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Original Study

Physical Function Differences Between the Stages From Normal Cognition to Moderate Alzheimer Disease

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A B S T R A C T

Objectives: We investigated the differences in the physical function test results across stages from normal cognition (NC) to moderate Alzheimer disease (AD) and how risk factors of physical function decline are correlated with the physical function test results.
Design: A cross-sectional study of outpatients at the Memory Disorder Outpatient Center of Japan's National Center of Geriatrics and Gerontology.
Participants: We enrolled 882 individuals aged ≥65 diagnosed with NC (n = 210), amnestic mild cognitive impairment (aMCI; n = 273), mild AD (n = 181) or moderate AD (n = 197).
Measurements: We measured the participants' results for functional reach (FR), the one-leg standing (OLS) test, the Timed Up and Go (TUG) test, tandem gait (TG), and grip strength (GS). A one-way analysis of covariance (ANCOVA) was used to identify significant differences among the groups' results on the physical function tests, controlling for age, sex, educational year, Mini-Nutritional Assessment, senior activity and exercise frequency, low-density lipoprotein, body mass index, free-fat mass index, and assistance for the TUG test. Multiple regression analysis was also used to investigate the correlation between these covariates and physical function tests results.
Results: The ANCOVA showed that FR, OLS, and TG were significantly worse among the individuals with aMCI, mild AD, or moderate AD compared with NC. However, TUG was significantly worse only in the moderate AD group compared with the NC, aMCI, and mild AD group. Multiple regression analysis showed that aging was correlated with poorer scores on all physical function tests, women had poorer scores on FR and GS than men, and low frequency of senior activity was significantly correlated with poorer scores on FR, OLS, and TG.
Conclusion: Postural impairment and instability on TG was seen in earlier AD stages compared with instability on TUG. As were the covariates of age and sex, senior activity frequency was significantly related to 2 or more physical function tests.

Alzheimer disease (AD) is the most common cause of cognitive impairment in elderly people and is associated with significant disability, requiring the substantial use of health care resources.[1] The decline in the physical functions of individuals with AD has been well documented,[2,3] and the reduced cognitive and physical functions of the increasing numbers of patients with AD worldwide are the basis of major social and public policy issues.[4]

Balance and gait disturbances have been shown to occur in relatively early stages of the progression of AD.[5] Many recent studies suggest that physical impairment is detectable among individuals with mild cognitive impairment (MCI) or the beginning signs of AD.[6]

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Gait and even simple standing are no longer considered merely automatic motor activity that is independent of cognition; in fact, gait and standing can be treated as a higher level of cognitive functioning. Grip strength (GS) is also reported to be a predictor of future cognitive decline among the elderly.[7] In addition, several studies support the hypothesis that physical impairments may precede the diagnosis of AD.[6] It also has been suggested that the decline in physical function of individuals with AD may represent a brain abnormality that cannot be identified by only neuropsychological tests.[8]

The diagnosis of pre-AD and AD is aided by many tools, such as neuropsychological and imaging tests. If more tools become available, they could help improve the patients' management and care and the guidance given to caregivers. Many tools to measure physical function have been developed and tested, but very little has been reported on the physical function differences according to the stage from normal cognition (NC) to AD. We therefore decided to investigate how physical function test results differ along the stages of progression from NC to AD.

In clinical settings, physicians often have to evaluate the physical function of a patient with AD with limited time, space, and staff. As the numbers of individuals with AD continue to increase worldwide, physicians can expect to see more patients with AD. A complete battery of physical function tests cannot always be conducted, due to time constraints and/or a patient's characteristics, whether at bedside or in a clinic. We therefore chose the following 5 tests in terms of easiness and convenience for clinical application: the functional reach (FR) test and the one-leg standing (OLS) test to evaluate an individual's postural function, the Timed Up and Go (TUG) test to evaluate his or her stability during normal gait,[9] the tandem gait (TG) test to evaluate the stability during different gait conditions, and GS to evaluate the upper extremity strength. These tests require little space and time to complete and are relatively easy to administer. For example, we decided to use the TUG test as a marker of balance during the patient's gait rather than straight path walking because the TUG test requires less space and is easier to measure, as the measurer does not have to move with the patient.

