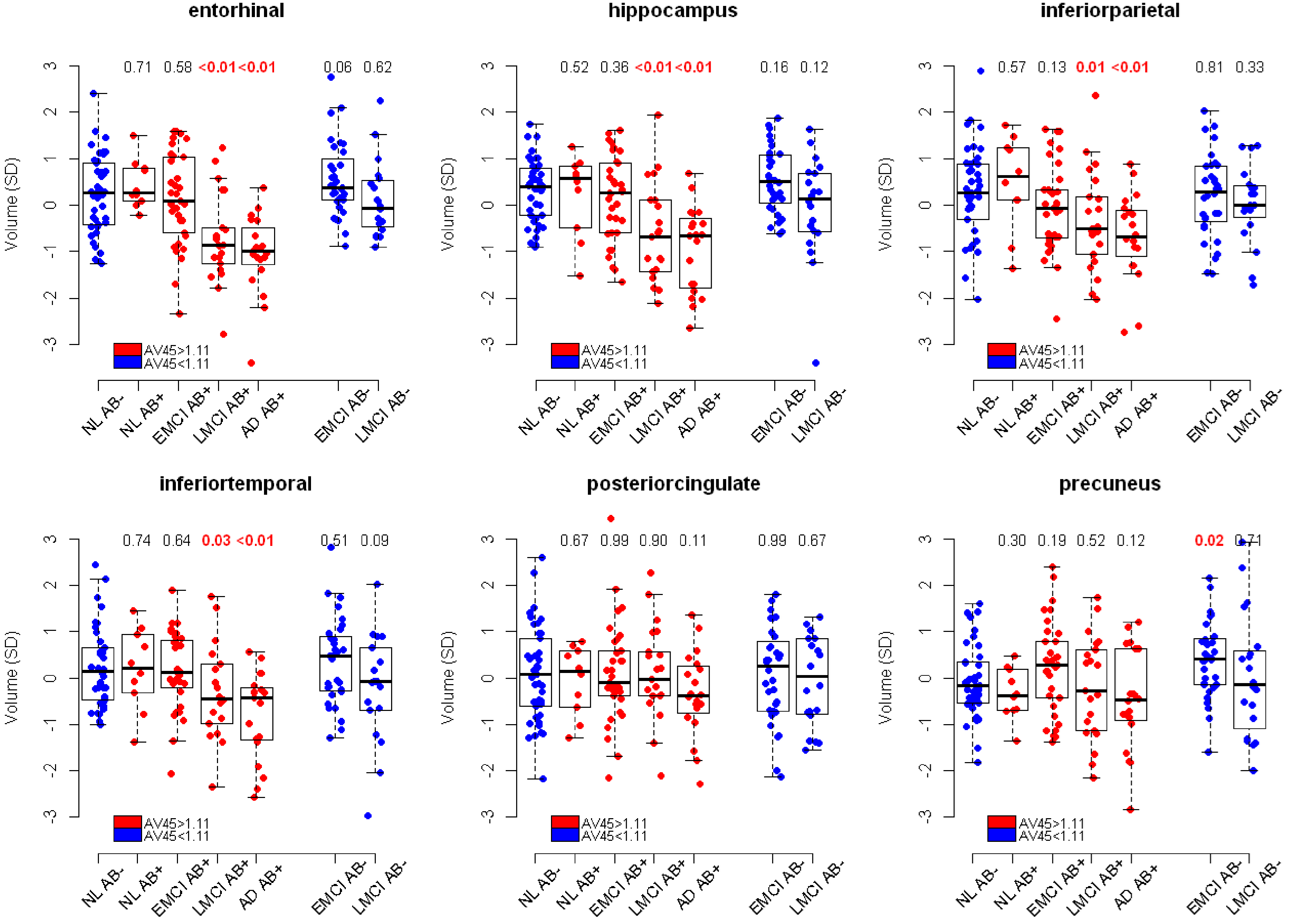
Groups	Region	ES ASL	ES VOL	DiffES	p
NL (N=51)	Entorhinal	0.23	0.06	-0.17	0.17
	Hippocampus	0.01	0.07	0.06	0.63
	Inferior parietal	0.18	0.24	0.05	0.58
	Inferior temporal	***0.32***	***0.01***	***-0.31***	***0.03***
	Posterior cingulate	0.15	0.04	-0.10	0.36
	Precuneus	0.09	0.06	-0.03	0.82
EMCI (N=65)	Entorhinal	0.27	0.14	-0.13	0.20
	Hippocampus	0.21	0.29	0.07	0.50
	Inferior parietal	0.11	0.15	0.04	0.70
	Inferior temporal	0.14	0.04	-0.09	0.34
	Posterior cingulate	0.17	0.06	-0.10	0.30
	Precuneus	0.12	0.10	-0.01	0.90
LMCI (N=41)	Entorhinal	0.28	0.48	0.20	0.12
	Hippocampus	0.11	0.42	0.30	0.04
	Inferior parietal	0.42	0.49	0.07	0.50
	Inferior temporal	***0.41***	***0.11***	***-0.30***	***0.03***
	Posterior cingulate	0.19	0.10	-0.09	0.46
	Precuneus	0.18	0.26	0.08	0.57

