ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

FUNDED BY NATIONAL INSTITUTE ON AGING

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

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John Hsiao, Neil Buckholz, Jesse Cedarbaum

Private Partners Scientific Board (PPSB)

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

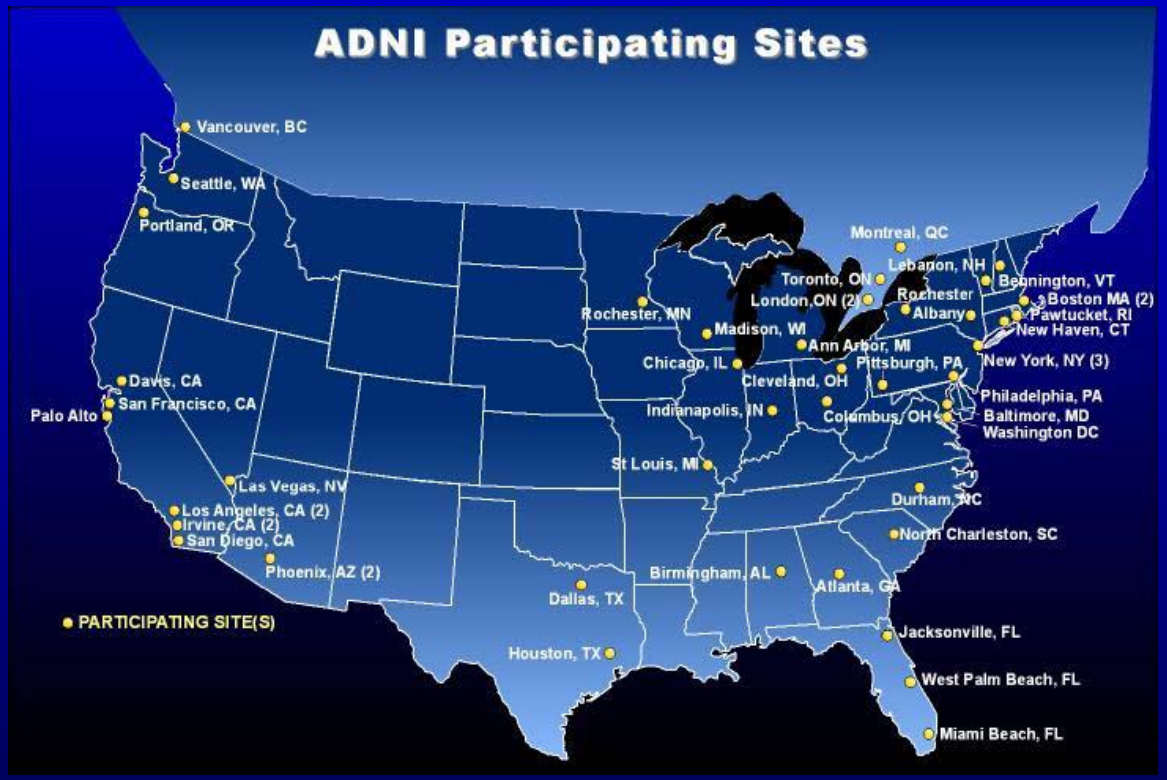
ADNI

2004-2013

Naturalistic study of AD progression

- **350 NORMAL**
- **150 SUB MEM C.**
- **850 MCI**
- **350 AD**

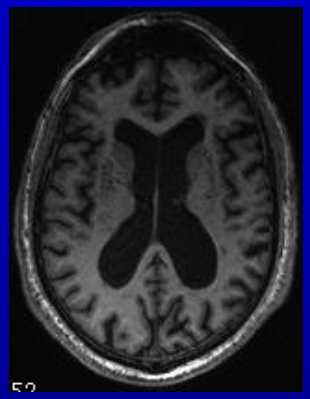
- **57 sites**
- **Clinical, blood, LP**
- **Cognitive Tests**
- **MRI: all types**
- **FDG/amyloid PET**
- **LP CSF Ab/tau**
- **Genetics**



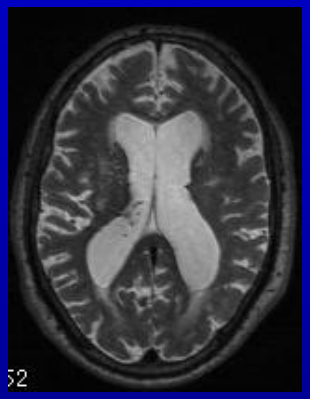
All data in public database: USC/LONI/ADNI: No embargo of data