Many factors may have contributed to the decline in an individual's physical function, such as undernutrition, smoking, alcohol consumption, medication, inactivity, diabetes mellitus, and obesity.[10] In the present study, we also investigated how these and other risk factors are correlated with physical function decline. We restricted our investigations of patients with MCI to only those with amnestic MCI (aMCI), which is the prodromal stage of AD. We suspected that individuals with severe AD would not be able to understand the test instructions, and thus we decided to narrow down the AD study population to those with mild or moderate AD.

In the present study, we decided to investigate the physical function differences among individuals with NC, aMCI, mild AD, and moderate AD after controlling covariates. We also looked at how the covariates are correlated with each physical function.

Methods

Participants

We enrolled 861 individuals who visited the Memory Disorder Outpatient Center of Japan's National Center of Geriatrics and Gerontology (NCGG) during the 15-month period from January 2011 to April 2012. The study participants were required to meet the following inclusion criteria: (1) aged 65 years or older; (2) diagnosed as having NC, aMCI, or AD; (3) had tried at least 1 of the physical function tests; (4) had a Mini-Mental State Examination (MMSE) score higher than 10. This study was approved by the NCGG Ethics Committee. Informed consent was obtained from all individuals before their enrollment in the study.

Clinical Measures

Age, sex, number of years of education, Mini-Nutritional Assessment (MNA) score (range 0–14; a score of $\leq$7 indicates malnutrition), and information about smoking (never smoker, current 1 pack per day smoker, current >1 pack per day smoker, or former smoker), alcohol consumption (none, occasionally, <40 g/d or >80 g/d), polypharmacy (defined as taking $\geq$5 types of oral medicine), fall experience (ie, having fallen down) within the past 12 months, frequency of participation in a senior activity at the local seniors' center (none, seldom, occasionally, or frequently), and exercise history (none, need assistance to move, 1 day/wk, or every day) were self-reported by the individuals and their caregivers. Systolic blood pressure was measured by an automatic blood pressure monitor at the time of physical assessment. We examined glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol from each person's blood sample.

The body composition (body weight; percentage body fat; fat-free mass [FFM]) of each participant was assessed using a Tanita Multi-Frequency Body Composition Analyzer MC-180 (Tanita, Tokyo, Japan). The Tanita is a scale that uses a bioelectrical impedance analysis (BIA) to determine the body composition. This BIA method provides simple, inexpensive, and reliable estimates of components of body composition. We calculated each person's body mass index (BMI) using the formula weight/height^2 (kg/m^2) and the FFM index (FFMI) using the formula FFM/height^2 (kg/m^2).

Assessment of Cognitive Function

Each person's cognitive function was measured by the MMSE,[11] the Category Fluency Test of the Hasegawa Dementia Rating Scale-Revised (HDS-R),[12] the Alzheimer's Disease Assessment Scale (ADAS),[13] the Frontal Assessment Battery (FAB),[14] Raven's Colored Progressive Matrices (RCPM),[15] the Digit Span Forward, Digit Span Backward test of the Wechsler Adult Intelligence Scales (WAIS)[16] as a clinical assessment of attention, and Logical Memory Tests I and II of the Wechsler Memory Scale-Revised (WMS-R).[17] Depression was estimated by the Geriatric Depression Scale 15 (GDS15).[18] All of the results of these cognitive tests were reviewed by a single neuropsychologist with more than 15 years of experience.

The diagnosis of MCI was based on the Petersen criteria.[19] A participant was further subtyped as having aMCI if his or her education-adjusted score on the WMS-R Logical Memory II was $\geq$1.5 SDs below his or her age-appropriate norm.[17] The diagnosis of AD was based on the US National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines.[20] Among the participants with AD, we defined those with an MMSE score >20 as having mild AD and those with an MMSE score of 10 to 19 as having moderate AD, as in earlier studies.[21,22]

Assessment of Physical Function

Postural function was evaluated by the FR and OLS tests. Each person's stability during normal gait was evaluated by the TUG test.[9] Their stability during gait with a narrow base of support in the medial or lateral direction was evaluated by the TG test.[23] The person's upper extremity strength was evaluated by GS testing the same day, with the use of a digital force gauge (ZP 500N; Imada, Toyohashi, Japan).[24] GS was not measured from the participants who had heart disease or uncontrolled blood pressure (systolic blood pressure is higher than 160 mm Hg). A previous study also used this criterion to

investigate the association between GS and resistance training.[25] We adopted this criterion because our participants were elderly and had many diseases and more frailty, considering the tests' influence on their chronic disease states.

