ORIGINAL ARTICLE

Functional Impairment in Elderly Patients With Mild Cognitive Impairment and Mild Alzheimer Disease

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Context: The original mild cognitive impairment (MCI) criteria exclude substantial functional deficits, but recent reports suggest otherwise. Identifying the extent, severity, type, and correlates of functional deficits that occur in MCI and mild Alzheimer disease (AD) can aid in early detection of incipient dementia and can identify potential mechanistic pathways to disrupted instrumental activities of daily living (IADLs).

Objectives: To examine the number, type, and severity of functional impairments and to identify the clinical characteristics associated with functional impairment across patients with amnestic MCI (aMCI) and those with mild AD.

Design: Study using baseline data from the Alzheimer's Disease Neuroimaging Initiative.

Setting: Multiple research sites in the United States and Canada.

Patients: Samples included 229 control individuals, 394 patients with aMCI, and 193 patients with AD.

Main Outcome Measure: The 10-item Pfeffer Functional Activities Questionnaire (FAQ) assessed function.

Results: Informant-reported FAQ deficits were common in patients with aMCI (72.3%) and AD (97.4%) but were rarely self-reported by controls (7.9%). The average severity per FAQ deficit did not differ between patients with aMCI and controls; both were less impaired than patients with AD ($P<.001$). Two FAQ items (remembering appointments, family occasions, holidays, and medications and assembling tax records, business affairs, or other papers) were specific (specificity estimate, 0.95) in differentiating the control group from the combined aMCI and AD groups (only 34.0% of patients with aMCI and 3.6% of patients with AD had no difficulty with these 2 items). The severity of FAQ deficits in the combined aMCI and AD group was associated with worse Trail Making Test, part A scores and smaller hippocampal volumes ($P<.001$ for both). Within the aMCI group, functionally intact individuals had greater hippocampal volumes and better Auditory Verbal Learning Test 30-minute delay and Trail Making Test, part A ($P<.001$ for each) scores compared with individuals with moderate or severe FAQ deficits. Patients with a high number of deficits were more likely to express the apolipoprotein ε4 allele (63.8%) compared with patients with no (46.8%) or few (48.4%) functional deficits.

Conclusions: Mild IADL deficits are common in individuals with aMCI and should be incorporated into MCI criteria. Two IADLs—remembering appointments, family occasions, holidays, and medications and assembling tax records, business affairs, or other papers—appear to be characteristic of clinically significant cognitive impairment. In patients with aMCI, impairment in memory and processing speed and greater medial temporal atrophy were associated with greater IADL deficits.

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FUNCTIONAL IMPAIRMENT IS A required criterion for the diagnosis of most major neuropsychiatric disorders, including dementia.[1,2] Decreases in functional ability in elderly individuals can adversely affect patients and caregivers and are associated with institutionalization.[3-8] Functional decline can occur as a result of several factors, including medical illness,[9,10] mood disorders,[11-14] and cognitive impairment.[15-17] Identifying the extent and severity of functional deficits that typically occur in each disorder can aid in early diagnosis, help in estimating prognosis, and improve treatment strategies.[18]

The term mild cognitive impairment (MCI)[19,20] is used to identify a stage of impairment that demonstrates considerable heterogeneity and is displayed by individuals at high risk for conversion to dementia.[19] The MCI criteria require reports of subjective memory deficits and a score 1.5 SDs below age-adjusted norms on a memory test (amnestic MCI [aMCI]) and require no "substantial interference with work, usual social activities, or other activities of daily living."[20] However, research has shown that individuals with

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Table 1. Baseline Characteristics for the Control, aMCI, and AD Groups[a]

Characteristic	Control Group (n=229)	aMCI Group (n=394)	AD Group (n=193)
Demographic			
Age, y	75.90 (5.00)	74.86 (7.40)	75.33 (7.48)
Educational level, y	16.04 (2.90)	15.65 (3.04)	14.71 (3.13)[c,d]
Sex, No. M/F (% F)	119/110 (48.0)	256/138 (35.0)[b]	102/91 (47.2)[d]
Neuropsychological scores			
MMSE	29.11 (1.00)	27.04 (1.78)[b]	23.34 (2.06)[c,d]
Logical Memory II, immediate recall	13.78 (3.47)	7.11 (3.16)[b]	4.07 (2.91)[c,d]
Logical Memory II, delayed recall	12.97 (3.57)	3.81 (2.66)[b]	1.27 (1.90)[c,d]
Trail Making Test, part A, s	36.45 (13.19)	44.85 (22.83)[b]	67.50 (36.43)[c,d]
Trail Making Test, part B, s	89.21 (44.26)	130.85 (73.77)[b]	197.95 (87.09)[c,d]
Digit Symbol	45.75 (10.20)	36.84 (11.12)[b]	26.94 (12.81)[c,d]
AVLT 30-min delay	7.39 (3.72)	2.84 (3.30)[b]	0.74 (1.62)[c,d]
Brain volumes, cm^3			
Hippocampal	7.22 (0.89)	6.35 (1.07)[b]	5.60 (1.05)[c,d]
Entorhinal cortex	3.80 (0.65)	3.29 (0.75)[b]	2.73 (0.71)[c,d]
CDR scores			
CDR sum of boxes	0.03 (0.12)	1.60 (0.89)[b]	4.30 (1.64)[c,d]
Median (range)	0 (0-0.50)	1.50 (0-5.00)	4.00 (1.00-9.00)
Function measure: FAQ			
Severity of deficits			
Mean	0.14 (0.60)	3.84 (4.47)[b]	12.99 (6.84)[c,d]
Median (range)	0 (0-6.00)	2.00 (0-21.00)	12.00 (0-30.00)
No. of deficits			
Mean	0.10 (0.38)	2.70 (2.69)[b]	6.97 (2.53)[c,d]
Median (range)	0 (0-2.00)	2.00 (0-10.00)	7.00 (0-10.00)
Severity per deficit			
Mean	1.25 (0.52) (n=18)	1.34 (0.43) (n=285)	1.78 (0.50) (n=188)[c,d]
Median (range)	1.00 (1.00-3.00)	1.17 (1.00-3.00)	1.75 (1.00-3.00)

