Exploration of a weighed cognitive composite score for measuring decline in amnestic MCI

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Background

- Neuropsychological batteries used widely
- Summarized using composite score
- Advantages:
  - Single summary measure
    - Interpretation
    - Multiple testing
  - Reduces floor and ceiling effects
  - Can detect subtle changes
  - Flexible in composition

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Background

- Current popular method:
  1. Standardize tests
  2. Average the standardized tests within domain
  3. Average the domains to create a single standardized measure
- Assumes equal performance
- Optimal in MCI due to AD?

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Study objectives

1. In aMCI, determine each domain's ability to classify clinically significant decline
2. Evaluate accuracy of averaged composite in classifying decline
3. Determine whether composite can be improved by weighting the domains

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Steps

1. Define the domains
2. Create domain-specific scores
3. Describe individual domain performance
4. Describe composite score performance
5. Compare results

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Step 1: Define cognitive domains

- Factor analysis of 10 neuropsych tests in UDS
  - UDS subjects with amnestic MCI at initial visit
  - Age ≥60
  - Primary language English
  - Non-missing test scores*
  - N=3,616
- Identify 4 factors

*Maximum (300) assigned for missing Trails B

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Factor analysis results

Test	Factor loading 1	2	3	4	Hypothesized domain
Logical Memory IA -Immediate	0.075	0.077	0.071	**0.525**	Episodic memory
Logical Memory IA- Delayed	0.079	0.171	0.041	**0.782**	Episodic memory
Digit Span-Forward	0.129	0.101	**0.573**	0.058	Working memory
Digit Span-Backward	0.211	0.086	**0.804**	0.078	Working memory
Animal Naming	0.223	**0.900**	0.121	0.091	Language
Vegetable Naming	0.198	**0.432**	0.081	0.206	Language
Boston Naming Test	0.359	**0.360**	0.121	0.162	Language
Trail Making Test A	**0.738**	0.163	0.096	0.054	Executive function
Trail Making Test B	**0.741**	0.179	0.268	0.111	Executive function
WAIS-R Digit Symbol	**0.701**	0.230	0.169	0.090	Executive function

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Step 2: Create domain-specific scores

- Reference group: mean and s.d. of test scores at initial visit from subjects with normal cognition
- For each test, subtract mean and divide by s.d.
- Average tests within domain
- Missing data:
  - ≤50% of tests within domain missing → average available tests
  - >50% missing → subject excluded

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Sample characteristics

Characteristic	Statistic*
Age (years)	76.2 (7.8)
Race: White	85.1%
Black	11.1%
Asian	1.4%
Multiracial	2.0%
Other or unknown	0.4%
Sex: Female	53.1%
Education (years)	15.3 (3.1)
Amnestic MCI Domain: Single	54.2%
CDR-SB	1.4 (1.1)
MMSE	27.2 (2.3)

*Sample characteristics are calculated from data observed at the UDS initial visit. Mean and (SD) are presented for continuous measures. Sample percentages are presented for categorical measures.

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Step 3: Describe domain performance

- 4 individual domains
- "Gold standard" = decline vs. stayed same
- Calculate the area under the ROC curve (AUC)
  - Outcome: diagnosis 1 year later (stayed aMCI vs. declined to primary probable AD dementia)
  - Predictor: domain-specific score at the initial visit

Initial visit:
Neuropsych tests

~1 year later:
aMCI vs. AD

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Status one year later

Status	N	(%)
Normal cognition	156	(8%)
Impaired not MCI	72	(4%)
Amnestic MCI*	**1,164**	**(63%)**
Non-Amnestic MCI	70	(4%)
Probable AD dementia*	**286**	**(15%)**
Possible AD dementia	69	(4%)
Dementia of another etiology	43	(2%)

*Used in main analysis

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Step 4: Describe composite score performance

- Averaging method:
  - Predictor: average standardized domain scores at initial visit

$$\frac{1}{4}\text{Domain}_1 + \frac{1}{4}\text{Domain}_2 + \frac{1}{4}\text{Domain}_3 + \frac{1}{4}\text{Domain}_4$$

  - Outcome: stayed aMCI vs. declined to AD dementia one year later

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Step 4: Describe composite score performance

- Weighted method:
  - Predictor: weights × standardized domain score from initial visit

$$w_1\text{Domain}_1 + w_2\text{Domain}_2 + w_3\text{Domain}_3 + w_4\text{Domain}_4$$

where $w_1 + w_2 + w_3 + w_4 = 1$ and

  - Calculated AUC for each combination where:

$$0 \le w_i \le 0.5 \quad \text{by } 0.05$$

  - Chose combination with highest AUC

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Step 5: AUC results

Predictor	AUC (95% CI)*
Domains	
Episodic memory domain	.69 (.66 - .72)
Language domain	.65 (.62 - .69)
Working memory domain	.54 (.51 - .58)
Executive function domain	.62 (.59 - .66)
Composites	
Average of domains	.69 (.66 - .72)
Maximizing AUC **	.73 (.70 - .76)

