Published in final edited form as:

J Alzheimers Dis. 2014 ; 39(3): 575–582. doi:10.3233/JAD-130524.

10-Minute Delayed Recall from the Modified Mini-Mental State Test Predicts Alzheimer's Disease Pathology

Scott A. Lyness^{a,*}, Ae Young Lee^b, Chris Zarow^a, Evelyn L. Teng^a, and Helena C. Chui^a

^aDepartment of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

^bDepartment of Neurology, Chungnam University, Daejeon, Korea

Abstract

We compared the sensitivity and specificity of two delayed recall scores from the Modified Mini-Mental State (3MS) test with consensus clinical diagnosis to differentiate cognitive impairment due to Alzheimer's disease (AD) versus non-AD pathologies. At a memory disorders clinic, 117 cognitively impaired patients were administered a baseline 3MS test and received a contemporaneous consensus clinical diagnosis. Their brains were examined after death about 5 years later. Using logistic regression with forward selection to predict pathologically defined AD versus non-AD, 10-min delayed recall entered first ($p = 0.001$), followed by clinical diagnosis ($p = 0.02$); 1-min delayed recall did not enter. 10-min delayed recall scores ≥ 4 (score range = 0–9) were 87% sensitive and 47% specific in predicting AD pathology; consensus clinical diagnosis was 82% sensitive and 45% specific. For the 57 patients whose initial Mini-Mental State Examination scores were ≤ 19 (the median), 3MS 10-min delayed recall scores ≥ 4 showed some loss of sensitivity (80%) but a substantial gain in specificity (77%). In conclusion, 10-min delayed recall score on the brief 3MS test distinguished between AD versus non-AD pathology about 5 years before death at least as well as consensus clinical diagnosis that requires much more comprehensive information and complex deliberation.

Keywords

Autopsy; consensus; dementia; memory disorders; Modified Mini-Mental State (3MS); neuropsychological tests; sensitivity and specificity

INTRODUCTION

Early and accurate diagnosis of Alzheimer's disease (AD) is important for treatment and management planning. An evidence-based review indicates that, using NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's

© 2014 – IOS Press and the authors. All rights reserved

*Correspondence to: Scott A. Lyness, Department of Neurology, Keck School of Medicine, University of Southern California, Health Sciences Campus, 1540 Alcazar Street, CHP 209-G, Los Angeles, CA 90033, USA. Tel.: +1 323 442 7793; Fax: +1 323 442 7790; lyness@usc.edu.

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1973>).

Disease and Related Disorders Association) clinical criteria for the diagnosis of probable or possible AD, the clinical-pathological correlation is about 90% sensitive and 56% specific [1]. It would be desirable to find a simpler yet efficacious and noninvasive method to clinically distinguish AD from non-AD cases to guide management and treatment.

In autopsy-confirmed samples, retrospective analysis of neuropsychological test scores consistently showed worse memory performance in the group clinically diagnosed with AD than the group without AD [2–10]. Further, where delayed recall was tested, the group with AD consistently performed worse than the group without AD [2, 4, 5, 7, 10]. There is indication that the memory component of screening tests for dementia such as the Mini-Mental State Examination (MMSE) [11] and Mattis Dementia Rating Scale [12] maybe useful in predicting AD pathology [5, 9, 13, 14], but no sensitivity and specificity values were reported.

Formal neuropsychological tests of memory often use longer word lists and several learning and recall trials (e.g., [15, 16]). While they are sensitive for detecting mild memory impairment, their difficulty and lengthy testing can be taxing or even overwhelming for patients with cognitive impairment or dementia usually seen at memory clinics. In the present study, we used a screening test of cognitive impairment, the Modified Mini-Mental State (3MS) test [17–19], that contains two delayed recall items, takes only about 10–15 minutes to administer, and has been used in several epidemiological studies (e.g., [20, 21]). We examined the efficacy of its 1-min delayed recall and 10-min delayed recall of three words in distinguishing AD brain pathology from other brain lesions. In addition, the predictive power of these two test scores was compared to that of the consensus clinical diagnosis [22] that included medical and family history, physical and neurological examination, mental status and neuropsychological examination, neuroimaging, and laboratory studies.

