Clinical Implications of Concordant and Discordant Beta-Amyloid and Neurodegenerative Abnormalities in Mild Cognitive Impairment

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Disclosures: Nothing to disclose

NIA-AA MCI Criteria

Diagnostic Category	Biomarker Driven Probability of AD Etiology	Presence of Cerebral Amyloidosis (PET, CSF)	Evidence of Neuronal Injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminite/untested	Conflicting/indeterminite/untested
MCI due to AD – Intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD – High likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al., *Alzheimer's & Dementia*, 2011

NIA-AA MCI Criteria

- Does not account for differing temporal resolution of biomarkers within and across class
- Conflicting results considered “uninformative”
  - What is the meaning of discordance between amyloid and neurodegenerative measures?
    - Likelihood of AD etiology?
    - Likelihood of progression?
  - Does it matter which measure (amyloid vs. neurodegenerative) is positive or negative?

To what degree do biomarkers differ in temporal resolution in the MCI stage?

- If cerebral amyloid deposition antecedent event and plateaus at early symptomatic stage
  - Expect limited temporal resolution for near-term clinical end-points
- If neurodegeneration tracks disease state in prodromal phase
  - Expect better near-term prediction

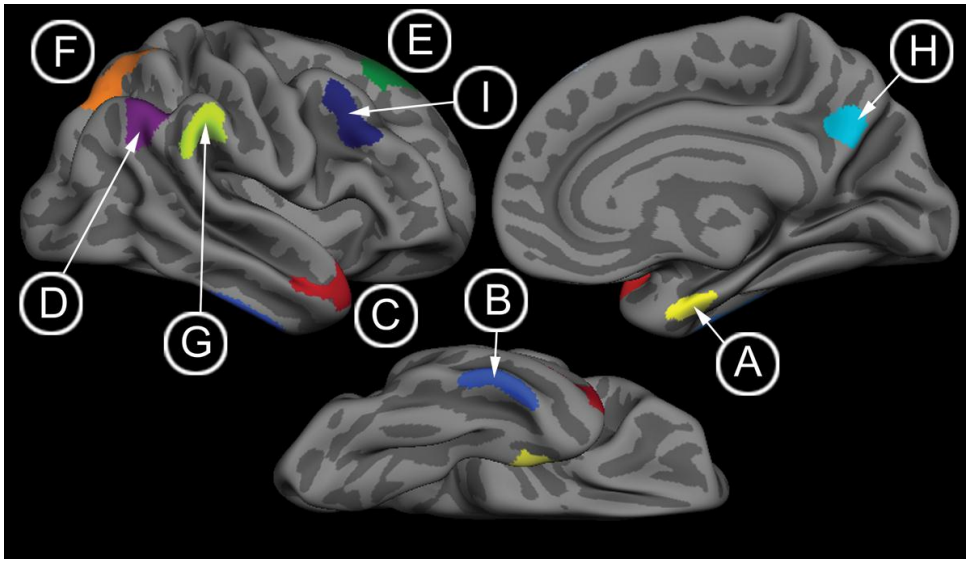
Temporal Prediction

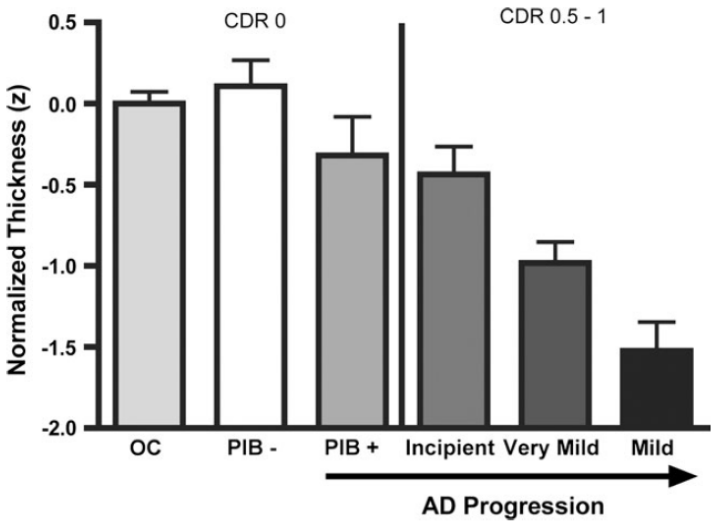
- ADNI MCI patients (n=156)
  - At least 1 year of follow-up
  - CSF biomarkers and adequate MRI available
    - Amyloid biomarker: CSF Aβ42
    - Neurodegenerative biomarkers: CSF t-tau, CSF p-tau, 'Cortical Signature of AD' structural marker
- Compare strength of prediction for 1-year and 3-year outcomes
  - The shorter the time-frame, the better neurodegenerative markers would perform