Abbreviations: AD, Alzheimer disease; aMCI, amnestic mild cognitive impairment; AVLT, Auditory Verbal Learning Test; CDR, Clinical Dementia Rating scale; FAQ, Pfeffer Functional Activities Questionnaire; MMSE, Mini-Mental State Examination.

[a] Data are presented as mean (SD) unless otherwise indicated. Neuropsychological scores are raw scores.

[b] Significant difference in post hoc comparisons between control individuals and patients with aMCI ($P<.01$).

[c] Significant difference in post hoc comparisons between controls and patients with AD ($P<.01$).

[d] Significant difference in post hoc comparisons between patients with aMCI and patients with AD ($P<.01$).

aMCI commonly have deficits in instrumental activities of daily living (IADLs).[21-28] Our group reported that in participants with MCI, baseline informant-reported functional deficits on the Pfeffer Functional Activities Questionnaire (FAQ)[25] were associated with a 4-fold increase in conversion to dementia during long-term follow-up.[29]

The goals of this study were to examine the number, type, and severity of functional impairments across patients with aMCI and those with mild Alzheimer Disease (AD), comparing them with healthy, cognitively intact control individuals; to identify the clinical characteristics that explain functional impairment in individuals with aMCI and mild AD; and to explore the neuropsychological and neuroanatomical profiles in relation to functional deficits in individuals with aMCI. Baseline data from the Alzheimer's Disease Neuroimaging Initiative (ADNI)[30] were used to address these goals.

METHODS

ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

Data used for preparation of this article were obtained from the ADNI database (http://adni.loni.ucla.edu/), a project launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, and various private pharmaceutical companies and nonprofit organizations as a $60 million, 5-year public-private partnership. The primary goal of the ADNI is to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

STUDY PARTICIPANTS

Data obtained from the ADNI in October 2009 were selected from screening or baseline visits of all participants who completed evaluations that included the key variables of interest to this report. The sample comprised 229 cognitively intact older adults, 394 individuals with aMCI, and 193 individuals with mild AD. The demographic, neuropsychological, and functional characteristics for these 3 groups are listed in **Table 1**.

Participants were enrolled if they were aged 55 to 90 years, had at least 6 years of educational attainment, spoke English or Spanish as their primary language, agreed to undergo longitudinal follow-up and neuroimaging tests, and had a study partner to monitor adherence. Cognitively intact participants had Mini-Mental State Examination (MMSE)[31] scores between 24 and 30, Clinical Dementia Rating (CDR)[32] scores of 0 (no dementia), and no significant memory concerns. The aMCI participants were classified as having single-domain or multidomain aMCI according to the Petersen criteria[19]: a CDR score of 0.5, MMSE scores between 24 and 30, 1 or more memory

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Table 2. Functional Deficits Per Item for the Control, aMCI, and AD Groups With Cochran-Armitage Linear Trend Test Results[a]

FAQ Item	Control Group, No. (%) (n=229)	aMCI Group, No. (%) (n=394)	AD Group, No. (%) (n=193)	Trend Test *z* Score
1. Writing checks, paying bills, or balancing checkbook	5 (2.2)	133 (33.8)	170 (88.1)	17.97
2. Assembling tax records, business affairs, or other papers[b,c]	4 (1.7)	169 (42.9)	176 (91.2)	18.47
3. Shopping alone for clothes, household necessities, or groceries	1 (.4)	73 (18.5)	137 (71.0)	16.19
4. Playing a game of skill such as bridge or chess or working on a hobby[c]	1 (.4)	86 (21.8)	119 (61.7)	14.27
5. Heating water, making a cup of coffee, or turning off the stove	0	30 (7.6)	53 (27.5)	9.14
6. Preparing a balanced meal	1 (.4)	78 (19.8)	125 (64.8)	14.98
7. Keeping track of current events[c]	1 (.4)	90 (22.8)	130 (67.4)	15.23
8. Paying attention to and understanding a television program, book, or magazine[c]	1 (.4)	84 (21.3)	114 (59.1)	13.83
9. Remembering appointments, family occasions, holidays, and medications[b,c]	8 (3.5)	216 (54.8)	175 (90.7)	18.01
10. Traveling outside the neighborhood, driving, or arranging to take public transportation[c]	2 (.9)	103 (26.1)	146 (75.6)	16.39

Abbreviations: AD, Alzheimer disease; aMCI, amnestic mild cognitive impairment; FAQ, Pfeffer Functional Activities Questionnaire.
[a] $P < .001$ for all items.
[b] Identified as a subset of functional items that reliably differentiates control individuals from a combined aMCI and AD group.
[c] Identified through bootstrapping techniques as the most reliable subset of functional items that differentiates controls from aMCI.

problems as verified by an informant, a memory score classified as abnormal (1.5 SDs below the age-adjusted cutoff) on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale–Revised,[33] and absence of a diagnosis of dementia as made by onsite physicians. Participants with mild AD had a CDR score of 0.5 or 1.0, had MMSE scores between 20 and 26, and met criteria for probable AD.[2] All participants had a Geriatric Depression Scale[34] score of less than 6 (no significant depression) and a modified Hachinski score[35] of 4 or less (no significant vascular impairment, including hypertension, stroke, and/or neurologic signs or symptoms). A more detailed account of the inclusion and exclusion criteria is available at http://www.adni.loni.ucla.edu/about/about-the-study/.

