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Stability of Different Subtypes of Mild Cognitive Impairment among the Elderly over a 2- to 3-Year Follow-Up Period

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Key Words
Cognitive subtypes · Mild cognitive impairment · Longitudinal prediction · Alzheimer's disease

Abstract
Background/Aims: To investigate the longitudinal stability and progression of different subtypes of mild cognitive impairment (MCI) in older adults. ***Methods:*** We classified 217 individuals with no cognitive impairment (NCI), amnestic MCI (aMCI) based on a single test (aMCI-1) or multiple tests (aMCI-2+), nonamnestic MCI (naMCI) based on a single test (naMCI-1) or multiple tests (naMCI-2+), or amnestic + nonamnestic MCI (a+naMCI), using their baseline neuropsychological test scores, and performed annual follow-up evaluations for up to 3 years. ***Results:*** None of the subjects with aMCI-2+ reverted to normal during follow-up, with 50% of these subjects remaining stable and 50% worsening over time. Similarly, less than 20% of subjects with aMCI-2+ and a+naMCI reverted to NCI during the follow-up period, whereas 50% of aMCI-1 and 37% with naMCI-1 reverted to NCI during this same period. ***Conclusion:*** Reversion to NCI occurs much more frequently when the diagnosis of MCI is based on the results of a single neuropsychological test than when it is based on the results of more memory tests. In epidemiological studies and clinical trials the diagnosis of MCI will likely be more stable if impairment on more than one test is required for amnestic and/or nonamnestic domains.

Introduction

Mild cognitive impairment (MCI), which is an intermediate state between normal cognition and dementia, is often considered to be a prodromal phase of various forms of progressive dementing disorders, such as Alzheimer's disease (AD), Lewy body disease, frontotemporal dementia and vascular dementia. A number of clinic-based and epidemiological studies have found that a diagnosis of MCI reverts to a state of no cognitive impairment (NCI) on follow-up evaluation in up to 40% of cases [1]. The ability to predict the likelihood of progression of MCI to dementia (of any etiology) has major implications for research in the field of MCI, especially with respect to the design of primary and secondary pre-

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vention trials using pharmacological and nonpharmacological methods.

The neuropsychological features that may predict which MCI subjects are likely to remain impaired versus those likely to progress to dementia include the severity of impairment on memory tests and the presence of impairment on both amnestic [1–5] and nonamnestic measures [6–13]. Alexopoulos et al. [14] found that 25% of subjects with amnestic MCI (aMCI), 38% with nonamnestic MCI (naMCI) and 54% with combined amnestic and nonamnestic MCI (a-naMCI) progressed to dementia within a 3.5-year period. However, Rountree et al. [15] observed no difference in rates of progression to dementia in a 4-year period for aMCI (56%) and naMCI (52%). More recently, Manly et al. [16] found that impairment in more than one cognitive domain was most predictive of progression from MCI to AD over a 4.5-year follow-up period.

The diagnosis of aMCI or naMCI is generally based on scores on cognitive tests that are at least 1.5 SD below age- and education-corrected norms on a neuropsychological test. The number of tests in the domain in which such impairment is discovered and the severity of impairment have not been typically used to further categorize MCI. However, the number of neuropsychological tests used to classify impairment in the amnestic and nonamnestic realms may determine the accuracy of prediction of likelihood of progression to dementia. Further, the specific types of measures used (e.g., list-learning memory test vs. those that assess recall of stories or visual designs) may also affect the accuracy of prediction of likelihood of progression to dementia.

Apart from neuropsychological measures, factors that may predict a high rate of progression of MCI to dementia include the subjects' age (older subjects are more likely to progress) and the presence of medial temporal lobe atrophy and/or white matter hyperintensities on neuroimaging [5, 13]. Specific biomarkers in the CSF and abnormal neuropsychiatric features including psychopathology, extrapyramidal signs and gait disorders also predict the rate of progression of MCI to dementia. While the presence of comorbid anxiety predicts progression to dementia [17], neither the presence of depression nor anxiety has been found to predict the likelihood of reversion to a normal cognitive state [5, 18]. Subjects diagnosed with MCI in community studies tend to have a higher reversion rate to normal than subjects recruited from memory disorders clinics, which, in general, have a higher baseline prevalence of AD [1] and have higher cognitive scores at baseline or have only impairment in a single cognitive domain [5, 16].

