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Item and Associative Memory in Amnestic Mild Cognitive Impairment: Performance on Standardized Memory Tests

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The earliest neuroanatomical changes in amnestic mild cognitive impairment (aMCI) involve the hippocampus and entorhinal cortex, structures implicated in the integration and learning of associative information. The authors hypothesized that individuals with aMCI would have impairments in associative memory above and beyond the known impairments in item memory. A group of 29 individuals with aMCI and 30 matched control participants were administered standardized tests of object–location recall and symbol–symbol recall, from which both item and associative recall scores were derived. As expected, item recall was impaired in the aMCI group relative to controls. Associative recall in the aMCI group was even more impaired than was item recall. The best group discriminators were measures of associative recall, with which the sensitivity and specificity for detecting aMCI were 76% and 90% for symbol–symbol recall and were 86% and 97% for object–location recall. Associative recall may be particularly sensitive to early cognitive change in aMCI, because this ability relies heavily on the medial temporal lobe structures that are affected earliest in aMCI. Incorporating measures of associative recall into clinical evaluations of individuals with memory change may be useful for detecting aMCI.

Keywords: aging, mild cognitive impairment, memory disorders, neuropsychological tests, associative memory

Amnestic mild cognitive impairment (aMCI) is characterized by an isolated memory decline in the context of otherwise normal cognition and daily functioning (recently reviewed by Feldman & Jacova, 2005; Petersen, 2004). Classification with aMCI represents a high risk factor for Alzheimer's disease (AD), as many individuals with aMCI develop AD within 3–6 years (Fisk, Merry, & Rockwood, 2003; Fisk & Rockwood, 2005; Petersen, 2004). Given the 3%–5% prevalence of aMCI among adults age 65 and older (Fisk et al., 2003; Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002), the presentation of these patients to geriatric or to memory clinics is not uncommon. Determining which cognitive tests are most sensitive in detecting aMCI has been of much interest to clinicians.

The earliest brain changes in aMCI, as measured by volume loss on magnetic resonance imaging, occur in the hippocampus and entorhinal cortex of the medial temporal lobes (reviewed in Masdeu, Zubieta, & Arbizu, 2005). These structures show increasing atrophy from normal aging to aMCI to AD (Du et al., 2001; Pennanen et al., 2004). Hippocampal and entorhinal atrophy are also sensitive predictors of progression to AD in individuals with aMCI (deToledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2000; Jack et al., 1999; Killiany et al., 2000). The primary cognitive consequence of changes in these brain regions is memory decline. In general, hippocampal and entorhinal volumes are correlated with performance on memory tests (Rodrigue & Raz, 2004; Rosen et al., 2003). There is evidence, however, that these brain regions are particularly important for specific types of memory, among them, associative memory.

Associative memory involves remembering relations among items of information; examples include remembering words that were paired together and remembering objects and their locations. Associative memory contrasts with item memory, which involves remembering the individual items, such as the words or the objects, independent of any other information associated with them at

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acquisition. Direct comparisons of these two types of memory indicate that the hippocampus and entorhinal cortex play a greater role in associative than in item memory, as seen in functional neuroimaging studies of healthy adults (Kirwan & Stark, 2004; Klingberg, Roland, & Kawashima, 1994; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001), in studies of focal lesions in humans (Mayes et al., 2004), and in animal studies (Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004). A dissociation between item and associative memory has been demonstrated in the normal aging process (e.g., Naveh-Benjamin, 2000), whereby older adults show greater age-related decline in associative than in item memory relative to young adults.