"Cortical Signature of AD"

- Attempt to capture pattern of cortical involvement associated with early AD
  - Perhaps more specific than MTL to AD-related changes
- Data-driven disease-specific ROI's
  - Regions with the highest effect size of cortical thickness difference in mild AD versus control sample
  - Replicated in 3 additional AD/control datasets (Dickerson et al., 2009)
  - Disease-defined ROI's may be more sensitive and specific than traditional ROI's
    - Disease may not obey anatomic boundaries

“Cortical Signature of AD”

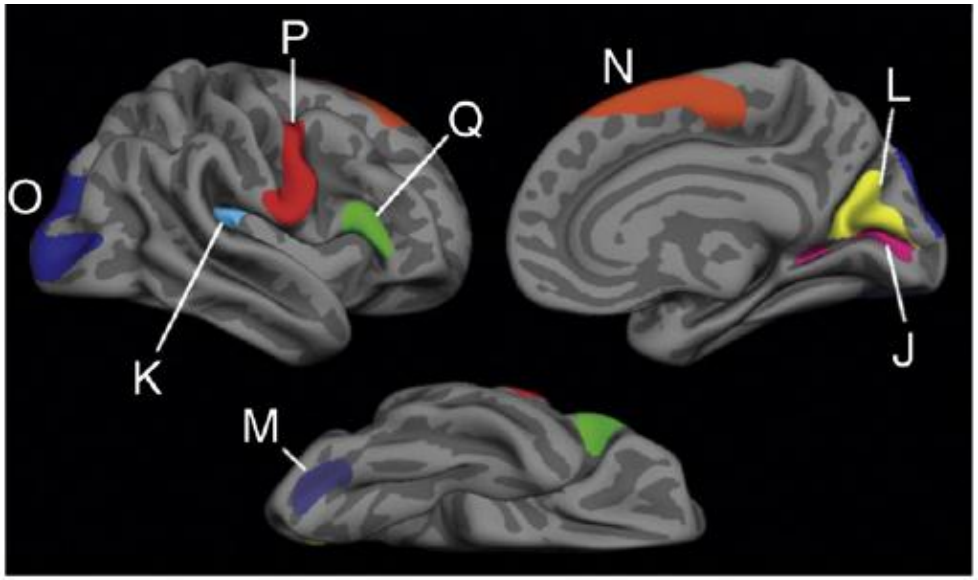




Dickerson et al., *Cerebral Cortex*, 2011

Cortical Signature of AD v1.1

- "Aging Signature"
  - 87 CN (M Age: 73.7)
  - 142 YC (M Age: 24.4)
- Variable age-effect on some AD Signature regions



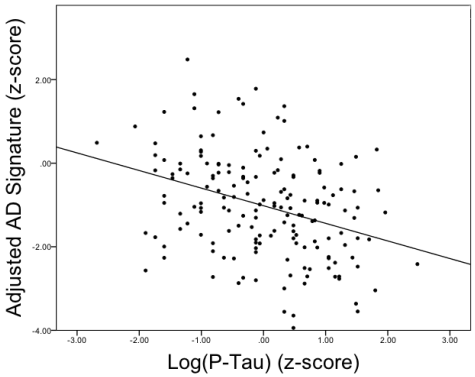
Bakkour et al., *NeuroImage*, 2013

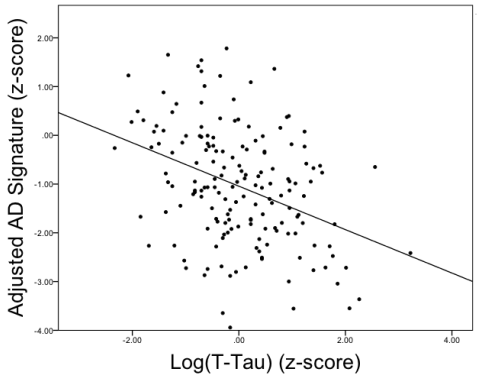
- Linear regression of Aging Sig on AD Sig in ADNI amyloid-neg controls
- **Adjusted AD Signature =** Residual AD Signature using the regression equation
- Potentially more pure measure of AD-specific change
  - Lower values – more significant AD related thinning relative to age effects

Adjusted AD Signature – Correlation with Age and CSF Molecular Markers

MCI Cohort (n=164)