For the FR test, we measured the distance in centimeters that the standing participant was able to reach forward from an initial upright posture to the maximal anterior leaning posture without moving or lifting the feet. The OLS test measures the time in seconds for the person to stand unassisted on one leg as long as possible with eyes open up to a maximum of 60 seconds. Each leg was tested, and we used the average of the left and right OLS times as the OLS time. In the TUG examination, we measured the time in seconds that it took for the person to rise from sitting on a standard chair, walk 3 m, turn, walk back to the chair and sit down. In the TG examination, we counted the number of steps while the person walked a straight line touching the heel of one foot to the toe of the other with each step. We also used the average of both sides' GS as the GS expressed in kilograms.[26]

No mobility assistance was provided during the FR, OLS, and TG tests, but the participants were allowed to use their cane or walker as needed during the TUG test only. When a participant could not try to undergo a test for whatever reason, the result was recorded as a missed value. However, once a participant attempted the FR, OLS, TUG, or TG test and the test administrator observed that the participant could not reach, walk, or maintain a position, the result was recorded as 0.

Statistical Analysis

We used an analysis of variance (ANOVA) to compare the means among the characteristics of the 4 subject groups (NC, aMCI, mild AD, and moderate AD). The distribution of frequencies for categorical variables was analyzed with the χ^2 test. We conducted an analysis of covariance (ANCOVA) with the Bonferroni post-test to identify significant differences among the results achieved by the 4 subject groups on the physical function tests (FR, OLS, TUG, TG, and GS), controlling for covariates and what kinds of covariates are correlated with the physical function test results. We used age, sex, educational year, MNA, participation in senior activities, exercise frequency, LDL, BMI, FFMI, and assistance for TUG as covariates because they were significantly different among the groups. We also investigated how these covariates are correlated with each physical function test by using a multiple regression analysis. Sex was coded as 1 = male or 2 = female. Frequency of participation in a senior activity at the local seniors' center was coded as 0 = none, 1 = seldom, 2 = occasionally, or 3 = frequently. Exercise frequency was coded as 0 = none, 1 = need assistance to move, 2 = 1 day per week, or 3 = every day. Assistance for TUG was coded as 0 = none or 1 = used a cane or walker. All analyses were performed using SPSS statistics software (ver. 17 for Windows; IBM SPSS Statistics, Chicago, IL) A P value less than .05 was considered significant.

Results

Clinical Characteristics

We enrolled 210 individuals with NC, 273 with aMCI, 181 with mild AD, and 197 with moderate AD. Their clinical characteristics are summarized in Table 1. There were significant differences among the groups regarding age (F [3, 857] = 31.2, $P < .001$), sex (χ^2 [3] = 19.9, $P < .001$), years of education (F [3, 844] = 20.5, $P < .001$), MNA score (F [3, 849] = 28.9, $P < .001$), participation in senior activity frequency (χ^2 [9] = 55.8, $P < .001$), exercise frequency (χ^2 [9] = 34.1, $P < .001$), LDL (F [3, 856] = 3.1, $P = .03$), BMI (F [3, 857] = 3.9, $P = .01$), FFMI (F [3, 836] = 12.5, $P < .001$), assistance needed for the TUG test (χ^2 [6] = 13.0, $P = .048$), and in all of the neuropsychological tests except the GDS15, as determined by the ANOVA and χ^2 test.

Differences in Physical Function Among the AD Stages

Of the total of 861 participants, 96.9% (n = 834) were able to try to complete the FR test, and among these 834 participants, the score of 4.0% (n = 33) was 0. Among the total group, 93.6% of participants' data (n = 781) without any missing covariates values were analyzed. The OLS test was attempted by 94.1% (n = 810), and among them 0.4% (n = 3) could not maintain the position at all; among these participants, the data of 93.8% participants (n = 760) without any missing covariates values was analyzed. The TUG test was completed by 99.1% (n = 854) participants, among whom 4.8% (n = 41) used a cane and 0.5% (n = 4) used a walker. Among the participants who completed the TUG test, the data of 93.7% participants (n = 800) without any missing covariate values were analyzed. The TG test was attempted by 99.5% (n = 857) of participants, among whom 16.5% (n = 141) could not walk at least 1 step; we analyzed the data of the 93.3% (n = 800) without any missing covariate values. The GS was measured in 56.3% (n = 485) of the participants, and we found that their minimum strength was 2.2 kg. Among them, 94.0% of participants' data (n = 456) without any missing covariate values were analyzed (Table 2).

