STRUCTURAL MRI IN AD AND MCI TRIALS

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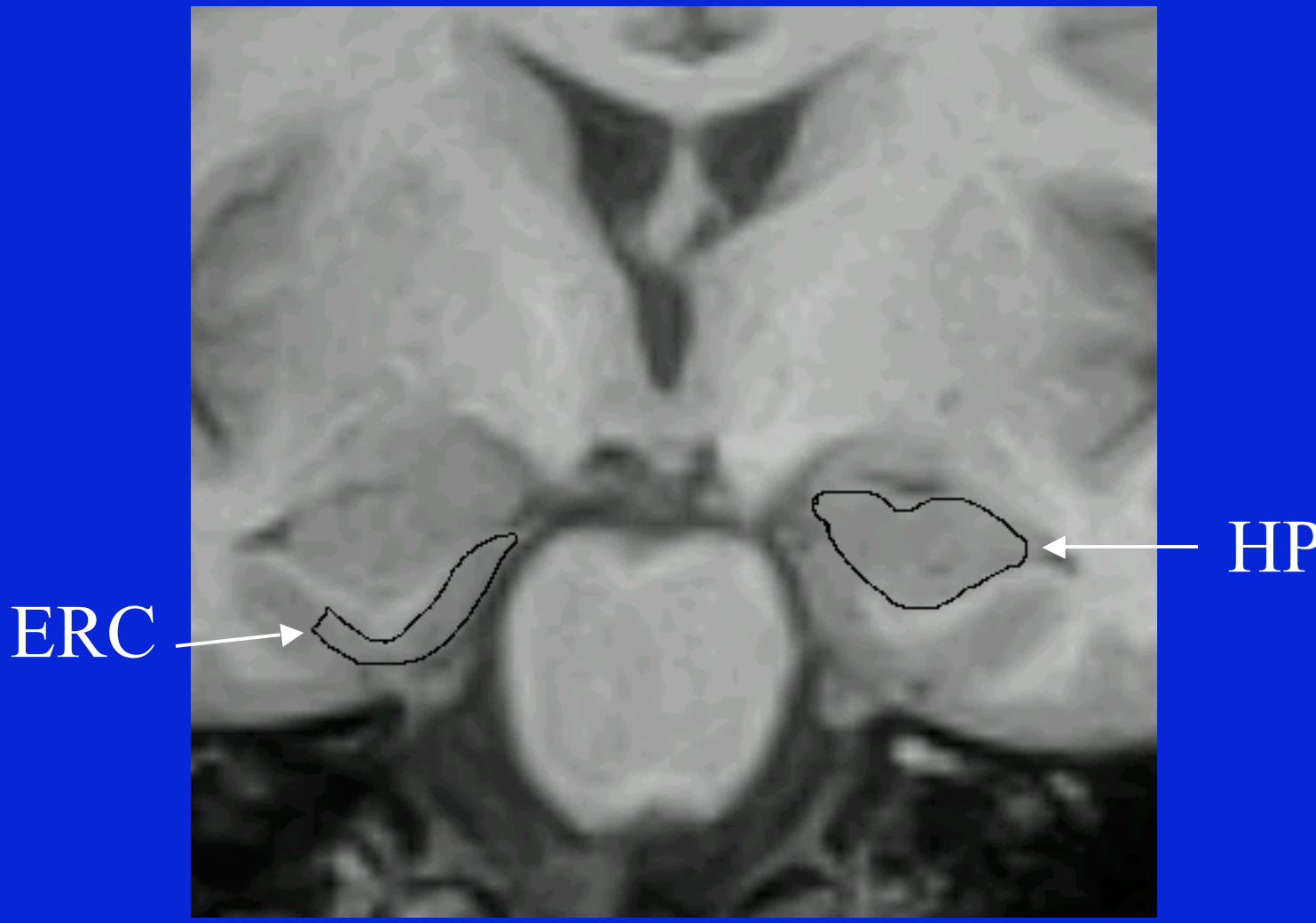
LONG TERM GOAL

- Identify a treatment which slows progression of AD
  - Preclinical development
  - Clinical studies
- Use effective treatments in AD prevention trials