	Age	Log(T-TAU)	Log(P-TAU)	ABeta
Aging Signature	r=-0.38 (p<0.001)	r=-0.05 NS	r=-0.04 NS	r=-0.06 NS
AD Signature	r=-0.30 (p<0.001)	r=-0.26 (p<0.01)	r=-0.21 (p<0.01)	r=-0.09 NS
Adjusted AD Signature	r=0.05 NS	r=-0.37 (p<0.001)	r=-0.35 (p<0.001)	r=0.22 (p<0.01)
Hippocampal Volume	r=-0.19 (p<0.05)	r=-0.04 NS	r=-0.03 NS	r=0.05 NS
Mean Cortical Thickness	r=-0.35 (p<0.001)	r=0.16 (p<0.05)	r=0.08 NS	r=0.02 NS





Dickerson & Wolk, *Frontiers in Aging Neuroscience,* 2013

Demographic and Biomarker Data by Outcome

	1 Year Outcome (n=156)	
	Stable (n=125)	AD (n=31)
Age	74.9 (7.6)	72.3 (6.9)
Gender	84 M: 41 F	17 M: 14 F
Education (yrs)	15.8 (3.0)	15.1 (3.2)
MMSE	27.5 (1.7)	26.7 (1.9)
CDR_SB	1.9 (0.8)	2.4 (0.9) **
CSF t-tau	101.5 (52.2)	112.9 (56.5)
CSF p-tau	34.2 (16.6)	42.3 (18.3) *
CSF Aβ	165.7 (55.3)	151.0 (38.6)
Adjusted AD Signature (z-score)	-0.82 (1.1)	-1.82 (1.3) ***

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Demographic and Biomarker Data by Outcome

	1 Year Outcome (n=156)		3 Year Outcome (n=111)	
	Stable (n=125)	AD (n=31)	Stable (n=63)	AD (n=48)
Age	74.9 (7.6)	72.3 (6.9)	74.7 (7.3)	74.3 (7.7)
Gender	84 M: 41 F	17 M: 14 F	47 M: 16 F	30 M: 18 F
Education (yrs)	15.8 (3.0)	15.1 (3.2)	15.6 (3.0)	15.6 (3.4)
MMSE	27.5 (1.7)	26.7 (1.9)	27.3 (1.8)	26.7 (1.9)
CDR_SB	1.9 (0.8)	2.4 (0.9) **	1.7 (0.6)	2.2 (1.0) **
CSF t-tau	101.5 (52.2)	112.9 (56.5)	96.5 (48.1)	117.1 (57.8) *
CSF p-tau	34.2 (16.6)	42.3 (18.3) *	32.8 (16.0)	40.5 (16.8) *
CSF Aβ	165.7 (55.3)	151.0 (38.6)	174.7 (55.3)	142.4 (35.7) **
Adjusted AD Signature (z-score)	-0.82 (1.1)	-1.82 (1.3) ***	-0.63 (1.1)	-1.26 (12) **

