Amyloid Imaging for Monitoring Clinical Trials

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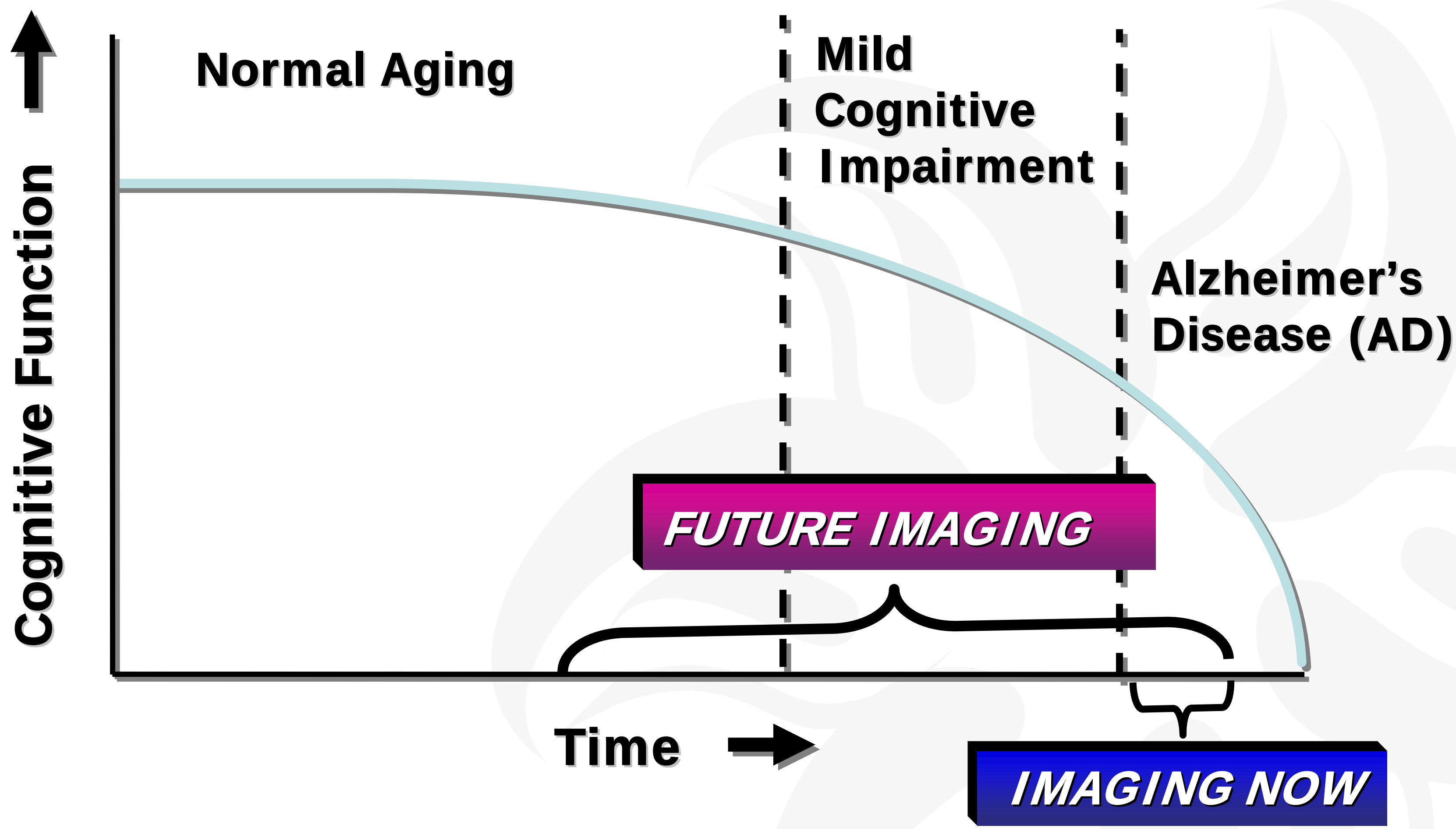
    - Co-inventor of FDDNP-PET (UCLA has licensed patent to Siemens)

Hypothetical Course of Brain Aging



Imaging Techniques and the Biological Processes They Measure

Imaging modality	**Biological process**
CT	**Atrophy, tumors**
MRI	**Atrophy, tumors, WM hyperintensity**
[F-18]FDG-PET	**Glucose metabolism**
[Tc-99m]Tc-HMPAO SPECT	**Blood flow**
[F-18]FDDNP-PET	**Amyloid plaques and tau tangles**
[C-11]PIB-PET	**Amyloid plaques**
[F-18]MPPF-PET	**Hippocampus, 5HT1A receptors**
Functional MRI	**Blood flow, functional connectivity**
DTI	**Neuronal connectivity, WM integrity**
MRS	**Metabolite concentrations**

Small et al. *Lancet Neurology*. 2008;7:161-72.

Issues to Consider

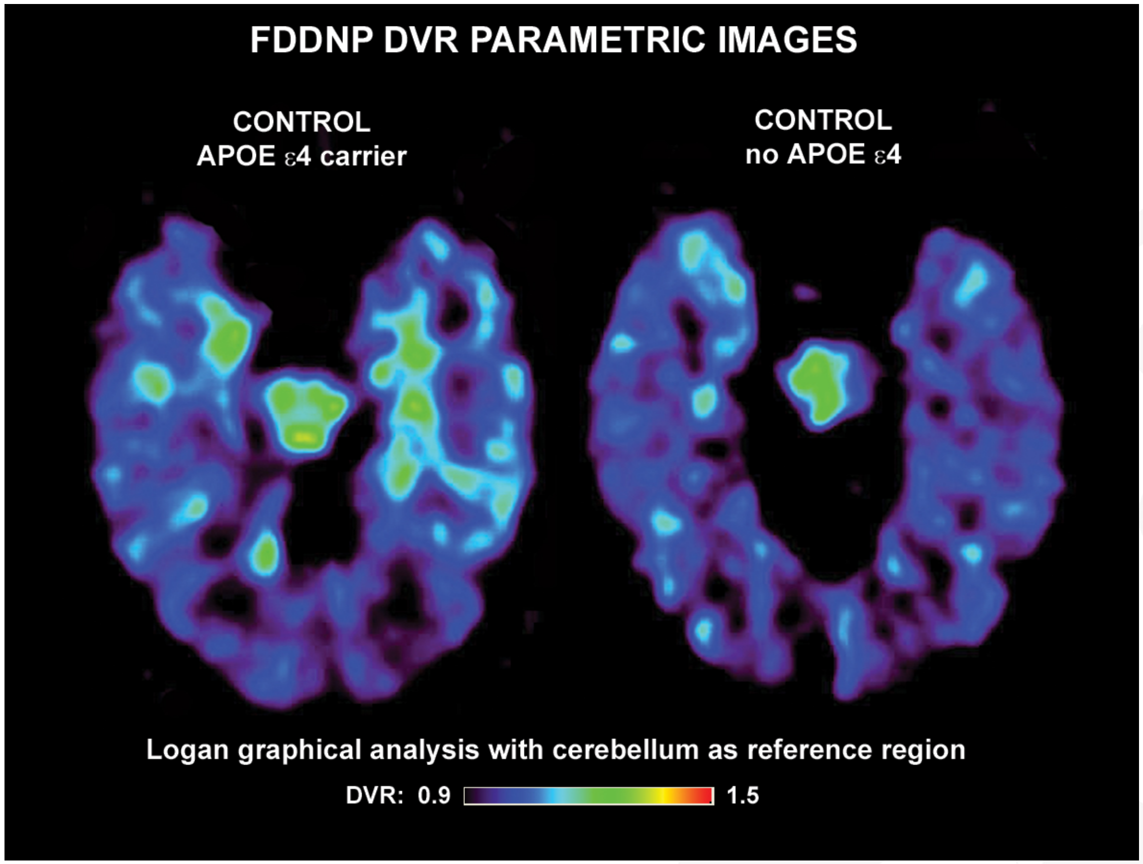
- What can amyloid PET contribute to clinical trials?
- What are some of the currently available probes and how do they differ?
- What studies are needed to demonstrate the utility of amyloid PET for clinical trials?
- What are some key methodological considerations for trial design?

