The Prospects of Neuroimaging for Early Detection in Alzheimer's Disease

Victor L. Villemagne, M.D.

Centre for PET, Austin Health
Department of Pathology, University of Melbourne
The Mental Health Research Institute of Victoria
Neurosciences Victoria
Melbourne, AUSTRALIA

The Normal Biology of Aging

Neurodegenerative Disorders in Older People

- Cognitive impairment, dementia
- Motor slowing, impaired movement
- Instability, falls, gait disturbance
- Sensory impairment (visual, auditory)

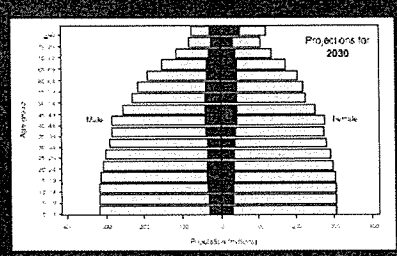
Australian Science and Technology Council Foresighting Study: 2010

Neurodegenerative diseases associated with abnormal protein conformations

(gain of toxic function)

Disease	Gene product
• Alzheimer's disease	APP and Aβ amyloid
• Creutzfeldt-Jakob disease	Prion protein
• ALS / MND	Superoxide dismutase
• Parkinson's disease	α-synuclein
• Huntington's disease	Huntingtin/PolyQ
• FTDP, PSP, CBD	Tau

Population Age Distribution



United Nations, 1999, and US Bureau of the Census, 2000

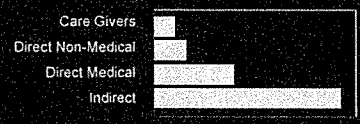
Background

- Alzheimer's disease represents the most common form of dementia syndrome
- Prevalence: 5% of individuals aged 65 years, 20–30% of 85-year olds
- With life expectancy increasing across the world, AD poses an increasing medical and socio-economic problem
- Treatment strategies are likely to be most effective if administered early
- No method of definitive early diagnosis, or predictive whether a person is likely to develop AD
  - Mild cognitive impairment (MCI): 40–60% develop AD

Economic Costs of AD in Australia, UK and USA

Currency	Com. Costs for AD Patients/annum
AUD	$ 13 billion
UKP	£ 21 billion
USD	$ 112 billion

Mean Costs/patient/annum for all stages of AD

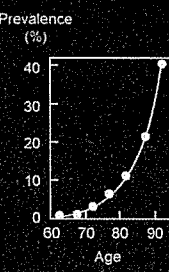


Total Costs/patient over 10 years

UAD = $2.7 million
UKP = £1.3 million
USD = $1.7 million

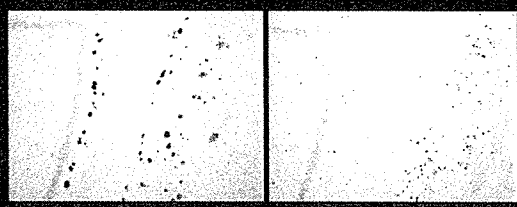
Risk Factors for AD

- Familial/ Genetic
  - Chromosome 21 (APP mutations)
  - Chromosome 19 (Apolipoprotein E)
  - Chromosome 14 (PS 1)
  - Chromosome 1 (PS 2)
- Down's Syndrome (Trisomy 21)
- Gene dosage: Aβ/APP gene
- Age
  - Exponential doubling of prevalence of AD with each decade after age 50 y



Neuropathological Hallmarks of AD

Senile Plaques (Aβ) | Neurofibrillary Tangles (tau)



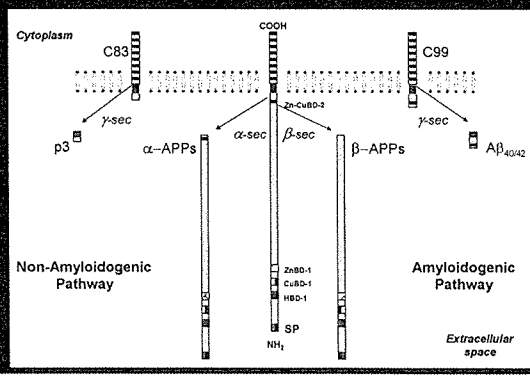
AD Neuropathology

(adapted from Braak & Braak, 1997)

Plaque Progression

NFT Progression

APP Cleavage

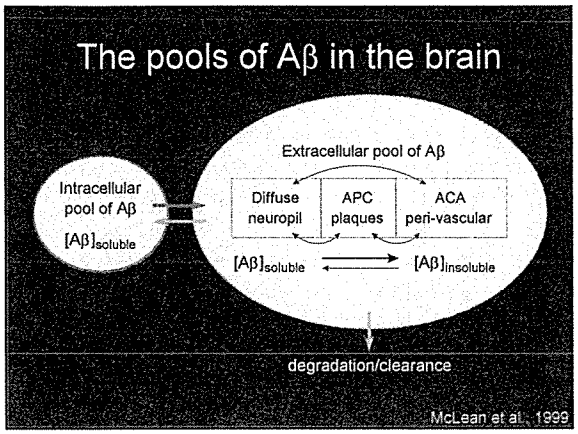


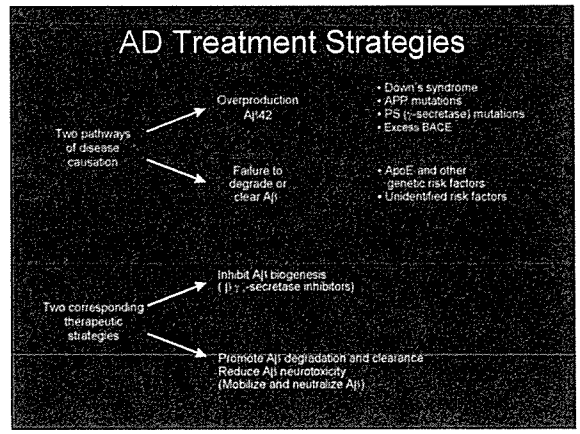
Aβ levels (μg/g)

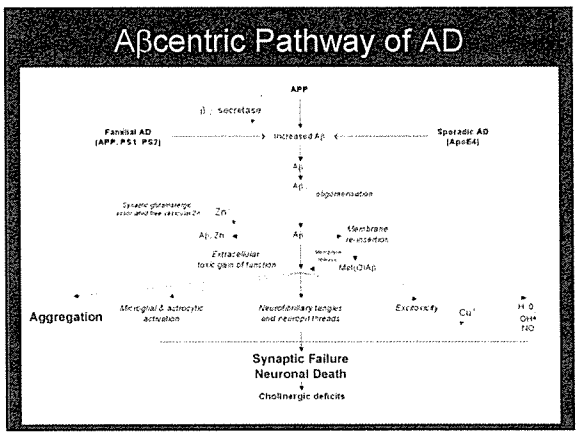
Frontal Cortex

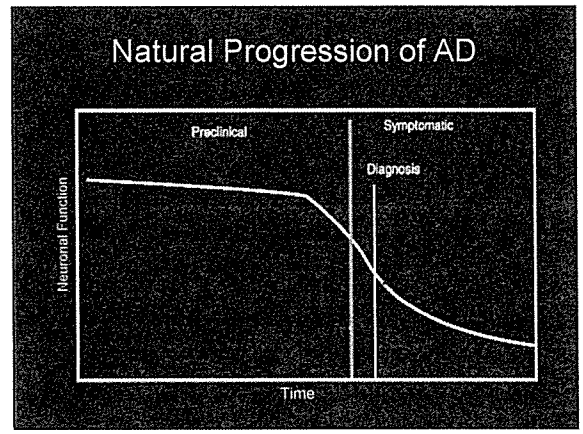
	Soluble Aβ (μg/g)	Insoluble Aβ (μg/g)	Proportion soluble (%)
Controls (n=18)	0.013±0.012	3.7±4.1	0.3
AD (n=18)	0.24±0.23*	34.4±35.3**	0.7
Fold increase	18	9	

