Biomarkers of Preclinical AD

Marilyn S. Albert, PhD
Department of Neurology
Johns Hopkins University

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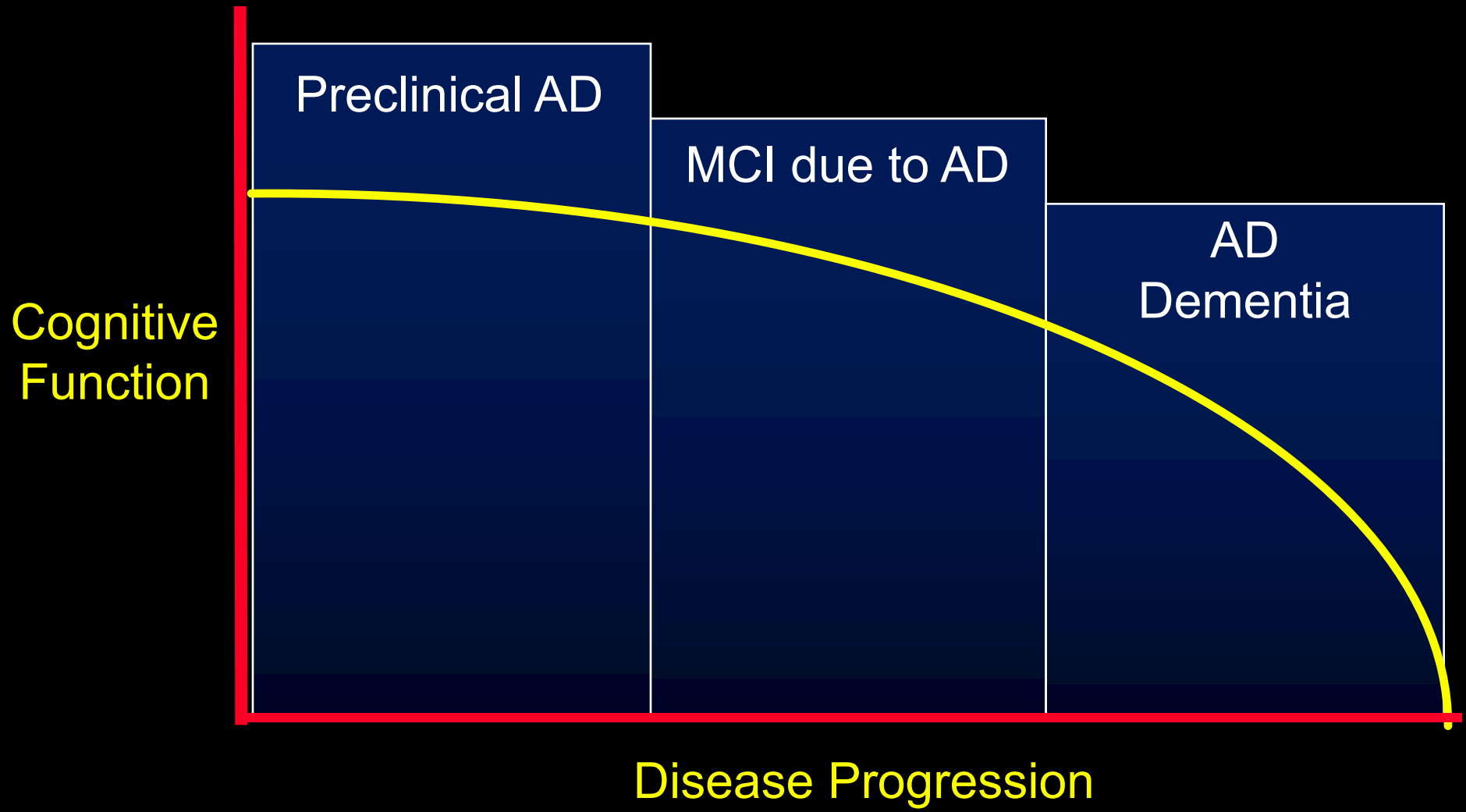
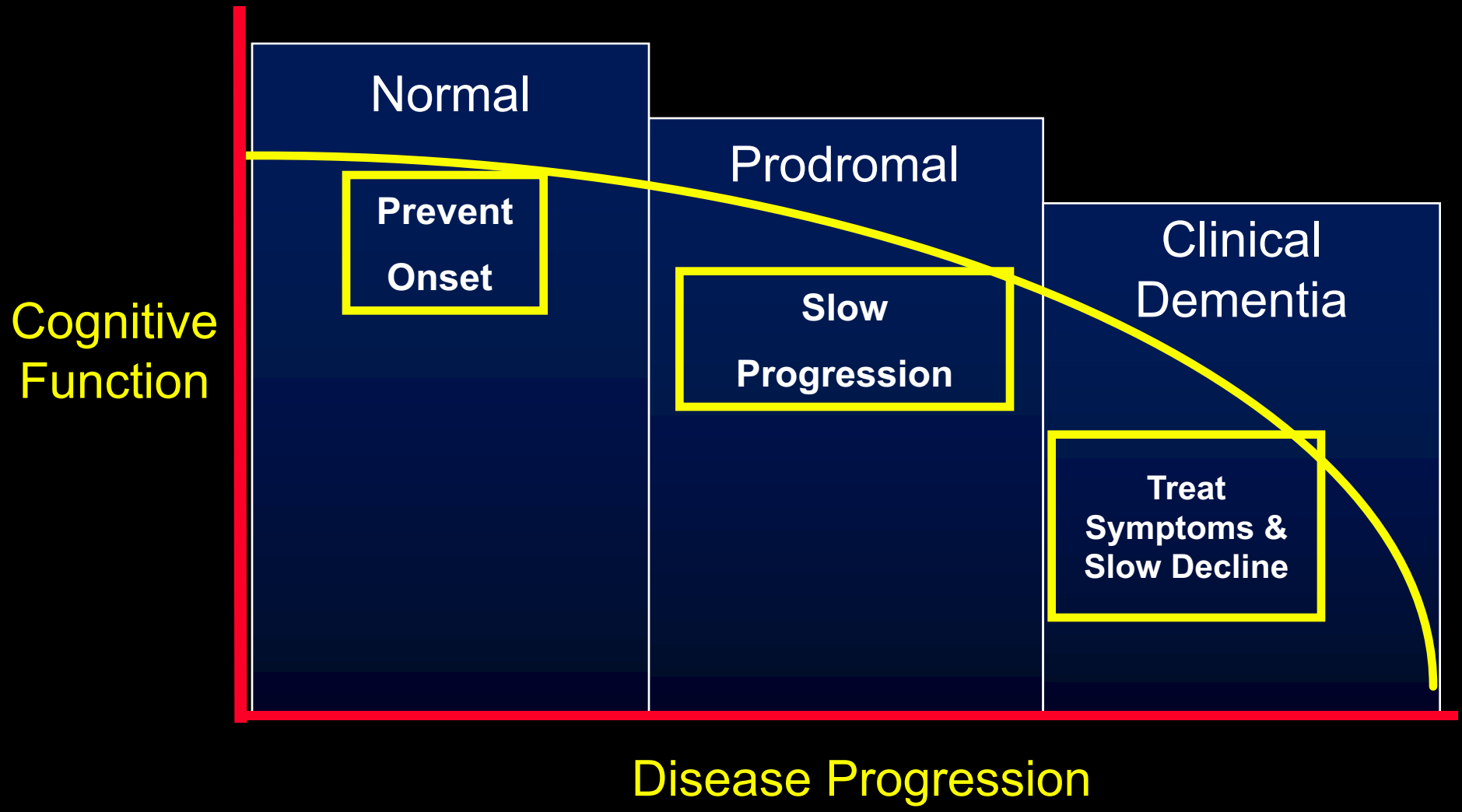
Biomarkers of Preclinical AD