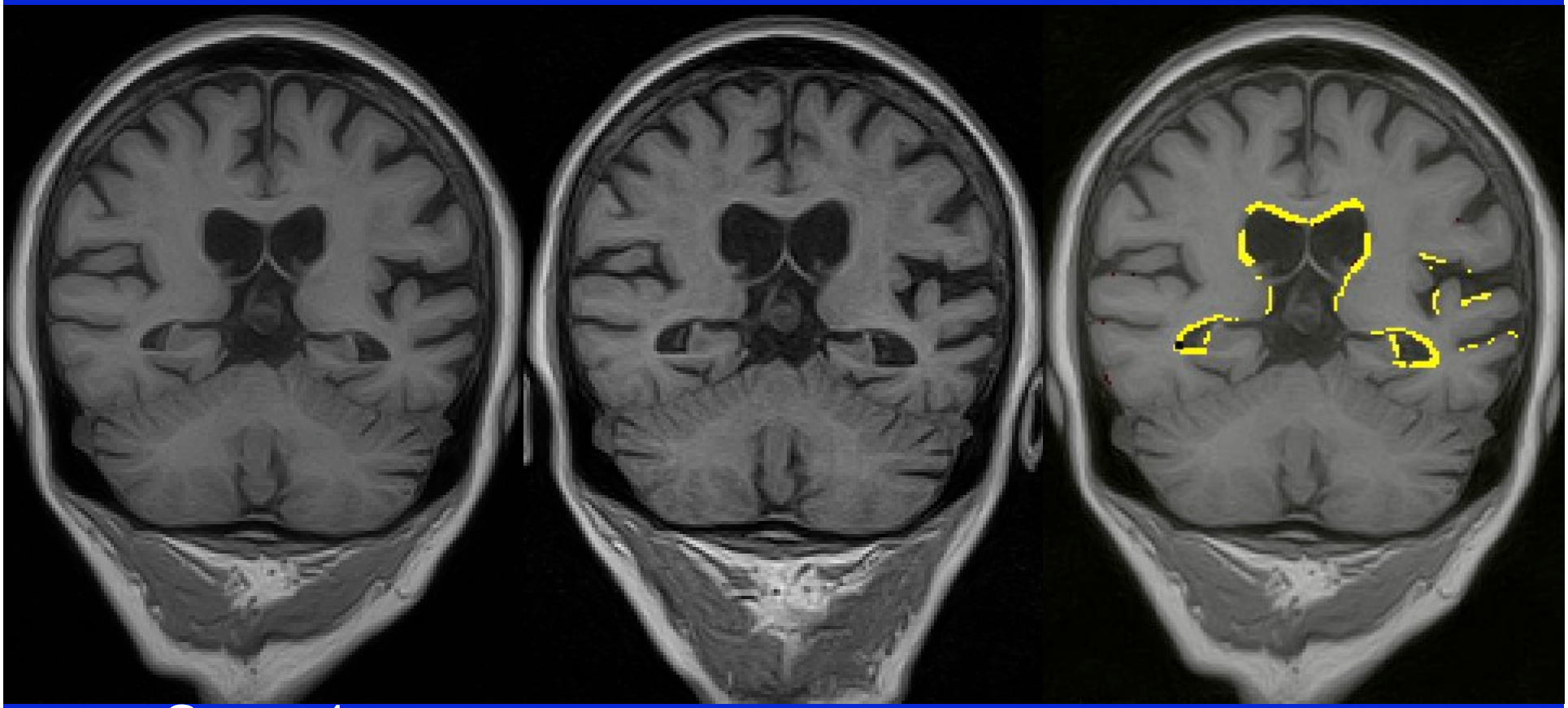
OVERALL MESSAGE

- Neurodegeneration causes brain shrinkage
- Structural imaging is *the* most sensitive/specific method to:
  - Determine the presence of
  - Monitor progression of
  - Determine treatment effects which slow neurodegeneration
- Its *very* important to distinguish between
  - Changes in brain function (PET, SPECT, MRS)
  - Progression of neurodegeneration (atrophy)

BOUNDARIES OF HIPPOCAMPUS AND ENTORHINAL CORTEX (ERC)