MATERIALS AND METHODS

Sample

This is a retrospective convenience study of 117 patients who presented with a chief complaint of memory or other cognitive impairment and came to autopsy at the Alzheimer's Research Centers of California (ARCC) at Rancho Los Amigos National Rehabilitation Center. All of them were administered a baseline 3MS test between July 1986 through January 2006, were given a clinical diagnosis close in time ($Mdn = 0.8$ months), and were later autopsied ($M = 4.5$ years) for brain pathology. During this period of time, an additional 88 patients came to autopsy but were excluded from this study because they did not have both baseline 3MS and clinical diagnosis, or were not found to be cognitively impaired. All participants or their surrogate decision makers signed informed consent to participate in the ARCC or the IVD (Ischemic Vascular Dementia) research programs and gave consent for autopsy. Both programs were approved by the institutional review board of Rancho Los Amigos National Rehabilitation Center.

The Modified Mini-Mental State (3MS) test

In comparison to the widely used MMSE, the 3MS test has (a) four additional items of reporting date and place of birth, generating names of 4-legged animals, assessing similarities, and a second delayed recall of three words at the end of the test and (b) more detailed testing and scoring on memory and some other items [17]. The 3MS test has a score range of 0–100, and can generate an estimated MMSE score with a score range of 0–30. In the MMSE, recent memory is assessed by requesting recall of three words after the participant is asked to do five serial subtractions or to spell a five-letter word backwards; only unaided recall is assessed, and correct recall of each word is given a score of 1. Thus the MMSE has a score range of 0–3 for the recall of three words. In the 3MS test, the first recall of three words is requested approximately 1 minute after their presentation, during which the participant is asked to count from 1 to 5 forward and backward, and to spell a 5-letter word forward and backward. For each word that is not correctly recalled, a category cue is provided, followed by three choices if needed; 3 points are given for unaided correct recall, 2 points are given for correct recall after category cueing, and 1 point is given for correct identification among 3 choices. Thus, the 3MS test has a score range of 0–9 for the recall of three words. In addition, during this “1-min delayed recall,” (a) if a participant has not chosen the correct word from three choices, he or she is told the correct answer, and (b) whenever a participant has not recalled all three words correctly without help (i.e., whenever the total score is <9), he or she is told the three words once more before proceeding to the next item. Therefore, this testing procedure for 1-min delayed recall also helps the participant to learn the three words more thoroughly. After approximately 10 minutes of other testing activities (at the end of the 3MS test), recall of the three words is requested for a second time. Again, for each word unaided recall is followed by category cueing and three choices when needed, and a score of 0–3 is given. Thus on the 3MS test, each of the 1-min and 10-min delayed recalls has a score range of 0–9.

Clinical diagnosis

Clinical diagnosis was based on history including informant interview, physical and neurological examinations, the 3MS test, and neuropsychological testing if MMSE >15. The neuropsychological test battery provided more detailed assessment of various cognitive domains and its administration required approximately 1.5 hours. In addition, the results of neuroimaging and laboratory studies were considered. A consensus clinical diagnosis was reached at a consensus conference involving several specialists in dementia.

The patients in this study were categorized into two groups: cognitively impaired but not demented (CIND) or demented. Those with CIND ($n = 15$) were divided between either amnesic ($n = 7$) or nonamnesic ($n = 8$). Those with dementia ($n = 102$) included the following etiologies according to the NINCDS-ADRDA criteria [22]: 79 AD (1 definite by brain biopsy, 40 probable, 15 possible, 23 mixed) and 23 non-AD (10 vascular, 7 Parkinson's disease or dementia with Lewy bodies [PD/DLB], 3 progressive supranuclear palsy or corticobasal ganglionic degeneration [PSP/CBGD], 2 frontotemporal disease or dementia [FTD] or Pick's, 1 not specified).

