# Value of Neuropsychological Tests, Neuroimaging, and Biomarkers for Diagnosing Alzheimer's Disease in Younger and Older Age Cohorts

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**OBJECTIVES:** To examine the influence of age on the value of four techniques for diagnosing Alzheimer's disease (AD).

**DESIGN:** Observational cohort study.

**SETTING:** Alzheimer's Disease Neuroimaging Initiative.

**PARTICIPANTS:** Individuals with mild cognitive impairment (MCI; n = 179), individuals with AD (n = 91), and normal controls (n = 105).

**MEASUREMENTS:** Neuropsychological tests, structural magnetic resonance imaging (MRI), amyloid-beta and tau in cerebrospinal fluid (CSF), and [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) for the diagnosis of MCI or AD. MCI was defined according to subjective memory complaints corroborated by an informant and an abnormal score on the delayed paragraph recall subtest of the Wechsler Memory Scale–Revised, a Mini-Mental State Examination score greater than 23, and a Clinical Dementia Rating score of 0.5. Participants with AD satisfied National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria of probable AD.

**RESULTS:** Neuropsychological tests and MRI were the most informative techniques, with 84% and 82% correct classifications, respectively, and areas under the receiver operating characteristic curve (AUCs) of 0.93 (90% confidence interval (CI) = 0.91–0.95) and 0.88 (90% CI = 0.85–0.91). FDG-PET and CSF assessments had 76% and 73% correct classifications, respectively, (AUC = 0.77, 90% CI = 0.71–0.83; AUC = 0.77, 90% CI = 0.73–0.82). These figures increased slightly when the techniques were combined. All analyses were repeated for the younger (<75) and older (≥75) halves of the sample. FDG-PET and CSF assessment were substantially less informative in the older cohort, and they did not add diagnostic information when all techniques were combined.

**CONCLUSIONS:** Structural MRI and neuropsychological assessment are diagnostic methods of first choice if AD is suspected. CSF and FDG-PET add little to these diagnostic techniques, especially in older adults. **J Am Geriatr Soc 59:1705–1710, 2011.**

**Key words: Alzheimer's disease; mild cognitive impairment; neuropsychological assessment; MRI; cerebrospinal fluid; FDG-PET**

Most clinical studies of Alzheimer's disease (AD) are conducted in people approximately 75 years old,[1] but only 7% of all people with AD are younger than 75.[2] This indicates a remarkable age bias in AD research.

With older age, the pathological characteristics of AD become less specific. At autopsy, plaques and tangles are found in many older people without dementia.[3] Accordingly, lower amyloid-beta and higher tau levels are found in the cerebrospinal fluid (CSF) of older than of younger control subjects.[4] Also, the association between apolipoprotein (ApoE) E4 and AD is weaker in people aged 70 and older than in younger individuals.[5] Finally, in very old adults with dementia, a mixed etiology of vascular dementia and AD seems to be more prevalent.[6–8] Consequently, it is important to examine the influence of age on diagnostic test characteristics in AD.

The diagnostic characteristics of neuropsychological, neurochemical, and neuroradiological techniques in young-old adults were compared with those of older-old adults using the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI).[9,10] It was expected that better diagnostic values would be found in younger than in older

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participants for all techniques. Furthermore, whether the effect of age differs between techniques was explored.

## METHODS

The National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations launched the ADNI in 2003 to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. ADNI has recruited participants from more than 50 sites across the United States and Canada. The goal of ADNI was to recruit 800 adults aged 55 to 90 to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years.[9,10] The ADNI sample is a clinic-based convenience sample.

### Participants

All participants from the ADNI database who had a lumbar puncture to obtain CSF were included. This was almost half of the sample (375 participants: 105 normal controls, 179 with MCI, and 91 with AD). All participants had undergone magnetic resonance image (MRI) scanning and neuropsychological testing, and 186 had a [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) scan (49 controls, 89 with MCI, and 48 with AD).