ADNI2
Multimodality Neuroimaging

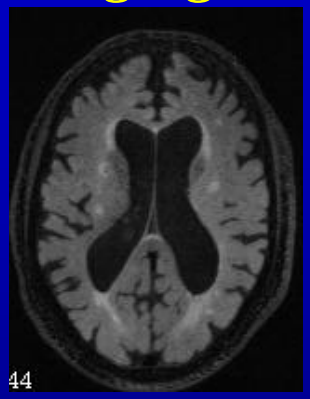
Structural imaging



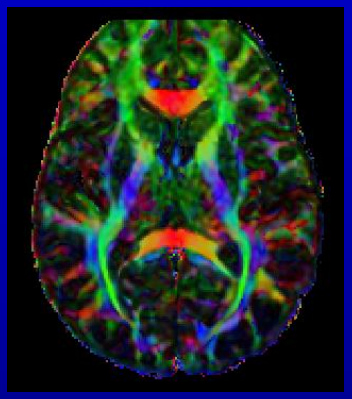
T_1 weighted



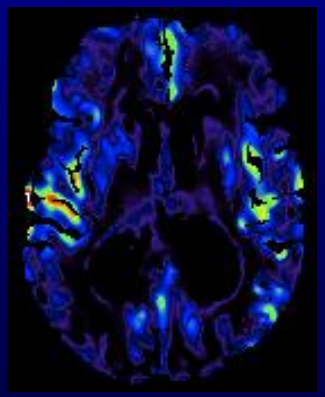
T_2 weighted



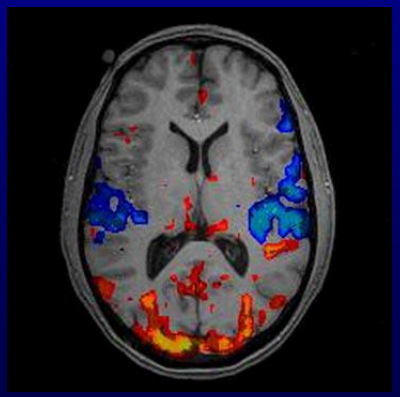
FLAIR



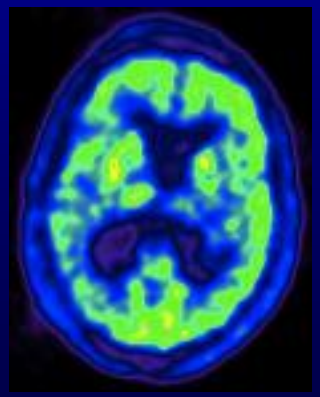
DTI



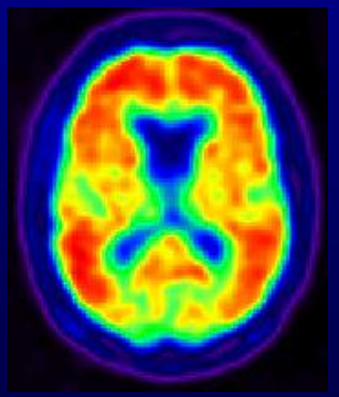
ASL MRI



fMRI



FDG PET



Amyloid PET

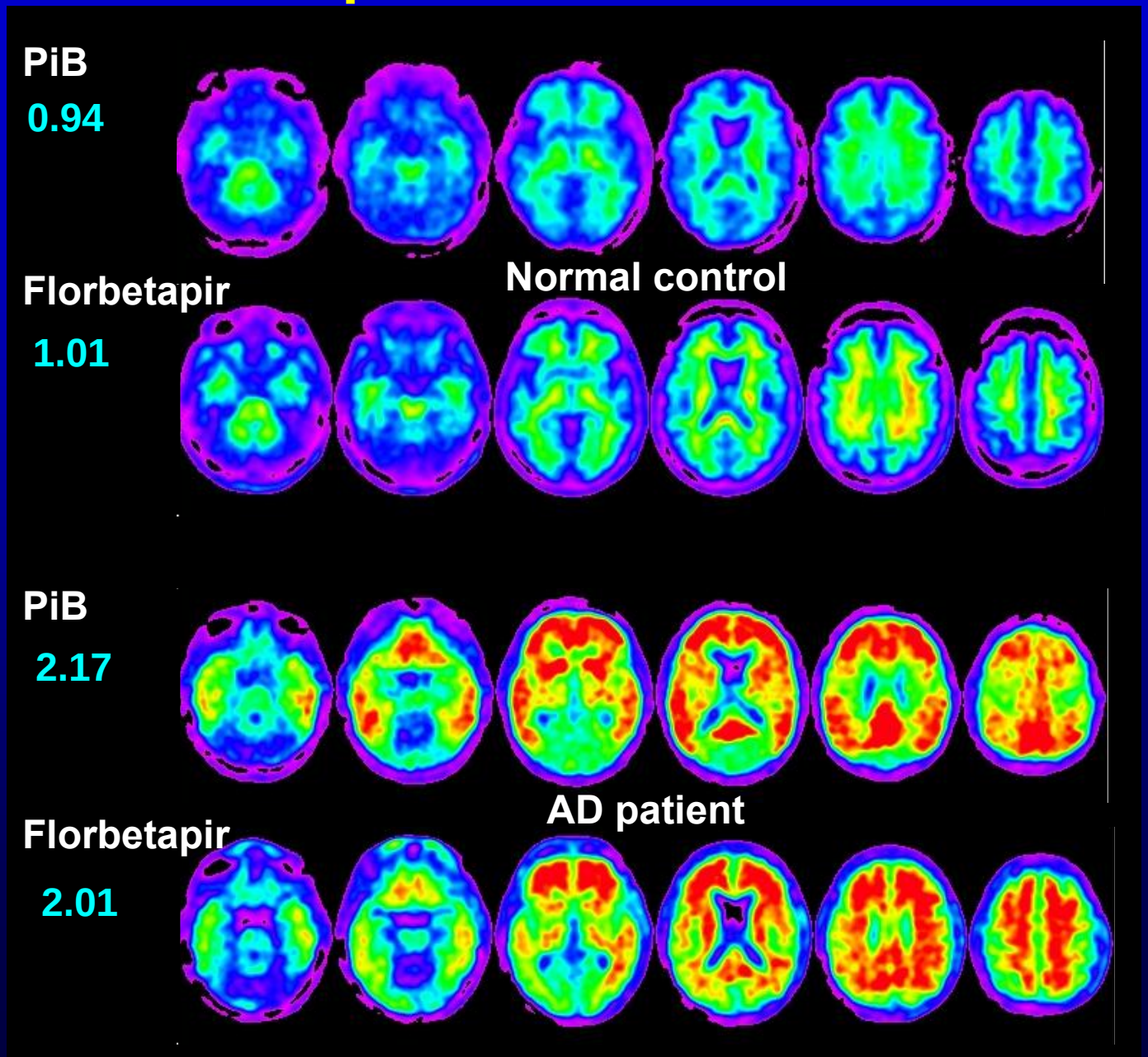
CONTRIBUTIONS OF ADNI

- Standardized methods for clinical trials
- Large multisite study amyloid imaging
- Acceptance of LPs
- MRI across vendors/ADNI phantom
- Data sharing without embargo: a model
- Data used for trial design: eg A4 and others
- GWAS and WGS
- World wide ADNI
- tau PET (in DOD ADNI)
- ADNI 3

OTHER ADNI or ADNI-LIKE PROJECTS

- DOD ADNI, DOD MCI ADNI, DOD Tau PET ADNI: 400 subjects total
- Depression ADNI
- Parkinson Progression Markers Initiative (PPMI)
- TRACK TBI
- DIAN