WHOLE BRAIN ATROPHY BOUNDARY SHIFT INTEGRAL



Scan 1

Scan 2
(1.8 yrs)

Whole brain
atrophy of
1%/yr

THE “MAJOR” ISSUES

- PHASE 2: How to detect a signal
  - Any signal at all
    - Biomarkers: blood, CSF
    - PET: FDG, Amyloid
  - A signal indicating disease modification
    - Most difficult
    - sMRI
- Finding dose

Phase 3

- Phase 3
  - Must be placebo vrs treatment
  - Structural MRI is an unvalidated surrogate which provides
    - Confirmatory evidence to primary outcome
    - Evidence for disease modification
    - Validate imaging by correlation with cognition

MRI/MRS ARE SURROGATES

- Imaging will not replace primary outcomes
- Unvalidated surrogates have great value:
  - Provide proof of concept
  - Confirm primary outcomes; helps with FDA
  - ***EVIDENCE OF DISEASE MODIFICATION***
- Surrogate "validation"
  - By correlating with primary outcomes, *longitudinally, across different treatments and classes of treatments*!
  - Once validated, surrogates become primary outcomes

STRUCTURAL MRI MAY DETECT DISEASE MODIFICATION

Structural MRI has “face validity”

AD is associated with atrophy

Hippocampal volume correlates with neuron counts

- Structural MRI correlates with cognition
- However, structural MRI not fully validated to detect disease modification

PROBLEMS WITH COGNITION/FUNCTION

- Poor test-retest reliability
- Intra-class correlation coefficient=0.6-0.8
- Poor reliability due to patient variability
  - Attention, Emotions
  - Physical status
- Reliability also differs between raters and sites
- These problems reduce power, increase sample size
- sMRI has high reliability: greater power

MODIFICATION OF DISEASE PROGRESSION VRS COGNITION ENHANCEMENT

- Structural MRI
  - Detects rate of brain atrophy
  - Detects drug effects which slow disease progression
- MRS (NAA), FDG PET, fMRI
  - Are affected by brain function
  - Do not distinguish between cognition enhancers and disease modifiers
- FDA understands/agrees with this

PET AND FUNCTIONAL MRI NOT SPECIFIC FOR NEURODEGENERATION

- Cholinesterase inhibitors increase brain metabolism
- This probably reflects improved brain function
- May not reflect changes of neurodegeneration
- Therefore, highly sensitive, not specific