There was a significant effect of each stage of AD on the participants' results on the FR (F [3, 767] = 8.9, $P < .001$), OLS (F [3, 746] = 5.8, $P = .001$), TUG (F [3, 785] = 4.6, $P = .004$), TG (F [3, 786] = 15.1, $P < .001$), and GS (F [3, 442] = 3.8, $P = .01$) after controlling for age, sex, educational year, MNA, senior activity frequency and exercise frequency, LDL, BMI, FFMI, and assistance needed for the TUG test (Table 3).

As shown in Table 2, the ANCOVA with Bonferroni post hoc tests revealed the following significant results. The FR distances were significantly lower in the participants with aMCI (28.4 ± 8.6, $P = .02$), mild AD (25.1 ± 9.7, $P < .001$) or moderate AD (23.2 ± 9.5, $P < .001$) compared with those with NC (31.1 ± 7.1). The OLS times were significantly worse in the participants with aMCI (18.9 ± 18.6, $P = .04$), mild AD (13.8 ± 14.2, $P = .003$), or moderate AD (11.0 ± 14.0, $P = .001$) compared with those with NC (25.6 ± 21.1). The TUG times were significantly lower in the participants with moderate AD (13.5 ± 5.0) compared with the NC participants (10.3 ± 8.6, $P = .045$), aMCI participants (10.7 ± 4.0, $P < .001$), and those with mild AD (12.2 ± 3.6, $P = .02$). The TG numbers of steps were significantly lower in the participants with aMCI (11.3 ± 7.9, $P = .003$), mild AD (8.2 ± 7.6, $P < .001$), or moderate AD (6.7 ± 7.6, $P < .001$) compared with those with NC (14.0 ± 7.4). The GS was significantly weaker in the participants with mild AD (18.6 ± 6.8, $P = .007$) or moderate AD (17.1 ± 6.4, $P = .02$) compared with those with aMCI (23.2 ± 7.8).

Correlation Between the Covariates and Physical Function

The covariates age (F [1, 767] = 47.2, $P < .001$), sex (F [1, 767] = 26.2, $P < .001$), and senior activity frequency (F [1, 767] = 6.0, $P = .01$) were significantly related to the FR results. The covariates age (F [1, 746] = 192.0, $P < .001$), senior activity frequency (F [1, 746] = 18.6, $P < .001$), and BMI (F [1, 746] = 4.9, $P = .03$) were significantly related to the participants' OLS results. The covariates of age (F [1, 787] = 21.3, $P < .001$) and assistance utilization (F [1, 787] = 36.0, $P < .001$) were significantly related to TUG. The covariates age (F [1, 786] = 62.9, $P < .001$), senior activity frequency (F [1, 786] = 4.9, $P = .03$), and LDL (F [1, 786] = 5.5, $P = .02$) were significantly related to the TG results. The covariates age (F [1, 442] = 54.7, $P < .001$), sex (F [1, 442] = 110.5, $P < .001$), and MNA (F [1, 442] = 6.0, $P = .01$) were significantly related to the GS results (Table 3).

A multiple linear regression was calculated to predict each physical function test results based on age, sex, educational year, MNA,

