ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Structural and functional Imaging as biomarkers in proof of concept trials and as a gene discovery tool

Steven G. Potkin
UC Irvine

ISCTM Disclosure Information

THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

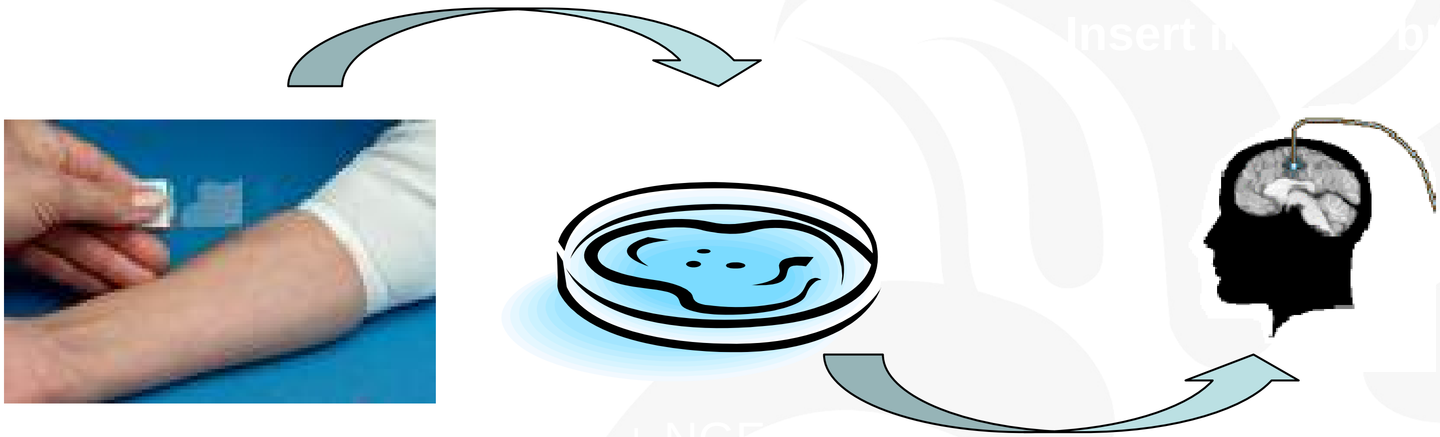
Grant/Funding

- Arena Pharmaceuticals
- AstraZeneca
- Bristol-Myers Squibb
- Diappon Sumitoma
- Elan
- Eli Lilly
- Forest Laboratories
- Janssen Pharmaceutica
- Novartis
- Organon
- Otsuka
- Pfizer
- Sanofi-Synthelabo
- ScheringPlough
- Roche
- Wyeth

Consultancy/Advisory Board/Honoraria

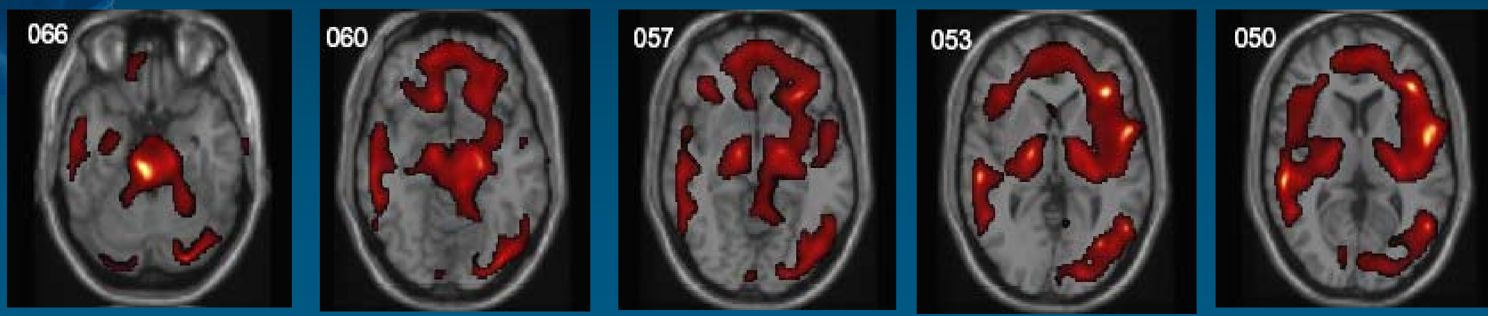
- Arena Pharmaceuticals
- AstraZeneca
- Bristol-Myers Squibb
- Janssen Pharmaceutica
- Novartis
- Organon
- Otsuka
- Pfizer
- Praecis
- Roche
- Vanda
- **Speakers Bureau**
- AstraZeneca
- Bristol-Myers Squibb
- Novartis
- Pfizer
- Otsuka

Gene Therapy: Proof of Concept



FDG PET to Monitor Gene Therapy

6 months low dose



12 months low dose

6 months high dose

Proof of Concept - Gene therapy

Why didn't it work??

Is the THEORY wrong?

Or is it the IMPLEMENTATION?

- **Was the transplantation successful?**
- **Are the gene products located appropriately?**
- **Was the dosing sufficient?**
- **Longitudinally: Is a booster treatment needed?**

GOALS OF ADNI

- To develop "validated surrogate markers" for early detection and to monitor progression of AD
- To develop improved biomarkers for AD clinical trials
- To validate these biomarkers by correlating with clinical progression/autopsy
- Funding $67 mil: $40 mil NIH, $27 M private

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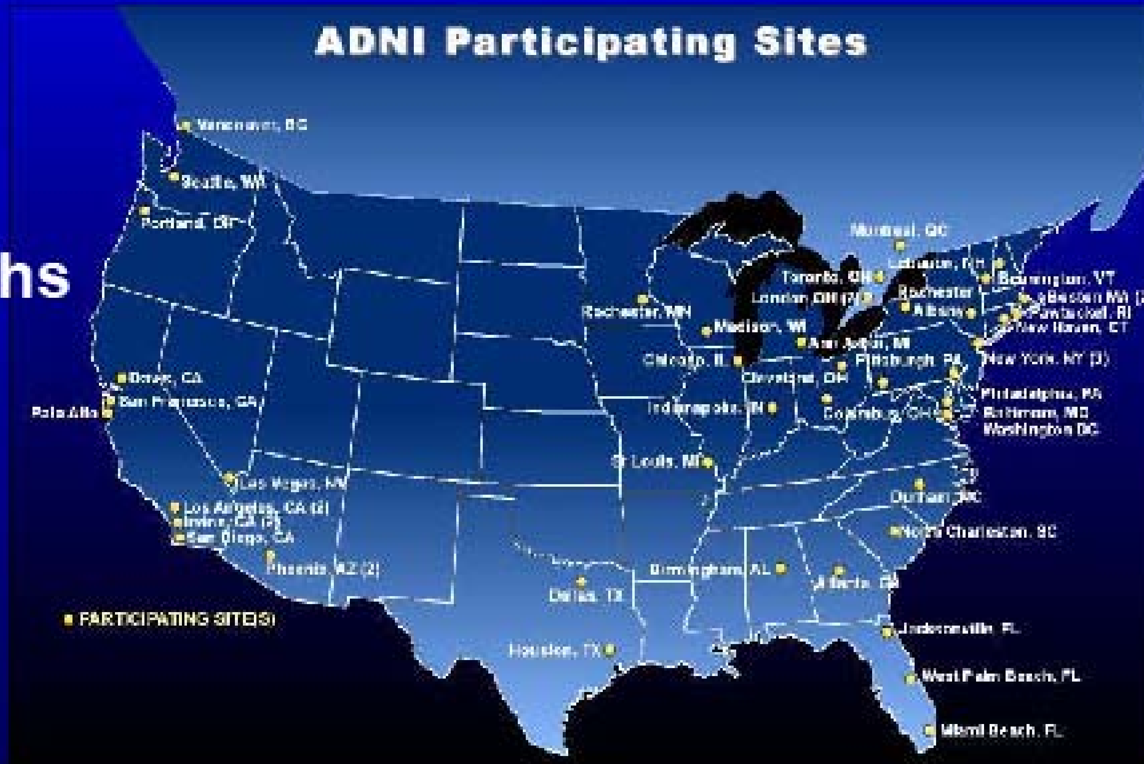
ADNI Sample

- Normals: MMSE 24-30; non-depressed
- MCI: cognitive impairment confined to memory complaint and objective loss on WMS-R with preserved ADLs
- Mild AD: MMSE 18-26; NINDS ADRDA probable AD

ADNI

Naturalistic study of AD progression

- 200 NORMAL 3 yrs
- 400 MCI 3 yrs
- 200 AD 2 yrs
- Visits every 6 months



- 57 sites
- Clinical, blood, LP
- Cognitive Tests
- 1.5T MRI

Some also have

- 3.0T MRI (25%)
- FDG-PET (50%)
- PiB-PET (approx 100)

Baseline Summaries

	n	ADAS-Cog	MMSE	CDR SOB
NL	229	6.11 (2.86)	29.11 (1.00)	0.03 (0.12)
MCI	390	11.08 (4.23)	26.98 (1.79)	1.62 (0.88)
AD	185	16.75 (5.75)	23.31 (2.03)	4.35 (1.59)
Overall	804	10.95 (5.75)	26.74 (2.67)	1.80 (1.83)

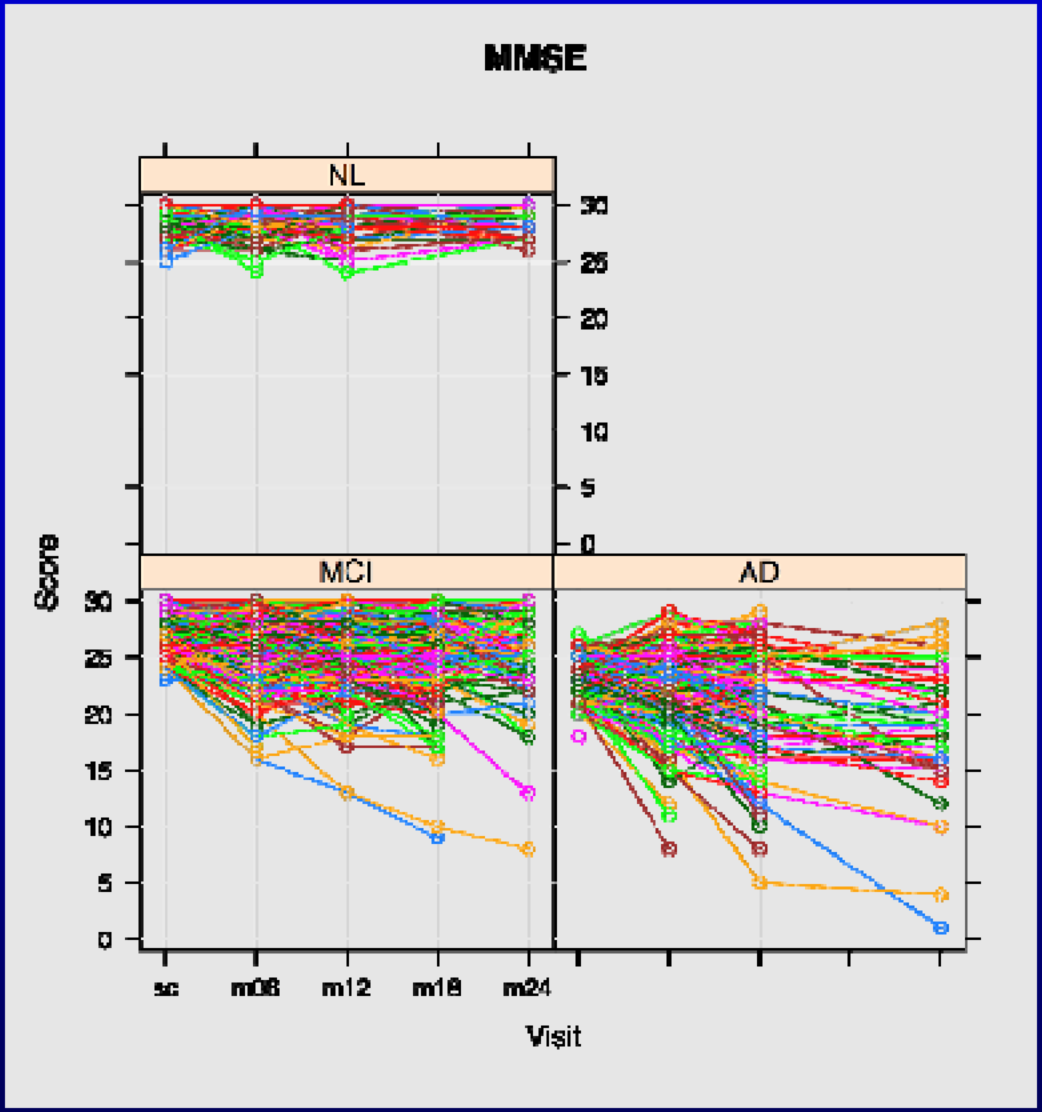
mean (sd)