Aβ has stronger effects on ASL-CBF than volume in inferior temporal cortex in NL and LMC

ASL-CBF, all groups compared to Aβ-negative NL



Volume, all groups compared to Aβ-negative NL



Aβ has different effects on ASL-CBF and volume during disease progression

Groups	Region	ES ASL	ES VOL	Diff ES	P
NL Aβ- (n=41) vs. NL Aβ+ (n=10)	entorhinal	0.17	0.13	-0.04	0.67
	hippocampus	0.01	0.08	0.07	0.51
	inferior parietal	0.15	0.16	0.02	0.85
	inferior temporal	***0.25***	***0.04***	***-0.21***	***0.08***
	posterior cingulate	0.07	0.04	-0.03	0.77
	precuneus	0.13	0.05	-0.09	0.47
NL Aβ- (n=41) vs. EMCI Aβ+ (n=33)	entorhinal	0.10	0.09	-0.01	0.88
	hippocampus	0.16	0.08	-0.08	0.41
	inferior parietal	0.12	0.13	0.01	0.89
	inferior temporal	***0.28***	***0.02***	***-0.25***	***0.02***
	posterior cingulate	0.05	0.02	-0.03	0.77
	precuneus	0.12	0.09	-0.03	0.73
NL Aβ- (n=41) vs. LMCI Aβ+ (n=20)	***entorhinal***	***0.14***	***0.47***	***0.34***	***0.01***
	hippocampus	***0.12***	***0.53***	***0.41***	***0.00***
	inferior parietal	0.40	0.27	-0.13	0.23
	inferior temporal	0.35	0.27	-0.08	0.39
	posterior cingulate	0.04	0.01	-0.03	0.74
	precuneus	0.16	0.06	-0.10	0.36
NL Aβ- (n=41) vs. AD Aβ+ (n=20)	***entorhinal***	***0.25***	***0.79***	***0.53***	***0.00***
	hippocampus	***0.21***	***0.81***	***0.60***	***0.00***
	inferior parietal	0.36	0.46	0.10	0.37
	inferior temporal	0.45	0.53	0.08	0.44
	posterior cingulate	0.14	0.21	0.07	0.47
	precuneus	0.37	0.20	-0.17	0.12

Conclusions

- Aβ pathology has strong effects on ASL-CFB
- Aβ effects ASL-CBF in all patient groups including normal controls
- Structural MRI of ERC and hippo is more sensitive than ASL-CBF to detect effects of Aβ-pathology in late disease stages
- ASL-CBF in some brain regions (inf temp ctx) **may be *more sensitive* than structural MRI** to detect early effects of Aβ-pathology

Aβ+ vs Aβ- classification accuracy (10-fold cross validation)