Potential Amyloid-PET Contribution to Clinical Trials

- Diagnostic accuracy of subjects included in a study
  - Clinical diagnosis
  - “Amyloid” diagnosis
  - Sample “enrichment” by combining with other biomarkers (e.g., APOE-4)
- Monitoring
  - Whether a particular treatment changes the brain amyloid signal
  - Dose of treatment

Example of APOE-4 Enrichment Strategy

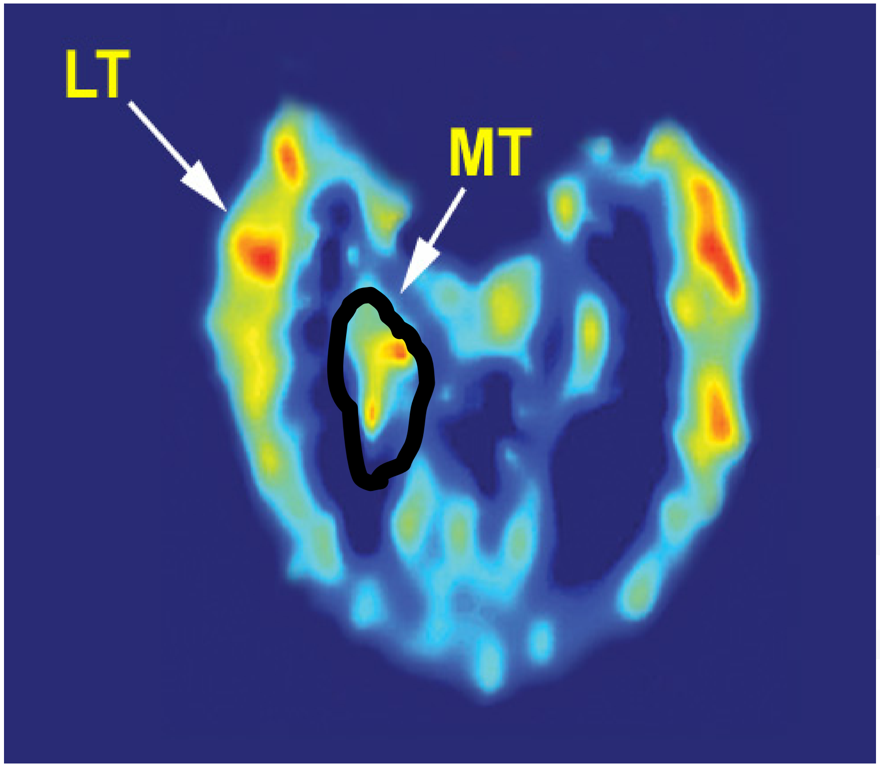
FDDNP Binding is Higher in Non-Demented People with the APOE-4 Genetic Risk for Alzheimer's Disease



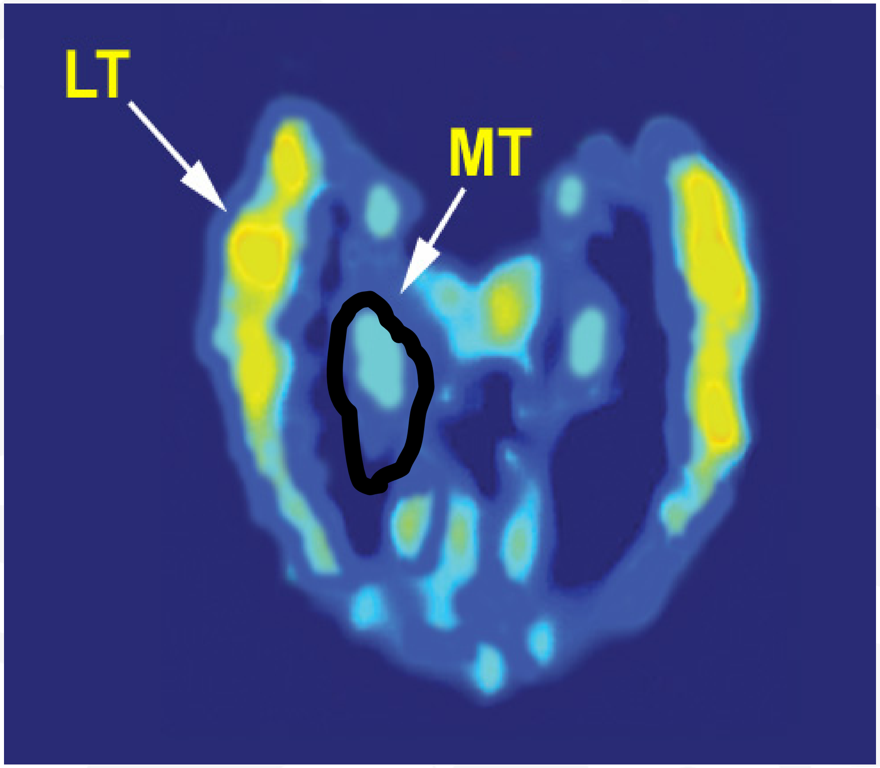
Small et al. Influence of cognitive status, age, and APOE-4 genetic risk on brain FDDNP-PET imaging in non-demented persons. *Arch Gen Psychiatry* (in press).

Example of Monitoring in Clinical Trials

Predicted Effect of *Anti-Tangle* Treatment on FDDNP Binding



Pre-Treatment



Post-Treatment

Amyloid Probes in Development

Reference	Imaging Compound	Imaging Technique	Study
Shoghi-Jadid et al	FDDNP	PET	Patients with AD
Friedland et al	Tc-10H3	SPECT	Patients with AD
Klunk et al	PIB	PET	Patients with AD
Mathis et al	BTA-1	PET	Baboons
Poduslo et al	MION-A	MRI	Mice PS
Poduslo et al	PUT-Gd-A	MRI	Mice PS
Wadghiri et al	Gd-DTPA-A	mMRI	Mice APP/PS
Mathis et al	BTA-1	Multiphoton	Mice APP/PS
Bacskai et al	Thioflavin-S	Multiphoton	Mice APP
Bacskai et al	PIB	Multiphoton	Mice APP

