The World of ADNI

Acknowledgements

Funded in part by Grant R13AG030995-01A1 from the National Institute on Aging

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Friday Harbor Psychometrics Workshop 2011

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NIA Alzheimer's Disease Neuroimaging Initiative

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MRI Core: Clifford Jack
PET Core: William Jagust
Infomatics Core: Arthur Toga
Biomarker Core: John Trojanowski
Biostatistics Core: Laurel Beckett
Genetics Core: Andy Saykin
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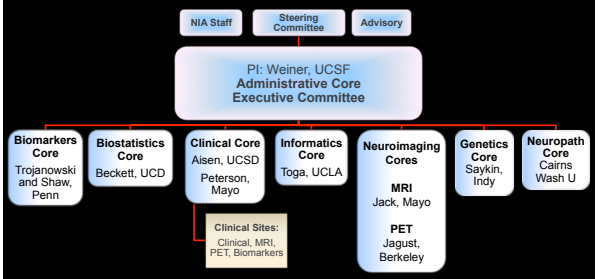
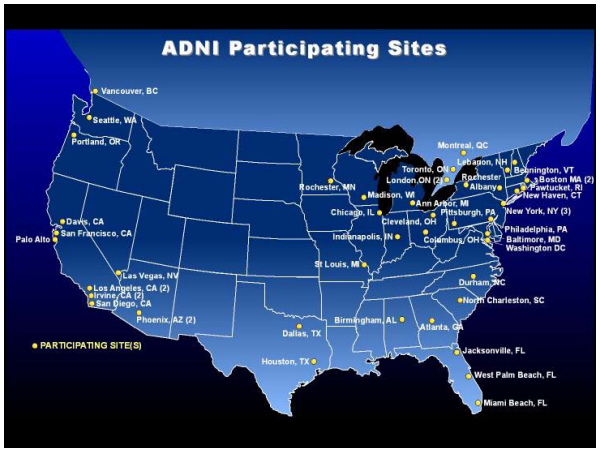
Industry Scientific Advisory Board: Enchi Liu (Janssen Alzheimer Immunotherapy)

Investigators, Coordinators, Participants at 60+ sites in North America

ADNI Organization





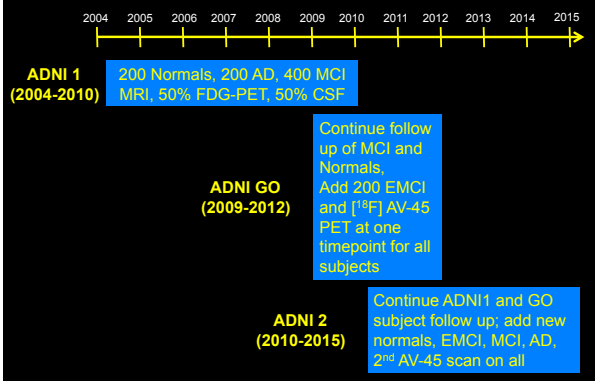
Key Features of ADNI

Testing of relatively well-established potential biomarkers for AD
Oriented towards improving clinical trial design and methodology

ADNI is not:
A study of AD diagnostic instruments
A general "neuroscience of aging" project

But
Defining biomarker dynamics involves development of models of disease

The 3 Stages of ADNI



ADNI 1 Goals

- Standardize the acquisition and analysis of biomarkers for AD for use in clinical trials
- Validate the use of biomarkers for measurement of disease outcomes
  - Power as a surrogate in clinical trials
  - Relationships between biomarkers
  - Associations with clinical severity

ADNI 1 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
- All subjects (age 55-90): 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 50% of subjects
- PIB "add on": 19 C, 19 AD, 65 MCI up to 3 years

GO and ADNI 2 Goals

- Continue ADNI 1 subjects and goals
  - Examine models of longitudinal biomarker change and relationships
  - Examine prognostic use of biomarkers
- Investigate earlier stages of preclinical AD (EMCI)
- Obtain 2 timepoints of amyloid-PET and FDG-PET
- DTI, ASL, fcMRI on 1/3 of subjects each
- Neuropathology to validate diagnosis
- Blood for DNA and RNA

ADNI GO Study Design EMCI

Recruit, define and characterize 200 EMCI:
CDR = 0.5, Meet MCI criteria but memory is 0.5 – 1.5 SD below education adjusted norms

