# Amnestic syndrome of the medial temporal type identifies prodromal AD

## A longitudinal study

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### ABSTRACT

**Objective:** To compare the power of tests assessing different cognitive domains for the identification of prodromal Alzheimer disease (AD) among patients with mild cognitive impairment (MCI).

**Background:** Given the early involvement of the medial temporal lobe, a precocious and specific pattern of memory disorders might be expected for the identification of prodromal AD.

**Methods:** A total of 251 patients with MCI were tested at baseline by a standardized neuropsychological battery, which included the Free and Cued Selective Recall Reminding Test (FCSRT) for verbal episodic memory; the Benton Visual Retention Test for visual memory; the Deno 100 and verbal fluency for language; a serial digit learning test and the double task of Baddeley for working memory; Wechsler Adult Intelligence Scale (WAIS) similarities for conceptual elaboration; and the Stroop test, the Trail Making test, and the WAIS digit symbol test for executive functions. The patients were followed at 6-month intervals for up to 3 years in order to identify those who converted to AD vs those who remained stable over time. Statistical analyses were based on receiver operating characteristic curve and Cox proportional hazards models.

**Results:** A total of 59 subjects converted to AD dementia. The most sensitive and specific test for diagnosis of prodromal AD was the FCSRT. Significant cutoff for the diagnosis was 17/48 for free recall, 40/48 for total recall, and below 71% for index of sensitivity of cueing (% of efficacy of semantic cues for retrieval).

**Conclusions:** The amnestic syndrome of the medial temporal type, defined by the Free and Cued Selective Recall Reminding Test, is able to distinguish patients at an early stage of Alzheimer disease from mild cognitive impairment non-converters. *Neurology*® 2007;69:1859–1867

### GLOSSARY

**AD** = Alzheimer disease; **AUC** = area under the curve; **CDR** = Clinical Dementia Rating; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised; **FCSRT** = Free and Cued Selective Recall Reminding Test; **IADL** = Instrumental Activities of Daily Living; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **ROC** = receiver operating characteristic; **WAIS** = Wechsler Adult Intelligence Scale.

In light of current drug development aimed at slowing Alzheimer disease (AD) progression, diagnosing AD at its prodromal stage is particularly important. Today, prodromal AD is integrated into the broad concept of mild cognitive impairment (MCI), a syndrome associated with many causes.[1,2] Recently, research has begun to focus on developing new tools, such as neuroimaging and CSF biomarkers, that could increase the specificity of the prodromal AD diagnosis.[3-6]

Screening tools used in memory clinics that serve the MCI population must fulfill several requirements: they should detect the specific features of the disease, have a high sensitivity and specificity for AD, and be reliable, reproducible, noninvasive, easy to

**Supplemental data at www.neurology.org**

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perform, and low cost. Moreover, with respect to therapy, screening tools must be able to predict short term disease progression so as to identify patients who will develop AD rapidly (i.e., patients who are in an active progression of the disease).

Accordingly, the use of cognitive and memory tests specific to AD may be effective. A specific memory profile has been reported in AD that is characterized by a diminished free recall ability that is only marginally improved by cueing.[7,8] Is this amnestic syndrome of the medial temporal type also present in incipient prodromal AD? What is the specific importance of impaired episodic memory in cognitive domains when identifying of prodromal AD? The Pre-Al study was designed to answer these questions and, accordingly, to provide cutoff scores for the diagnosis of prodromal AD.

## METHODS

**Subjects.** Between March 2001 and June 2002, subjects with memory complaints and MCI were recruited and followed up semiannually during 3 years. Subjects came from memory clinics of 14 centers expert in the field of AD and dementia across France (see Acknowledgment). All subjects were living independently in the community at the time of their baseline evaluation. Each subject signed an informed consent form after the nature of the procedures had been fully explained. The study was approved by the Ethics Committee of Salpêtrière Hospital and supported by the French Ministry of Health. Patients were enrolled on the basis of the following criteria: 1) a subjective memory complaint screened through questionnaire on self-perceived forgetfulness in daily activities or in recent events.[9] The memory complaint questionnaire included two sections: Section A provides information concerning spontaneous self awareness of general memory functions, Section B provides scores for specific aspects of memory in reference to a previous level of functioning; 2) an objective memory impairment documented by at least one word missing at the three-word recall of the Mini-Mental State Examination (MMSE),[10] or a score less than 29 on the Isaac-set test, or both[11]; 3) a preservation of general cognitive functioning documented by an MMSE score between 25/30 and 29/30; 4) a normal score or only one item impaired at the first level in the four Instrumental Activities of Daily Living (IADL) (ability to use the telephone, independence for transportation, self-administration of medication, ability to handle finances), which has been shown to be predictive of rapid conversion to dementia in the PAQUID study[12]; and 5) the absence of the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R) criteria for dementia.[13] Selection of the tests used to define MCI was based on the results obtained in the PAQUID study.[14,15] Brain scan or MRI performed within the last 6 months before inclusion was required to exclude patients with focal lesions, including brain tumor, subdural hematoma, stroke, and CNS infection. Patients with small subcortical lesions (less than 2 cm in diameter) that were clinically and historically silent and patients with diffuse symmetric periventricular lucencies were not excluded. Patients with depressive symptoms documented by a score of the Montgomery-Asberg Depression Rating Scale[16] $> 20$, and, more generally, patients with medical conditions which could interfere with memory performance or follow-up were excluded. Among the 279 patients screened, 251 fulfilled the inclusion criteria and were included.

