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Defining Mild Cognitive Impairment: Impact of Varying Decision Criteria on Neuropsychological Diagnostic Frequencies and Correlates

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Abstract

Objective—To examine the impact of varying decision criteria on neuropsychological diagnostic frequencies and on their correlates.

Design—Descriptive and correlational study.

Setting—Florida Alzheimer's Disease Research Center.

Participants—A sample of 373 individuals with comprehensive baseline analyses participating in a longitudinal study of cognitive decline and early Alzheimer's disease.

Measurements—MCI diagnoses were made on the basis of four sets of decision criteria created by crossing two approaches: varying the number of impaired test results required for a diagnosis within any domain (1 test versus 2) and varying the performance level required to determine impairment (1.5 or 2 SDs below the normative mean) for any test.

Results—Under each criteria set, single-domain amnesic MCI was the most frequent MCI diagnosis. MCI global and subtype diagnosis frequencies were inversely related to the stringency of the criteria. The single test-1.5 SD criterion identified the largest number of cases as qualifying for an MCI diagnosis, and the two test-2.0 SD cutoff identified the fewest. Across all sets of criteria, we found significant positive associations between neuropsychological diagnoses and CDR score categories. Significant relationships between diagnoses and both APOE genotype and MRI ratings of medial temporal atrophy application were found only for the two test-1.5 SD and two test-2.0 SD cutoffs.

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Conclusion—MCI diagnosis frequencies are substantively affected by the stringency of the criteria, but the relative rankings of MCI subtype diagnoses are fairly consistent regardless of the stringency of the criteria. Significant associations of neuropsychological diagnoses with independent markers such as APOE genotype and medial temporal atrophy are only found with more stringent criteria, suggesting that a coherent network of associations reflecting cognitive decline occurs with more restrictive definitions for impairment.

Keywords

Mild cognitive impairment; neuropsychological tests; cognition; aging; Alzheimer's disease

Although numerous researchers have addressed the period of accelerated cognitive decline preceding formal diagnosis of dementia, Petersen and his colleagues (1) were the first to provide a detailed operational definition of this syndrome, which they termed Mild Cognitive Impairment (MCI). In their original presentation, Petersen et al. defined MCI as a condition characterized by the self-report of a memory problem, normal activities of daily living, normal general cognitive function, abnormal memory functioning, and the failure to meet criteria for dementia. Petersen et al. showed that the cognitive performance of the MCI patients was equivalent to control subjects except for memory. Memory performance for the MCI group was similar to that of an early Alzheimer's disease (AD) group. In this study and subsequent follow-up studies, Petersen et al. showed that the conversion rate to formal diagnosis of AD was approximately 12% per years, providing additional support for the hypothesis that MCI was a precursor to AD (2,3). Subsequently, however, broader definitions of MCI have been considered. The current MCI diagnostic typology now includes nonamnestic and multiple cognitive domain subtypes (4). Additionally, the definition of MCI has been amended to require a) a report of cognitive decline by self- or informant-report in combination with impairment on objective cognitive performance measures *or* evidence of decline over time on objective cognitive performance measures and b) preserved basic activities of daily living *and* no more than minimal impairment in complex instrumental activities.

There continue to be diagnostic challenges that critically affect accurate calculation of MCI prevalence rates, which have varied between 3% and 19% (5), and of conversion rates to AD and other dementias, which have varied between 1 and 19% annually (6-8). Further, up to 40% of MCI cases either do not convert to dementia or revert to a cognitively normal state on follow-up (9,10), possibly because of methodological differences in conducting and interpreting the objective assessment of cognitive performance.