EMCI Exam baseline, 6, 12 months

EMCI 3T MRI at baseline, 3, 6, 12 months

CSF and blood (Aβ, DNA, RNA) on all EMCI

ADNI GO Study Design (2)

Continue annual clinical follow up of all normal and MCI subjects in ADNI 1

[^{18}F]Florbetapir (AV-45) PET and FDG-PET on all subjects at one timepoint

Annual 1.5T MRI on MCI and normals from ADNI 1

CSF on all EMCIs and all subjects with CSF in ADNI1

Blood samples (Aβ, DNA, RNA) on all subjects

ADNI 2 Study Design New Subjects

Enroll: 150 new normal, 100 EMCI, 150 MCI, 150 AD

Obtain 2 Florbetapir-PET and FDG PET scans on all new subjects (2 years apart)

Annual clinical evaluation on normals, EMCI, MCI
3T MRI at baseline, 3, 6, 12 months and yearly
CSF and RNA annually

Annual clinical evaluation for AD up to 24 months
3T MRI at baseline, 3, 6, 12, 24 months
CSF and RNA at baseline and 24 months

ADNI 2 Study Design Follow Up Subjects

Continue annual clinical follow up of all normal, EMCI and MCI subjects from ADNI 1 and GO

Obtain a second Florbetapir-PET and FDG-PET scan on all subjects from ADNI1 and GO 2 years after initial scan

Annual 3T MRI on all subjects from ADNI GO

Annual 1.5 T MRI on all subjects from ADNI 1

ADNI Technical Achievements

Standardize MRI structural image acquisition

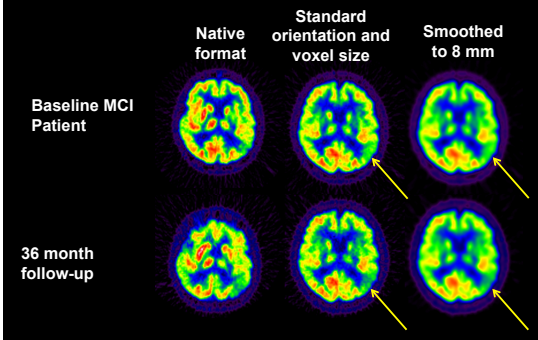
Standardize FDG-PET and amyloid-PET image acquisition

Standardize collection, shipping, aliquoting and curation of biofluids, characterize variability

Definition of EMCI

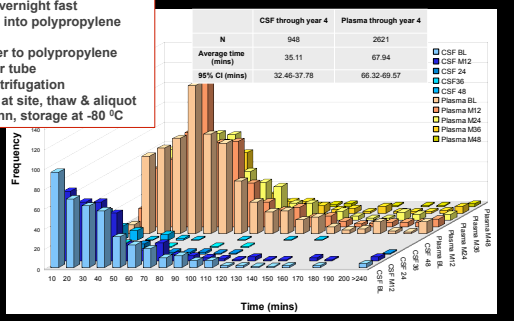
Archiving, logging, tracking all clinical and image data with full public availability

ADNI FDG Image Processing



Pre-Analytical Issues are Critical: CSF & Plasma Collections For ADNI

- After overnight fast
- Collect into polypropylene tube
- Transfer to polypropylene transfer tube
- No centrifugation
- Freeze at site, thaw & aliquot at UPenn, storage at -80 ^{0}C



Number of biofluids collected as of 6/30/2010: 13,122
Number of aliquots in biofluid bank: 126,681

ADNI MRI Data

Dx	#	BL	M3	M6	M12	M18	M24	M36	M48	M60
N	249	226	0	201	193	0	98	127	47	4
EMCI	140	124	75	34	0	0	0	0	0	0
MCI	415	388	0	349	324	179	200	146	40	0
AD	193	185	0	154	140	0	69	0	0	0
Total	997	923	75	738	657	179	367	273	87	4

ADNI FDG-PET Data

Dx	#	BL	M6	M12	M18	M24	M36	M48	M60
N	249	103	94	85	0	84	69	54	19
EMCI	140	92	0	0	0	0	0	0	0
MCI	415	206	188	177	154	142	112	57	4
AD	193	95	86	74	0	58	0	0	0
Total	997	496	368	336	154	284	181	111	23