NEUROPSYCHOLOGICAL ASSESSMENT

At baseline, participants underwent an extensive neuropsychological battery. We selected specific cognitive measures a priori because they assess cognitive functions shown in prior research[15-17] to correlate with functional impairment; these measures include the Trail Making Test, parts A and B;[36] the Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale–Revised;[37] and the Auditory Verbal Learning Test (AVLT).[38]

FUNCTIONAL ASSESSMENT

The FAQ[25] is a 10-item IADL measure (**Table 2**). Self-reports of functional deficits were collected for controls, but informant reports were collected for the aMCI and AD groups. Each item is rated from 0 (no difficulty or independent) to 3 (dependent). Analyses classified functional impairment in 1 of 3 ways: total severity (total sum score from all 10 items; range, 0-30), total number of deficits (total sum score of dichotomized items, with 0 indicating no difficulty and 1 indicating any difficulty; range, 0-10),[26] and average severity per deficit (total severity divided by total number of deficits). The means and standard deviations for each and selected medians (with ranges) are listed in Table 1.

IMAGING VOLUME DERIVATIONS

Hippocampal (derived by adding right and left hippocampal volumes), entorhinal, and intracranial volumes were downloaded from postprocessed image analysis using FreeSurfer, version 4.3.0, by researchers at the University of California, San Francisco; the data are available at http://adni.loni.ucla.edu/. We used the cross-sectional baseline data recommended for use by the ADNI investigators. A detailed account of the volume derivation process is located at http://www.loni.ucla.edu/twiki/bin/view/ADNI/ADNIPostProc.

STATISTICAL ANALYSES

Analysis of variance or χ^2 tests were used to detect group differences for continuous and categorical variables. Analysis of covariance was used for group comparison on all brain volumetric measures with intracranial volume as the covariate. A stepwise selection procedure for item selection from a unidimensional scale was used to identify a subset of FAQ items that best differentiated controls from patients with aMCI.[39] To obtain a reliable subset of items classifying the 2 groups with accuracy similar to that of the full scale, we applied the procedure with a significance criterion of .05 for item contribution to the subset classification accuracy to 500 bootstrap samples, including the item response data of the controls and patients with aMCI randomly sampled with replacement from the study sample, choosing the items most frequently selected (included in >50% of bootstrap samples). The area under the receiver operating characteristic curve was used to compare the usefulness of the identified FAQ subset with the full 10-item FAQ in differentiating controls and patients with aMCI. In addition, for potential clinical applicability, the sensitivity and specificity of a 2-item subset were assessed. Linear regression models were used to examine the relationship between the FAQ and demographic, physical, depression, neuropsychological, and neuroimaging characteristics in a combined aMCI and AD group and in the aMCI group only. Within the aMCI group, linear models were used to calculate the covariate-adjusted means of the neuropsychological and neuroimaging variables identified in the linear regression analysis across the 3 categorized ordinal classes of number of FAQ deficits and severity of FAQ deficits (a functionally intact group and the functionally impaired group split into categories based on number and severity of functional deficits). In post hoc group comparisons, Bonferroni correction on the false-positive error rate was used to account for multiple comparisons. Multinomial logistic regression models for the trichotomized functional severity and number of func-

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tional deficits scores were used to assess the simultaneous effect of the neuropsychological, genetic, and neuroimaging variables identified in the linear regression analysis.

RESULTS

EXTENT AND SEVERITY OF FUNCTIONAL DEFICITS ACROSS COGNITIVELY IMPAIRED GROUPS

Demographic, neuropsychological, and functional variables (Table 1) differed significantly by group with the exception of age. Item distributions among the 10-item FAQ showed an increased number of functional deficits across study groups (F_{2813}=494.99, $P<.001$): 7.9% of controls, 72.3% of informants for the aMCI group, and 97.4% of informants for the mild-AD group reported 1 or more functional deficit. In the AD group, 87.0% of informants reported 4 or more total deficits. As indicated in Table 1, total severity scores of functional impairment significantly increased across groups (F_{2813} = 438.60, $P<.001$). The average level of severity per deficit did not differ, however, between the control (mean [SD], 1.25 [0.52]) and aMCI (mean [SD], 1.34 [0.43]) groups, but the mild-AD group (mean [SD], 1.78 [0.50]) had greater average severity per functional deficit than both of the other groups (F_{2488}=56.27, $P<.001$). Informant-reported deficits in the aMCI sample were fewer and milder in severity than those reported for the mild-AD group. In fact, 78.7% of informants for the aMCI group endorsed 0 (no difficulty) or 1 (patient has difficulty but still does the task by himself/herself) on each of the 10 FAQ items; this finding contrasts with that of 25.4% to 66.3% of informants of the mild-AD group who reported a score of 2 (requires assistance) or 3 (dependent) for 8 of the 10 FAQ items (only 12.4% and 15.5% of informants from the mild-AD group reported a score of 2 or 3 on item 5 [heating water, making a cup of coffee, turning off the stove] and item 8 [paying attention to and understanding a television program, book, or magazine], respectively).