There is no standard protocol for cognitive assessment in diagnosing MCI, and the neuropsychological batteries employed in studies to date vary in the number of cognitive domains assessed beyond memory (e.g., language, executive function, visual-spatial/perceptual ability, attention), procedures for assessing memory (e.g., verbal list learning and retention, prose paragraph recall, memory for visually-presented designs), criteria for determining the presence of impairment on a single cognitive measure (e.g., performance falling at 1 SD versus 1.5 or 2 SDs below normative means), and in criteria for determining impairment across multiple same-domain cognitive measures (e.g., requiring impaired performance on one versus two language measures). The few studies that have examined the impact of these decisions (11-15) have shown substantial effects on the frequency of diagnosed cases of MCI. The most comprehensive of these studies was recently reported by Jak et al. (16), who conducted cross-sectional and longitudinal analyses of a small cohort of neurologically normal, community-dwelling older adults. At baseline and followup the participants were diagnosed as normal or as having MCI by means of five different strategies based on the number of neuropsychological tests considered in the diagnosis and

the level of performance required to define impairment. Their results showed that the number of participants diagnosed as having MCI ranged from 10 to 74% of the sample, depending on the stringency of the criteria for interpreting cognitive impairment. Examination of classification agreement at baseline using different strategies, and of agreement across time within strategies, revealed a complex pattern of results. Notably, however, the most conservative strategy for diagnosing MCI (requiring a performance that was 1.5 SDs below the normative mean in more than two marker tests for a domain) had the greatest stability longitudinally.

In this study we conducted a constructive replication of the Jak et al. baseline analyses, using data from a large sample of elderly individuals who are participating in a longitudinal study of cognitive decline and Alzheimer's disease. This sample is well-characterized and allowed us to determine neuropsychological diagnostic frequencies as well as examine associations with independent clinical diagnoses, APOE genotypes, and clinical ratings of MRI-based medial temporal atrophy.

METHOD

Participants

Data for the present study were obtained from the database of the Florida Alzheimer's Disease Research Center (FADRC), an ongoing longitudinal study of normal individuals, elderly with MCI or cognitive impairment without dementia, and cases of early-stage Alzheimer's disease. FADRC participants are required have a Mini Mental State Exam (MMSE) (17) score > 19, have a stable medical status, be fluent in English or Spanish, and have at least six years of formal education. Individuals with active neoplastic disease or psychiatric disorders affecting cognition (e.g., schizophrenia, alcohol abuse) are excluded from participation. At the time of these analyses the sample consisted of approximately 467 individuals who had been consented and had initiated the baseline evaluation. The complete baseline evaluation consists of a thorough (medical, psychiatric, and psychosocial) history, structured clinical interviews including the Clinical Dementia Rating Scale (CDR) (18), comprehensive neuropsychological evaluation, MRI, laboratory tests, and blood draws for genotyping and biochemical analyses. In the FADRC protocol, clinical diagnostic interviews are conducted by physicians (neurologists or geropsychiatrists) and neuropsychological measures are administered by trained psychometricians under the supervision of neuropsychologists. All other histories, surveys, and questionnaires are administered by trained research staff. Clinical diagnostic interviews are conducted without knowledge of neuropsychological test results, MRI findings, or APOE genotype.

For this study, only data from the initial baseline evaluation were used; no data from subsequent evaluations were examined. Diagnoses therefore reflect diagnostic status at the point of entry into the FADRC study. Participant records from the ADRC baseline database were selected for analysis if the following conditions were met: 1) Geriatric Depression Scale (GDS) (19) score < 11, 2) age > 59, 3) complete data for all neuropsychological test measures, 4) Caucasian, and 5) first and primary language being English. Conditions 4 and 5 were used to avoid the influence of disparities in the quality of normative comparison data for neuropsychological measures that would be expected due to race and ethnicity. These inclusion criteria resulted in a study sample of 373 participants. The FADRC study is approved by an Institutional Review Board, and all participants whose data were used in these analyses provided informed consent.