**Procedures.** Patients were seen at 6-month intervals for 3 years and underwent the following standardized procedures.

**Clinical and functional assessment.** Baseline and follow-up 6-month evaluation, performed by trained clinicians, included family history of dementia, record of medical events (cardiovascular disease, hypertension, diabetes, dyslipidemia, and stroke), current treatment, and complete neurologic examination including blood pressure after a 10-minute rest. Activities of daily life were rated with the IADL scale during an interview with the patient and a knowledgeable collateral source (a spouse or a child).[17] Memory complaint was assessed by a specific questionnaire.[9] Depression was assessed by the MADRS and anxiety by the Goldberg Scale.[16,18] The Clinical Dementia Rating scale (CDR) was completed at each visit during follow-up.[19]

During the follow-up, when conversion to dementia was suspected and diagnosed in a given center, the diagnosis was further reviewed by an Expert Committee composed of neurologists (n = 3), neuropsychologists (n = 3), geriatricians (n = 3), and psychiatrists (n = 3). They determined whether clinical criteria for dementia were satisfied using DSM-III-R criteria.[13] Demented subjects were further classified using established criteria for AD,[20] vascular dementia, dementia with Lewy bodies, and frontotemporal dementia.

**Neuropsychological performance testing.** In addition to clinical and functional assessment every 6 months, all subjects were tested at inclusion and annually by a standardized neuropsychological battery. In cases of a suspected conversion at any of the evaluations, the patient underwent an additional neuropsychological evaluation 6 months later in order to confirm the conversion. Cognitive tests were selected to assess a broad range of cognitive abilities commonly affected by aging and AD. The battery took approximately 90 minutes and included the Free and Cued Selective Reminding Test (FCSRT) for verbal episodic memory,[21] the Benton Visual Retention Test for visual memory,[22] the DENO 100 and Verbal Fluency (letter S and category: fruit in 2 minutes) for language,[23] the Serial Digit Ordering Test and Double Task of Baddeley for working memory,[24,25] Wechsler Adult Intelligence Scale (WAIS) Similarities for conceptual elaboration,[26] the Stroop Test,[27] and the Trail Making test and WAIS Digit Symbol Test for executive functions.[26,28]

The FCSRT was selected because it is based on a semantic cueing that allowed us to control for an effective registration of the list of words and to facilitate the retrieval from stored information. The FCSRT was administered according to the procedure described by Grober and Buschke.[21] The 16 items to be learned were presented four at a time on successive cards. Items were represented in each quadrant by a word (e.g., grapes) that goes with a unique category cue

(e.g., fruit). The subject was asked to name and point aloud each item (e.g., grapes) after its cue (fruit) was aurally presented. After all four items were identified correctly, the card was removed, and immediate cued recall of the four items was tested by presenting the cues again in order to control for encoding. Once immediate recall for a group of four items was completed, the next set of four items was presented. This first phase of the test permits control of encoding and provided a score called immediate recall. Then, the memory phase was performed by three successive recall trials, each preceded by 20 seconds of subjects counting backward to obtain recall from long-term memory. Each recall trial consisted of two parts. First, each subject had up to 2 minutes to freely recall as many items as possible. Next, an aurally presented semantic category ("what was the name of the fruit?") was provided for those items that were not spontaneously retrieved by the patient. This provided a free recall score and a total recall score, which was the sum of free and cued recall. This memory phase provides three successive free recall and total recall scores for a maximum of $16 \times 3 = 48$. To evaluate the efficacy of semantic cues to facilitate retrieval from stored information, we defined an Index of Sensitivity of Cueing, which was determined by the score of (free recall − total recall)/(free recall − 48). After a 30-minute delay, filled by other nonverbal tests, a delayed recall was proposed to the patient with the same procedure of free and cued recall, providing a delayed free recall and a total delayed score with a maximal score of 16.

**Statistical analysis.** All statistical analyses were conducted using SAS software version 8.2. The primary outcome of the study was conversion to dementia of the Alzheimer type according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. The onset of AD was defined as the date when the diagnosis was made. In order to compare demographic, clinical, and neuropsychological data at baseline between the converted MCI group and the stable MCI group, we performed a logistic regression analysis controlling for age, sex, and educational level.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminating power of the different neuropsychological tests and clinical characteristics for conversion to dementia. The area under the curve (AUC) was used as a measure of the overall performance of the ROC curve (with a 95% CI). Moreover, it was determined whether the AUC values were statistically different using a nonparametric method for correlated samples (Delong's method). Finally, optimum cutoff points of neuropsychological tests were calculated by selecting the point on the ROC curve that maximized both sensitivity and specificity. We first studied for each test the joint effect of adding age, sex, or education (data not shown). Age was the only factor which was important for this maximization and was therefore considered for the determination of the optimal cutoff for each score in table 3. The joint effect of combining two scores on this maximization was evaluated. Then, Kaplan-Meyer curves were used to illustrate the differences in progression to AD between the two groups of patients below or under the optimum cutpoint point of neuropsychological tests. We used Cox proportional hazards models to estimate separately the effects of the different neuropsychological factors on the relative risk of conversion from MCI to AD (relative risk is expressed with a 95% CI). Time of diagnosis was modeled using age, sex, and level of education, as covariate along with whether the subject scored at or below the cutoff defined in ROC analysis. ROC analysis was performed on the whole sample and after exclusion of subjects with early withdrawal.