Table 2 lists the percentage of deficits by item within each diagnostic group. Although few controls self-reported any functional deficits on the individual FAQ items, informants for the aMCI group most commonly reported deficits for item 1 (writing checks, paying bills, or balancing checkbook; 33.8%), item 2 (assembling tax records, business affairs, or other papers; 42.9%), and item 9 (remembering appointments, family occasions, holidays, and medications; 54.8%). These 3 items increased markedly in frequency on the Cochran-Armitage linear trend tests from controls to patients with aMCI to patients with AD, but the frequency of other items, such as item 5 (heating water, making a cup of coffee, turning off the stove), increased less so across groups (Table 2). To identify those items that most commonly differentiated the control and aMCI groups, an item selection process was used. The subset selected had a median size of 6; the 6-item subset (items 2, 4, 7, 8, 9, and 10) was the most frequently selected in the 500 bootstrap samples and differentiated the control and aMCI groups with classification accuracy (0.6998) similar that of the full 10-item scale (0.7067).

The evaluation of 6 IADLs (including the ability to assemble tax records, business affairs, or other papers; to play a game of skill such as bridge or chess or work on a hobby; to keep track of current events; to pay attention to and understand a television program, book, or magazine; to remember appointments, family occasions, holidays, and medications; and to travel outside the neighborhood, drive, or arrange to take public transportation) does not represent a marked time savings compared with the 10-item FAQ for use in clinical practice. Two of these 6 items were selected in each of the 500 bootstrap samples. These 2 items (assembling tax records, business affairs, or other papers; and remembering appointments, family occasions, holidays, and medications) were highly effective in discriminating the control group from a combined aMCI and mild-AD group. Although only 3.5% (n=12) of healthy controls reported deficits on 1 of these 2 items (no controls reported deficits in both), 66.0% of informants for the aMCI group and 96.4% of informants for the mild-AD group reported deficits on 1 of these 2 items; 85.5% of the mild-AD group had informant-reported deficits on both items. Comparing controls with the combined aMCI and AD groups, these numbers are reflected in the sensitivity (0.76 vs 0.81) and specificity (0.95 vs 0.92) estimates comparing the 2-item FAQ and 10-item FAQ, respectively, with a cut point of 1 functional deficit or more.

The control group consisted of cognitively intact older adults who used self-report assessments, thereby making it difficult to compare these rates with those reported by informants for the aMCI and AD groups. Therefore, healthy controls were excluded from subsequent analyses.

FACTORS ASSOCIATED WITH FUNCTIONAL DEFICITS IN aMCI AND MILD-AD GROUPS

The bivariate relationships in the combined aMCI and AD groups between functional impairment and demographics (age, sex, and educational level), physical health (Hachinski score, which assesses history of hypertension, stroke, and neurologic signs and symptoms), depression (Geriatric Depression Scale), brain volumes (intracranial, hippocampal, and entorhinal cortex volumes), apolipoprotein (*APOE*) ε*4* allele status (present or absent), and neuropsychological variables (Trail Making Test, parts A and B; AVLT 30-minute delay; and Digit Symbol) showed significant associations between functional impairment and brain volumes, *APOE* ε*4* status, and the neuropsychological variables ($P<.01$). Linear regression analyses in the combined aMCI and AD group were used to identify variables associated with functional impairment after controlling for all other independent variables. Three aspects of functional impairment served as outcome variables in separate analyses: total severity score, total number of deficits, and average severity per deficit score. In each regression analysis the demographic, physical health, depression, brain volume, genetic, and neuropsychological variables were entered simultaneously into the model. The independent variables explained 30.8% of

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the variance in total severity ($F_{13\,545}$ = 18.65, $P < .001$), 29.4% of the variance in total number of deficits ($F_{13\,545}$ = 17.44, $P < .001$), and 17.8% of the variance in average severity per deficit ($F_{13\,438}$ = 7.30, $P < .001$). Two independent variables were significant in each of the analyses: hippocampal volume ($P_{total\ severity} < .001$; $P_{total\ number} < .001$; $P_{severity\ per\ deficit} = .001$) and Trail Making Test, part A score ($P_{total\ severity} = .001$; $P_{total\ number} < .001$; $P_{severity\ per\ deficit} = .004$). Three other independent variables were associated with total severity and total number of deficits: age ($P_{total\ severity} = .044$; $P_{total\ number} = .008$), AVLT 30-minute delay score ($P_{total\ severity} = .004$; $P_{total\ number} < .001$), and entorhinal cortex volume ($P_{total\ severity} = .03$; $P_{total\ number} = .048$). The effect of these independent variables remained significant and the R^2 virtually unchanged when the independent variables that did not contribute to the models were excluded.

