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Lower-Extremity Function in Cognitively Healthy Aging, Mild Cognitive Impairment, and Alzheimer's Disease

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Abstract

Objective—To examine differences in lower-extremity function in cognitive healthy older persons, older persons with mild cognitive impairment (MCI), and older persons with Alzheimer's disease (AD).

Design—Descriptive study.

Setting—University Alzheimer's disease clinical and research program.

Participants—Older persons (N=66) were studied (mean age, 76.7y); 22 were cognitively normal, 22 were diagnosed with probable MCI, 22 were diagnosed with probable AD.

Interventions—Not applicable.

Main Outcome Measures—Lower-extremity function was assessed by the four-meter walk test (4MWT), Timed Up & Go (TUG) test, and sit-to-stand (STS) test.

Results—Analysis of variance, adjusting for covariates, revealed that performance on the 4MWT was significantly lower in the MCI and AD groups as compared with controls. TUG test performance was worse in the AD group compared with controls. No significant group differences were found for STS performance.

Conclusions—These results suggest an association between cognitive impairment and lower-limb function in older persons Walking speed could be evaluated for its possible utility in screening older persons at risk for cognitive impairment and falls.

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Keywords

Aging; Alzheimer disease; Cognition; Gait; Rehabilitation

Gait disturbance is a symptom in advanced stages of AD.[1,2] There is, however, growing evidence that lower-extremity disturbances are also present in milder stages of the disease[2] and may be related to level of cognitive impairment.[3] In older persons, lower-extremity function (eg, walking) involves intention and the integration of higher cortical sensory information, and thus impairment in cognition may also impair walking.[4] Alternatively, lower-extremity function impairments, for example gait impairments, may even predict future cognitive decline and dementia.[3,5] Because persons with impaired lower extremity functioning are also at high risk for adverse events such as falls, institutionalization, and death,[6] improved early identification of lower-extremity impairment is important in order to identify those risks.

Results of previous research examining the differences in lower-extremity function among persons with AD or MCI and cognitively healthy adults have, however, been equivocal. Some studies have shown greater lower limb function impairments in persons with MCI compared with controls,[3,7–9] while others have not.[10–12] Similarly, some studies have reported significant differences between persons with MCI and persons with AD,[3,10] while others have not.[8,9,11,12] The inconsistency of these findings may be attributable to methodologic factors: the use of different study populations, diagnostic criteria, sample sizes, and motor function measurements. It is noteworthy that possible moderating factors, in other words, factors that may affect lower-limb function such as osteoporosis,[3,10,11,13] parkinsonian signs,[7,8,11,13] and depressive symptoms[14] were not uniformly considered across all studies. The purpose of the present study was to compare performance on different lower-extremity function tests in a well-characterized group of persons with MCI or AD and demographically matched controls, while taking into account covariates such as comorbid conditions, parkinsonian signs, and depressive symptoms.

METHODS

Participants (N=66) were a subset of a large research registry, which longitudinally follows older persons with and without cognitive impairment. The design and selection criteria of the research registry have been described elsewhere.[15,16] Briefly, all participants underwent annual neurologic examination and extensive neuropsychologic evaluation. Inclusion criteria for the current study required that participants be (1) community-dwelling, (2) English speaking, (3) ambulatory, and (4) cognitively normal, MCI, or AD, based on a multidisciplinary consensus diagnosis. In anticipation of this analysis, participants also had to perform at least 1 lower-extremity function test. Participants were excluded if they had a history of major psychiatric illness (eg, schizophrenia) or head injury involving loss of consciousness for more than 5 minutes. The study was approved by the local institutional review board. All participants and their study partners provided written informed consent.

Diagnoses for participants were based on a multidisciplinary consensus team conference, including board certified neurologists, neuropsychologists, and a nurse practitioner. Participants were diagnosed with MCI (n=22) if they had a self-report or informant report of cognitive decline, an objectively determined cognitive impairment, and a lack of dependence in instrumental activities of daily living.[17] Objective cognitive impairment was defined as falling at least 1.5 SDs below available age-corrected normative data on primary variables in the neuropsychologic test battery, which also included the Unified Data Set of the National Alzheimer's Coordinating Center.[18] Participants with MCI all had a CDR[19] of 0.5. All persons with AD (n=22) met widely accepted criteria[1] for probable AD and had CDR scores at or above

