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Physical factors underlying the association between lower walking performance and falls in older people: A structural equation model

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ABSTRACT

The purpose of this study was to determine the interrelationships between lower limb muscle performance, balance, gait and falls in older people using structural equation modeling. Study participants were two hundred and thirteen people aged 65 years and older (mean age, 80.0 ± 7.1 years), who used day-care services in Japan. The outcome measures were the history of falls three months retrospectively and physical risk factors for falling, including performance in the chair stand test (CST), one-leg standing test (OLS), tandem walk test, 6 m walking time, and the timed up-and-go (TUG) test. Thirty-nine (18.3%) of the 213 participants had fallen at least one or more times during the preceding 3 months. The fall group had significantly slower 6 m walking speed and took significantly longer to undertake the TUG test than the non-fall group. In a structural equation model, performance in the CST contributed significantly to gait function, and low gait function was significantly and directly associated with falls in older people. This suggests that task-specific strength exercise as well as general mobility retraining should be important components of exercise programs designed to reduce falls in older people.

1. Introduction

Falling is the leading cause of severe injury, such as hip fracture, in older people (Lord et al., 2001), and fall-related fractures are recognized as the third most important factor used in calculating care insurance for frail older people in Japan (Ministry of Health, Labour and Welfare, 2002). Many studies have identified physical risk factors for falls, including: muscle weakness (Whipple et al., 1987; Tinetti et al., 1988; Campbell et al., 1989; Nevitt et al., 1989; Robbins et al., 1989; Studenski et al., 1991), inability to maintain static or dynamic balance (Overstall et al., 1977; Brocklehurst et al., 1982; Tinetti et al., 1988; Campbell et al., 1989; Nevitt et al., 1989; Studenski et al., 1991; Clark et al., 1993; Lord et al., 1994), reduced walking speed (Himann et al., 1988; Campbell et al., 1989; Nevitt et al., 1989), and poor tandem gait (Buchner and Larson, 1987; Nevitt et al., 1989). Falls result from interactive etiological factors, not simply from the additive effects of multiple pathologies or physical disabilities. It is clear from the evidence that at least a previous fall and/or poor balance and a gait disorder may be predictive of those at highest risk (NICE, 2004). Furthermore, muscle weakness makes a considerable contribution to falling and is a marker of physical functioning in older people (Perell et al., 2001).Muscle weakness, poor balance, and lower walking performance are independently associated with falling in older people. De Rekeneire et al. (2003), for example showed with multivariate logistic regression models that white race, slow 6 m walking speed, poor standing balance, inability to do five chair stands, urinary incontinence, and poor leg muscle strength are independently associated with falling in older men. If these physical risks are independently associated with falling, exercise programs that improve muscle strength and balance and include gait exercises, should be effective in preventing falls in older people. Despite this being evident in individually tailored exercise programs for preventing falls (Campbell et al., 1997, 1999; Robertson et al., 2001), the effects of single component exercise programs are not clear. Furthermore, the published evidence suggests that the interaction between falls, muscle weakness, poor balance, and lower walking performances in older people is unclear. It would therefore be useful to identify the interactions between risk factors for falls on the one hand and the occurrence of

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falls on the other, because a better understanding of these interactions will allow for more effective targeting of intervention strategies.

The purpose of this study was to explore the interrelationships among measures of physical function and falls in older people using structural equation modeling. A structural equation model was developed based on a theoretical model of the relationships between falls and the physical measurements previously found to be associated with the risk of falling (Perell et al., 2001; NICE, 2004). To select the structural equation model, we considered the WHO classification of disabilities and our previous study (WHO, 1980; Lord et al., 1996). In this classification, the parameters are separated into the following two categories: lower muscle function and poor balance resulting from impaired sensorimotor functions; and lower functional mobility resulting from lower muscle and balance functions. Thus, the structural equation model was constructed in two stages by explanatory variables that were associated with falls. We considered that lower muscle function and poor balance were indirectly associated with falls and lower functional mobility was directly associated with falls because approximately 65% of falls occur during ambulation or during postural transfers (Tinetti et al., 1988; Arnold and Faulkner, 2007).

2. Subjects and methods

2.1. Participants

The participants were 213 people aged 65 years or older (65–96 years) who had used day-care services in Japan in the previous year. The exclusion criteria for the study were an inability to walk independently or perform the physical assessments, or cognitive impairment (3 or more errors on a validated mental status questionnaire, Kahn et al., 1960). Table 1 shows the characteristics of the study participants, which includes dependence in activities of daily living (ADL) and the MOS Short-Form 8-Item Health Survey™ (SF-8) (Fukuhara and Suzukamo, 2004). The dependent status in toileting, incontinence, and climbing/descending stairs was evaluated as basic ADL. The SF-8 as a measurement of health related quality of life was scored on the norm-based metrics, standard value 50 points and standard deviation 10 points, using Excel macro-program.

Informed consent was obtained from all participants prior to the commencement of study participation. The Ethics Committee of the Tokyo Metropolitan Institute of Gerontology approved the study protocol.

2.2. Measurements

2.2.1. Falls

A fall was defined as an event that resulted in a person coming to rest unintentionally on the ground or other lower level, not as the result of a major intrinsic event or an overwhelming hazard (Nevitt et al., 1989). Participants or their caregivers recorded via a questionnaire falls experienced in the previous three months. A three-month period was chosen as it has been shown that under estimation of fall history results from the use of longer-term recall methods in older adults (Cummings et al., 1988).

Table 1
Characteristics of the participants.

Parameters	
Age (year): median (IQR)	81.0 (12.0)
Female, *n* (%)	130 (61.0)
Dependent in ADL, *n* (%)	
Toileting	2 (0.9)
Incontinent	10 (4.7)
Climbing/descending stairs	62 (29.1)
Mental status questionnaire (error response), median (IQR)	1.0 (2.0)
SF-8, median (IQR)	
Summary score for physical component[a], mean ± S.D.	45.4 ± 10.6
Summary score for mental component[a], mean ± S.D.	49.3 ± 11.3

[a] *Note*: There were 10 missing values.

2.2.2. Physical assessments

All participants were assessed for functional lower limb strength with the CST, 5 times, for balance function with the OLS and tandem walk tests, and for functional mobility with the 6 m walking time and TUG-test. The assessment measures were conducted by day-center staff who had nursing, allied health or similar qualifications. Prior to the commencement of the study, all staff received training from the authors (HS and MS) in the correct protocols for administering all of the assessment measures included in the study. The assessors conducted introduction and practice of the physical assessments to facilitate understanding of the tests to the participants before the tests. The assessors were not blinded to fall data.

The CST is traditionally used as a measure of lower limb muscle function (Csuka and McCarty, 1985) and is included in a number of comprehensive falls risk assessment tools (Tinetti, 1986; Berg et al., 1992; Smith, 1994). The CST task in this study involved sitting down and standing up five times from a standing position. The participants who could not sit to stand without support were permitted to use their arms. The task in the CST was completed as quickly as possible and the time taken, in seconds, was the score. The CST is usually performed without using one's arms. However, we used the results of the CST with and without arms as the CST to ensure sufficient participants.