Individuals were included if they were in good physical and mental health. Normal participants had intact memory (assessed using delayed paragraph recall of the Wechsler Memory Scale–Revised; WMS-R), a Mini-Mental State Examination (MMSE)[11] score greater than 23, and a Clinical Dementia Rating (CDR) of 0. Participants with MCI had subjective memory complaints corroborated by an informant and by an abnormal score on the delayed paragraph recall subtest of the WMS-R, a MMSE score greater than 23, and a CDR of 0.5, not satisfying consensus criteria for dementia. Participants with AD had abnormal memory scores on delayed paragraph recall, MMSE scores between 20 and 26, a CDR of 0.5 or 1, and satisfied National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria of probable AD. Participants who used drugs with anticholinergic or opioid properties were excluded, but use of estrogens, cholinesterase inhibitors, and vitamin E was allowed if the dose remained stable. For details on inclusion and exclusion criteria, see[10,12].

### Neuropsychological Evaluation

To avoid circular reasoning, only neuropsychological tests that were not used for defining the groups (WMS-R paragraph recall, MMSE) were analyzed, which left the following tests: Rey Auditory Verbal Learning Test (RAVLT; total number of words reproduced in five learning trials; number of words reproduced after a delay of $\sim$ 30 minutes), category fluency (number of animals and vegetables named in 1 minute each), Boston Naming Test, Trail Making Test Parts A and B, Digit Symbol Substitution Test (DSST), Digit Span forward and backward from the Wechsler Adult Intelligence Scale, the Clock Drawing task (free drawing and copying), and the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-cog; total score and immediate and delayed word recall). For test references, see[10,12].

### Cerebrospinal Fluid

CSF biomarker variables included amyloid-beta$_{1\text{-}42}$; total tau; and tau phosphorylated at threonine 181, in pg/mL (p-tau$_{181p}$), as well as ratios (t-tau:A-beta$_{1\text{-}42}$, p-tau$_{181p}$:A-beta$_{1\text{-}42}$). Analysis was done using the xMAP platform (Luminex Corp, Austin, TX) and INNO-BIA AlzBio3 reagents as previously described[13,14] and specified.[10]

### MRI

Structural MRI scans (1.5-T) were acquired at multiple ADNI sites using a standardized MRI protocol.[15] Total brain volume; ventricular volume; and volumes of the left and right hippocampi, fusiform gyri, middle and inferior temporal lobes, entorhinal cortices, and inferior lateral ventricles were obtained using voxel-based morphometry.[16,17] Because an earlier study did not find significant differences between left and right structures in the ADNI data,[18] the mean of left and right volumes of each structure were used.

### FDG-PET

Using FDG-PET acquired, controlled, and analyzed according to the ADNI protocol, region of interest (ROI) approaches (University of California at Berkeley) resulted in a set of five regions located in the right and left angular gyri, bilateral posterior cingulate gyrus, and left middle and inferior temporal gyrus. Because these ROIs were highly correlated,[19] they were averaged across participants. This composite ROI was used in the present analyses.

### Statistical Analyses

All variables were corrected for age, sex, and education based on the regression weights in the normal control group. Age and education were centered at the median. The number of variables was reduced by examining which variables of each technique best differentiated between normal controls and participants with AD using separate logistic regressions for each of the techniques in the control and AD groups. The variables of each technique were entered in a stepwise forward manner. This analysis was then repeated combining all variables that were significant in the separate logistic regressions. These analyses were then repeated with the significant variables only, this time comparing the normal controls with the cognitively abnormal participants (the combined MCI and AD participant groups).

To examine the effect of age, the sample was stratified according to median age, and the analyses were repeated in both halves. Receiver operating characteristics (ROCs) of predicted probabilities of each logistic regression were analysed to calculate the area under the ROC curve (AUC) to enable comparison of the four techniques and their combinations.

$P \leq .05$ was considered significant. All analyses were conducted using SPSS 18.0 (SPSS, Inc., Chicago, IL).

## RESULTS

The characteristics of this subsample (Table 1) were comparable with those of the entire ADNI sample.[12] Almost all participants with AD (95%) had a CDR score of 1.