Although item memory and associative memory have not been directly compared in aMCI, memory tests that involve some type of associative learning do appear to be sensitive to memory changes in individuals with aMCI and in similar participant groups. For example, individuals with aMCI had difficulty learning associations between objects and actions in a subject-performed-task paradigm (Karantzoulis, Rich, & Mangels, 2006). The learning of word pairs on the Associate Learning subtest of the Wechsler Memory Scale was impaired in patients with very mild or questionable AD (Duchek, Cheney, Ferraro, & Storandt, 1991; Storandt & Hill, 1989). Similarly, the ability to learn associations between abstract patterns and their spatial locations was poorer in a group of older adults with longitudinal memory decline than it was in those without memory decline (Collie, Myers, Schnirman, Wood, & Maruff, 2002). Associative memory, however, is clearly dependent on item memory, because one cannot remember associations if the items themselves have been forgotten. Thus, an interesting question arises as to whether associative memory is impaired after accounting for decreased item recall among individuals with aMCI.

Given that changes in brain structures that are specifically implicated in associative memory appear early in aMCI, a pattern of impaired associative memory after controlling for impaired item memory would provide a behavioral correlate consistent with these early neuroanatomical changes. Objective evidence of such a pattern would also be potentially useful in clinical evaluations aimed at identifying individuals with aMCI, particularly if item and associative memory measures can be derived from the same memory tests. Advantages of using memory tests that are standardized include their wide availability to clinicians, the standardization of administration procedures, the presence of psychometric information (such as reliability and validity), and their familiarity to many clinicians.

In this study, we investigated the memory performance of individuals with aMCI on two standardized memory tests: the Brief Visuospatial Memory Test—Revised (BVMT–R; Benedict, 1997), as a measure of object–location associative recall, and Digit Symbol incidental recall from the Wechsler Adult Intelligence Test–III (Wechsler, 1997), as a measure of symbol–symbol associative recall. Although both tests provide information about item and associative recall within tasks, they differ in many respects, including the type of associative information presented, the intentionality of learning, and the number and duration of exposures to the stimuli to be learned. By using these diverse tasks, we were able to determine whether our findings were robust when using different stimuli and procedures for testing associative memory.

On the basis of previous evidence of brain regions involved in aMCI and in associative memory, we expected that individuals with aMCI, relative to matched control participants, would show an impairment in associative recall above and beyond their impairment in item recall. Because, as previously discussed, associative memory is dependent on item memory, we controlled for item recall by measuring associative recall only for those items that were recognizably recalled. To provide preliminary evidence that may be of use in clinical neuropsychological assessment, we present information about the sensitivity and the specificity of these associative measures in the detection of aMCI.

Method

Participants

Recruitment and classification of participants. Two groups of older adults participated: healthy (i.e., non-memory-impaired) control participants and individuals with single-domain aMCI. Both groups were screened by interview for medical and for psychiatric disorders, medications affecting cognition, and substance use. All were screened for current mood disorders by self-report questionnaires (Geriatric Depression Scale; Yesavage et al., 1983; Hospital Anxiety and Depression Scale; Snaith & Zigmond, 1994).

Control participants were recruited from community talks and from databases of research volunteers. To be considered healthy, they were required to score within the normal range for their age on tests of general cognitive status (i.e., Mini-Mental State Examination, MMSE; Folstein, Folstein, & Fanjiang, 2000; Folstein, Folstein, & McHugh, 1975) and of immediate and delayed verbal memory on a word-list learning test (i.e., Hopkins Verbal Learning Test—Revised, HVLT–R; Brandt & Benedict, 2001). As can be seen in Table 1, on average, MMSE scores were near the ceiling of 30 points and mean HVLT–R scores were within one standard deviation of the mean vocabulary score.

Individuals with aMCI were recruited from physician referrals and from newspaper advertisements. Clinical evaluation and consensus by two neuropsychologists were used for classification of individuals with single-domain aMCI according to criteria by Petersen (2004). These criteria include the presence of a new memory complaint, objective evidence of memory impairment, normal general cognitive functioning, no substantial interference with normal activities, and no dementia. Presence of a new memory complaint and absence of substantial interference with normal activities were determined from structured interviews with the individual (in all cases) and with a family member whenever possible (i.e., 52% of our final sample). Interview questions probed subjective memory ability (i.e., past and current level of ability) and level of independence in various daily activities (on the basis of Lawton & Brody, 1969). Evidence of an objective memory impairment was obtained by cognitive testing with the HVLT–R, Rey–Osterreith Complex Figure recall (Spreen & Strauss, 1998), Logical Memory (Wechsler, 1987), and Verbal Paired Associates (Wechsler, 1987). As recommended by Petersen (2004), we considered memory impairment to be present when an individual obtained memory scores that were lower than expected on the basis of age, education, and intellectual function, and no particular cutoff score was used. Specifically, we required that the age-corrected scaled score (age SS) on at least two memory tests be considerably lower than was the age SS for verbal IQ. For exam-