The OLS test consisted of attempting to stand on one leg for 120 s. For the OLS, two trials were performed and the maximum time obtained was the final score. The participants performed the OLS task on preferred leg. The OLS test has confirmed reliability (Curb et al., 2006). The tandem walk test measures participants' ability to walk with the feet placed in the tandem position (one foot directly in front of the other) during the double support period of the gait cycle. The constraint placed on the foot position presents a challenge to the postural control system, as the base of dynamic support is significantly reduced, causing a reduction in medio-lateral stability (Lord et al., 2001). The tandem walk test was measured by counting the number of successful steps while the participants walked toe to heel. The scoring method is similar to the functional gait assessment which has confirmed reliability (Wrisley et al., 2004). In this study, participants attempted twice to walk for a maximum of ten steps.

Slowed gait speed has previously been associated with an increased risk of falls (Imms and Edholm, 1981; Bootsma-van der Wiel et al., 2002) and it is a factor that is included in several falls risk assessment scales with a variety of protocols (Podsiadlo and Richardson, 1991; Piotrowski and Cole, 1994). In this study, the participants walked once on a flat surface at their "comfortable walking speed" for 6 m. Two markers indicated the start and end of the 6-m path. A 3-m approach was allowed before reaching the start marker so that the participants were walking at their normal pace within the timed path. The participants were also instructed to continue walking past the end of the 6-m path for a further 3 m to ensure that their walking pace was consistent throughout the task. The time taken to complete the task, measured in seconds, was the score.

The TUG test was measured once at the participant's comfortable pace. The TUG test includes basic mobility skills, including rising from a chair, walking 3 m, turning, returning to the chair and sitting down. Podsiadlo and Richardson (1991) validated the TUG in 60 elderly patients at a geriatric day hospital. It correlates significantly with the Berg balance scale (BBS) ($r = 0.81$), gait speed ($r = 0.61$), and the Barthel index (BI) ($r = 0.78$). The TUG test is one of the most frequently utilized test of gait for assessing fall risk in older people (NICE, 2004). If a walking aid was usually used inside the home, then the walking aid was used during the 6-m walking test and the TUG test.

2.2.3. Statistical analysis

The participants were categorized into faller and non-faller groups based on their three-month fall histories. Mann–Whitney test and χ^2 test were used to compare the differences in age, sex, physical tests, and using arms during the CST task between the faller and non-faller groups because these variables showed non-normally distribution for Kolmogorov–Smirnov test. Spearman correlation coefficient was calculated for setting up a structural equation model. A structural equation model provides estimates of the magnitude and significance of the hypothesized simultaneous causal connections between the risk factors and falls. Structural equation modeling is an extension of the general linear model, in which a hypothesis-driven diagram is constructed to explain the direction of associations between multiple dependent variables simultaneously (Stevens, 1996). Our hypothesized model in interrelation between falls and physical tests was composed of two stages: direct relationship between falls and physical tests; and indirect relationships mediated by gait performance between falls and the CST and balance. The absolute and relative goodness of fit were then assessed using the χ^2 statistic, the Tucker–Lewis index (TLI), and the comparative fit index (CFI). Variables with non-normally distribution were $\log_{10}$ transformed in structural equation modeling. Descriptive and basic statistical analyzes of the data were performed using the SPSS 15.0 software package (SPSS Inc., Chicago, USA), and Analysis of Moment Structures (AMOS) Graphics Version 7 software (Small Waters Corp., Chicago, USA) was used to investigate structural equation modeling.

3. Results

3.1. Differences in age, sex, physical tests, and using arms during the CST task between the faller and non-faller groups

During the three-month follow-up period, 39 participants (18.3%) experienced at least one fall. The fall group had significantly slower 6 m walking speed and took significantly longer to undertake the TUG test than the non-faller group (Table 2). There were no significant differences on the other physical measurements and using arms during the CST task between the faller and non-faller groups.

3.2. Relationship between physical tests

Slight correlations were shown between the CST and the 6 m-walking time and TUG, and between the OLS and tandem walk, 6-m-walking time and TUG ($r = -0.18$ to 0.39). The 6-m-walking time and TUG correlated moderately in the older participants ($r = 0.69$) (Table 3).

Table 2
Comparison of age, sex, and physical assessments between fallers and non-fallers.

Parameters	Non-fall group	Fall group	*p* value
Age (year), median (IQR)	81.0 (11.0)	80.0 (16.0)	0.964
Sex, *n* (%)			
Male	64 (77.1)	19 (22.9)	0.167
Female	110 (63.2)	20 (15.4)	
CST (s), median (IQR)	12.0 (6.1)	12.1 (7.7)	0.834
OLS (s), median (IQR)	4.0 (6.0)	3.0 (4.0)	0.310
Tandem walk (step), median (IQR)	4 (8.3)	2.0 (8.0)	0.125
6-m-walking time (s), median (IQR)	7.6 (4.6)	9.4 (4.5)	0.012
TUG (s), median (IQR)	13.3 (6.0)	16.0 (10.0)	0.030

Table 3
Correlation matrix of physical performance measurements.

Parameters	CST	OLS	Tandem walk	6m-walking time	TUG
CST	1.00	−0.05	0.06	0.37**	0.39**
OLS		1.00	0.34**	−0.18*	−0.23**
Tandem walk			1.00	−0.13	−0.12
6m-walking time				1.00	0.69**
TUG					1.00

* $p < 0.05$.
** $p < 0.01$.

3.3. Interrelationships between functional lower limb strength, balance, gait and falls

The structural equation model is shown in Fig. 1. Standardized regression weights are shown for the associations between each variable. Functional lower limb strength and balance function contributed significantly to gait function, and low gait function was significantly associated with falls in the older participants. The χ^2 test was not significant ($\chi^2 = 2.9$, df = 6, $p = 0.82$), indicating a good model fit. The TLI value (1.06) and the CFI value (1.00) also indicated a good model fit.

4. Discussion

The faller group showed significantly decreased performances in the 6 m-walking time and TUG test as a gait performance compared to the non-faller group although functional lower limb strength and balance did not show significant differences between the groups. The walking speed at a comfortable pace was the best test for use as a screening tool of falls in frail older adults when feasibility and validity were considered (Shimada et al., 2009). The TUG test is widely used as a measure to screen for fall risk, and recent studies support the predictive ability of this test for use with older people (Large et al., 2006; Kristensen et al., 2007). These significant tests showed moderate correlation in the older participants. The results suggest that the gait tests (TUG and 6m walking speed) were better at discriminating between older fallers and non-fallers than the CST, OLS, and tandem walk tests.

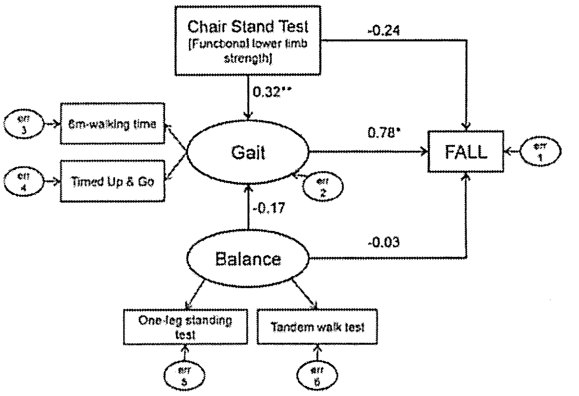

Fig. 1. The structural equation model illustrating the association between falls and the risk factors for falling. The structural equation model was constructed in two stages by explanatory variables that were associated with falls. The two stages included lower muscle function and poor balance resulting from impaired sensorimotor functions and lower functional mobility resulting from lower muscle and balance functions. *Notes*: *$p < 0.05$, **$p < 0.01$, standardized regression weights are shown for the associations between each variable.