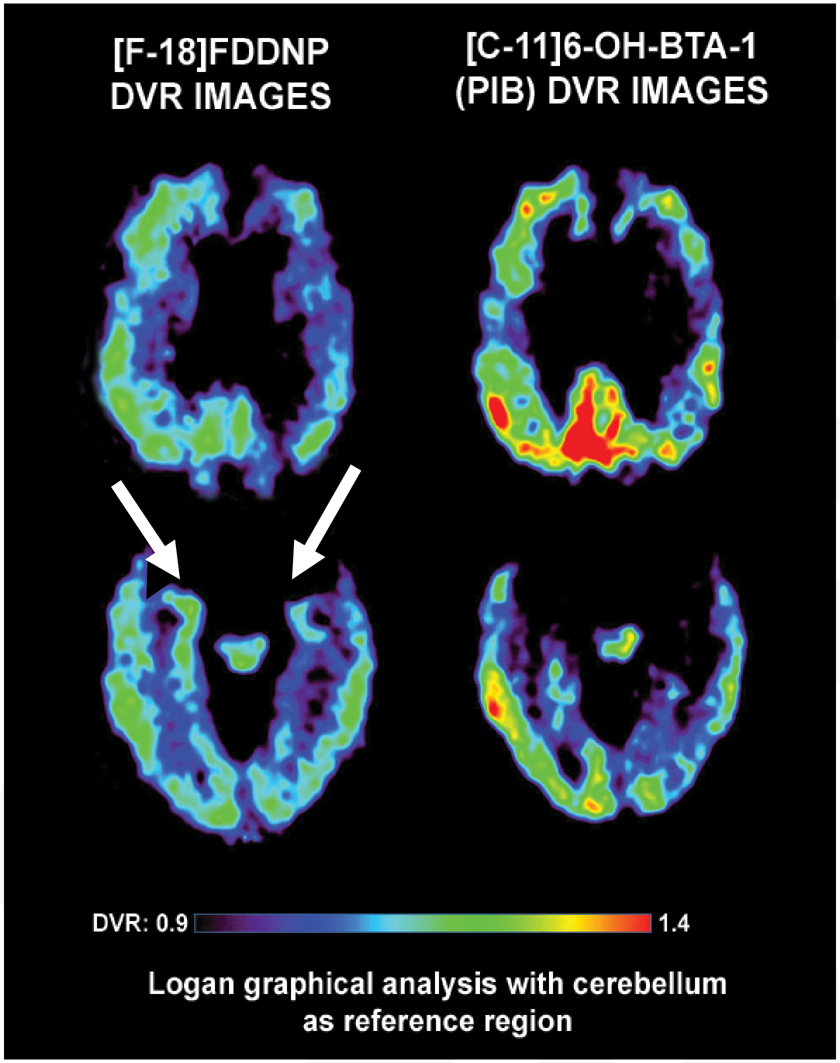
Adapted from Nordberg A. *Lancet Neurology* 2004

Differences Among Some Probes

Compound	Company	Target	Radiolabel
FDDNP	Siemens	Amyloid, Tau	F-18
PIB	GE	Amyloid	C-11
AV-45	Avid	Amyloid	F-18
SB-13		Amyloid	C-11

FDDNP and PIB (BTA) Imaging in a Patient with AD

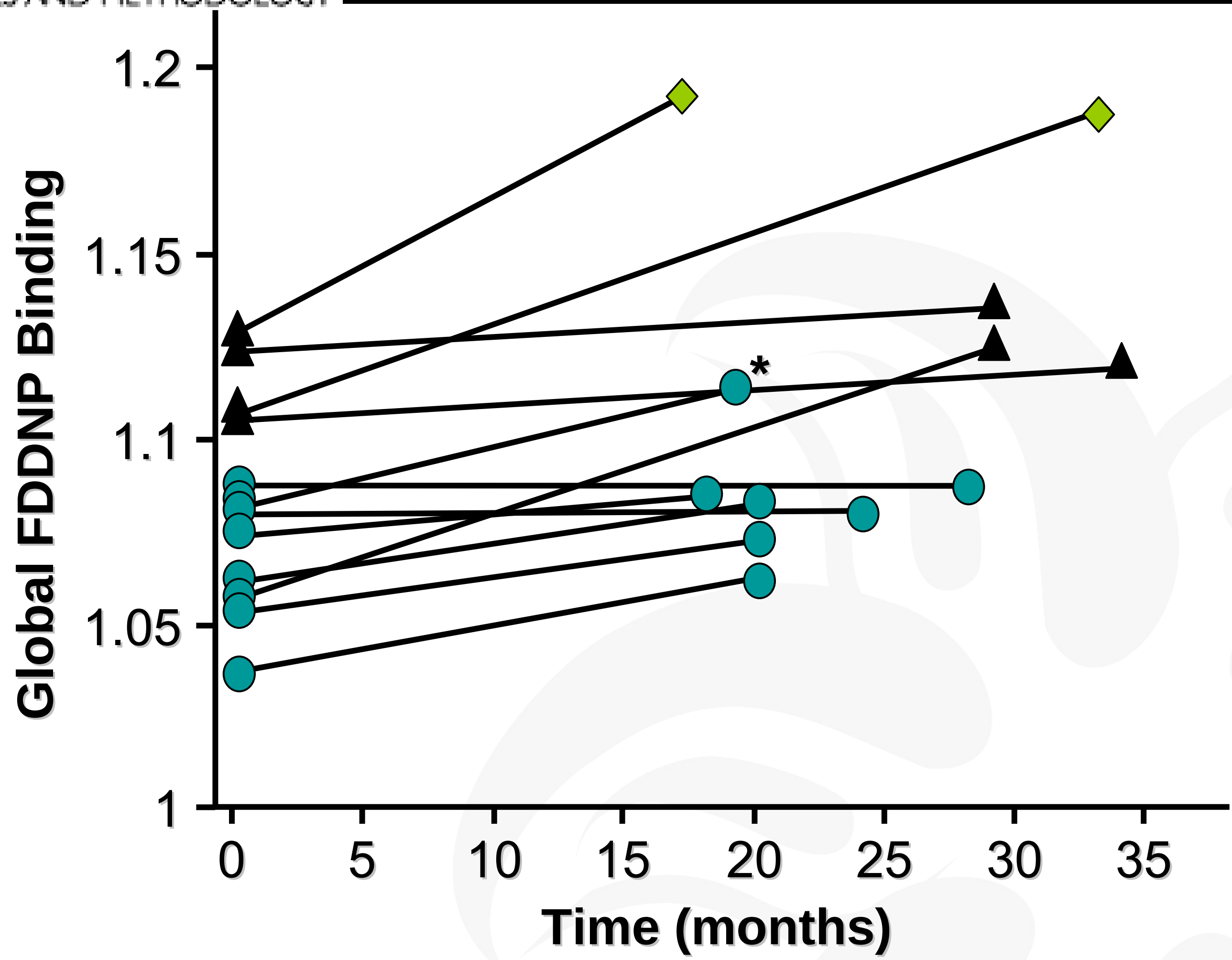
Medial temporal signal (arrows) observed in FDDNP but not BTA scanning in same patient



Studies Needed to Demonstrate Utility

- Differential diagnosis
  - Comparing AD, MCI, Normals
  - Comparing different forms of dementia
- Longitudinal studies
  - Showing that probe changes along with disease progression
- Treatment studies
  - Showing that signal decreases with treatment
  - Showing that disease improves with treatment