Table 1
Characteristics and Physical Functions of the 4 Groups of Participants

	n	NC	n	aMCI	n	Mild AD	n	Moderate AD	*P*
Age, y	210	74.5 (5.8)	273	76.3 (6.0)	181	78.8 (5.7)	197	79.4 (5.6)	<.001
Female, n (%)	210	120 (57)	273	161 (59)	181	129 (71.2)	197	146 (74)	<.001
Education, y	210	11.8 (2.8)	272	11.1 (2.5)	176	10.6 (2.5)	190	9.8 (2.4)	<.001
MNA score	205	11.7 (1.9)	271	11.4 (2.0)	180	10.5 (2.3)	197	9.9 (2.4)	<.001
Smoking, n (%)	202		268		179		196		
Never		173 (85.6)		224 (83.6)		153 (85.5)		174 (88.8)	
<1 pack/d		8 (4.0)		12 (4.5)		9 (5.0)		5 (2.6)	
>1 pack/d		1 (0.5)		3 (1.1)		1 (0.6)		3 (1.5)	
Former		20 (1.0)		29 (10.8)		16 (8.9)		14 (71.4)	.8
Alcohol, n (%)	202		267		179		196		
None		125 (61.9)		175 (65.5)		126 (70.4)		145 (74.0)	
Occasionally		47 (23.3)		45 (16.9)		28 (15.6)		28 (14.3)	
<40 g/d		28 (13.9)		45 (16.9)		20 (11.2)		19 (9.7)	
>80 g/d		2 (1.0)		2 (0.7)		5 (2.8)		4 (2.0)	.054
Polypharmacy, n (%)	209	70 (33.5)	272	100 (36.8)	180	66 (36.7)	194	64 (33)	.8
Fall experience, n (%)		69 (33)		81 (29.7)		54 (30)		73 (37)	.6
Senior activity, n (%)	198		267		179		196		
None		78 (39.4)		122 (45.7)		100 (55.9)		134 (68.4)	
Seldom		28 (14.1)		30 (11.2)		26 (14.5)		19 (9.7)	
Occasionally		57 (28.8)		79 (29.6)		42 (23.5)		39 (19.9)	
Frequently		35 (17.7)		36 (13.5)		11 (6.1)		4 (2.0)	<.001
Exercise, n (%)	201		269		177		196		
None		30 (14.9)		63 (23.4)		57 (32.2)		61 (31.1)	
Need assistance		1 (0.5)		2 (0.7)		0 (0.0)		3 (1.5)	
1 d/wk		53 (25.1)		77 (28.6)		54 (30.5)		63 (32.1)	
Every day		117 (58.2)		127 (47.2)		66 (37.3)		69 (35.2)	<.001
SBP, mm Hg	204	153.6 (24.4)	265	152.3 (26.9)	180	153.8 (25.9)	195	153.1 (25.7)	.9
Blood samples									
HbA1c, %	179	6.0 (0.7)	252	6.0 (0.9)	173	6.0 (0.8)	185	6.1 (1.2)	.8
LDL, mg/dL	210	102.6 (53.9)	273	110.3 (45.3)	181	116.6 (42.2)	196	112.8 (47.4)	.03
HDL, mg/dL	174	112.9 (91.2)	252	119.5 (81.9)	172	131.0 (96.4)	183	120.8 (103.1)	.3
Body composition									
BMI	210	23.4 (14.9)	273	22.4 (3.4)	181	21.5 (3.6)	197	20.9 (3.1)	.01
PBF	207	25.1 (8.6)	269	24.7 (8.9)	174	25.3 (9.1)	190	23.6 (8.1)	.2
FFMI	207	16.6 (1.8)	269	16.6 (1.9)	174	15.9 (1.9)	190	16.3 (1.9)	<.001
Assistance for TUG	210		271		180		193		
None		204 (97.1)		265 (97.1)		166 (91.7)		181 (91.9)	
Cane		5 (2.4)		7 (2.6)		14 (7.7)		15 (7.6)	
Walker		1 (0.5)		1 (0.4)		1 (0.5)		1 (0.5)	.048
Neuropsychological tests									
MMSE	210	28.0 (2.1)	273	24.7 (3.1)	181	22.7 (2.2)	197	15.9 (2.6)	<.001
ADAS	181	5.4 (3.1)	273	10.4 (3.9)	166	15.1 (4.5)	167	21.5 (6.6)	<.001
RCPM	175	29.5 (3.9)	254	26.5 (4.9)	154	24.2 (5.5)	150	19.1 (5.5)	<.001
CFT	210	4.8 (0.8)	273	3.9 (1.7)	180	3.2 (2.0)	195	2.1 (2.0)	<.001
FAB	178	13.1 (3.3)	267	11.2 (2.7)	163	10.3 (2.8)	156	8.0 (2.9)	<.001
DSF	180	5.8 (1.2)	271	5.5 (1.1)	164	5.3 (1.0)	167	5.0 (1.2)	<.001
DSB	180	4.0 (1.0)	271	3.6 (0.9)	164	3.4 (0.9)	166	2.9 (1.1)	<.001
LM I	181	16.8 (6.2)	273	7.1 (4.7)	166	4.5 (3.6)	167	2.4 (2.4)	<.001
LM II	181	11.9 (6.2)	273	2.0 (3.1)	165	0.7 (1.7)	165	0.2 (0.7)	<.001
GDS15	210	4.1 (3.0)	273	4.3 (3.0)	181	4.3 (2.8)	197	4.2 (2.8)	.9