Predictors	**ACC**	**PPV**	**NPV**
Demographics	0.65±0.03	0.67±0.03	0.66±0.04
Demographics & ApoE	0.69±0.08	0.73±0.09	0.70±0.10
Demographics & sMRI*	0.79±0.05	0.81±0.06	0.80±0.07
Demographics & ASL-MRI*	0.75±0.11	0.76±0.12	0.78±0.10
Demographics & sMRI & ApoE*	0.83±0.03	0.85±0.02	0.83±0.04
Demographics & ASL-MRI & ApoE*	0.80±0.06	0.82±0.06	0.82±0.02

Effects of traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) on Alzheimer's disease (AD) in veterans using imaging and biomarkers in the AD Neuroimaging Initiative (ADNI)

Michael Weiner, MD
San Francisco VA Medical Center
University of California, San Francisco

EFFECTS OF TRAUMATIC BRAIN INJURY AND PTSD ON AD IN VIETNAM WAR VETERANS: ADNI

A STUDY OF
BRAIN AGING
IN VIETNAM WAR
VETERANS

TWO GRANTS FROM THE DOD

- We have two grants from the DOD
  - Effects of traumatic brain Injury and Post traumatic stress disorder on AD in Vietnam veterans using ADNI
  - Effects of traumatic brain Injury and Post traumatic stress disorder on AD in Vietnam veterans with MCI using ADNI
  - Total of 400 subjects in both grants together

Recruitment Effort

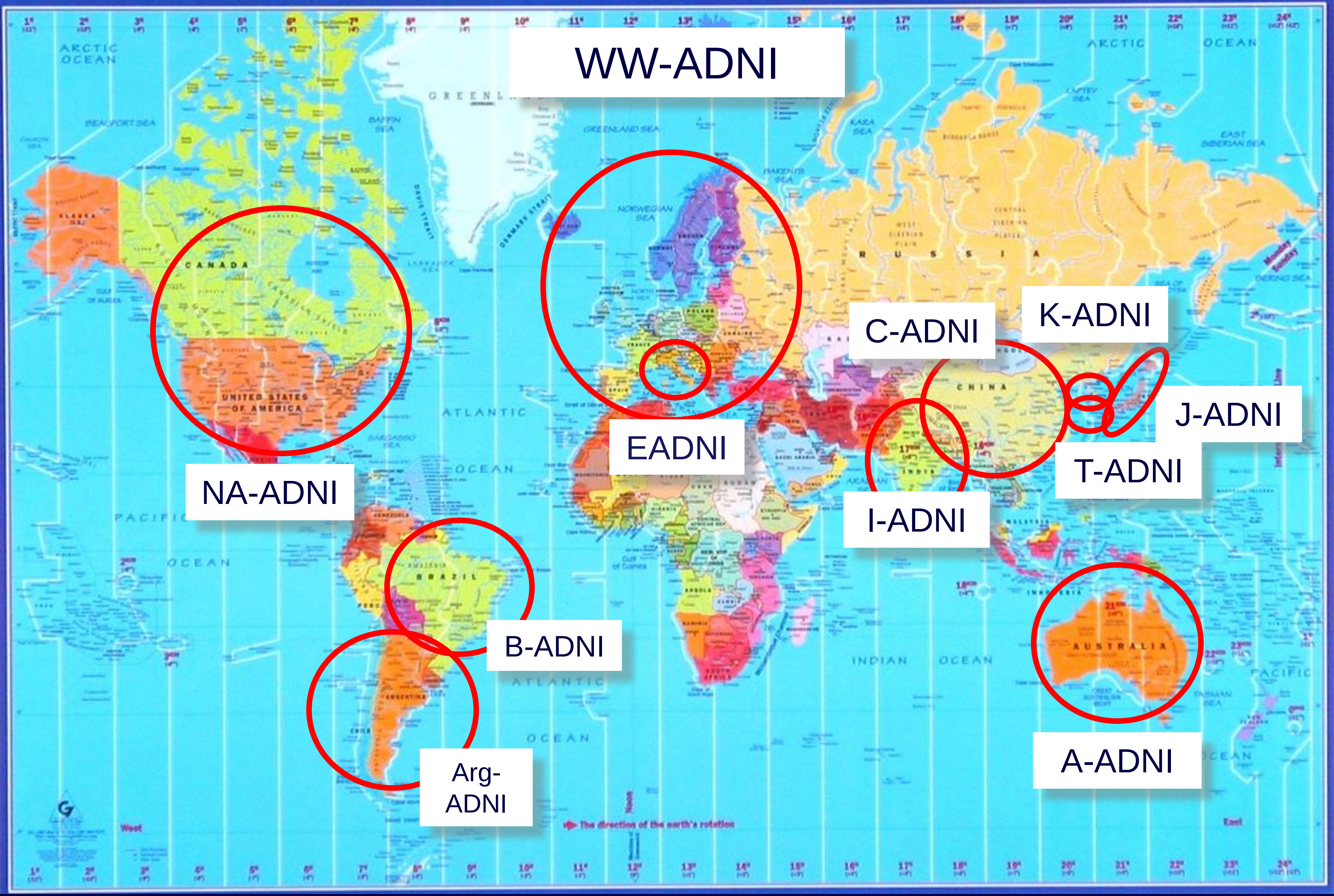
Mail Effort	Call Effort	Status of 673 Screens	Status 214 Consents	Status 123 Received
4,728 Brochures Mailed	1,894 Subjects Called	459 (68.2%) Excluded	40 (18.7%) Declined	27 (22.0%) Excluded
589 (12.4%) "YES"	302 (15.9%) Decline	**214 (31.8%) Sent Consent**	51 (23.8%) Waiting	**96 (78%) SCID CAPS**
201 (4.3%) "NO "	**673 (35.5%) Screened**		**123 (57.5%) Received**	