Table 1
Participant Demographics, Descriptive Cognitive Variables, and Standard Performance Measures for the Two Tests of Interest, the BVMT–R and Digit Symbol

Variable	Control (n = 30)		aMCI (n = 29)	
	M	*SD*	*M*	*SD*
Demographics				
Age (years)	75.2	5.7	75.1	7.0
Education (years)	14.1	3.3	14.3	2.6
Sex (% female)	57		55	
Descriptive cognitive variables				
MMSE	28.6	1.2	27.8	1.7*
Vocabulary age SS	13.8	2.8	14.4	2.5
Digit Span age SS	11.6	2.9	12.6	3.9
Trail Making Test–Part B age SS	12.2	2.7	11.5	2.3
HVLT–R immediate recall age SS	10.7	1.7	6.2	2.2*
HVLT–R delayed recall age SS	11.8	1.7	3.8	3.2*
Tests of interest				
BVMT–R immediate recall age SS	9.9	2.4	5.3	2.5*
BVMT–R delayed recall age SS	10.7	2.2	5.3	3.2*
Digit Symbol coding age SS	12.0	3.1	10.4	2.0*

Note. BVMT–R = Brief Visual Spatial Memory Test—Revised; aMCI = amnestic mild cognitive impairment; MMSE = Mini-Mental State Examination; SS = scaled score; HVLT–R = Hopkins Verbal Learning Test—Revised.
* Denotes group differences where $p < .05$.

ple, as seen in Table 1, mean HVLT–R age SSs were 2–3 standard deviations lower than was the mean vocabulary age SS in this group. Normal general cognitive functioning was confirmed by cognitive screening with the MMSE or the Dementia Rating Scale–II (Jurica, Leitten, & Mattis, 2001) and by a cognitive assessment with the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Digit Span (Wechsler, 1997), Rey–Osterreith Complex Figure copy, and the Trail Making Test (Spreen & Strauss, 1998). The final criterion of "no dementia" was determined by taking into consideration all of the previous criteria; it hinged on the criterion of no significant functional impairment (Petersen, 2004). In addition, we performed a careful review of each participant's background information, current medical conditions, self-reported mood, and cognitive assessment to ascertain that no medical or psychiatric condition (other than possible incipient AD) accounted for the memory impairment.

Participant groups. The final sample included 30 healthy control participants and 29 individuals with aMCI. Descriptive demographic and cognitive variables from the participant groups are presented in Table 1. There were no significant group differences in age, $t(57) = 0.08$, $p = .94$, $d = 0.02$; education, $t(57) = -0.23$, $p = .82$, $d = 0.06$; or sex, $\chi^2(1, N = 59) = 0.01$, $p = .91$. On the MMSE, the control group obtained significantly higher scores than did the aMCI group, $t(57) = 2.29$, $p = .026$, $d = 0.55$, although both groups scored in the normal range. General verbal ability on the vocabulary test (Wechsler, 1997) was above average for many participants and was not significantly different between groups, $t(57) = -0.79$, $p = .44$, $d = 0.23$. Immediate and delayed verbal recall on the HVLT–R was average in the control group, and memory in the aMCI group was well below average (i.e., approximately 1–1.5 standard deviations below the mean for their age and more than 2 standard deviations below their verbal IQ estimates). As expected on the basis of grouping criteria, immediate and delayed HVLT–R scores were higher in the healthy older group than in the aMCI group, $t(57) = 8.88$, $p < .001$, $d = 1.77$, and $t(57) = 12.03$, $p < .001$, $d = 3.26$, respectively.