1.0. The cognitively normal controls (n=22) were selected from the larger registry and matched for age, sex, and education to the persons with MCI and AD, without knowledge of neuropsychologic or lower-extremity test performance. The neuropsychologic performance of the cognitively healthy controls was within the normal range (as determined by published normative data), and each control participant had a CDR of 0. Global cognitive functioning was determined by the MMSE.20

Covariates

Medical histories, which were completed by the nurse practitioner, provided information about participant height, weight, and comorbid conditions. A summary score of comorbidity[21] was calculated based on the presence of the following conditions: diabetes, hypertension, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, stroke, and rheumatoid arthritis. Because parkinsonian signs are frequently present in MCI and AD, [2] the motor subsection of the UPDRS was also included as a covariate.[22] Because walking speed may be related to the level of depression in older persons,[14] we sought to control for depressive symptoms, as measured by the Geriatric Depression Scale.[23]

Lower-Extremity Function Tests

Lower-extremity function tests were chosen based on their clinical utility, low costs, and restricted time to administer Tests were administered by trained neurologists, research nurses, or students. Because diagnoses were based on a multidisciplinary consensus team conference that took place after the assessment, testers were unaware of the participants' cognitive diagnosis.

Four-meter timed walk test—For the 4MWT procedure, the participant walks a straight 4-m distance at a normal pace of ambulation.[24] Persons are allowed to use a walking aid, if necessary. No practice trial is included, but the outcome measure is the mean duration of 2 attempts, converted to walking speed (m/s). Walking speed is associated with adverse events and cognition in healthy older adults.[4,25]

Timed Up & Go—In the TUG test, participants stand up from a seated position without the use of their hands, walk for 3m, turn, and return to sit in the chair, again without the use of the hands.[26] No practice trial is included, but the mean number of seconds required to perform the test across 2 trials forms the outcome variable. The TUG test is a reliable and valid test for quantifying functional mobility.[26]

Sit-to-stand test—In the STS test, the participant is requested to stand up and sit down in a chair as often as possible in 30 seconds while keeping the arms crossed across the chest.[27] STS score was formed by the total number of sit-to-stands. The STS is considered a reliable test to measure lower body strength.[27] Measurement of the ability to quickly sit and stand has proven to predict falls in healthy older persons.[28]

Statistical Analysis

A sample size calculation was performed based on the effect sizes of previous studies in which MCI and AD groups were compared with controls. Differences in walking speed between AD groups and controls showed large effect sizes.[10,12] We used the software application G*Power, version 3.0;[29,a] a Cohen *d* of 0.8, alpha at .05, power (1-β) at .80; and 3 covariates to show a total sample size of 64 persons. Therefore, the current sample size of 66 provided sufficient

[a]G*Power; Prof. Dr. Axel Buchner, Institut für Experimentelle Psychologie, Heinrich-Heine-Universität, Gebäude 23.03, Universitätsstr. 1, 40225 Düsseldorf, Germany.

power to detect significant group differences. Between-group differences for demographic characteristics were examined by analyses of variance, chi-square tests, or nonparametric Mann-Whitney *U* tests. Between-group differences in lower-extremity functioning were evaluated by analyses of covariance, adjusting for comorbid medical conditions summary score, parkinsonian signs (UPDRS), and depressive symptoms (Geriatric Depression Scale). For all omnibus tests, simple pairwise planned contrasts were used to explore significant group differences. Alpha was set a priori at .05. Effect sizes were estimated by Cohen *d* and partial eta squared (η^2).[30] Data were analyzed using SPSS version 15.[b]

RESULTS

Sample characteristics for each diagnostic group are provided in table 1; prevalence of comorbid conditions is provided in table 2. Overall, the sample had a mean age ± SD of 76.7 ±8.3 years (range, 51–91) and a mean education level ± SD of 15.2±2.8 years (range, 8–21). There were 13, 14, and 12 women in the control, MCI, and AD groups, respectively. There were no between-group differences with respect to age ($F_{2,63}$=.06, *P*=.944), sex (χ^2_2=.38, *P*=.829), education ($F_{2,63}$=.53, *P*=.591), height ($F_{2,54}$=.05, *P*=.948), weight ($F_{2,53}$=.38, *P*=.689), or use of assistive devices (χ^2_2=1.06, *P*=.366). As expected, groups did significantly differ on MMSE score ($F_{2,63}$=44.40, *P*<.001; AD<MCI, AD<cognitively healthy controls, MCI=cognitively healthy controls) and depressive symptoms ($F_{2,63}$=3.83, *P*=.027; MCI>cognitively healthy controls, MCI=AD; normal controls=AD). The between-group differences in total comorbidity and UPDRS score were not significant ($F_{2,63}$=.16, *P*=.852 and $F_{2,63}$=2.64, *P*=.079, respectively).