The data are mean (SD) or n (%). HbA1c is expressed in National Glycohemoglobin Standardization Program (NGSP).
CFT, Category Fluency Test; DSB, Digit Span Backward; DSF, Digit Span Forward; PBF, percentage body fat; SBP, systolic blood pressure.

participation in senior activities, exercise frequency, LDL, BMI, FFMI, and assistance for TUG. As shown in Table 4, the AD stages ($\beta = -0.2$, $P < .001$), age ($\beta = -0.2$, $P < .001$), sex ($\beta = -0.2$, $P < .001$), and senior activity ($\beta = 0.08$, $P = .01$) were significantly correlated with FR results ($R^2 = 0.2$, $F[10, 770] = 20.9$, $P < .001$). The AD stage ($\beta = -0.1$, $P < .001$), age ($\beta = -0.5$, $P < .001$), senior activity ($\beta = 0.1$, $P < .001$) and BMI ($\beta = -0.07$, $P < .03$) were significantly correlated with OLS ($R^2 = 0.3$, $F[10, 749] = 34.5$, $P < .001$). The AD stage ($\beta = 0.1$, $P = .002$), age ($\beta = 0.2$,

Table 2
Physical Function Test Results According to Cognitive Status

	Mean ± SD								*P*					
	n	NC	n	aMCI	n	Mild AD	n	Moderate AD	NC vs aMCI	NC vs Mild AD	NC vs Moderate AD	aMCI vs Mild AD	aMCI vs Moderate AD	Mild AD vs Moderate AD
FR	188	31.1 ± 7.1	254	28.4 ± 8.6	160	25.1 ± 9.7	179	23.2 ± 9.5	.02	<.001	<.001	.03	.003	.37
OLS	192	25.6 ± 21.1	253	18.9 ± 18.6	152	13.8 ± 14.2	163	11.0 ± 14.0	.04	.003	.001	.2	.07	.2
TUG	194	10.3 ± 8.6	261	10.7 ± 4.0	164	12.2 ± 3.6	181	13.5 ± 5.0	.96	.3	.045	.018	<.001	.02
TG	194	14.0 ± 7.4	258	11.3 ± 7.9	165	8.2 ± 7.6	183	6.7 ± 7.6	.003	<.001	<.001	.008	.001	.2
GS	109	23.8 ± 8.2	150	23.2 ± 7.8	91	18.6 ± 6.8	106	17.1 ± 6.4	.3	.08	.3	.007	.02	.7

Table 3
Correlations Between the Covariates and Physical Function Test Results

Covariate	Sum of Squares	df	Mean Square	F	*P*	η^2
FR						
AD stage	1797.1	3	599.0	8.9	<.001	0.03
Age	3179.9	1	3179.9	47.2	<.001	0.06
Sex	1770.2	1	1770.2	26.2	<.001	0.03
Senior activity	405.1	1	405.1	6.0	.01	0.008
Error	51699.2	767	67.4			
OLS						
AD stage	4127.1	3	1375.7	5.8	.001	0.02
Age	45207.1	1	45207.1	192.0	<.001	0.2
Senior activity	4385.3	1	4385.3	18.6	<.001	0.02
BMI	1160.3	1	1160.3	4.9	.03	0.007
Error	175616.7	746	235.4			
TUG						
AD stage	361.1	3	120.4	4.6	.004	0.02
Age	620.0	1	620.0	21.3	<.001	0.03
Use of assistance	1046.7	1	1046.7	36.0	<.001	0.04
Error	22904.6	787	29.1			
TG						
AD stage	2440.0	3	813.3	15.1	<.001	0.06
Age	3378.9	1	3378.9	62.9	<.001	0.07
Senior activity	264.3	1	264.3	4.9	.03	0.006
LDL	296.5	1	296.5	5.5	.02	0.007
Error	42240.7	786	53.7			
GS						
AD stage	350.1	3	116.7	3.8	.01	0.03
Age	1677.9	1	1677.9	54.7	<.001	0.1
Sex	3387.8	1	3387.8	110.5	<.001	0.2
MNA	185.2	1	185.2	6.0	.01	0.01
Error	13553.1	442	30.7			

η^2, the effect size.