To provide sensitivity and specificity of the cutoff based on a test normative approach, according to categorization of aging, we further conducted analyses in two strata according to median of age: younger than the age of 72 (111 patients with 14 converted) or older than the age of 72 (106 patients with 45 converted).

**RESULTS** At study entry, 251 patients (151 female/100 male) with a mean age of 72.0 years (±5.4) were included. Education level was 10.8 ± 4 years. Among these 251 patients, 28 withdrew early from the study: 17 had no follow-up, and 11 had only one visit at 6 months without conversion to dementia. Because of uncertainty about their cognitive status over time, these 28 patients with early withdrawal were excluded from the ROC curve analysis. Of the remaining 223 subjects, 65 patients converted to dementia: dementia of the Alzheimer type in 59 cases and non-AD dementia in 6 cases. As AD was the primary outcome of the study, these patients with non-AD dementia were excluded from further statistical analyses.

Among the MCI population at baseline, 48% of the patients met the two cognitive criteria for inclusion in terms of the MMSE word recall and IST; of the remaining patients 39% met only the MMSE criterion, and 12% met only the IST criterion; 87% of patients had no IADL changes, and 13% had one item impaired at the first level (table 1).

Among the AD cases (referred as MCI-AD converters), 85% of patients (n = 50) converted

**Table 1** Inclusion criteria of the MCI population at baseline (n = 217)

| | % (n) |
|---|---|
| Memory complaint | 100 (217) |
| Objective memory impairment | |
| Impairment in both MMSE word recall* and IST | 48 (104) |
| Impairment in IST | 12.4 (27) |
| Impairment in MMSE word recall | 39.6 (86) |
| IADL | |
| No IADL change | 87.1 (189) |
| Minor IADL change† | 12.9 (28) |

*At least on word missing at the three-word recall of the Mini-Mental State Examination (MMSE).
†Only one item impaired at the first level in one of the four IADL. The four items included ability to use telephone, independence for transportation, self-administration of medication, and ability to handle finances.
MCI = mild cognitive impairment; IST = Isaac Set Test; IADL = Instrumental Activities of Daily Living.

**Table 2** Baseline comparisons between MCI-AD converters and stable MCI

| | MCI–non AD (n = 158) | MCI–AD (n = 59) | Group comparison (adjusted *p* value) |
|---|---|---|---|
| Age | 70.9 ± 5.4 | 74.8 ± 4.1 | <0.0001 |
| Education (% Bachelor) | 44.3 | 39.0 | 0.39 |
| Sex ratio (% male) | 39.9 | 45.8 | 0.61 |
| Family history of dementia (%) | 33.5 | 30.5 | 0.45 |
| MMSE | 27.7 ± 1.3 | 26.9 ± 1.2 | <0.0001 |
| Isaac Set Test | 28.2 ± 5.9 | 25.7 ± 5.2 | 0.03 |
| Goldberg scale | 3.1 ± 2.5 | 2.4 ± 2.3 | 0.2 |
| MADRS | 6.9 ± 4.6 | 6.6 ± 5.3 | 0.9 |
| Questioner of memory complaint | 15.4 ± 7.5 | 15.9 ± 10 | 0.86 |
| Subscore of spontaneous memory complaint | 2.1 ± 0.9 | 1.8 ± 1 | 0.053 |
| FCSRT free recall | 25.2 ± 6.2 | 13.6 ± 5.9 | <0.0001 |
| FCSRT total recall (free and cued recall) | 44.3 ± 3.8 | 31.0 ± 9.9 | <0.0001 |
| Intrusion (%) | 57 | 13.6 | <0.0001 |
| Serial digit learning test | 82.2 ± 8.7 | 71.8 ± 17.2 | 0.0002 |
| WAIS digit symbol test | 10.8 ± 2.7 | 9.9 ± 2.4 | 0.07 |
| Trail Making test A | 53.4 ± 24.6 | 63.7 ± 27 | 0.28 |
| Trail Making test B | 138.7 ± 78.1 | 191.8 ± 89 | <0.009 |
| Stroop test (inhibition condition) | 29.4 ± 9.1 | 25.0 ± 9.3 | 0.14 |
| Benton Visual Retention Test | 11.9 ± 1.9 | 10.8 ± 2.2 | 0.002 |
| Free delayed recall | 9.6 ± 3.0 | 3.7 ± 2.7 | <0.0001 |
| Total delayed recall | 15.1 ± 1.7 | 10.3 ± 4.2 | <0.0001 |
| False recognition ≥ 1 (%) | 6.3 | 39 | <0.0001 |
| WAIS similarities | 12.7 ± 3.4 | 10.6 ± 3.9 | <0.0001 |
| Verbal fluency (letter S) | 18.3 ± 6.4 | 15.8 ± 6.3 | 0.04 |
| Verbal fluency (category) | 17.0 ± 4.5 | 12.7 ± 3.7 | <0.0001 |
| DENO 100 | 89.7 ± 7.1 | 84.1 ± 10 | 0.0003 |
| Double task of Baddeley | 94.6 ± 11.6 | 93.5 ± 13.7 | 0.9 |