BIOSTAT CORE: Laurel Beckett, Danille Harvey, Anthony Gamst, Mike Donohue

POWER COMPARISONS

POWER OF CLINICAL/COGNITIVE TESTS
25% CHANGE 1YR STUDY (2 ARM)

Cognitive test	Sample size: AD	Sample size: MCI
CDR sum of boxes	424	764
ADAS-COG 11	467	1982
Verbal learning 5 trials	849	8297



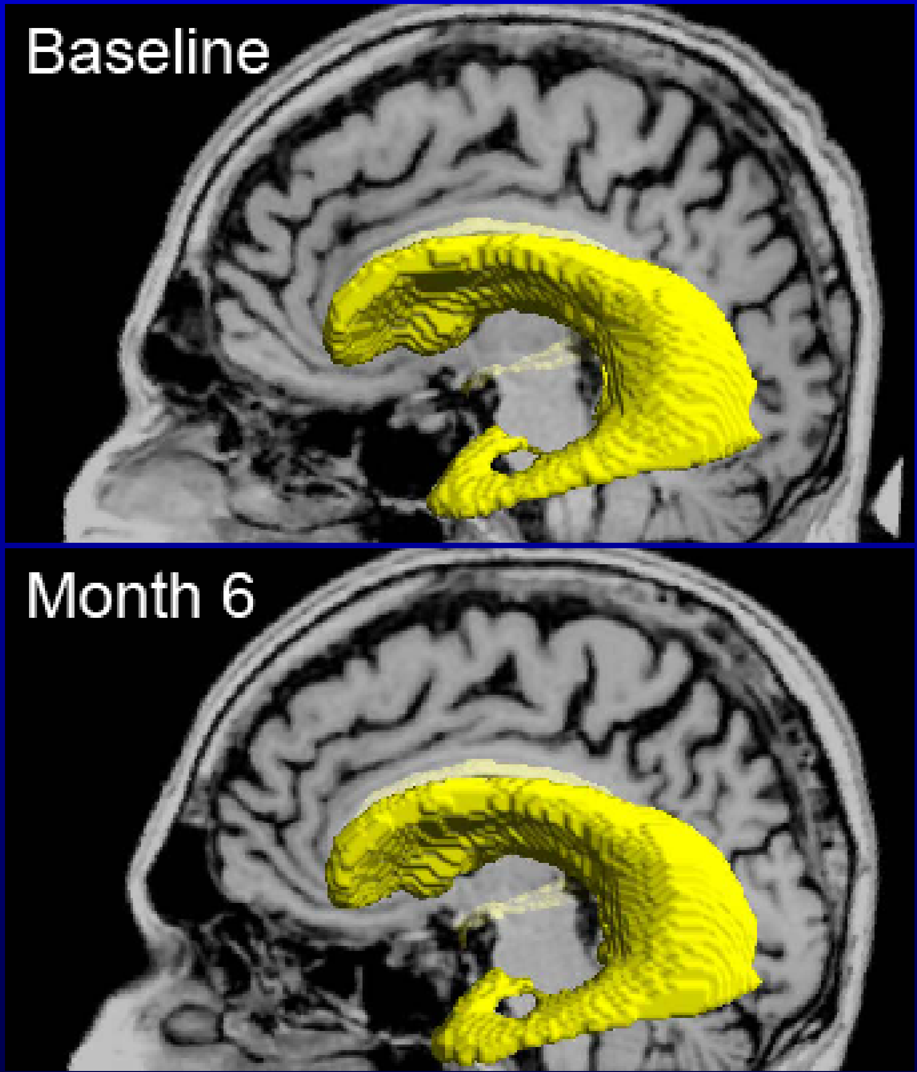
MCI → AD 26%

AUTOMATED VENTRICULAR VOLUME

Nestor, Bartha, Borrie

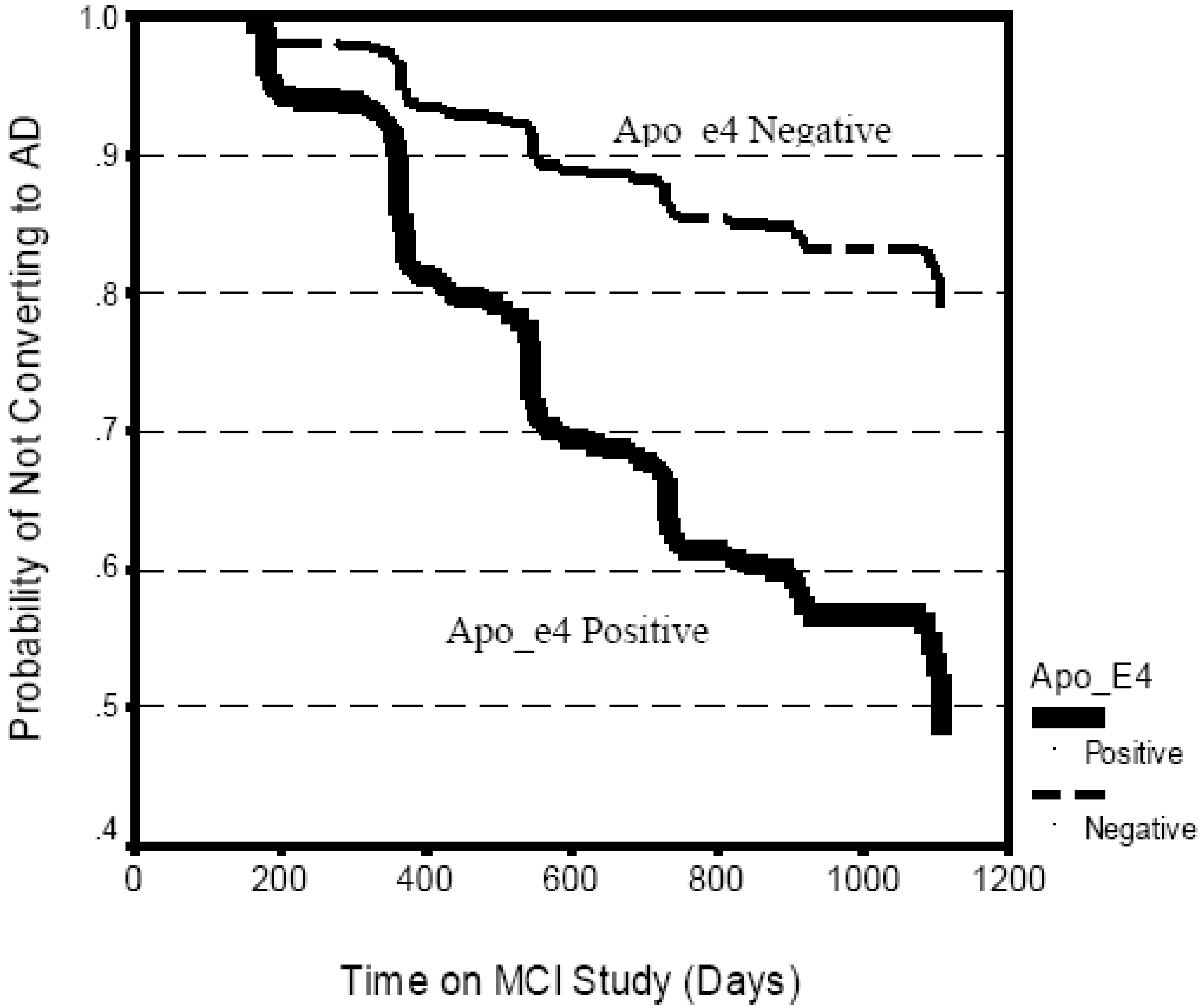
Group	Absolute Change (cm^3)	Percent Change
NEC	**0.6 ± 1.4***	**1.5 ± 4.3***
MCI	**1.6 ± 2.4***	**3.4 ± 6.1***
AD	**2.6 ± 2.0***	**5.7 ± 4.9***

* All groups significantly different ($p<0.01$)

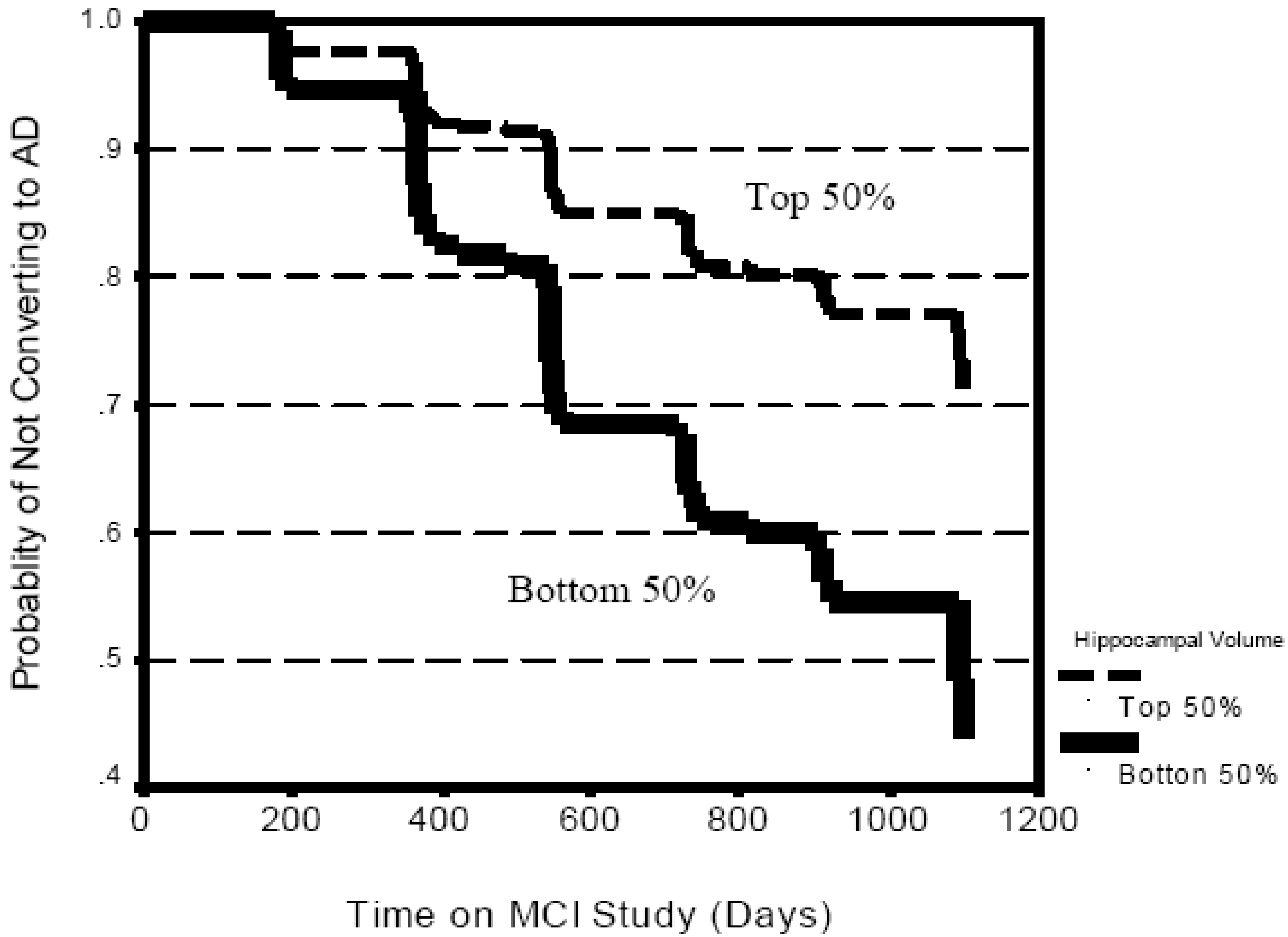


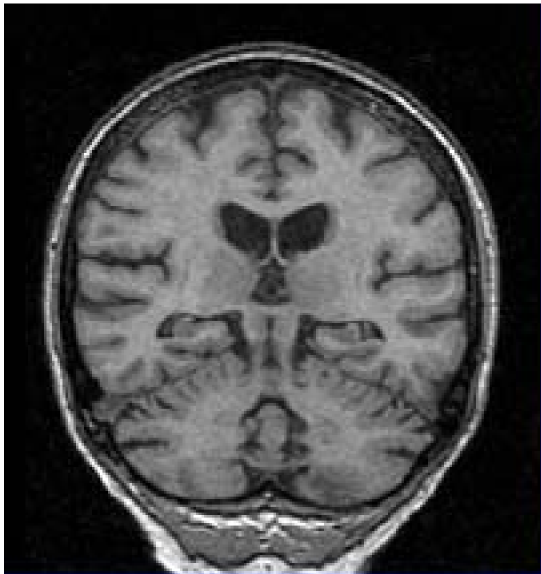
Nestor, S., *et al.*, Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's Disease Neuroimaging Initiative database. Brain. Published July 11, 2008, doi:10.1093/brain/awn146