*Calculated using DeLong DeLong method

**Weights are (0.50, 0.40, 0.00, 0.10) for standardized episodic memory, language, working memory, and executive function

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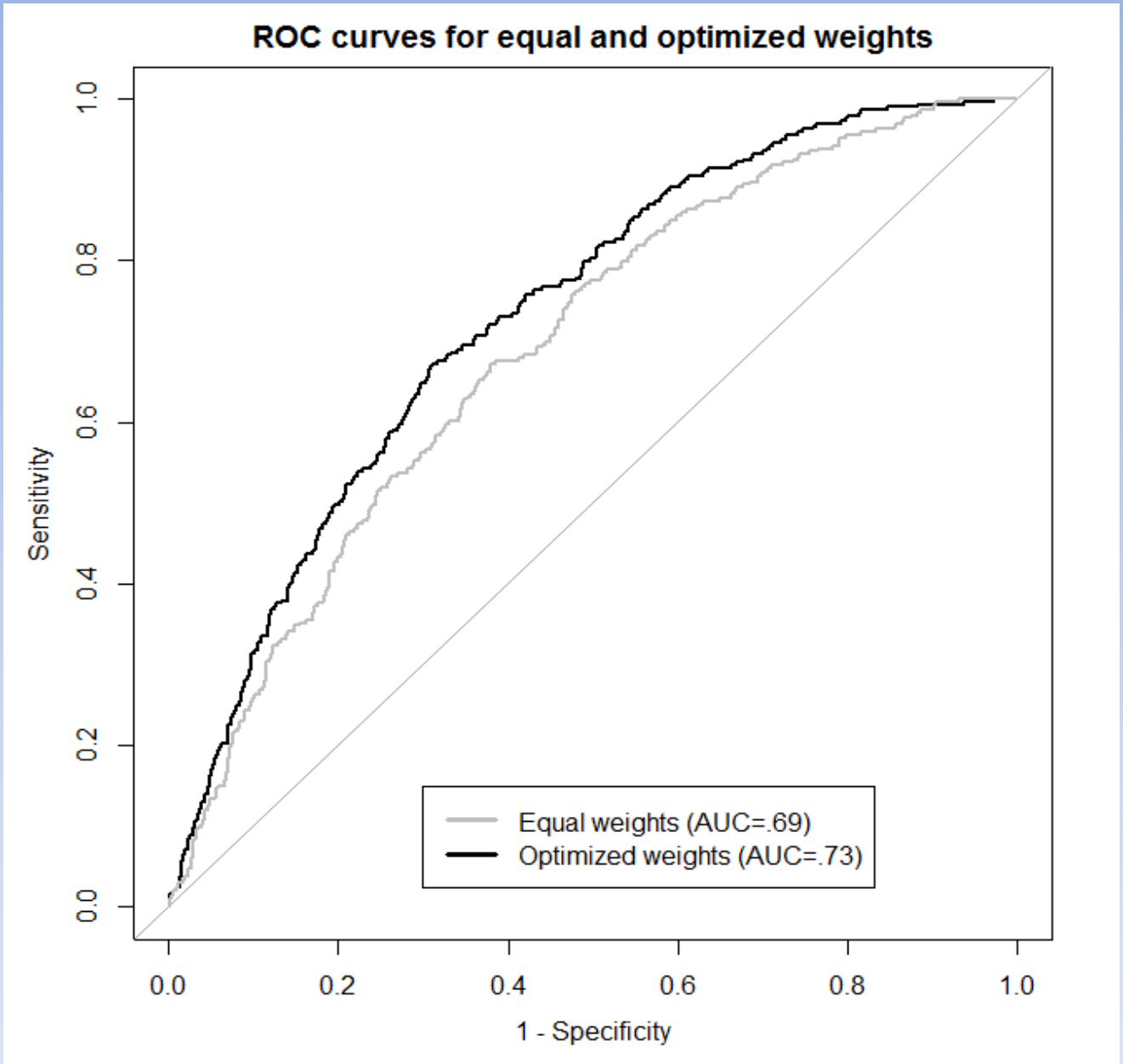

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Summary

- Episodic memory and language > working memory and executive function as subjects decline from aMCI to AD dementia
- Focusing on these domains could lead to more precise measurement of clinical decline
- Potential for disease-specific composite scores

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Words of caution

- Heterogeneity in clinical expression
- Generalizability of UDS neuropsych battery
  - Limited in episodic memory
  - No visuospatial test
  - Did not control for age, education, etc.
  - Handling of missing data
- Selection of weights needs to depend on research goals
  - Cross-sectional vs. longitudinal
  - Clinical progression timeline

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