In this study, we evaluated the rate of reversion of different subtypes of MCI to NCI over a 3-year period based on the number of tests used to classify subjects as aMCI or naMCI at the baseline evaluation. We hypothesized that subjects classified as aMCI or naMCI, based on impairment on a single neuropsychological measure (i.e., aMCI-1 and naMCI-1), would have a higher rate of reversion to NCI on follow-up than subjects classified on the basis of two or more tests in any single cognitive domain (i.e., aMCI-2+ and naMCI-2+).

Methods

Community-dwelling subjects over 60 years of age (n = 433), with and without memory complaints, participated in a study investigating neuropsychological predictors of cognitive decline in the elderly. Recruitment of subjects was from two main sources: (1) a free memory screening program (65% of the sample) and (2) the Wien Center for Alzheimer's Disease and Memory Disorders in Miami Beach, Fla. (35% of the sample). All subjects were required to have global scores of 0.5 or less on the Clinical Dementia Rating (CDR) [19] scale. Of the 433 subjects initially recruited, 399 individuals had complete data from a neuropsychological battery administered in the patient's primary language (English or Spanish). The administered neuropsychological tests were as follows:

(1) Memory: Total recall of the three-trial Fuld Object Memory Evaluation (FOME) [20]; Delayed Recall of Logical Memory from the third edition of the Wechsler Memory Scale (WMS-LM-DR) [21], and Immediate Recall and Delayed Recall of Visual Reproduction from the revised edition of the Wechsler Memory Scale (WMS-VR-IR and WMS-VR-DR) [22].
(2) Language: Category Fluency (CFT) (i.e., animals, fruits, and vegetables) [23].
(3) Visuospatial skills: Block Design from the third edition of the Wechsler Adult Intelligent Scale (WAIS-BD) [24].
(4) Executive function: Controlled Oral Word Association Test (FAS) [25] and Trails B of the Trail Making Test (TMT-B) [26].

All test scores were considered relative to appropriate age- and education-normative data for English- and Spanish-speaking older adults, as described previously [27, 28]. The threshold for impairment for all amnestic and nonamnestic tests was at least 1.5 SD below the mean for that test. The subjects were not classified by their cognitive complaints on the CDR but rather by their baseline neuropsychological scores as follows:

(1) NCI: All memory and nonmemory tests deviated less than 1.5 SD below expected values relative to age- and education-related norms and the overall neuropsychological profile was deemed as normal by the neuropsychologist.
(2) Amnestic MCI based on a single test (aMCI-1): One memory measure was found to be 1.5 SD or greater below expected values, while all nonmemory measures were less than 1.5 SD below expected values.
(3) Amnestic MCI based on a multiple tests (aMCI-2+): Two or more memory measures were found to be 1.5 SD or greater

Table 1. Demographic characteristics of study sample with 2- to 3-year follow-up

	Normal cognition (n = 84)	Amnestic impairment (n = 26)	Nonamnestic impairment (n = 52)	Mixed cognitive impairment (n = 56)	F value or χ^2 value
Age, years	75.63 ± 4.9	76.73 ± 6.3	76.87 ± 5.7	77.93 ± 5.9	1.94
Education, years	14.12 ± 3.7[a]	13.96 ± 4.6[a, b]	12.42 ± 4.0[a, b]	11.71 ± 4.1[b]	4.88***
Gender: female, %	72.6	50	80.8	38.2	26.84***
Language: English, %	65.5	57.7	55.8	54.5	2.14
Follow-up, months	36.72 ± 2.1[a]	31.04 ± 6.7[b]	31.63 ± 6.7[b]	31.82 ± 5.8[b]	16.35***
Baseline MMSE	27.55 ± 2.0[a]	26.81 ± 3.0[a, b]	26.06 ± 2.4[a, b]	25.44 ± 3.3[b]	8.00***

Means with different alphabetic superscripts are statistically significant at $p \leq 0.05$ by the Scheffé procedure. *** $p \leq 0.001$.

below expected values, while all nonmemory measures were less than 1.5 SD below expected values.