Tests are presented in order of their administration.
MCI-AD converters = patients with mild cognitive impairment (MCI) who converted to Alzheimer disease (AD) dementia during the 3-year follow-up; stable MCI = patients with MCI who did not convert to AD during the 3-year follow-up; MMSE = Mini-Mental State Examination; FCSRT = Free and Cued Selective Recall Reminding Test; WAIS = Wechsler Adult Intelligence Scale.

to AD within the first 2 years (9 in the first 6 months, 14 in 1 year, 17 in 18 months, 10 in 2 years), 4 in 30 months, and 5 in the third year.

ROC curve analysis was thus performed in 217 patients (MCI-AD converters n = 59, conversion rate of 27.2% (59/217); MCI-non AD n = 158). Their mean follow-up was 31.0 ± 10.5 months (5.6 to 50.4).

**Baseline characteristics.** Baseline characteristics of the cohort according to the outcome are shown in table 2. We described demographic and neuropsychological data at the initial visit in patients who developed AD (MCI-AD converters, n = 59) and those who did not (stable MCI, n = 158). At baseline, the two groups differed in age (74.8 ± 3.9 years and 70.7 ± 5.4 years; $p < 0.0001$). There was no difference in gender, education, or family history of dementia (table E-1 on the *Neurology*® Web site at www.neurology.org). No significant differences were observed in anxiety and depression scores or in the memory complaint scale. However, patients who did not develop dementia had a slightly higher level of spontaneous memory than patients who developed AD ($p = 0.053$). Medical history and comorbidity were similar in both groups. No difference between systolic or diastolic arterial tension was noticed between the two groups. Baseline psychometric performances were significantly lower in MCI-AD converters compared to MCI-non AD for all neuropsychological tests except for the WAIS Digit Symbol Test and the Double Task of Baddeley.

**Table 3** Receiver operating characteristic analysis: Demographic factors and neuropsychological tests associated with incident AD dementia

| | AUC | CI (AUC) | *p* Value | Cutoff | Se | Sp |
|---|---|---|---|---|---|---|
| Age | 0.72 | (0.65, 0.79) | | | | |
| Age + gender | 0.72 | (0.65, 0.79) | 0.21 | | | |
| Age + education | 0.72 | (0.65, 0.79) | 0.79 | | | |
| Age + gender + education | 0.73 | (0.66, 0.80) | 0.49 | | | |
| FCSRT total recall* | 0.94 | (0.91, 0.97) | <0.0001 | 40 | 79.7 | 89.9 |
| FCSRT index of cueing* | 0.93 | (0.89, 0.96) | <0.0001 | 71 | 78.0 | 84.8 |
| FCSRT free recall* | 0.92 | (0.88, 0.96) | <0.0001 | 17 | 71.2 | 91.8 |
| FCSRT delayed free recall* | 0.92 | (0.89, 0.96) | <0.0001 | 6 | 76.3 | 90.5 |
| FCSFT delayed total recall* | 0.89 | (0.85, 0.94) | <0.0001 | 14 | 69.5 | 88.6 |
| FCSRT number of intrusions* | 0.87 | (0.81, 0.92) | <0.0001 | 2 | 64.4 | 85.4 |
| Verbal fluency (category)* | 0.80 | (0.74, 0.87) | 0.003 | 13 | 55.9 | 82.3 |
| WAIS similarities* | 0.78 | (0.72, 0.85) | 0.04 | 11 | 49.2 | 72.2 |
| FCSRT false recognition* | 0.78 | (0.71, 0.84) | 0.002 | 1 | 20.3 | 98.1 |
| Serial digit learning test* | 0.77 | (0.7, 0.84) | 0.04 | 80 | 57.6 | 67.7 |
| DENO 100* | 0.76 | (0.7, 0.83) | 0.07 | 89 | 55.9 | 67.7 |
| Benton Visual Retention Test* | 0.76 | (0.69, 0.83) | 0.07 | 11 | 42.4 | 77.2 |
| Trail Making test B* | 0.75 | (0.68, 0.82) | 0.09 | 138 | 62.7 | 67.1 |
| WAIS digit symbol test* | 0.74 | (0.67, 0.81) | 0.15 | 10 | 37.3 | 71.5 |
| Stroop test (inhibition condition)* | 0.74 | (0.67, 0.81) | 0.22 | 59 | 52.5 | 58.2 |
| Verbal fluency (letter S)* | 0.74 | (0.67, 0.81) | 0.19 | 17 | 57.6 | 56.3 |
| Trail Making test A* | 0.73 | (0.66, 0.8) | 0.36 | 53 | 62.7 | 58.9 |
| Double task of Baddeley* | 0.72 | (0.65, 0.79) | 1.00 | 94 | 50.8 | 56.3 |

Areas under the curve (AUC) are presented with their 95% CI. *p* Values are given for comparison between AUC values for age and for each factor added. Optimal cutoff was determined for each neuropsychological test associated with incident AD dementia. Results for tests are presented in order of statistical power.
*Age is included in models for computing AUC.
AD = Alzheimer disease; FCSRT = Free and Cued Selective Recall Reminding Test; WAIS = Wechsler Adult Intelligence Scale.