Neuropsychological Measures and MCI Diagnostic Criteria

Three neuropsychological performance measures were examined in each of five cognitive domains. Table 1 lists the neuropsychological measures by domain and the source of normative data used to establish cutoff scores for determining ‘impairment’ for each test. Two approaches were used in generating strategies for examination. In the first, we varied the requirement for the number of impaired test results that were necessary for a diagnosis of MCI within any domain (1 test versus 2). In the second, we varied the performance level that was required to determine impairment (1.5 or 2 SDs below the normative mean) for any test. Crossing these two approaches created four sets of decision criteria for making a diagnosis of MCI. Using all five cognitive domains, we evaluated the neuropsychological test protocols with each of these sets to make one of five MCI diagnoses: normal (no diagnosis), single-domain amnesic, single-domain nonamnesic, multiple domain amnesic, and multiple-domain nonamnesic. For comparison purposes we also made a neuropsychological diagnosis of dementia, which required impairment in memory and at least one other domain using the 2 SD cutoff for determination of impairment under either the one or two-test requirement conditions. Normative impairment values (1.5 or 2 SDs) for each neuropsychological measure were based on widely recognized and commonly used published studies (see Table 1).

Correlational and Diagnostic Variables

To examine the effect of the different decision sets, we examined the association of the neuropsychological diagnostic results with MRI ratings of medial temporal atrophy, presence of an APOE E4 allele, CDR global score, and clinician diagnosis. The CDR was completed by a neurologist or geriatric psychiatrist without reference to results of MRIs, genotyping, or neuropsychological test findings. MRIs were obtained on a 1.5 Tesla MRI machine using proprietary 3-D MP-RAGE (Siemens) or 3-D SPGR (General Electric) sequences. Scans were acquired in the coronal plane and images were reconstructed as 1.5 mm thick contiguous slices. A visual rating system (20) was employed by an experienced rater to make bilateral estimates of regional atrophy of brain structures. In previous work, the inter-rater kappa values for the hippocampus, the entorhinal cortex, and the perirhinal cortex ranged between 0.75 and 0.94, with intra-rater reliabilities ranging from 0.87 to 0.93. The average score for the coronal slices of these three structures at the level of the mammillary body constituted the medial temporal atrophy score for the right (MTA-R) and left (MTA-L) hemispheres, respectively. Genotyping for APOE was performed by standard protocol (21). CDR global score was calculated using the algorithm recommended by Morris (18).

RESULTS

The sample consisted of 198 females (53.1%) and 175 males (46.9%), with an average age of 74.2 (SD = 6.0) and mean number of years of total education of 14.7 (SD = 2.9). Table 2 presents the results of applying the four sets of neuropsychological diagnostic criteria to the results of neuropsychological tests representing each of the five cognitive domains. Regardless of the diagnostic criteria the memory domain is most frequently impaired (11.3% to 36.2%). Executive and language domains have largely equivalent percentages of impaired performance, each at a level below that of the memory domain. The lowest percentages across diagnostic criteria occur for the visual-spatial and attention domains. For all domains and the category of no impairment, the pattern of frequencies is the same across decision sets: the single test- 1.5 SD cutoff identifies the largest number of impaired domains followed in order by the single test-2.0 SD cutoff, two test-1.5 SD cutoff, and the two test-2.0 SD cutoff.

Table 3 presents the diagnoses produced by the application of the four sets of neuropsychological diagnostic criteria to the results of neuropsychological tests representing each of the five cognitive domains. In order to examine the difference in proportions of global diagnoses (Normal, MCI, Demented) across diagnostic criteria, we treated the diagnoses as markers (or rankings) of pathology (Normal = 1, MCI= 2, Demented=3) and then conducted nonparametric analyses using the Friedman test. The overall analysis indicated a significant ($\chi^2 = 336.49$, $df = 3$, $p < .001$) difference in proportions of these diagnoses across the four sets of criteria. Followup pairwise Friedman tests, each conducted with alpha set at .01 to control for the number of analyses conducted, showed that each of the sets of diagnostic criteria was significantly different from every other set ($df = 1$, all $ps < .001$). The frequency of the global MCI diagnosis is highest for the single test- 1.5 SD cutoff criterion and decreases across the remaining sets of criteria in the following order: single test-2.0 SD cutoff, two test-1.5 SD cutoff, and the two test-2.0 SD cutoff. Because of the small number of diagnoses that occurred for some diagnostic criteria, we were not able to analyze differential frequencies for MCI subtypes. In general, however, the pattern of frequencies suggests that amnesic MCI is more frequent than nonamnesic MCI across sets of criteria, with the exception of the single test-2 SD criteria. Chi-square analyses examining the proportion of cases diagnosed in each set of decision criteria is significantly different for all pairwise comparisons of diagnosis (Normal, MCI all subtypes, Demented) ($df = 3$, all $p < .001$)