When a structural equation model was devised to illustrate the causal relationship between falls and the physical study measures, gait function (as measured by the TUG and 6 m walk tests) was directly associated with falls. Additionally, functional lower limb strength (as measured with the CST) was included in the model as a significant underlying explanatory variable of gait function which was indirectly associated with falls. These results suggest that of the variables included in this analysis, gait function was the strongest correlate of falls and it was underpinned by tests of functional lower limb strength, which indirectly affected the occurrence of falls. The validity of the model in this study is supported by a previous study which identified lower limb muscle strength as a predictors of variable gait parameters (Lord et al., 1996). Moreover, rising from a chair and sitting down, which are components of the CST task, includes the TUG task.

One of the limitations of this study was that falls were measured retrospectively with a self-report method, which is known to be less accurate than prospective measurement. This may have led to an underreporting of falls in the study sample, although the participants only recalled the history of falls over three months. Second, we acknowledge that, because the study design excluded the frailest people who were immobile and could not undergo the physical examinations and people with cognitive impairment, the primary findings regarding the relationship between falls and the parameters tested cannot be generalized to these groups. Third, the structural equation model was constructed from the CST, OLS, tandem walk test, 6-m walking time, and TUG tests. Thus, the result of our model is limited by the measurement variables.

These study results have implications for the prevention of falls in older people. The model developed suggests the importance of gait interventions in preventing falls and that exercise programs which aim to reduce fall risk factors should include specific gait training elements.

In summary, the structural equation model revealed the associations between reduced performances in the CST and balance and falls were mediated primarily by impairments in gait function. This suggests that task-specific strength and balance training as well as general mobility retraining should be important components of exercise programs designed to reduce falls in older people.'

Conflict of interest statement

None.

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Imaging of Glucose Uptake During Walking in Elderly Adults

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Abstract: Gait disorders have been identified as one of the most influential physical impairments associated with deterioration in daily living activities among the elderly. A better understanding of the mechanisms responsible for gait disorders is important for developing intervention strategies for the elderly. In recent years, positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG) have been used to monitor glucose uptake by skeletal muscle during exercise. This review discusses recent studies in which FDG PET has been used to measure muscular glucose uptake, differences between young adults and the elderly in muscular glucose uptake during walking, and the usefulness of FDG PET for determining the effects of exercise intervention in the elderly.

Keywords: FDG, positron emission tomography, aged, gait disorder, skeletal muscle, exercise, physical activity.

INTRODUCTION

Healthy elderly people have less muscle mass, strength, and power production than healthy young people [1-5]. These differences are associated with a slower gait speed, shorter step length, shorter swing phase, and less range of motion at the hip, knee, and ankle joints during walking in the elderly [6-16]. A decrease in walking speed is associated with an increase in the need for assistance with daily living activities [17,18], falls [19-21], and nursing home admission [22]. Many studies have been conducted to identify the characteristics of the gait of the elderly.

Kinesiological studies have found that healthy elderly people carry out locomotor tasks at a level closer to their maximal torque-producing capabilities than young adults [23]. The increase in muscular activation during walking is a potential cause of decreased physical activity [24] because sustained walking may be limited, not by general exhaustion, but by the onset of fatigue in any of the participating muscles. Any decrease in physical activity has adverse effects on physical and psychological functions in elderly people [25,26]. Therefore, local muscle energy expenditure appears to be more important than global expenditure in determining movement and physical activity in the elderly [27].

In recent years, positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG) has been used to monitor cumulative muscle activity during exercise and to provide images of the spatial distribution of skeletal muscle metabolism [28-32]. PET is a method to detect gamma ray emitted from administered radiochemical compound such as FDG, and therefore a quantitative measurement of the spatial distribution of FDG is available. The purpose of this review is to examine whether FDG PET is useful for studying the gait of the elderly and for developing rehabilitation programs.

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MUSCLE ACTIVITY DURING WALKING IN THE ELDERLY

Winter *et al.* reported that one of the most critical changes with age is a reduction in stride caused by a lower plantar flexor power burst in the terminal stance phase of the gait cycle [11]. Neptune *et al.* suggested that a reduced power burst in the plantar flexor affects swing initiation and trunk progression during the late stance of the gait cycle and trunk stabilization in the early stance of the gait cycle [33]. The reduced power in the plantar flexor redistributes muscle activity and power with aging and is accompanied by increased output of the hip musculature and decreased output of the musculature of the more distal joints. DeVita and Hortobagyi reported that healthy elderly people produced 279% more work at the hip, 39% less work at the knee, and 29% less work at the ankle during the gait cycle compared with healthy young adults [34]. Therefore, advanced age is associated with a redistribution of joint torques and power in which the elderly use their hip extensors more and their knee extensors and ankle plantar flexors less than young adults when walking [34]. The compensatory response to decreased ankle power output appears to emanate from the hip muscles in healthy elderly individuals [15,34] and elderly individuals with a lower extremity disability [35,36]. A recent analysis using a musculoskeletal model showed that the power output of the plantar flexors is of particular importance for maintaining a normal walking pattern because it is able to compensate for many musculoskeletal deficits, including diminished muscle strength in the hip and knee flexors and extensors and increased hip joint stiffness [37].

An increase in the compensatory activity of proximal muscles is associated with an increase in neural stimuli to the muscles involved in walking and enhanced coactivation of the opposing muscles [23,38]. Excessive coactivation increases the metabolic cost of exercise. Mian *et al.* reported that antagonist muscle coactivation is greater in the elderly than in young adults, and that coactivation is moderately correlated with the metabolic cost of walking [39]. The increase in coactivation in the elderly during gait may be a compensatory mechanism for joint stiffness and thereby enhance stability [38]. This may be necessary because of low muscle strength and stiffness in the elderly, which would render them less able to recover quickly from a fall or from loss of dynamic stability. These results suggest that rehabilitation or preventive exercise programs should consider focusing on increasing or maintaining plantar flexor activity during walking, which appears critical for maintenance of normal walking mechanics [37]. Accurate measurement of muscle activity during walking is required to develop exercise programs for elderly people who exhibit compensatory responses or coactivation.

GLUCOSE UPTAKE IN SKELETAL MUSCLES DURING WALKING

Several noninvasive modalities have been used to acquire information on skeletal muscle function *in vivo*. Magnetic resonance (MR) imaging techniques are noninvasive and can be used to characterize the motion and mechanics of contracting skeletal muscle *in vivo* [40-42] but cannot be used to measure its metabolic activity. Electromyography (EMG) has been used to evaluate muscle activity, and amplitude-based algorithms have strong associations with metabolic cost. However, some of the elderly are not able to achieve maximal contractions [43], and quantification requires normalization of EMG amplitude to a maximal voluntary contraction EMG amplitude. Moreover, surface EMG is inappropriate for evaluating the activities of deep muscles such as the gluteus minimus. Kinetic analysis has also used to examine muscle activity during walking. However, this technique provides limited information on the etiology of the metabolic cost of walking because it cannot measure isolated synergistic muscular activities.

