

Why ADNI?

Neuroimaging in the Early Detection, Tracking and Treatment of Alzheimer's Disease

Eric M. Reiman, MD

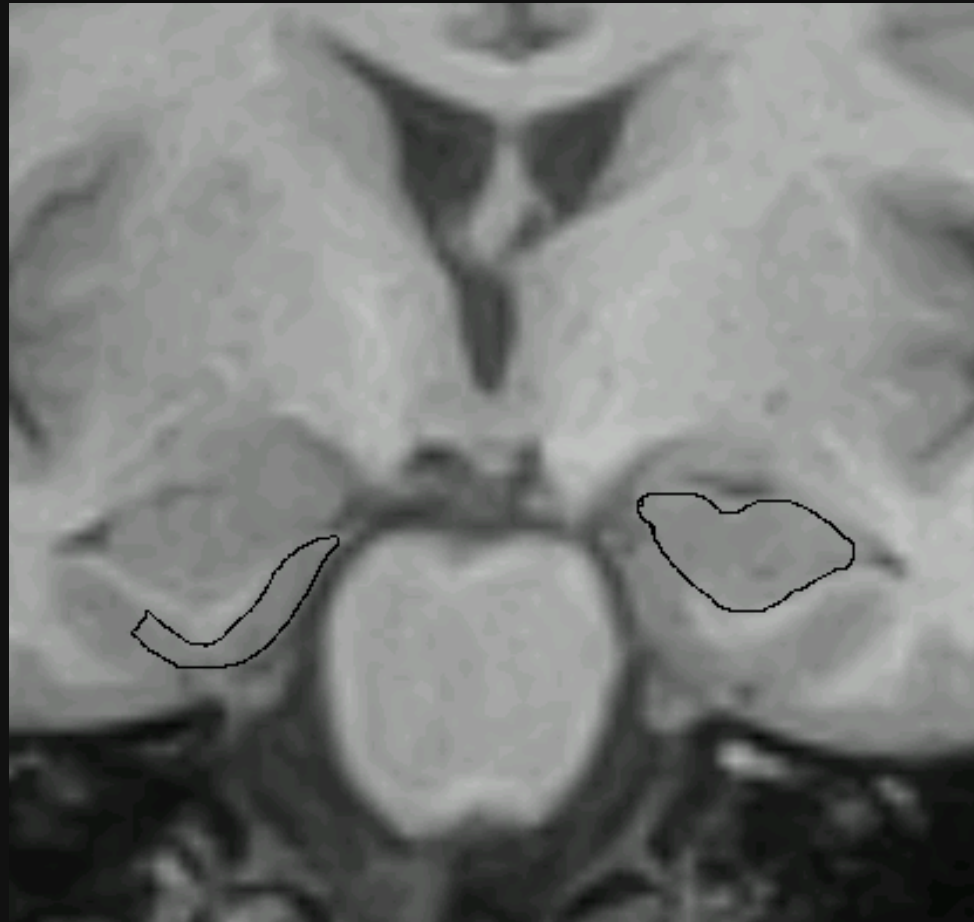
**Banner Good Samaritan Medical Center
University of Arizona
Translational Genomics Research Institute
Arizona Alzheimer's Disease Consortium
Phoenix, Arizona, USA**

Volumetric MRI in the Study of AD

- **Declines in brain volume**
 - entorhinal cortex & hippocampal atrophy
 - whole brain atrophy
- **Progressive & correlated with dementia severity**
- **Predicts clinical decline & histopathological diagnosis of AD**
- **Parallels the onset of MCI , predicts rate of conversion to probable AD**
- **Promising roles in the evaluation of AD disease-slowing & prevention therapies**
- **Whole brain atrophy rates may be better than medial temporal lobe atrophy in clinical trials**

MRI in the Assessment of Entorhinal and Hippocampal Atrophy

Entorhinal Cortex

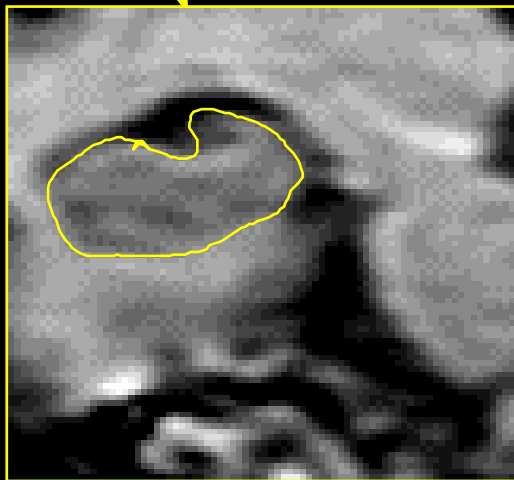
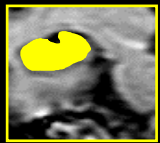
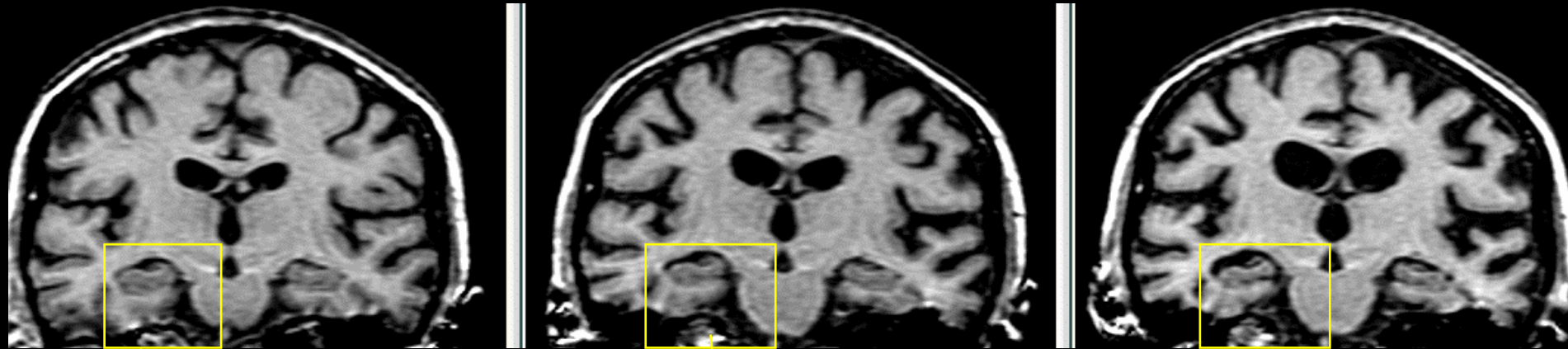


Hippocampus

Courtesy of Mike Weiner

Serial Coronal MRI's from a Patient with Initially Mild AD

(courtesy of Nick Fox)