Table 4 presents descriptive statistics and cross tabulations for the CDR global score, APOE E4 status, MTA ratings, and diagnoses generated by application of the four sets of diagnostic criteria to the neuropsychological test results. The CDR global score was significantly associated with APOE E4 status ($\chi^2 = 9.37$, $df = 2$, $p < .01$), with higher scores associated with greater frequency of an E4 allele. An ANOVA of MTA ratings by CDR score categories was significant for both left ($df = 3$, 277; $F = 16.86$, $p < .0001$) and right ($df = 3$, 277; $F = 22.44$, $p < .0001$) hemispheres, with higher scores associated with greater atrophy. An ANOVA of MTA ratings by APOE genotypes was not significant for left MTA ratings ($df = 1$, 178; $F = 2.99$, $p > .05$), but was significant for right MTA ratings ($df = 1$, 178; $F = 10.56$, $p < .001$), with the presence of an APOE E4 allele associated with greater atrophy.

For all sets of criteria, χ^2 tests revealed a significant association between neuropsychological diagnosis and CDR score categories ($df = 4$, all $ps < .001$). The association between diagnosis and the presence of an APOE E4 allele was not significant using the one test-1.5 SD ($\chi^2 = 5.64$, $df = 2$, $p > .05$) or the one test-2.0 SD ($\chi^2 = 4.84$, $df = 2$, $p > .05$) cutoff; however, it was significant for the two test-1.5 SD ($\chi^2 = 18.10$, $df = 2$, $p < .001$) and two test-2.0 ($\chi^2 = 16.07$, $df = 2$, $p < .001$) cutoffs. ANOVAs testing differences in MTA ratings among diagnoses (normal, MCI, demented) were significant for both left and right hemispheres for each of the four criteria sets (all $ps < .001$). However, only for the two test-1.5 SD and two test-2.0 SD criteria sets did posthoc analyses (Tukey's b) reveal that the MCI group had significantly higher MTA ratings ($ps < .05$) than the normal group.

DISCUSSION

We examined the impact of different decision criteria on generating neuropsychological diagnoses in a large sample of elderly individuals participating in a longitudinal study of cognitive decline and dementia. Specifically, four sets of diagnostic criteria were applied to scores from neuropsychological tests in five cognitive domains. These criteria required an impaired performance on either one or two tests with impairment being defined as a score below a cutoff set at either 1.5 or 2.0 SDs below the age-adjusted mean based on a large normative sample. At the domain level the results were consistent across criteria sets in

showing that the memory domain was the most frequently impaired domain. For all domains and the category of no impairment, the same pattern of impairment frequencies was found: using more stringent criteria (i.e., requiring impairment at the 2.0 SD cutoff or impairment on two tests) reduces the frequency of impairment. This result is not surprising from a statistical standpoint and replicates the findings of previous studies (1,15).

Because the neuropsychological diagnoses were based solely on the pattern of impairment across cognitive domains, examination of the distribution of neuropsychological diagnoses revealed findings that paralleled those for the domains. Under three of the four criteria sets, single-domain amnesic MCI was the most frequent MCI subtype diagnosis. This finding is consistent with some (6,22), but not all (7), studies that have employed varying criteria in establishing a neuropsychological diagnosis of MCI.