- Brief overview of challenges in identifying individuals with preclinical AD
- Recent findings from the BIOCARD Study
  - Cognitive tests demonstrating change during preclinical AD
  - Evaluating measurement parameters that maximize sensitivity to preclinical disease
  - Modeling changepoints of biomarkers during preclinical AD
- Future directions

Progression of Alzheimer's Disease



Therapeutic Implications of Disease Course



Identifying The Earliest Phases of AD
Challenges

- Need to follow cognitively normal individuals over time to determine which changes are predictive of onset of clinical symptoms consistent with AD
- If you examine cross-sectional relationships associated with short term change cannot be sure if they will be predictive of disease progression
- Most of the measures you would want to examine change with age
- Change that might reflect disease-related alterations are extremely slow during the earliest phases of AD

Identifying the Earliest Phases of AD
Challenges

- By definition, you are looking for: measures / biomarkers that might reflect underlying progression of disease when clinical symptoms are minimal
- Must: (1) collect a wide range of measures that are likely to reflect the underlying disease process, (2) follow cognitively normal individuals for a very long time, (3) have skilled clinicians to evaluate outcomes, so you can be fairly sure the 'outcomes' reflect MCI due to AD, (4) need to have enough 'outcomes' that statistical analyses are feasible

Potential Biomarkers for Preclinical AD

Based on Decades of Research

- Cerebrospinal fluid (CSF) – provides measure of both amyloid beta peptide (Abeta), total tau and phosphorylated tau (hallmarks of AD pathology)
- Magnetic resonance imaging (MRI) – indirect measure of neuronal loss (e.g., regional brain volumes)
- Cognitive Testing – indirect measure of impact of synaptic changes on cognition (sometimes considered a biomarker)
- [Amyloid and tau imaging (using PET) also provides measure of Abeta and tau accumulation]

Identified in MCI and Dementia due to AD

BIOCARD Study at NIH

- Study Design
  - Enroll cognitively normal individuals (n=349)
  - Primarily middle age
  - Approximately 3/4 with family history of AD
  - Annual cognitive and clinical assessments
  - Collect CSF and structural MRI – bi-annually
- Overarching Goal of Study
  - Examine predictors of progression from normal cognitive status to mild impairment and/or dementia (focus on AD)
- Initially Conducted at NIH (1995 – 2005)
  - NIMH - Geriatric Psychiatry Branch (PI, Trey Sunderland)

Enrolled over time

BIOCARD Study at JHU

- Johns Hopkins team funded to continue study – July 2009
  - U19 with specific goals
  - Re-enroll cohort – find them, re-initiate participation
  - Conduct annual clinical and cognitive evaluations, and collect blood
  - Analyze current status of subjects in relation to previously collected data and resources
    - **Cognitive and clinical data (electronic files and 56 boxes)**
    - **CSF specimens and blood (in 5 freezers)**
    - **MRI scans (digital scans on hard drive)**
  - Refunded in 2014 to continue follow-up and collect more CSF, MRIs and amyloid imaging