Brain tissue preparation and pathological classification

At autopsy, the brain was removed and weighed, then fixed in 10% neutral buffered formalin for at least two weeks. Tissue was blocked and processed according to methods recommended by the Consortium to Establish a Registry for Alzheimer Disease (CERAD) [23]. Tissue blocks were obtained from the hippocampus, middle frontal, superior temporal, inferior parietal, and occipital lobes, as well as the nucleus basalis, substantia nigra, and locus ceruleus. The blocks were dehydrated in alcohol, embedded in paraffin, and sectioned at 10 microns. Sections were stained with hematoxylin and eosin, cresyl violet, Bielschowsky silver, and Congo Red. The stained sections were examined microscopically by board-certified neuropathologists. We examined the substantia nigra for Lewy bodies in hematoxylin and eosin stained sections but did not use immunocytochemical staining against α -synuclein. Ischemic lesions are known to be heterogeneous in distribution. The blocking protocol was developed to assess AD pathology but all sections were examined for infarcts (which included a few representative sections of basal ganglia and deep white matter).

The autopsy classification of AD was based on the finding of widespread neurofibrillary tangles in hippocampus and neocortex (Braak & Braak stage IV) [24], as well as abundant neuritic plaques in neocortex. Braak & Braak stage IV (hippocampal stage) was chosen because of its expectation to be associated with significant memory impairment. Hippocampal sclerosis (HS) was defined by complete loss of pyramidal neurons with gliosis in cornu ammonis-1 (CA-1). The classification of cerebrovascular disease, PD/DLB, HS, PSP/CBGD, FTD/Pick's, and prion disease were made by the neuropathologists based on neuropathological features characteristic of these disorders.

Two of the authors (HC and CZ) reviewed the macroscopic and microscopic reports from the neuropathologists. Using the National Institute on Aging-Reagan criteria [25], the brains were assigned into an AD category ($n = 79$) or into a non-AD category ($n = 38$). The AD category included intermediate and high likelihood AD ($n = 60$), AD + cerebrovascular brain injury (CVBI) ($n = 14$), AD + HS ($n = 4$), and AD + DLB ($n = 1$). The non-AD category included HS ($n = 8$), CVBI ($n = 7$), PD/DLB ($n = 7$), PSP/CBGD ($n = 5$), abnormal brain without clearly definable cause ($n = 3$), FTD/Pick's ($n = 2$), Creutzfeldt-Jakob disease ($n = 2$), or normal brain ($n = 4$). We did not rate the severity of non-AD pathology or attempt to assess its relative contribution to cognitive impairment. The pathological classification of AD versus non-AD was based exclusively on the macro- and microscopic examinations by neuropathologists without knowledge of the 3MS scores.

Statistical analyses

Sensitivity and specificity were computed to compare accuracy between the two 3MS memory scores and clinical diagnosis in predicting AD pathology outcome.

Logistic regression modeled the probability of a pathology-based classification of AD versus non-AD. The three predictors were clinical diagnosis (AD dementia, including amnesic CIND, versus non-AD dementia, including nonamnesic CIND) and the 1- and 10-min delayed recall scores on the 3MS test (each with a score range of 0–9). Logistic models were run with all predictors entered simultaneously, and also with a forward selection procedure.

Receiver operating characteristic (ROC) curves were computed. An estimated probability of an event serves as a cutpoint for predicting the response (AD pathology). Sensitivity and 1 – specificity are computed from these estimated probabilities and graphed as the ROC curve. Areas under the curves (AUC) were compared using nonparametric methods [26].

Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). Continuous data are presented as mean and SD, $M (SD)$. Probability levels ≤ 0.05 were considered statistically significant.

RESULTS

The demographic and clinical characteristics of the sample are summarized in Table 1. On average, patients died around age 80, had some college education, and started showing symptoms of illness 10 years before death; the interval between the baseline 3MS test and death was about 5 years; the total score of the baseline 3MS test was 56 out of 100, with an estimated MMSE score of 18 out of 30. The average score on 1- and 10-min delayed recall was each about 3 out of 9. Clinical diagnoses ranged from mild cognitive impairment (CIND) to clear dementia.

Accuracy of clinical diagnosis

The correspondence between the consensus clinical diagnosis and the pathology-based classification is shown in Table 2. Among the patients clinically diagnosed to have nonamnesic CIND or amnesic CIND, their pathology-based classification included 38% and 57% AD cases, respectively. Among the patients clinically diagnosed to be non-AD dementia or AD dementia, their pathology-based classification included 48% and 77% AD cases, respectively.