Baseline

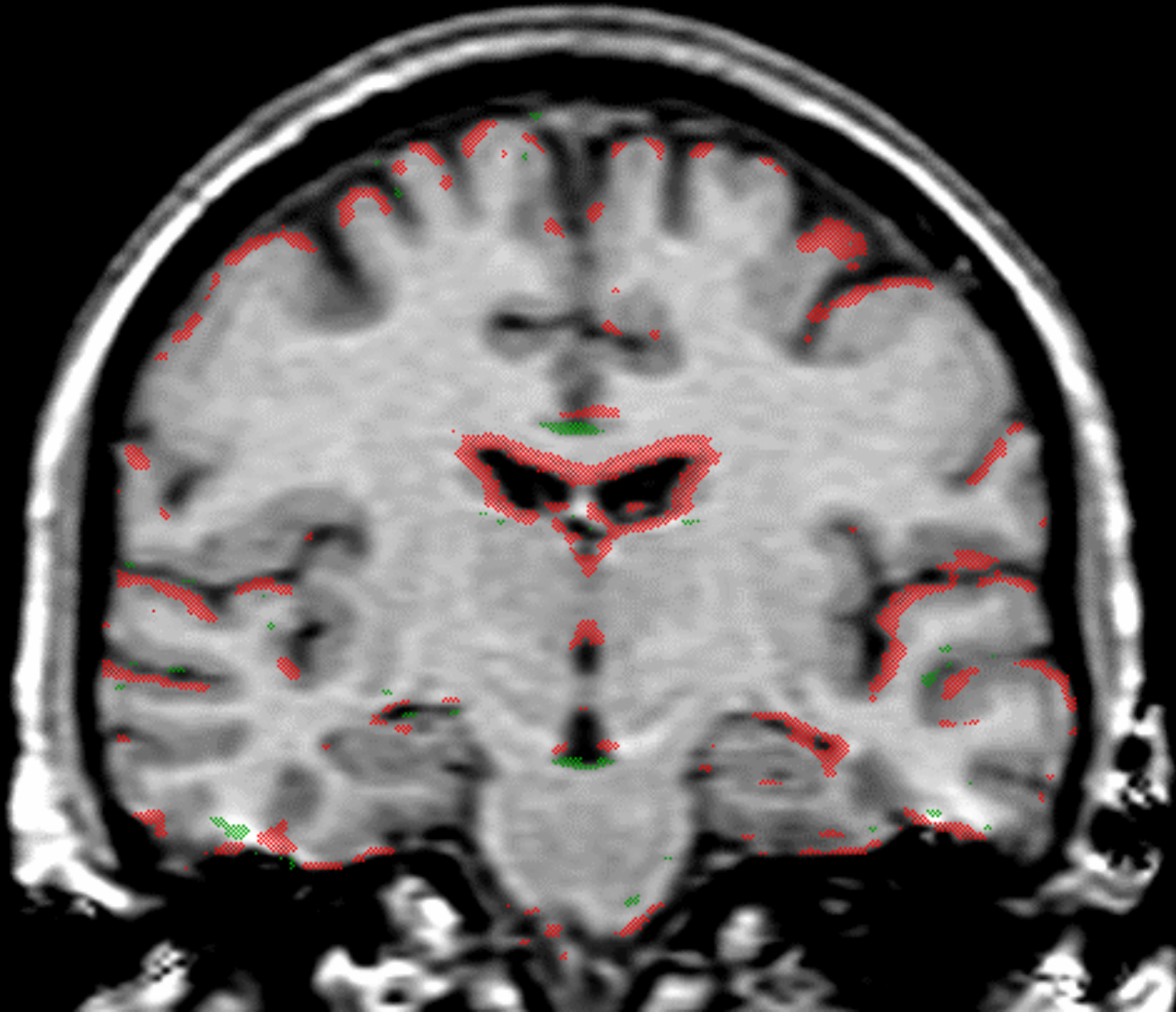


18 months

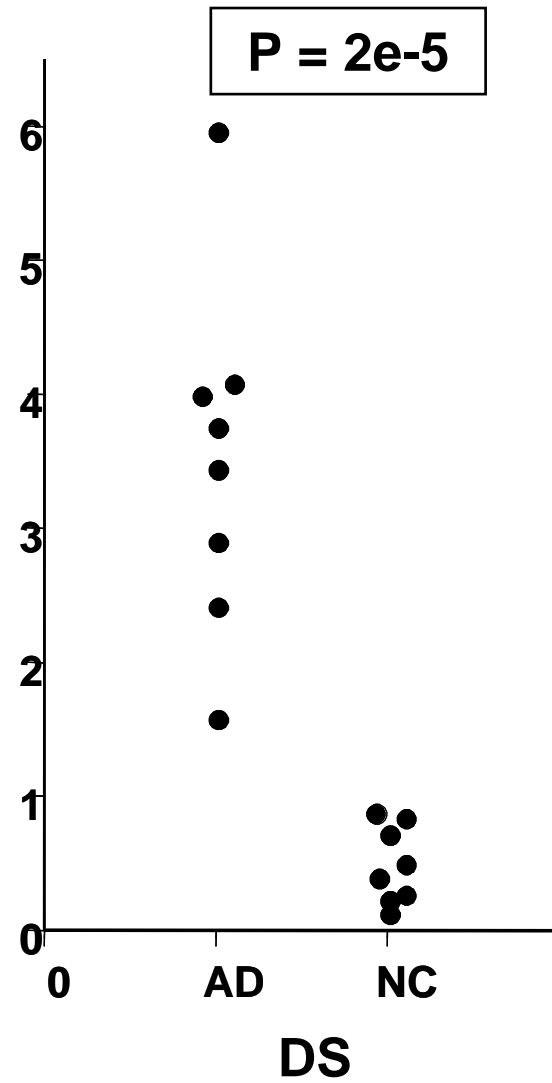
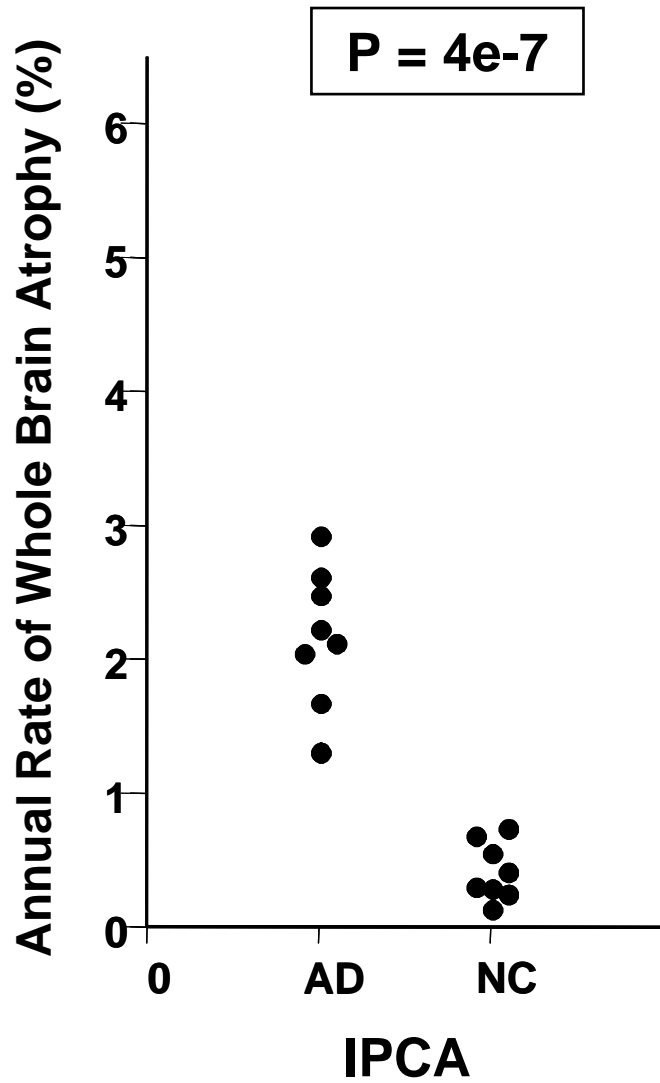