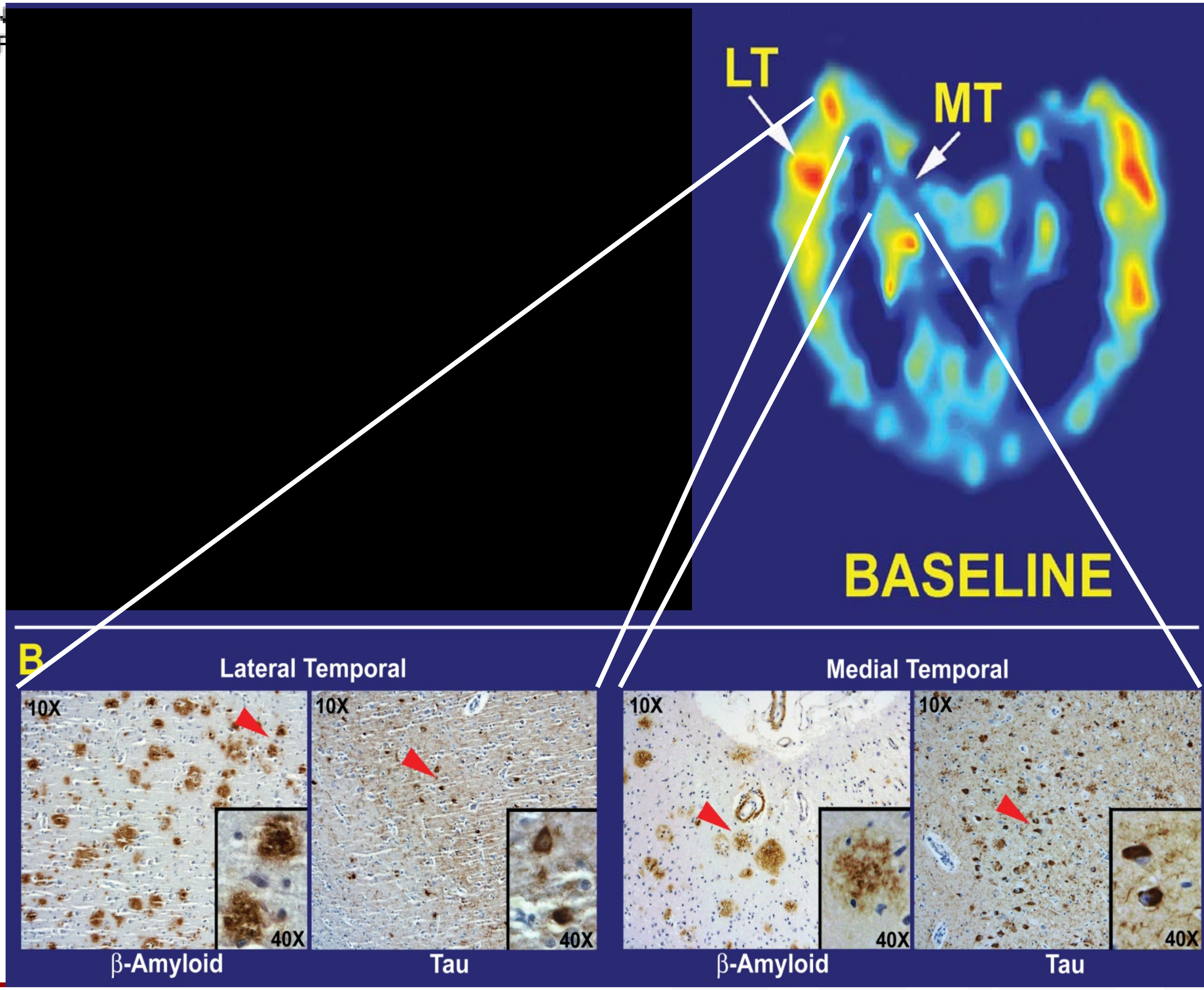
FDDNP Binding Increases With Clinical Progression



Small et al. *N Engl J Med* 2006;355:2652-63.

Circle = CTL; triangle = MCI; diamond = AD.

Regional Tau/Amyloid Differences



Small et al. *N Engl J Med* 2006:355:2652-63.

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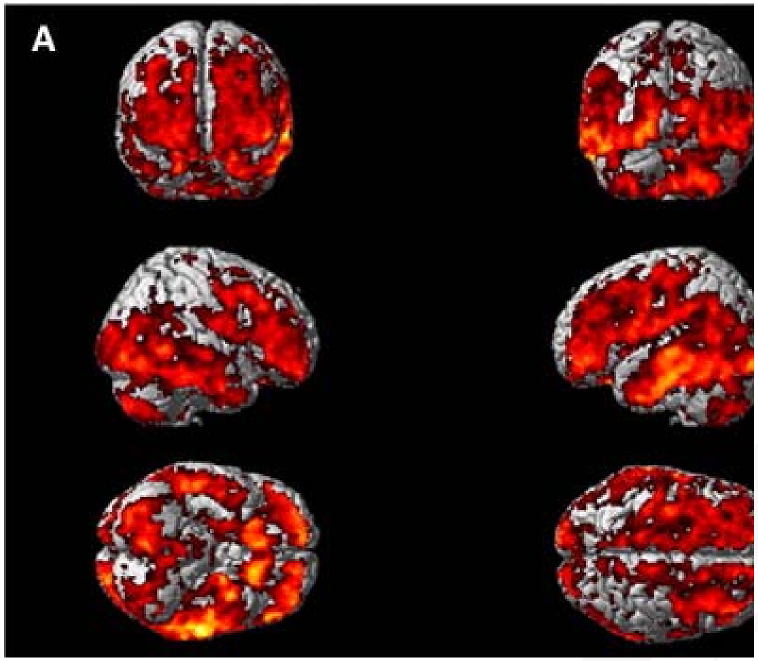
Probe/Disease Correlations: Beyond the Amyloid Hypothesis

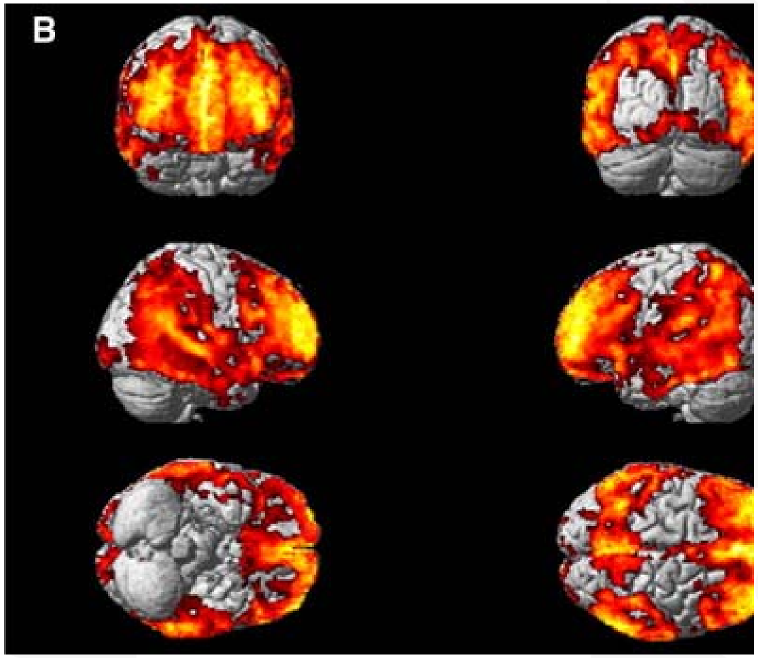
- Study of activated microglia marker, [11C](R)PK11195-PET, and amyloid marker [11C]PIB-PET
  - Both probes showed differences in cortical signal between AD and controls
  - MMSE scores in AD subjects correlated with levels of cortical microglial activation but not with amyloid load
- Recent studies of anti-amyloid treatments have not succeeded (e.g., Flurizan) or are showing mixed results (e.g., bapineuzumab)

Edison et al. Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* 2008.