(4) Nonamnestic MCI based on a single test (naMCI-1): All memory measures were found to be less than 1.5 SD below expected values, but one nonmemory measure was 1.5 SD or greater below expected values.

(5) Nonamnestic MCI based on multiple tests (naMCI-2+): All memory measures were found to be less than 1.5 SD below expected values, but two or more nonmemory measures were 1.5 SD or greater below expected values.

(6) Amnestic + nonamnestic MCI (a+naMCI): One or more memory tests and one or more nonmemory tests were found to be at least 1.5 SD or greater below expected levels.

Subjects were reevaluated annually and rediagnosed, blind to the initial diagnosis, using the same classification system for a period of up to 3 years. Those subjects who became demented did not receive additional annual follow-ups. The final diagnosis was the classification at the last available follow-up evaluation.

Statistical Analyses

A primary aim of the study was to determine the relative stability and progression of cognitive impairment among different neuropsychological subtypes diagnosed at baseline. Differences in proportions between the groups were analyzed using a series of χ^2 analyses. This allowed for comparison of (1) the percentage of subjects who either remained impaired or reverted to NCI among those whose classification of impairment was based on a single or multiple tests and (2) the percentage of subjects who remained stable versus those who transitioned to a more impaired or less impaired state among those initially classified on the basis of amnestic or nonamnestic impairment and on the basis of single or multiple tests.

A series of post hoc one-way analyses of variance was conducted to determine whether groups with a high reversion rate to a normal state at follow-up differed with regard to the baseline neuropsychological test scores. We also employed stepwise multivariate discriminant analysis and logistic regression to determine if these approaches could identify any factors that might distinguish between those subjects who evidenced deterioration versus those who remained stable or improved over time.

Results

One hundred thirty-four of 237 participants classified as cognitively impaired at baseline were followed up to a 3-year period. If subjects progressed to dementia by DSM-IV criteria at the year 2 follow-up, they were no longer followed and neuropsychological data at that time point were utilized in analyses of the data. Similarly, year 2 neuropsychological data were used for subjects who did not have neuropsychological data available for year 3. As indicated in table 1, there were no significant differences with regard to cognitively impaired groups regarding mean follow-up time.

Eighty-four of the 162 subjects, initially classified as normal, were followed for 3 years for descriptive purposes. However, since they could not by definition revert to a cognitively improved state, they were not included in χ^2 analyses that evaluated improvement, no change or improvement among those with initial cognitive impairment at baseline.

As indicated in table 1, there was no age difference between the groups. There was a preponderance of females in the NCI and naMCI groups as compared to the aMCI and a+naMCI groups. NCI subjects were followed for a longer period (approximately 3 years) than the other study groups (approximately 2.5 years) and NCI subjects had more education and higher MMSE scores than did the a+naMCI group.

As depicted in table 2, outcomes differed among groups based on the type of impairment at baseline [(χ^2; d.f. = 4) = 20.83; $p < 0.001$]. Fifty percent of those classified at baseline as aMCI-1, 37% of naMCI-1, none (0%) of aMCI-2+, 18% of naMCI-2+ and 9% of a+naMCI were reclassified as NCI on follow-up evaluation, indicating

that impairment on only single cognitive measures, particularly memory, was associated with reversion to a cognitively normal state over time. The CDR global score or sum of boxes at baseline did not differ between those who reverted to NCI versus those who did not upon follow-up evaluation among aMCI-1, naMCI-1 subjects or other groups. Further, logistic regression for 50% of aMCI-1, 37% of naMCI-1, none (0%) of aMCI-2+, and 18% of naMCI groups indicated a lack of associated demographic factors such as age, education, primary language or gender in the percentage of subjects experiencing reversion to a normal state. The 5 subjects with a+naMCI who reverted to a normal state had lower levels of educational attainment and were younger than the majority of a+naMCI participants who remained stable. A discriminant function analysis was conducted comparing all subjects who had declined to those who had remained stable. Neither age, education, gender nor other demographic variables were predictive of those subjects who evidenced decline versus those who remained stable or reverted to a less impaired cognitive state.