APOE4 and Transition

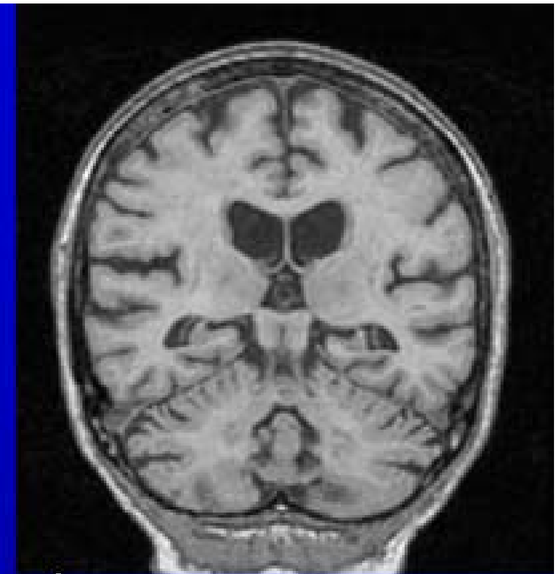


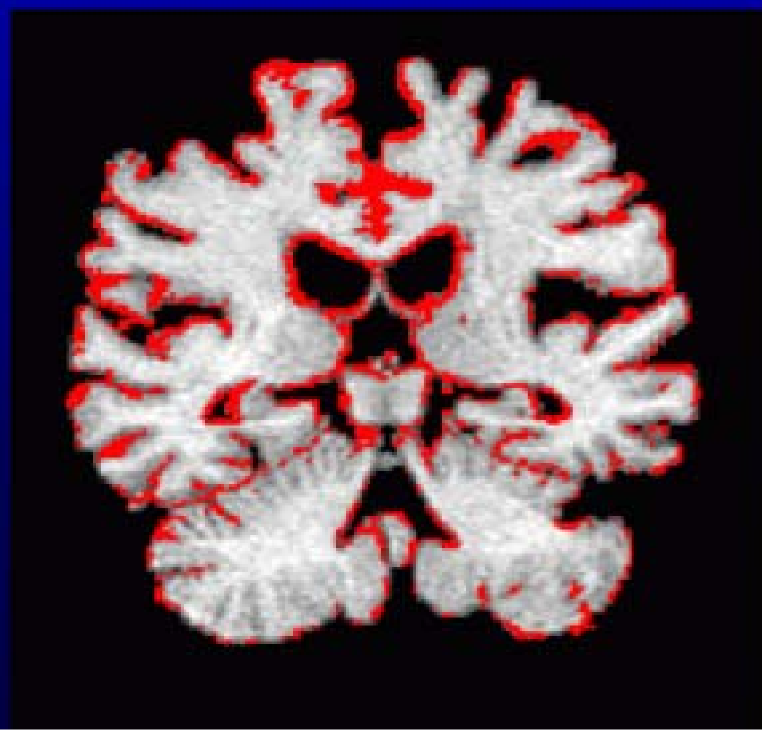
Hippocampal Atrophy and Transition





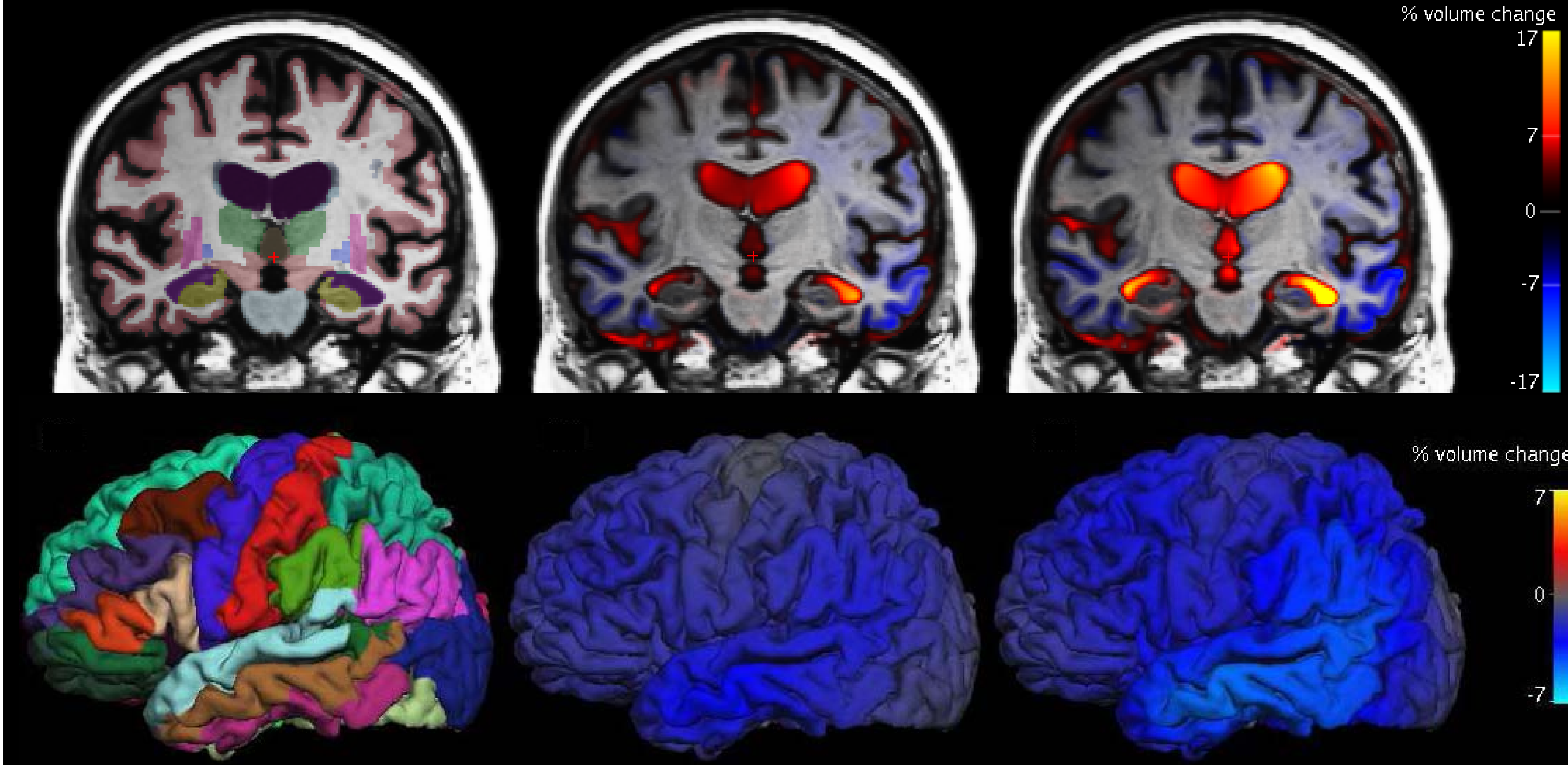
Boundary Shift Integral
Nick Fox et al





Quantification of Longitudinal Change

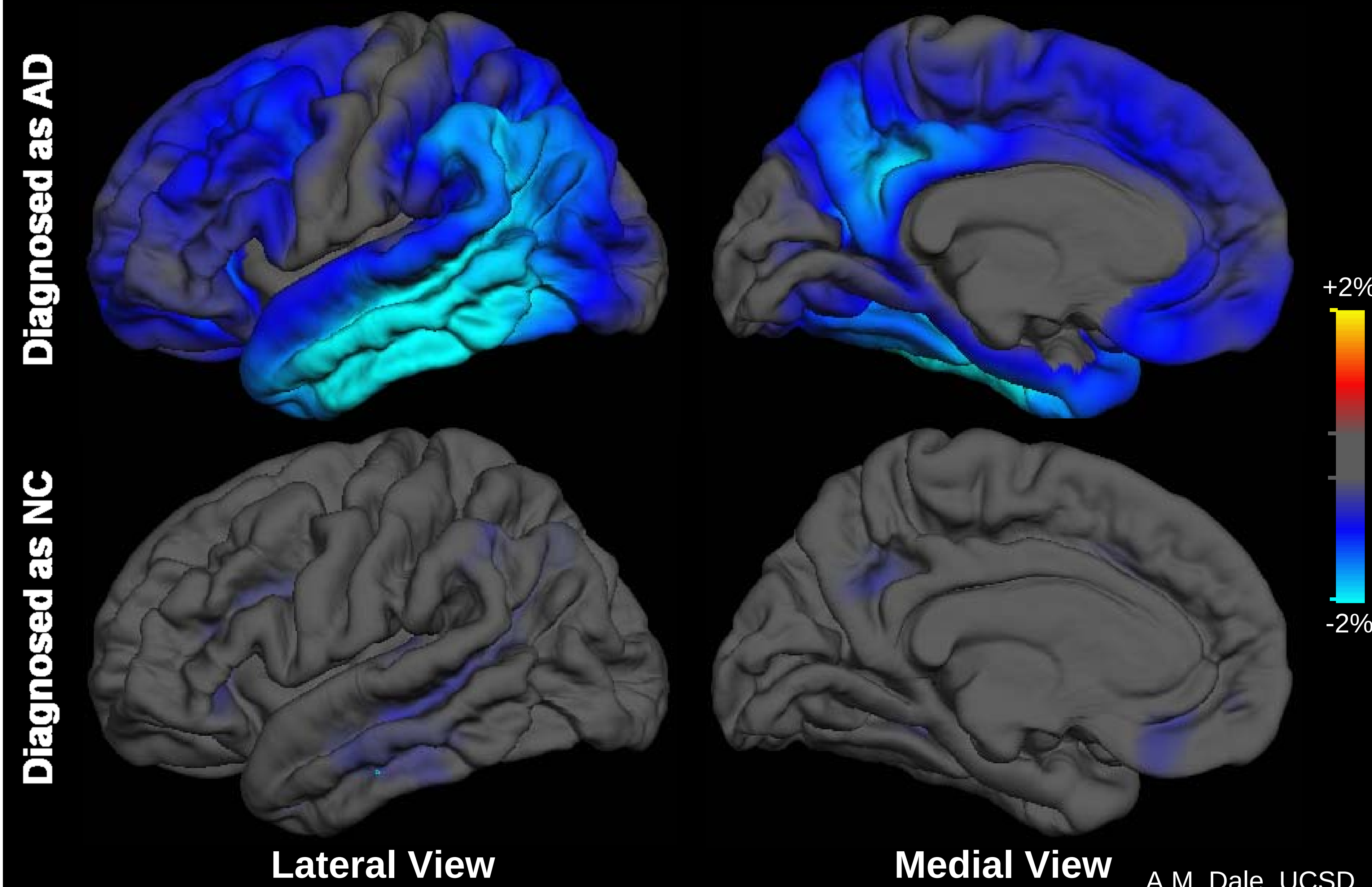
Individual ADNI Subject (70 y.o. Female, Diagnosed with MCI)