ADNI PIB-PET Data

Dx	#	BL	M6	M12	M18	M24	M36	M48	M60
N	249	0	0	17	0	17	13	2	0
EMCI	140	0	0	0	0	0	0	0	0
MCI	415	15	1	51	0	47	27	2	0
AD	193	5	0	15	0	14	0	0	0
Total	997	20	1	83	0	78	40	4	0

ADNI Florbetapir-PET Data

Dx	#	BL	M6	M12	M18	M24	M36	M48	M60	Any
N	249	1	0	0	0	0	0	35	21	57
EMCI	140	107	0	0	0	0	0	0	0	107
MCI	415	1	0	0	0	0	6	49	6	62
AD	193	0	0	0	0	0	0	0	0	0
Total	997	109	0	0	0	0	6	84	27	226

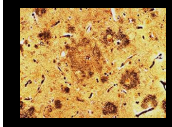
ADNI CSF Data

Dx	#	BL	M12	M24	M36
N	249	114	94	22	15
EMCI	140				
MCI	415	195	154	44	8
AD	193	100	74	17	0
Total	997	409	322	83	23

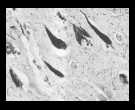
Pathway to Decline

Trigger (misfolded, excessive, aggregated proteins) → Neurodegeneration → Neurological Dysfunction

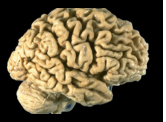
Alzheimer's disease: The Amyloid Hypothesis



β-amyloid



Tau pathology
Synapse loss



Cognitive Decline and Dementia

ADNI Conceptual Model

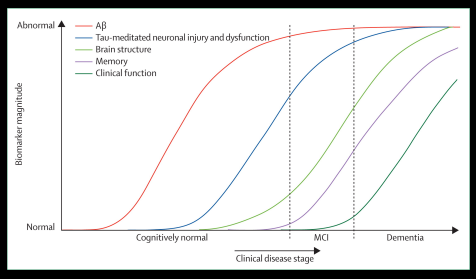
Aβ is the earliest detectable biomarker change
- This does not mean Aβ causes AD

Initiates "downstream" structural and functional events
- synaptic alterations/hypometabolism
- tau/NFTs
- regional atrophy

Cognitive and clinical change are late effects

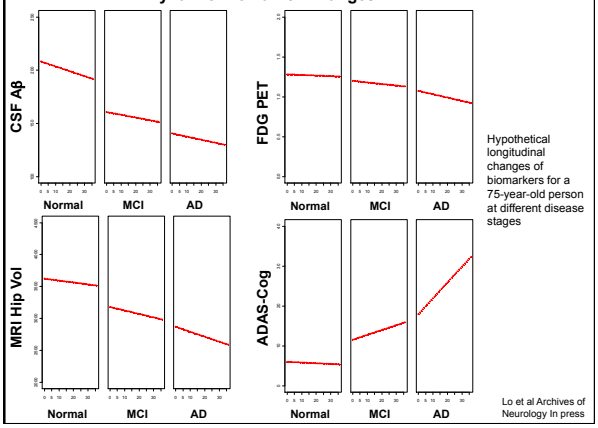
Jack et al, Lancet Neurology 2010

Dynamic Biomarkers in the AD Pathological Cascade



Jack et al, Lancet Neurology 2010

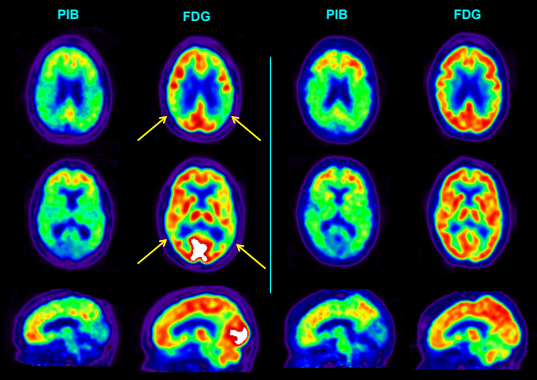
Dynamic Biomarker Changes in ADNI



Hypothetical longitudinal changes of biomarkers for a 75-year-old person at different disease stages

Lo et al Archives of Neurology In press

Demented or Not?