In FDG PET analysis, FDG is taken up by cells from circulation through glucose transporters 1–4 and is phosphorylated into FDG-6-phosphate by hexokinase, the first enzyme in the glycolysis pathway [44]. Because FDG-6-P is a poor substrate for glucose-phosphate isomerase, which converts glucose to fructose, and a lack of the enzyme for dephosphorylation, FDG-6-P escapes from further metabolism and is trapped within the cells [45], and can be detected using gamma ray emission [46]. Furthermore, FDG facilitates assessment of muscular activity because the half-life of ^{18}F is relatively long (109.8 min) compared with that of other positron-emitting tracers, which makes it ideal for observing cumulative muscle activity over a long period. Its demerits are a transient measurement is impossible. FDG PET can also be used to compare task-specific muscle activity because FDG uptake is closely correlated with exercise intensity [30,47,48]. For instance, Pappas *et al.* reported the results of regression analysis between normalized biceps FDG uptake and the number of repetitions of elbow flexion performed with 2 lb and 10 lb weights. Statistically significant positive correlations were found for both the 2 lb ($r = 0.899$) and 10 lb ($r = 0.958$) weights. The slopes of the 10 lb and 2 lb regression lines were 0.029 and 0.006, respectively. The ratio of the slopes for the 10 lb and 2 lb weights was 4.94, nearly equivalent to a fivefold ratio between the external forces produced by the elbow flexors for these two loads [47].

Oi *et al.* analyzed muscular activity during level walking in healthy young adults using FDG PET [31]. They found that the activity of the lower leg muscles was higher than that of the thigh muscles at self-selected speeds during a 15 min trial. We confirmed their findings in a recent study [32], providing good evidence that FDG PET is an appropriate method for measuring muscle activity during walking and identifying differences in muscle activity between young adults and the elderly during walking [49]. The subjects walked on a treadmill during 50 minutes. All young subjects could walk at the target walking speed of 4.0 km/h. However, all 10 elderly subjects could not walk at the target speed so the walking speed was reduced to achievable levels between 1.86 and 3.54 km/h. FDG (young: 361 ± 21 MBq, elderly: 367 ± 30 MBq) was injected 30 minutes after the start of the walking. From 35–80 minutes after the FDG injection, PET scans of the area from the crista iliaca to the planta were conducted in six overlapping bed positions. The images were reconstructed with a filtered-back-projection algorithm using a second-order low-pass filter with a cutoff frequency of 1.25 cycles/cm. Fig. (**1**) shows representative FDG PET images for a young adult and an elderly. The elderly had significantly increased glucose uptakes in the semitendinosus, biceps femoris, iliacus, gluteus minimus, gluteus medius, and gluteus maximus muscles. FDG uptake ratios between the elderly and young adults for the semitendinosus, biceps femoris, iliacus, gluteus minimus, gluteus medius, and gluteus maximus muscles were 3.02, 3.19, 1.66, 1.64, 3.68 and 3.05, respectively [49]. The elderly exhibited higher glucose metabolism in the hamstrings and hip muscles during walking than young adults. In contrast, distal muscles such as the planter flexors had lower FDG uptake ratios in the elderly compared with young adults, although the difference was not statistically significant. Of the distal muscles, the soleus had the lowest FDG uptake ratio (0.47). These findings on cumulative muscle activities during walking support previous kinesiological studies [11,34] and suggest that efficient muscle activity of the hamstrings or hip muscles during walking improves walking efficiency and results in a normal walking pattern in the elderly. Intervention studies are required to confirm this hypothesis.

FDG PET AS A TOOL FOR EVALUATING INTERVENTION EFFECTS

Walking exercise is attractive to elderly people because it is familiar and more convenient than many other sports and recreational activities [50,51]. Intervention studies have shown that strength or endurance training can improve measures of gait such as walking speed in elderly people [52-56]. It also improves physical fitness, particularly cardiovascular fitness and cognitive functions [57]. A better understanding of the effects of muscle activity during walking by exercise interventions may facilitate the development of targeted exercise programs.

Evaluation of a Walking Aid Using FDG PET

We previously described muscle activity in the elderly with or without a walking aid using FDG PET [58]. The walking aid involved a robotic stride assistance system (SAS) (Honda R & D Co. Ltd, Wako, Japan), which con-