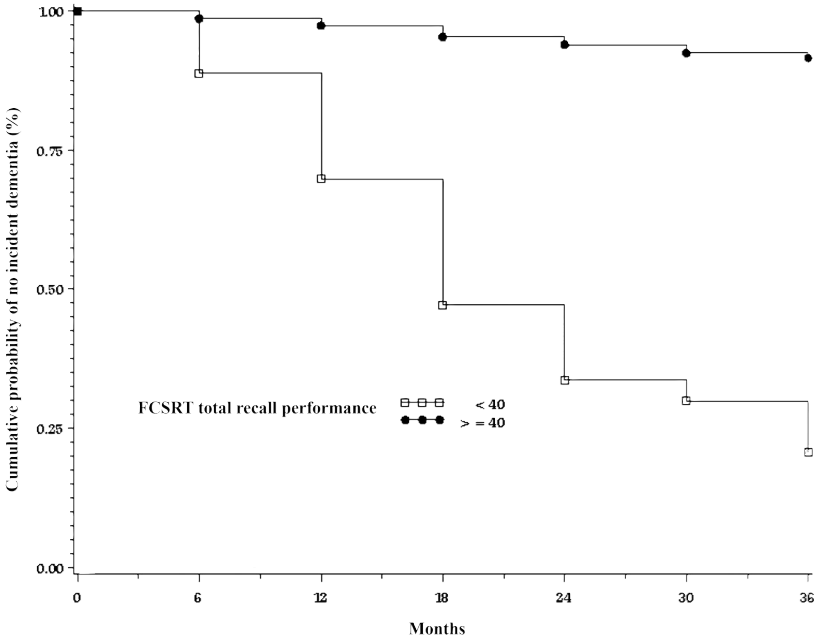
**Determination of the optimal neuropsychological cutoff for predicting AD dementia.** A first ROC curve analysis showed that only age changed the statistical level, whereas sex and level of education did not. Results are presented in table 3. The ROC analysis provides information about the more sensitive and specific neuropsychological tools which can predict the development of AD dementia. The FCSRT scores (total recall, index of cuing free recall, free recall, delayed free recall, delayed total recall, and number of intrusions) all have the best areas under the curve with AUC values higher than 0.87. Then, only Verbal Fluency (category), WAIS Similarities, and the Serial Digit Learning Test add significant information to predict the incidence of AD dementia (compared to a model with age only) with AUC between 0.77 and 0.80. All other tests did not add significant information.

We further tried to increase accuracy by combining different neuropsychological performances. No combination significantly improved the accuracy of the models presented in table 3.

The significant threshold of subscores of the FCSRT for identifying MCI-AD converters at baseline was 17/48 for free recall, 40/48 for total recall, 6/16 for delayed free recall, 14/16 for total delayed recall, and 71% for index of sensitivity of cueing (table 3). Respective sensitivity and specificity are also presented in table 3. High sensitivity and specificity were provided by the different FCSRT scores, total recall being the score with the highest sensitivity (79.7%), with a specificity of 89.9%. The highest specificity is for free recall (91.8%), with sensitivity equal to 71.2%. In addition to the FCSRT scores were the Verbal Fluency scores, but these values were far less sensitive and specific than those of the FCSRT subscores (sensitivity = 55.9%, specificity = 82.3%).

**Relation between baseline neuropsychological performance and risk of developing AD.** The Kaplan-Meier survival curves (figure) graphically show the dramatic difference in the development of AD dementia between the groups, according to the

**Figure** Kaplan-Meyer survival curves for the development of Alzheimer disease (AD) dementia in patients with mild cognitive impairment for subjects with or without amnestic syndrome of the medial temporal type




The curves show the dramatic difference in the development of AD dementia between groups, according to the initial performance on Free and Cued Selective Recall Reminding Test total recall. Receiver operating characteristic analysis was performed on the whole sample (n = 251 patients).

initial performance on FCSRT total recall, as defined above. For FCSRT total recall, 75% of the subjects under the threshold of 40/48 converted to AD at the end of the 3-year follow-up, compared to 8% of those who were above the cutoff, and 52% vs 5% converted at 18 months. The Kaplan-Meier survival curves according to the initial performance on FCSRT free recall and index of cueing are available in figures E-1 and E-2.

The multivariate Cox proportional hazards models controlling for age show that there was a significant difference in the probability of progression from MCI to AD between the patients with baseline FCSRT total recall under 40/48 and those above (relative risk 12.0, 95% CI 6.24 to 23.2; $p < 0.0001$; table 4, figure). Relative risk for subjects with FCSRT cueing below 71% was equal to 10.0 (95% CI 5.3 to 18.75, $p < 0.0001$). In contrast, the relative risk for subjects with a category fluency score under the cutoff was equal to 2.77 (95% CI 1.59 to 4.84, $p = 0.003$). The other relative risks are listed in table 4.

**Complementary analyses.** We further conducted analyses in two strata according to median of age. We further conducted analyses in two strata according to age (younger and older than age 72). AUC order was similar in the two age classes, whereas different cutoffs were obtained for some tests but not for all of them (table 5).