McLean et al., 1999









The Search for Biomarkers

- Biomarkers are based on genotypical or phenotypical characteristics that can be objectively measured and evaluated as indicators of normal or pathological biological processes, as well as pharmacologic responses to a drugs
- Despite the promise of recent advances in molecular neurosciences, the early detection of neurodegenerative diseases like AD, especially the identification of at-risk individuals before the development of the typical phenotype, will require several biomarkers to ensure presymptomatic diagnosis and, ultimately, intervention with disease-modifying medications during the presymptomatic period

Types of Biomarkers

Antecedent Biomarkers: used to identify the risk of developing a disease

Diagnostic Biomarkers: aid in identifying disease

Prognostic Biomarkers: predict disease course, including response to therapy

Biomarkers

- *Genetic* genes that are either causative or associated with functional mechanisms that are disease specific
- *Neuroimaging* provide non-invasive measurement of the altered molecular pathway allowing early diagnosis, monitoring of therapy and disease progression
- *Biochemical* Modern array-based technologies allow targeting biochemical deficits more effectively for identification of markers of disease in serum and CSF
- *Clinical* Longitudinal studies of AD and MCI subjects allows the identification the earliest changes in *serial* neuropsychological evaluations

Ideal Biomarker

"The ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases; it should have a diagnostic sensitivity >80 percent for detecting AD and a specificity of >80 percent for distinguishing other dementias; it should be reliable, reproducible, noninvasive, simple to perform, and inexpensive."

AlzForum

Potential Roles for Amyloid Imaging

- Accurate diagnosis of AD
- Early diagnosis and intervention when minimally impaired
- Investigate the spatial and temporal pattern of Aβ deposition and its relation to disease progression and cognitive decline
- Subject selection for anti-Aβ trials
- Monitor the effectiveness of anti-Aβ therapy

Ideal Amyloid Ligand

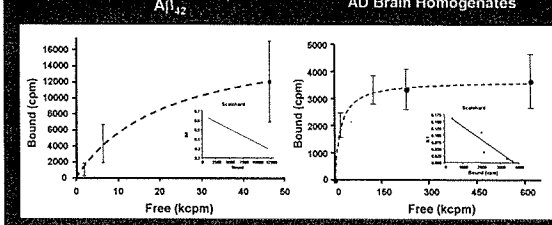
- Easily labeled with ^{18}F, ^{99m}Tc, ^{123}I
- Lipid soluble (crosses BBB)
- High affinity and selectivity for Aβ plaques
- Slow dissociation from binding site
- Rapidly cleared from blood
- Not metabolized
- Provide quantitative and reproducible information about Aβ burden in the brain

In Vitro Binding Criteria

- Saturable Binding
- Specific Binding
- Stereoselectivity
- Appropiate Co-Localization w/IHC

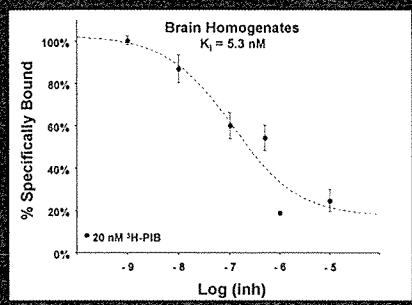
PIB as a marker of Aβ plaques

^3H-PIB *in vitro* saturation binding studies



PIB as a marker of Aβ plaques

^{3}H-PIB *in vitro* inhibition studies



PIB as a marker of Aβ plaques

Immunofluorescence (IF)/Immunohistochemistry (IHC) analysis of PIB binding to Aβ plaques

PIB

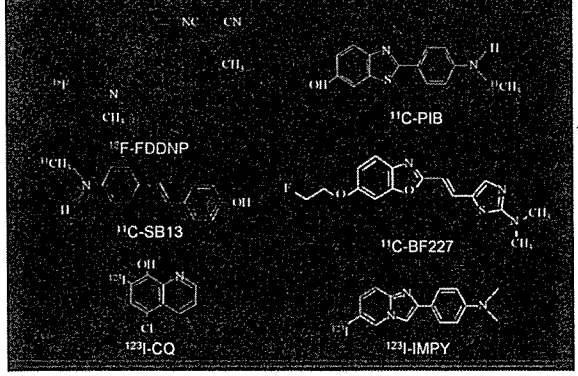
ThS

In vivo Aβ Amyloid Imaging

Aβ Ligand Strategies

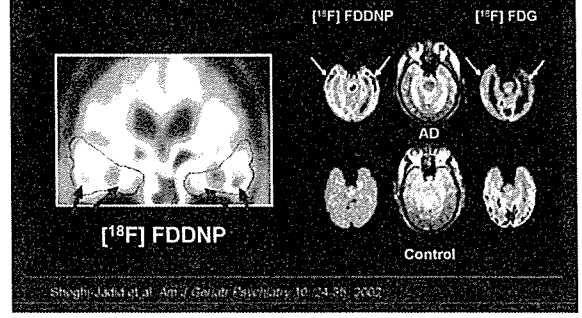
- Histological Dyes
  - Thioflavin T
  - Congo Red
  - Chrysamine G
  - Acridine Orange
- NSAID Derivatives
- MPACs
- Aβ Fragments
- Antibodies

Aβ Imaging in Humans

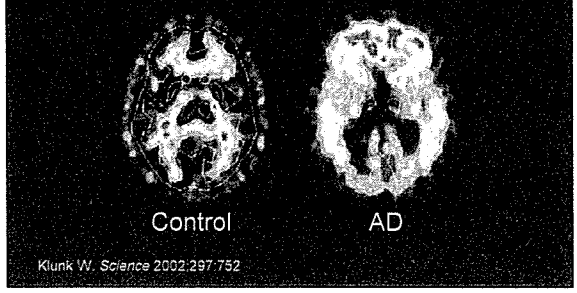


Aβ Amyloid Imaging

[^{18}F] FDDNP

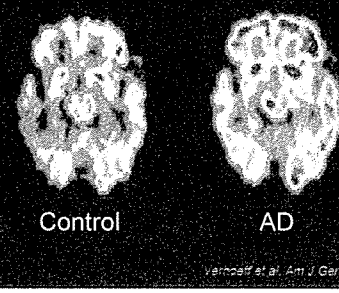


Aβ Amyloid Imaging
[^{11}C] 6-OH-BTA-1 (PIB)