LONGITUDINAL IMAGING

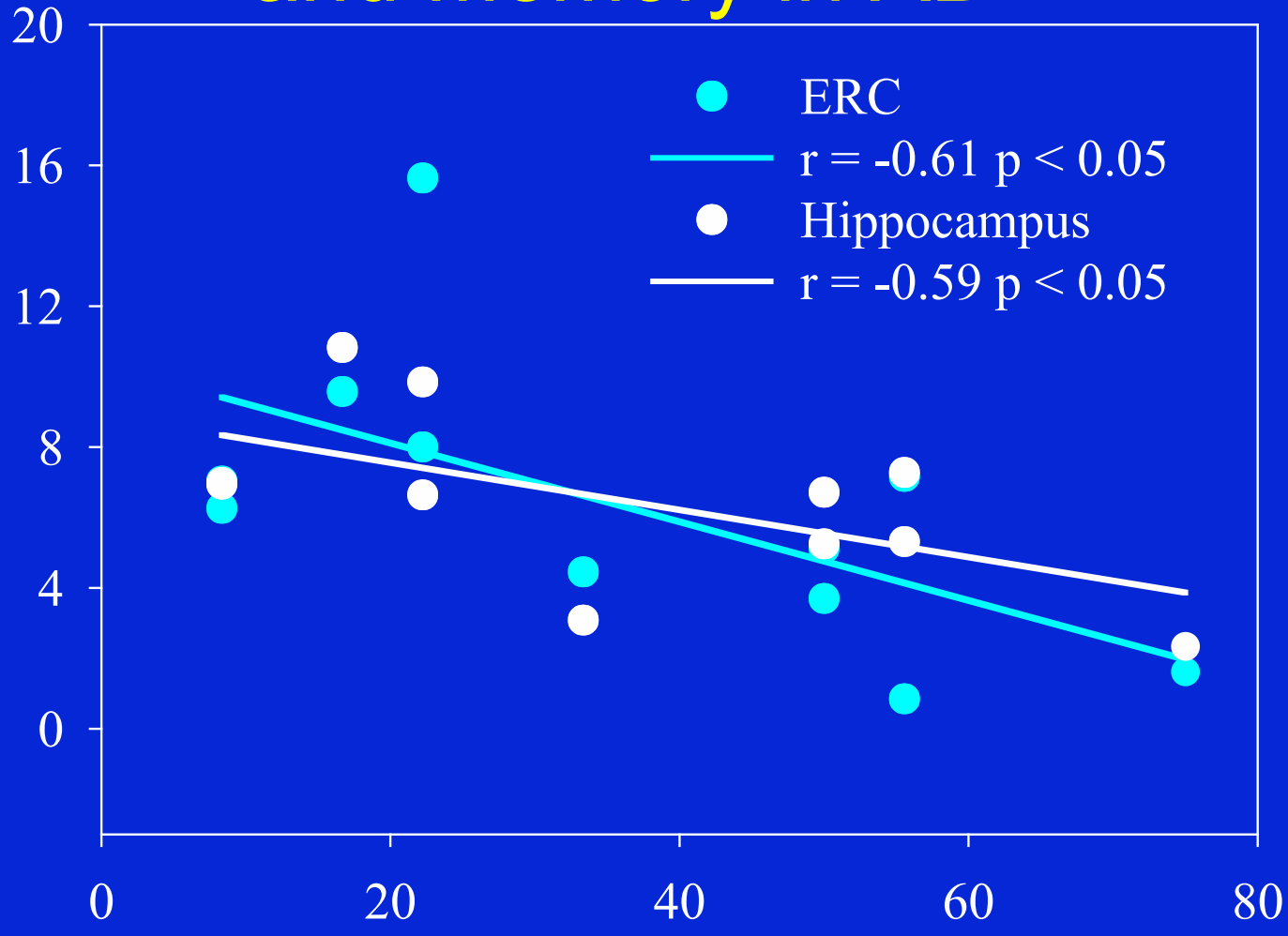
- *Only* approach towards understanding the course of progression
- Critical for clinical trials
  - develop methods to provide maximum power
- Critical for early detection
  - Distinguish AD etc. from normal aging

Atrophy Rates in Normal Aging and AD

	CN (N=23)	AD (N=19)	COV
ERC Rate	1.4 ± 2.0‡	7.1 ± 3.2*†	0.45
HP Rate	0.8 ± 1.7‡	5.9 ± 2.4*†	0.41
BSI_CORT	0.4 ± 0.3‡	0.7 ± 0.6**	0.86
BSI_VENT	0.1 ± 0.1‡	0.6 ± 0.4*	0.67
BSI_TOTAL	0.5 ± 0.4‡	1.3 ± 0.8*	0.62
CGM Rate	-0.1 ± 4.4	3.1 ± 5.9	1.9

Data as mean ± SD (%/yr), Coefficient of variation (COV) is in AD
* $p < 0.01$, ** $p < 0.05$, Rate is greater in AD than CN (t-test)
† $p < 0.05$ rate of ERC is higher than that of HP in AD (pair t-test)
‡ $p < 0.05$ Rate is larger than zero in CN (one sample t-test)
Entorhinal cortex (ERC), hippocampus (HP), cortical BSI (BSI_CORT), ventricular BSI (BSI_VENT), Total BSI (BSI_TOTAL),

Relationship between Atrophy Rates of ERC and Hippocampus and Memory in AD*



*DLR = Delayed List Recall at baseline; Includes AD patients with DLR > 0

Effects of cerebrovascular disease (lacunes) on atrophy rates in healthy elderly controls