Anatomical Segmentation **Change over 6 Months** **Change over 12 Months**

A.M. Dale, UCSD

Mean Cortical Thickness Change over 12 Months



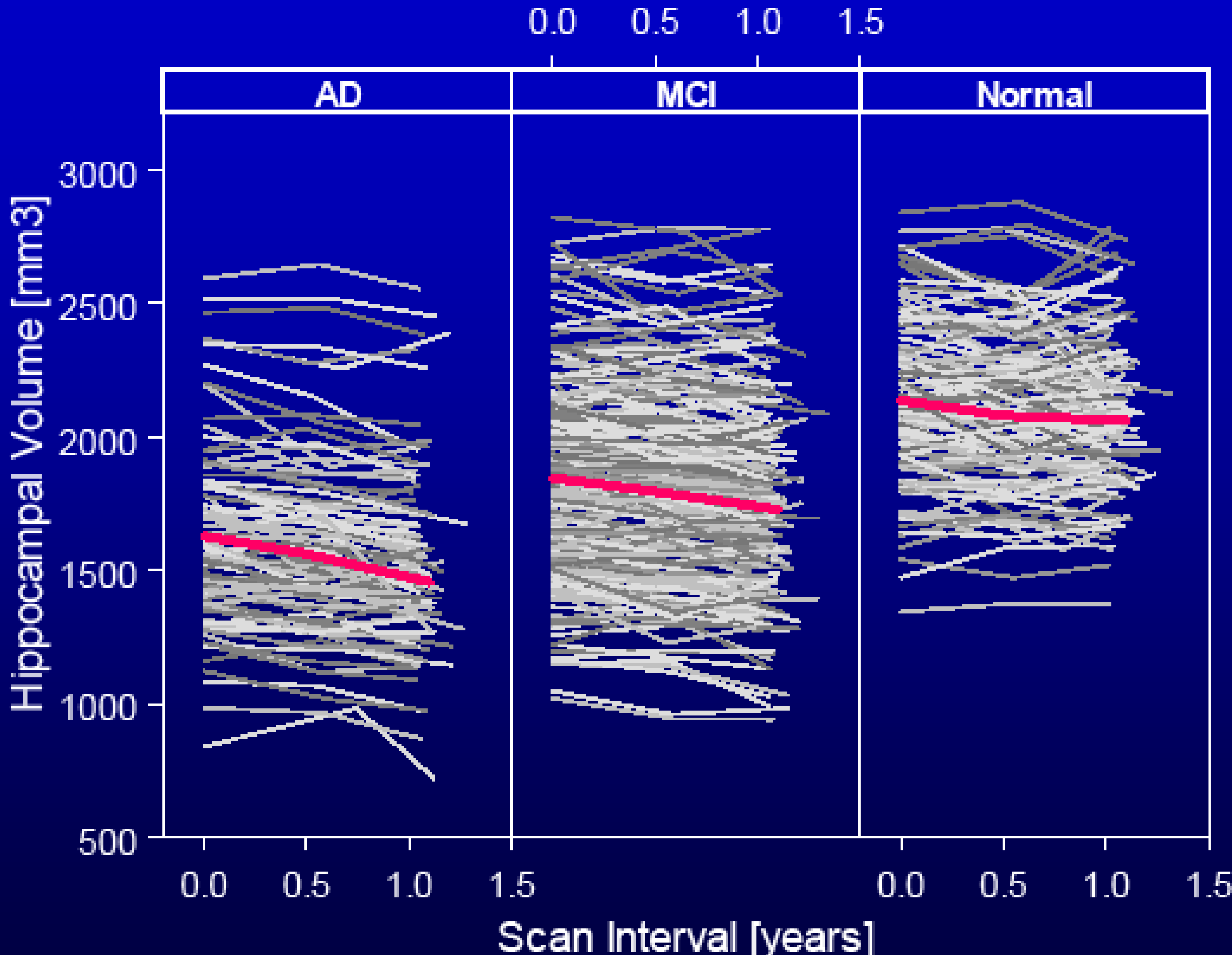
A.M. Dale, UCSD

Rates of Hippocampal Volume Loss

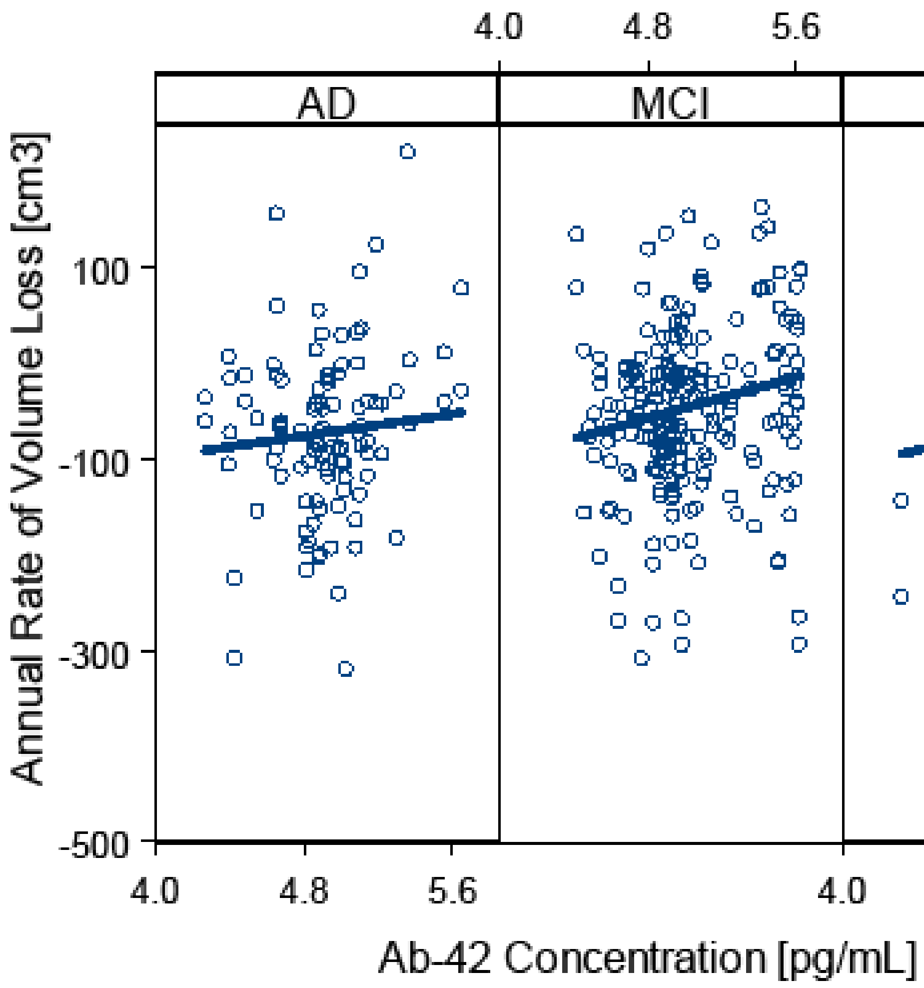
	Normal	MCI	AD
Baseline [mm^3]			
Left	2115 ± 26	1810 ± 24	1600 ± 34
Right	2158 ± 28	1880 ± 25	1656 ± 38
Rates [mm^3/year]			
0 – 6 month	**(-1.2%)**	**(-2.7%)**	**(-3.8%)**
Left	-27.3 ± 18.1	-48.2 ± 11.6*	-56.8 ± 15.0*
Right	-28.1 ± 18.0	-52.2 ± 11.6*	-76.5 ± 19.2*
6-12 month	**(-0.8%)**	**(-2.9%)**	**(-6.3%)**
Left	-19.5 ± 22.4	-51.0 ± 12.4*	-112.7 ± 18.0*
Right	-17.5 ± 24.7	-62.7 ± 14.1*	-97.5 ± 21.3*

Presented at ICAD in a Talk: APOE 4 session

Individual Trajectories of Hippocampal Volume Loss



Effects of CSF Ab-42 (log transformed) on annual rate of hippocampal atrophy.



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Estimated sample size for 25% slope reduction, AD (n=34)

Lab	MRI Measure	Sample size / gp
Dale	Left Mid Temporal	47
Dale	Whole Brain	49
Fox	DBC BSI % Change	61
Studholme	% Change (Temporal)	70
Dale	Left hippo	68
Dale	Ventricles	88
Fox	Ventricles/Brain	96
Schuff	Avg hipp vol	160
Alexander	Left Mid Temporal	184
Thompson	Avg Jaco Pre-sp Temp	275
Alexander	Left Hippo Formation	336

Estimated sample size for 25% slope reduction. MCI (n=76)

Lab	MRI Measure	Sample size / gp
Studholme	% Change (Temporal)	98
Dale	Left Hippo	102
Fox	DBC BSI % Change	118
Dale	Whole Brain	125
Fox	Ventricles/Brain	130
Dale	Ventricles	156
Alexander	Left Mid Temporal	213
Alexander	Left Hippo Formation	230
Dale	Left Mid Temporal	252
Thompson	Avg Jaco Pre-sp Temp	536
Schuff	Avg hipp vol	732

Correlations of change in MRI with change in ADAS-COG: AD

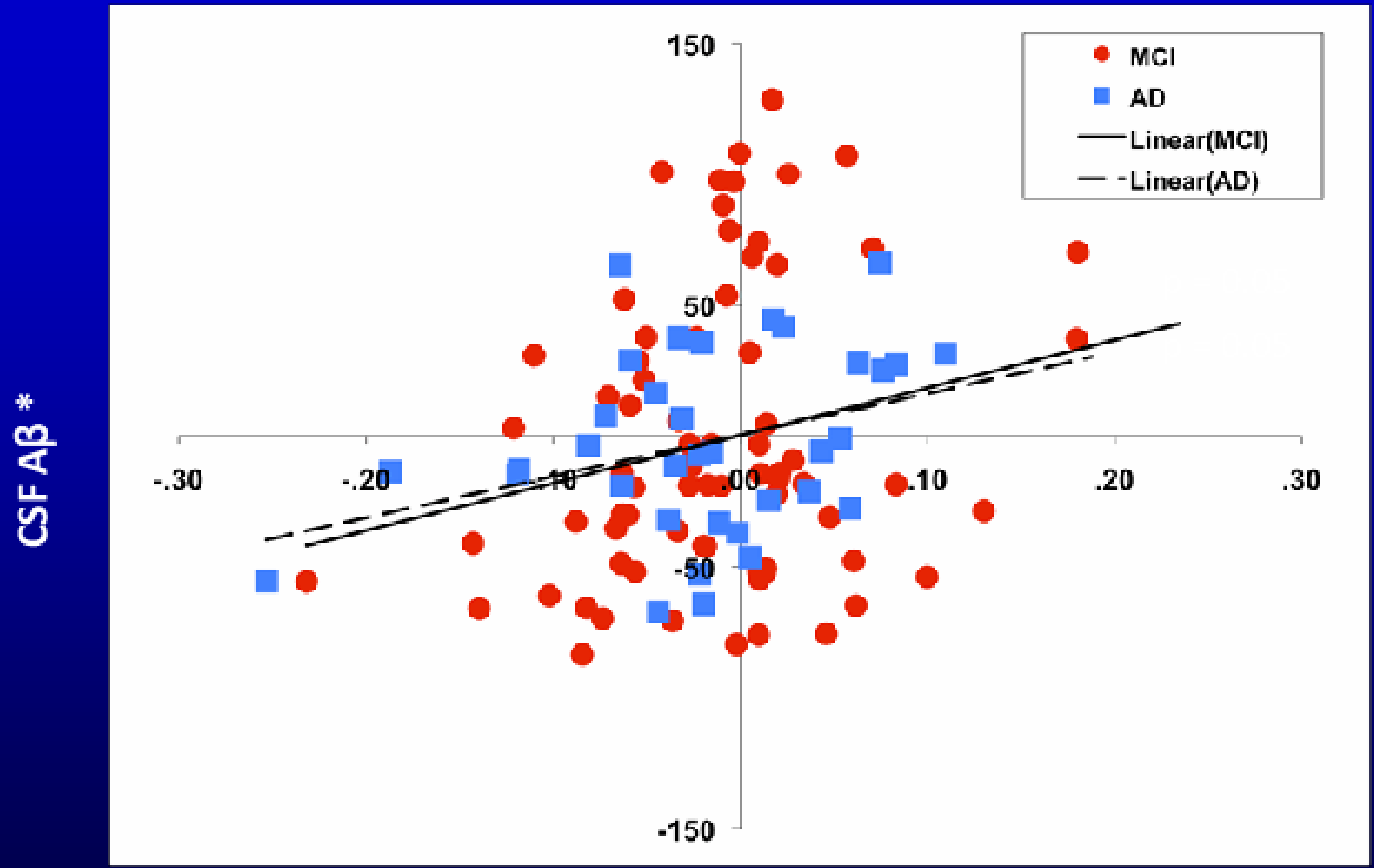
Lab	Measure	Correlation
Dale	Whole Brain	-0.57
Studholme	% Change (Temporal)	-0.21
Dale	L Mid Temp	-0.38
Fox	DBC BSI % Change	0.33
Schuff	Avg Hippo	0.23
Dale	R Hippo	0.24
Alexander	L Hippo Formation	0.17
Fox	Ventricles/Brain	0.18
Dale	Ventricles	0.14
Thompson	Avg Jacobian (Temporal)	0.11
Alexander	Mid Temp	0.09