**DISCUSSION** The main objective of this study was to determine which predictive tool is most effective for diagnosing prodromal AD. Because AD at its early stage and the MCI diagnosis are often confused, we specifically wanted to enroll patients whose memory complaints more or less corresponded with the MCI definition, so as to cover the entire spectrum of the MCI population seen in a memory clinic whose clientele includes patients with prodromal AD and patients with stable MCI with subjective complaints. To achieve this objective, patients were included on the basis of the following: 1) memory complaint; 2) a global cognitive efficiency documented by MMS score between 25/30 and 29/30[10]; 3) the absence of dementia[13]; 4) normal activity in daily living or only minor changes[12,17]; and 5) mild quantitative impairments of cognitive function measured by either the Isaac Set Test or at least one word missing in the word recall MMSE, or both.[10,11] The Set Test is a categorical fluency test which utilizes executive function and semantic memory, both impaired in very mild AD.[29,30] Moreover, executive dysfunction is a frequent cognition domain altered in MCI and aging, and is associated with a high risk for dementia.[31,32] Word recall on MMSE reflects impairment of long-term memory and is a predicting factor for AD in patients with mild MCI.[33,34] Cognitive criteria used permitted us to include MCI with both memory and attention impairment.

We observed a high rate of early converters during follow-up (27% of the MCI population, 23% during the first 2 years), a result that differs from the current epidemiologic survey of the MCI population that reports a homogeneous rate of annual conversion.[1] The high rate of early conversion allows us to conclude that prodromal AD was already present among patients with MCI at baseline. It follows, therefore, that the best predictors of an AD conversion can be considered as a diagnostic tool for prodromal AD. Accordingly, the FCSRT appears to be the best neuropsychological test for detecting AD at its prodromal stage.

At the early stage of AD, neuropathologic changes are already present in medial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex),[35,36] areas critical for long-term episodic memory. Episodic memory deficit is a constant, precocious, and reliable neuropsychological marker of AD in relation to early involvement of medial temporal structures.[8,37]

**Table 4** Relative risk associated with each cutoff point score

| | β | Ect (β) | p | RR | CI |
|---|---|---|---|---|---|
| FCSRT total recall | 2.507 | 0.334 | <0.0001 | 12.26 | (6.37, 23.60) |
| FCSRT index of cueing | 2.329 | 0.322 | <0.0001 | 10.26 | (5.47, 19.28) |
| FCSRT free recall | 2.160 | 0.307 | <0.0001 | 8.68 | (4.76, 15.82) |
| FCSRT delayed free recall | 2.365 | 0.322 | <0.0001 | 10.64 | (5.66, 20.01) |
| FCSRT delayed total recall | 1.977 | 0.288 | <0.0001 | 7.22 | (4.11, 12.70) |
| FCSRT number of intrusions | −1.703 | 0.316 | <0.0001 | 0.18 | (0.10, 0.34) |
| Verbal fluency (category) | 1.043 | 0.293 | 0.0004 | 2.84 | (1.60, 5.04) |
| WAIS similarities | 1.166 | 0.288 | <0.0001 | 3.21 | (1.82, 5.64) |
| FCSRT false recognition | −1.374 | 0.273 | <0.0001 | 0.25 | (0.15, 0.43) |
| Serial digit learning test | 0.635 | 0.268 | 0.177 | 1.89 | (1.12, 3.19) |
| DENO100 | 0.642 | 0.271 | 0.0179 | 1.90 | (1.12, 3.23) |
| Benton Visual Retention Test | −0.242 | 0.066 | 0.0002 | 1.27 | (1.12, 1.45) |
| Trail Making test B | −0.837 | 0.282 | 0.0030 | 0.43 | (0.25, 0.75) |
| WAIS digit symbol test | 0.493 | 0.295 | 0.0943 | 1.64 | (0.92, 2.92) |
| Stroop test (inhibition condition) | 0.214 | 0.276 | 0.4379 | 1.24 | (0.72, 2.13) |
| Verbal fluency (letter S) | 0.377 | 0.271 | 0.1652 | 1.46 | (0.86, 2.48) |
| Trail Making test A | −0.550 | 0.281 | 0.0500 | 1.58 | (0.33, 1.00) |

FCSRT = Free and Cued Selective Recall Reminding Test; WAIS = Wechsler Adult Intelligence Scale.

Longitudinal studies in the elderly or in those with MCI showed that a long-term memory deficit consistently predicts incident dementia.[32,33,38,39]

**Table 5** Optimal cutoff point determined for each neuropsychological test associated with incident AD dementia by age groups