Although not used for group classification, the typical clinical scores derived from our targeted memory tasks are provided in Table 1 for descriptive purposes. In the control group, performance was within the average range on all BVMT–R and Digit Symbol measures. In the aMCI group, BVMT–R recall was in the borderline impaired to low average range; performance on Digit Symbol coding, although lower than in the control group, was well within the average range.

Procedures

All participants underwent an evaluation consisting of a clinical interview and administration of standardized cognitive tests. We derived object item recall scores and object–location associative recall scores from the BVMT–R. We calculated symbol item recall scores and symbol–symbol associative recall scores from Digit Symbol incidental recall. Because raw associative recall scores are dependent on the number of items recalled, we also calculated "corrected" association scores to provide information about associative recall after accounting for item recall, as described subsequently.

Object–location recall. Standard administration procedures (Benedict, 1997) were used. Briefly, a 2-by-3 array of six simple geometric figures was presented for 10 s on each of three learning trials. Immediately following each presentation, we tested free recall by asking the participant to reproduce the figures as accurately as possible in their correct locations on a blank sheet of paper. Approximately 25 min after the final learning trial, we tested delayed recall by asking the participant to draw the figures in their correct locations.

To score each trial, consistent with standardized scoring rules (Benedict, 1997), the scorer first determined the correspondence between each produced figure and the presumed target figure. If any target figure was produced more than once on any given trial, only the figure with the highest overall score was used. Similarly, if an inaccurately produced figure could reasonably correspond to more than one target figure, it was considered to correspond to the target figure for which it would obtain the highest overall score. We calculated separate item recall and associative recall scores. To decrease the dependence of these measures on each other, we scored item accuracy regardless of location, and we scored association regardless of item accuracy (although for the latter, the item was required to be at least recognizable so we could determine whether it was in the correct location).

Item scores were based in part on the criteria in the manual. Each figure was given 1 item point if it was drawn accurately (i.e., if it met criteria for "full credit" as described in the manual), regardless of location. No item points were awarded for recognizable but inaccurately drawn figures (i.e., those described as "partial credit" in the manual) or for unrecognizable figures. The maximum

item recall score was thus 6 for each trial. To score object–location association, consistent with the scoring manual, the scorer imposed a 2-by-3 matrix on the reproduced figures in whatever manner maximized the location scores (without rotating the matrix more than 45°). For each recognizable or accurate figure, 1 associative point was awarded if the figure was drawn in the correct location on the matrix. No points were awarded for figures drawn in incorrect locations or for unrecognizable or missing figures. The raw associative memory score was the sum of associative points, with a maximum of 6 for each trial. To correct for the number of items recalled, we calculated the corrected associative score as the mean object–location associative score for each item that was recognizably (but not necessarily completely accurately) drawn. The corrected associative recall score thus ranged from 0 to 1.

Because this strict scoring system, which required that items and locations be recalled with complete accuracy to receive a point, could have masked subtle group differences in item and in associative recall, we also created a more lenient scoring system. We rescored drawings by allotting partial credit (i.e., a half point) on item recall for figures that were recognizable but were not perfectly drawn (called "partial credit" in the BVMT–R manual) and on associative recall for figures that were drawn in a location adjacent (either horizontally or vertically) to the target location. Full credit (i.e., 1 point) was awarded for completely accurate item and associative recall, as described previously.

Symbol–symbol recall. Standard administration procedures (Wechsler, 1997) were used. Participants were presented with a sheet of paper. In a row on the top of the sheet was a key showing the digits 1 to 9, each paired with a simple nonnumeric symbol (e.g., + and =); below this, filling the remainder of the page, were rows of digits paired with blank spaces. After completing several sample items, the participants filled the blank spaces with the symbol that went with each digit; they worked as quickly as possible and referred to the key as necessary. They were stopped after 120 s or after they had completed the first four rows, whichever occurred last. (For the large majority of individuals in both groups, the stopping point was four rows, as described subsequently.)