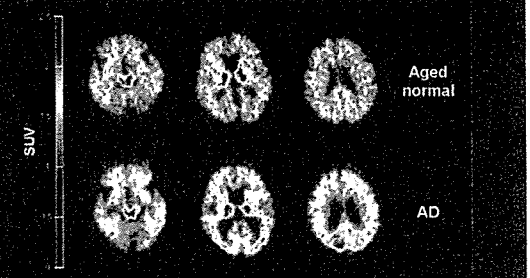
Klunk W. *Science* 2002;297:752

Aβ Amyloid Imaging
^{11}C-SB13



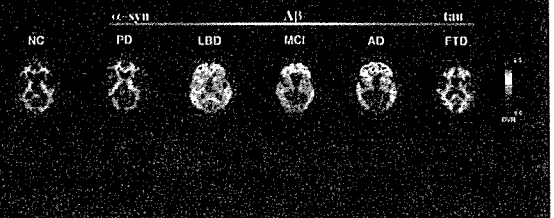
Verhoeff et al. Am J Geriatr Psychiatry, 2004

[^{11}C]BF-227



Kudo, Okamura, Furumoto et al. J Nucl Med. I

Aβ Amyloid Imaging
^{11}C-PIB



Villemagne et al. Neuroradiology Journal, 2006

AIMS
Overview

- Determine Aβ burden using ^{11}C-PIB PET in healthy ageing, mild cognitive impairment, Alzheimer's disease and other dementias
- Correlate Aβ burden to clinical features, cognitive status and glucose metabolism
- Evaluate the diagnostic utility of PIB PET
- Compare Aβ burden as measured by ^{11}C-PIB with previously established neuropathological findings in AD

Methods

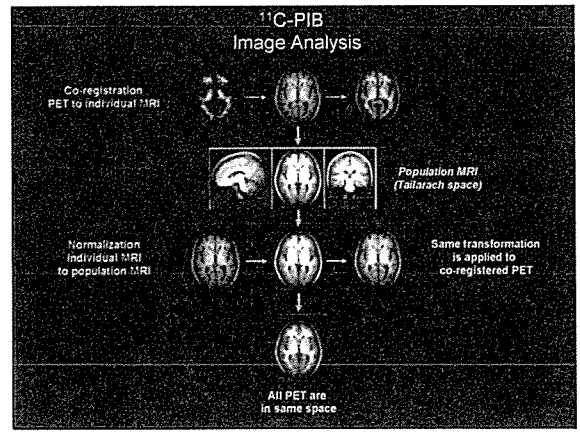
- 34 age-matched healthy controls (HC)
- 43 subjects meeting criteria for MCI (*Petersen et al., 2001*)
- 66 subjects with dementia
  - 44 subjects with NINCDS-ADRDA criteria for probable AD
  - 12 subjects meeting criteria for DLB (*McKeith et al., 1996*)
  - 10 subjects meeting criteria for FTD (*Neary et al., 1998*) + MRI & FDG
- 1 subject with Parkinson's disease

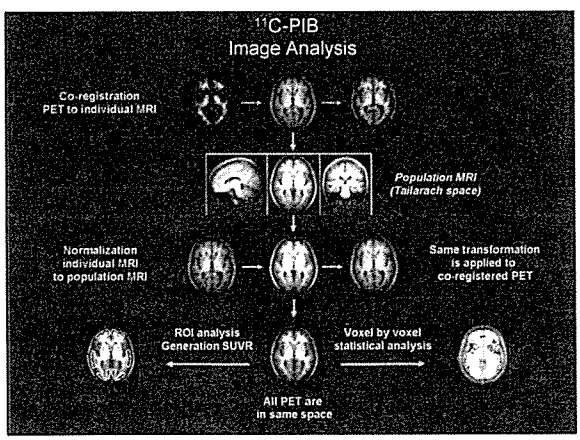
Extensive Neuropsychological Evaluation
(including CDR, MMSE, CVLT II, CAT Fluency, Rey Figure, etc)

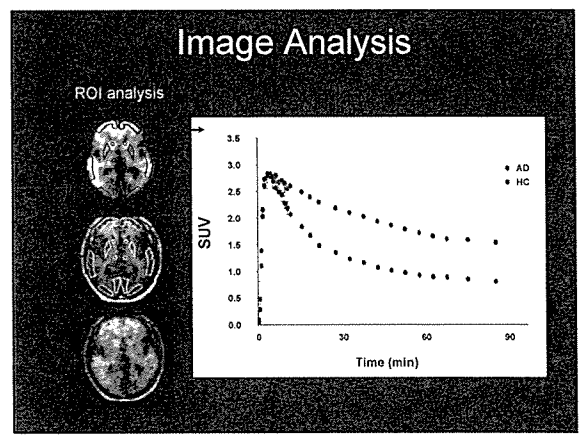
MRI: SPGR scans for screening and PET-MR co-registration

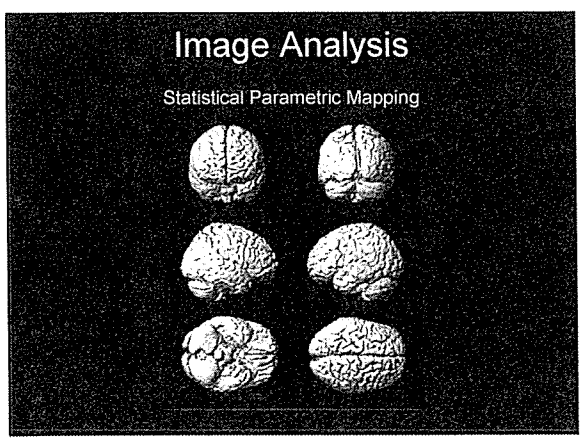
Methods

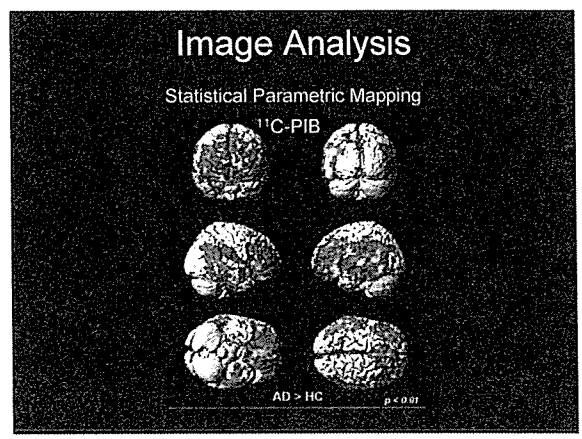
- PET
  - 10 mCi of ^{11}C-PIB iv
  - Sequential imaging from 0 to 90 min (n=68)
  - Equilibrium imaging 40-70 mpi (n = 78)
- Image Analysis
  - ROIs placed on co-registered MRI
  - Generation of time-activity curves (TAC)
- Calculation of Region to Cb Ratios ($SUVR_{40-70}$)
- Calculation of Distribution Volume Ratio (DVR)
  - Graphical analysis w/Cb as input function
  - *(Logan et al., 1996; Price et al., 2005)*
- Statistical Analysis:
  - *Wilcoxon Signed-Ranks test*
  - *Dunnet's test against controls*
  - *Tukey-Kramer HSD for group means*
  - *Pearson correlation between Aβ burden and clinical parameters*











Evaluation and Optimization of a Simplified Quantification Approach for ^{11}C-PIB

Objective

Evaluate a minimally invasive method for Aβ burden quantification in the human brain, suitable for routine clinical application, using ^{11}C-PIB and PET