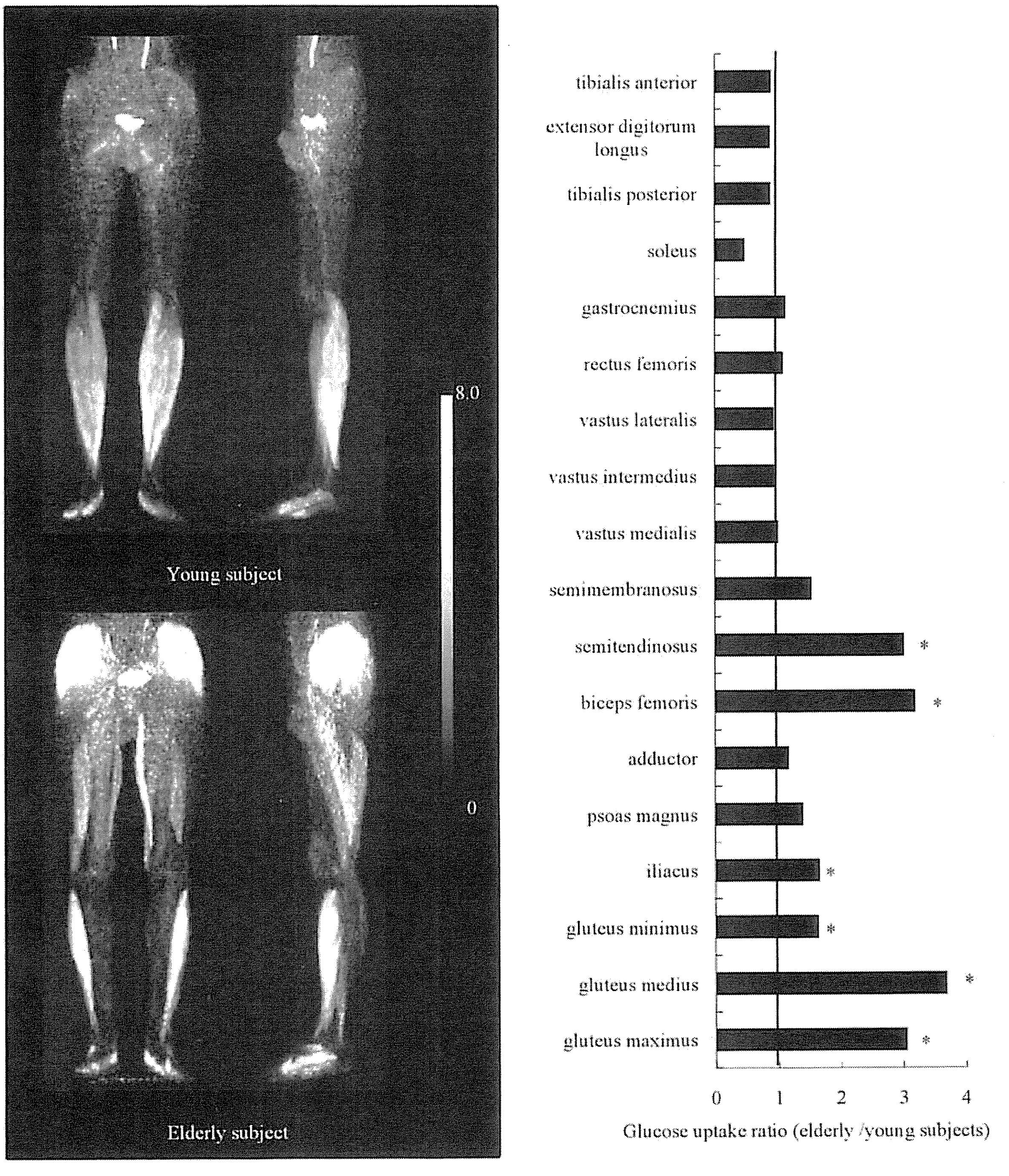

Fig. (1). FDG PET images taken after walking in young and elderly subjects.
*$p<.05$, **$p<.01$
In left FDG PET images, the above and below panels show projection images in young and elderly subjects, respectively. The elderly had significantly increased glucose uptakes in the semitendinosus, biceps femoris, iliacus, gluteus minimus, gluteus medius, and gluteus maximus muscles. The white color at the center of the pelvis resulted from accumulation of FDG in the bladder. Right bar chart shows FDG uptake ratios between the elderly and young adults in the lower skeletal muscles.

trolled the walk ratio (stride length/cadence) and provided supportive power to the thigh during walking [32]. Additional supporting information about the SAS may be found in the online version of our previous article (Movie S1) [59].

Fig. (2) shows representative FDG PET images taken after walking with or without the SAS. Glucose utilization in the lower-extremity muscles was evident after walking. There was no significant difference in the FDG uptakes of the lower skeletal muscles with or without the SAS, but the walk ratio, which was lower than the optimized walk ratio, and walking speed were improved by the SAS. These results suggest that the SAS can facilitate efficient walking patterns in respect of muscle activity. The improved walk ratios of elderly subjects may have increased the torque of their hip joints through the assistance provided by the SAS to the thigh. Therefore, the increased walk ratio was elicited without activating lower-extremity muscle activity. As these findings were revealed by FDG PET analysis, this technique may be useful for evaluating other walking aids or rehabilitation tools.

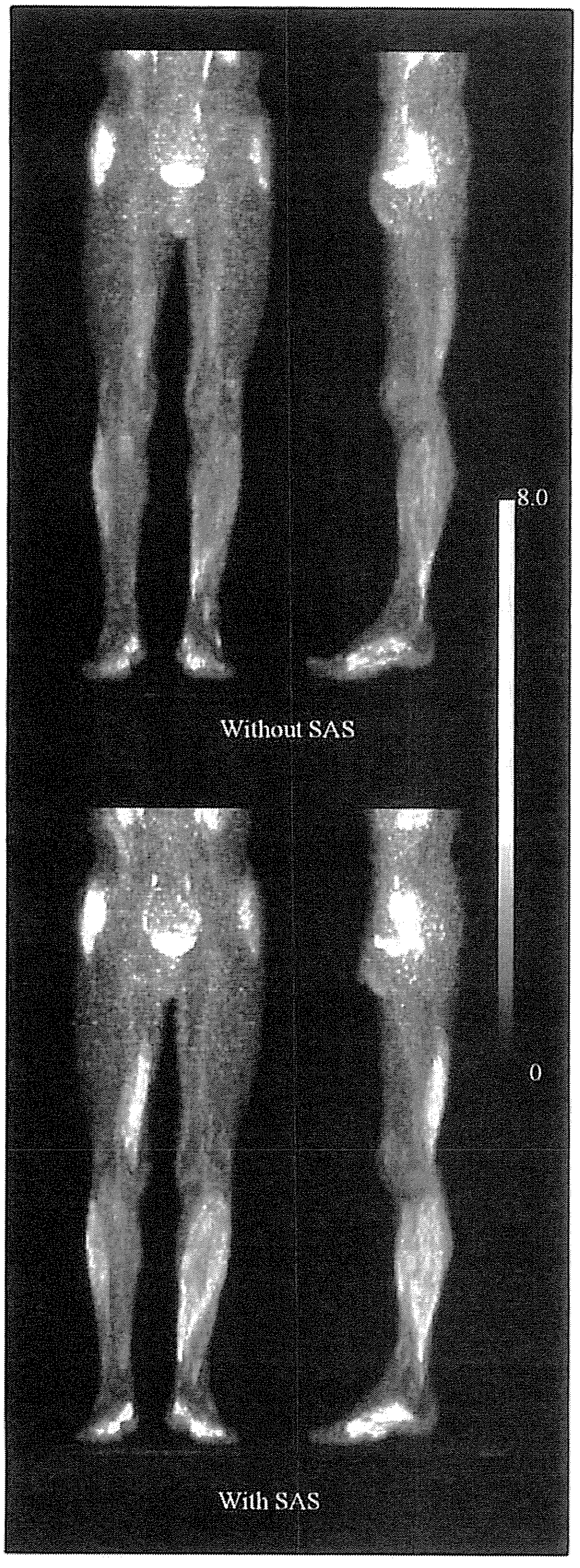

Fig. (2). FDG PET images taken after walking without or with the SAS.
FDG PET images taken after walking without or with the SAS were shown above and below panels, respectively. There was no significant difference in the FDG uptakes of the lower skeletal muscles with or without the SAS, although the walk ratio and walking speed were improved by the SAS.

Evaluation of Exercise Intervention Using FDG PET

The purpose of our next study was to assess the effects of a walking program for the elderly using the SAS. Fifteen subjects participated in a three-month walking program using the SAS, involving two 90 min supervised sessions per week. For FDG PET analysis of the walking program, subjects walked for 50 min at a comfortable speed on a circular indoor walking track without the SAS. Fig. (3) shows representative FDG PET images taken before and after the exercise intervention [59]. FDG uptake by the gluteus minimus, gluteus medius, and rectus femoris was significantly lower after the intervention than the one before it, although walking speed during FDG PET measurements increased after the intervention. In contrast, the lower distal muscles such as the medial gastrocnemius and soleus showed higher FDG uptakes after the intervention than those before it, although the difference was not statistically significant.

The SAS automatically lends horizontal force to the thigh to facilitate an optimal walk ratio and the SAS may help the elderly to learn how to use their muscles more efficiently. The consecutive stimuli provided by the SAS may help the elderly to adopt an efficient walking pattern. This study suggests that FDG PET is an appropriate tool for identifying intervention effects in terms of the glucose metabolism of muscles.