Immediately following this coding trial, two incidental learning tests were administered. We tested item recall by providing a blank writing area and asking participants to produce from memory as many of the symbols as they could recall, regardless of the digits with which the symbols were paired. A point was awarded for each symbol that was drawn accurately, and the total possible item recall score was 9. We tested associative recall by giving participants a sheet of paper with two rows of digits (each row contained all 9 digits) and asking them to produce from memory the symbols that were paired with each digit. For the present study, we examined only a single row, whichever contained the highest score. The raw association score was the number of symbols correctly paired with a digit, for a total possible score of 9. To correct for the number of items recalled, we calculated the corrected association score as the number of correctly paired symbols divided by the number of correctly recalled symbols. The corrected association score thus ranged from 0 to 1.

Data analyses

For both tasks, we addressed our primary hypothesis in two ways: (a) We tested for interactions between group and recall type (item vs. association). For the object–location task, we conducted a repeated measures ANOVA with one between-subjects variable (groups: control vs. aMCI) and two within-subjects variables (recall type: item vs. association; trials: 1, 2, 3, and delayed). For symbol–symbol recall, we conducted a repeated measures ANOVA with one between-subjects variable (groups: control vs. aMCI) and one within-subjects variable (recall type: item vs. association). (b) Because raw associative scores are at least somewhat dependent on item scores, we tested for group differences in associative recall scores corrected for item recall. For corrected object–location associative recall, a repeated measures ANOVA was conducted with one between-subjects variable (groups: control vs. aMCI) and one within-subjects variable (trials: 1, 2, 3, and delayed). For corrected symbol–symbol associative recall, we used a t test to assess group differences. To provide descriptive information, we also examined main effects and post hoc paired comparisons or t tests of individual variables. In addition, we created receiver-operating characteristic (ROC) curves and examined their coordinates to determine cutoff scores for each task that produced the most equivalent sensitivity and specificity values for identifying aMCI.

Results

Scores obtained by the two groups on the targeted measures of item and of associative recall are presented in Table 2. As a measure of effect size for each variable, Cohen's d is provided.

Object–Location Recall

A comparison of item and of raw associative recall scores shows a significant group difference favoring control participants, $F(1, 57) = 52.14$, $p < .001$, $\eta_p^2 = .48$, and a significant main effect of recall type, with lower scores on item recall than on raw associative recall, $F(1, 57) = 386.60$, $p < .001$, $\eta_p^2 = .87$. Of importance was a significant interaction between group and recall type, $F(1, 57) = 30.41$, $p < .001$, $\eta_p^2 = .35$. The interaction reflects significant group differences on both recall types that were greater for raw associative recall, $F(1, 57) = 77.22$, $p < .001$, $\eta_p^2 = .58$, than for item recall, $F(1, 57) = 17.69$, $p < .001$, $\eta_p^2 = .24$.

There was also a main effect of trial, with higher scores on later trials, $F(3, 171) = 96.52$, $p < .001$, $\eta_p^2 = .63$, and an interaction between group and trial, $F(3, 171) = 10.03$, $p < .001$, $\eta_p^2 = .15$. Post hoc tests showed that, for both groups, scores increased significantly over the three learning trials (all ps $< .002$). An examination of the scores and effect sizes in Table 2 shows that the Group × Trial interaction was due to a greater learning slope in the control group than in the aMCI group, which resulted in larger group differences on the later learning trials and on the delayed trial. There was no three-way interaction between group, recall type, and trial, $F(3, 171) = 1.16$, $p = .32$, $\eta_p^2 = .02$.

We reran these analyses using our more lenient scoring system, which allotted partial credit for objects and for object–location pairs that were close but not completely accurate. These analyses resulted in the same pattern of findings for all main effects and interactions.