PROFILES OF INFORMANT-REPORTED FUNCTIONAL IMPAIRMENT IN THE aMCI GROUP

To identify variables uniquely associated with functional deficits in the aMCI stage, linear regression analyses were conducted with the aMCI group with total severity and total number of functional deficit scores serving as the outcome variables. As in the combined aMCI and AD analysis, the demographic, physical health, depression, brain volume, genetic, and neuropsychological variables were entered simultaneously into the model. The independent variables explained 13.3% of the variance in total severity ($F_{13\,365}$=4.29, $P < .001$) and 13.2% of the variance in total number of deficits ($F_{13\,365}$=4.28, $P < .001$). Hippocampal volume ($P_{total\ severity} = .01$; $P_{total\ number} = .03$); AVLT 30-minute delay score ($P_{total\ severity} = .04$; $P_{total\ number} = .01$); and Trail Making Test, part A score ($P_{total\ severity} = .009$; $P_{total\ number} = .005$) predicted each of the functional outcomes. Digit Symbol score predicted total severity ($P = .03$) but not total number of deficits ($P = .28$). Status regarding *APOE ε4* predicted total number of deficits ($P = .049$) but not total severity ($P = .09$). The effect of these independent variables remained significant and the R^2 virtually unchanged when the independent variables that did not contribute to the models were excluded.

To investigate these relationships further comparing individuals with aMCI who have and those who do not have functional impairment, analyses of covariance and post hoc comparisons adjusting for age, sex, and educational level (and intracranial volume in the hippocampal volume analysis) were conducted for the 6 independent variables (including age) identified as significant in the linear models (**Figure 1** and **Figure 2**). Total functional severity scores were categorized into 3 groups: functionally intact (total severity scores=0; n=109), mild (total severity scores, 1-4; n=162), and moderate to severe (total severity scores ≥5; n=123). The functionally intact and mild severity groups performed more strongly on the Trail Making Test, part A ($P < .001$), Digit Symbol test ($P < .001$), and AVLT 30-minute delay ($P_{intact} < .001$ and $P_{mild} = .001$, respectively) than the moderate to severe group;the adjusted means for the functionally intact group did not differ from the mild group on the Trail Making Test, part A ($P = .36$) and Digit Symbol test ($P = .07$) but differed on AVLT 30-minute delay ($P = .01$; Figure 1A and B). The adjusted mean hippocampal volumes in the functionally intact group were larger than those in the moderate to severe group ($P < .001$) and the mild group, although the latter did not reach significance ($P = .06$); the adjusted mean hippocampal volume for the mild group was larger than that in the moderate to severe group ($P = .02$; Figure 2A), although the difference did not reach the Bonferroni corrected significance level.

Similar analyses of covariance and post hoc comparisons (Figures 1 and 2) were conducted for total number of functional deficits categorized into 3 groups: functionally intact (total deficits, 0; n=109), few deficits (total deficits, 1-3; n=155), and high number of deficits (total deficits, ≥4; n=130). Again, the functionally intact group differed from the high deficit group regarding Trail Making Test, part A scores ($P < .001$); AVLT 30-minute delay scores ($P < .001$); and hippocampal volume ($P < .001$; Figure 1C and D and Figure 2B). A higher percentage of individuals had positive expression for the *APOE ε4* allele in the high deficit group (63.8%) compared with the functionally intact (46.8%) or few deficit (48.4%) groups.

Finally, multinomial logistic regression analyses assessed the simultaneous effect of these significant independent variables on the trichotomized functional severity and the number of functional deficit groups, with the functionally intact group serving as the reference category in each analysis with age, sex, educational level, and intracranial volume entered as covariates into each model. **Table 3** lists the odds ratios for the group comparisons in the models. These comparisons mirror the results of the post hoc analyses: the functionally intact group performed better on the Trail Making Test, part A ($P = .006$) and the AVLT 30-minute delay ($P < .001$) than the moderate to severe and high deficit groups ($P < .001$ for Trail Making Test, part A and AVLT 30-minute delay) in each logistic model; the functionally intact group also had greater hippocampal volume than the moderate to severe ($P = .02$) and high deficit ($P = .04$) groups. None of the functionally intact vs few deficit group or functionally intact vs mild severity group comparisons were significant (Table 3).

COMMENT

EXTENT AND SPECIFIC FUNCTIONAL IMPAIRMENTS ACROSS GROUPS

Functional impairment is necessary to make a diagnosis of dementia,[2] but the Petersen criteria for MCI stipulate no "substantial" functional impairments.[19,20] The present study, however, found that 72.3% of informants of individuals with aMCI reported 1 or more deficits in daily functioning compared with 97.4% with mild AD and 7.9% of self-reported healthy controls. This proportion of functional impairment in the aMCI group is consistent with previous findings identifying IADL deficits in patients with MCI.[15,17,21,22,26,28,29] The severity of these impairments, however, was mild; that is, individuals with aMCI show difficulty in IADL functioning, but this difficulty does not require the assistance of others. Only 1.8% to 21.3% of