FUTURE DIRECTIONS

FDG PET analysis is noninvasive and is useful for studying cumulative muscle activity during exercise. However, because it cannot be automated and the measurement cost is high, it is difficult to apply to large samples or in clinical or community care settings. As a methodological issue of FDG PET, a kinetic analysis has a possibility to give us more quantitative information such as glucose transporter and hexokinase, although the kinetic analysis requires arterial blood sampling and it is a demerit of this approach. Clarification on whether increased muscle metabolism in the elderly is associated with muscle weakness, neuromuscular incoordination, kinesiological factors, daily living activity level, or dysfunctional physiological factors is required to facilitate targeted intervention. Future studies are required to develop a FDG PET system for analysis of muscular activity and to identify relationships between glucose uptake of muscles used quantitative FDG PET analysis and physical or behavioral variables.

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Ethical Approval: The ethics committee of the Tokyo Metropolitan Institute of Gerontology approved the protocol for all our researches which were referred by present paper.

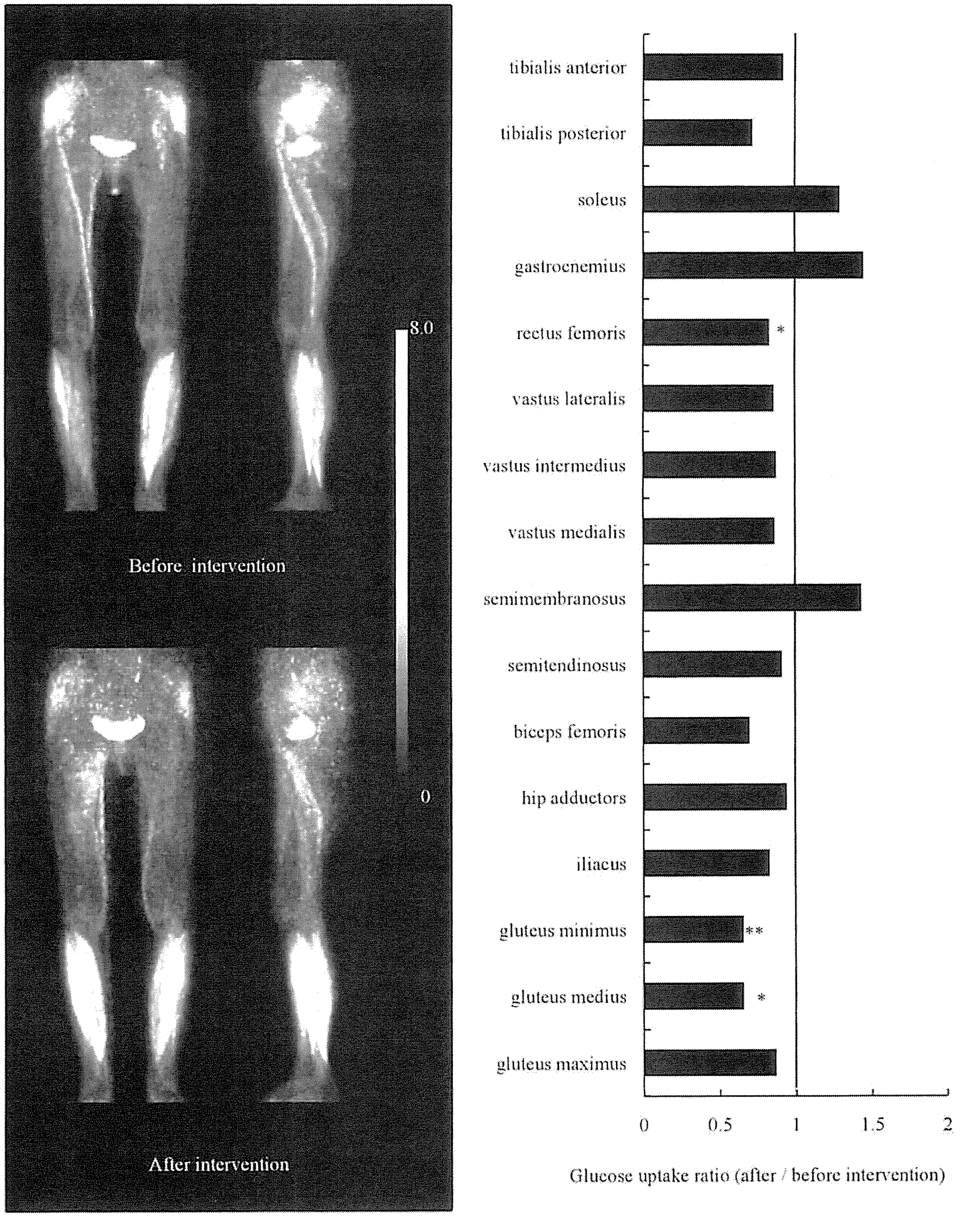

Fig. (3) FDG PET images of elderly women before and after the intervention.
$^*p<.05$, $^{**}p<.01$
The left and right panels show projection images of FDG PET and FDG uptake ratios between after and before intervention, respectively. FDG uptake by the gluteus minimus, gluteus medius, and rectus femoris was significantly lower after the intervention than before it.

CONFLICT OF INTEREST

The author has no financial or any other kind of personal conflicts with this paper.

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ORIGINAL ARTICLE

The Association Between Decline in Physical Functioning and Atrophy of Medial Temporal Areas in Community-Dwelling Older Adults With Amnestic and Nonamnestic Mild Cognitive Impairment

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ABSTRACT. Makizako H, Shimada H, Doi T, Yoshida D, Ito K, Kato T, Shimokata H, Washimi Y, Endo H, Suzuki T. The association between decline in physical functioning and atrophy of medial temporal areas in community-dwelling older adults with amnestic and nonamnestic mild cognitive impairment. Arch Phys Med Rehabil 2011;92:1992-9.

Objective: To examine whether declining performance in aspects of physical functioning, including lower extremity muscle strength, 1-legged balance, walking speed, and exercise capacity, is associated with atrophy of medial temporal areas in community-dwelling older adults with mild cognitive impairment (MCI).

Design: Cross-sectional study.

Setting: General community in Japan.

Participants: Community-dwelling older adults 65 years and older with a Clinical Dementia Rating of 0.5 or memory complaints were enrolled in this study. This study examined 34 participants with amnestic MCI (aMCI) and 58 nonamnestic MCI (non-aMCI) participants.

Interventions: Not applicable.

Main Outcome Measures: The following physical performance tests were conducted: muscle strength of knee extension, 1-legged standing time, 5-m walking test, and 6-minute walk test (6MWT). The *z* scores of the voxel-based specific regional analysis system for Alzheimer's disease were determined to assess the degree of atrophy in the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC).

Results: In the aMCI group, 6MWT performance was associated with MTA-ERC atrophy (β=–.462, P=.014) after controlling for age. In the stepwise multiple regression analyses, 6MWT and body mass index were found to be significant determinants of MTA-ERC atrophy in all participants (R^2=.275), as well as the aMCI and non-aMCI groups when analyzed separately (R^2=.418 and R^2=.216, respectively).

Conclusions: A decline in exercise capacity was found to be more closely associated with atrophy of the MTA-ERC compared with other aspects of physical functioning in older adults with MCI, especially the amnestic type. These findings suggest that it is important for future studies to investigate the effects of increased aerobic activity and improved fitness on brain volume in older adults at risk of developing dementia.

Key Words: Cognition; Entorhinal cortex; Memory; Physical fitness; Rehabilitation.