Florbetapir and PIB in ADNI

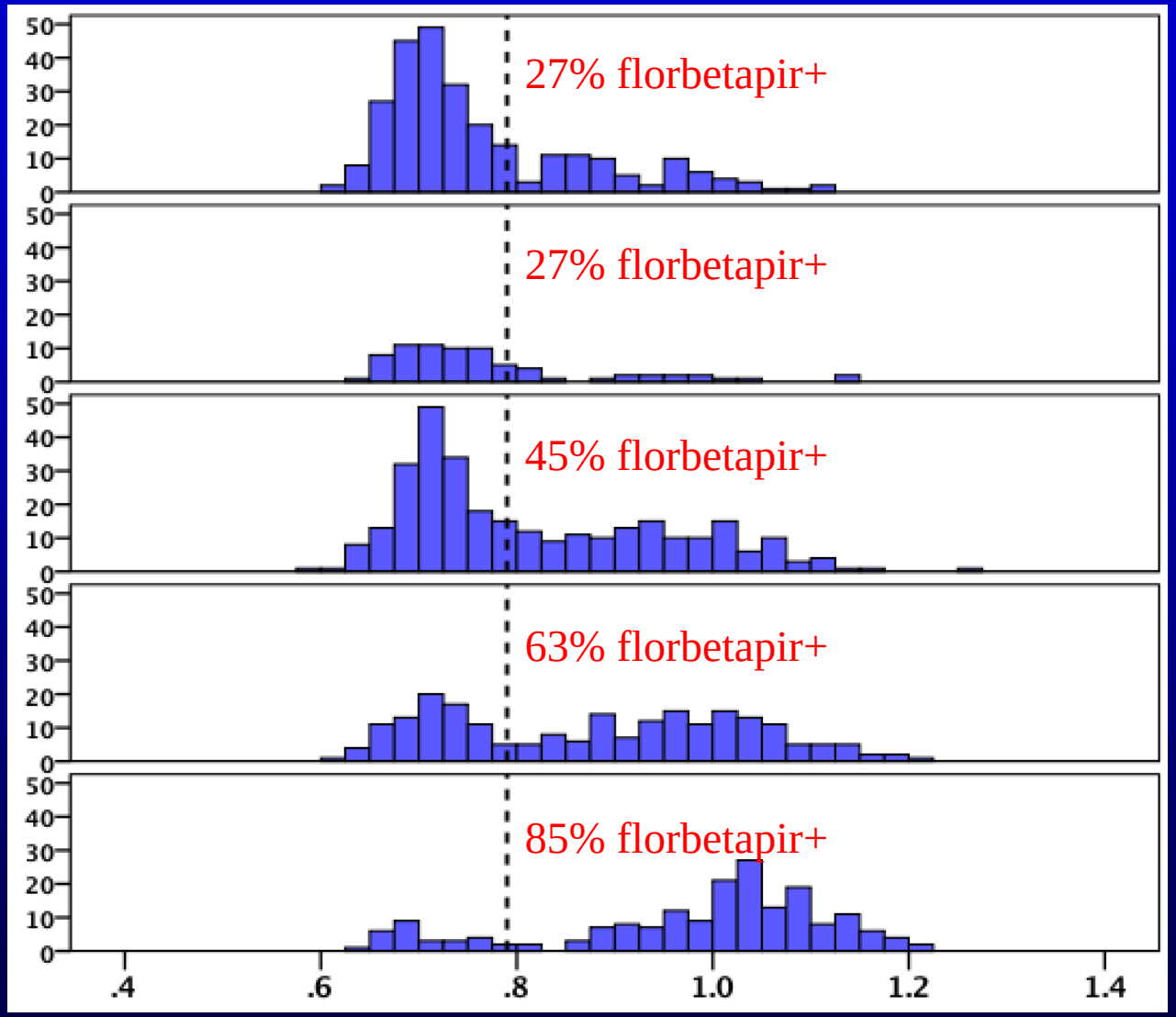


MEASUREMENT OF AMYLOID AND TAU IN CEREBROSPINAL FLUID

AD (n=102)	Tau	$A\beta_{1-42}$	P-Tau_{181P}	Tau/$A\beta_{1-42}$	P-Tau_{181P}/$A\beta_{1-42}$
Mean±SD	122±58	143±41	42±20	0.9±0.5	0.3±0.2
MCI (n=200)					
Mean±SD	103±61	164±55	35±18	0.8±0.6	0.3±0.2
NC (n=114)					
Mean±SD	70±30	206±55	25±15	0.4±0.3	0.1±0.1

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.
For AD vs MCI:p<0.005, Tau; p<0.01, $A\beta_{1-42}$; p<0.01, P-Tau $_{181P}$; p<0.0005, Tau/$A\beta_{1-42}$; p<0.005, P-Tau $_{181P}$/$A\beta_{1-42}$. Mann-Whitney test