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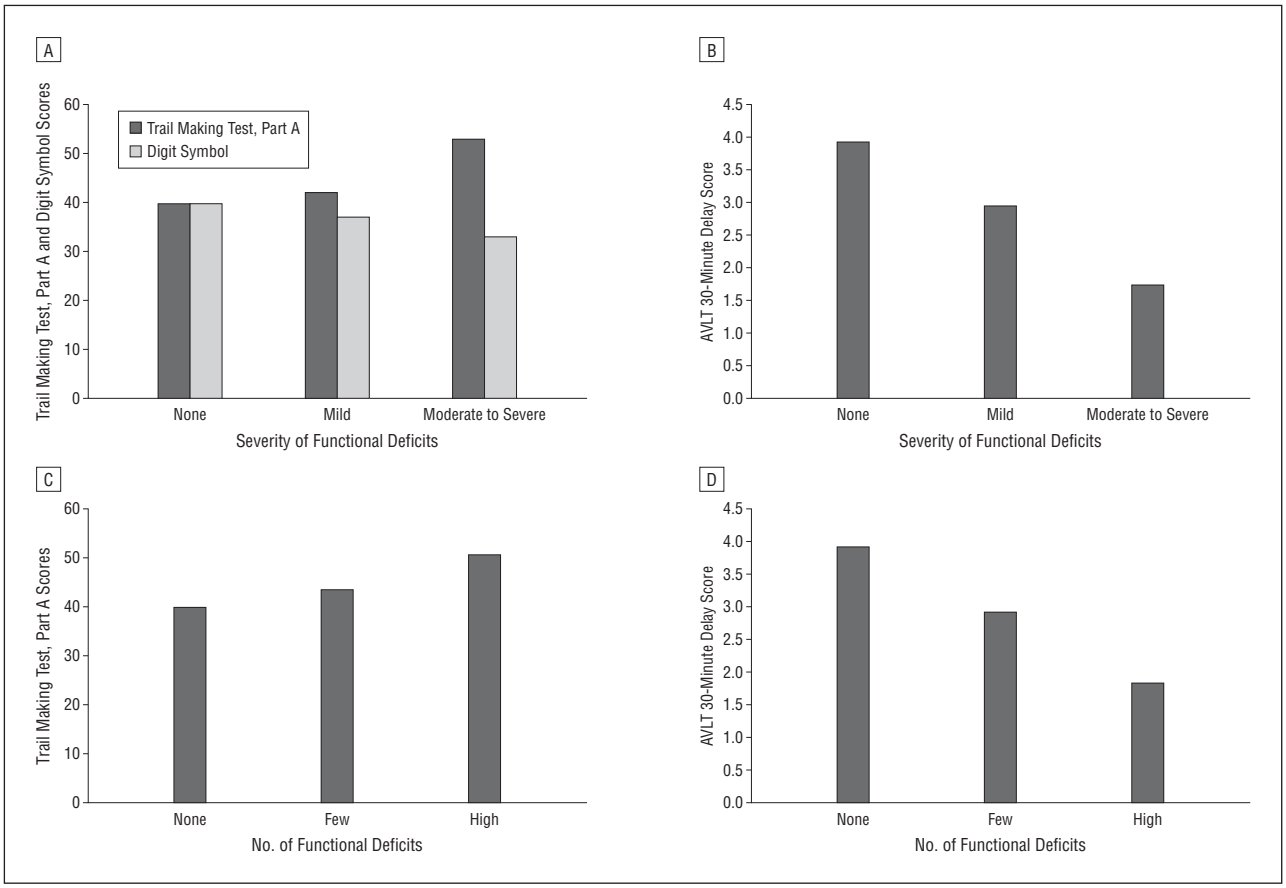

Figure 1. Post hoc adjusted mean comparisons of neuropsychological predictors of functional deficits in the amnestic mild cognitive impairment sample. Means are adjusted for age, sex, and educational level. A, Severity of functional deficits for scores on the Trail Making Test, part A and the Digit Symbol test. B, Severity of functional deficits for scores on the Auditory Verbal Learning Test (AVLT) 30-Minute Delay test. C, Number of functional deficits for scores on the Trail Making Test, part A. D, Number of functional deficits for scores on the AVLT 30-Minute Delay test. A significant difference was found in post hoc comparisons between no deficits and mild or few deficits for the severity of functional deficits and the number of functional deficits as measured by the AVLT 30-minute delay. A significant difference was found in post hoc comparisons between no deficits and moderate to severe or high deficits for all measures. A significant difference was found in post hoc comparisons between mild or few and moderate to severe or high deficits for all measures. Severity groups were defined as follows: no deficits, 0; mild severity, 1-4; and moderate to severe, 5 or more. Number of deficit groups was defined as follows: no deficits, 0; few deficits, 1-3; and high deficits, 4 or more ($P<.0167$; Bonferroni corrected).

informants reported that individuals with aMCI require assistance or were dependent per the IADLs assessed. This finding contrasts with those of patients with mild AD, of whom 12.4% to 66.3% of informants reported that those patients required assistance or were dependent per most of the IADLs assessed. Thus, physicians should be sensitive to mild informant-reported deficits at the aMCI stage, which is often a precursor to the diagnosis of dementia.

To aid physicians in the ability to detect impairment early in the dementia process, we identified 6 IADLs that distinguished controls from individuals with aMCI. Two of these items in particular, remembering appointments, family occasions, holidays, and medications and assembling tax records, business affairs, or other papers, may improve the ability of physicians to briefly identify aMCI functional impairment. These 2 items were highly specific in their ability to differentiate controls from the 2 combined cognitively impaired groups. Only 34.0% of individuals with aMCI (and 3.6% of individuals with AD) have intact informant-reported functioning on both items. These findings highlight the types of daily activities that are disrupted during different stages of cognitive impairment and specifically identified 2 daily tasks that physicians can use to differentiate controls from cognitively impaired individuals.