The frequency of MCI and of MCI subtypes was found to be inversely related to the stringency of the criteria sets. The single test- 1.5 SD cutoff identifies the largest number of cases as qualifying for an MCI diagnosis, followed in order by the single test-2.0 SD cutoff, two test-1.5 SD cutoff, and the two test-2.0 SD cutoff. These findings are consistent with those reported by Jak et al. (11) and by Busse et al. (16), who also found this pattern of results when examining variations of the stringency of cutoff scores in generating MCI diagnoses.

Substantive relationships were found among the CDR, APOE, and MTA variables. These results replicate the findings of numerous previous studies, thus speaking to the internal validity of the study and providing the foundation for examining the relationship between the sets of criteria and each of these variables. Across all sets of criteria, we found significant positive associations between neuropsychological diagnoses and CDR score categories. A different pattern of results was found for the association between diagnosis and the presence of an APOE E4 allele. Application of the one-test criteria (either at the 1.5 SD or 2.0- SD cutoff) did not reveal a relationship between diagnosis and APOE genotype; however, application of the two test sets of criteria did produce evidence of a significant relationship for both the two test-1.5 SD and two test-2.0 SD cutoffs. Because the presence of an APOE E4 allele is a fairly robust risk factor for AD, is a predictor of conversion from MCI to AD (23), and is selectively associated with loss of episodic memory in the elderly (24), this result parallels that reported by Loewenstein et al. (14) and suggests that use of two-test criteria might more accurately identify true early AD phenotypes. Analysis of the relationship between sets of criteria and MTA ratings revealed findings largely in parallel with those for the APOE analyses. Only for the two-test sets of criteria did the MCI cases have significantly higher MTA ratings than controls. Medial temporal atrophy is a substantive predictor of conversion from MCI to AD (25,26). This association with a biomarker for conversion would support the position that more stringent criteria for neuropsychological diagnosis might serve to provide as better indicators of early AD.

This study has several strengths, including the sample size, the availability of several neuropsychological measures in each of five cognitive domains, and the presence of independent clinical and biological markers of decline. Nevertheless, several caveats are in order. Because the recruitment procedures for the FADRC included multiple methods, including public announcements, referrals from memory disorder clinics, and word-of-mouth efforts, the frequencies of MCI and MCI subtype diagnoses should not be considered to be estimates of population prevalence. A further limitation of the study is that the sample was relatively highly educated and thus may have had greater cognitive reserve than the age-based normative samples used to determine cutoff scores for the decision criteria.

It should be noted that our criteria required impairment on either one or two tests within each domain. Because we had three measures within each domain, the frequencies of MCI and MCI subtype diagnoses are likely higher than would be the case if we had only administered one or two tests within each domain. It is well established that the greater the number of tests examined within a domain, the greater the probability of obtaining single or multiple test scores that will fall below a given cutoff score (12). We did not examine the use of a cutoff score set at 1.0 SD. If a measure has a normal distribution in a healthy population, a normative cutoff score of 1.0 SD identifies 16% of healthy individuals as impaired, a percentage we consider too high to allow meaningful specificity in the assessment of cognitive decline leading to AD. Cutoff scores at the 1.0 or even .5 SD level might, however, have value in conjunction with clinical or biological markers.

In summary, this study suggests that the frequencies of MCI diagnoses and subtype diagnoses are substantively affected by the stringency of the neuropsychological criteria, but the relative rankings of MCI subtype diagnoses are fairly consistent regardless of the stringency of the criteria. Because most neuropsychological test data typically have quasi-normal distributions, these findings are not very notable: more stringent criteria capture fewer cases at the tail ends of the distributions and there are therefore fewer cases being defined as impaired. More important, however, is the fact that significant associations of neuropsychological diagnoses with independent markers such as APOE genotype and MTA are only found with more stringent criteria, suggesting that a coherent network of associations reflecting cognitive decline occurs with more restrictive definition for impairment.