Further analyses among the MCI subgroups showed that the outcome among aMCI-1 was 56% less impaired, 25% unchanged and 19% more impaired, whereas among aMCI-2+, none were less impaired, 50% were unchanged and 50% were more impaired [(χ^2; d.f. = 2) = 8.7; $p < 0.02$]. Outcome among nonamnestic groups did not depend on the number of tests showing impairment. Among naMCI-1, 24% were unchanged and 29% were more impaired, whereas among naMCI-2+, 55% were unchanged and 27% were more impaired on follow-up [(χ^2; d.f. = 2) = 4.3; p = 0.18]. Since there were no differences in age, education, gender and primary language among subjects with one amnestic or nonamnestic impairment versus those persons with more than one such impairment, the obtained frequencies appeared to be related solely to differences in the initial cognitive state rather than reflecting any effect of baseline demographic characteristics. The frequency of progression to a CDR score of 1.0 or greater (indicative of dementia) was 1% for NCI, 0% for aMCI-1 and naMCI-2+, 2% for naMCI-1, 20% for aMCI-2+ and 12.5% for a+naMCI.

The vast majority of the subjects with initial cognitive impairment demonstrated stability or worsening of neuropsychological status over time; half of the subjects with aMCI-1 reverted to an NCI state. Neuropsychological measures at baseline were higher for aMCI-1 subjects who reverted to NCI versus those who remained stable or worsened over time. Since demographic variables were not different among aMCI-1 subjects or naMCI-1 subjects who remained stable or who deteriorated, these were not entered as covariates in ANOVA models. Those who reverted to NCI had a lower time to completion on Trails B (92.4 ± 40.9 vs. 153.4 ± 50.1 s) [F(1,14) = 7.0; $p < 0.02$] and higher scores on WMS-VR-IR (26.5 ± 5.4 vs. 19.9 ± 5.5) [F(1,14) = 5.9; $p < 0.03$]. Among naMCI-1 subjects, predictors of reversion to NCI were higher scores on WMS-VR-IR (27.6 ± 6.7 vs. 22.7 ± 6.2) [F(1,39) = 5.8; $p < 0.03$)] and WMS-VR-DR (22.7 ± 7.9 vs. 17.9 ± 6.5) [F(1,39) = 6.1; $p < 0.02$].

Table 2. Cognitive outcome at 2–3 years' follow-up among cognitively impaired subjects

Initial cognitive classification	No cognitive impairment at follow-up, %	Impaired cognition at follow-up, %
aMCI-1 (n = 16)	50.0	50.0
aMCI-2+ (n = 10)	0	100.0
naMCI-1 (n = 41)	36.6	63.4
naMCI-2+ (n = 11)	18.2	81.8
a+naMCI (n = 56)	8.9	91.1

χ^2 (d.f. = 4) = 20.83; $p \leq 0.001$. aMCI-1, aMCI-2+, naMCI-1, naMCI-2+ and a+naMCI are defined in Methods.

Among 84 subjects diagnosed as NCI at baseline, 18% became cognitively impaired during the follow-up period (11% with naMCI-1; 2% with aMCI-1; 1% with aMCI-2+, and 4% with a+naMCI). Since the level of educational impairment was less for those who became impaired versus those who remained unimpaired, this was entered as a covariate in ANOVA models. The neuropsychological predictors of progression to some form of MCI were higher time to completion on Trails B (126.3 ± 62.9 vs. 89.9 ± 33.7 s) [F(1,79) = 11.12; $p < 0.001$] and lower WMS-VR-IR scores (22.7 ± 5.4 vs. 28.5 ± 5.2) [F(1,81) = 11.61; $p < 0.001$].

Discussion

The main objective of the current study was to examine the stability or progression of different types of neuropsychological impairment among older community-dwelling adults. Consistent with expectations, the presence of impairment in both amnestic and nonamnestic domains, as well as impairment on more than one test in a single domain, especially the memory domain, predict-

ed continuing cognitive impairment on follow-up evaluation 2–3 years later. In contrast, impairment on one memory or one nonmemory neuropsychological test was far less likely to be associated with stable or worsening cognitive impairment. One half of those subjects initially presenting with a single amnestic impairment on one test and over a third of subjects with a single nonamnestic cognitive impairment were classified as cognitively normal upon follow-up.