36 months

Computation of Brain Atrophy from Sequential MRIs



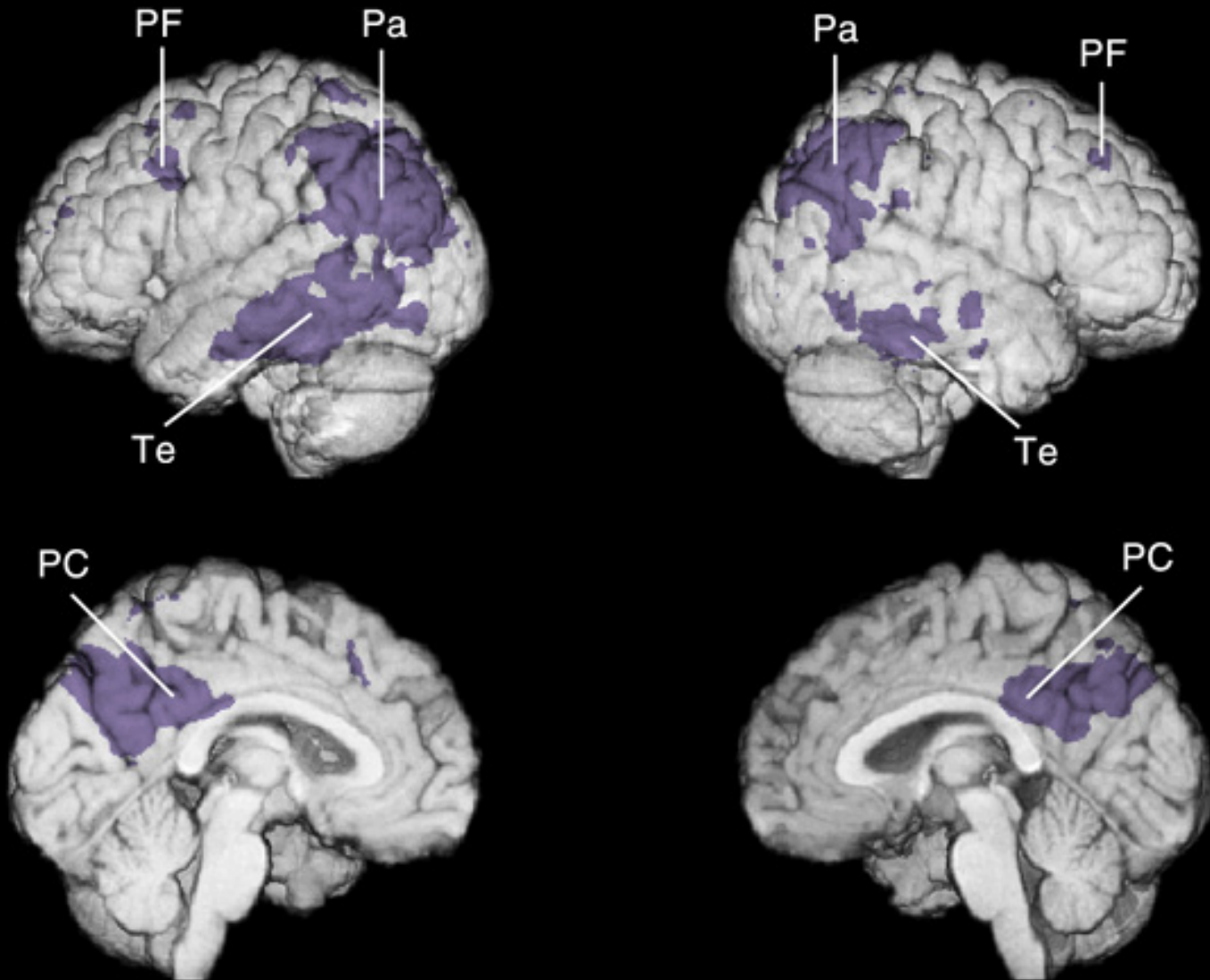
Courtesy of Nick Fox



FDG PET in the Study of AD

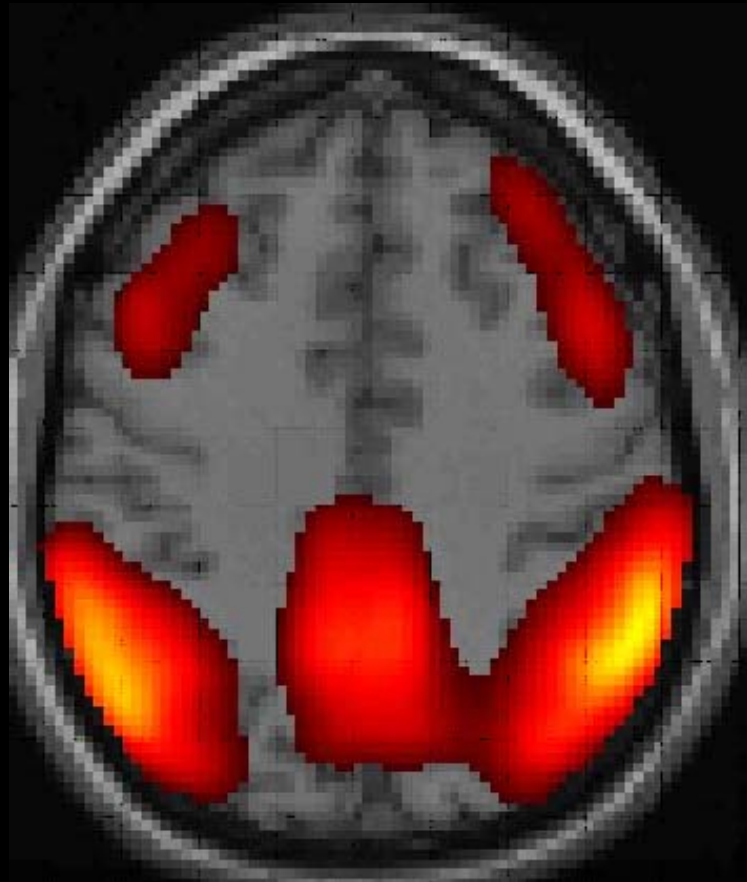
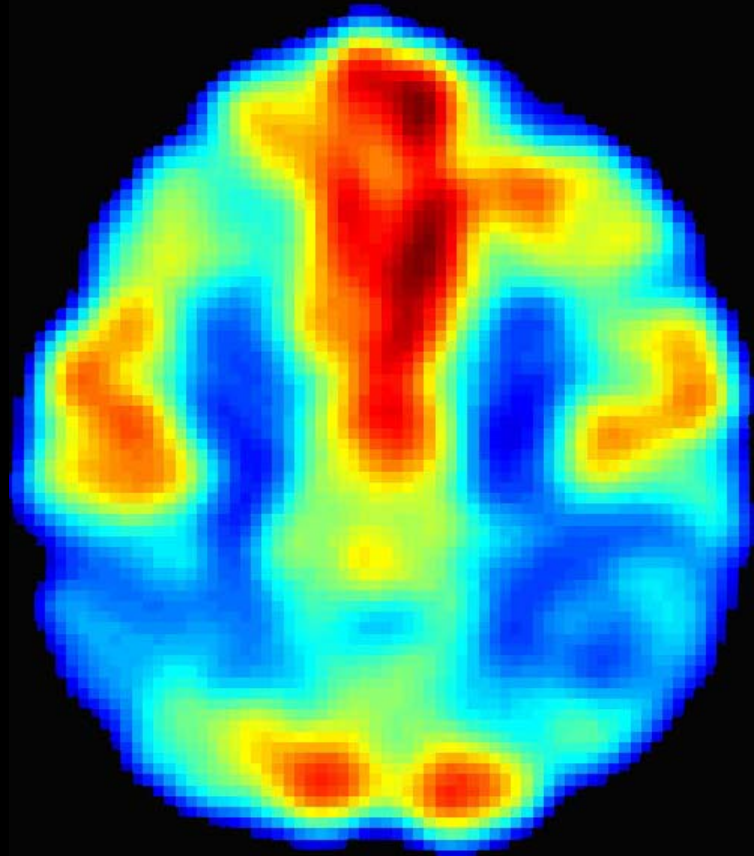
- **Characteristic & progressive CMRgl declines**
 - posterior cingulate, parietal & temporal cortex
 - prefrontal cortex & whole brain metabolism
- **Correlated with dementia severity & progressive**
- **Predicts clinical decline & histopathological diagnosis of AD**
 - Clinically indicated in some patients with dementia
- **Predicts higher rate of conversion from MCI to probable AD**
 - Not yet clinically indicated in patients with MCI
- **Early and progressive CMRgl declines in cognitively normal APOE ϵ 4 carriers**
- **Promising roles in the discovery of AD disease-slowing & prevention therapies**