Table 2 shows all variables used in the present analyses, including effect sizes of the group differences.

### Selection of Variables

Logistic regression analysis of the neuropsychological tests comparing normal controls with participants with AD selected ADAS-cog delayed word recall, DSST, category fluency (vegetables), and ADAS-cog total score (in this stepwise order). The a priori classification success without any additional testing is 55% in this sample (105 of 196 participants classified correctly as normal). This increased to an a posteriori success of 99% correct after neuropsychological examination, with a proportion of 98% explained variance (Nagelkerke R-square). The AUC was 0.998 (90% confidence interval (CI) = 0.995–1.000).

The logistic regression analysis of CSF variables selected the total tau:amyloid-beta ratio and subsequently amyloid-beta, with an increase in classification success to 78% correct, 47% explained variance, and AUC of 0.86 (90% CI = 0.81–0.90).

The corresponding analysis of MRI variables selected entorhinal cortices, hippocampi, inferior temporal lobes, and whole brain volume. Classification success increased to 88% correct, with 73% explained variance and AUC of 0.94 (90% CI = 0.92–0.97).

The composite ROI of temporal areas, angular gyri, and cingulate that was used for FDG-PET yielded a classification success of 81%, with 57% explained variance and AUC of 0.89 (90% CI = 0.83–0.94).

The analysis combining neuropsychological tests, MRI, and CSF assessment selected ADAS-cog delayed word recall, DSST, fluency (vegetables), inferotemporal volume, ADAS-cog total score, and entorhinal volume. Amyloid-beta and tau/ amyloid-beta ratio were not included in the model. The classification success was 100% correct. The AUC was 1. When FDG-PET was added to this analysis, ADAS-cog delayed word recall, ADAS-cog total score, hippocampal volume, and fluency (vegetables) were selected; FDG-PET ($P = .83$) was not entered into the model. The classification success remained 100% correct; AUC was 0.992 (90% CI 0.989–1.000).

### Effects of Age

The sample was stratified at the median into younger than 75 (younger) and aged 75 and older (older). The MCI group was added to the AD participant group to form a cognitively abnormal group (n = 270) that was contrasted with the normal control group. With this group division, the a priori classification success of any analysis is 72% (270 abnormal participants in a group of 375 participants).

The same logistic regression and ROC analyses were repeated for each of the four techniques and for the techniques combined. All significant variables were entered into the models (Table 3).

For MRI and neuropsychological assessment, diagnostic characteristics did not differ between the younger and older cohorts. For the CSF and FDG-PET assessments, there was a distinct effect of age. The AUCs for the tau/amyloid-beta ratio and for the composite ROI of FDG-PET were significantly higher in younger than in older participants. Percentage of explained variance of these techniques was also considerably larger in the younger than in the older group.

Overall, the neuropsychological evaluation had the largest AUCs and the highest percentages of explained variance and correct classifications. Its AUCs were significantly higher than those of the CSF and FDG-PET assessments, except for FDG-PET in the younger subgroup. The diagnostic indices were slightly better for combinations of neuropsychological, CSF, and MRI than the neuropsychological assessment alone. Addition of FDG-PET did not improve the model in the older subgroup.

In the older cohort, the best diagnostic results were obtained with only two predictors: hippocampal volume and memory performance. CSF assessment and FDG-PET did not add to the distinction between cognitively normal and MCI/AD in this old group.