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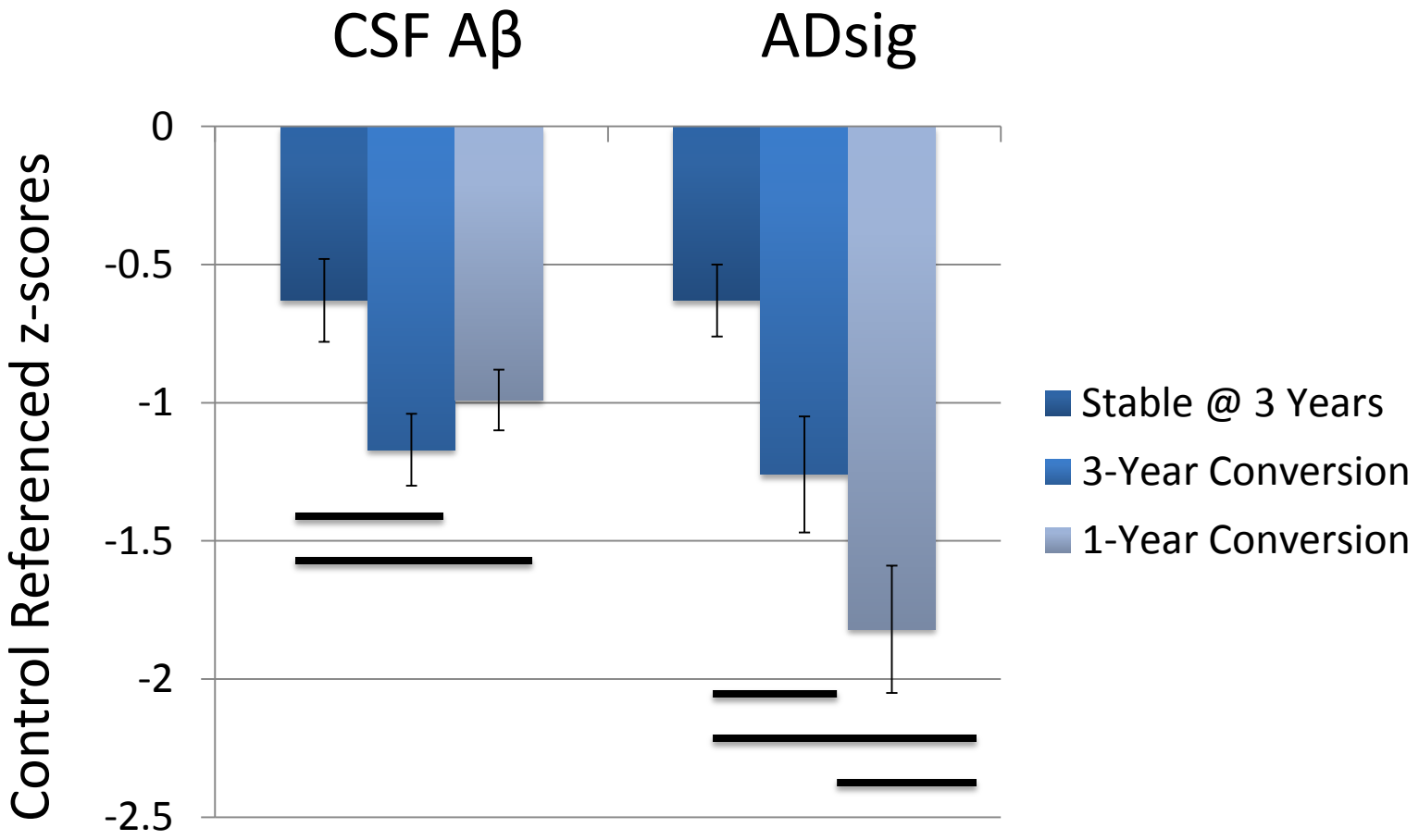
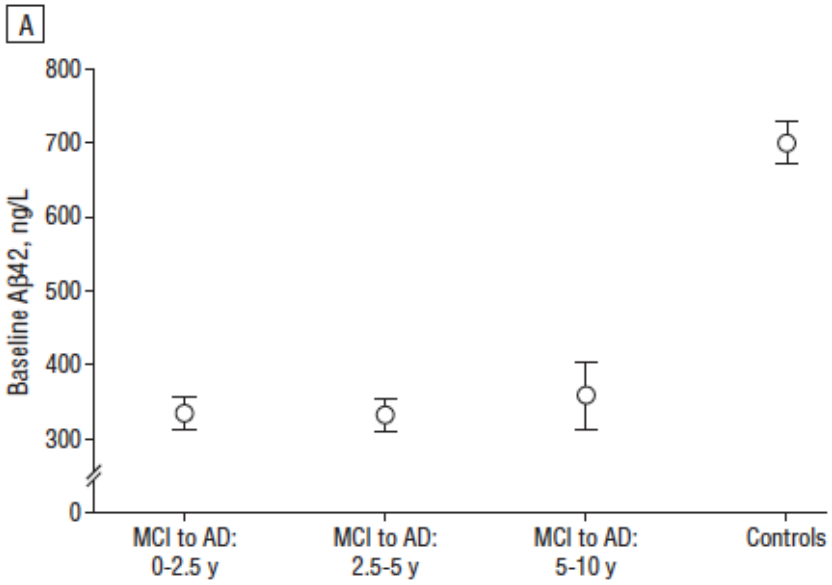
Relationship of CSF Aβ and Cortical Signature to Time of Progression