On the measure of object–location associative recall corrected for item recall, there was a main effect of group favoring control participants, $F(1, 55) = 13.99$, $p < .001$, $\eta_p^2 = .20$. (Two partic-

Table 2
Mean Scores and Standard Deviations for Item and Associative Recall

Recall type	Control (n = 30) *M*	Control (n = 30) *SD*	aMCI (n = 29) *M*	aMCI (n = 29) *SD*	*d*
Item recall					
Object recall					
Trial 1	1.1	1.0	0.6	0.7	0.58
Trial 2	1.9	1.4	1.0	0.8	0.79
Trial 3	3.0	1.3	1.6	1.4	1.07
Delay	2.4	1.3	1.1	1.3	1.09
Symbol recall	7.1	1.3	5.0	1.5	1.53
Raw associative recall					
Object–location recall					
Trial 1	3.1	1.5	1.6	1.1	1.17
Trial 2	5.1	0.9	2.8	1.2	2.15
Trial 3	5.5	0.9	3.2	1.2	2.29
Delay	5.5	0.9	2.7	1.7	2.17
Symbol–symbol recall	5.5	1.7	2.0	1.8	1.98
Corrected associative recall					
Object–location recall					
Trial 1	0.84	0.23	0.72	0.37	0.38
Trial 2	0.96	0.11	0.81	0.23	0.89
Trial 3	0.97	0.10	0.82	0.19	1.02
Delay	0.98	0.10	0.77	0.27	1.13
Symbol–symbol recall	0.77	0.19	0.39	0.37	1.34

Note. Item scores ranged from 0 to 6 for object recall and 0 to 9 for symbol recall. Raw associative recall scores had the same ranges. Corrected associative recall scores ranged from 0 to 1. aMCI = amnestic mild cognitive impairment; d = Cohen's d as a measure of effect size.

ipants with aMCI were dropped from these analyses because no items were recognizable on one of the learning trials.) There was a main effect of trial, $F(3, 165) = 4.86$, $p = .003$, $\eta_p^2 = .08$, but no interaction between group and trial, $F(3, 165) = 1.40$, $p = .245$, $\eta_p^2 = .03$. Post hoc tests showed that for the combined groups, the first learning trial was lower than the other trials (all ps $< .006$), and there were no significant differences between the other trials (all ps $> .08$).

Symbol–Symbol Recall

A comparison of item and of raw associative recall scores showed a significant overall group difference favoring control participants, $F(1, 57) = 62.22$, $p < .001$, $\eta_p^2 = .52$, and a significant main effect of recall type, with higher scores on item recall than on raw associative recall, $F(1, 57) = 121.81$, $p < .001$, $\eta_p^2 = .68$. Of importance was a significant interaction between group and recall type, $F(1, 57) = 10.22$, $p = .002$, $\eta_p^2 = .15$. The interaction reflects significant group differences on both recall types that were greater for raw associative recall, $t(57) = 7.62$, $p < .001$, $d = 1.98$, than they were for item recall, $t(57) = 5.93$, $p < .001$, $d = 1.53$.

Consistent with this, an analysis of symbol–symbol associative recall corrected for item recall showed a significant group difference favoring control participants, $t(57) = 4.99$, $p < .001$.

Although the control group was faster than the aMCI group in pairing the symbols during the encoding phase (see Digit Symbol coding scores in Table 1), the better recall in the control group was not due to more exposures to the symbol–symbol pairs. In both groups, few participants were fast enough to continue past the fourth row. The average (mean, median) number of trials completed was equivalent in the aMCI group (73.1, 73.0) and in the control group (74.0, 73.0).

Sensitivity and Specificity

Sensitivity and specificity were calculated separately for each task. For the object–location task, we calculated a total score by considering all four trials together. For the control and the aMCI groups, respectively, the mean and the standard deviation were 8.4 (4.0) and 4.3 (3.6) for the total item (i.e., object) recall scores, were 19.2 (3.4) and 10.3 (4.4) for the total raw object–location associative recall scores, and were .95 (.10) and .77 (.18) for the total corrected associative recall scores.