**Table 1. Demographic and Clinical Characteristics of Participants**

| Characteristic | Normal (n = 105) | Mild Cognitive Impairment (n = 179) | Alzheimer's Disease (n = 91) | *P*-Value |
|---|---|---|---|---|
| Female, % | 48.6 | 34.6 | 42.9 | .06* |
| Age, mean ± SD | 75.5 ± 5.3 | 74.2 ± 7.5 | 74.7 ± 7.8 | .32† |
| Education, years, mean ± SD | 15.8 ± 2.9 | 15.8 ± 2.9 | 15.3 ± 3.3 | .29† |
| Mini-Mental State Examination score, mean ± SD (range 0–30)[11] | 29.1 ± 1.0 | 26.9 ± 1.8 | 23.5 ± 2.0 | <.001‡ |
| Geriatric Depression Scale score, mean ± SD (range 0–15)[20] | 0.9 ± 1.1 | 1.7 ± 1.4 | 1.7 ± 1.4 | <.001‡ |
| Modified Hachinski score, mean ± SD (range 0–18)[21] | 0.6 ± 0.7 | 0.6 ± 0.8 | 0.6 ± 0.7 | .84‡ |

* Chi-square.
† Analysis of variance.
‡ Kruskal-Wallis test.
SD = standard deviation.

**Table 2. Neuropsychological, Cerebrospinal Fluid (CSF), Magnetic Resonance Imaging (MRI), and [18F]Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Measures in Normal Controls and Participants with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)**

| | | Mean ± Standard Deviation | | |
|---|---|---|---|---|
| **Measure** | **Partial $\eta^2$** | **Control (n = 105)** | **MCI (n = 179)** | **AD (n = 91)** |
| Neuropsychological tests* | | | | |
| Rey Auditory Verbal Learning Test | | | | |
| Total 5 trials (maximum 75) | .43 | 43.0 ± 8.5 | 30.3 ± 8.6 | 23.7 ± 7.5 |
| Delayed recall (maximum 15) | .39 | 7.2 ± 3.4 | 2.6 ± 3.0 | 1.0 ± 2.0 |
| Fluency, number | | | | |
| Animals | .17 | 19.6 ± 5.8 | 16.1 ± 4.9 | 13.0 ± 5.1 |
| Vegetables | .30 | 14.4 ± 3.8 | 10.9 ± 3.4 | 8.2 ± 3.3 |
| Boston Naming Test total correct (maximum 30) | .12 | 27.6 ± 2.5 | 25.7 ± 4.0 | 23.6 ± 5.5 |
| Trail Making Test, seconds | | | | |
| Part A | .17 | 36.7 ± 13.8 | 45.4 ± 23.1 | 70.4 ± 39.5 |
| Part B | .24 | 89.8 ± 42.4 | 133.7 ± 74.6 | 198.5 ± 87.3 |
| Digit Symbol Substitution Test (maximum 93) | .27 | 46.0 ± 8.6 | 37.3 ± 11.4 | 26.7 ± 12.5 |
| Digit Span, number of items | | | | |
| Forward | .01 | 8.6 ± 2.1 | 8.3 ± 2.0 | 7.8 ± 1.9 |
| Backward | .10 | 7.0 ± 2.3 | 6.2 ± 2.0 | 4.9 ± 1.9 |
| Clock Drawing test (maximum 5) | .12 | 4.6 ± 0.7 | 4.1 ± 1.0 | 3.5 ± 1.2 |
| Alzheimer's Disease Assessment Scale—Cognitive Subscale, error scores | | | | |
| Word recall | .46 | 2.9 ± 1.2 | 4.6 ± 1.4 | 6.1 ± 1.4 |
| Delayed recall | .52 | 3.0 ± 1.7 | 6.3 ± 2.3 | 8.5 ± 1.6 |
| Total score | .44 | 6.4 ± 2.9 | 11.7 ± 4.6 | 18.0 ± 6.1 |
| Cerebrospinal fluid† | | | | |
| Tau, pg/mL | .13 | 70.7 ± 30.5 | 104.2 ± 62.1 | 122.5 ± 57.1 |
| Amyloid-beta 142, pg/mL | .16 | 203.1 ± 54.5 | 163.4 ± 54.2 | 142.4 ± 40.4 |
| Phosphorylated tau 181P | .11 | 25.2 ± 14.9 | 35.7 ± 18.4 | 42.4 ± 20.3 |
| Tau/amyloid-beta ratio | .14 | 0.39 ± 0.26 | 0.76 ± 0.63 | 0.93 ± 0.48 |
| Phosphorylated tau/amyloid beta ratio | .13 | 0.15 ± 0.13 | 0.26 ± 0.18 | 0.33 ± 0.19 |
| MRI volumes† | | | | |
| Whole brain volume, $mm^3$ | .04 | 996,083 ± 98,674 | 995,560 ± 107,745 | 954,043 ± 105,429 |
| Ventricular volume, $mm^3$ | .06 | 36,916 ± 18,641 | 45,726 ± 22,050 | 50,181 ± 22,788 |
| Hippocampus, $mm^3$ | .28 | 3,634.6 ± 407.3 | 3,188.5 ± 520.9 | 2,933.1 ± 520.7 |
| Inferior lateral ventricle, $mm^3$ | .17 | 1,164.5 ± 444.9 | 1,576.5 ± 756.9 | 2,050.8 ± 1,076.7 |
| Medial temporal lobe | .22 | 2.58 ± 0.16 | 2.45 ± 0.19 | 2.30 ± 0.22 |
| Inferior temporal lobe | .23 | 2.61 ± 0.16 | 2.48 ± 0.20 | 2.32 ± 0.22 |
| Fusiform gyrus | .18 | 2.37 ± 0.15 | 2.26 ± 0.17 | 2.14 ± 0.23 |
| Entorhinal cortex | .28 | 3.26 ± 0.32 | 2.93 ± 0.44 | 2.58 ± 0.45 |
| FDG-PET mean of regions of interest†,‡ | .26 | 1.29 ± 0.13 | 1.19 ± 0.13 | 1.09 ± 0.10 |