The results of this study support recent proposals to modify the Petersen criteria for MCI to reflect these deficits in complex instrumental functions.[40,41] Although basic activities of daily living usually remain intact in aMCI, mild IADL deficits often appear to occur in aMCI. The aMCI group in this study was rigorously defined according to the Peterson criteria for aMCI,[19] yet it still represents a heterogeneous stage of cognitive impairment. Other classification systems have been used to define cognitive impairment, and each of these systems is likely to differ in the extent and severity of IADL deficits and each identifies slightly different clinical courses and outcomes.[42] These findings represent a reminder that the MCI classification system denotes a continuum of impairment, and impairments based on the extent and severity of daily functioning can play an important role in defining where on this continuum a cognitively impaired individual can be classified. Greater functional deficits, associated with greater medial temporal atrophy, memory, and processing speed deficits, can aid practicing physi-

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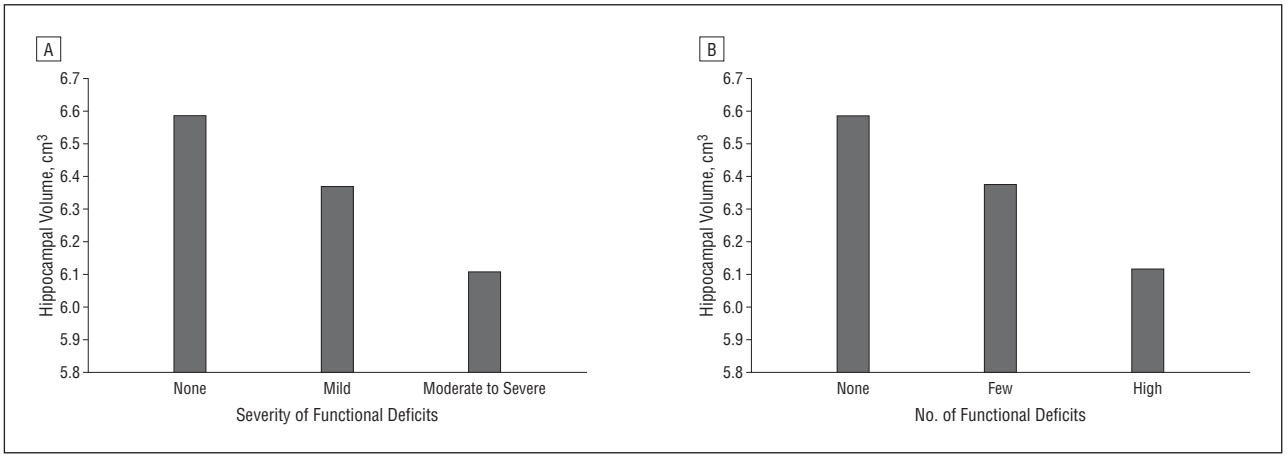

Figure 2. Post hoc adjusted mean comparisons of neuroanatomical predictors of functional deficits in the amnestic mild cognitive impairment sample. Means are adjusted for age, sex, educational level, and intracranial volume in the hippocampal volume analysis. A, Severity of functional deficits. B, Number of functional deficits. A significant difference was found in post hoc comparisons between no deficits and moderate to severe or high deficits. Severity groups were defined as follows: no deficits, 0; mild severity, 1-4; moderate to severe, 5 or more. Number of deficit groups were defined as follows: no deficits, 0; few deficits, 1-3; and high deficits, 4 or more ($P < .0167$; Bonferroni corrected).

Table 3. Covariate-Adjusted Odds Ratios (95% Confidence Intervals) for FAQ Deficit Class Comparisons Within the aMCI Group[a]

	Number of FAQ Deficits		Severity of FAQ Deficits	
Predictor	**Few Deficits vs None**	**High Deficits vs None**	**Mild vs None**	**Moderate to Severe vs None**
Hippocampal volume per 1000 cm^3	0.828 (0.610-1.124)	0.711 (0.510-0.991)[b]	0.828 (0.614-1.118)	0.679 (0.485-0.950)[b]
Trail Making Test, part A	1.009 (0.994-1.024)	1.027 (1.012-1.042)[c]	1.003 (0.986-1.022)	1.025 (1.007-1.044)[d]
AVLT 30-min delay	0.946 (0.873-1.024)	0.832 (0.750-0.924)[c]	0.951 (0.878-1.030)	0.809 (0.723-0.905)[c]
APOE ε4	0.944 (0.556-1.605)	1.706 (0.957-3.042)	. . .	. . .
Digit Symbol	. . .	. . .	0.993 (0.964-1.023)	0.984 (0.951-1.018)

Abbreviations: aMCI, amnestic mild cognitive impairment; *APOE*, apolipoprotein, AVLT, Auditory Verbal Learning Test; ellipses, not applicable; FAQ, Pfeffer Functional Activities Questionnaire.
[a] Covariates adjusted for age, sex, educational level, and intracranial volume.
[b] $P < .05$.
[c] $P < .001$.
[d] $P < .01$.

cians and researchers in interpreting the point in the predementia stage in which the patient should be classified and can help predict the speed at which the condition of that patient will convert to dementia.[26,29] Aiding in earlier identification of the disease stage can lead to earlier enrollment of patients in clinical trials for treatment of cognitive impairment, earlier financial and estate planning, the designation of health care proxies, and the preparation of families for the future responsibility and cost of providing care for the patient. These findings show that even mild disruptions in daily functioning may be an important clinical indicator of disease and represent the latter phases of disease progression within the MCI classification system for cognitive impairment.[43]

FACTORS ASSOCIATED WITH FUNCTIONAL DEFICITS IN COGNITIVELY IMPAIRED INDIVIDUALS

Past studies have identified strong associations between functional impairment and medical illness,[9,10] mood disorders,[11-14] and cognitive impairment.[15-17] This study found that functional impairment (total severity, total number, and average severity per deficit) was associated with smaller hippocampal volumes and decreased processing speed in the combined aMCI and AD group. Functional severity and total number of functional deficits were also associated with worse memory performance per the AVLT 30-minute delay and decreased entorhinal cortex volumes.