BIOCARD Cohort

- Characteristics of Cohort at Baseline
  - Total Number of Enrollees = 349
  - Age at Entry: M = 57.2 (middle age)
  - Females: 57.6%
  - Education: M = 17 yrs
  - Mini-Mental State Exam: M= 29.5
  - ApoE-4 positive: 33.6%
  - Dementia in family member: 75%

BIOCARD Study - Progress To Date

- Re-enrollment and evaluation of subjects
  - Consensus diagnoses on 90% of cohort (~ 30 deceased) – some followed almost 20 yrs, minimum follow-up is 10 yrs (mean ~ 11 yrs)
  - Approximately 60 have developed symptoms and received diagnosis of MCI or dementia due to AD
  - Biomarker analyses completed to date looking at:
    - CSF measures
    - MRI measures
    - Cognitive test scores

BIOCARD Research Team
Johns Hopkins

Marilyn Albert, PhD
Timothy Brown, BS
Qing Cai, BS
Ann Ervin, PhD
Leonie Farrington, RN
Rebecca Gottesman, MD
Maura Grega, RN
Alden Gross, PhD
Corinne Pettigrew, PhD
Guy McKhann, MD
Michael Miller, PhD
Abhay Moghekar, MD
Susumu Mori, PhD
Richard O'Brien, MD, PhD
Tilak Ratnanather, PhD
Gay Rudow, RN
Ned Sacktor, MD
Roberta Scherer, PhD
Ola Selnes, PhD
Anja Soldan, PhD
Juan Troncoso, MD
R. Scott Turner, MD
Mei-Chang Wang, PhD
Laurent Younes, PhD

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Cognitive tests demonstrating change during preclinical AD

Cognitive Test Battery

GENERAL	VISUOCONSTRUCTION
Mini-Mental State	Rey Complex Figure Copy
ATTENTION	Block Design (WAIS-R)
Digit Span (WAIS-R)	EXECUTIVE
MEMORY/NEW LEARNING	Trail Making Test B
California Verbal Learning Test	Letter Fluency (F,A,S)
Logical Memory (WMS-R)	Category Fluency (animals, vegetables)
Verbal Paired Associates (WMS-R)	PSYCHOMOTOR SPEED
Rey Complex Figure Recall	Digit Symbol (WAIS-R)
LANGUAGE	Trail Making Test A
Boston Naming (30-item)	MOTOR SPEED
	Grooved Pegboard*

Individual Domains

Data Analytic Approach

- Outcome variable: time to onset of clinical symptoms
- Main Goals:
  1. **Is baseline value related to time to onset of clinical symptoms?**
  2. **Does rate of change in values prior to onset of clinical symptoms differ for stable and progressing groups?**
- Cox regression models
  - **Model baseline and time-dependent rate of change**
  - **Primary statistical measure = Hazard Ratio**
- Similar approach for Cognitive, CSF, and MRI data
  - **Used z scores so HR could be compared across measures**
  - **'Baseline' approximately 6 years before onset of symptoms**

Baseline Sample Characteristics

Subjects in Cognitive Analysis

	Remained normal (N = 208)	Progressed to MCI or AD (N = 60)
Age (SD)	55.4 (9.6) years*	62.4 (10.9) years*
Gender, females (%)	63.0%	56.7%
Education (SD)	17.3 (2.3) years	16.6 (2.3) years
Ethnicity, Caucasian (%)	98.6%	91.7%
ApoE-4 carriers	33.2%	45.8%
MMSE, mean score (SD)	29.6 (0.7)	29.4 (1.0)

Albert et al., 2014

Cognitive measures and relative risk of progression

Baseline score and Rate of change in score

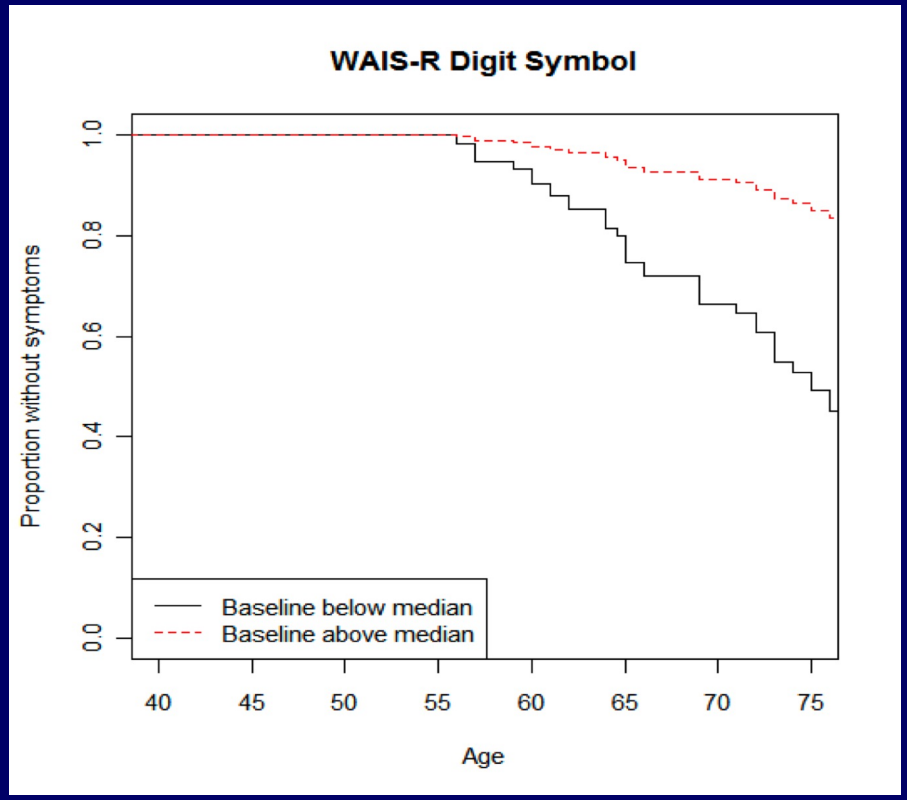
Variable	Baseline HR	Baseline p - value	Rate HR	Rate p - value
Episodic Memory				
Paired Associates -Immediate	0.53	0.0001	0.37	0.001
Paired Associates - Delayed	0.63	0.0004	0.63	0.016
Logical Memory - Immediate	0.59	0.0005	0.58	0.024
Logical Memory - Delayed	0.48	0.0001	0.54	0.009
Logical Memory - % Retention	0.56	0.0001	0.54	0.001
Rey Figure Recall	0.62	0.0008	0.49	0.001
Other Measures				
Digit-Symbol Substitution	0.41	0.0001	0.47	0.001
Boston Naming Test	0.57	0.0001	0.69	0.001
Block Design (WAIS-R)	0.53	0.0001	0.40	0.014