* All group differences significant at $P < .001$, except Digit Span forward ($P = .08$; analysis of covariance (ANCOVA) corrected for age, education, and sex); post hoc analyses (least significant difference (LSD)): all groups different at $P < .05$.

† All group differences significant at $P < .001$ (ANCOVA corrected for age and sex); post hoc analyses (LSD), all groups different at $P < .05$.

‡ Arbitrary units based on *z*-scores.

## DISCUSSION

Contrary to expectation, these results show that structural neuroimaging and neuropsychological assessment do not lose diagnostic value with older age. With older age, MRI volumetry of temporal lobe structures and assessment of memory and attention retain diagnostic value for prevalent MCI or AD. FDG-PET neuroimaging and CSF biomarkers, on the contrary, appear to lose diagnostic value when applied in an older age cohort. The result with respect to CSF replicates earlier findings.[4] In the group aged 75 and older, the tau/amyloid-beta ratio still conveyed some information on prevalent MCI or AD. A greater prevalence of multiple brain pathologies explain this better than plaques and tangles alone with increasing age.[3,7,22] If this explanation is correct, it implies that, in older participants, conversion to dementia may be due to disease processes other than formation of plaques and tangles (e.g., vascular damage) while clinically mimicking AD.

To simulate clinical practice, the data were used "as is" without searching for particular patterns that might be

**Table 3. Results of Logistic Regression and Receiver Operating Characteristic (ROC) Curve Analyses Comparing Diagnostic Techniques in Younger and Older Age Cohorts with Respect to the Distinction Between Cognitively Normal and Abnormal (Mild Cognitive Impairment or Alzheimer's Disease)**