Measure	No lacunes	Lacunes	p	ES
Age [years]	73.4 ± 6.9	75.6. ± 5.8	N.S.	-
MRI scan interval [years]	3.4 ± 1.1	3.2 ± 1.0	N.S.	-
Hippo. Annual Volume Loss	1.04 ± 1.70	2.21 ± 2.35	0.025	0.58
ERC Annual Volume Loss	1.48 ± 2.98	3.02 ± 2.27	N.S.	0.59
Brain Annual Volume Loss (BSI)	0.38 ± 0.18	0.55 ± 0.30	0.009	0.71

ES = Effect Size

Sample size estimates to detect differences equaling 50% or 25% of observed median

with 90% probability and an alpha level of 0.05 using two-sided *t*-tests among MCI patients

	Observed median	SD (on transformed scale)	Sample size to detect effect size of 50%	Sample size to detect effect size of 25%
Hippocampus	-2.55	16.13	24	102
Entorhinal cortex	-5.97	72.72	21	91
Whole brain	-0.63	1.91	32	130
Ventricle	3.29	0.44	16	69
CDR	0.54	0.33	311	1277
MMSE	-0.47	1.31	658	2628

Cliff Jack:Neurology

SAMPLE SIZE/ARM OF 20% TREAMENT EFFECT ONE YEAR TRIAL

	80% power (One tail)	80% power (Two tail)	90% power (One tail)	90% power (Two tail)
ERC Rate	64	82	89	109
HP Rate	52	66	71	88
BSI_VENT	58	74	81	99

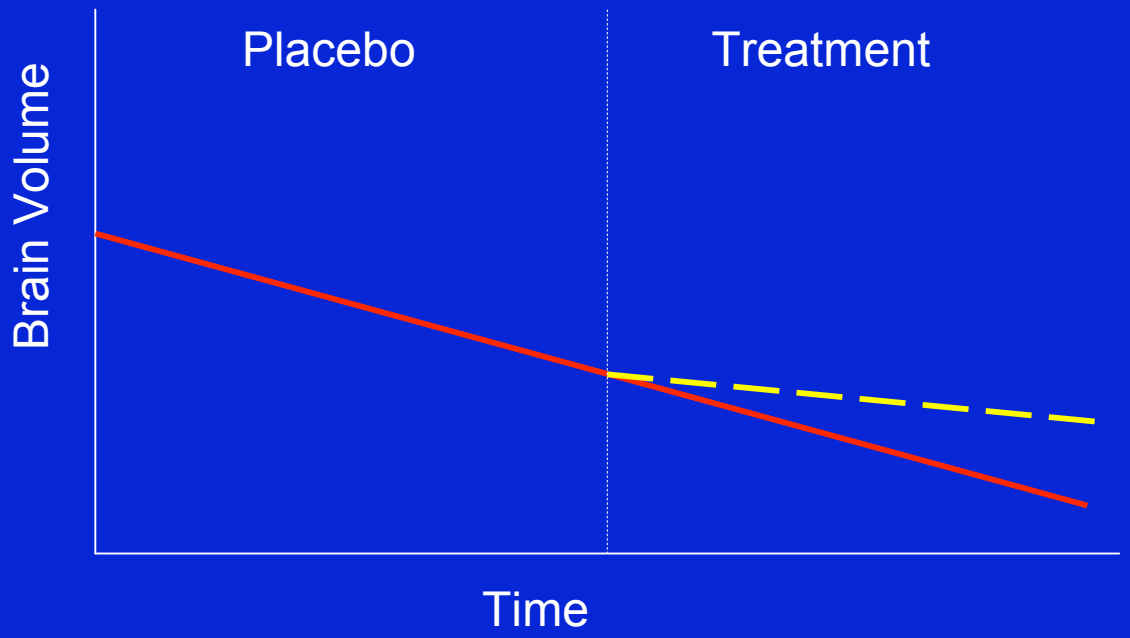
Entorhinal cortex (ERC), hippocampus (HP), ventricular BSI (BSI_VENT). Calculated from data on 20 AD subjects. Interscan interval = 1.8

HOW TO IMPROVE POWER TO DETECT TREATMENT EFFECTS

- Use subject as their own control
- Determine sources of variance and predictors of change
  - Develop a model which incorporates predictors: should have more predictive power
  - This can be used in Phase 2, possibly in phase 3

RANDOMIZED START-IMAGING TRIAL

Subjects can be entered **before** treatment is available



This approach greatly improves statistical power!