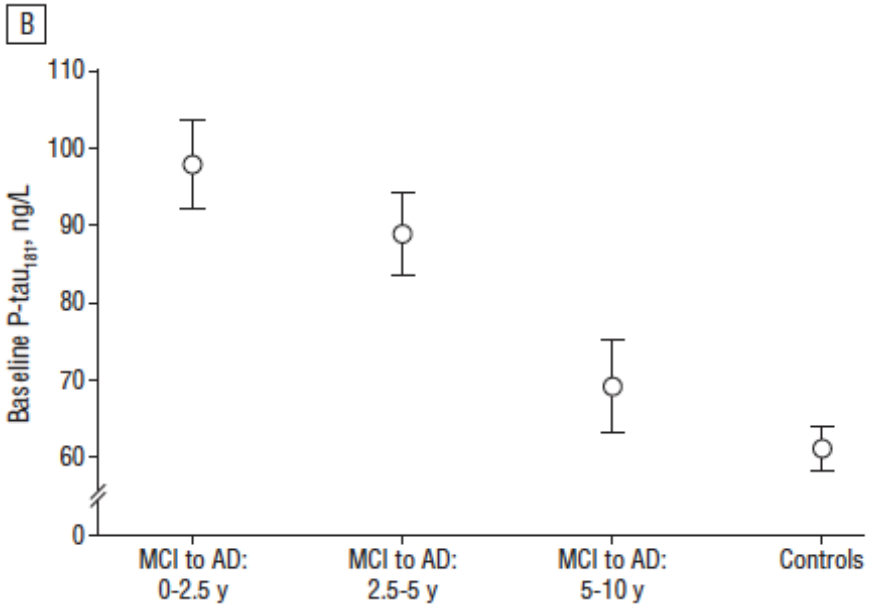
Dickerson & Wolk, *Frontiers in Aging Neuroscience*, 2013

PTAU Tracks Timing of Conversion

Cerebral Amyloid: CSF Aβ



Neurodegeneration: CSF phospho-tau



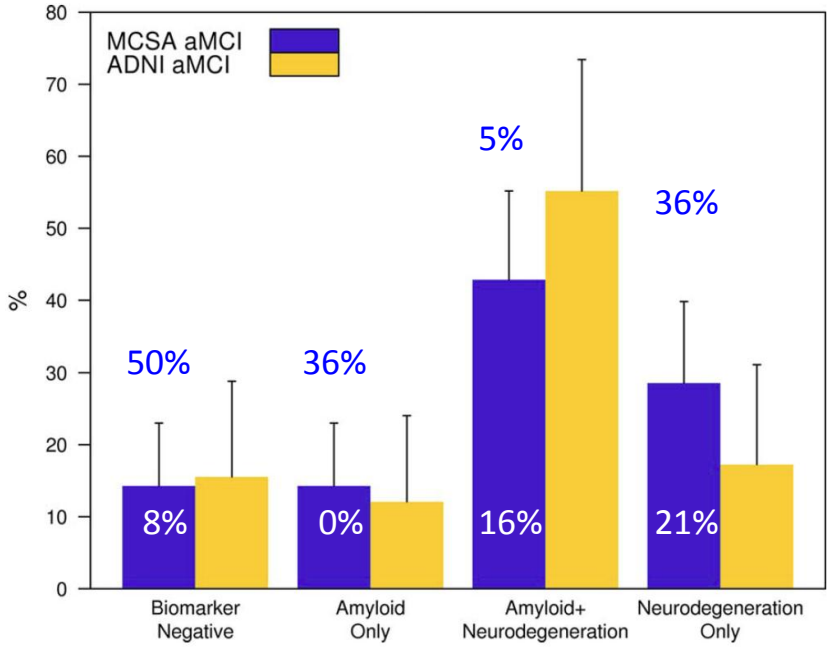
Buchhave et al., *Archives Gen Psychiatry*, 2011

Categorization Based on Cutoffs of Amyloid and Neurodegenerative Biomarkers

- Concordant Findings
  - Amyloid negative, neurodegeneration negative
    - Consistent with non-AD etiology
  - Amyloid positive, neurodegeneration positive
    - Consistent with high likelihood AD
- Discordant Findings
  - Amyloid positive, neurodegeneration negative
    - Consistent with model, but potentially earlier disease stage
    - Is it consistent to have sx's of MCI symptoms without obvious neurodegeneration?
  - Amyloid negative, neurodegeneration positive
    - Suspected non-AD pathology? Different pathway?

Outcomes in MCI Based on Biomarker-Defined Groups

- Petersen et al., Annals of Neurology, 2013
  - Mayo Clinic Study of Aging (n=126); ADNI (n=58)
  - PiB PET, FDG PET, and Hippocampal volume
  - Neurodegeneration = abnormal FDG PET and/or Hippocampal volume
  - Cut-offs were 10th percentile of AD distribution