Clinical diagnoses were dichotomized as AD (including 79 AD dementia and 7 amnesic CIND) versus non-AD (including 23 non-AD dementia and 8 nonamnesic CIND). Likewise, pathological classifications were also dichotomized as 79 AD (including 60 AD only and 19 AD with additional pathology) versus 38 non-AD (including 34 non-AD pathology and 4 normal brain). The clinical-pathological correspondence between the dichotomized categories is summarized in Table 3 and shows that the clinical diagnosis of AD, made approximately 5 years before death, had a sensitivity of 82% and specificity of 45% for pathology-based classification of AD.

Differences between pathology-based AD versus non-AD patients

Table 4 compares the demographic and screening variables between neuropathology verified AD versus non-AD patients. Statistically significant differences were found for the interval between baseline 3MS test and death, where the group with AD survived about 1.5 years longer. The group with AD also scored lower on 3MS 10-min delayed recall.

Logistic regression

Three predictors (clinical diagnosis, 1-min delayed recall, and 10-min delayed recall) were entered to predict pathological outcome (AD was the referent, versus non-AD). Interval between baseline 3MS test and death was included as a covariate.

To test for collinearity among the three predictors and covariate (interval to death), the variance inflation factor (VIF) was examined. VIF was considerably <10 , indicating little evidence for collinearity [27]. VIF = 2.65 for 1-min delayed recall, 2.60 for 10-min delayed recall, and 1.05 for both clinical diagnosis and interval.

Rank biserial correlations were computed for the association between the two recall measures and clinical diagnosis. The correlation between 1-min delayed recall and clinical diagnosis was 0.18 and between 10-min delayed recall and clinical diagnosis was 0.16. For both associations, therefore, the proportion of variance accounted for (r^2) was about 3%.

When all three predictors and the covariate were entered simultaneously to predict pathology-based outcome (AD versus non-AD), the overall model was statistically significant, Wald $\chi^2(4) = 19.0$, $p = 0.0008$. For the individual variables, 10-min delayed recall (Wald $\chi^2 p = 0.007$), clinical diagnosis ($p = 0.02$), and interval to death ($p = 0.03$) were statistically significant, 1-min delayed recall was not ($p = 0.15$). In logistic regression with forward selection, 10-min delayed recall entered first ($p = 0.001$), followed by interval to death ($p = 0.006$), and then clinical diagnosis ($p = 0.02$); 1-min delayed recall did not enter.

Receiver operating characteristic curves

ROC curves were drawn for the three predictors (see Fig. 1). The AUC for 3MS 10-min delayed recall (AUC = 0.65) was larger ($p = 0.01$) than that of its 1-min delayed recall (AUC = 0.57), but not different ($p = 0.82$) from that of clinical diagnosis (AUC = 0.64).

A cutpoint at 4 (meaning scores ≥ 4 indicates AD) for 10-min delayed recall resulted in the best combination of sensitivity and specificity (87% sensitive, 47% specific) for AD pathology. Table 5 displays sensitivity and specificity, positive and negative likelihood ratios, and AUC for the cutpoints for 10-min delayed recall. AUC is largest at the cutpoint of 4.

Ancillary data analysis

Five sets of additional data analyses were performed to further clarify our findings.

First, to examine whether the main findings differed between the two groups with poorer or better general cognitive level at baseline 3MS testing, the 117 patients were divided into two subgroups at the median of their initial MMSE score (≤ 18 versus >19), and data analysis was repeated for each subgroup. Logistic analyses showed that for MMSE ≤ 18 ($n = 60$; 44 AD, 16 non-AD), the overall model with three predictors was not statistically significant, Wald $\chi^2(3) = 3.6$, $p = 0.30$. In contrast, for the subgroup with MMSE >19 ($n = 57$; 35 AD, 22 non-AD), the overall model with three predictors and one covariate (interval to death) was statistically significant, Wald $\chi^2(4) = 14.7$, $p = 0.005$. 10-min delayed recall was

statistically significant ($p = 0.008$), as well as interval to death ($p = 0.02$) (clinical diagnosis $p = 0.14$). With the cutpoint at 4 for 10-min delayed recall, sensitivity = 80% and specificity = 77% for AD pathology. For the clinical diagnosis predictor, sensitivity = 80% and specificity = 50% for AD pathology.