Enrollment Effort

Status of 96 SCID/CAPS	Cohort of 44 Referrals	Clinic of 44 Referrals
31 (32.3%) Failed	**7 (15.9%) TBI only**	**•Banner, N=2 •Rush, N=4 •Stanford, N=4 •UCSD, N=1 •UCSF, N=22 •URMC, N=7 •USC, N=3 •Wisconsin, N=1**
21 (21.9%) Scheduled	**29 (65.9%) PTSD only**	
44 (45.8%) Referred to Clinic	**8 (18.2%) Both TBI & PTSD**	

DATA SHARING

- All ADNI raw and processed data is shared on the internet with no embargo
- UCLA/LONI/ADNI under direction of Dr Arthur Toga
- ADNI has resulted in 636 manuscripts, 329 of which are now published
- This unprecedented data sharing is a model for future science


WW-ADNI
NA-ADNI
EADNI
C-ADNI
K-ADNI
J-ADNI
T-ADNI
I-ADNI
B-ADNI
Arg-ADNI
A-ADNI
ARCTIC OCEAN
ATLANTIC
OCEAN
PACIFIC
OCEAN
INDIAN OCEAN
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The direction of the earth's rotation
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East

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These slides and much more at
ADNI-INFO.ORG

All data at
www.loni.ucla.edu/ADNI/

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Takeda
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

alzheimer's association
Alzheimer's Drug Discovery Foundation

Private partners committed more than $45 million to AD research through ADNI1 and ADNI2

FNIH Foundation for the National Institutes of Health

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Clinical Trial Comm & Recruit	Genny Mathews
ADCS IT	Baoyuan Zhao

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University of South Florida, Tampa	Amanda Smith, MD	Jill Ardila

Publications

1) Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, Trojanowski JQ, Toga AW, Becket L: Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Dementia, 1: 55-66, 2005.
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5) Mueller SG, Weiner MW, Thal LJ, Peterson RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L: Alzheimer's Disease Neuroimaging Initiative. Advances in Alzheimer's and Parkinson's Disease. 183-189, 2008.
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