Tracer Kinetics

Quantification Strategies

Full Kinetic

Graphical

Equilibrium

- Continuous Infusion
- Delayed scanning
- Pseudoequilibrium

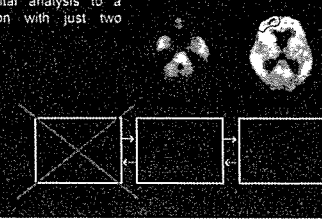
Tracer Kinetics

- Highly invasive
- Sometimes not possible
- Difficult for some patient populations or in serial/longitudinal studies

Reduces the compartmental analysis to a single differential equation with just two unknowns

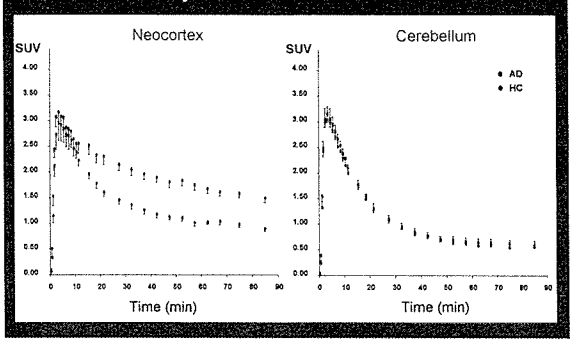
$$\frac{dC_2}{dt} = k_1 C_1(t) - k_2 C_2(t)$$

$$\frac{dC_2}{dt} = k_1 C_1(t) \otimes e^{-k_2 t}$$



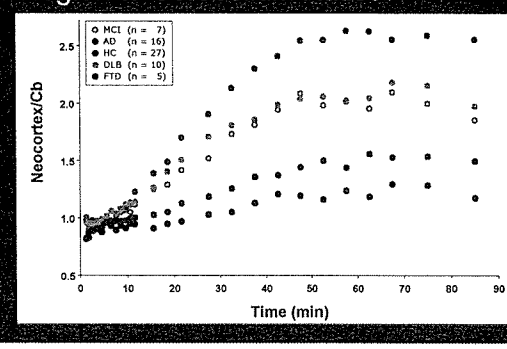
Tracer Kinetics

Time-Activity Curves



Tracer Kinetics

Region to Cerebellum Ratios



Tracer Kinetics

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Tracer Kinetics

Quantification Strategies

Full Kinetic

Equilibrium

- Continuous Infusion
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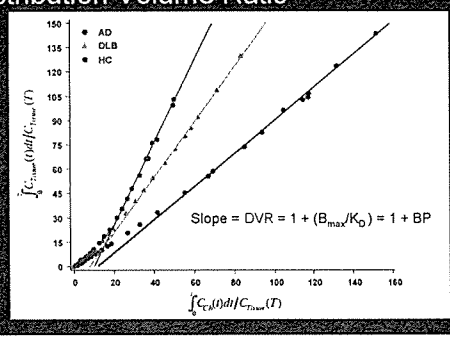
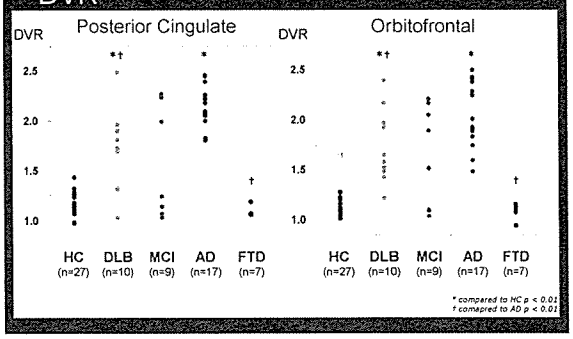
Tracer Kinetics

Distribution Volume Ratio



Aβ burden Quantification

DVR



Tracer Kinetics

Quantification Strategies

Full Kinetic

Graphical

- Continuous Infusion
- Delayed scanning
- Pseudoequilibrium

Tracer Kinetics

Quantification Strategies

Full Kinetic

Graphical

- Continuous Infusion
- Pseudoequilibrium

Tracer Kinetics

Equilibrium Scanning

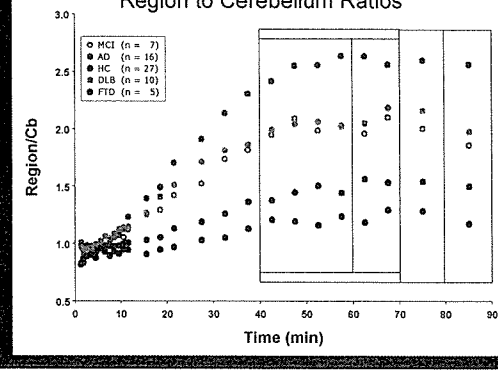
^{11}C-PIB

$\frac{ROI}{Cb}$ = = BP +1 = (B_{max}/K_D) +1

40-70 min
post-injection

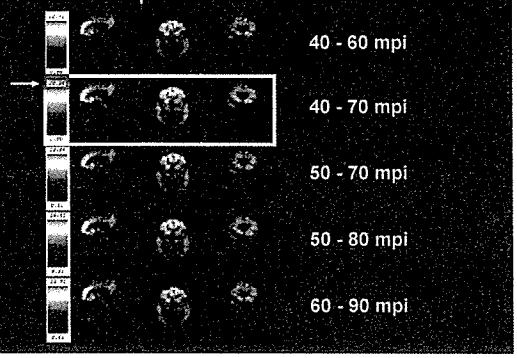
^{11}C-PIB

Region to Cerebellum Ratios



^{11}C-PIB

Simplified Quantification



^{11}C-PIB

Simplified Quantification

Neocortical DVR vs $SUVR_{40\text{-}70}$

40-60 min	***0.992***
40-70 min	***0.988***
50-70 min	***0.976***
50-80 min	***0.970***
60-90 min	***0.946***

(n = 70)

^{11}C-PIB

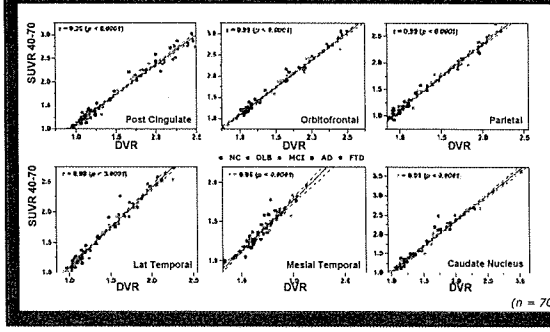
Neocortical $SUVR_{40\text{-}70}$
Effect Size
AD vs HC

40-60 min	***1.81***
40-70 min	***1.79***
50-70 min	***1.73***
50-80 min	***1.72***
60-90 min	***1.76***

(n = 70)

^{11}C-PIB

DVR vs $SUVR_{40\text{-}70}$

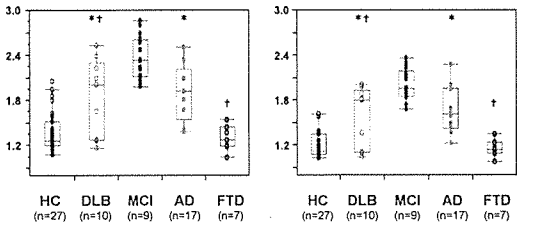


(n = 70)

Aβ burden Quantification

$SUVR_{40-70}$ DVR

Neocortex



Summary

- Both graphical (DVR) and simplified equilibrium scanning approaches (SUVR) using the cerebellum as input function allow reliable and reproducible quantitative statements on Aβ burden in the brain, requiring no blood sampling
- Summed SUV_{40-70} images provide the highest count-rate PET images, appropriate for visual analysis
- DVR is highly correlated with $SUVR_{40-70}$ ($r > 0.95$)

Conclusions

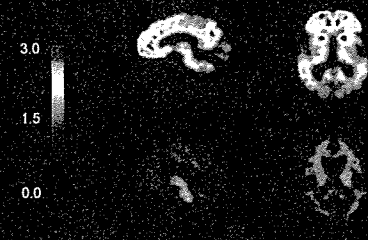
- SUVR40-70 values obtained from a single 30-min ^{11}C-PIB PET scan appear:
  - *acceptable for quantification of Aβ burden*
  - *suitable for clinical studies particularly in the elderly and cognitively impaired who may not be able to tolerate a prolonged scan,*
  - *allow maximizing resources by using a single cyclotron run to provide two individual doses to be injected 35 min apart*
- A simple quantification strategy, based on equilibrium scanning will further facilitate widespread clinical application of the technique.