Second, to assess whether the comparisons were strongly influenced by specific non-AD pathology subgroups, we systematically removed each of the non-AD subgroups (including normal brain) in turn; the results were essentially the same as reported above. We would have liked to compare AD pathology with each of the other pathology groups such as HS only ($n = 8$) or CVBI only ($n = 7$), but their n s were too small for reliable statistical analysis. Likewise, from the AD pathology group, we systematically removed AD + CVBI ($n = 14$), AD + HS ($n = 4$), and AD + DLB ($n = 1$) in turn, and then removed all three AD + subgroups at once. The conclusions for the predictor variables were identical to the model where the AD-only subgroup was combined with the AD + subgroups: 10-min delayed recall was the strongest predictor, followed by clinical diagnosis; 1-min delayed recall was not statistically significant.

Third, to check whether other items on the 3MS test were also useful in predicting AD pathology, the 15 individual item scores from the 3MS test, along with interval to death as a covariate, were regressed onto AD pathology using a forward selection model. 10-min delayed recall ($p = 0.002$) was the only statistically significant predictor to enter.

Fourth, to check to what extent the predictive power of the 3MS 10-min delayed recall was due to the delay interval or to the detailed testing and scoring for memory, performance on the 10-min delayed recall was rescored using the MMSE scoring method. For each word, one point was given unaided correct recall, and 0 point was given otherwise. When this 0–3 points rescored variable was substituted for the 0–9 points 10-min delayed recall variable originally used in the logistic regression, this 0–3 points variable was less predictive than the original 0–9 points variable for AD pathology ($p = 0.03$ versus $p = 0.007$), but it was still more predictive than clinical diagnosis or 1-min delayed recall.

Fifth, to check whether AD pathology is associated with more forgetting than non-AD pathology between 1- and 10-min delayed recall, a difference score between 10-min delayed recall and 1-min delayed recall was calculated for each patient. The group with AD recalled fewer words ($M = -0.7$, $SD = 1.8$) at 10-min delayed recall whereas the group with non-AD recalled more words ($M = +0.2$, $SD = 1.8$). The difference between the two mean difference scores was statistically significant, $t(115) = -2.57$, $p = 0.01$.

DISCUSSION

10-min delayed recall, but not 1-min delayed recall, was predictive of neuropathologically-verified AD. Our results also showed that the sensitivity and specificity of 10-min delayed recall from the baseline 3MS test (87%, 47%) was comparable to the contemporaneous consensus clinical diagnosis (82%, 45%) in predicting AD versus non-AD pathology. The consensus clinical diagnosis was based on history, informant report, physical and neurological examinations, laboratory, and neuroimaging, as well as the 3MS and other

neuropsychological test results. As part of this large amount of information, the score on 3MS 10-min delayed recall apparently did not strongly influence clinical diagnosis; the association between the score on 3MS 10-min delayed recall and clinical diagnosis of AD versus non-AD was weak (rank biserial correlation = 0.16; proportion of variance accounted for is only about 3%). It is possible that the recall results may have affected decisions to include or exclude patients in some diagnostic groups more than others, but this was not evaluated in this study.

Specificity was poor for both 3MS 10-min delayed recall and the clinical diagnosis in the total sample. This means that about half of those classified with non-AD pathology also performed poorly on the 10-min delayed recall, or were clinically diagnosed with AD. This poor specificity is comparable to what is reported in the literature for clinical-pathological correlation (e.g., [1, 28]), prior to the use of genetic risk factors, metabolic imaging, and cerebrospinal fluid biomarkers.

However, for a subset of higher functioning patients presenting with MMSE 19 (median), a score 4 on 10-min delayed recall was associated with improved specificity (from 47% to 77%) and lower sensitivity (from 87% to 80%) for AD pathology. This finding suggests that as severity of dementia progresses, differential patterns of amnesic versus nonamnesic cognitive impairment (i.e., response to cueing, rate of forgetting) disappear. In contrast, no appreciable improvement in specificity (from 45% to 50%) was noted in the higher functioning group for the consensus clinical diagnosis predictor. This suggests that the value of added information for clinical diagnosis (e.g., neuroimaging and laboratory testing) is independent of severity of dementia.