TUG test scores were missing for 1 participant with MCI and 4 participants with AD, but these persons did not differ significantly on any of the main characteristics from the persons who did perform this test. STS scores were missing for 3 participants with MCI and 7 participants with AD. These 10 participants did not differ on any of the main characteristics, except for a significantly lower MMSE score (mean, 22.6), compared with persons who did perform this test (mean, 27.1) (z=−2.02, *P*=.044).

The analysis of covariance revealed a significant between-group difference in 4MWT performance (ie, walking speed) ($F_{2,59}$=4.76, *P*=.012, partial η^2=.14), such that both MCI (*P*=.041) and AD (*P*=.004) groups had significantly lower scores than the control group.. TUG test performance did reveal a significant between-group difference ($F_{2,55}$=3.34, *P*=.043, partial η^2=.11). Post hoc tests suggest only the AD group differed from the control group (*P*=.012). Finally, there was no significant difference between groups for STS test performance ($F_{2,50}$=.70, *P*=.502, partial η^2=.03). See table 3 for more information.

DISCUSSION

The present results suggest that there are differences between cognitively healthy control, MCI, and AD groups in walking speed (4MWT); differences between controls and AD patients in functional mobility (TUG); and that there are no between-group differences for lower body strength (STS) With respect to walking speed, persons with MCI and AD showed a slower speed compared with cognitively healthy controls. This finding is consistent with 1 other study that revealed differences between these 3 groups.[3] Although walking speed was significantly slower in persons with MCI com pared with controls in another study,7 2 additional investigations did not show such a difference.10,12 However, these 2 latter studies did not take comorbid medical conditions into account. It is noteworthy however, that another study showed that after controlling for parkinsonian signs, use of walking aids, and activities of daily living,

[b]SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

older persons with dementia walked faster compared with controls.[31] These authors state that this finding may reflect frontal lobe disinhibition. The latter, in turn, may be the result of periventricular white matter lesions, for which risk factors are cardiovascular diseases.[32] In the study by Van Iersel et al,[31] persons with vascular dementia and frontotemporal dementia were also included, who may have shown frontal disinhibition in particular. In contrast, in our AD group, only half had hypertension, and other cardiovascular diseases were not common.

In the present study, mobility function was worse in the AD group compared with both MCI and control groups, which is in agreement with findings from other studies.11,33 It is noteworthy that all groups in the present study showed slower performance than expected on the TUG test. More specifically, the mean number of seconds to perform the test in the control group was actually lower than the cut-off score that is traditionally used for this test in the older population (10s).26 However, higher cutoff scores (12s) have been suggested for older women. 34 Notably, higher cutoff scores (>13.5s) have been reported for older persons particularly at risk for falls.35 In view of the mean TUG scores of the AD group in our study, it is not surprising that people with AD are particularly at risk for falls.4

The lack of a between-group difference in lower-body strength is in contrast with the findings of another study.[3] The high number of missing values in the current analysis, however, resulted in insufficient power (observed power=.16), thus limiting the possibility to detect a potential between-group difference. On the other hand, the difference between control and MCI groups showed a moderate effect size[30] (see table 3), which suggests that there may be clinical significance to this finding. Also, the persons who did not perform this test had significantly lower MMSE scores compared with the people who did, and one might expect those people to have performed worse.

It has been suggested that differences in lower-extremity function across the cognitive aging spectrum may be explained by atrophy of a network including the dorsolateral prefrontal cortex, cingulate gyrus, parietal association areas, basal ganglia, and medial temporal lobes, particularly the hippocampus.2,4 Several brain imaging studies found support for such a network involved in both cognition and lower-extremity function. For example, a computerized tomography study revealed that impaired motor performance was associated with temporal lobe atrophy.[36] Additionally, another imaging study showed an association between higher activity in brain regions that are involved in complex cognitive functions (including the pre-frontal cortex and the hippocampus), and increasing complexity of gait.[37]

The current study extends the existing literature by using well-characterized participants with a clear diagnosis based on widely used criteria by multidisciplinary consensus, including demographically matched controls, controlling for covariates, and analyzing the different lower-extremity function tests separately to evaluate which test best detected between-group differences. The results suggest that walking speed may be a measure sensitive enough to assess lower-extremity function impairments in MCI and AD. Reduced walking speed is associated with adverse events, including falls, in healthy older adults and AD patients.[4,25] Therefore, adding a lower-extremity function measure to clinical assessment protocols may be useful for identifying those persons at greatest risk.