Data-driven regions improve over pre-specified ROI in voxel-based methods (TBM and VBM)

Lab	MRI Measure	Sample size/gp	
		AD	MCI
Thompson	Avg Jaco Pre-Sp Temp	275	536
Thompson	TBM region	67	73
Alexander	L Mid Temp (Pre-sp)	184	213
Alexander	L Hippo Formation (Pre-sp)	336	230
Alexander	VBM region	40	77

Results for data-driven regions not directly comparable until validated independently on separate test set

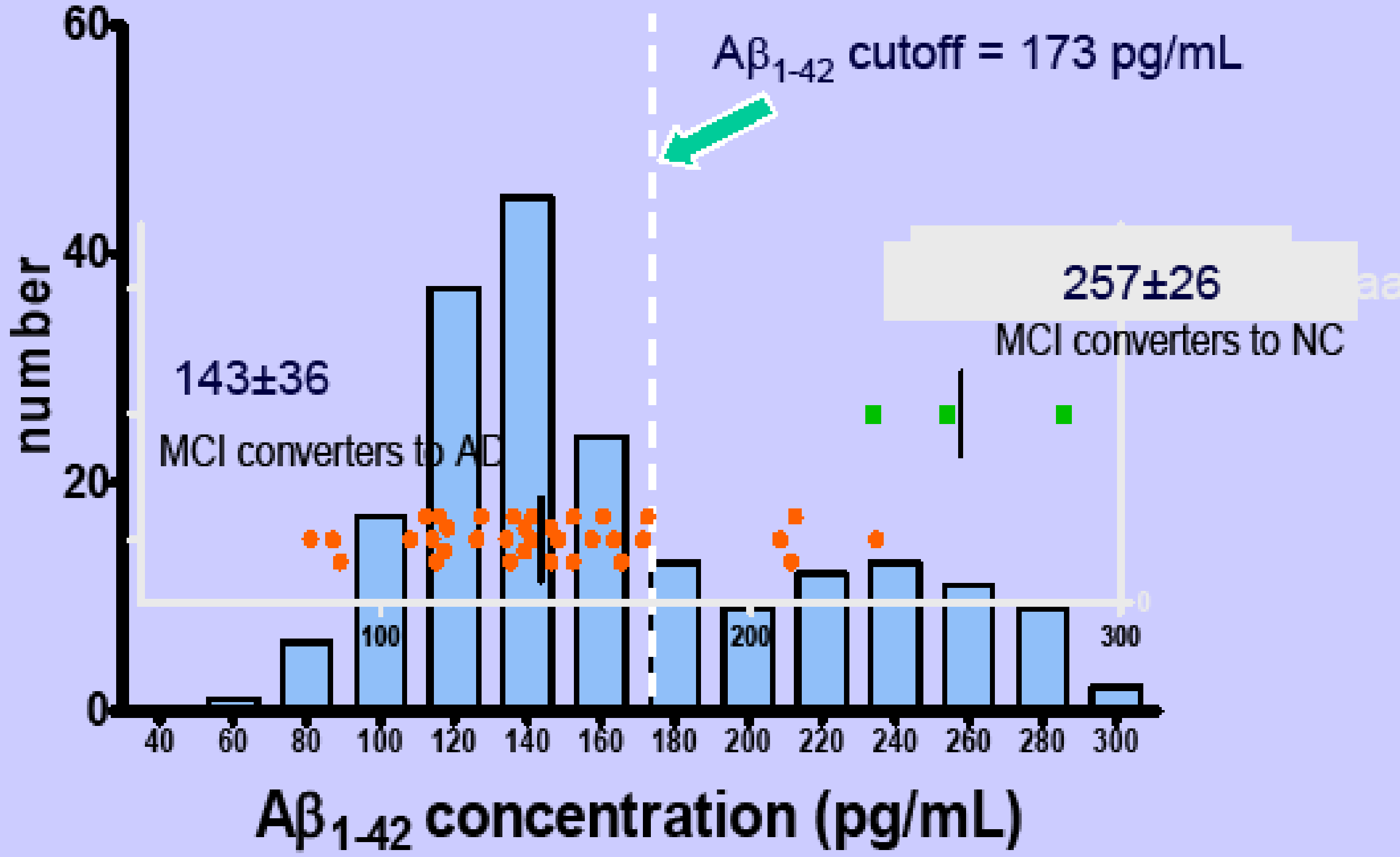
Change in Right Temporal ROI correlates with CSF Aβ for MCI *and* AD patients



← Greater decline   Right Temporal ROI change*   Less decline →

*corrected for age, education, and baseline Right Temporal mean

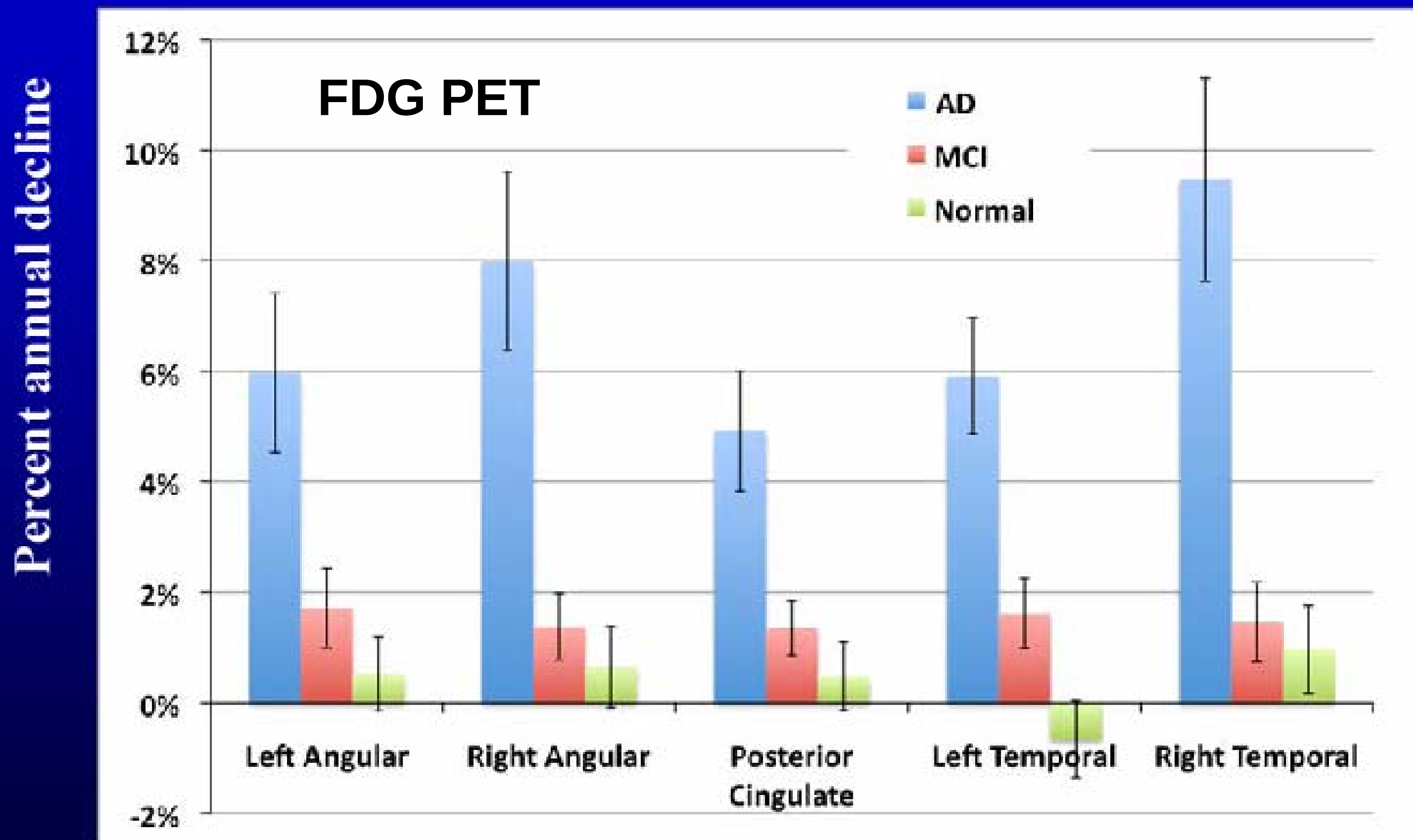
MCI converters to AD at YEAR 1(n=34)



Aβ 42 Quartiles and Annual Brain Change (2 Labs)

	< 159.2 (worst)	**(159.2, 217)**	**(217, 252.8)**	**> 252.8 (best)**
Dale	-7986 (8932)	-1892 (3800)	-3204 (5470)	-4455 (4980)
Fox	-11.9 (13.4)	-3.2 (12.7)	-5.3 (9.5)	-5.3 (10.3)

AD Patients show greater annual decline in glucose metabolism than MCI or Normal subjects