Uptake in AD Vs. Controls



[11C](R)PK11195



[11C]PIB

Edison et al. Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* 2008.

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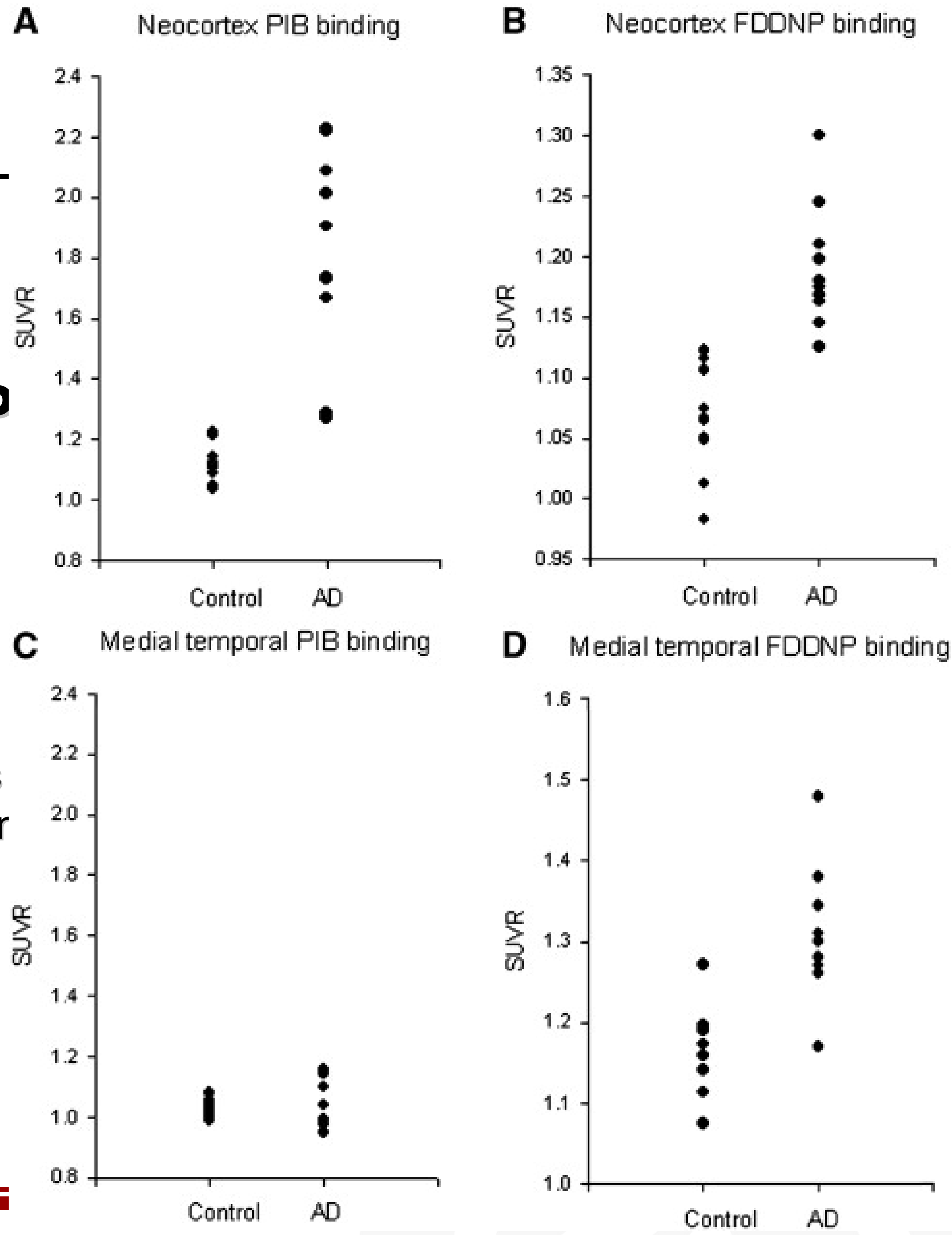
Tau Imaging May Facilitate Prevention Strategies

- Study of patients with AD, MCI and Normals using both PIB-PET and FDDNP-PET
  - Strong FDDNP binding, but negligible PIB binding in medial temporal cortex (amygdala, hippocampus, parahippocampal gyrus)
  - Both probes showed differences in cortical signal between AD and controls
  - Normal subjects had significant FDDNP binding in the medial temporal cortex, which correlated inversely with episodic memory measures
- Recent anti-tau treatments show promise (e.g., methylene blue [TauRx], AL-108 [Allon Therapeutics])

Shin et al. Multitracer PET imaging of amyloid plaques and neurofibrillary tangles in Alzheimer's disease *NeuroImage* 2008.

PIB and FDDNP Binding in AD and Controls



Shin et al. Multitracer PET imaging of amyloid plaques and neurofibrillary tangles in Alzheimer's disease *NeuroImage* 2008.

Key Methodological Considerations

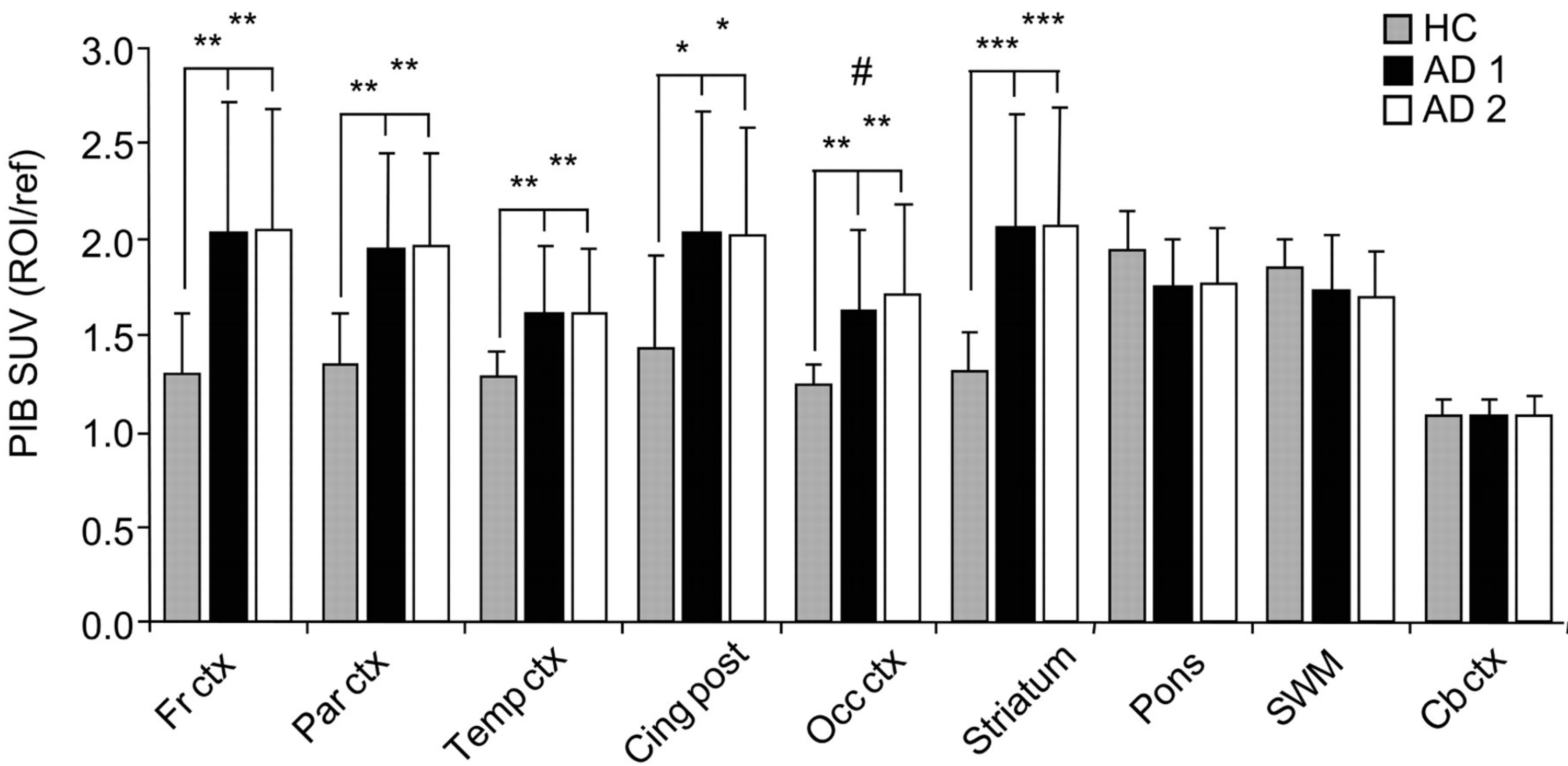
- Study duration
  - How long does it take to observe change?
  - Rate of change of probe in AD, MCI, Controls
  - Correlation of probe change rate and cognitive change rate
  - Estimated effect size for treatment
- Method of analysis
  - Region of interest
  - Partial volume correction
  - Head motion correction
  - 3-D surface projection mapping