RR = 0.41: The hazard of clinical symptom onset is reduced by a factor of 0.41 (i.e., by 59%) for each standard deviation increase in the test score.

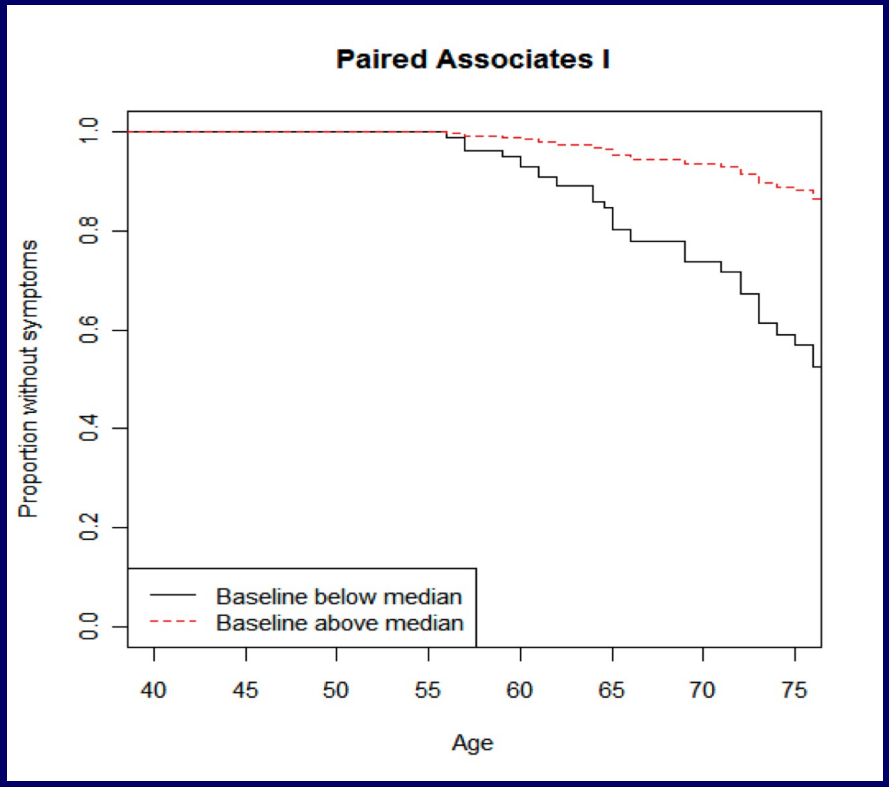
---9/17 tests---

Digit Symbol and Paired Associates

Cox regression ‘survival’ curves



HR = .41
p=.0001



HR = .53
p = .0001

Composite Cognitive Score

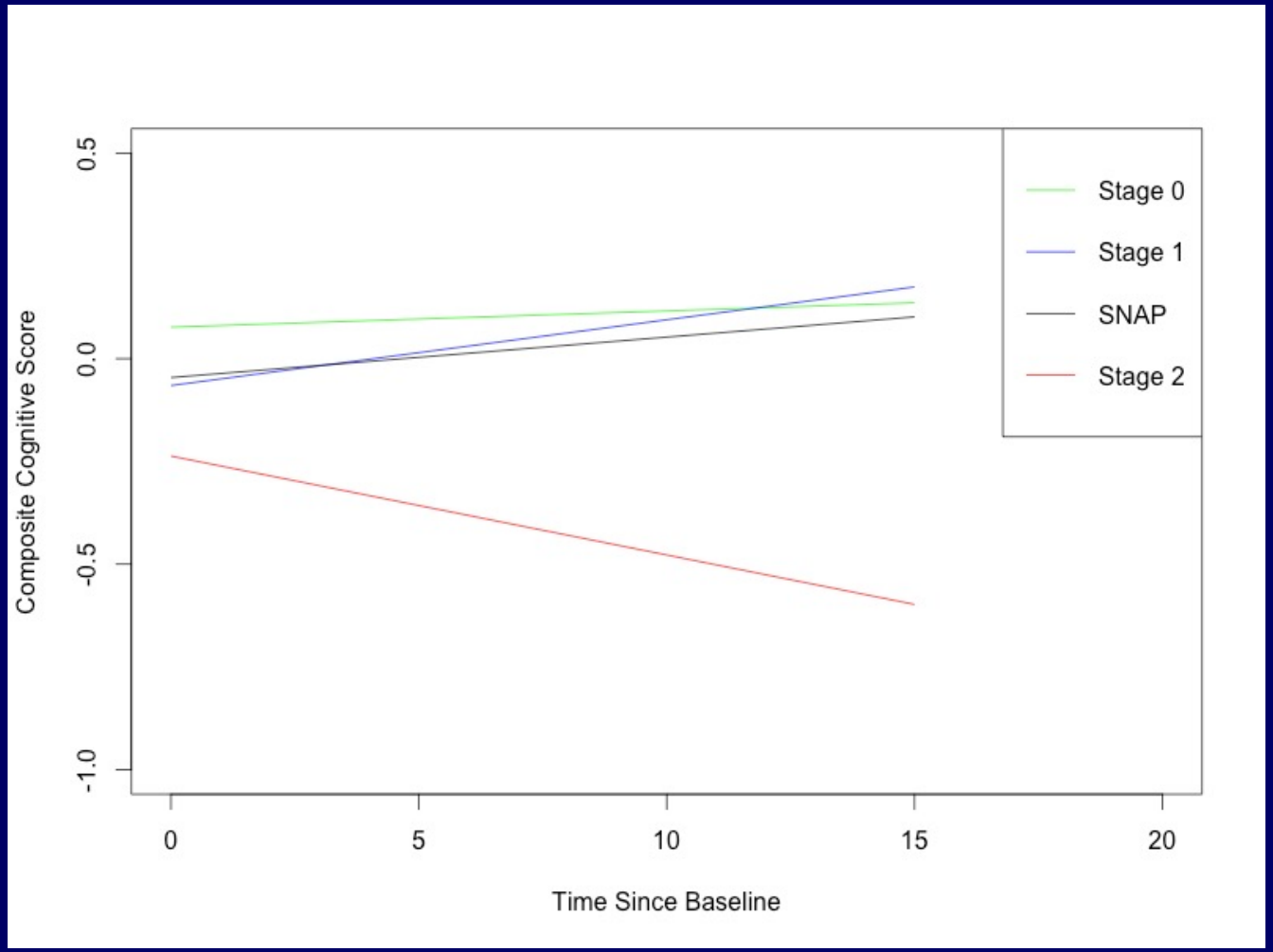
- Cox Multivariate Model – combination of variables at baseline associated with time to onset of symptoms
  - Digit Symbol Substitution (WAIS): $p < 0.0001$
  - Paired Associates (WAIS), Immed Recall: $p = 0.008$
  - Logical Memory (WMS), Delayed: $p = .003$
  - Boston Naming: $p = .001$

- Create Composite Cognitive Score for Future Analyses
  - Z scores for each test
  - Composite Score: mean of Z scores for the 4 tests

- Example: Group subjects based on hypothesized stages during preclinical AD (Stage 0,1,2 and SNAP – using CSF values) and look at relationship to change over time in composite score

Groups Based on CSF Levels at Baseline

Relationship to Change in Composite Cognitive Score



Evaluating Measurement Parameters that Maximize Sensitivity to Disease

Combining Biomarkers to Quantify Severity of Underlying Disease

- No single biomarker domain appears to have sufficient accuracy for prediction on an individual basis.
- Can CSF, MRI and cognitive measures be combined to indicate who is at highest risk for progression to provide guidance for measures to use for subject selection in clinical trials?
- Can CSF, MRI and cognitive measures be combined to provide guidance for measures to be used in tracking response to treatment in a clinical trial?

Biomarkers From Baseline Evaluated to Date

Cox Models – Time to Onset of Symptoms

- CSF
  - CSF Abeta 42; HR = 0.66, p = .008
  - CSF p-tau; HR = 1.54, p = .004
  - CSF p-tau/Abeta; HR = 1.51, p = .007
- MRI
  - Entorhinal cortex volume; HR = 0.73, p = .02
  - Hippocampal volume (R); HR = 0.76, p = .05
- Cognitive Tests
  - Digit Symbol, Logical Memory (p = .0001)
  - Paired Associates, Boston Naming (p = .0001)