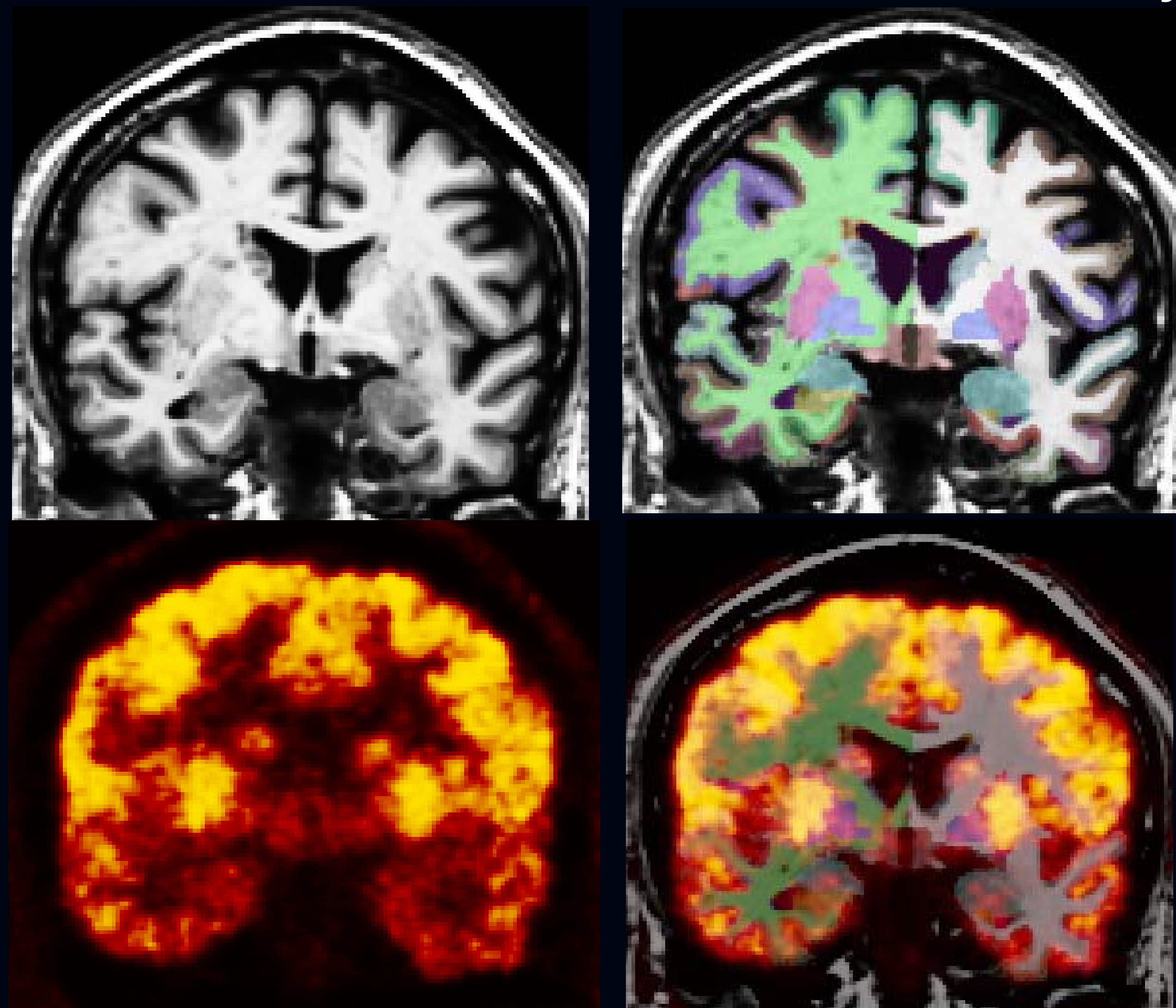


Structural ROIs Applied to FDG PET

"Raw" | FreeSurfer ROI Overlay

MRI

PET



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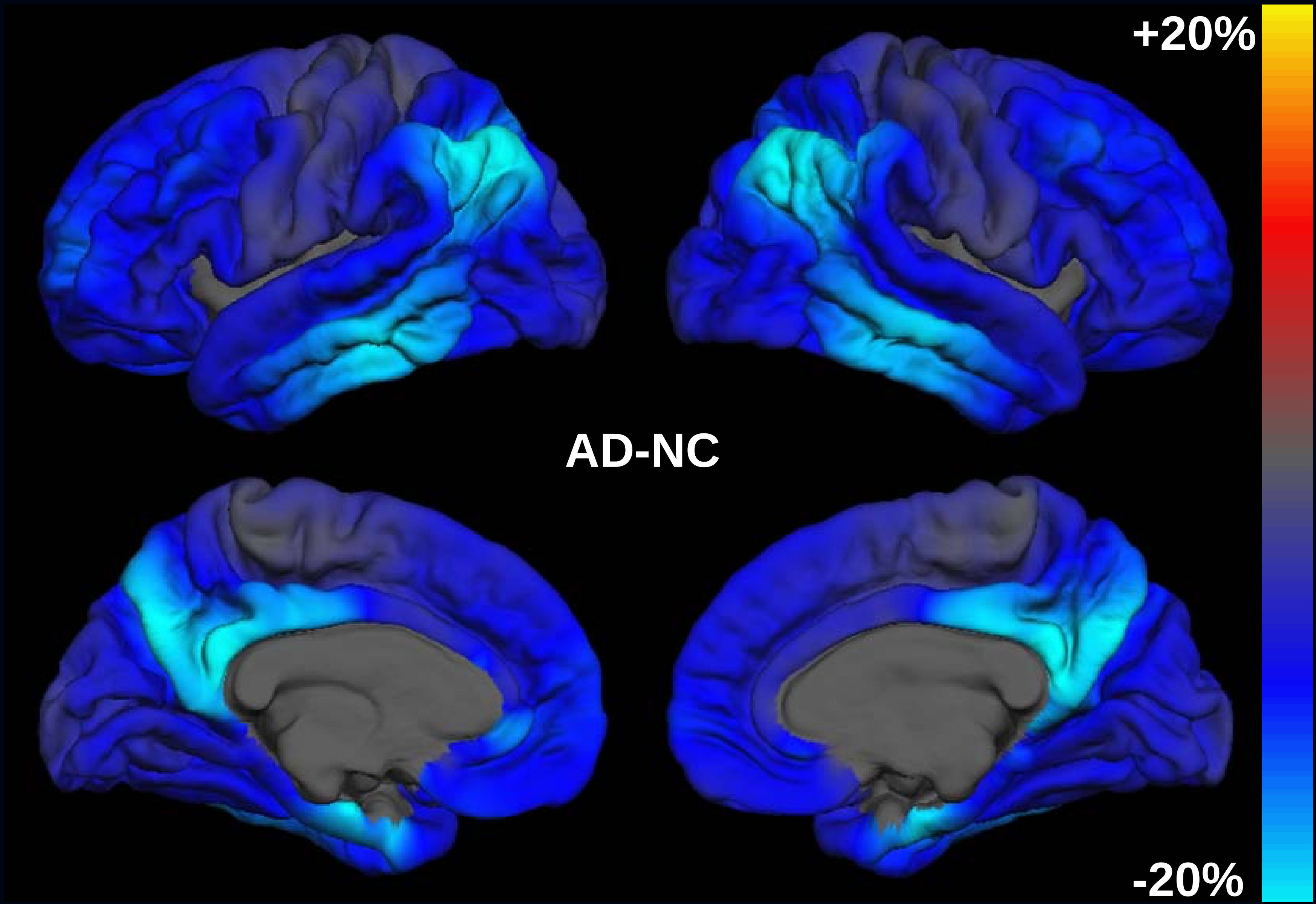
Cross-Sectional FDG PET Difference in ADNI



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Estimated sample sizes to detect 25% reduction in rate of FDG PET change: AD (n=32)

Laurel Beckett, Danielle Harvey: Biostat Core

Lab	PET Measure	Sample size / gp
Reiman	Functional ROI	160
Foster	Pixels > 3SD below NL	403
Jagust	Right Angular	513
Jagust	Right Temporal	566
Foster	Pixels > 2 SD below NL	910
Jagust	Bilat Cingulum Post	1216
Foster	Average Assoc Cortex	1272
Jagust	Left Temporal	1272
Foster	Avg Front Assoc Cortex	1433
Jagust	Left Angular	2261

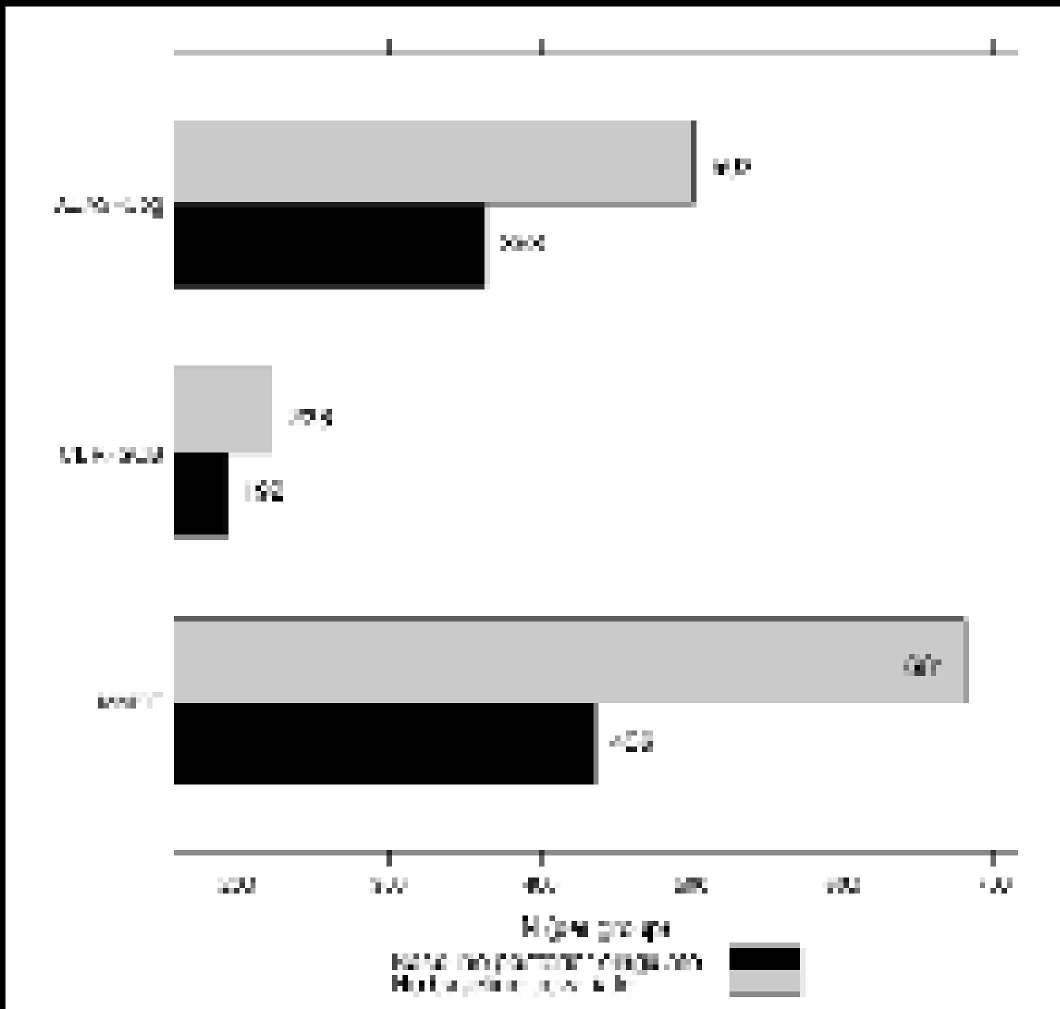
Correlations of change in PET with change in ADAS-COG in AD

Lab	Measure	Correlation
Reiman	Functional ROI	-0.34
Jagust	Bilat Cingulum Post.	-0.26
Jagust	Right Angular	-0.23
Jagust	Left Angular	-0.23
Foster	Avg Front Assoc. Cortex	-0.22
Foster	Avg Assoc Cortex	-0.20
Jagust	Left Temporal	-0.16
Jagust	Right Temporal	-0.06
Foster	>2 SD below NL	0.07
Foster	>3 SD below NL	0.09

Estimated sample sizes to detect 25% reduction in FDG PET change: MCI (n=79)

Lab	PET Measure	Sample size / gp
Reiman	Functional ROI	626
Foster	>3 SD below NL	830
Foster	>2 SD below NL	2033
Foster	Average assoc	3077
Foster	Average frontal	5674
Jagust	Left angular	>10,000
Jagust	Bilat. cing. post.	>10,000
Jagust	Left temporal	>10,000

Baseline Posterior Cingulate Metabolism Lowers Sample Size in MCI



- Random effects model for data at baseline, 6, 12, 18 and 24 months
- Inclusion of baseline posterior cingulate metabolism as a covariate increases power

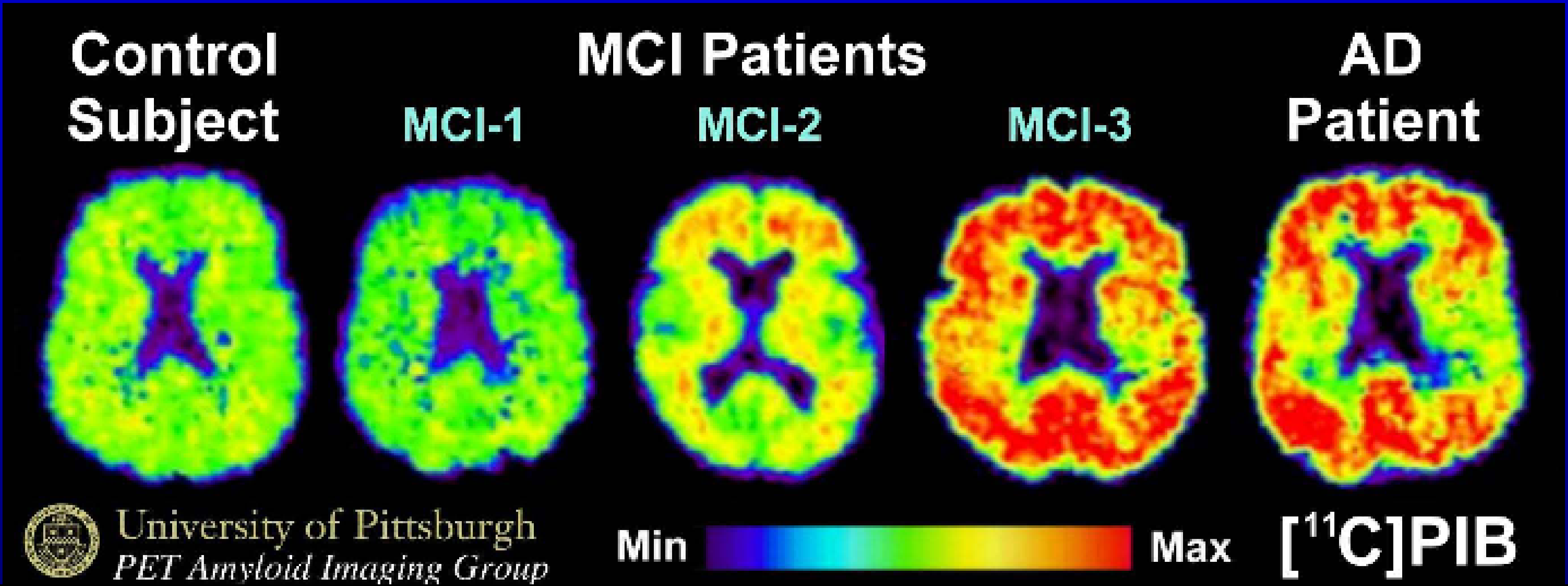
Number of patients per group needed to detect a treatment effect in a functionally defined ROI (P=0.05) with 80% power using FDG PET in a 12-month RCT*