Amyloid PET status by diagnosis



Normal
N=266

SMC
N=74

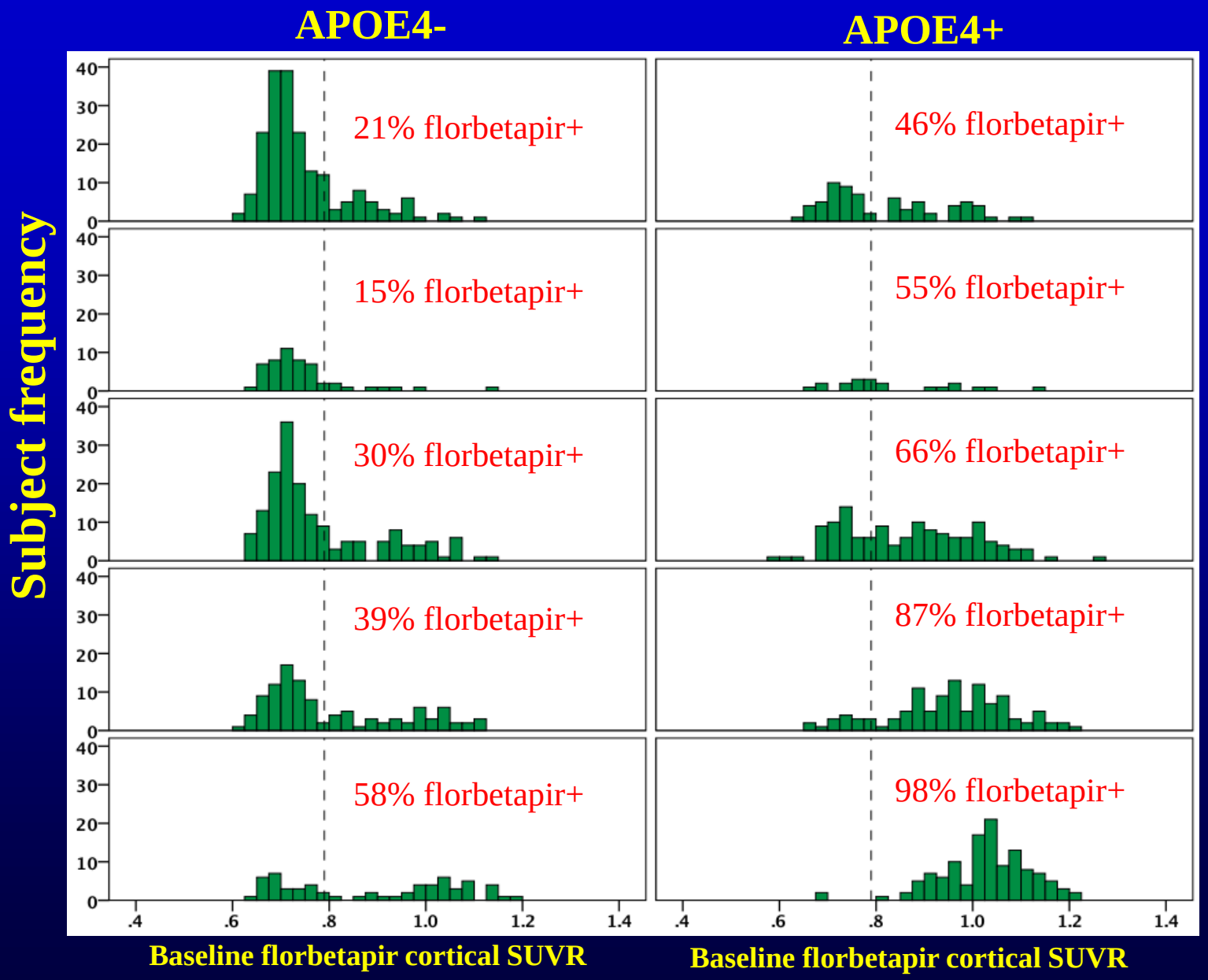
Early MCI
N=302

Late MCI
N=219

AD
N=187

Total N=1048

Florbetapir by APOE4 status



Normal
N=265

SMC
N=72

Early MCI
N=299

Late MCI
N=219

AD
N=184

Total
N=1039

EFFECTS OF AMYLOID STATUS ON CONVERSION RATE

- Conversion of MCI to AD dementia in 2-3 years
- 25% of MCI who were amyloid +
- 2% of MCI who were amyloid-
- Conclusion: amyloid in the brain predicts faster decline and conversion to dementia!
  - This applies to normal subjects, subjects with MCI, and subjects with dementia!
- Therefore clinical trials are helped by “amyloid phenotyping”

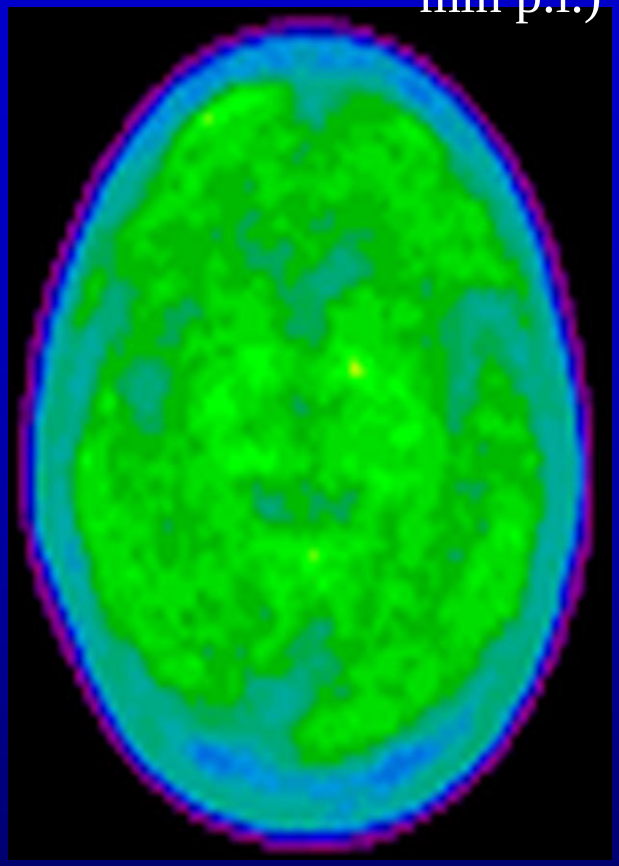
PLANNING FOR ADNI3

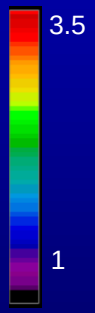
- NIA and Pharma have expressed interest in continuing ADNI: ADNI 3 2016-2021
- Continue to follow existing subjects
- Add tau PET
- Multimodality MRI at all sites
- Mass spec analysis of CSF Abeta
- Computer based neuropsych testing