CMRgl Abnormalities in Probable Alzheimer's Dementia

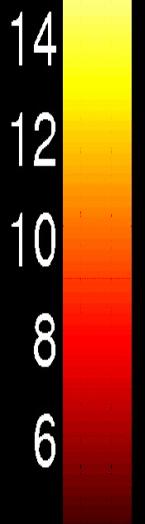


From Reiman et al, *New Engl J Med* 1996

PET in the Diagnosis of Alzheimer's Disease



Z-score

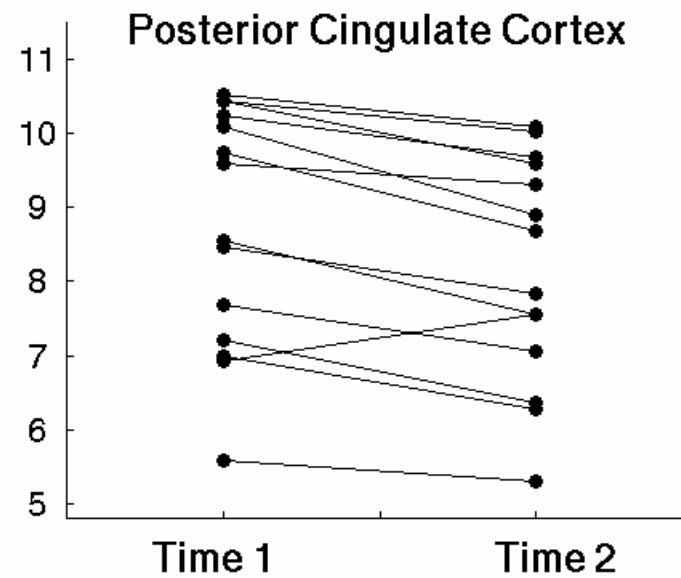
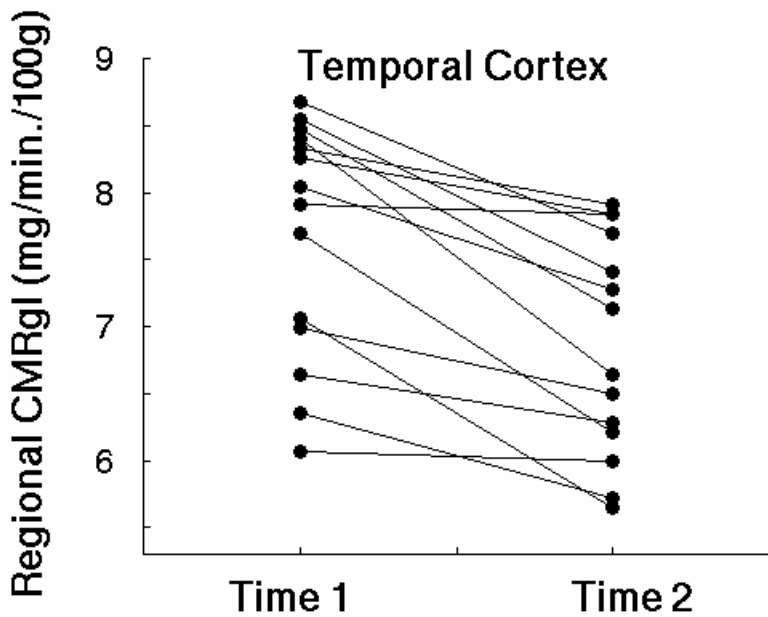
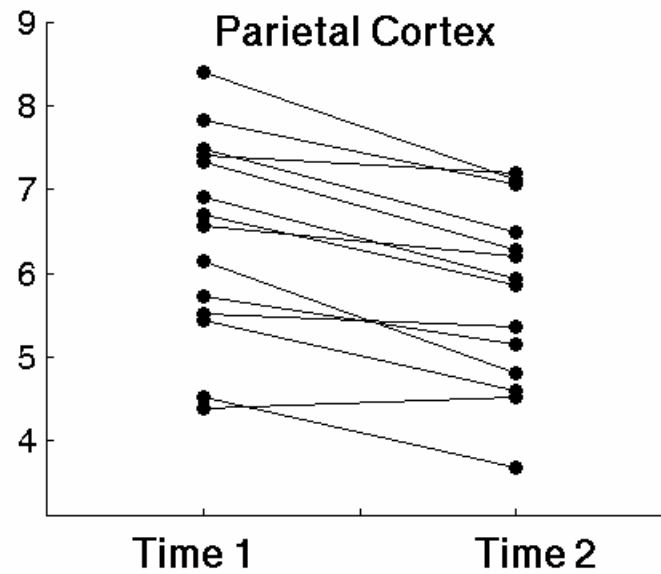
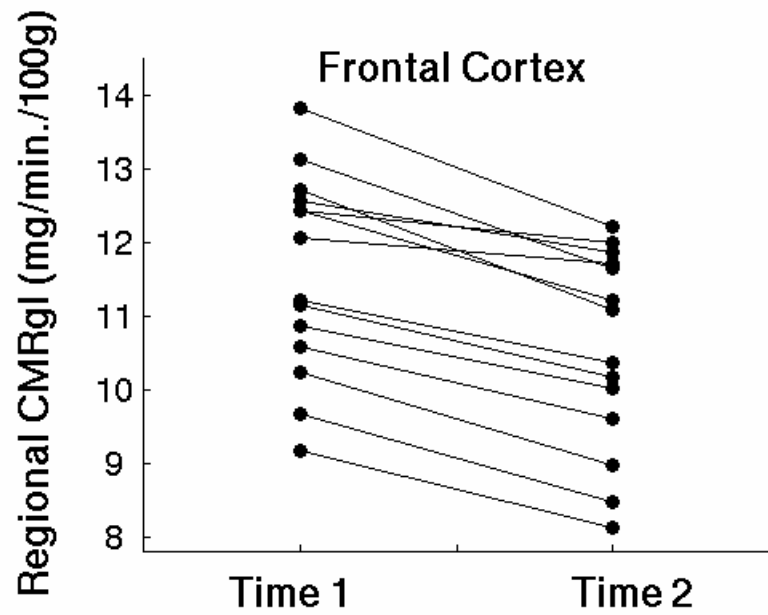


Alzheimer's Dementia: Maximal Percent CMRgl Declines in One Year

Region	Atlas Coordinates			Z-Score	% Annual Decline*
	x	y	z		
Frontal	-48	6	40	5.20	9.1±3.4
Parietal	-64	-42	36	4.14	10.9±6.9
Temporal	-68	-14	-12	3.91	10.4±6.7
Cingulate	-2	-42	28	3.62	6.6±5.5
Global	---	---	---	-----	4.2±4.6

*Mean ± SD, percent decline from baseline CMRgl

Alexander et al, *Am J Psychiatry* 2002



Number of AD Patients per Treatment Group Needed to Detect an Effect with 80% Power in One Year

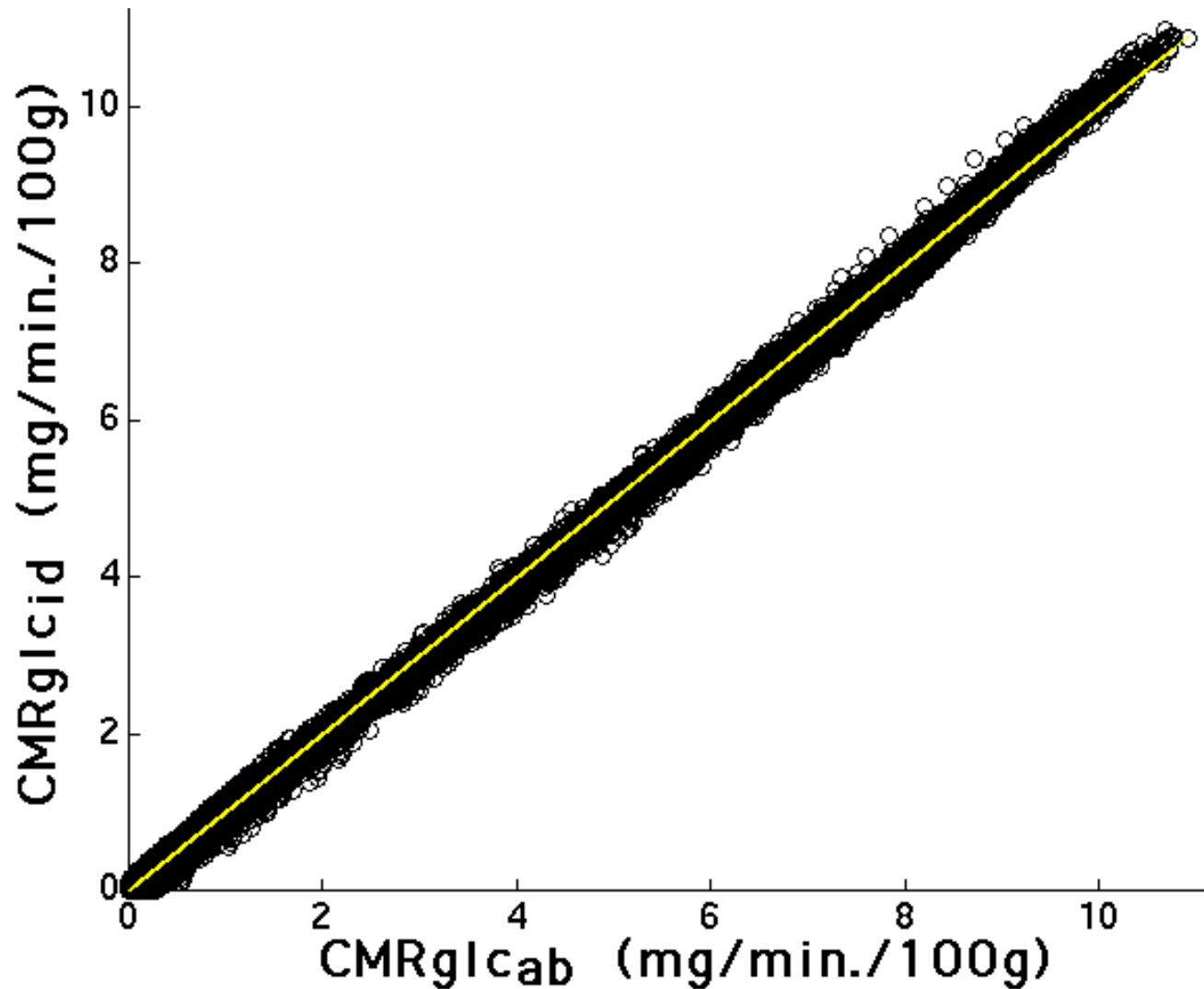
	Treatment Effect			
	20%	30%	40%	50%
Frontal	85	38	22	14
Parietal	217	97	55	36
Temporal	266	119	68	44
Cingulate	343	153	87	57
Combined	62	28	16	10

P=0.01 (two-tailed)