Removing either normal brain ($n = 4$) or any particular subtype of non-AD pathology from data analysis did not change the findings, and removing any particular or all AD groups with mixed non-AD pathology also did not change the findings. Furthermore, other items in the 3MS test were not useful in predicting AD pathology. The unique usefulness of the 10-min delayed recall in predicting AD pathology was due partly to detailed testing and scoring, and partly to the longer delay interval. For patients without AD pathology, recall of the three words improved from the first (1-min delayed) to the second (10-min delayed) recall, which may have represented a learning effect. In contrast, patients with AD pathology showed a decline between first and second recall, consistent with impaired learning or rapid forgetting as has been described previously in the literature [29, 30].

Our findings are consistent with neuropsychological studies showing that patients with AD perform more poorly on delayed recall than patients without AD diagnosed by neuropathologic finding [2, 4, 5, 7, 10]. They are also consistent with the power of delayed recall as well as cued recall tests to distinguish cerebrospinal fluid profiles consistent with AD [31]. Neuropsychological tests of learning and memory typically employ lists of 10 to 15 words presented over several learning trials, as part of a larger test battery requiring more than an hour to administer. The advantage of the 3MS test is that it can be administered in only about 10 minutes and is better tolerated by patients with cognitive impairment.

Recently published revised consensus criteria recognize the prominence of memory impairment for the clinical diagnosis of AD [32]. However, the criteria do not capitalize on the amnesic features of the memory impairment (i.e., poor response to cueing, flat learning curve, as well as rapid forgetting) associated with AD.

Limitations of our study include the following: First, this is a convenience sample of autopsied cases, and the findings may not be generalizable to all patients presenting to a memory clinic. The sensitivity and specificity we observed may depend on the particular mix of pathology cases and memory impairment in our sample. Second, our group with non-AD pathology comprised a heterogeneous group of neurodegenerative pathology as well as normal appearing brain. The number of cases for each classification of non-AD subtype was small and it is possible that a much larger sample size for a specific non-AD classification would change the results.

Strengths of the present study include autopsy confirmation of a good-sized sample of patients with AD versus patients without AD. The objectively tested and scored 10-min delayed recall from the brief 3MS test is a cost-effective screening tool for AD, especially for mildly impaired patients, in primary care settings.

Acknowledgments

Supported by National Institutes of Health (P01 AG12435, P50 AG05142) and the State of California Department of Health Services (DHS 94-20356).

References

1. Chui, H.; Lee, A. Clinical criteria for dementia subtypes. In: Qizilbash, N.; Schneider, L.S.; Chui, H.; Tariot, P.; Brodaty, H.; Kaye, J.; Erkinjuntti, T., editors. Evidence-Based Dementia Practice. Oxford, England: Blackwell Science; 2003. p. 106-119.
2. Grossman M, Libon DJ, Forman MS, Massimo L, Wood E, Moore P, Anderson C, Farmer J, Chatterjee A, Clark CM, Coslett HB, Hurtig HI, Lee VM-Y, Trojanowski JQ. Distinct antemortem profiles in patients with pathologically defined frontotemporal dementia. Arch Neurol. 2007; 64:1601-1609. [PubMed: 17998442]
3. Hamilton JM, Salmon DP, Galasko D, Delis DC, Hansen LA, Masliah E, Thomas RG, Thal LJ. A comparison of episodic memory deficits in neuropathologically-confirmed dementia with Lewy bodies and Alzheimer's disease. J Int Neuropsych Soc. 2004; 10:689-697.
4. Heyman A, Fillenbaum GG, Gearing M, Mirra SS, Welsh-Bohmer KA, Peterson B, Pieper C. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to establish a registry for Alzheimer's disease, Part XIX. Neurology. 1999; 52:1839-1844. [PubMed: 10371532]
5. Kraybill ML, Larson EB, Tsuang DW, Teri L, McCormick WC, Bowen JD, Kukull WA, Leverenz JB, Cherrier MM. Cognitive differences in dementia patients with autopsy-verified AD Lewy body pathology, or both. Neurology. 2005; 64:2069-2073. [PubMed: 15985574]
6. Liscic RM, Storandt M, Cairns NJ, Morris JC. Clinical and psychometric distinction of frontotemporal and Alzheimer dementias. Arch Neurol. 2007; 64:535-540. [PubMed: 17420315]
7. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, Jagust WJ, Chui HC. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. Brain. 2007; 130:731-739. [PubMed: 17267522]
8. Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, Boone K, Ellis W, Miller C, Miller BL. Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. Neurology. 2002; 58:1608-1615. [PubMed: 12058087]