$P < .001$), and assistance for TUG ($\beta = 0.2$, $P < .001$) were significantly correlated with TUG ($R^2 = 0.1$, $F[10, 788] = 11.1$, $P < .001$). The AD stage ($\beta = -0.2$, $P < .001$), age ($\beta = -0.3$, $P < .001$), senior activity ($\beta = 0.07$, $P = .03$), and LDL ($\beta = 0.08$, $P = .02$) were correlated with TG ($R^2 = 0.2$, $F[10, 789] = 19.6$, $P < .001$). The AD stage ($\beta = -0.1$, $P = .01$), age ($\beta = -0.3$, $P < .001$), sex ($\beta = -0.5$, $P < .001$), and MNA ($\beta = 0.09$, $P = .02$) were correlated with GS ($R^2 = 0.5$, $F[10, 445] = 48.0$, $P < .001$).

Discussion

The Physical Function Differences Among the Groups

The results of this study demonstrated that the individuals' postural impairment and instability during TG were seen at an earlier stage than instability during normal gait or GS.

Our findings are in agreement with some previous similar studies. Although some investigators reported no differences between the results of those with aMCI or NC on postural function tests such as TG and the Berg Balance Scale,[27] other studies showed that individuals with aMCI or mild AD had significantly poorer scores on OLS and TG compared with cognitively intact individuals.[28] It was also reported that among individuals with aMCI, although gait velocity was not impaired, other parameters such as stride length and swing time were impaired.[29] In addition, although several research groups reported that GS is correlated with cognitive decline or can be a predictor of future cognitive decline,[30,31] it was also suggested that lower-extremity impairments may be better indicators of impaired cognitive status than upper extremity impairment.[32] In the present study, the GS was lower at the later stages compared with the postural function tests. However, it must be noted that the GS results in our participants were lower than those of the other 4 tests in part because GS was not measured in the participants who had uncontrolled blood pressure or heart disease.

AD degeneration starts from the hippocampus[33] at the stage of aMCI, which is reported to be correlated with vestibular dysfunction.[34] In patients with MCI or mild AD, as their AD degeneration was observed to spread from the hippocampus to the precuneus, parietal, occipital, and temporal association area and frontal areas, an early loss of attention and other executive functions preceding deficits in sensorimotor and peripheral function, slowed reaction time, and visual spatial skills were also observed,[35] and these deficits resulted in postural instability.[36,37] The white matter lesion that spreads with AD degeneration also was reported to be correlated with a deterioration in postural function.[38]

However, it would seem that having only one sensory impairment does not lead to a normal gait deficit, because some people with a particular impairment develop one or more of their other functions to cover the impairments.[39] For example, a one-year longitudinal study found significant changes in mean stride length and double support among those with mild AD.[40] In a gait cycle consisting of a stance and swing phase of one leg, there are two periods, the initial and terminal double support, when both feet are in contact with the floor. Double support is the sum of these two periods. The authors of that study proposed that patients with AD are making a substantial compensation for decreased balance, as double support is used to control their stability between steps, and the compensation increases when their balance is threatened. People also must pay attention to use both legs properly for balance compensation.[41] It also has been argued that patients with AD tend to make increased use of their relatively unaffected somatosensory system (a reallocation of resources) once the visual system has deteriorated too much.[2]

Table 4
Results of Multiple Regression Analysis for Physical Function

Dependent Variable	FR		OLS		TUG		TG		GS	
Explanatory Covariates	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
AD stage	−0.2	<.001	−0.1	<.001	0.1	.002	−0.2	<.001	−0.1	.01
Age	−0.2	<.001	−0.5	<.001	0.2	<.001	−0.3	<.001	−0.3	<.001
Sex	−0.2	<.001	−0.05	.3	−0.004	.9	−0.08	.054	−0.5	<.001
Education	0.06	.08	0.009	.8	0.03	.4	−0.07	.06	0.01	.7
MNA	0.03	.5	−0.02	.6	−0.04	.3	−0.003	.9	0.09	.02
Senior activity	0.08	.01	0.1	<.001	−0.07	.055	0.07	.03	0.06	.09
Exercise	0.03	.4	0.009	.8	−0.03	.5	0.04	.2	0.02	.6
LDL	0.03	.3	0.05	.1	−0.06	.1	0.08	.02	0.02	.6
BMI	−0.04	.3	−0.07	.03	0.05	.2	−0.04	.3	−0.03	.3
FFMI	−0.09	.056	−0.05	.3	0.0	.99	0.005	.9	0.09	.08
Assistance for TUG	-	-	-	-	0.2	<.001	-	-	-	-
	$R^2 = 0.2$, F = 20.9 ($P < .001$)		$R^2 = 0.3$, F = 34.5 ($P < .001$)		$R^2 = 0.1$, F = 11.1 ($P < .001$)		$R^2 = 0.2$, F = 19.6 ($P < .001$)		$R^2 = 0.5$, F = 48.0 ($P < .001$)	