No adjustment for normal aging effects or subject attrition

Alexander et al, *Am J Psychiatry* 2002

FDG PET Quantification Using an Image-Derived Carotid Artery Input Function



Chen et al, *J Cereb Blood Flow Metab* 1998

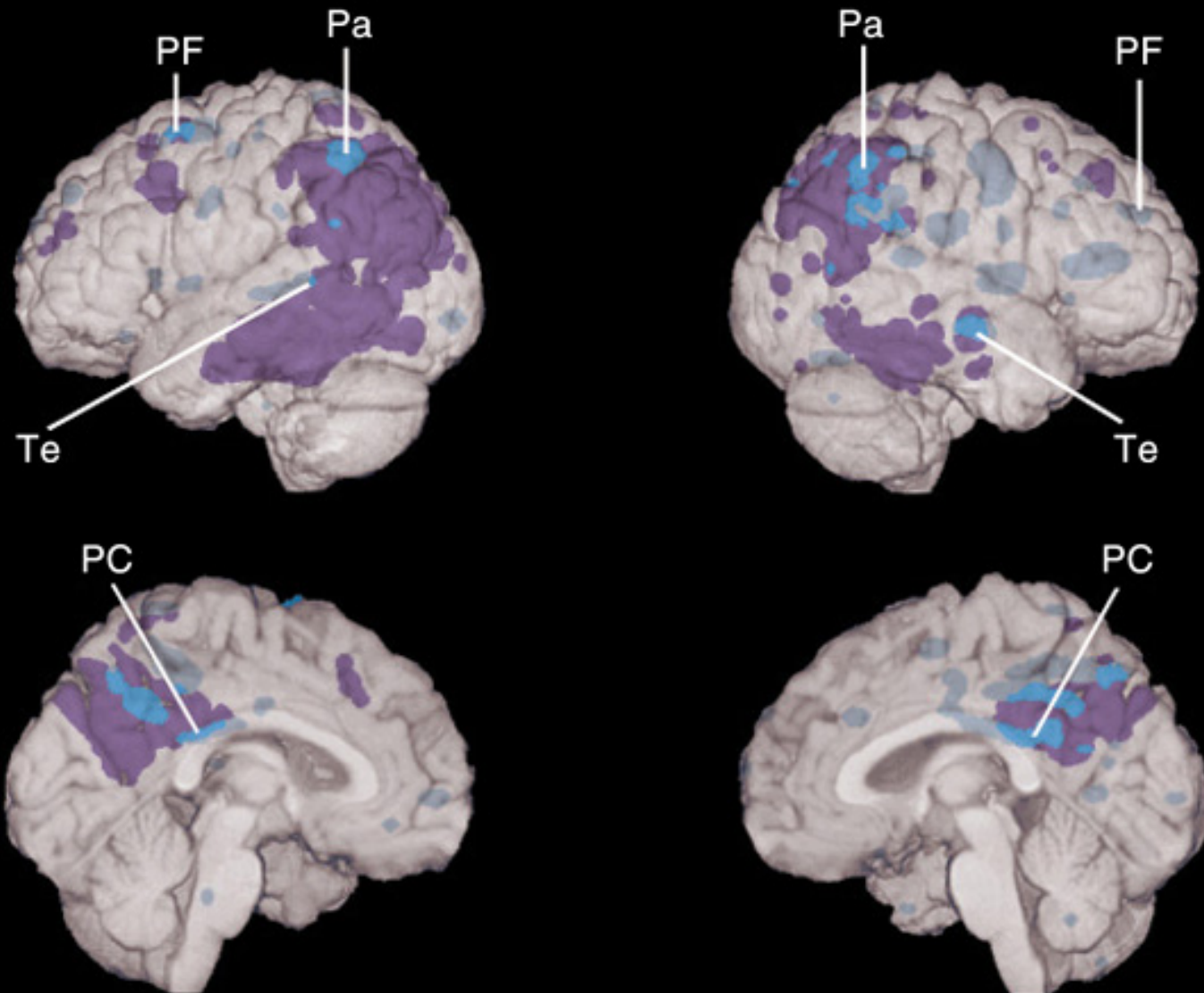
Baseline CMRgl Reductions and One-Year CMRgl Declines in Amnestic MCI

- **22 patients with MCI**
 - Petersen criteria, CDR 0.5, baseline MMSE 28, mean age 70
 - 8 (36%!) converted to probable AD, 12 remained stable, 2 excluded
- **Patients who converted to probable AD**
 - Baseline rCMRgl reductions in comparison to NCs & stable MCIs
 - One-year rCMRgl declines, some of which were greater than those in the stable MCIs (e.g., in right prefrontal cortex)
- **Analyses of the aggregate MCI group are pending**
 - Including estimates of statistical power for clinical trials

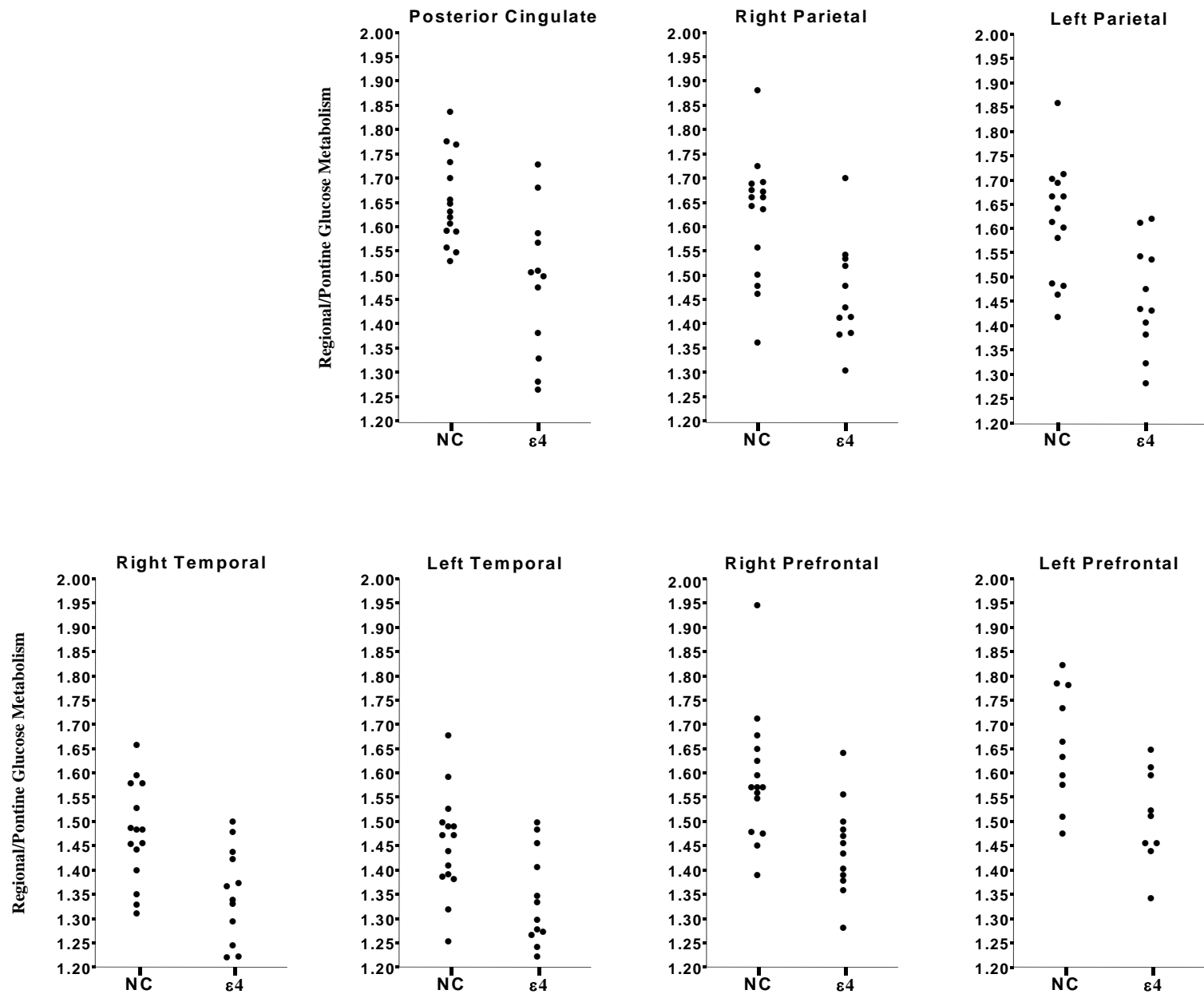
APOE ϵ4 Copies	Prevalence	Alzheimer Risk	Onset Age
0	73%	20%	84
1	24%	47%	75
2	3%	91%	68