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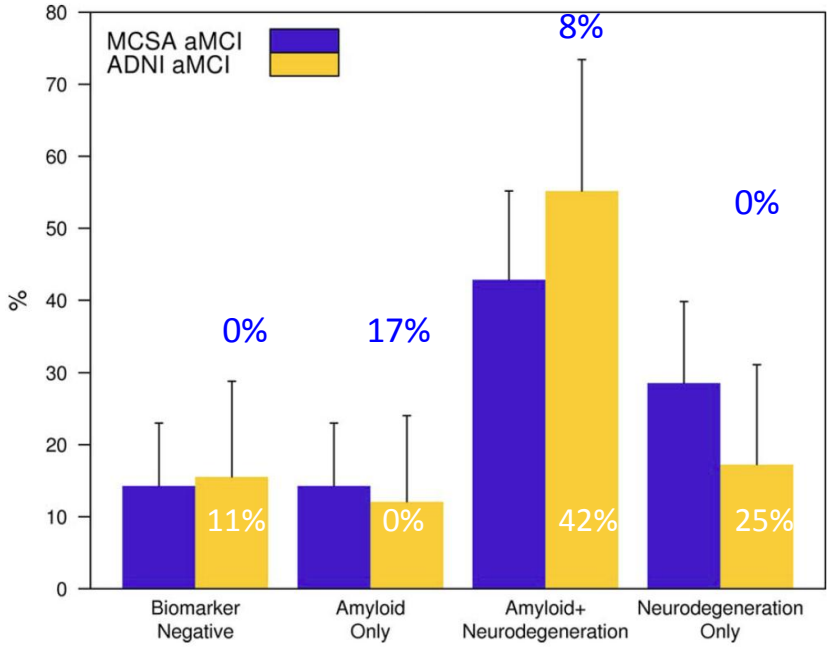
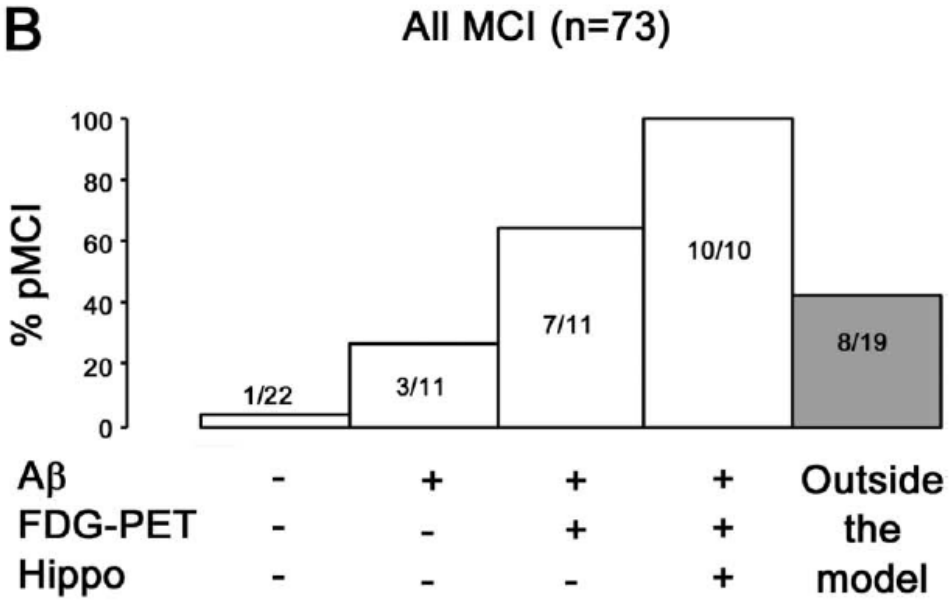


