Predicting Alzheimer's disease development: A comparison of cognitive criteria and associated neuroimaging biomarkers

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BACKGROUND. Currently, there exist multiple criteria for diagnosing mild cognitive impairment (MCI).[1,2,3] All require the presence of "objective impairment" in one or more cognitive domains, typically including memory. Four critical issues need clarification regarding the operationalization of "objective cognitive impairment":

1 ***What cut-off?*** *-1, -1.5 or -2 SD?* 2 ***How many tests?*** *Is one sufficient?* 3 ***Test other domains?*** *Language, executive functions?* 4 ***Consider biomarkers?*** *Genetic? Imaging?*

PARTICIPANTS

- 494 non-demented seniors with 24-month follow-up from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

COGNITIVE MEASURES

- Mini-Mental State Exam (MMSE)
- Logical Memory Story A – Delay (LM-II)
- Auditory Verbal Learning Test – Delay (AVLT)
- Category Fluency (animals)
- Boston Naming Test (BNT)
- Trails A & B (B/A ratio was used)

BIOMARKERS

- APOEε4 status
- Hippocampal (HP) & whole brain volume (BPF)
- White-matter hyperintensity (WMH) volume
- Ventricular cerebrospinal fluid (vCSF)

Main predictors. Six binary variables were created:

- Score < -1 SD × 1 memory test
- Score < -1.5 SD × 1 memory test
- Score < -2 SD × 1 memory test

} **LM-II *or* AVLT**

- Score < -1 SD × 2 memory tests
- Score < -1.5 SD × 2 memory tests
- Score < -2 SD × 2 memory tests

} **LM-II *and* AVLT**

RESULTS

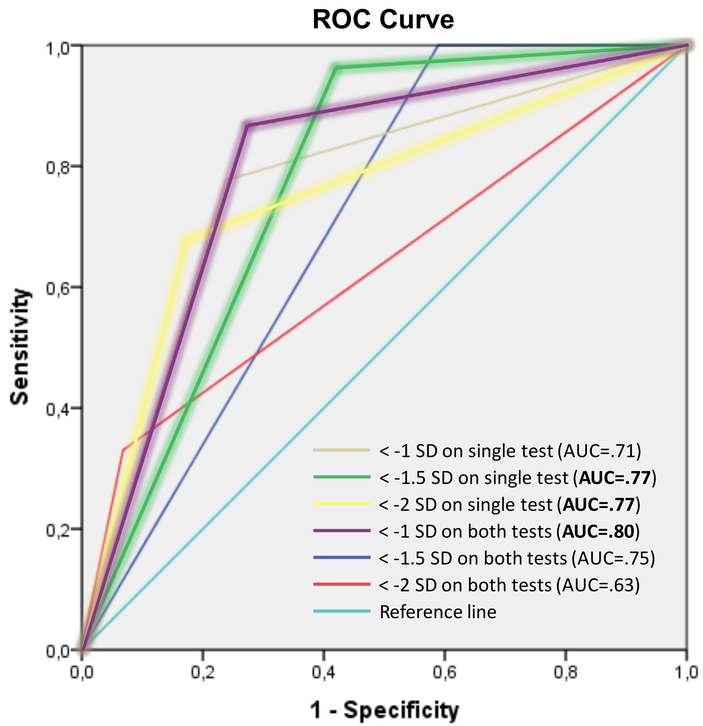

Figure 1. Areas under the curve (AUC) for six cut-offs.

Figure 2. Sensitivity, specificity and accuracy of different cut-off scores in 494 non-demented participants at baseline.

Table 1. Variables predicting Alzheimer's disease at 24 months in addition to selected cut-off scores.

Predictor	< -1 SD on two tests	< -1.5 SD on one test	< -2 SD on one test
Block 1: Main predictors			
Age	*p* = .146	*p* = .997	*p* = .403
Education	*p* = .780	*p* = .870	*p* = .668
Sex	*p* = .662	*p* = .917	*p* = .528
MMSE	*p* <.001	*p* <.001	*p* <.001
Selected cut-off	*p* <.001	*p* <.001	*p* <.001
Block 2: Non-memory tests			
Category Fluency	*p* = .227	*p* = .163	*p* = .211
BNT	*p* = .167	*p* = .109	*p* = .052
Trails B/A ratio	*p* = .130	*p* = .033	*p* = .017
Block 3: Biomarkers			
APOE ε4 (1 allele)	*p* = .055	*p* = .055	*p* = .060
APOE ε4 (2 alleles)	*p* = .016	*p* = .021	*p* = .019
Total HP volume	*p* = .326	*p* = .081	*p* = .115
BPF	*p* = .123	*p* = .030	*p* = .078
WMH	*p* = .121	*p* = .654	*p* = .609
vCSF	*p* = .240	*p* = .687	*p* = .382

CONCLUSION. Episodic memory impairment in MCI should be defined as scores **<-1 SD** on at least **two measures**. If one test is used, a more stringent cut-off should be applied and **executive functioning** abilities or **whole-brain volume** should be considered. When possible, **APOEε4 status** should be ascertained to optimize prediction of conversion to dementia.

1. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH: **The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease**. *Alzheimers Dement* 2011, **7**:270–279.
2. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. 5th edition. Arlington, VA: American Psychiatric Publishing; 2013.
3. Petersen RC: **Mild cognitive impairment as a diagnostic entity**. *J Intern Med* 2004, **256**:183–194.

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
ADNI Defining Alzheimer's Disease
AUCC Association des universités et collèges du Canada / Association of Universities and Colleges of Canada
Heart & Stroke Foundation Canadian Partnership for Stroke Recovery

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