ROC curves for both memory tasks are presented in Figure 1. For both the object–location and the symbol–symbol task scores, the area under the ROC curve was higher for the raw associative recall scores (.93 and .91, respectively) than it was for the corrected associative recall scores (.80 and .83, respectively) or for the item recall scores (.79 and .86, respectively). This finding indicates that sensitivity and specificity will be highest for raw associative recall, and this was the measure we used for our calculations. For both associative recall tasks, the raw scores were not highly correlated with age in the control group; their small effect sizes, $r(28) = -.25$ and $-.26$, were not significant with our sample size of 30 (ps = .18 and .16). This is perhaps not surprising, given range restrictions due to the narrow age span of 66–87 years and the fact that most participants were high functioning. Because of this finding, cutoff scores for calculating sensitivity and specificity were not age corrected.

Cutoff scores for each task were selected as those that produced the most equivalent sensitivity and specificity scores. The cutoff score for object–location associative recall was 14.5. This score showed a sensitivity of 86% (i.e., 25 of 29 participants with aMCI scored below the cutoff) and a specificity of 97% (i.e., 29 of 30 control participants scored above the cutoff). The overall accuracy of classifying participants with aMCI and control participants was 92% (95% confidence interval = 84%–99%). For symbol–symbol associative recall, the cutoff score was 3.5. This score showed a sensitivity of 76% (i.e., 22 of 29 participants with aMCI scored below the cutoff) and a specificity of 90% (i.e., 27 of 30 control participants scored above the cutoff). The overall accuracy of classification was 83% (95% confidence interval = 74%–93%). Measures of item recall produced lower sensitivity and specificity values. For object item recall, these values were 69% and 67%, respectively. For symbol item recall, the sensitivity of 79% was similar to that of associative recall, but the specificity of 70% was notably lower.

Discussion

We measured item and associative memory within the same episodic memory tests among participants with aMCI and matched control participants. As hypothesized, we found an associative

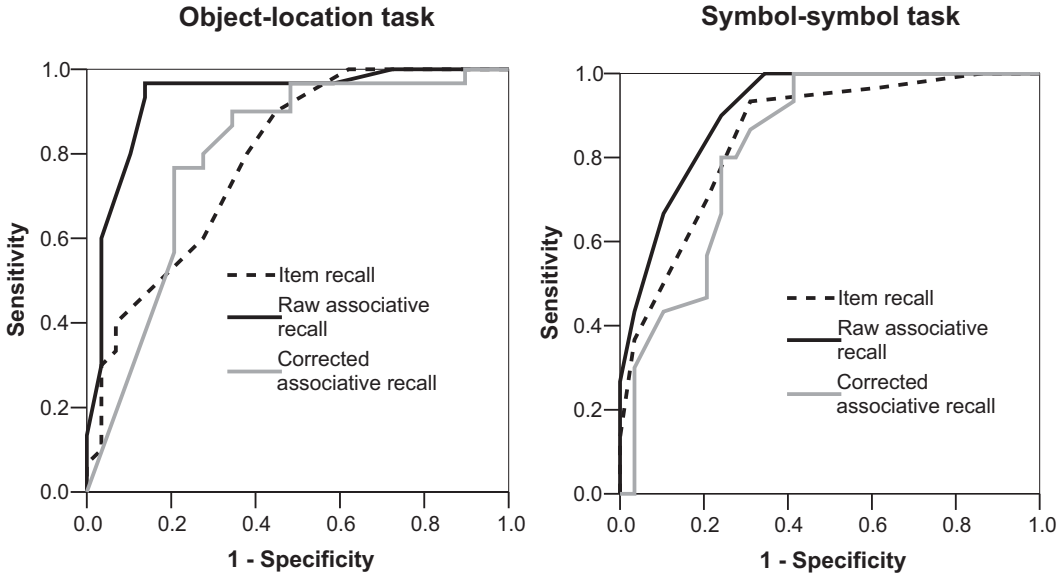

Figure 1. Receiver-operating characteristic curves plotting sensitivity and specificity values for item recall and for associative recall.