Another approach is to enrich with rapid progressors

MOST IMPORTANT QUALITY CONTROL

- Within scanner reliability
  - problem of dimensional drift: phantoms
- Software and hardware upgrades
  - phantoms to maintain consistency
- Between scanner consistency
- Within and between rater error in manual measurements
- Biological variability currently ?

PROBLEMS WITH SMRI FOR AD TREATMENT TRIALS

- What are the best ways to acquire and analyze the data?
  - Acquisition issues: sequences (T1, T2?)
  - Quality control issues: use of phantoms?
  - Processing issues: which region(s) to measure and with which method?
    - Hippocampus, ERC, whole brain, manual, semiautomated, fully automated???

MORE PROBLEMS WITH SMRI FOR AD TREATMENT TRIALS

- Validation:
  - If sMRI detects a slowing of atrophy, does this mean that the patients clinical course is slowed?
  - If sMRI dosnt detect a slowing of atrophy, does this mean that there is no disease modification?
  - May differ between types of treatments, and stage of disease

NIA ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)

Michael W Weiner

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Ronald Petersen

Clifford Jack

William Jagust

Arthur Toga

John Trojanowski

Laurel Beckett

Ronald Thomas

GOALS OF THE ADNI LONGITUDINAL MULTISITE OBSERVATIONAL STUDY

- Develop “standards” for imaging
- Improve methods for clinical trials
- Determine the optimum methods for acquiring and processing images
- “Validate” imaging and biomarker data by correlating with neuropsych and behavioral data
- Provide a data base and biological samples for PHARMA

OVERALL GOALS

Major goal is *collection of data and to establish a brain imaging and biomarker database*

- Also development of improved methods for trials
- Clinical Core, Neuroimaging Core: public access
- Emphasis on MCI, with some AD and controls
- Processing of MRI, PET, and biomarkers

FUNDING

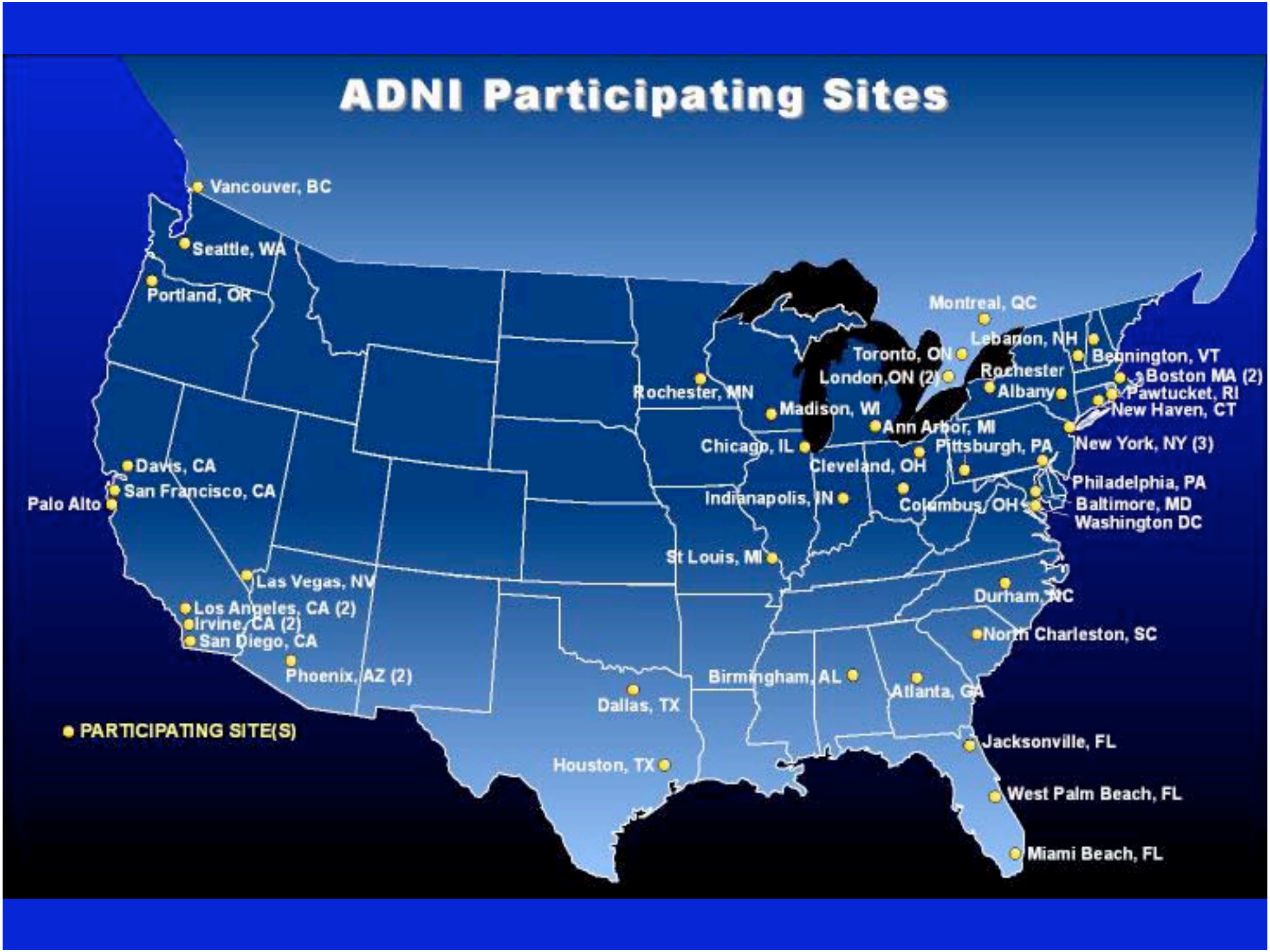
- $12 million/yr, 5 years:
- Total funding $ ~60 million
  - $40 Million provided by NIH
  - ~$20 Million provided by industry