Corder et al, Science 1993

CMRgl Abnormalities in 20-39 y.o. $\epsilon 3/\epsilon 4$'s

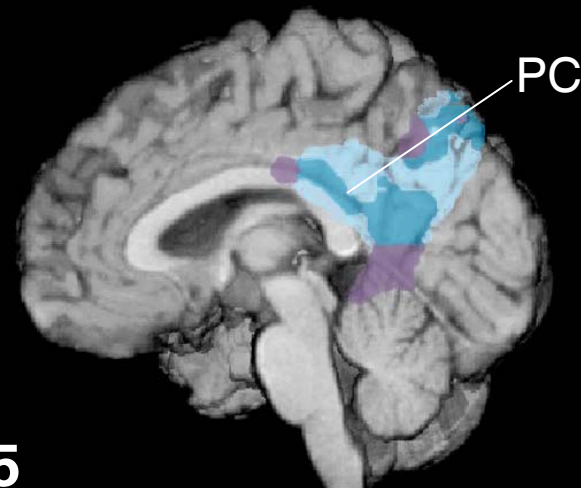
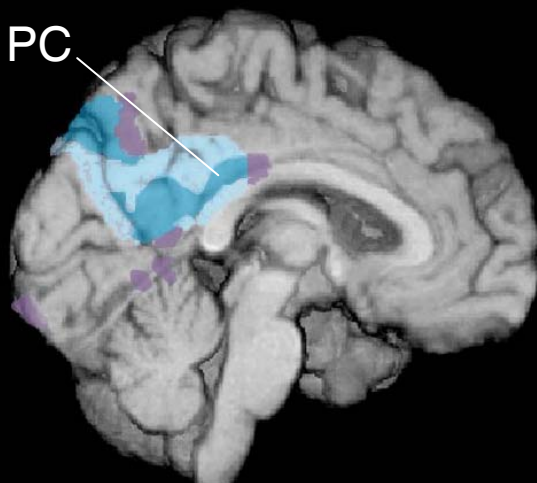
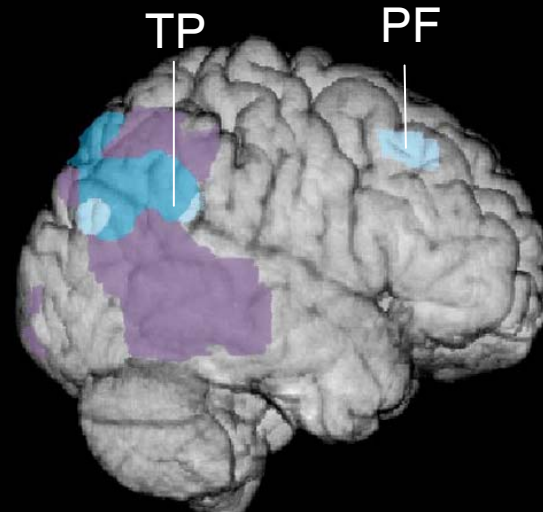
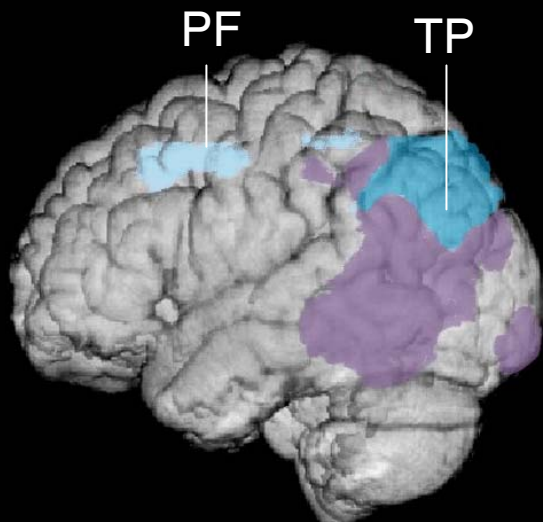


Reiman et al, *PNAS* 2004

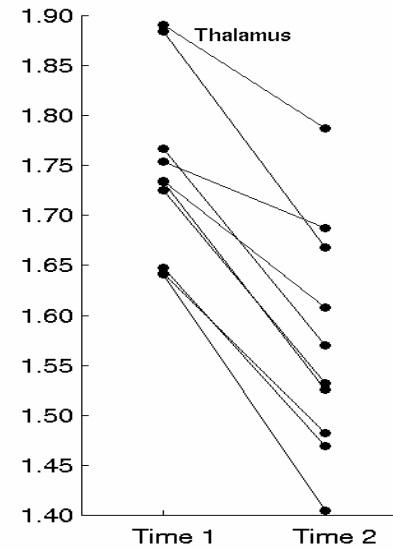
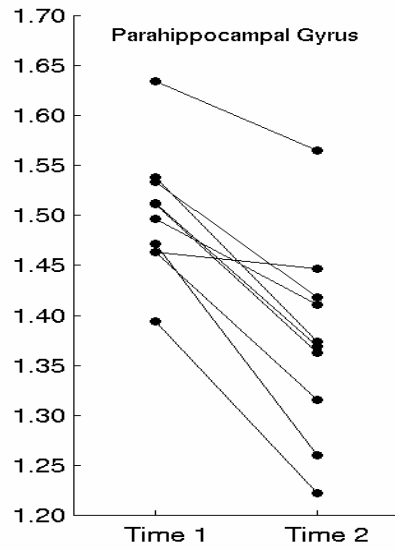
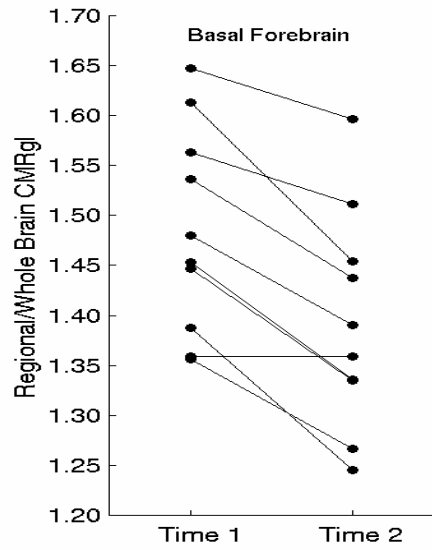
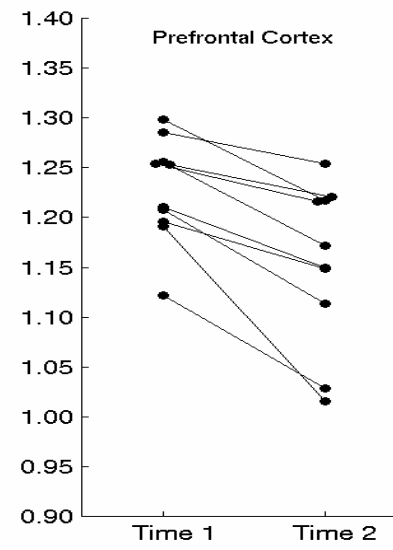
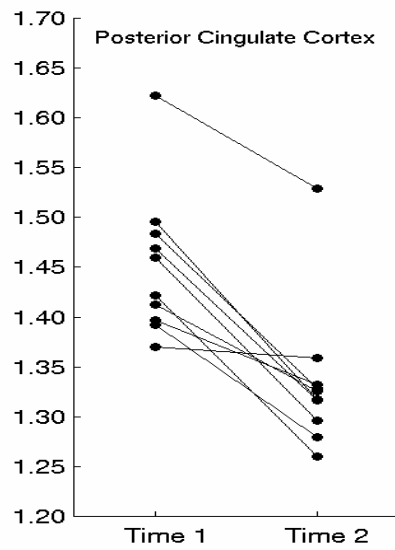
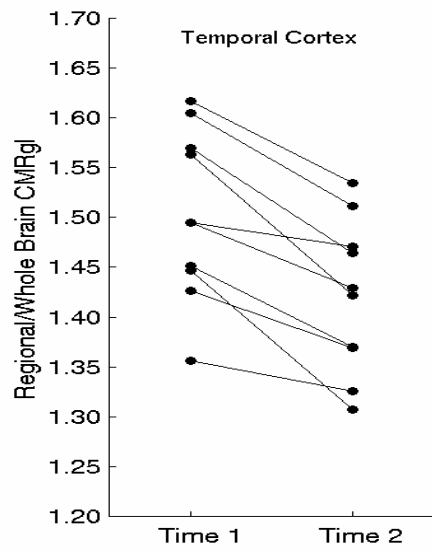