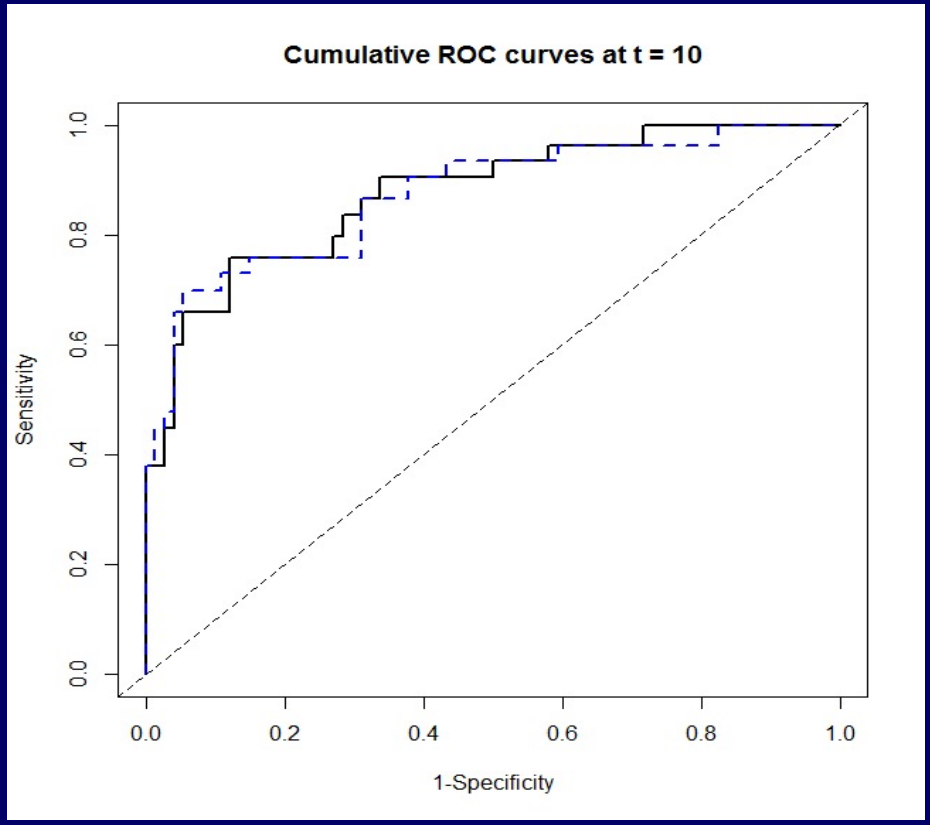
Moghekar, et al, 2013; Soldan et al, in press; Albert et al, 2014

Combining Biomarkers to Identify Individuals Likely to Progress within 5yr Timeframe

- Goal: Combine measures at baseline so that prediction of outcome for an individual 5 years later is possible
- Identified 'best' measures from each domain (i.e., CSF, MRI, cognitive) based on prior findings
- Time dependent ROC method - examined combinations from different perspectives
- Least invasive to most invasive, least expensive to most expensive, 'best combination' for prediction, adjusted for demographics (using AIC criterion)

Analytic Method – Li et al., 2012

Combination of Measures - ROC Analysis



Best Model:
Sensitivity = .80
Specificity = .75
AUC = .85

5 years after entry

Best Model

Addition of each domain added significantly to accuracy of prediction

Dashed line = weighted combination of: Genetics (ApoE-4), + cognitive (Digit Symbol and Paired Associates, immediate recall) + CSF (CSF ptau) + MRI (R EC thickness + R hippo) adjusted by age and education

Preclinical AD Severity Score

- Goal: develop a continuous measure by combining biomarkers that might reflect underlying severity of disease during preclinical phase of AD
- Combine measures from 3 domains: (1) CSF measures, (2) MRI measures, (3) Cognitive tests
- Combine measures across multiple visits (i.e., Visit 1, 3 and 5) anticipating that this longitudinal data would capture changes in severity
  - Data collapsed across visits, but adjustments made for inter-correlation within individuals

Preclinical AD Severity Score

- Used latent trait methods (similar to factor analysis) to create a composite measure that might reflect underlying severity of disease
- Fitted lines come from longitudinal modeling of individual scores