ADNI Image Data

3-D volumes that reflect anatomy (MRI), glucose metabolism or Aβ deposition (PET)

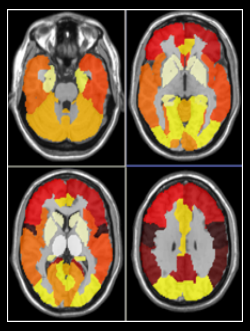
All image volumes can be processed to yield quantitative continuous measures of brain volumes or PET tracer uptake

- PET data is normalized to an "unaffected" brain region
- Continuous measures can be segmented

Image volumes themselves can be used as dependent measures on a voxelwise level

- May be exploratory, type I error

MR Processing Methods: Freesurfer Cortical Parcellation



Cortical and hippocampal volumes used as dependent variables

Power of Cognitive Tests: Detect a 25% Change in 1 year (2 ARM) in AD

Test	Sample Size		
MMSE	803		
RAVLT	607		
ADAS	592		
CDR SOB	449		

Power of Cognitive Tests: Detect a 25% Change in 1 year (2 ARM) in MCI

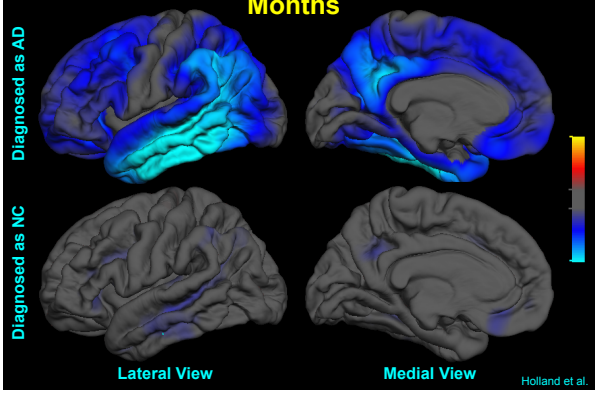
Test	Sample Size			
RAVLT	6056			
ADAS	4547			
MMSE	3879			
CDR SOB	853			

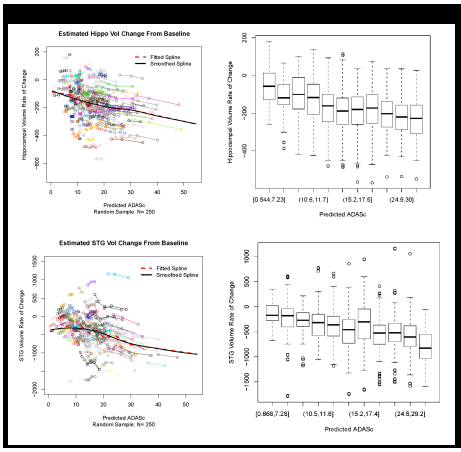
MRI as Surrogate Outcome in AD (N=128)

Lab	Variable	N / arm	N.S. differ		
Alexander	L hippo form	268			
Alexander	L mid temp	191			
Schuff-FS	Ventricles	133			
Fox	Ventricle ch%	129			
Fox	VBSI	128			
Fox	DBCBSI %	127			
Studholme	% change	70			
Schuff-FS	Hippocampus	50			

Sample size to detect 25% reduction in rate of change with 80% power and $\alpha = 0.05$

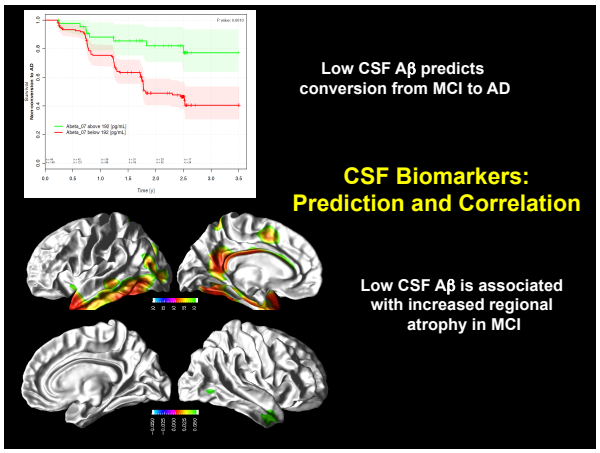
Mean Cortical Thickness Change over 12 Months