Outcomes in MCI Based on Biomarker-Defined Groups

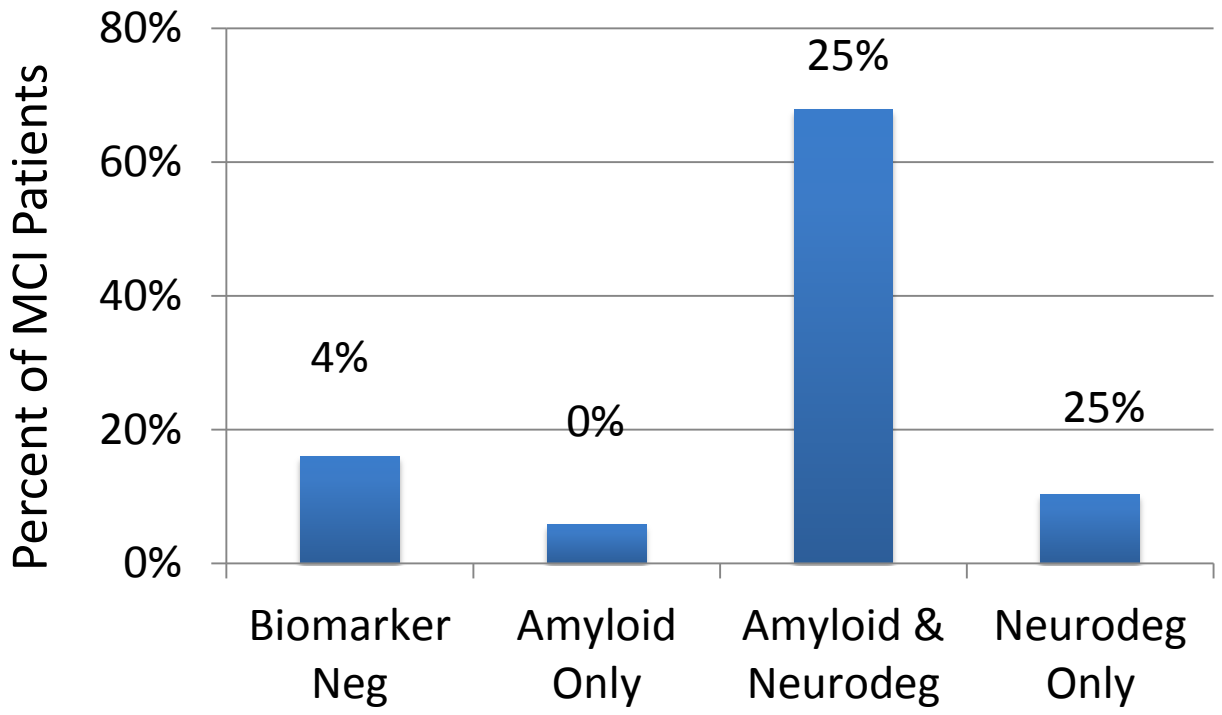
- Prestia et al, Neurology, 2013 (n=73)
  - CSF Aβ, FDG PET, and Hippocampal volume
    - Applied standard cutoffs for center
  - Divided into groups that were proposed to fit or be "Outside the Model" (e.g. hippo atrophy, but normal amyloid)



- 15 patients "Outside of the Model" had positive neurodegenerative markers, but negative amyloid
  - 7 converted to AD (47%)

MCI Biomarker Groups

- Neurodegeneration positive
  - AD Signature and/or CSF PTAU (≥ 23 pg/ml)
- Amyloid positive
  - CSF Aβ (<192 pg/ml)



Demographics of Amyloid Negative Patients

	All	Stable @ 1-Year (n=35)	AD @ 1-Year (n=5)
Age	75.6 (8.5)	76.5 (8.2)	69.1 (9.0)+
Gender	30 M: 10 F	27 M: 8 F	3 M: 2 F
Education (yrs)	15.7 (2.9)	15.8 (3.1)	15.2 (1.0)
MMSE	27.2 (1.9)	27.3 (1.8)	26.8 (2.6)
CDR_SB	1.8 (0.7)	1.7 (0.6)	2.4 (1.1)*
CSF t-tau	67.0 (25.4)	66.4 (26.5)	70.1 (17.7)
CSF p-Tau	21.1 (8.8)	20.4 (16.6)	26.0 (13.8)
CSF Aβ	240.4 (24.2)	242.8 (24.1)	223.0 (18.3)+
Adjusted AD Signature (z-score)	-0.57 (1.18)	-0.34 (0.92)	-2.16 (1.64)***

What is Etiology of Each Group

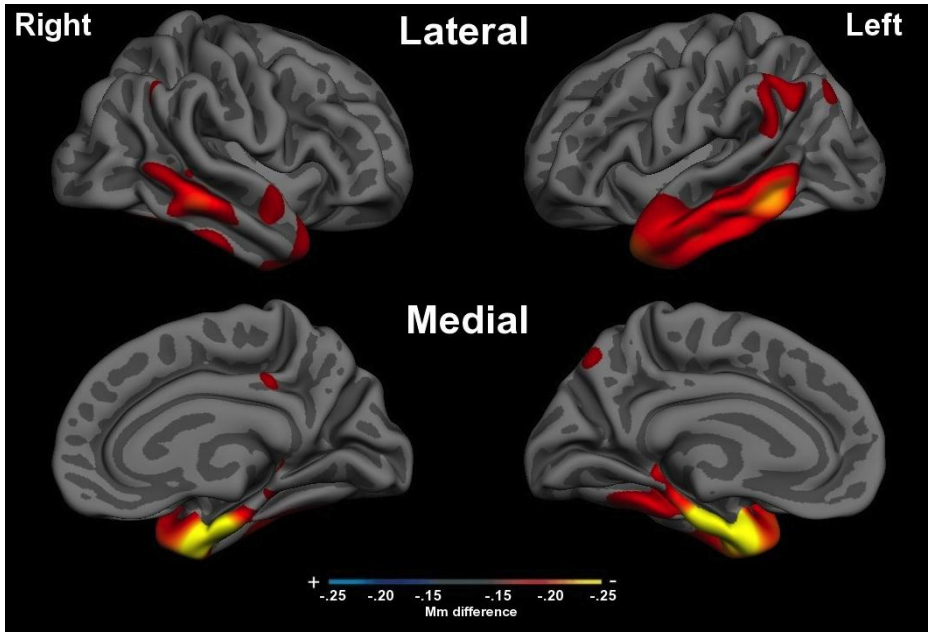
- All biomarkers negative
  - Non-AD neurodegeneration; non-neurodegenerative
  - Likely very heterogeneous group
- Amyloid + Neurodegeneration
  - High likelihood of AD and high conversion rate
- Amyloid only
  - Earlier in disease course
  - Reduced reserve
  - Amyloid pathology may not be primary cause (age-associated memory loss)
  - Low nearer-term conversion rate