| | ≤72 y (n = 111) | | | >72 y (n = 106) | | |
|---|---|---|---|---|---|---|
| | Cutoff | Se | Sp | Cutoff | Se | Sp |
| FCSRT total recall | 40 | 71.4 | 91.8 | 39 | 75.6 | 93.4 |
| FCSRT index of cueing* | 70 | 71.4 | 88.7 | 74 | 80 | 82 |
| FCSRT free recall | 17 | 57.1 | 94.8 | 17 | 75.6 | 86.9 |
| FCSRT delayed free recall* | 8 | 78.6 | 81.4 | 6 | 77.8 | 88.5 |
| FCSFT delayed total recall* | 13 | 50 | 92.8 | 14 | 68.9 | 85.2 |
| FCSRT number of intrusions* | 1 | 78.6 | 55.7 | 1 | 88.9 | 59 |
| Verbal fluency (category)* | 14 | 42.9 | 18.6 | 13 | 40 | 27.9 |
| WAIS similarities* | 11 | 57.1 | 67 | 11 | 46.7 | 80.3 |
| FCSRT false recognition* | 1 | 42.9 | 96.9 | 1 | 37.8 | 88.5 |
| Serial digit learning test* | 83 | 35.7 | 41.2 | 78 | 42.2 | 26.2 |
| DENO 100* | 91 | 50 | 39.2 | 89 | 42.2 | 39.3 |
| Benton Visual Retention Test* | 12 | 42.9 | 44.3 | 11 | 53.3 | 21.3 |
| Trail Making test B* | 143 | 42.9 | 22.7 | 159 | 42.2 | 34.4 |
| WAIS digit symbol test* | 9 | 28.6 | 76.3 | 11 | 44.4 | 63.9 |
| Stroop test (inhibition condition)* | 59 | 42.9 | 67 | 55 | 46.7 | 55.7 |
| verbal fluency (letter S)* | 13 | 71.4 | 14.4 | 16 | 46.7 | 34.4 |
| Trail Making test A* | 46 | 42.9 | 46.4 | 58 | 35.6 | 42.6 |
| Double task of Baddeley* | 98 | 7.1 | 57.7 | 99 | 33.3 | 68.9 |

AD = Alzheimer disease; Se = sensitivity; Sp = specificity; FCSRT = Free and Cued Selective Recall Reminding Test; WAIS = Wechsler Adult Intelligence Scale.

Poor performance on free recall predicts future dementia for at least 5 years before diagnosis of AD in initially nondemented elderly community volunteers.[39] Our study shows that impairment of free recall, total recall, and index of sensitivity of cueing can identify prodromal AD in patients with MCI with a high sensitivity of 79.7% and a specificity of 89.9%. At 36 months, the probability of developing AD dementia for patients with MCI who fulfilled both criteria defined by free and total recall was 90%, while it was 5.6% for those who did not fulfill both criteria. By comparison, biomarkers including a combination of CSF concentrations of total tau (T-tau) and amyloid beta 1-42 yielded a sensitivity of 95% and a specificity of 83%.[3] Hippocampal volume reduction and glucose metabolic reduction in the temporo-parietal neocortex and in the anterior and posterior cingulate gyrus may predict future conversion of patients with MCI to AD with an estimated accuracy of 69 to 77% and 94%.[4,40] However, MRI brain volume or metabolism reductions can be observed in other causes of dementia, and these methods require intensive skilled labor. Visual qualitative estimates of medial temporal atrophy, which are easier to perform routinely, predict the progression of MCI to dementia with a sensitivity of 68% and specificity of 69%.[5,6]

The main characteristic of the FCSRT is to assess verbal episodic memory with semantic cueing that permits one to control for encoding and to facilitate retrieval in order to isolate the storage capacities of the patients. The cued recall technique, used in the FCSRT, is aimed at enhancing the recall performance by presentation of semantic cues that help for encoding and for retrieval processes. By construction, the FCSRT can isolate the amnesic syndrome of the medial temporal type defined by 1) a very poor free recall and 2) a decreased total recall because of insufficient effect of cueing.[2,8] The low performance of total recall, despite facilitation of retrieval, indicates a poor storage of information. This memory pattern differs from functional and subcortico-frontal memory disorders which are characterized by a low free recall performance with normal total recall because of good efficacy of cueing.[41] The ability to benefit from cues mainly reflects an impairment in strategies to retrieve stored information, as in frontotemporal dementia,[42] depression,[43] vascular dementia,[44] and subcortico-frontal dementia.[41] These data are in accordance with a clinico-metabolic correlation study in AD demonstrating that performance on free recall was correlated with metabolic activity in frontal regions,

while performance on cued recall was correlated with residual metabolic activity in bilateral parahippocampal regions.[45] Among other tests, while almost all psychometric performances were significantly impaired in declining MCI compared to stable MCI, only categorical verbal fluency, WAIS similarities, and serial digit learning test performances were associated with incident dementia. Previous community-based studies have shown that attention processing and mental speed can consistently predict which patients will develop dementia.[14,46] However, the PreAl study was designed to reflect the activity in the memory clinic, and therefore the population was clinical in character rather than community-based. Accordingly, the results of our investigations differed from those conducted at the community level. In contrast to results obtained in the PAQUID study,[46] the Benton Visual Retention Test, a test of visual memory, had a low sensitivity in our study even though we used the same procedure that evaluates immediate recognition.

Although ApoE4 status was not measured in the PreAl study, family history was not associated with an increased risk of AD in our cohort.

We acknowledge the fact that the cutoffs determined in this sample are related to the population of our sample recruited in memory clinics, with subjective cognitive complaints and precise inclusion criteria. However, these results highlight the superiority of specific memory tests in the diagnosis of AD at a predementia stage.