Reiman et al, *PNAS* 2004

Correlations Between APOE ϵ 4 Gene Dose and Regional Hypometabolism



P < 0.005



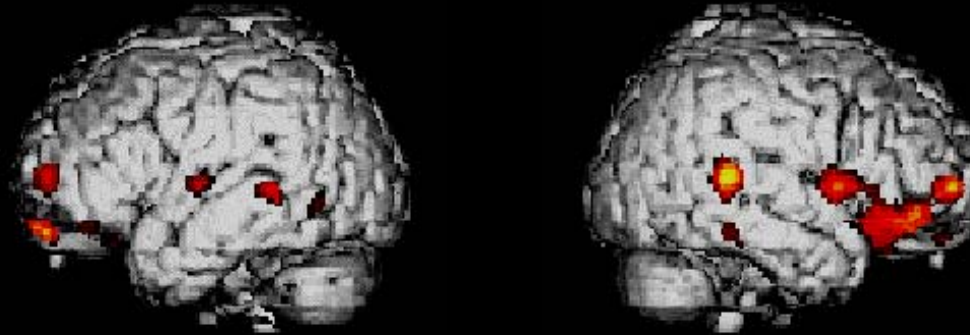
Number of Cognitively Normal APOE-3/4's per Treatment Group Needed to Detect an Effect with 80% Power in Two Years

	Treatment Effect			
	20%	30%	40%	50%
Thalamus	78	35	21	14
Parahippocampal	129	58	33	22
Cingulate	130	58	33	22
Temporal	155	70	40	27
Basal Forebrain	167	75	43	29
Prefrontal	179	80	46	29
Combined	39	19	12	8

P=0.01 (two-tailed), uncorrected for multiple comparisons

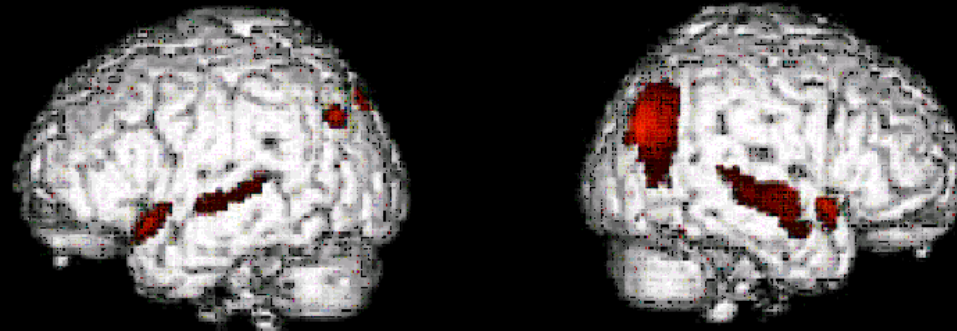
Two-Year CMRgl Declines in Cognitively Normal APOE ϵ 4 Carriers

Reiman et al, *PNAS* 2001



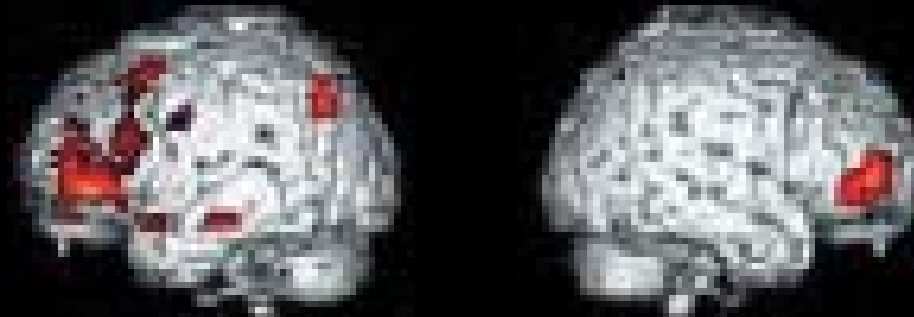
Two-Year CMRgl Declines in APOE ϵ 4 Carriers with Memory Concerns

Small et al, *PNAS* 2000



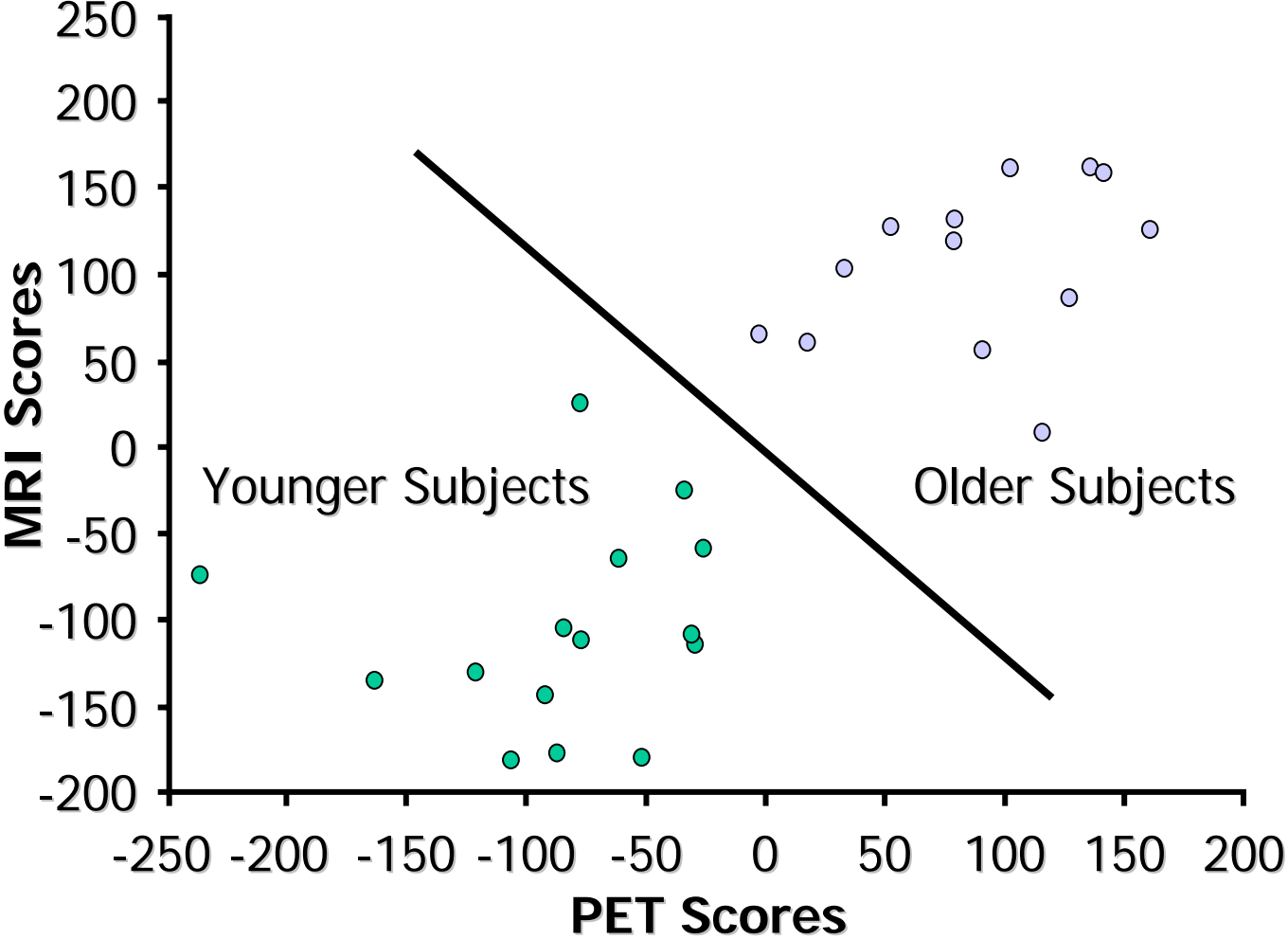
One-Year CMRgl Declines in MCI patients Who Developed Probable AD