What is Etiology of Neurodegeneration Only Group?

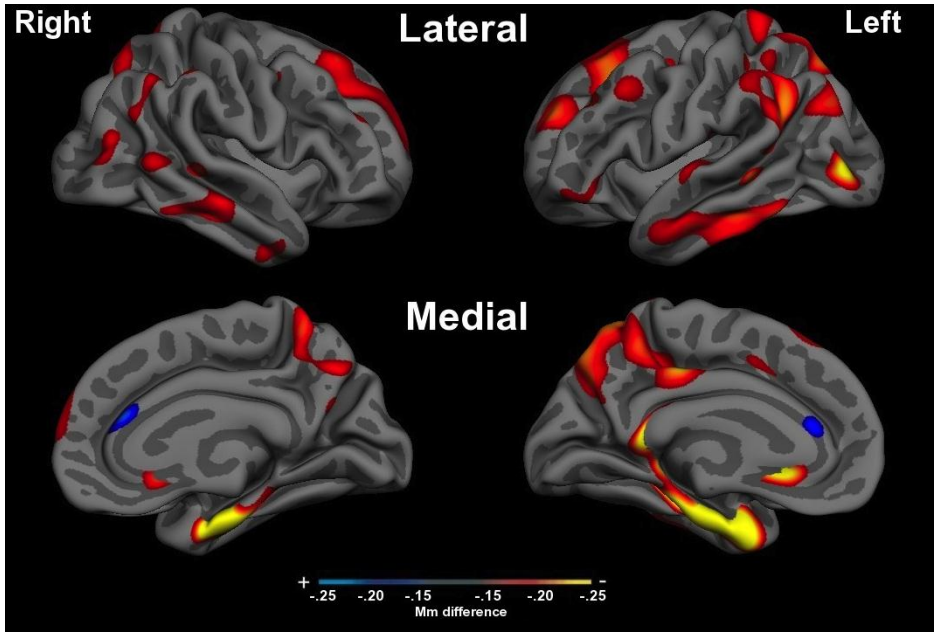
- Non-AD pathology (TDP-43? Tauopathy? Hippocampal sclerosis?)
  - But they exhibit AD specific markers
    - AD Sig correlates with t-tau ($r=0.40$, $p<0.01$) and p-tau ($r=0.35$, $p<0.05$)
- Mixed pathologies with AD
  - Lower threshold of amyloid pathology to reach neurodegenerative/clinical milestones
- AD, but with modification of the typical biomarker cascade
  - False negative amyloid measure? Diffuse plaques?
  - Relatively more prominent neurofibrillary degeneration (extreme is tangle-only dementia)
- Likely heterogeneous

Average Cortical Thinning Relative to Controls

Amyloid + Neurodegeneration (n=114)



Neurodegeneration Only (n=16)



Conclusions

- Neurodegenerative markers provide finer grade prediction of timing to clinical endpoints in MCI
  - Structural markers more informative than CSF
  - Supports temporal ordering of biomarker cascade model
- Concordant positive biomarker findings across molecular and neurodegenerative measures best predictor of conversion and likely most homogeneous group
- Other combinations less clear with regard to etiology
  - In particular, neurodegeneration only group displays high rate of conversion and relatively specific AD pattern despite absence of biomarker evidence of cerebral amyloidosis
  - Cutoffs may significantly influence categories and outcomes

Thank You!!

All work done in collaboration with Brad Dickerson at MGH

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