The occurrence of a single amnestic or single nonamnestic neuropsychological impairment at one point in time did not appear to be a particularly useful predictor of stability or progression of cognitive deficits in this study. It was also not possible to predict which aMCI-1 and naMCI-1 subjects would progress or remain stable based on demographic factors such as age, education or on the basis of CDR global or sum of box scores.

The finding that with amnestic impairment on two or more memory measures subjects were more likely to have stable deficits or to have progressive cognitive deficits on follow-up relative to those with impairment on only one test, is consistent with other studies. It has been demonstrated that those with more severity of impairment are more likely to worsen cognitively and to progress to dementia as compared to subjects with lesser impairment [14, 16]. In contrast, the same was not true for those with nonamnestic deficits. Subjects' impairment on multiple nonamnestic tests did not evidence a differential pattern of stability of impairment compared to subjects with only one nonamnestic test impaired.

Although initial demographic factors were not related to patterns of deterioration, we found that scores on neuropsychological tests with a visual or speed of processing component (i.e. WMS-VR, TMT-B, WAIS-BD) were higher for aMCI-1 and naMCI-1 subjects who reverted to normal versus those subjects who were unchanged or would decline. This suggests that more deleterious outcomes were associated with greater neuropsychological impairment within these subgroups. Subjects with multiple amnestic impairments or mixed amnestic and nonamnestic impairments never or rarely reverted to a cognitively normal state.

Albert et al. [6] found that only 4% of individuals with amnestic multiple domain MCI reverted to normal over a 3-year period. We have previously reported that the presence of multiple amnestic and nonamnestic deficits decreases the likelihood of a reversion to NCI [27]. Manly et al. [16] observed that in a community setting of 564 subjects initially classified as MCI, 38% of individuals with impairment in a single cognitive domain at baseline no longer met MCI criteria during an average 4.5-year follow-up.

In summary, the present study indicates that impairment on one or more tests within a specific cognitive domain predicts continuing cognitive impairment over time. The main limitation of this study is that the classification of impairment, using 1.5 SD below the mean for every test, does not guarantee equivalence in the severity of impairment across cognitive domains and tests. However, it should be noted that the findings in this study are based on commonly used neuropsychological measures that have been used in numerous studies in which a 1.5-SD cutoff for cognitive impairment has been the standard for establishing or confirming cognitive impairment. It might also be argued that amnestic and nonamnestic cases with a single versus multiple memory impairment showed a greater reversion to a normal state simply because they had less global cognitive impairment. This is unlikely, however, since post hoc tests indicated no statistically significant MMSE differences between amnestic and nonamnestic groups with single versus multiple impairments.

It might also be argued that the number of subjects in some of the groups was relatively modest and follow-up was not of sufficient duration to determine the stability or progression of cognitive impairment for all-subjects. Cognitive decline may take a quadratic rather than a linear form, so it will be important to follow these subjects over time. Our subject sample did include those who were recruited from an outpatient memory disorders clinic and those who were recruited from the-community by word of mouth. There was no statistically significant difference in outcome for subjects recruited from the memory disorders clinic versus community sources. In addition, in subgroups in which there were a sufficient number of subjects from each referral source to allow evaluation of the impact of the referral source there was no effect on longitudinal outcome. However, larger sample sizes would allow a determination of the generalizability of the results of the present study.

In clinical and research settings it is important to determine the likelihood of progression, stability or reversal of cognitive deficits among older adults. The findings in this study suggest that multiple impairments on memory tests or on both memory and nonmemory tests are associated with poorer outcomes, whereas single amnestic or single nonamnestic deficits appear much less predictive of permanent or progressive deficits, even

after accounting for the initial CDR score. Future studies should examine other possible contributing factors (e.g., neuroimaging findings, subject's clinical history) that could increase accuracy of prediction of outcome in individuals with amnestic or nonamnestic impairment.

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