STUDY DESIGN

- MCI (n= 400): 0, 6, 12, 18, 24, 36 months
- AD (n= 200): 0, 6, 12, 24 months
- Controls (n= 200): 0, 6, 12, 24, 36 months
- Clinical, MRI (1.5 T) at all time points
- FDG PET at all time points in 50%
- 3 T MRI at all time points in 25%
- Blood and urine at all time points from all subjects, CSF from 20% of subjects less often

IMAGING INFOMATICS

- Goal is rapid public access of *all raw and processed data*
- Art Toga at LONI will receive all QA'd MRI and PET data
- Images for processing downloaded from LONI, and results uploaded to LONI
- All image data will be available from LONI
- Clinical data base at ADCS/UCSD will be linked


ADNI Participating Sites
Vancouver, BC
Seattle, WA
Portland, OR
Montreal, QC
Lebanon, NH
Toronto, ON
Bennington, VT
London,ON (2)
Rochester
Boston MA (2)
Rochester, MN
Albany
Pawtucket, RI
Madison, WI
New Haven, CT
Ann Arbor, MI
Chicago, IL
Pittsburgh, PA
New York, NY (3)
Davis, CA
Cleveland, OH
San Francisco, CA
Philadelphia, PA
Palo Alto
Indianapolis, IN
Columbus, OH
Baltimore, MD
Washington DC
St Louis, MI
Las Vegas, NV
Durham, NC
Los Angeles, CA (2)
Irvine, CA (2)
North Charleston, SC
San Diego, CA
Phoenix, AZ (2)
Birmingham, AL
Atlanta, GA
Dallas, TX
PARTICIPATING SITE(S)
Jacksonville, FL
Houston, TX
West Palm Beach, FL
Miami Beach, FL

TIME LINE

- Preparatory Phase Oct –April 2005
- Patient enrollment begins April-July 2005
- Enrollment ends July 2006.
- Completion 2009

CONCLUSION

- Structural MRI appears to be the most sensitive/specific measure of neurodegeneration
- sMRI is an unvalidated biomarker for MCI and AD studies
- ADNI will provide a huge data base, will help design and power MCI/AD trials, and will lead towards a validated biomarker

CO-INVESTIGATORS

- Andrew Maudsley
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- Frank Ezekiel
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