	Treatment Effect				
	20%	25%	30%	40%	50%
AD (n=22)	62	40	28	17	11
MCI (n=64)	633	406	283	159	103

*The estimates exclude scans from the HRRT & HiRez Biograph systems.
The MCI-related ROI has not been optimized yet, which may increase statistical power furthe

PIB in Controls, MCI, AD

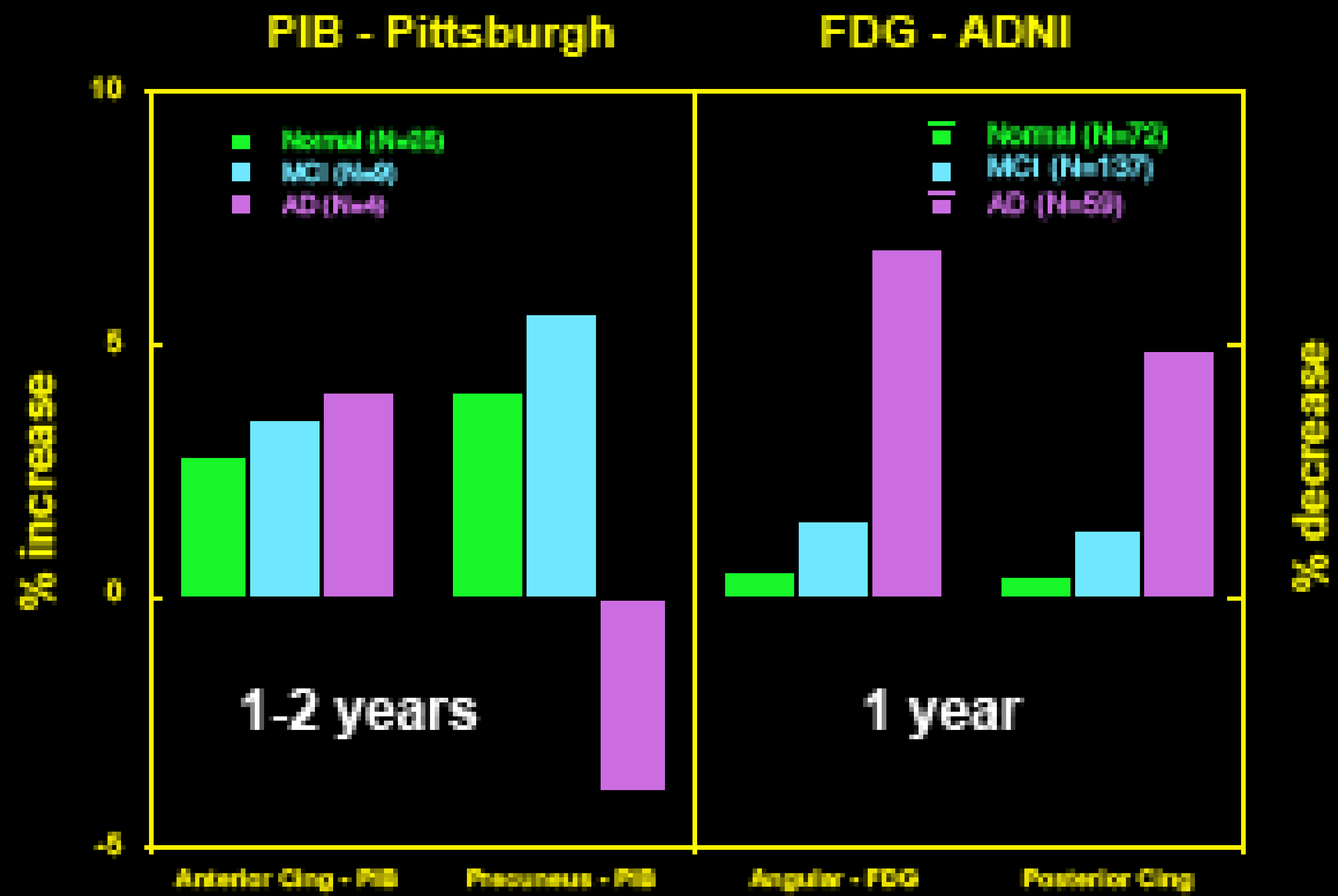
Chet Mathis, U Pittsburgh



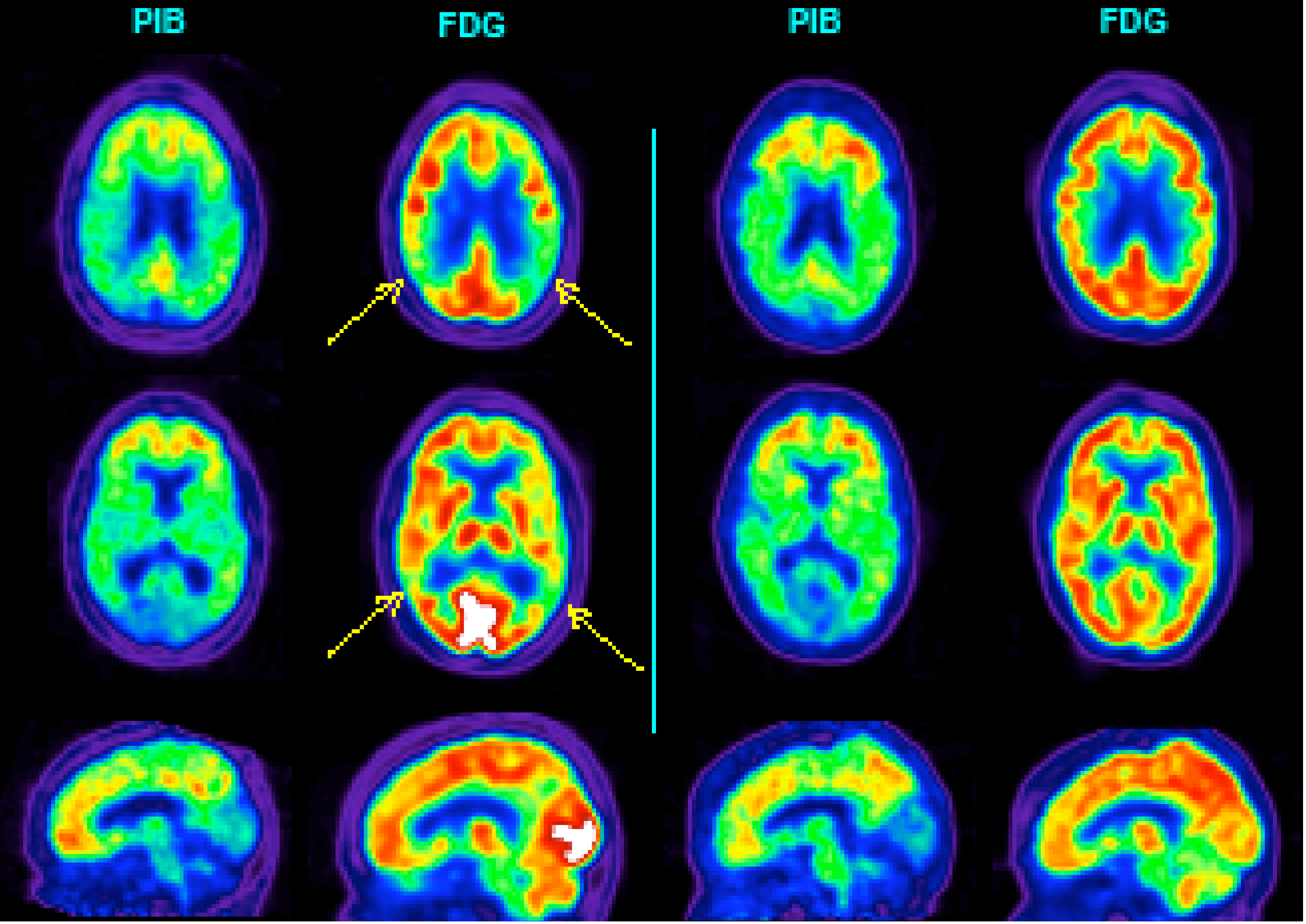
Some MCI's have control-like PIB retention, some have AD-like retention, and some have intermediate retention

Price et al., JCBFM 2005
Lopresti et al., J Nucl Med, in press

Longitudinal Change PIB and FDG



Demented or Not?



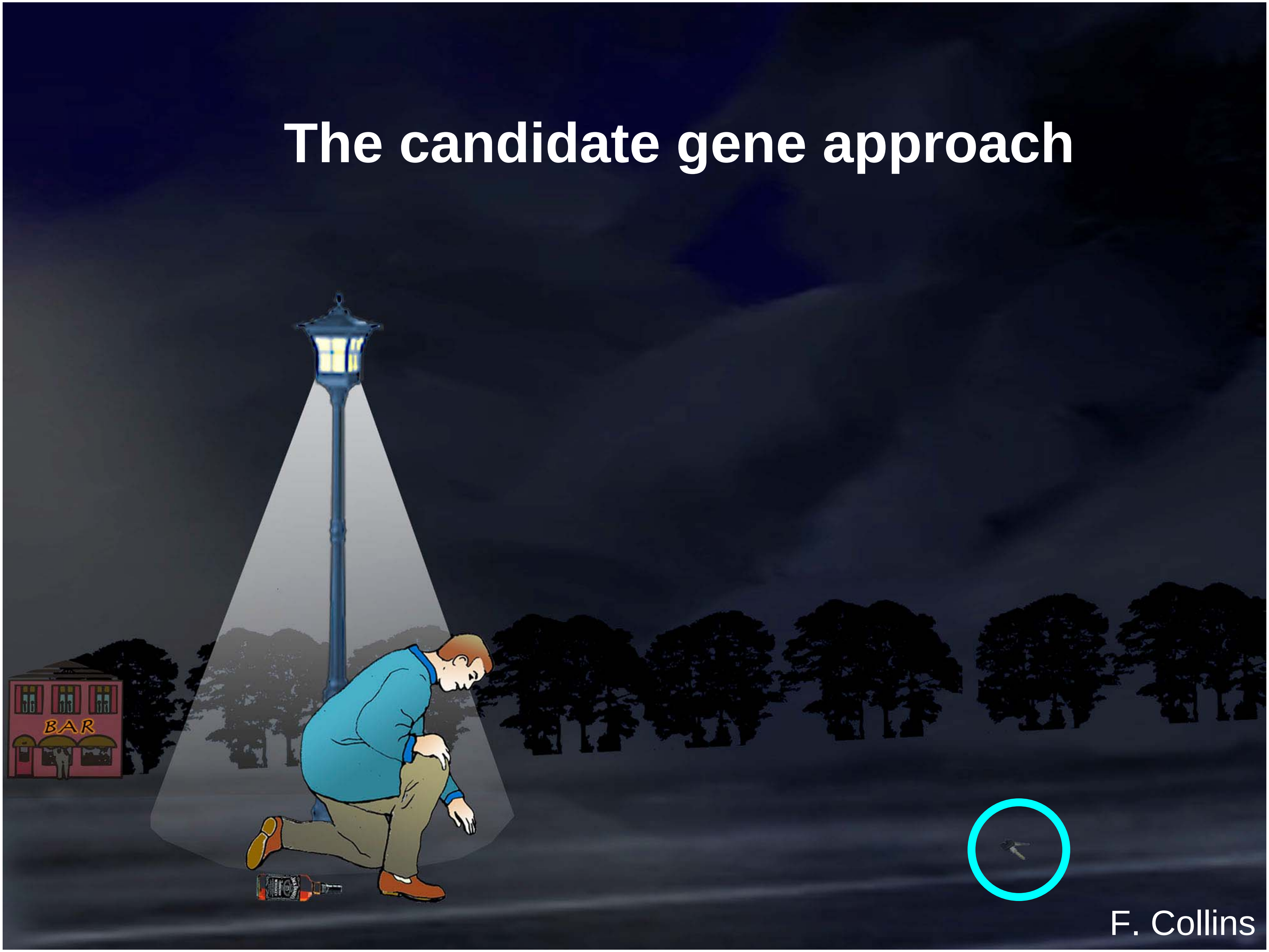
Imaging Genetics

Imaging Genetics: combination of imaging, genetic and clinical data

- Candidate approach begins with a gene of interest and use brain imaging to understand the gene effects
- Imaging as a strategy to find unknown risk genes

  Fundamentally different from a standard candidate gene approach

  New approach uses brain imaging as a quantitative phenotype and identifies which SNP influence it in the context of a GWAS


The candidate gene approach
BAR
F. Collins


The genome wide association approach
F. Collins

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New Approach Quantitative Trait