In vivo Aβ Amyloid Imaging in Alzheimer's disease

AIMS

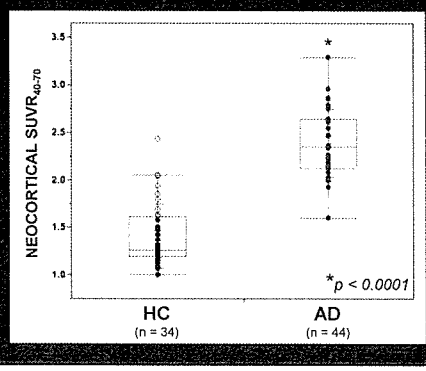
- Determine Aβ burden using ^{11}C-PIB PET in Alzheimer's disease age-matched controls
- Correlate Aβ burden to clinical features, cognitive status and glucose metabolism
- Evaluate the diagnostic utility of PIB PET
- Correlate Aβ burden as measured by PET with neuropathology and IHC studies

^{11}C-PIB PET

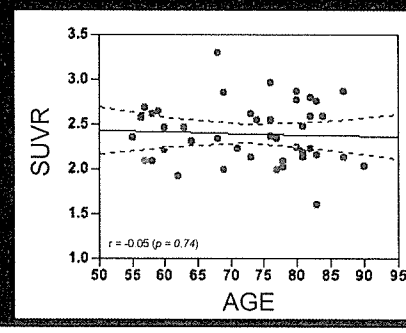


Summed images: 40–70 minutes post-PIB injection

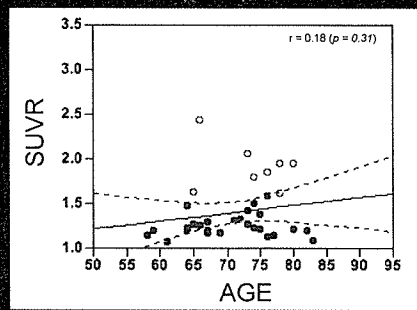
Aβ burden Quantification



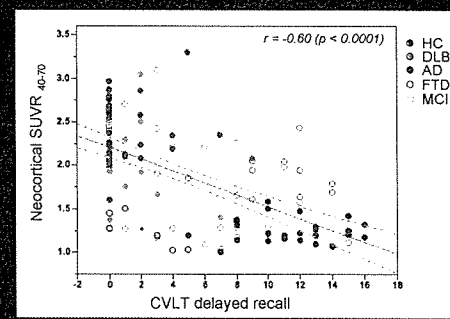
PIB vs Age
AD
(n = 44)



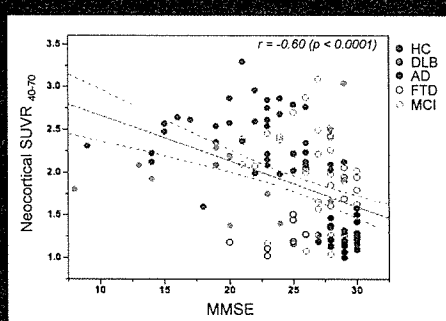
PIB vs Age
HC
(n = 34)



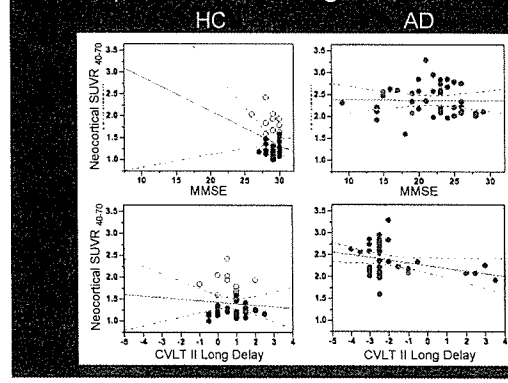
^{11}C-PIB
Memory impairment vs Aβ burden



^{11}C-PIB
Disease severity vs Aβ burden



Aβ burden and Cognitive Status

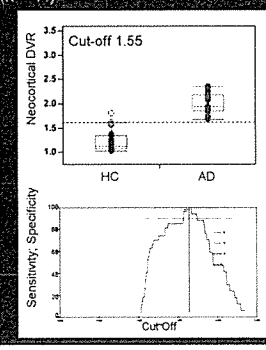


^{11}C-PIB PET
$SUVR_{40-70}$

	HC	AD
Frontal Ctx	1.4	2.5
Posterior Cingulate	1.5	2.6
Caudate Nuc	1.5	2.7
Mesial Temp	1.4	1.6
Occipital	1.4	1.9
White Matter	1.9	1.8

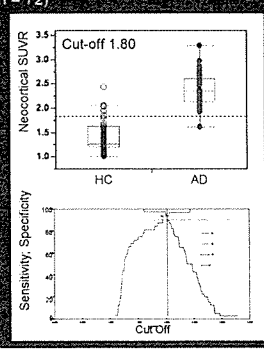
PIB DVR for Diagnosis of AD
ROC analysis
(n = 44)

Sensitivity = 1.00
Specificity = 0.85
Accuracy = 0.91
Prevalence = 0.39
PPV = 0.81
NPV = 1.00
+LK = 6.75
- LK = 0.00

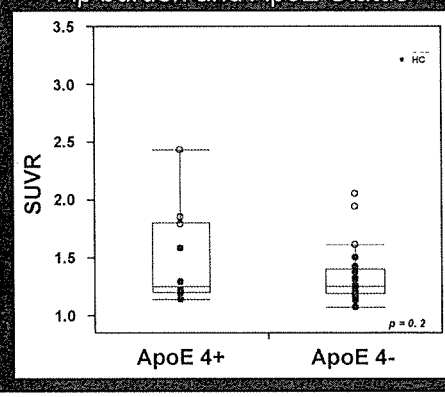


PIB SUVR for Diagnosis of AD
ROC analysis
(n = 72)