MILD COGNITIVE IMPAIRMENT (MCI) is a heterogeneous condition associated with the transitional phase between normal cognitive aging and Alzheimer's disease (AD).[1,2] Prospective data have also indicated that physical frailty and lower physical performance may be associated with an increased risk of MCI among older people.[3-6]

Several previous studies have indicated that aspects of physical performance, such as gait dysfunction,[7,8] reduced postural stability,[9] and decline in cardiorespiratory fitness,[10] are related to structural changes of the brain (eg, leukoaraiosis,[7] medial temporal lobe atrophy,[9] whole-brain volume decline[10]) in older people. In addition, a prospective, observational cohort study indicated that muscle weakness was associated with an increased risk of developing AD and MCI.[4] However, these analyses did not include indices of multidimensional physical abilities such as muscle strength, mobility, balance, or fitness for examining subjects with MCI. There are few data on the

List of Abbreviations

AD	Alzheimer's disease
aMCI	amnestic mild cognitive impairment
apoE4	apolipoprotein Eϵ4
BMI	body mass index
GDS	Geriatric Depression Scale
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MTA-ERC	medial temporal areas, including the entorhinal cortex
OLS	1-legged standing
6MWT	6-minute walk test
VSRAD	voxel-based specific regional analysis system for Alzheimer's disease
WMS-R	Wechsler Memory Scale–Revised
WS	walking speed

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relationship between brain atrophy and multidimensional physical functioning in older adults with MCI.

Severe hippocampal and entorhinal cortex deterioration is found to occur in AD, and the prodromal state of MCI has been examined with regard to neuropathologic substrates (eg, neuritic plaques, neurofibrillary tangles, hippocampal atrophy) in numerous studies.[11-13] However, it is difficult to quantitatively evaluate atrophy of the medial temporal lobe including the hippocampal and entorhinal cortex by visual inspection. On the other hand, volumetric assessment of the entorhinal cortex in routine clinical practice requires time-consuming region-of-interest analysis, which is dependent on the expertise of the examiners, and lacks an automated volume measurement technique.[14] To resolve this difficulty, Matsuda et al[14-16] recently developed a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), and an automated software program. In the VSRAD, z scores are used as an indicator reflecting the degree of atrophy in the medial temporal areas including the entorhinal cortex (MTA-ERC) for the diagnosis of early AD. Hirata et al[15] found a high level of accuracy (87.8%) for discriminating patients with very early AD at the MCI stage from normal control subjects using z scores in the VSRAD. Determining which aspects of physical function are more closely related to MTA-ERC atrophy among older people at risk of developing dementia may be useful for planning intervention programs. Clinical randomized trials suggest that participating in aerobic exercise, physical activity, or resistance training regimens can help to restore the neural and cognitive decay manifested in individuals without cognitive decline[17,18] but at risk of dementia.[19,20] Therefore, physical performance, especially exercise capacity and muscle strength, may be closely related to brain atrophy in subjects with MCI.

We examined the relationships between multidimensional physical performance and brain atrophy, particularly in bilateral medial temporal areas in older adults with MCI, using a cross-sectional design. Furthermore, we performed analyses comparing amnestic MCI (aMCI) and nonamnestic MCI (non-aMCI) participants, because aMCI is likely to progress to AD.[2,21] Although there are few data on differences in multidimensional physical performance between aMCI and non-aMCI older adults, a decline in physical performance may be related to the atrophy of brain areas important for memory earlier in aMCI. We hypothesized that there would be a difference in the association of multidimensional physical performance and brain atrophy between aMCI and non-aMCI participants.

METHODS

Participants

Participants were recruited from 2 volunteer databases (n=1543), which included elderly individuals 65 years and older, selected either by random sampling or when they attended a health check in Obu, Japan. For inclusion, all participants were required to meet the definition of MCI using Petersen criteria.[22] A total of 528 potential participants exhibiting a Clinical Dementia Rating of 0.5 or a memory complaint were enrolled in the first eligibility assessments. Of these, 135 participants underwent the second eligibility assessments, including neuropsychological tests, physical performance tests, face-to-face interviews, and scanning with magnetic resonance imaging (MRI). Criteria for inclusion into this study required that the participant was 65 years or older, living independently in the community (ie, no impairment of activities of daily living), and Japanese speaking, with sufficient hearing and visual acuity to participate in the examinations, and general cognitive functioning (Mini-Mental State Examination [MMSE][23] scores between 24 and 30). Exclusion criteria included a history of major psychiatric illness (eg, schizophrenia or bipolar disorder), other serious neurologic or musculoskeletal diagnoses, and clinical depression (Geriatric Depression Scale [GDS][24] score ≥10). In addition, we excluded 8 participants who could not complete the physical performance tests. Finally, 92 participants satisfied the inclusion criteria, and their data were analyzed in the present study.

Participants were classified into aMCI and non-aMCI groups. Of the 92 participants, 34 exhibited an objectively determined memory impairment, as assessed via education-adjusted scores on the Wechsler Memory Scale–Revised (WMS-R) Logical Memory II, and were included in the aMCI group.[25,26] The non-aMCI participants (n=58) did not have any objective memory impairment as measured by education-adjusted scores on the WMS-R Logical Memory II scale. However, they exhibited a Clinical Dementia Rating of 0.5 or a memory complaint, and met the definition of MCI using Petersen criteria (not normal for age, not demented, cognitive decline, and essentially normal functional activities).[22] This study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants provided written informed consent. The purpose, nature, and potential risks of the experiments were fully explained, and all subjects gave written, informed consent before participating in the study.

Physical Performance Tests

The following physical performance tests were conducted: isometric knee extension strength, 1-legged standing (OLS) time, walking speed (WS), and 6-minute walk test (6MWT). For physical performance tests, we chose physical functions that previous studies suggested to be related to a risk of developing dementia and structural age-related changes in the brain.[4,7-9,27,28] In addition, we were careful to choose tests that could be conducted safely and easily in a clinical setting with older adults who have MCI. All physical performance tests were performed by licensed and well-trained physical therapists.

Isometric knee extension strength was tested twice using a dynamometer.[a] Knee extension was measured while the participant was sitting on a chair with a backrest and the knee flexed to 90°. A testing pad was attached to the front lower leg of the participant and strapped to the leg of the chair. The participant was instructed to push the pad with maximal strength. Licensed and well-trained physical therapists confirmed compensatory movement and assessed muscle strength. Participants practiced several times before data collection. Two trials were conducted, and the peak force of the higher score was recorded. Isometric knee extension torque was normalized against the moment arm and body mass (Nm/kg) in the data analysis.

The OLS test is a commonly used balance assessment of postural stability. For the OLS test, we asked participants to look straight ahead at a dot 50cm in front of them, then to stand on their preferred leg with their eyes open and hands down alongside the trunk. OLS balance was measured as the length of time (0–60s) participants were able to stand on 1 leg. The better of the 2 trials was used for statistical analysis.

WS was measured using a 5-m walking test. The usual WS of the participants was measured over an 11-m straight and level path. The time taken (in seconds) to pass the 5-m mark on the path was used as the participant's score. A 3-m approach was allowed before the starting marker, and an additional 3m of space was provided after the end marker of the 5-m path to ensure a usual walking pace throughout the task. Participants were instructed to walk the 11-m path at their usual walking pace. The time to complete the 5-m walking test was measured once. A previous study[29] reported that this walking test has a high level of reproducibility.