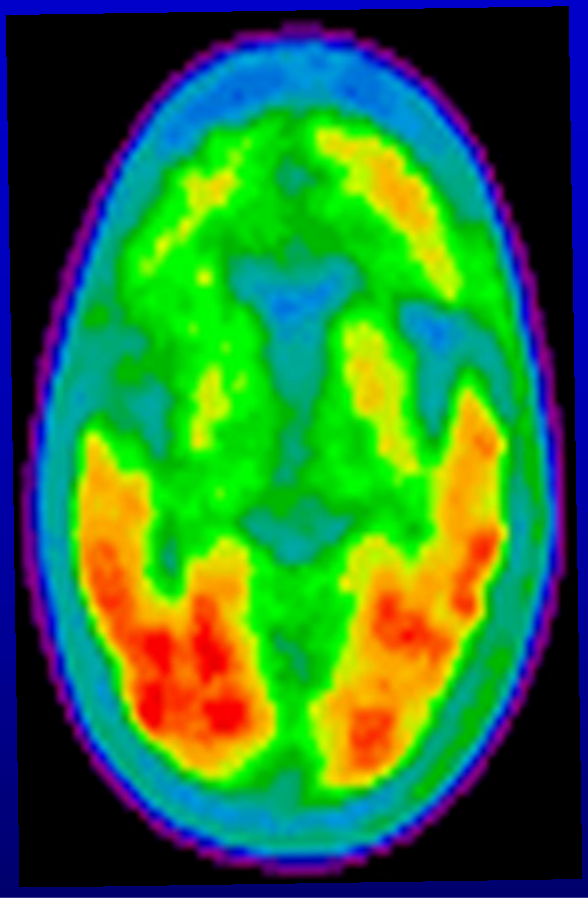
EMERGING IMPORTANCE OF TAU PET SCANS

- Many autopsy pathology studies have shown that tau tangles highly correlate with
  - Synapse loss
  - Neuron loss
  - Memory loss, cognitive decline
- Tau can be measured in cerebrospinal fluid
- Tau can now be detected by PET scans

[18F]-T807 PET (80-100 min p.i.)







Healthy Control

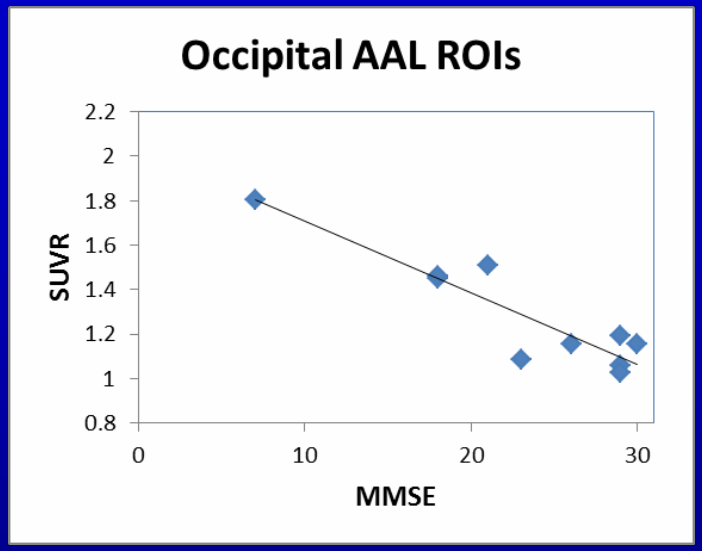
(58 years old)