Within the aMCI group, the associations among memory deficits (as measured by the AVLT 30-minute delay and decreased hippocampal volume), processing speed decrements (per Trail Making Test, part A score), and greater functional impairment again were identified. Distinct heterogeneity was observed within the aMCI group illustrated in the post hoc and logistic models. Although the trends across groups for the severity and number of functional deficits analyses showed that with increasing deficits in daily activities, impairment in memory and processing speed and medial temporal atrophy worsened, the strongest difference was observed between the functionally intact and moderate to severe or high deficit groups. The moderate to severe and high number of

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functional deficits groups with aMCI had greater hippocampal atrophy and impairment in memory and speed of processing compared with the functionally intact individuals with aMCI.

These results illustrate 2 possible mechanistic pathways that contribute to functional impairment in cognitively impaired individuals. One potential pathway, memory dysfunction, is represented by neuropsychological measures (ie, the AVLT 30-minute delay) and neurobiological markers (ie, increased medial temporal atrophy). This finding is consistent with past findings showing increased atrophy in the 2 areas of the brain consistently associated with AD, the hippocampus and the entorhinal cortex.[29,44,45] Speed of processing marks the second potential pathway associated with functional impairment. Processing speed declines with age.[46,47] Although researchers have focused on the association between executive dysfunction and daily functional deficits,[48] the present study concurs with recent findings by Wadley and colleagues,[15] who showed that individuals with aMCI differed from healthy controls in speed of processing on a financial performance measure. These findings intimate that gradual decreases in processing speed that occur with normal aging may accelerate in individuals with incipient dementia. We speculate that processing speed decrements may mark the initial onset of milder deficits in daily functioning, but executive dysfunction may lead to more severe impairments in daily functioning as the disease progresses. Longitudinal data need to be examined to test this hypothesis.

The status of *APOE ε4*, a genetic marker shown to increase risk of developing Alzheimer disease,[49] was associated with an increased number of informant-reported functional deficits in the aMCI group. Those individuals with aMCI who had a positive expression for the *APOE ε4* allele had a greater number of functional deficits, although not more severe deficits, than those without the *APOE ε4* allele. Individuals with an *APOE ε4* allele may be predisposed to earlier onset of impairments in daily functioning, consistent with the increased risk of incipient dementia conferred by the presence of the *APOE ε4* allele.[49] However, these disruptions in daily activities do not require overt assistance by or overall dependence on spouses, family members, or friends.

The study has some design limitations. It used carefully selected individuals who agreed to participate in a research study with intensive serial procedures during an extended period. Part of the selection criteria included the exclusion of significant depressive symptoms or coexisting medical disorders, such as vascular impairment. Although the present study illustrated that functional deficits partly overlap with cognitive deficits (specifically, memory impairment and processing speed deficits)[15,16] and in part may be considered a consequence of these impairments, the moderate amount of explained variance between functional and cognitive deficits in this study and another[50] suggests that other factors contribute to the development of these deficits. Possible contributing factors to increased functional deficits include physical[10] and psychological[14] comorbidities, but these comorbidities were excluded in this sample. The exclusion of moderate to severe depression, in particular, hinders generalizability of these findings because depression is common in patients with cognitive impairment, and the bidirectional relationship between depression and functional impairment is well established.[51] The use of different assessment methods (self-report for controls and informant report for the aMCI and mild-AD groups) makes cross-comparisons between the cognitively impaired and cognitively intact groups difficult. Previous research has shown that self-reports can underreport symptoms in part due to worsening cognitive impairment and awareness,[17,21,26] but informant reports in AD may overreport symptoms perhaps due to caregiver burden.[52] Performance-based measures[53] may reflect more accurately the ability of the patient to perform specific behaviors, although this remains to be established; performance-based measures were not evaluated in this study.

In conclusion, this study shows that mild deficits in daily activities are common in the aMCI stage of cognitive impairment and that this impairment should be considered in the MCI criteria. Functionally impaired individuals with aMCI had greater medial temporal atrophy and deficits in memory and processing speed compared with functionally intact individuals with aMCI. Future research should investigate the onset and course of functional impairment longitudinally to discern whether deficits in memory and processing speed or greater medial temporal atrophy are associated with the onset and progression of functional deficits during the disease process.

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Correction

Errors in Table. In the Original Article titled "A Double-blind Randomized Controlled Trial of Olanzapine Plus Sertraline vs Olanzapine Plus Placebo for Psychotic Depression: the Study of Pharmacotherapy of Psychotic Depression (STOP-PD)" by Meyers et al, published in the August 2009 issue of the *Archives* (2009;66[8]:838-847), the data in Table 2 in the tardive dyskinesia row are incorrect. The correct data are as follows: All Patients, No. (%): 11 (4.3); Older Patients, No. (%): 6 (4.2); Younger Patients, No. (%): 5 (4.3); χ^2_1=0.0004; and P=.99. This article was corrected online.

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