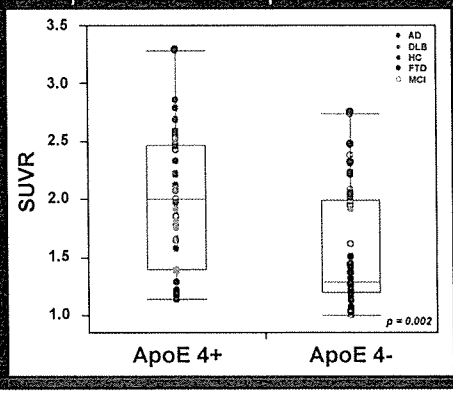
Sensitivity = 0.98
Specificity = 0.84
Accuracy = 0.92
Prevalence = 0.56
PPV = 0.89
NPV = 0.96
+LK = 6.24
- LK = 0.03



Aβ burden and ApoE Status



Aβ burden and ApoE Status

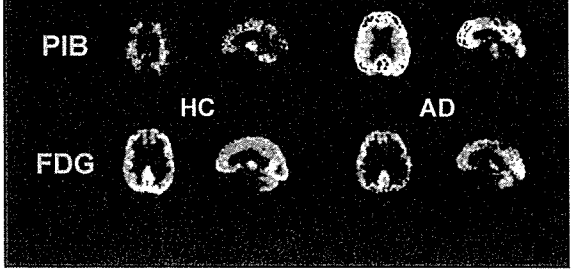


^{11}C-PIB and ^{18}F-FDG
in the Diagnosis of Alzheimer's Disease

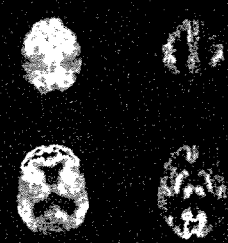
Background

- Lack of accurate tests for Alzheimer's Disease (AD)
- Gold standard: post-mortem demonstration of Aβ plaques and NFTs
- Clinical assessment (Knopman et al 2001)
  - Probable AD: sensitivity 80%, specificity 70%
  - Possible AD: sensitivity 93%, specificity 48%
- No blood test available at present
- Structural neuroimaging (CT and MRI) neither sensitive nor specific
- Functional neuroimaging (FDG PET)
  - Sensitivity: 85%, Specificity: 70% - 90% (Silverman et al. 2004)

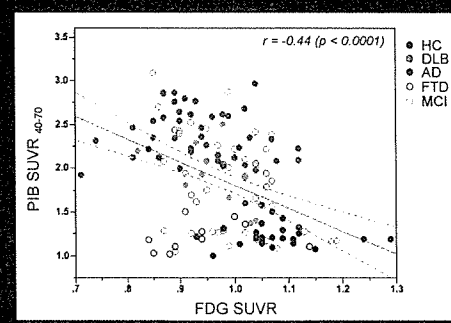
^{11}C-PIB and ^{18}F-FDG in the diagnosis of Alzheimer's disease



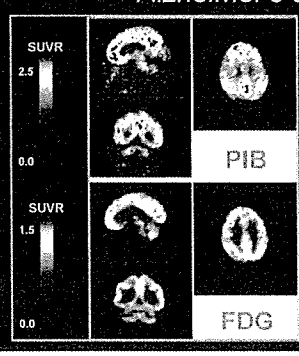
^{11}C-PIB - ^{18}F-FDG AD



^{11}C-PIB - ^{18}F-FDG Neocortex



^{11}C-PIB and ^{18}F-FDG in the diagnosis of Alzheimer's disease



AD
(79 yo, MMSE 27)

Diagnostic Accuracy

PIB vs FDG

	SENSITIVITY	SPECIFICITY	ACCURACY	*Reader agreement (κ)*
PIB VISUAL	0.98	0.89	*0.90*	*0.84*
FDG VISUAL	0.80	0.68	*0.72*	*0.56*
PIB DVR	1.00	0.92	*0.95*	
FDG SUVR	0.92	0.80	*0.86*	

Mean of 3 readers
15 AD & 25 age-matched controls

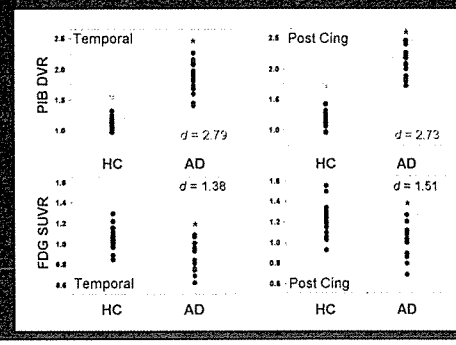
Effect of Age on Visual Diagnostic Accuracy

Age	FDG SENSITIVITY	FDG SPECIFICITY	FDG ACCURACY	PIB ACCURACY
< 75 yo (mean age 61 yo)	1.00	0.79	*0.85*	*0.87*
> 75 yo (mean age 81 yo)	0.63	0.44	*0.53*	*0.94*

Mean of 3 readers
15 AD & 25 age-matched controls

Diagnostic Power

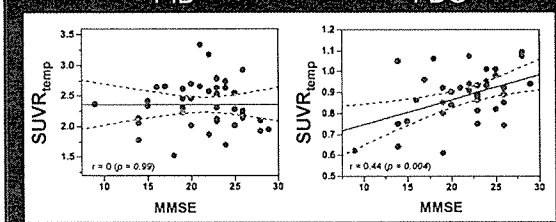
PIB vs FDG



Aβ Burden and Glucose Metabolism vs Disease Severity

AD

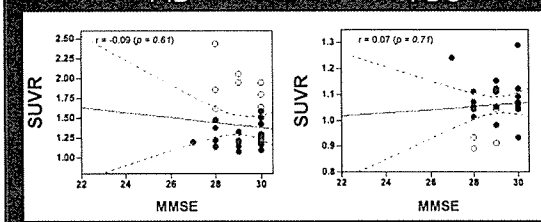
PIB FDG



Aβ Burden and Glucose Metabolism vs Disease Severity

HC

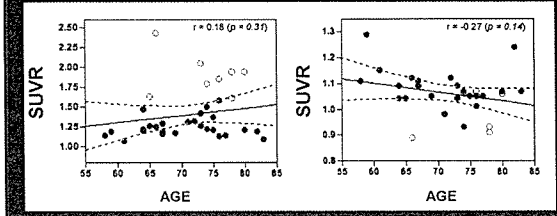
PIB FDG



Aβ Burden and Glucose Metabolism vs Age

HC

PIB FDG



Summary

- The quantitative analysis of PIB PET revealed robust differences in DVR between AD and HC
- Accuracy of PIB is limited by cortical PIB retention, retention thatmay represent preclinical Alzheimer's disease
- Visual interpretation of a 30-minute PIB PET image had similar accuracy to quantitative analysis of a 90 minute dynamic scan,
- PIB PET visual reading was more accurate than FDG PET
- The inter-observer agreement was excellent for PIB, and was higher than for FDG
- Visual reading of FDG scan has higher diagnostic accuracy in a younger population, while PIB results are not affected by age
- Glucose hypometabolism correlates with dementia severity but PIB uptake does not

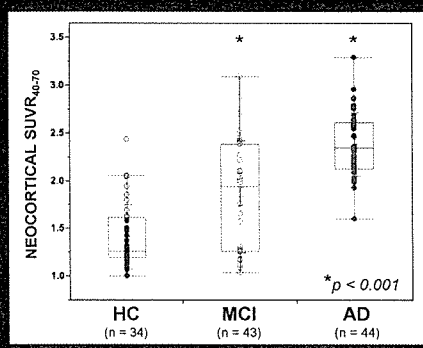
Conclusions

Visual interpretation of PIB images:

- accurately distinguishes AD from controls and is not affected by age or disease severity
- has similar accuracy to quantitative analysis
- appears superior to visual reading of FDG images with better reader agreement, sensitivity and specificity, particularly in older subjects.