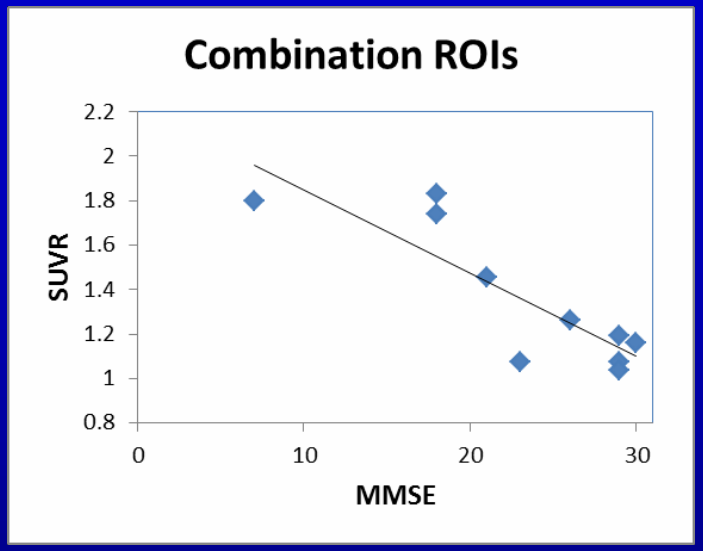
Alzheimer's Disease Subject

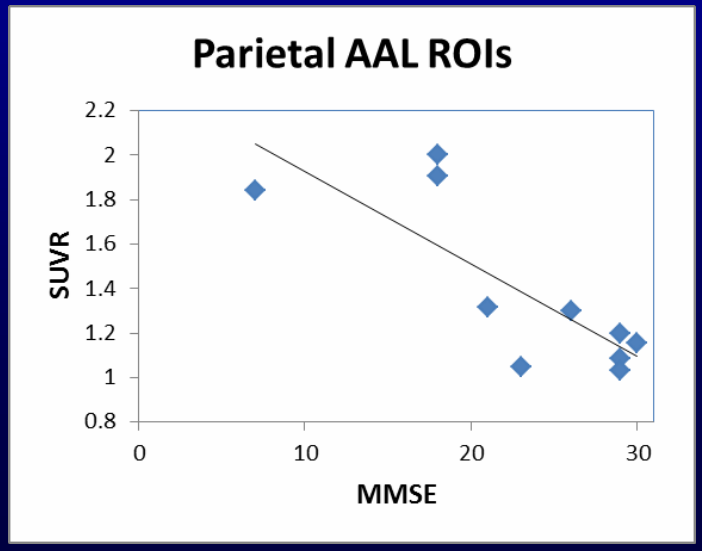
(72 years old, MMSE = 7)

Chien, D. T.; Kolb, H.C. et al. J. Alzheimer's Disease, 2012, 34, 457-468Xia, C.F.; Kolb, H.C. et al. Alzheimer's & Dementia, 2012, in pressZhang, W.; Kolb, H.C. et al. J. Alzheimer's Disease 2012, 31, 601-612

Relationship of MMSE to T807 Uptake by Region: All Subjects







Region	Correlation
Occipital	-0.918
Parietal	-0.798
Combo	-0.854

ADNI 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
- Data widely used for design of clinical trials
- This unprecedented data sharing is a model for future science

OBSTACLE TO EFFECTIVE TREATMENTS

- The high costs of clinical trials
- Solution: subject recruited, assessed, screened and longitudinal monitored on the internet
- A pool of longitudinally monitored subjects
- Using a website greatly reduces costs

The Brain Health Registry:

An Internet-Based Registry for

Recruitment, Assessment, & Longitudinal Monitoring

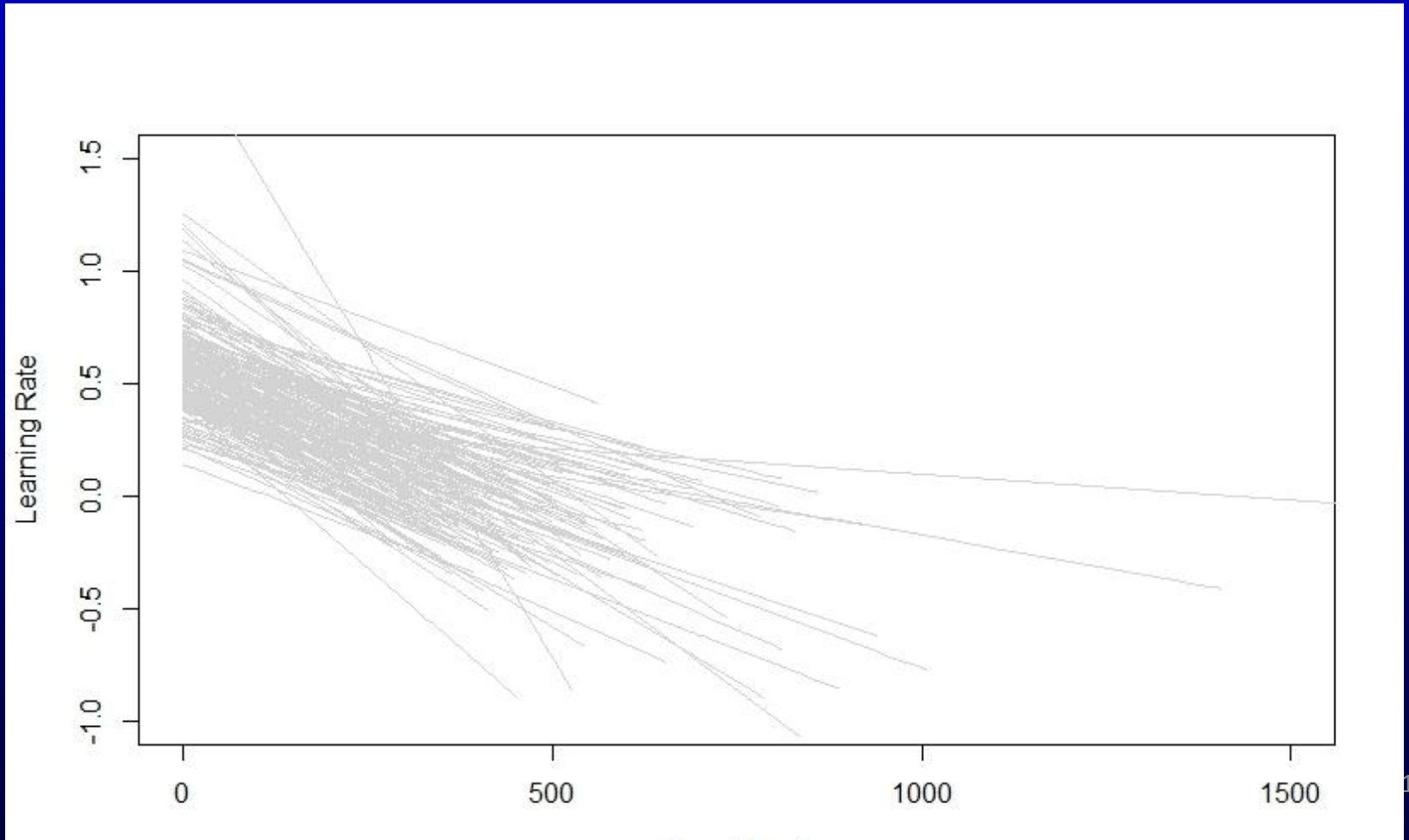
for Clinical Neuroscience Research

COGSTATE RESULTS ON 2500 SUBJECTS

				Unadjusted	Full Model	
	Data	Response	Predictor	p-value	Estimate	p-value
1	Cogstate	Working Memory	Age	<0.001	0.03	<0.001
2			Gender	0.21	0.01	<0.001
3			Education	0.54	-0.005	0.30
4			Family History	<0.001	0.005	0.11
5			Memory Problem	0.02	0.03	0.001
6			Memory Concern	<0.001	0.009	0.007
7		Attention	Age	<0.001	0.02	<0.001
8			Gender	0.70	0.004	0.13
9			Education	0.93	-0.01	0.01
10			Family History	<0.001	0.004	0.06
11			Memory Problem	<0.001	0.03	<0.001
12			Memory Concern	<0.001	0.01	<0.001
13		Learning	Age	<0.001	-0.03	<0.001
14			Gender	0.001	0.007	0.13
15			Education	0.01	0.03	<0.001
16			Family History	0.72	0.006	0.21
17			Memory Problem	<0.001	-0.05	<0.001
18			Memory Concern	0.001	-0.02	<0.001
19		Psychomotor	Age	<0.001	0.03	<0.001
20			Gender	<0.001	0.03	<0.001
21			Education	0.41	-0.005	0.2
22			Family History	0.001	-0.001	0.76
23			Memory Problem	0.001	0.04	<0.001
24			Memory Concern	<0.001	0.01	0.003
25	Lumos	GoNoGo	Age	<0.001	31.32	<0.001
26			Gender	0.009	16.51	<0.001
27			Education	0.55	-5.00	0.30
28			Family History	0.007	-0.03	0.11
29			Memory Problem	0.007	25.19	0.001
30			Memory Concern	<0.001	15.28	0.007
31		Memory Span	Age	<0.001	-0.46	<0.001
32			Gender	0.36	-0.17	0.13
33			Education	0.09	0.19	0.01
34			Family History	0.001	-0.05	0.06
35			Memory Problem	0.002	-0.42	<0.001
36			Memory Concern	0.002	-0.12	<0.001
37		Reverse Memory Span	Age	<0.001	-0.58	<0.001
38			Gender	0.39	-0.21	0.13
39			Education	0.35	0.17	<0.001
40			Family History	0.008	-0.02	0.21
41			Memory Problem	0.12	-0.29	<0.001
42			Memory Concern	0.01	-0.10	<0.001
43		Trails B	Age	<0.001	10639	<0.001
44			Gender	0.03	-891	<0.001
45			Education	<0.001	-8050	0.2
46			Family History	<0.001	2702	0.76
47			Memory Problem	0.02	2882	<0.001
48			Memory Concern	<0.001	6631	0.003

EXISTING DATA SET OF LONGITUDINAL COMPUTER GAME SCORES:LUMOSITY

LOWER 25TH OF DECLINING ELDERS



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Lilly
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SYNARC — Start here, finish first.
Takeda
IXICO
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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

ADNI IS FUNDED BY NIA

These slides and much more at ADNI-INFO.ORG

All data at

www.loni.ucla.edu/ADNI/