Longitudinal Data

- FDDNP
  - Follow up data (2.4 yrs) on 23 subjects (12 MCI, 11 Controls)
  - MCI – significant decline in posterior cingulate, medial temporal and frontal regions
  - Controls – significant decline in medial and lateral temporal regions
  - Cognitive decline correlated with regional FDDNP decline
- PIB
  - Follow-up data (2.0 yrs) on 14 AD patients
  - FDG-PET measures and cognitive measures decline
  - PIB-PET retention was stable

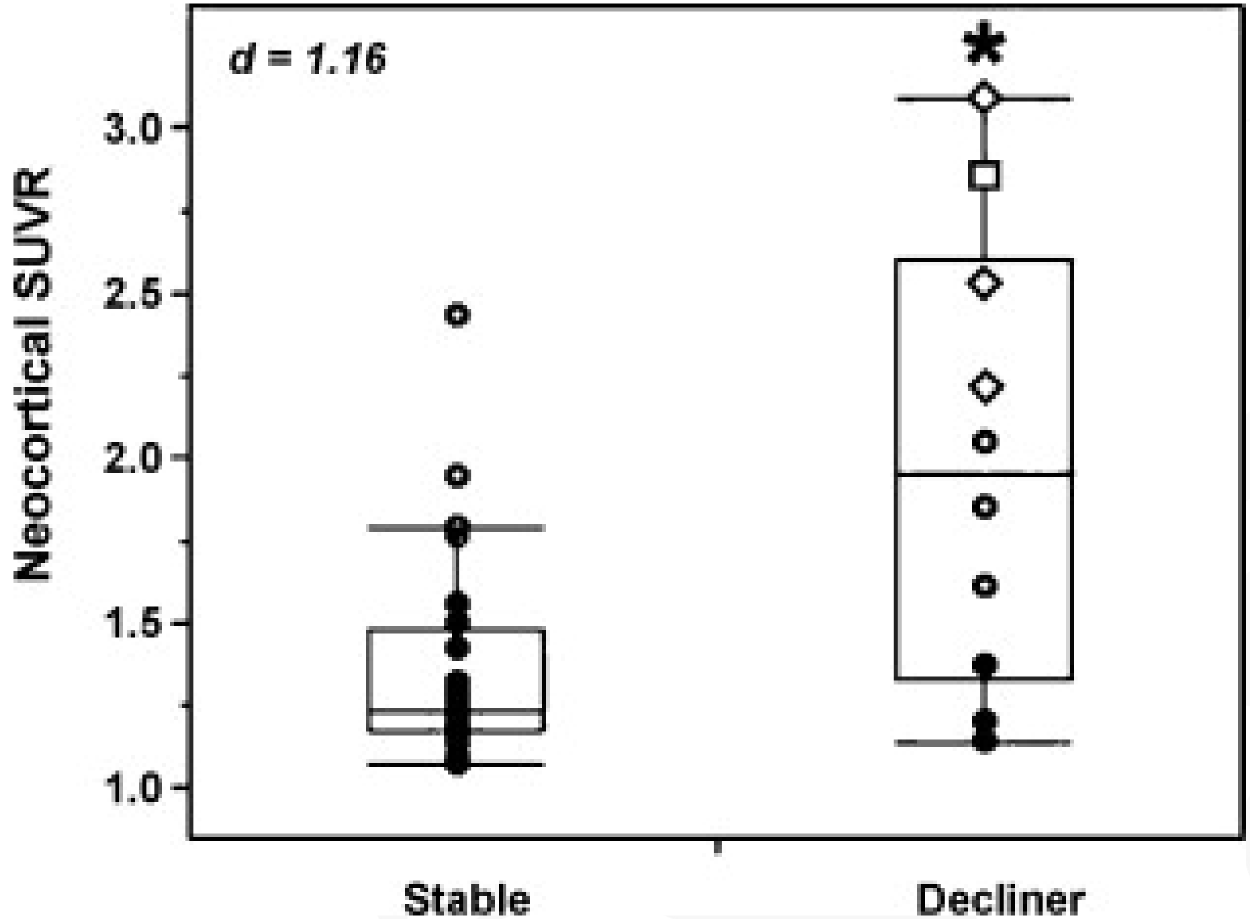
Engler et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006;129:_2856-66.