9. Salmon DP, Galasko D, Hansen LA, Masliah E, Butters N, Thal LJ, Katzman R. Neuropsychological deficits associated with diffuse Lewy body disease. *Brain Cogn.* 1996; 31:148–165. [PubMed: 8811990]
10. Wang LY, Leverenz JB, Larson EB, Vavrek DA, Kukull WA, McCormick W, Bowen JD, Teri L, Montine T, Tsuang DW. Cognitive impairment in older adults without dementia: Clinical and pathologic outcomes in a community-based sample. *J Geriatr Psychiatry Neurol.* 2009; 22:256–265. [PubMed: 19433862]
11. Folstein MF, Folstein SE, McHugh PR. '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]
12. Mattis, S. DRS Dementia Rating Scale Professional Manual. Odessa, Florida: Psychological Assessment Resources, Inc.; 1988.
13. Connor DJ, Salmon DP, Sandy TJ, Galasko D, Hansen LA, Thal LJ. Cognitive profiles of autopsy-confirmed Lewy body variant vs pure Alzheimer disease. *Arch Neurol.* 1998; 55:994–1000. [PubMed: 9678318]
14. Rascovsky K, Salmon DP, Hansen LA, Galasko D. Distinct cognitive profiles and rates of decline on the Mattis dementia rating scale in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *J Int Neuropsych Soc.* 2008; 14:373–383.
15. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, Kurland LT. Mayo's older Americans normative studies: Updated AVLT norms for ages 56 to 97. *Clin Neuropsychol.* 1992; 6(Suppl. 001):83–104.
16. Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. San Antonio, Texas: Pearson; 1987.
17. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiat.* 1987; 48:314–318.
18. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry.* 2007; 78:790–799. [PubMed: 17178826]
19. Khachaturian AS, Gallo JJ, Breitner JCS. Performance characteristics of a two-stage dementia screen in a population sample. *J Clin Epidemiol.* 2000; 53:531–540. [PubMed: 10812327]
20. Canadian Study of Health and Aging Working Group. Canadian study of health and aging: Study methods and prevalence of dementia. *Can Med Assoc J.* 1994; 150:899–913. [PubMed: 8131123]
21. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA.* 2002; 288:1475–1483. [PubMed: 12243634]
22. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* 1984; 34:939–944. [PubMed: 6610841]
23. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L. The consortium to establish a registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology.* 1991; 41:479–486. [PubMed: 2011243]
24. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging.* 1995; 16:271–278. [PubMed: 7566337]
25. The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. *Neurobiol Aging.* 1997; 18 Suppl. 1(4):S1–S2. [PubMed: 9330978]
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics.* 1988; 44:837–845. [PubMed: 3203132]
27. Kutner, MH.; Nachtsheim, CJ.; Neter, J. Applied Linear Regression Models. 4th edition. Boston: McGraw-Hill/Irwin; 2004.

28. Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, Hyman BT, Crain B, Tang MX, Phelps CH. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's disease centers consortium on apolipoprotein E and Alzheimer's disease. *N Engl J Med*. 1998; 338:506–511. [PubMed: 9468467]
29. Hart RP, Kwentus JA, Harkins SW, Taylor JR. Rate of forgetting in mild Alzheimer's-type dementia. *Brain Cogn*. 1988; 7:31–38. [PubMed: 3345267]
30. Kramer JH, Mungas D, Reed BR, Schuff N, Weiner MW, Miller BL, Chui HC. Forgetting in dementia with and without subcortical lacunes. *Clin Neuropsychol*. 2004; 18:32–40. [PubMed: 15595356]
31. Wagner M, Wolf S, Reischies FM, Daerr M, Wolfsgruber S, Jessen F, Popp J, Maier W, Hull M, Frolich L, Hampel H, Perneczky R, Peters O, Jahn H, Luckhaus C, Gertz HJ, Schroder J, Pantel J, Lewczuk P, Kornhuber J, Wiltfang J. Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology*. 2012; 78:379–386. [PubMed: 22238414]
32. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia 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; 7:263–269. [PubMed: 21514250]

Fig. 1. Receiver operating characteristic (ROC) curves for 3MS 10-min delayed recall, 3MS 1-min delayed recall, and clinical diagnosis, in distinguishing AD from non-AD pathology. $N = 117$.