memory impairment in aMCI above and beyond the known item memory impairment. That is, our aMCI group performed worse than did the control group in item recall of objects and of symbols; this is not surprising, given that aMCI is classified on the basis of item memory. Significantly, however, there were greater group differences in associative recall of object–location and of symbol–symbol pairs than in item recall, both when we examined them using interactions and when we used a measure of associative recall that controls for item recall. The finding of overall memory impairment with particularly impaired associative memory is consistent with the early, regionally specific atrophy of the hippocampus and entorhinal cortex in aMCI (see Masdeu et al., 2005), given that these regions are known to be important for memory in general and have a particularly critical role in associative memory.

The same pattern of findings was obtained on both of the recall tasks, which differed in several respects. One task required the intentional formation of associations between different types of information (i.e., objects and their locations) across three presentation trials and four recall trials. The other task involved incidental formation of associations between similar types of information (i.e., symbols) after 4–9 continuous presentations of each pair and a single recall trial. Associative recall scores from the two tasks produced similar overall accuracy rates for discriminating individuals with aMCI and for healthy older adults. The fact that we obtained the same findings on two diverse tasks provides preliminary evidence that the associative memory impairment obtained is a generalizable finding across different test stimuli and procedures.

On the object–location task, associative recall in the control group approached ceiling-level performance (i.e., raw score of 6, corrected score of 1.0) after the first trial (see Table 2). This made it statistically more difficult to find group differences and interactions, and we likely would have found even larger group differences had this ceiling effect not been present. Clearly, even with this psychometric limitation, the group differences were sufficiently robust for detection. The symbol–symbol recall task, on the other hand, did not show a ceiling effect, and performance on this task showed the same general pattern of group differences.

We provide preliminary information about the clinical usefulness of calculating associative memory scores from standardized tests of object–location recall (i.e., BVMT–R) and symbol–symbol recall (i.e., Digit Symbol incidental recall) as part of the neuropsychological assessment of possible aMCI. Our ROC curve analyses (i.e., areas under the curve) indicated numerically better classification of individuals to groups when we used measures of associative recall as opposed to measures of item recall. When we used specific cutoff scores, our associative recall tasks correctly classified 76% and 86% of the aMCI group and 90 and 97% of the control group on the symbol–symbol and the object–location tasks, respectively. These measures of sensitivity and specificity were notably higher than were similar measures calculated with item recall scores, with the exception of sensitivity of item recall of symbols, which was similar to the sensitivity of associative recall. Thus, on the symbol–symbol task, the benefit of examination of associative recall over item recall comes primarily in terms of specificity or of accurate classification of controls.

Our estimates of sensitivity and of specificity were derived from a sample consisting of approximately equal numbers of individuals with and without aMCI. This 50% prevalence rate may be representative of some clinic samples but is much higher than the prevalence of aMCI in the general population of older adults (i.e., 3%–5%; Fisk et al., 2003; Hänninen et al., 2002). Because lower prevalence rates decrease positive predictive values, the sensitivity and the specificity of these scores would be lower when samples were drawn from the general population. Clearly, these two memory tasks would not take the place of a full cognitive assessment, but including measures of associative recall could increase the accurate detection of aMCI in selected samples.

In conclusion, we present data consistent with the idea that, because of early neuroanatomical changes in the hippocampus and entorhinal cortex in aMCI, the ability to integrate associative information in memory may be the earliest cognitive change in the evolution of Alzheimer's dementia. Moreover, our results provide preliminary evidence in support of the use of associative memory testing in clinical evaluations aimed at identifying individuals with aMCI. Our ongoing research focuses on recognition (rather than recall) of associative information. Because associative recall is limited by the number of items recalled, the use of associative recognition paradigms will permit us to examine memory for all items, not just those explicitly recalled.

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