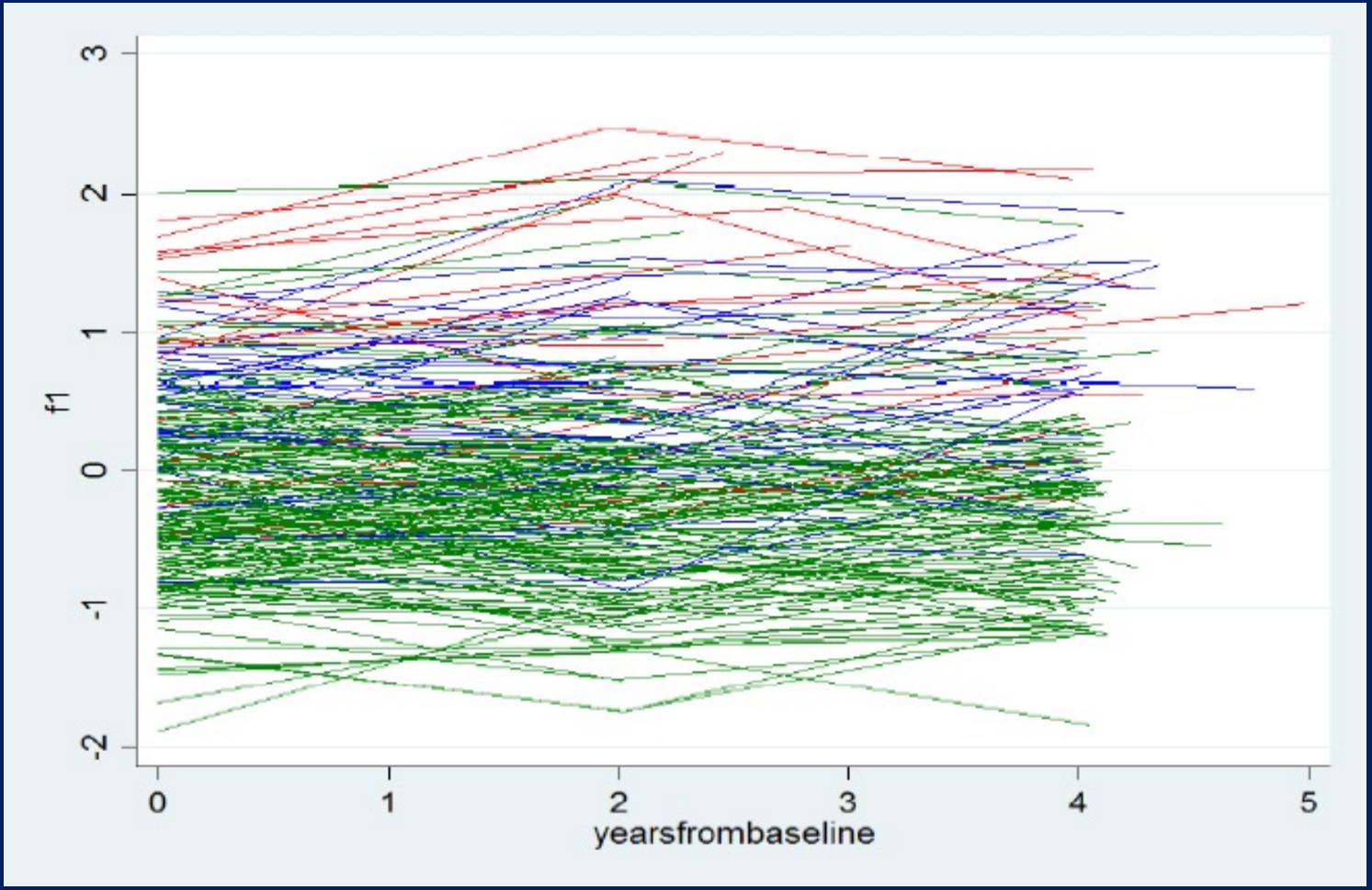
Gross, Leousatkos et al, in preparation

Preclinical AD Severity Score

Severity Scores - Color Coded by Dx Outcome

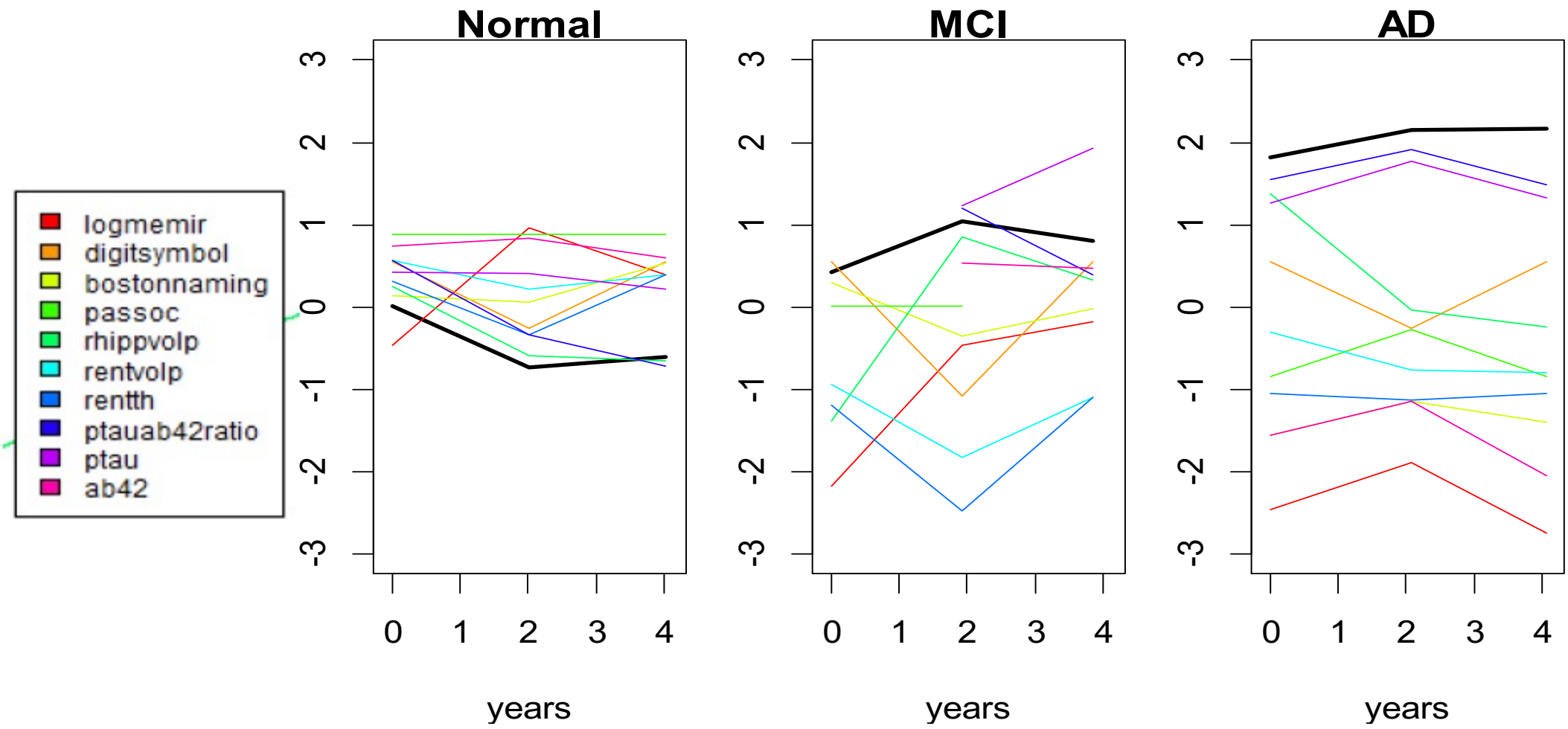
Legend

- Normal
- MCI
- AD



Examples of Individuals

Stayed Normal, Progressed to MCI , Progressed to Dementia



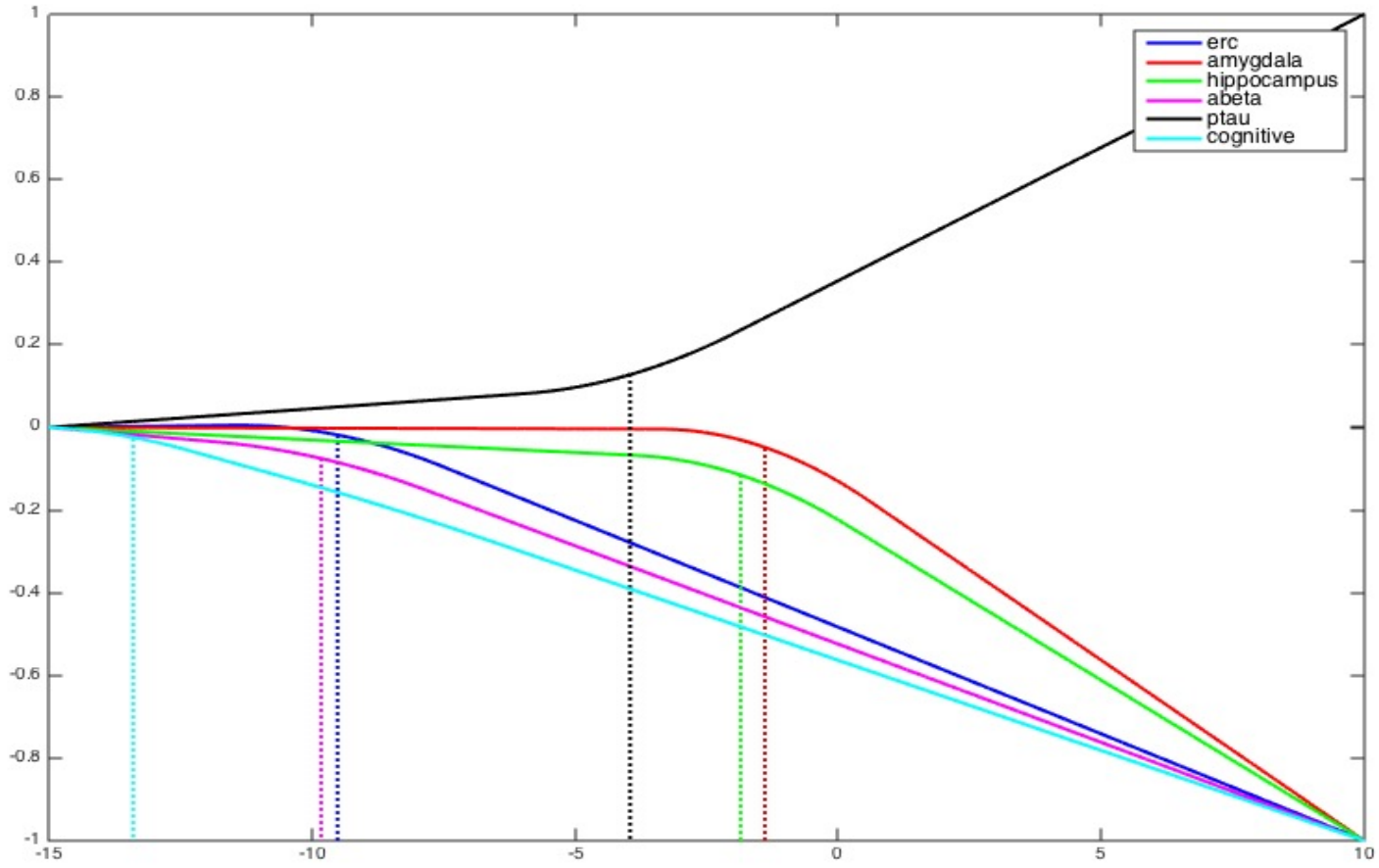
Modeling Changepoints of Biomarkers during Preclinical AD

Order of Changes During Preclinical AD
Recent Findings

- Goal: Identify the order in which biomarker changes occur during preclinical AD to improve understanding of disease
- Developed 'change point' method – identify point at which acceleration of change occurs
- Examined measures previously shown to be good predictors from each domain (CSF, MRI, cognitive)

Method – Younes et al., 2013

Ordering of Changes in Biomarkers



Future Directions

- Identify additional measures that can be added to existing models for: (1) predicting onset of symptoms and (2) tracking response to treatment
  - Potential measures in CSF or blood: lipids, cytokines, synaptic markers, etc
  - Potential imaging measures: additional changes in volume or shape on MRI, regional accumulations of amyloid and tau on PET, DTI measures, rs-fMRI;
  - Potential cognitive measures: computerized assessments of contextual cueing, pattern separation, etc