Table 1Demographic and clinical characteristics of the patients ($N = 117$, 56 men and 61 women)

Variables	<i>M (SD)</i>	Range
Age at death, years	80.8 (9.9)	39–98
Education, years ^a	12.6 (4.1)	0–23
Illness duration, years ^a	9.8 (4.6)	2–30
Interval from baseline 3MS test to death, years	4.5 (2.9)	0.2–14
Baseline 3MS score	56.0 (22.8)	1–94
1-min delayed recall	3.2 (2.8)	0–9
10-min delayed recall	2.8 (2.7)	0–9
Estimated MMSE score	17.6 (7.1)	0–29

3MS, Modified Mini-Mental State; MMSE, Mini-Mental State Examination.

^a
 $n = 116$.

Table 2

Association between clinical diagnosis and pathological classification

Clinical diagnosis	Pathological classification
8 nonamnesic CIND→	3 AD (38%) 4 non-AD (50%) 1 normal brain (12%)
7 amnesic CIND→	4 AD (57%) 1 non-AD (14%) 2 normal brain (29%)
23 non-AD dementia→	11 AD ^a (48%) 12 non-AD (52%)
79 AD dementia→	61 AD (77%) 17 non-AD ^b (22%) 1 normal brain (1%)

CIND, cognitively impaired but not demented.

^a 8 had a classification of definite AD and 3 had a classification of AD + cerebrovascular brain injury.^b 6 were classified with hippocampal sclerosis.

Table 3Correspondence between clinical diagnosis and pathological classification of AD versus non-AD ($N = 117$)

Clinical diagnosis ^a	Pathological classification ^b	
	AD	Non-AD
	No. of patients	
AD	65	21
Non-AD	14	17
Total	79	38

Sensitivity (65/79) = 82%; Specificity (17/38) = 45%.

^a AD includes AD dementia and amnestic CIND; Non-AD includes non-AD dementia and nonamnestic CIND.^b Non-AD includes non-AD pathology and normal brain.

Table 4

Comparisons between neuropathologically-verified AD and non-AD patients

Variables	AD <i>n</i> = 79 48% men <i>M</i> (<i>SD</i>)	Non-AD <i>n</i> = 38 47% men <i>M</i> (<i>SD</i>)	<i>t</i>	<i>p</i>
Age at death, years	80.5 (9.4)	81.3 (11.0)	−0.39	0.69
Education, years	12.4 (4.5)	12.9 (3.2) ^a	−0.58	0.57
Illness duration, years	10.2 (4.0)	9.0 (5.6) ^a	1.10	0.28
Interval from baseline 3MS test to death, years	5.0 (2.8)	3.5 (2.9)	2.70	0.009
Baseline 3MS score	54.3 (22.2)	59.6 (23.9)	−1.15	0.25
1-min delayed recall	2.9 (2.7)	3.7 (3.1)	−1.36	0.18
10-min delayed recall	2.2 (2.3)	3.9 (3.2)	−2.99	0.004
Estimated MMSE score	17.2 (7.0)	18.3 (7.2)	−0.78	0.44

3MS, Modified Mini-Mental State; MMSE, Mini-Mental State Examination.

^a
n = 37.

Table 5

Cutpoints for 10-min delayed recall and sensitivity, specificity, positive (LR+) and negative likelihood ratios (LR-), and area under the curve (AUC) (N = 117; 79 AD pathology, 38 non-AD pathology)

10-min delayed recall	Sensitivity %	Specificity %	LR+	LR-	AUC
0	29	74	1.11	0.96	0.514
1	44	68	1.40	0.81	0.564
2	66	66	1.92	0.52	0.658
3	81	53	1.71	0.36	0.668
4	87	47	1.66	0.27	0.674
5	89	32	1.30	0.36	0.601
6	92	26	1.25	0.29	0.594
7	95	16	1.13	0.32	0.554
8	96	11	1.08	0.36	0.534
9	100	0	1	-	-

-, not computable.