With the course of AD, degeneration spreads throughout the brain, including the frontal and primary motor area or association area.[42] At the late AD stage, as less brain area is involved in autonomic adjustments during moving, the compensation for the more impaired balance may become difficult. Although the mechanisms underlying our present findings are unclear, we believe that individuals with aMCI or mild AD still have the ability to compensate for impaired balance as long as they walk normally using the intact brain region. When they walk in a TG, they cannot adjust their stride length or double support. We believe this is a reason why the number of steps in the TG test was lower among our participants with aMCI and mild AD. We suspect that individuals with more than mild AD may have impairments in the complex motor skills and limb coordination that are necessary for compensation.

The Correlation Between the Covariates and Physical Function Test Results

ANCOVA showed that age, sex, and senior activity frequency were significantly correlated with 2 or more physical function test results. Furthermore, multiple regression analysis showed that aging was significantly correlated with poorer scores on all physical function tests. Women had significantly poorer scores on FR and GS. Low frequency of senior activity was significantly correlated with poorer score on FR, OLS, and TG. The contribution of aging to the decline in humans' physical function is well known. Regarding gender, it is well documented that muscle strength of men is generally stronger than that of women. Interestingly, our present results showed that low frequency of senior activity was correlated with both postural function impairment and instability in TG. A longitudinal cohort study (part of the Rush Memory and Aging Project) revealed that less-frequent participation in social activities was associated with a more rapid rate of motor function decline in old age.[43] The basis for the finding of an association between senior activity and postural function impairment and instability during TG is uncertain. The same Rush project team has reported that loneliness was associated with more rapid motor decline.[44] That team speculated that loneliness is correlated with poor self-regulation, which may lead to poor eating habits and/or decreased exercise that would cause a physical function decline. Participation in senior-focused activities may combat or even prevent loneliness among the participants. The Rush team also proposed that senior activity may contribute to improved physical function by increasing neuronal plasticity and protecting against tissue damage.[45] Conversely, those with physical dysfunction may hesitate to attend these senior activities. Regarding our findings that BMI was significantly correlated with OLS, it is notable that obesity has been reported to be a risk factor for postural function impairment.[46] Regarding our finding that MNA was significantly correlated with GS, nutrition is also well known to contribute to muscle strength.[47]

Study Strength and Limitations

To our knowledge, this is the first study to identify FR, OLS, and TG impairment at earlier AD stages compared with impairments in TUG. We used a large sample and many covariates. We restricted the dementia cases to AD cases because we believe that restricting the cases to only AD gave us more clinically useful information than a consideration of all patients with dementia, who would have various pathological backgrounds.

This study has some limitations, including its cross-sectional design and lack of longitudinal data. More longitudinal studies are needed to explore the physical function decline in AD. Second, we did not use elaborate equipment to determine the details of gait parameters, such as stride length, center of gravity sway, variability, and gait abnormality. Such a level of detail regarding gait may help identify the previously mentioned underlying mechanisms in greater detail. Third, it may be more complex to perform the TUG task than the straight path walking because in the TUG test the individual must get up from a chair and make a U-turn, which might have affected the observed discrepancy between the associations of gait and postural tests in this study. Finally, the GS achievement rate was low in our study population. Our exclusion criteria for GS might be relatively strict. In future studies, a physical function test that has a higher achievement rate than the GS test is needed.

Conclusions

We conclude that postural impairment and instability in TG were seen at earlier AD stages compared with normal gait impairments. As were the covariates of age and sex, senior activity frequency was significantly related to 2 or more physical function tests. The elucidation of the underlying mechanisms and longitudinal studies are needed, as these will lead to strategies that will prevent the functional decline of patients with AD.

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