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## REFERENCES

1. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
2. Dubois B, Albert ML. Amnestic MCI or prodromal Alzheimer's disease? Lancet Neurol 2004;3:246–248.
3. Hansson O, Zetterberg H, Buchhave P, et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet 2006;5:228–234.
4. Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. J Neurol Neurosurg Psychiatry 2002;72:491–497.
5. Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 2004;63:94–100.
6. DeCarli C, Frisoni GB, Clark CM, et al. Qualitative estimates of medial temporal atrophy predict progression of mild cognitive impairment to dementia. Arch Neurol 2006;64:108–115.
7. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900–903.
8. Tounsi H, Deweer B, Ergis AM, et al. Sensitivity to semantic cuing: an index of episodic memory dysfunction in early Alzheimer disease. Alzheimer Dis Assoc Disord 1999;13:38–46.
9. Al Aloucy J, Dalla Barba G, Roudier M. Metamemory, self-awareness and anosognosia in patients with mild cognitive impairment, mild Alzheimer's disease and control healthy older adults. Neurology 2006;66(suppl 2):A129. Abstract S16.005.
10. 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.
11. Isaac B, Kennie AT. The Set-Test as an aid to the detection of dementia in old people. Br J Psychiatry 1973;45: 957–962.
12. Barberger-Gateau P, Dartigues JF, Letenneur L. Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. Age Ageing 1993; 22:457–463.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (rev. 3rd ed). Washington, DC: American Psychiatric Association, 1987.
14. Fabrigoule C, Rouch I, Taberly A. Cognitive process in preclinical phase of dementia. Brain 1998;121:135–141.
15. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002; 59:1594–1599.
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389.
17. Lawton MPL, Brody EM. Assessment old older people: self-maintaining an instrumental activities of daily living. Gerontologist 1969;9:179–186.
18. Goldberg DP, Hillier VF. A scaled version of the General health (part anxiety) Questionnaire. Psychol Med 1979;9:139–145.
19. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43: 2412–2414.
20. McKhann G, Drachman D, Folstein M, et al. 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.
21. Grober E, Buschke H. Genuine memory deficits in dementia. Dev Neuropsychol 1987;3:13–36.
22. Benton AL. The revised visual retention test: clinical and experimental applications. 3rd edition. New York: Psychological Corporation, 1963.

23. Kremin H, Perrier D, De Wilde M. DENO-100–Paradigme expérimental et test clinique de dénomination contrôlée: effet relatif de 7 variables expérimentales sur les performances de 16 sujets atteints de maladies dégénératives. Rev Neuropsychol 1999;9:439–440.
24. Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 1991;114:2095–2122.
25. Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. Attentional control in Alzheimer's disease. Brain 2001; 124:1492–1508.
26. Wechsler D. The Wechsler Adult Intelligence Scale–Revised. San Antonio: Psychological Corporation, 1981.
27. Stroop J. Studies of interferences in serial verbal reactions. J Exp Psychol 1935;18:643–662.
28. Reitan R. Validity of the Trail Making test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–276.
29. Salmon DP, Thomas RG, Pay MM, et al. Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals. Neurology 2002;59:1022–1028.
30. Adlam AL, Bozeat S, Arnold R, Watson P, Hodges JR. Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. Cortex 2006;42:675–684.
31. Amieva H, Jacqmin-Gadda H, Orgogozo JM, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. Brain 2005;128:1093–1101.
32. Tierney MC, Yao C, Kiss A, McDowell I. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology 2005;64:1853–1859.
33. Small BJ, Fratiglioni L, Viitanen M, Winblad B, Backman L. The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. Arch Neurol 2000;57:839–844.
34. Meyer J, Xu G, Thornby J, Chowdhury M, Quach M. Longitudinal analysis of abnormal domains comprising mild cognitive impairment (MCI) during aging. J Neurol Sci 2002;201:19–25.
35. Delacourte A, David JP, Sergeant N, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–1165.
36. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405.
37. Deweer B, Lehericy S, Pillon B, et al. Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. J Neurol Neurosurg Psychiatry 1995;58:590–597.
38. Elias MF, Beiser A, Wolf PA, et al. The preclinical phase of metamemory, self-awareness and anosognosia in patients with mild cognitive impairment, mild Alzheimer's disease and control healthy older adults Alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol 2000;57:808–813.
39. Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. Neurology 2000;54:827–832.
40. Mosconi L, Perani S, Sorbi K, et al. MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. Neurology 2004;63:2332–2340.
41. Pillon B, Blin J, Vidailhet M, et al. The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology 1995;45:1477–1483.
42. Lavenu I, Pasquier F, Lebert F, Pruvo JP, Petit H. Explicit memory in frontotemporal dementia: the role of medial temporal atrophy. Dement Geriatr Cogn Disord 1998;9:99–102.
43. Fossati P, Coyette F, Ergis AM, Allilaire JF. Influence of age and executive functioning on verbal memory in patients with depression. J Affect Disord 2002;68:261–271.
44. Traykov L, Baudic S, Raoux N, et al. Patterns of memory impairment and perseverative behavior discriminate early Alzheimer's disease from subcortical vascular dementia. J Neurol Sci 2005;229–230:75–79.
45. Lekeu F, Van der Linden M, Chicherio C, et al. Brain correlates of performance in a free/cued recall task with semantic encoding in Alzheimer disease. Alzheimer Dis Assoc Disord 2003;17:35–45.
46. Amieva H, Letenneur L, Dartigues JF, et al. Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. Dement Geriatr Cogn Disord 2004;18:87–93.