Imaging Phenotype = Genotype + Group + (Genotype *Group)

Imaging Phenotype is activation or volume in ROI

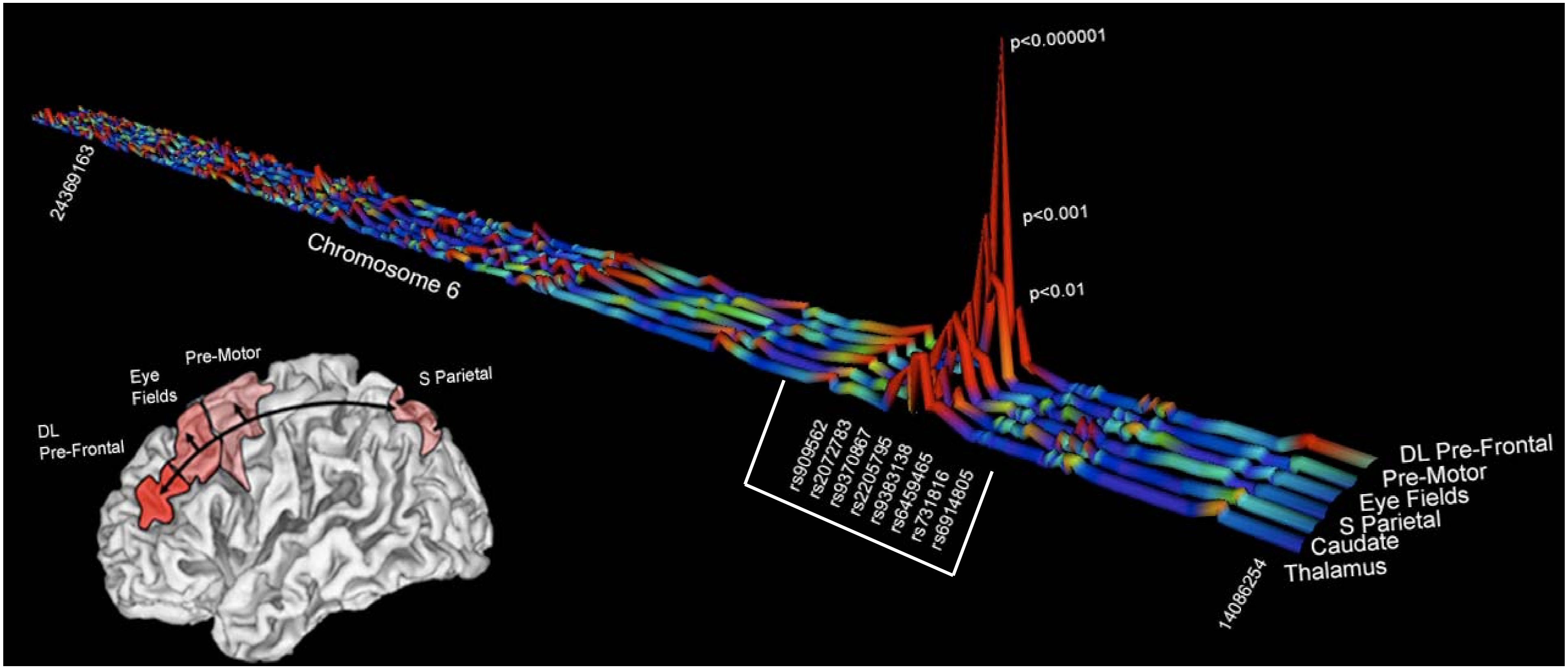
Genotype = SNP_1

Group= converts/noconverters

Determine which SNPs or genotypes influence these functional differences by a series of GLM

GLM can be expanded to consider covariates like age, education, medication, smoking, as well as gene-gene interaction

Genome-wide scans & neuroimaging



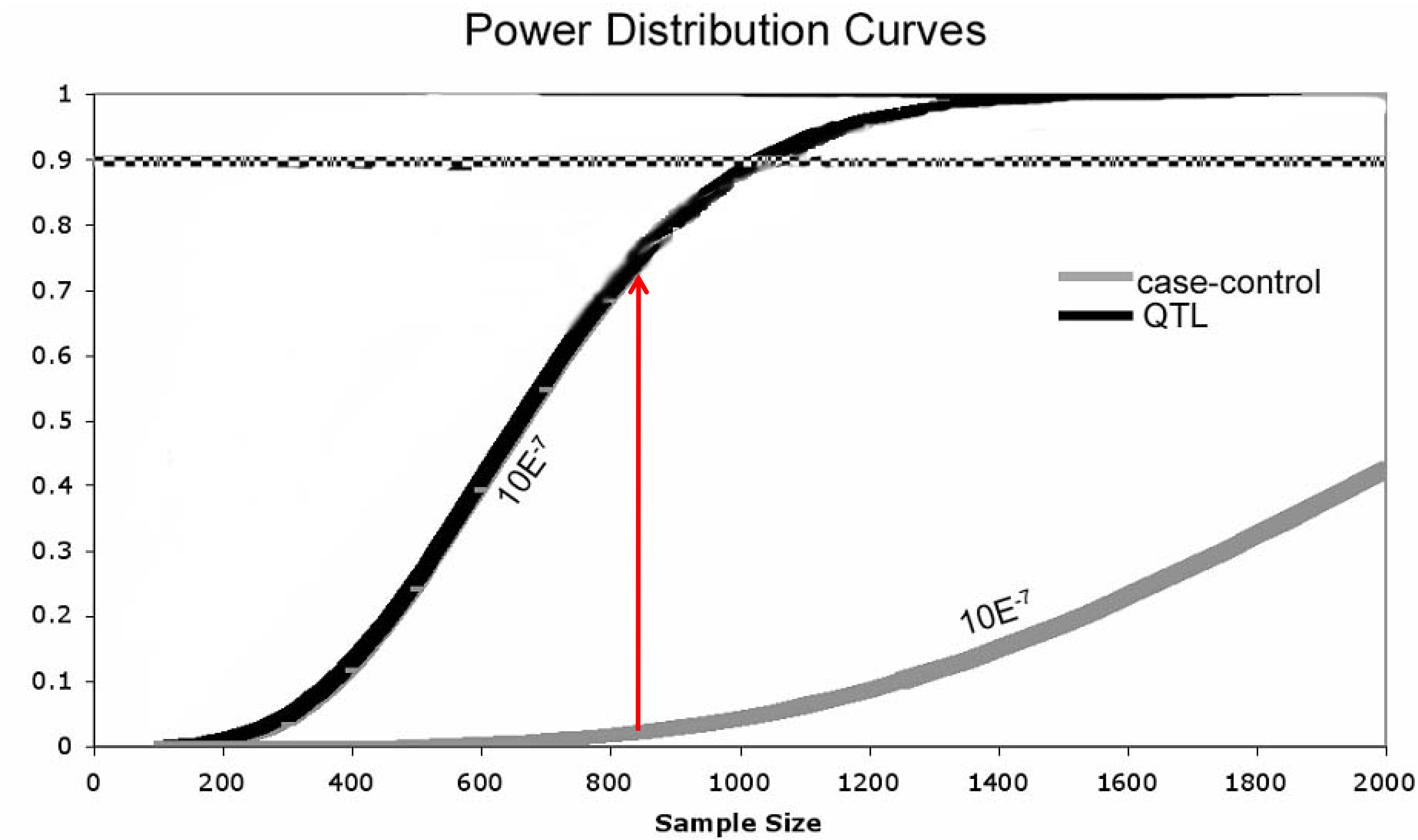
Looking down 10 million base pairs on Chromosome 6 to discover the genes that cause schizophrenia.

<u>New gene detected in white bracket.</u>

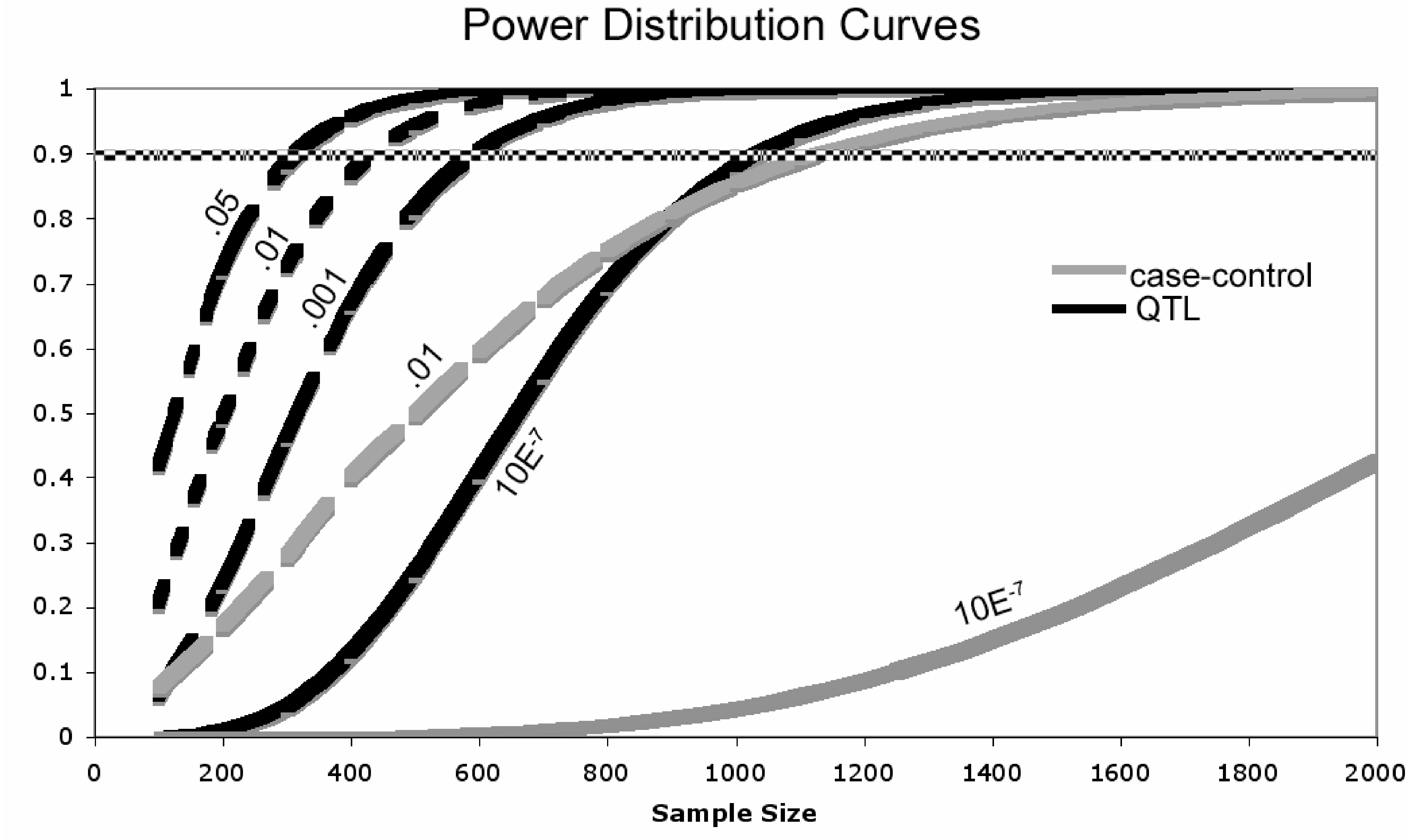
Peaks point to SNPs that influence fMRI brain activation in various brain regions

From: S. Potkin, D. Keator, F. Macciardi, J. Fallon, J. Turner

QTs increase power and reduce needed sample sizes



QTLs increase power and reduce needed sample



Imaging Biomarkers

Proof of Concept: MOA or clinical result

Choose biomarkers based on 'a fit for purpose' :

- •Sample enrichment, drug effect, MOA, supportive data,
- •Surrogate outcome: MRI reflect underlying pathology MS
- •Biomarkers highly correlated: unvariate v multivariate

Discrepancies between biomarkers

- •Diagnosis, severity, progression, MCI v AD

Difficulty in Prespecifying Details of Outcome Measures and Statistical Threshold Details

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Use of Biomarkers

- Biomarker enrichment strategies for clinical trials
  MCI or AD not the same: amyloid imaging, hippocampal atrophy, hypometabolism on PET, and reduced CSF beta amyloid and increased tau; AP0E
- Clinical endpoint not sensitive enough.
- Detection of disease-modifying effects of emerging therapies in presymptomatic or minimally symptomatic populations.