PIB-PET 2-Year Longitudinal Study in AD



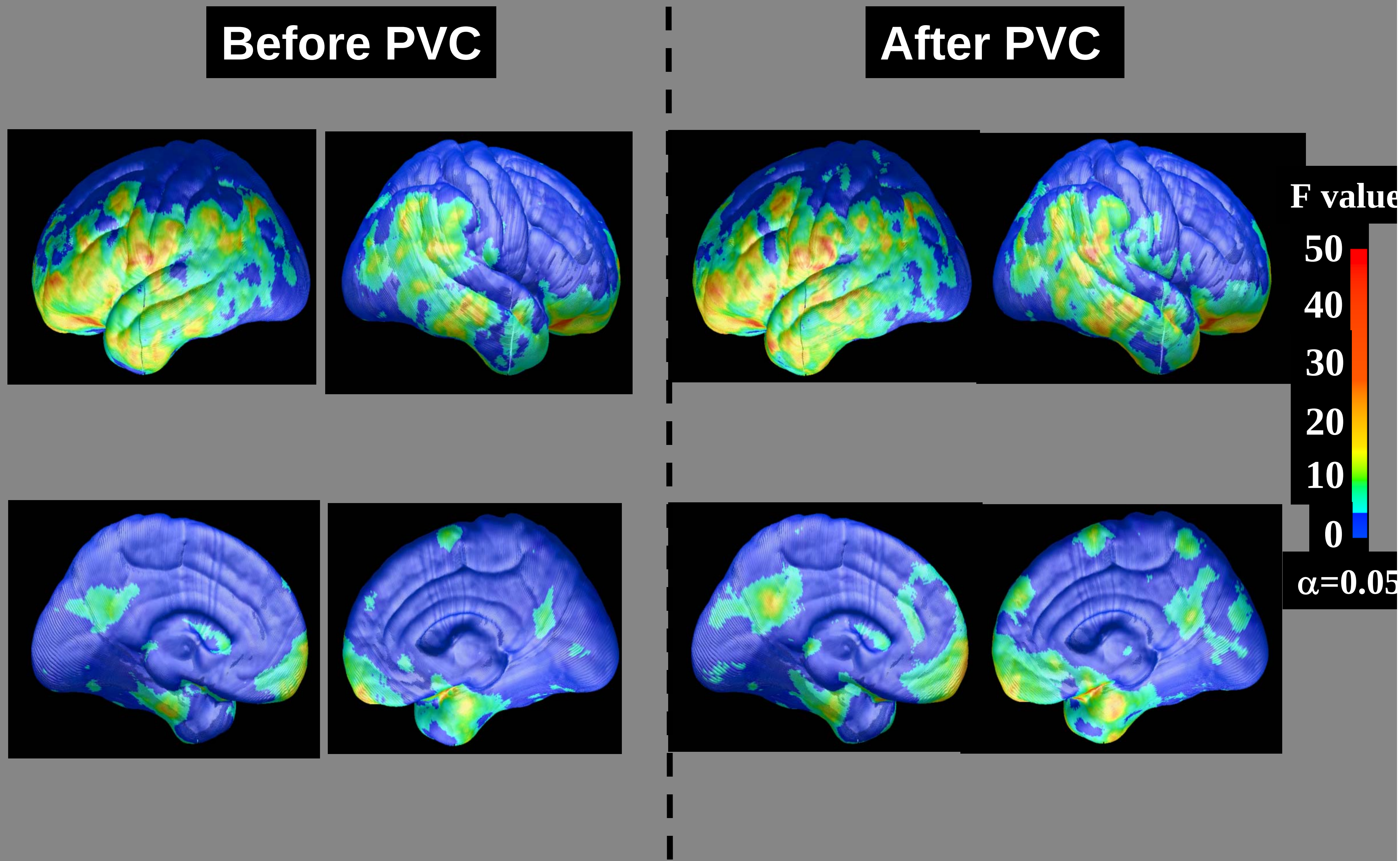
Engler et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006;129:_2856-66.

High PIB-PET Binding May Predict Future Decline

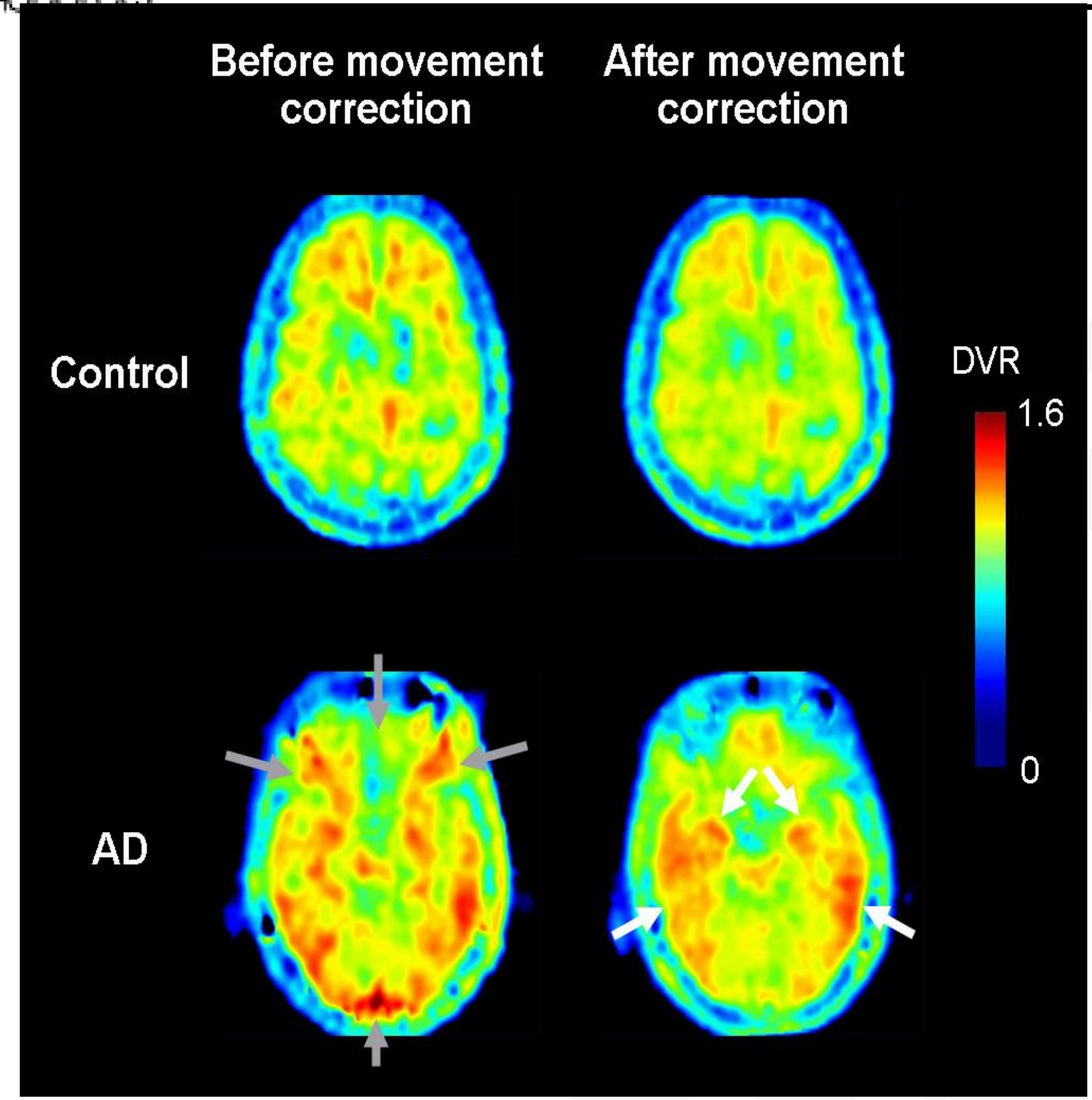


Villemagne et al. Aβ deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease . Neuropsychologia. 2008;46:_1688-97.