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REFERENCES

1. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment - clinical characterization and outcome. *Arch Neurol* 1999;56:303–308. [PubMed: 10190820]
2. Jack CR, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurol* 1999;52:1397–1403.
3. Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol* 2004;61:59–66. [PubMed: 14732621]
4. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment - beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med* 2004;256:240–246. [PubMed: 15324367]
5. Panza F, D'Introno A, Colacicco AM, et al. Current epidemiology of mild cognitive impairment and other predementia syndromes. *Am J Geriatr Psychiatry* 2005;13:633–644. [PubMed: 16085779]
6. Farias ST, Mungas D, Reed BR, et al. Progression of mild cognitive impairment to dementia in clinic-vs community-based cohorts. *Arch Neurol* 2009;66:1151–7.
7. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* 2007;23(68):288–91. [PubMed: 17242334]
8. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;119:252–65. [PubMed: 19236314]
9. Ganguli M, Dodge HH, Shen C, et al. Mild cognitive impairment, amnesic type: an epidemiologic study. *Neurology* 2004;63:115–121. [PubMed: 15249620]

10. Comijs HC, Dik MG, Deeg DJ, et al. The course of cognitive decline in older persons: results from the longitudinal aging study Amsterdam. *Dement Geriatr Cogn Disord* 2004;17:136–142. [PubMed: 14739534]
11. Busse A, Bischkopf J, Riedel-Heller SG, et al. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Br J Psychiatry* 2003;182:449–54. [PubMed: 12724250]
12. Brooks BL, Iverson GL, Holdnack JA, et al. Potential for misclassification of mild cognitive impairment: a study of memory scores on the Wechsler Memory Scale-III in healthy older adults. *J Int Neuropsychol Soc* 2008;14:463–78. [PubMed: 18419845]
13. Brooks BL, Iverson GL, White T. Substantial risk of “Accidental MCI” in healthy older adults: base rates of low memory scores in neuropsychological assessment. *J Int Neuropsychol Soc* 2007;13:490–500. [PubMed: 17445298]
14. Loewenstein DA, Acevedo A, Small BJ, et al. Stability of different subtypes of mild cognitive impairment among the elderly over a 2- to 3-year follow-up period. *Dement Geriatr Cogn Disord* 2009;27:418–23. [PubMed: 19365121]
15. Loewenstein DA, Acevedo A, Agron J, et al. The use of amnesic and nonamnesic composite measures at different thresholds in the neuropsychological diagnosis of MCI. *J Clin Exp Neuropsychol* 2007;29:300–7. [PubMed: 17454350]
16. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry* 2009;17:368–75. [PubMed: 19390294]
17. Folstein MF, Folstein SE, McHugh PR, et al. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198. [PubMed: 1202204]
18. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–4. [PubMed: 8232972]
19. Yesavage JA, Brink TL, Rose TL, et al. Development and validity of a Geriatric Depression Scale: A preliminary report. *J Psychiatr Res* 1983;17:37–49. [PubMed: 7183759]
20. Urs R, Potter E, Barker W, et al. Visual rating system (VRS) for assessing magnetic resonance images (MRIs): A tool in the diagnosis of MCI and Alzheimer’s Disease. *J Comput Assist Tomogr* 2009;33:73–78. [PubMed: 19188789]
21. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet* 1991;337:1158–1159. [PubMed: 1674030]
22. Saxton J, Snitz BE, Lopez OL, et al. Functional and cognitive criteria produce different rates of mild cognitive impairment and conversion to dementia. *J Neurol Neurosurg Psychiatry* 2009;80:737–43. [PubMed: 19279031]
23. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol* 2005;62:975–80. [PubMed: 15956169]
24. Boyle PA, Buchman AS, Wilson RS, et al. The APOE epsilon4 allele is associated with incident mild cognitive impairment among community-dwelling older persons. *Neuroepidemiol* 2010;34:43–9.
25. Ferreira LK, Diniz BS, Forlenza OV, et al. Neurostructural predictors of Alzheimer’s disease: A meta-analysis of VBM studies. *Neurobiol Aging*. in press.
26. Risacher SL, Saykin AJ, West JD, et al. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort: Alzheimer’s Disease Neuroimaging Initiative (ADNI). *Curr Alzheimer Res* 2009;6:347–61. [PubMed: 19689234]
27. Brandt, J.; Benedict, RHB. *Hopkins Verbal Learning Test-Revised*. Psychological Assessment Resources; Odessa, FL: 1991.
28. Weschler, D. *Wechsler Memory Scale*. 3rd Ed. The Psychological Corporation; San Antonio, TX: 1997.
29. Kaplan, E.; Goodglass, H.; Weintraub, S. *The Boston Naming Test*. Lea & Febiger; Philadelphia, PA: 1983.
30. Benton AH. Problems of test construction in the field of aphasia. *Cortex* 1967;3:32–58.

31. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's older Americans normative studies: category fluency norms. *J Clin Exp Neuropsychol* 1998;20:194–200. [PubMed: 9777473]
32. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643–661.
33. Weschler, D. Wechsler Adult Intelligence Scale. 3rd Ed. The Psychological Corporation; San Antonio, TX: 1997.
34. Reitan RM. Validity of the Trailmaking Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271–276.
35. Benton, AL.; Hamsher, K.; Varney, N., et al. Judgement of Line Orientation Test. University of Iowa; Iowa City, IA: 1983.
36. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's older americans normative studies: WMS-R norms for ages 56-94. *The Clin Neuropsychologist* 1992;6:49–82.
37. Ivnik RJ, Malec JF, Smith GE, et al. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. *The Clin Neuropsychologist* 1996;10:262–278.
38. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol* 1999;14:167–177. [PubMed: 14590600]
39. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's older americans normative studies: Category fluency norms. *Clin Exp Neuropsychologist* 1998;20:194–200.

Table 1

Neuropsychological test domains, measures, and normative reference samples used to determine cutoff scores

Domain	Test	Measure/Normative Sample Reference
Memory	Hopkins Verbal Learning Test ²⁷	Delayed recall trial score ²⁷
	Wechsler Memory Scale ²⁸	Visual Reproduction II score ³⁶
	Wechsler Memory Scale	Logical Memory II score ³⁶
Language	Boston Naming Test ²⁹	Total correct ³⁷
	FAS ³⁰	Total words ³⁸
	Category Fluency ³¹	Total words ³⁹
Executive Function	Stroop Test ³²	Color -Word Trial score ³⁷
	Wechsler Adult Intelligence Scale ³³	Digit Symbol total score ³³
	Trail-Making Test ³⁴	Trails B time ³⁷
Visual-spatial	Wechsler Adult Intelligence Scale	Block Design score ³³
	Judgment of Line Orientation ³⁵	Total correct ³⁷
	Wechsler Memory Scale	Visual Reproduction I score ³⁶
Attention	Wechsler Adult Intelligence Scale	Digit Span total score ³³
	Stroop Test	Word Trial score ³⁷
	Trail-Making Test	Trails A time ³⁷

Table 2

Participants meeting neuropsychological criteria for impairment by cognitive domain

	Neuropsychological Criteria							
	Single test				Two tests			
	1.5 SD cutoff		2 SD cutoff		1.5 SD cutoff		2 SD cutoff	
Cognitive Domain	N	%	N	%	N	%	N	%
Memory	135	36.2	80	21.4	70	18.8	42	11.3
Executive	73	19.6	40	10.7	23	6.2	13	3.5
Language	84	22.5	46	12.3	26	7.0	17	4.6
Visual-Spatial	48	12.9	30	8.0	7	1.9	2	0.5
Attention	52	13.9	22	5.9	10	2.7	4	1.1
None	172	46.1	250	67.0	286	76.7	314	84.2