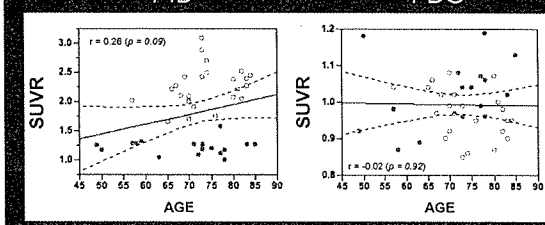
^{11}C-PIB and ^{18}F-FDG in Mild Cognitive Impairment

Aβ burden Quantification



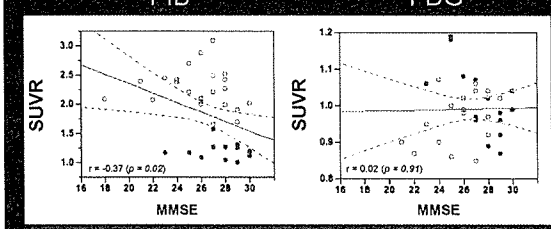
Aβ Burden and Glucose Metabolism vs Age

MCI

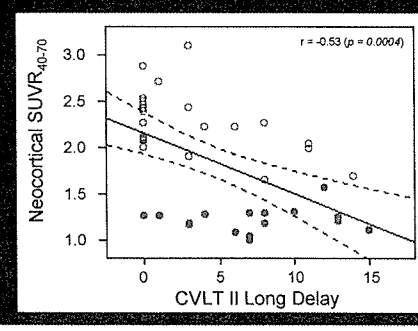


Aβ Burden and Glucose Metabolism vs Disease Severity

MCI



^{11}C-PIB Memory impairment vs Aβ burden MCI



Correlation with Neuropathology

Post Mortem Studies of Senile Plaques

- density does not correlate well with dementia severity.
- present in cognitively intact older persons (30% of those aged >75).
- present in most cases of Dementia with Lewy Bodies (DLB) (10-15% have none).
- not present in FTD

^{11}C-PIB PET SUVR$_{40-70}$

	HC		AD	
Frontal Ctx	1.4	⟶	2.5	(80%)
Posterior Cingulate	1.5		2.6	(80%)
Caudate Nuc	1.5		2.7	(86%)
Mesial Temp	1.4	⟶	1.6	(14%)
Occipital	1.4		1.9	(36%)
White Matter	1.9		1.8	(-8%)

In Vitro Quantification

Frontal Ctx

	HC		AD	
Image Quantification	0.006	⟶	0.044	⟶ (617%)
WB insoluble fraction (IF)	117	⟶	269	⟶ (130%)
ELISA Aβ_{40} IF	0.3	⟶	3.8	⟶ (1146%)
ELISA Aβ_{42} IF	6.7	⟶	12.9	⟶ (91%)

Aβ burden and plaque deposition

PIB binding matches histopathology of Aβ

HC HC MCI AD

Braak Stages (1997) A B C

^{11}C-PIB PET Imaging in the Differential Diagnosis of Dementia

Background

- Prevalence of dementia
  - Alzheimer's Disease – 60-70%
  - Dementia with Lewy Bodies - 15%
  - Frontotemporal Dementia - 15%
  - Multi-infarct dementia – 5%
  - Mixed Vascular/Alzheimer's Dementia
  - Movement Disorders - PD, CBD, PSP
- Clinical diagnosis is 85% sensitive in established dementia but only 40-60% specific for AD vs other dementias
- Aβ deposition precedes cognitive decline by up to 10 years:
  - Aβ plaques present in 25% of normal persons aged 75
  - this equals the prevalence of AD at age 85
  - In Down's Syndrome Aβ plaques precede dementia

Results

Clinical Data

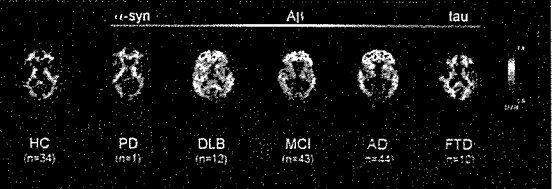
	HC	DLB	AD	MCI	FTD
	(n=34)	(n=13)	(n=44)	(n=43)	(n=10)
AGE	71 ± 7	72 ± 6	73 ± 10	72 ± 9	68 ± 10
FEMALE: MALE	16:18	4:9	24:20	23:20	4:6
MMSE	29.2 ± 1	21.5 ± 7*	21.3 ± 4*	26.6 ± 3*	24.3 ± 2*
CDR	0	1.5 ± 0.8*	1.1 ± 0.6*	0.5 ± 0.1*	0.8 ± 0.7*

* Statistically significant results compared to controls ($p < 0.05$)

^{11}C-PIB

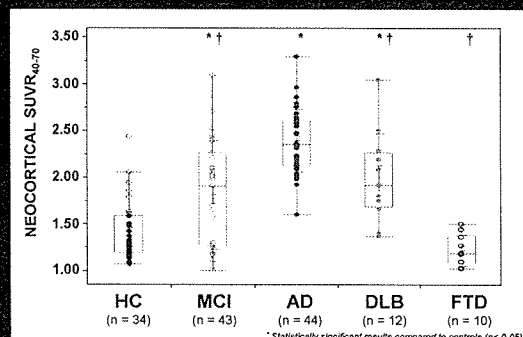
Neurodegenerative diseases associated with protein misfolding

TOTAL PIB Studies (27/02/2007) = 183



Stroke (n=26)
K channelopathy (n=1)

Aβ burden Quantification



(n = 143)

* Statistically significant results compared to controls ($p < 0.05$)

† Statistically significant results compared to AD ($p < 0.05$)

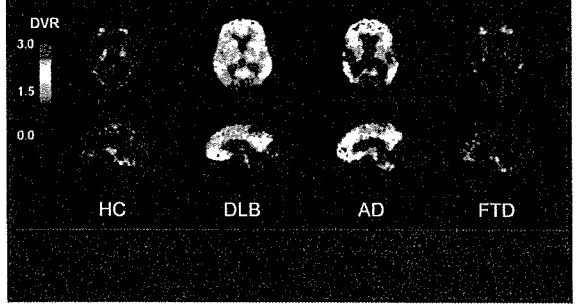
^{11}C-PIB PET
$SUVR_{40-70}$

	HC (n=34)	MCI (n=43)	AD (n=44)	DLB (n=12)	FTD (n=10)
Frontal Ctx	1.4	1.9*	2.5*	2.2*	1.2
Parietal Ctx	1.3	1.7*	2.3*	1.7*	1.2
Temporal Ctx	1.4	1.8*	2.4*	2.0*	1.2
Post Cingulate	1.5	2.0*	2.6*	2.2*	1.2
Caudate Nuclei	1.5	2.0*	2.7*	2.1*	1.3
Mesial Temp	1.4	1.5	1.6*	1.5	1.2
Occipital	1.4	1.6	1.9*	1.6	1.4
Midbrain	1.9	1.8	1.9	1.8	1.7
White Matter	1.8	1.8	1.8	1.8	1.6