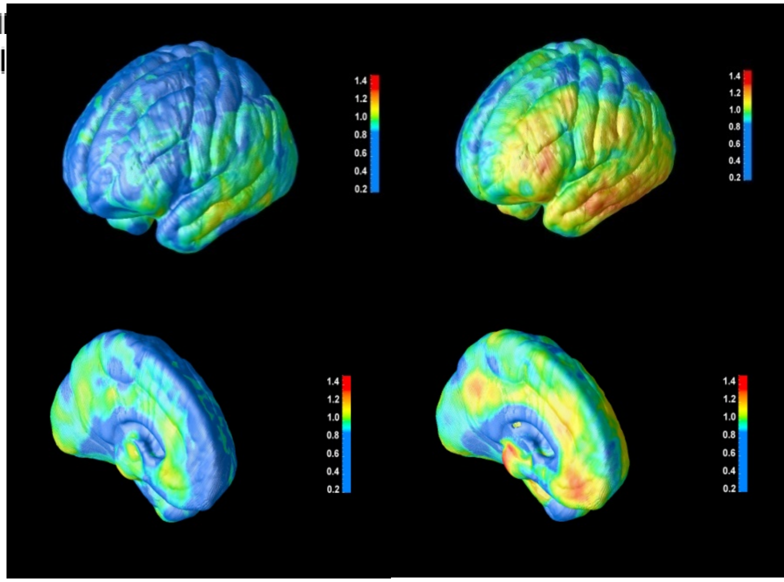
Partial Volume Correction: FDDNP Vs. MMSE



Head Motion Correction



3-D Display of Atrophy and Pathology

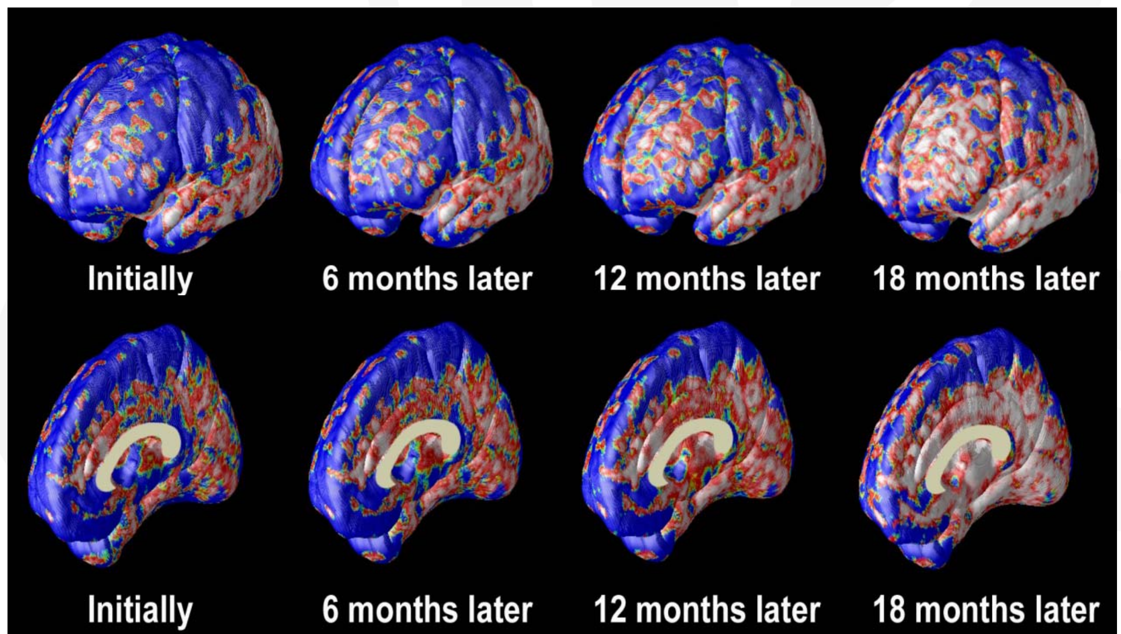


Amyloid and Tau Pathology with [F-18]FDDNP-PET

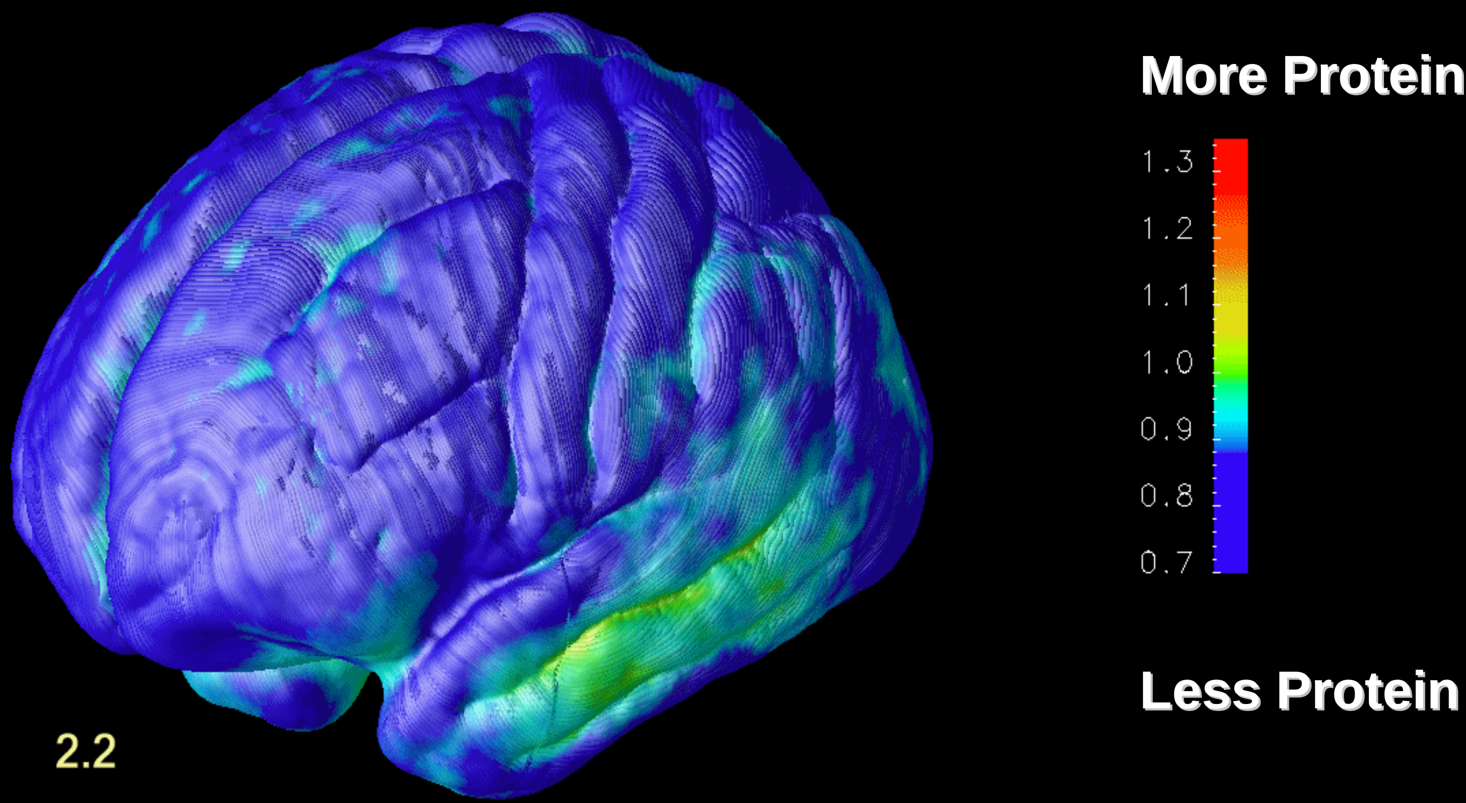
Small G, Barrio JR, et al, NEJM, 2006)

MRI: Cortical Thinning

(Thompson PM, J. Neurosci , 2003)



FDDNP Shows Full Picture of Progression of Neurodegeneration



Regression of surface projections of FDDNP-PET scans of 20 subjects (8 controls, 6 MCIs, 6 ADs)

Issues for Discussion

- What can amyloid PET contribute to clinical trials?
- What studies are needed to demonstrate the utility of amyloid PET for clinical trials?
- How do we best address the key methodological considerations when designing clinical trials?