Drzezga et al, *Eur J Nucl Med Mol Imaging* 2003



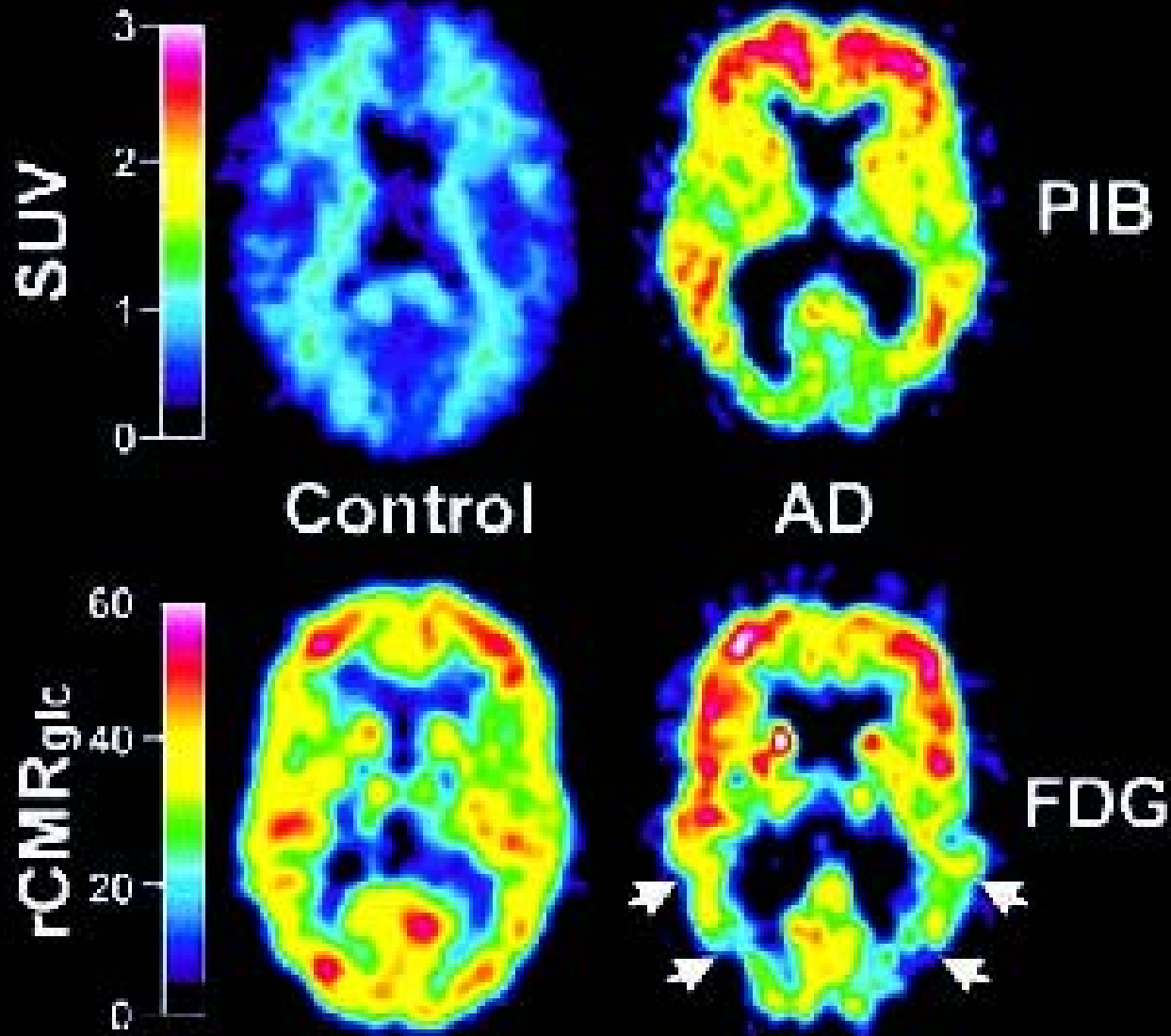
P < 0.001

Linking Functional and Structural Brain Images With Multivariate Network Analyses Using the Partial Least Square Method



Chen et al 2004 (abstract)

Amyloid Imaging



Amyloid Imaging: Promising Radioligands

- **[18F] FDDNP (JR Barrio, GW Small et al, UCLA)**
 - Lipophilic, binds in vitro to synthetic A β fibrils
 - Binds in postmortem brain to fibrillar A β , diffuse A β , and NFTs
 - PET: Increased binding in parietotemporal cortex
 - Unlike Congo Red and Thioflavin-T, competes with NSAID binding to fibrillar A β
- **[11C] PIB (WE Klunk, CA Mathis et al, Univ Pittsburgh)**
 - Benzothiazole derivative with high affinity for fibrillar A β
 - Lipophilic, low non-specific binding
 - PET: Increased binding in frontal & parietotemporal cortex
 - [18F]-labeled ligand in development
- **[11C] SB-13 (HF Kung et al, Univ Pennsylvania)**
 - Stilbene derivative with high affinity for fibrillar A β
 - Competes with PIB but not FDDNP binding in vitro
 - PET: Binding properties similar to PIB in AD patients versus controls
- **[125I] IMPY (HF Kung et al, Univ Pennsylvania)**
 - Binding properties similar to [11C] SB-13 in vitro

PET Measurements of AD Neuropathology

Extraordinary Promise

- The evaluation of putative “plaque busters”
- The identification of persons likely to benefit from these treatments
- Helping to test the amyloid hypothesis

Current Challenges

- To further develop & test radiotracer methods for the quantitative assessment of fibrillar A β density
- To directly compare these radiotracers in patients & controls
- To determine whether fibrillar A β binding measurements can...
 - Track the progression of AD
 - Predict the clinical progression & neuropathological diagnosis of AD in patients with dementia & MCI
- To compare the time-course of neuropathological, FDG PET, & MRI changes in patients with AD & MCI & non-impaired at-risk persons
- To further develop & test radiotracer methods for the quantitative assessment of NFT density & other neuropathological features
- Patience, persistence & support for this important endeavor

Why ADNI?

The Promise of MRI & FDG PET in Clinical Trials

- **Volumetric MRI & FDG PET are the best established imaging techniques in the early detection & tracking of AD**
- **Emerging roles in the evaluation of putative disease-slowing and prevention therapies**
 - Greater statistical power than clinical ratings in proof-of-concept (e.g., early Phase II) trials
 - Potential to support a disease-slowing indication (e.g., in Phase III trials)
 - Potential to help determine a sub-set of patients most likely to benefit from the treatment (e.g., to enrich clinical trials)
- **Promising roles in predicting the rate of conversion from MCI to probable AD**
 - Permitting shorter clinical trials in which conversion to probable AD isn't the primary endpoint
 - Possible future role in the differential diagnosis of MCI

Why ADNI?

Helping to Fulfill this Promise

- **Standardized procedures for clinical trials**
 - Needed to compare data from different persons & centers, compare findings from different studies, & conduct clinical trials
- **An accessible database**
 - To compare different methods & measurements, helping to establish the best ones to use in clinical trials
 - To develop & test improved image-analysis algorithms
 - To improve the early detection & tracking of AD through the use of complementary datasets
- **Biological specimens**
 - To relate imaging findings to other promising biomarkers
- **To further characterize & compare the statistical power of PET & MRI in multi-center clinical trials**
- **To help determine how baseline measurements & short-term changes predict subsequent rates of clinical decline & conversion from MCI to probable AD**

ADNI: Experimental Design

- **800 subjects**
 - 200 AD: 0, 6, 12, 24 months
 - 400 amnesic MCI: 0, 6, 12, 18, 24, 26 months
 - 200 normal controls: 0, 6, 12, 24, 36 months
- **45-50 sites**
- **Volumetric MRI**
 - 1.5T in all subjects
 - 3T in ~25% of subjects
- **FDG PET (resting state)**
 - Non-quantitative PET in ~50% of all subjects
 - Quantitative PET in ~25% of PET subjects (~25% of all subjects)
- **Biological specimens**
 - Blood and urine at all time points
 - CSF from ~20% of subjects at fewer time points

ADNI Components

- **Administrative Core – UCSF**
 - Weiner (ADNI Director)
- **Clinical Core – UCSD**
 - Thal, Albert, DeKosky, Morris, Petersen, Salmon, Tariot, Salmon, others
- **MRI Core – Mayo**
 - Jack, Alexander, Bernstein, Dale, DeCarli, Felmlee, Fox, Schuff, Studholme, others
- **PET Core – Berkeley, Michigan, Arizona**
 - Jagust, Bandy, Foster, Koeppe, Reiman, others
- **Biomarkers Core – Penn**
 - Trojanowski, others
- **Informatics Core – UCLA for QA'd images, UCSD for clinical data**
 - Toga (LONI), others
- **Statistics Core – UCSD**
 - Beckett, Gamst
- **45-50 Sites**
- **Industry Scientific Advisory Board**
 - Snyder, others

ADNI and the ADCs

- **Enrolling interested subjects in brain donation programs?**
- **Subsequently enrolling interested subjects in clinical cores?**
- **Proposal to be presented by John Morris to the ADNI Steering Committee on April 11, 2005**

Anticipated Challenges

Subject recruitment

Subject retention

Imaging upgrades

Informatics

Communication/coordination

Schedule

Conclusions

- **Volumetric MRI & FDG PET have great promise in...**
 - the early detection & tracking of AD
 - the evaluation of putative disease-slowing & prevention therapies
- **ADNI is intended to help fulfill this promise**
- **We recognize the challenges and remain open to your suggestions**

Acknowledgements

- **Our ADNI stakeholders**
 - **Leaders**
 - Mike Weiner, Leon Thal, Cliff Jack, William Jagust
 - Neil Bucholtz, Susan Molchan
 - **Our colleagues**
 - **Our sponsors**
 - NIA (U01 AG024904)
 - NIBIB
 - NIH Foundation, Industry Partners, Alzheimer's Association
- **My research partners**
 - **My colleagues**
 - **My sponsors**
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 - NIMH (R01 MH057899)
 - Alzheimer's Association
 - State of Arizona