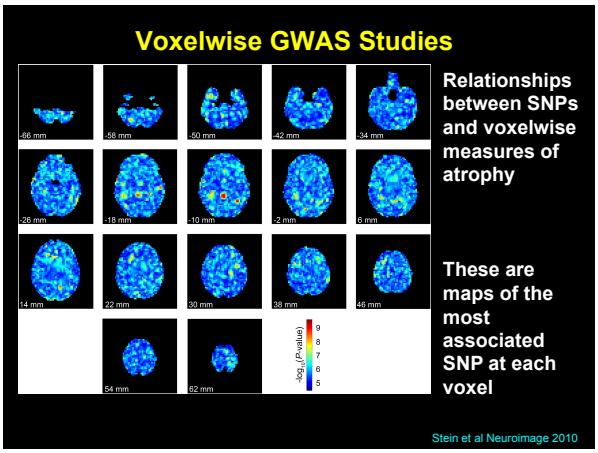


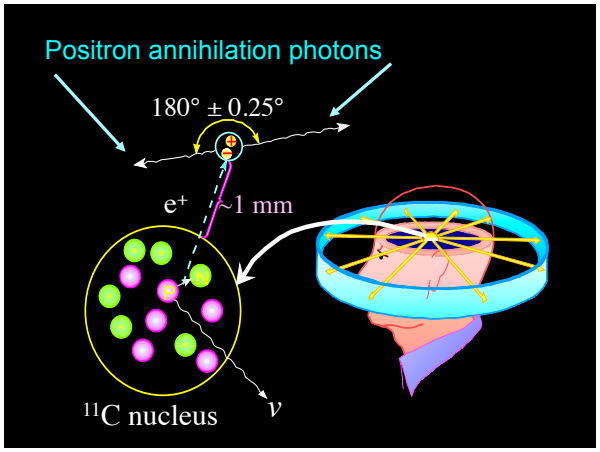


Hippocampal volume loss as a function of cognitive impairment

Sup Tem Gyrus volume loss as a function of cognitive impairment







What happens during a PET scan?

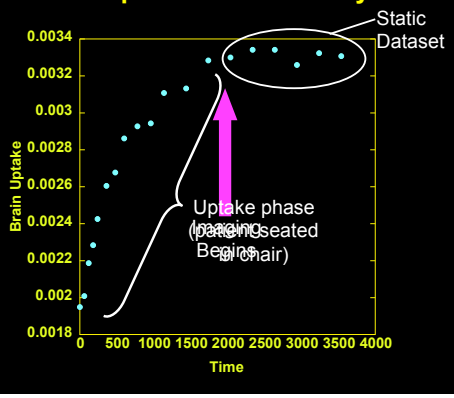
Subject receives an intravenous injection of a radiotracer (technologist inserts iv, Nuclear Medicine MD supervises injection)

The radiotracer circulates and is taken up by brain

Timing and %uptake depend upon the tracer

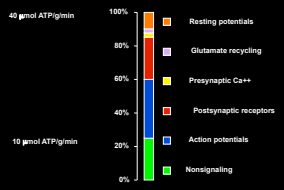
Data usually collected at a time after injection that depends on pharmacokinetics/equilibrium of tracer

Example: FDG-PET Study



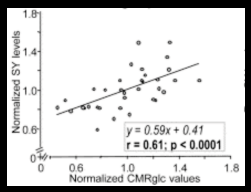
Glucose Metabolism and Synapses

Cortical Neuronal Energy Utilization



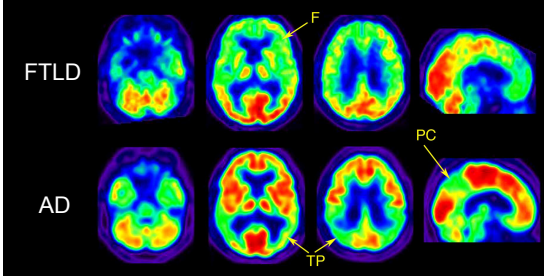
Attwell and Laughlin, JCBF 2001
(rodent, glutamatergic neuron)

Glucose Metabolism vs Synaptophysin



Rocher et al, Neuroimage 2003

FDG-PET in Alzheimer's and FTLD



F = frontal cortex, TP = Temporoparietal cortex,
PC = posterior cingulate/precuneus

PET Analytic Approaches

Full kinetic models
- requires blood sampling/not done in ADNI

Regions-of-interest
- Normalization to an "unaffected" brain region (pons, cerebellum)

Voxel-based (SPM)
- Statistical models with brain volumes as dependent measure (also normalized)