Study Limitations

The present study has several limitations. First, the number of lower-extremity function tests included in the assessment was limited, and the selection of some tests warrants attention. For instance, the 4MWT was used instead of assessing walking speed based on a longer distance, which may have decreased measurement accuracy relative to a longer test.[38] In future studies without the restriction of limited space, the use of a longer walking distance is recommended. Also, measuring walking speed at various velocities may offer interesting information

concerning gait variability.[39] Additionally, more sophisticated experimental measures of lower-extremity performance may be superior in detecting small changes. However, the current measures are cost-effective, easy to administer, and more feasible in clinical practice. In the current study, participant selection could be considered a second limitation. Participants were not excluded based on any comorbid condition that might negatively affect lower-extremity function, such as stroke[3] or peripheral neuropathy.[7] Persons with stroke were not excluded in view of the frequent co-occurrence of cerebrovascular disease and AD.[40] Comorbid conditions that could affect lower-limb function are numerous but can be present among participants of all 3 groups. Therefore, in the analyses concerning lower-extremity function, comorbid conditions were controlled for statistically. Finally, the cross-sectional design of the study precludes any determination of either the longitudinal course of lower-extremity functioning or the predictive accuracy of lower-extremity performance on future cognitive decline.

CONCLUSIONS

The present study suggests that differences exist in certain aspects of lower-extremity function between controls, persons with MCI, and persons with AD. Also, the current findings support the further exploration of walking speed as a quickly and easily applied screening tool to identify older persons at risk for cognitive impairment and falls.

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List of Abbreviations

4MWT	4 meter walk test
AD	Alzheimer's disease
CDR	Clinical Dementia Rating
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
STS	sit-to-stand
TUG	Timed Up & Go
UPDRS	Unified Parkinson's Disease Rating Scale

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Table 1

Demographics of the Participants

Characteristic	Controls	MCI	AD
Age (y)	76.5±7.4 (59–89)	76.3±8.1 (51–91)	77.1±9.6 (53–91)
Education (y)	15.3±2.5 (12–21)	14.7±2.7 (11–20)	15.5±3.1 (8–20)
MMSE	29.4±0.9 (27–30)	28.4±1.5 (24–30)	21.6±4.8 (13–28)
Height (cm)	163±11 (135–178)	163±9 (140–178)	164±10 (146–183)
Weight (kg)	72.4±13.0 (47–91)	71.5±10.8 (48–98)	68.9±12.7 (54–92)
Depressive symptoms	0.8±1.3 (0–4)	2.7±2.5 (0–8)	2.1±2.8 (0–11)
UPDRS	1.6±3.3 (0–12)	2.1±3.7 (0–13)	4.5±6.0 (0–17)
Total comorbidity (n)	0.8±0.7 (0–2)	0.8±1.0 (0–4)	0.7±1.0 (0–3)

NOTE. Values are mean ± SD (range) unless otherwise noted.

Table 2

Prevalence of Comorbid Conditions

Comorbid Condition	Controls	MCI	AD
Diabetes mellitus	2	2	2
Hypertension	14	12	9
Congestive heart failure	1	1	1
Chronic obstructive pulmonary disease	1	2	0
Stroke	0	0	2
Rheumatoid arthritis	0	0	0

NOTE. Values are n.

Table 3

Statistical Results of the Analyses of Covariance of the 3 Lower-Extremity Function Tests

	Groups			Contrasts					
	Controls	MCI	AD	C-MCI		C-AD		MCI-AD	
	Mean ± SD	Mean ± SD	Mean ± SD	*P*	Cohen *d*	*P*	Cohen *d*	*P*	Cohen *d*
4MWT (m/s)	0.87±0.2	0.75±0.1	0.71±0.2	.04	0.84	<.01	0.91	.33	0.27
TUG (s)	10.39±3.1	12.3±2.3	13.60±4.6	.22	0.70	.01	0.83	.17	0.36
STS (n)*	11.61±4.0	9.63±3.2	10.23±3.9	.25	0.55	.68	0.35	.50	0.17

NOTE. Values were adjusted for depressive symptoms, comorbid medical conditions, and parkinsonian signs.

Abbreviation: C, controls.

*Values indicate the number of stands.

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