Table 3

Neuropsychological diagnoses by differing sets of neuropsychological diagnostic criteria

Diagnosis	Single test, cutoff =			Two tests, cutoff =					
	1.5 SD ^a		2 SD ^a	1.5 SD ^a		2 SD ^a		2 SD ^a	
	N	%	N	N	%	N	%	N	%
Normal ^b	172	46.1	250	286	76.7	314	84.2		
MCI, all subtypes ^b	155	41.6	77	75	20.1	47	12.6		
Demented ^b	46	12.3	46	12	3.2	12	3.2		
MCI-all amnesic subtypes	89	23.9	34	58	15.5	30	8.0		
MCI-amnesic domain only	54	14.5	34	40	10.7	30	8.0		
MCI- amnesic plus other domain(s)	35	9.4	0	18	4.8	0	0.0		
MCI-all nonamnesic subtypes	66	17.7	43	17	4.6	17	4.6		
MCI-single nonamnesic domain only	46	12.3	33	13	3.5	15	4.0		
MCI-multiple nonamnesic domains	20	5.4	10	4	1.1	2	0.5		

^aProportion of Normal, MCI all subtypes, and Demented diagnoses is significantly different for all pairwise comparisons of decision criteria at $p < .001$.

^bProportion of cases diagnosed in each set of decision criteria is significantly different for all pairwise comparisons of diagnosis at $p < .001$.

Table 4

Relationships among neuropsychological diagnostic frequencies, CDR scores, APOE E4 status, and MTA ratings

						MTA Rating			
	CDR Global Score %			APOE Status %		Left		Right	
	0	0.5	1+	E4 Positive	E4 Negative	Mean	SD	Mean	SD
CDR Global Score									
0				21.4	78.6	0.6	0.8	0.7	0.8
0.5				33.0	67.0	0.9	0.8	0.8	0.8
1+				57.1	42.9	2.1	1.3	2.3	1.2
APOE Status									
E4 Positive	35.3	52.9	11.8			0.8	1.0	1.0	1.1
E4 Negative	52.7	43.7	3.6			0.6	0.8	0.5	0.7
Neuropsychological Diagnostic Groups									
Single test, 1.5 SD criteria									
Normal	66.1	33.9	0.0	21.6	78.4	0.7	0.8	0.7	0.8
MCI-all subtypes	41.6	53.2	5.1	32.1	67.9	0.7	0.8	0.8	0.7
Demented	10.9	63.0	26.1	43.5	56.5	1.6	1.1	1.5	1.3
Single test, 2.0 SD criteria									
Normal	60.5	39.5	0.0	24.4	75.6	0.7	0.8	0.7	0.8
MCI-all subtypes	35.1	54.5	10.4	34.5	65.5	0.7	0.7	0.8	0.8
Demented	10.9	63.0	26.1	43.5	56.5	1.6	1.1	1.5	1.3
Two tests, 1.5 SD criteria									
Normal	59.9	39.1	1.1	22.0	78.0	0.7	0.8	0.7	0.8
MCI-all subtypes	16.0	66.7	17.4	53.2	46.8	1.3	1.1	1.2	1.1
Demented	0.0	66.7	33.3	37.5	62.5	1.7	1.0	1.6	1.2
Two tests,									

										MTA Rating			
	CDR Global Score %				APOE Status %		Left		Right				
	0	0.5	1+	E4 Positive	E4 Negative	Mean	SD	Mean	SD				
2.0 SD criteria													
Normal	57.4	41.0	1.6	24.1	75.9	0.7	0.8	0.7	0.8				
MCI-all subtypes	6.4	70.2	23.4	61.5	38.5	1.4	1.0	1.4	1.1				
Demented	0.0	66.7	33.3	37.5	62.5	1.7	1.0	1.6	1.2				