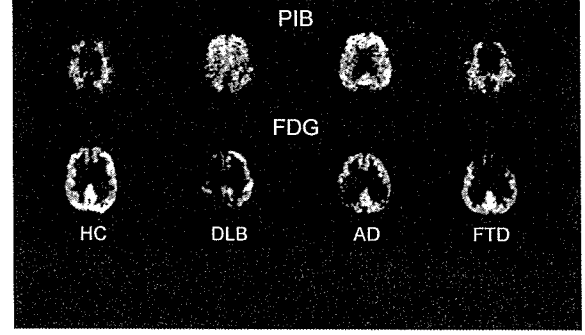
* Statistically significant results compared to controls ($p < 0.05$)

Results

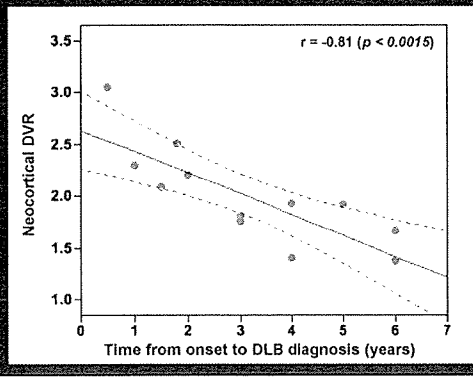
^{11}C-PIB PET



Results



Aβ burden and Clinical Onset



Summary

Imaging of Aβ accurately reflects the neuropathology of amyloid plaque deposition

Aβ accumulation appears to occur very early in the development of AD and does not correlate with the severity of dementia

PIB is not a marker of dementia severity

PIB will allow earlier and more accurate diagnosis of AD

This will allow earlier intervention and monitoring of specific anti-Aβ therapy improving the chances for a successful outcome

Longitudinal studies to more clearly define the patterns of Aβ deposition in the development of dementia are warranted

Summary

- All AD subjects showed extensive cortical and striatal Aβ burden but no correlation with the severity of cognitive impairment
- 59% of MCI and 23% of HC showed cortical Aβ with one HC subsequently progressing to MCI
- 60% of MCI convert to AD
- Mean age of controls is 72. Prevalence of AD at age 85 is 20-30%.

This supports the hypothesis that Aβ deposition occurs well before the onset of AD and can be detected with PIB PET

Summary

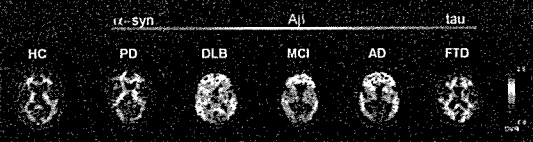
- DLB has variable and lower Aβ burden than AD despite worse cognitive function
- PIB PET cannot distinguish reliably between AD and DLB
- Greater Aβ burden was associated with more rapid development of the full DLB phenotype

This is consistent with the role of Aβ in promoting aggregation and exacerbation of α-synuclein dependent neuronal injury

- FTD showed a similar pattern of PIB retention as HC

PIB PET will assist in the differential diagnosis of AD from FTD

Summary



Our findings are consistent with a spectrum of neurodegenerative diseases associated with misfolded proteins.

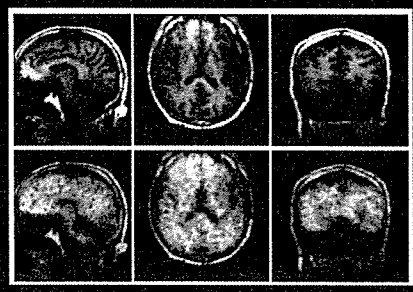
^{11}C-PIB PET demonstrates a robust increase in cortical retention in dementias associated with cortical Aβ amyloid deposition.

DLB BRAIN

Correlation of in vivo

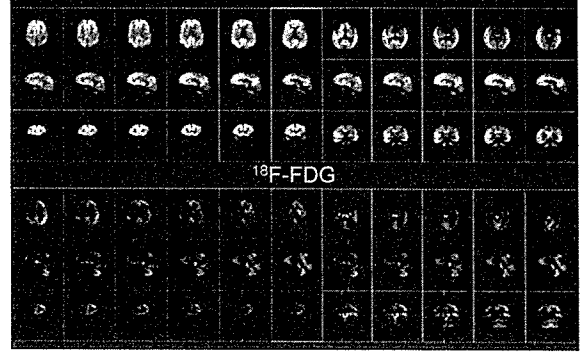
PIB PET vs Postmortem IHC levels

DLB BRAIN



DLB BRAIN

^{11}C-PIB



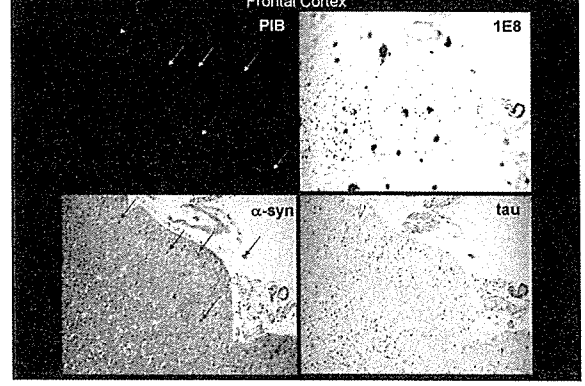
DLB BRAIN

^{11}C-PIB

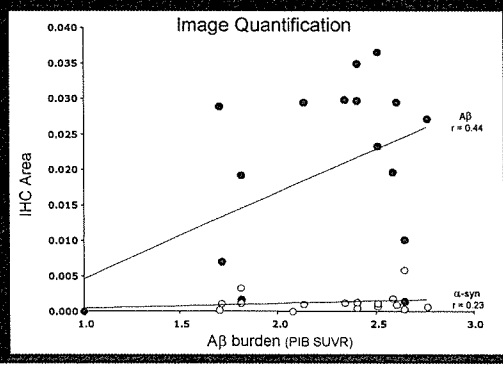
	DLB PIB SUVR	HC PIB SUVR	Z score
Superior Dorsolateral Prefrontal	2.14	1.31 ± 0.31	2.66
Somatosensory	1.82	1.25 ± 0.20	2.78
Parietal	2.03	1.29 ± 0.25	2.94
Posterior Cingulate	2.60	1.50 ± 0.36	3.07
Anterior Cingulate	2.59	1.52 ± 0.41	2.59
Ventral Dorsolateral Prefrontal	2.41	1.41 ± 0.37	2.69
Caudate Nuclei	2.64	1.46 ± 0.31	3.80
Putamen	2.10	1.45 ± 0.31	2.11
Thalamus	1.82	1.62 ± 0.23	0.86
Orbitofrontal	2.35	1.41 ± 0.32	2.94
Gyrus Rectus	2.76	1.55 ± 0.49	2.45
Temporal	2.51	1.37 ± 0.28	4.06
Mesial Temporal	1.72	1.36 ± 0.18	1.98
Occipital	1.71	1.40 ± 0.18	1.74
Midbrain	1.84	1.90 ± 0.21	-0.28
Pons	2.06	2.19 ± 0.26	-0.51
White Matter	2.08	1.84 ± 0.29	0.84

DLB Brain

Frontal Cortex

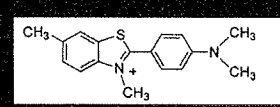


PIB vs IHC in DLB brain



In vitro Characterisation of PIB binding to α-synuclein.

Thioflavin T



PIB