| | Young (<75) | Older (≥75) | All Subjects |
|---|---|---|---|
| Neuropsychology | | | |
| Explained variance, % | 63 | 69 | 65 |
| Correct, % | 84 | 85 | 84 |
| AUC (90% CI) | 0.92 (0.89–0.95) | 0.94 (0.92–0.97) | 0.93 (0.91–0.95) |
| Significant predictors | ADAS delayed recall, DSST fluency | ADAS total and delayed recall, DSST | ADAS total and delayed recall, DSST fluency |
| CSF | | | |
| Explained variance, % | 39 | 17 | 26 |
| Correct, % | 77 | 70 | 73 |
| AUC (90% CI) | 0.83 (0.78–0.88) | 0.71 (0.65–0.78) | 0.77 (0.73–0.82) |
| Significant predictors | tau/amlyoid-beta ratio | tau/amlyoid-beta ratio | tau/amlyoid-beta ratio |
| MRI | | | |
| Explained variance, % | 47 | 47 | 47 |
| Correct, % | 84 | 83 | 82 |
| AUC (90% CI) | 0.88 (0.84–0.92) | 0.88 (0.84–0.92) | 0.88 (0.85–0.91) |
| Significant predictors | Hippocampi WBV inferior-temporal | Hippocampi inferior-temporal | Hippocampi WBV inferior-temporal |
| [18F]fluorodeoxyglucose PET | | | |
| Explained variance, % | 41 | 10 | 23 |
| Correct, % | 79 | 75 | 76 |
| AUC (90% CI) | 0.86 (0.80–0.92) | 0.69 (0.59–0.79) | 0.77 (0.71–0.83) |
| Combined, no PET | | | |
| Explained variance, % | 65 | 67 | 66 |
| Correct, % | 84 | 86 | 85 |
| AUC (90% CI) | 0.93 (0.90–0.96) | 0.95 (0.92–0.97) | 0.94 (0.92–0.95) |
| Significant predictors | ADAS delayed recall | ADAS total and delayed recall | ADAS total and delayed recall, DSST fluency |
| Combined, with PET | | | |
| Explained variance, % | 74 | 72 | 63 |
| Correct, % | 92 | 88 | 85 |
| AUC (90% CI) | 0.96 (0.93–0.99) | 0.95 (0.92–0.98) | 0.93 (0.90–0.96) |
| Significant predictors | Fluency PET | ADAS delayed recall hippocampi | ADAS delayed recall fluency |

Explained variance = Nagelkerke R-square; % correct = % correct classifications (a priori success rate = 72%); AUC = area under the ROC curve; CI = confidence interval; ADAS = Alzheimer's Disease Assessment Scale cognitive subscale, DSST = Digit Symbol Substitution Test; WBV = whole brain volume; PET = positron emission tomography; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

more diagnostically informative than raw data. The only exception was the tau/amyloid-beta ratio, which is frequently applied in clinical settings also. The ADNI database provides voxel-based morphometry, which is more precise than visual inspection of relevant brain structures, but more-advanced techniques such as high-dimensional pattern classification of MRI[23] and mathematical identification of biomarker signatures[24] were not used. Neither was PET Pittsburgh Compound B scanning included, because it was performed in a small number of participants, which precluded proper analysis of age effects.

A limitation of the present analysis is that the ADNI project focuses on AD at the exclusion of non-AD disorders. Moreover, the participants were mostly uncomplicated AD cases in an early stage of the disease. Thus, the present analyses contain an artificial discrimination. Second, because it was desired to analyze a series of tests on the same participants, data on only half of the ADNI sample could be used, because a limited number of participants consented to lumbar puncture. The FDG-PET results are based on an even smaller sample, resulting in less statistical power.

A final potential caveat concerns the possible circularity in the logic of this comparison of diagnostic techniques. A clinical diagnosis of MCI or AD is based on behavioral characteristics, cognitive symptoms in particular. This may benefit neuropsychological assessment in comparisons like these. Although cognitive tests that were used for the diagnostic classification were excluded, the remaining tests correlate strongly with these tests.

The differential effect of age on the diagnostic value of atrophy visible on MRI and of CSF measures is consistent with a recent neuropathological study that documented a weaker association between pathological changes related to AD and older age, whereas in contrast, cerebral atrophy maintained a relationship with dementia also in participants aged 75 and older.[3] Perhaps this more-pronounced neocortical signature of AD at younger ages also explains why FDG-PET has considerable discriminative value in younger but not older adults.

## CONCLUSION

Structural MRI and neuropsychological assessment are the prime methods of diagnostic examination if AD is suspected, and CSF and FDG-PET add little to these diagnostic techniques, especially in older adults with MCI or dementia, who constitute the vast majority.

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