Participants' exercise capacity was quantitatively measured using the 6MWT. The 6MWT is used to measure the maximum distance that a person can walk in 6 minutes.[30] The 6MWT is a modification of the 12-minute walk-run test originally developed by Cooper,[31] and is commonly used as an assessment of exercise capacity. The 6MWT is useful for predicting maximal oxygen uptake related to cardiorespiratory fitness and is easily administered in clinical settings.[32] Participants were asked to walk from end to end, covering as much ground as they could during the allotted time, without running. Participants were instructed to walk as far as possible in 6 minutes along a 10-m course, and the test was performed under the supervision of a physical therapist. Each minute, participants were informed of the time elapsed and were given standardized encouragement. The distance (in meters) walked in 6 minutes was recorded.

MRI Procedure and Voxel-Based MRI Analysis

We determined the atrophy of MTA-ERC using VSRAD software,[b] which yields a z score as the end point for the assessment of medial temporal lobe volume. MRI was performed using a 1.5-T system.[c] Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1700ms; echo time, 4.0ms; flip angle 15°, acquisition matrix 256×256, 1.3-mm slice thickness). According to the VSRAD procedure proposed by Matsuda[14] and Hirata,[15] the acquired MRI images were reformatted to gapless 2-mm, thin-slice transaxial images.

In the voxel-based MRI analyses, the first anatomic standardization used affine transformation. The normalized MRI images were then segmented into gray matter, white matter, cerebrospinal fluid, and other components using a modified version of the clustering algorithm, the maximum likelihood "mixture model" algorithm. The segmentation procedure involved a calculation for each voxel using a Bayesian probability of belonging to each tissue class based on a priori MRI information with a nonuniformity correction. The segmented gray matter images were then subjected to an affine and nonlinear anatomic standardization using an a priori gray matter template. The anatomically standardized gray matter images were smoothed with an isotropic Gaussian kernel 12mm full width at half maximum to exploit the partial volume effects, so as to create a spectrum of gray matter intensities. Gray matter intensities are equivalent to the weighted average of gray matter voxels located in the volume fixed by a smoothing kernel. Each gray matter image of the participants was compared with the mean and SD of gray matter images from healthy volunteers collected in an earlier study,[15] using voxel-by-voxel z-score analysis after voxel normalization to global mean intensities: z score = (control mean − individual value)/(control SD), as reported in several previous studies.[15,33] The VSRAD software contained the MRI data of normal control subjects with a wide age range and could automatically compare the gray matter intensities of the MRI data on a voxel-by-voxel basis between experimental subjects and age-comparable normal control subjects. The z score thus reflected the degree of atrophy in bilateral MTA-ERC. For a reliable criterion of z values, Hirata[15] demonstrated automated voxel-based analysis using a z-score value in the bilateral MTA-ERC after anatomic standardization of gray matter images. The programs calculate the area under the receiver operating characteristic curves. Accuracy was .949 (95% confidence interval, .880–.982) or 87.8%. Higher z scores indicate clearer MTA-ERC atrophy, and a z score of less than 1.0 means that hardly any atrophy of the MTA-ERC is observed.[33]

Statistical Analysis

Student t tests or a chi-square test (to test for sex differences) were used to compare the demographic, neuropsychological measures, physical performance scores, and z scores of the VSRAD between the aMCI and non-aMCI groups. Pearson correlation coefficients were calculated to assess simple relationships between MTA-ERC atrophy and physical performance tests. Linear regression analysis was used to assess the relationships between the variables while controlling for age to minimize the confounding influence of age-related changes in brain atrophy, and standardized β values were calculated. We evaluated the association between MTA-ERC atrophy and other factors using stepwise multiple regression analyses, and adjusted R^2 values were calculated. Statistical analyses were performed using SPSS for Windows, version 17.0.[d] Statistical significance was set at .05 for all analyses.

RESULTS

Table 1 summarizes the characteristics of the aMCI and non-aMCI groups. Mean ± SD age and education years in all

Table 1: Participants' Demographic Information

Characteristics	All Participants (n=92)	aMCI Group (n=34)	Non-aMCI (n=58)	P
Age (y)	74.4±6.3	75.4±6.6	73.8±6.1	.24
Women	49 (53.3)	15 (44.1)	34 (58.6)	.18
BMI (kg/m²)	23.4±3.2	22.4±2.9	24.0±3.2	.02*
Education (y)	10.7±2.5	11.3±2.7	10.4±2.2	.07
Knee extension strength (Nm/kg)	1.2±0.5	1.2±0.5	1.1±0.4	.24
OLS (s)	36.7±23.4	38.4±23.4	35.8±23.7	.61
WS (m/s)	1.1±0.2	1.1±0.2	1.2±0.3	.10
6MWT (m)	374.0±69.4	364.1±70.7	379.7±68.6	.30
MMSE (score)	27.0±1.9	27.0±1.9	26.9±2.0	.78
Logical Memory II (score)	5.5±4.3	1.2±1.3	8.0±3.5	<.01†
GDS (score)	3.0±2.3	3.0±2.4	3.1±2.3	.89
Atrophy of the medial temporal areas (z score)	1.4±1.0	1.4±1.0	1.4±0.9	.96

NOTE. Values are mean ± SD, n (%), or as otherwise indicated.
*P<.05; †P<.01.

Table 2: Relationships Between Physical Performance Scores and Atrophy of Medial Temporal Areas (n=92)

	aMCI (n=34)		Non-aMCI (n=58)	
Dependent Variable	Simple Correlation (r)	Age-Controlled (β)	Simple Correlation (r)	Age-Controlled (β)
Knee extension strength	−.10	.13	−.03	−.01
OLS	−.35*	−.05	−.08	.17
WS	−.46†	−.30	−.15	.03
6MWT	−.58†	−.46*	−.37†	−.26

NOTE. Pearson's r values represent the simple correlation between the atrophy of medial temporal areas and the dependent variables. Standardized β values represent the correlation between the atrophy of medial temporal areas and each dependent variable after controlling for age.
*$P<.05$; †$P<.01$.

participants were 74.4±6.3 and 10.7±2.5 years, respectively. The aMCI group exhibited a statistically significant lower body mass index (BMI) (aMCI=22.4±2.9kg/m^2, non-aMCI=24.0±3.2kg/m^2; $P=.020$) and lower Logical Memory II scores (aMCI=1.2±1.3 points, non-aMCI=8.0±3.5 points; $P<.001$) compared with the non-aMCI group. There were no statistically significant between-group differences in age, sex, education, knee extension strength, OLS, WS, 6MWT, MMSE, GDS, or MTA-ERC atrophy.

Simple correlations were examined between MTA-ERC atrophy and physical performance tests in each group (table 2). OLS, WS, and 6MWT scores were associated with MTA-ERC atrophy in the aMCI group (OLS, $r=-.35$, $P=.048$; WS, $r=-.46$, $P=.006$; 6MWT, $r=-.58$, $P<.001$). In the non-aMCI group, MTA-ERC atrophy was only associated with 6MWT scores ($r=-.37$, $P=.004$). Both groups exhibited statistically significant correlations between MTA-ERC atrophy and exercise capacity levels (fig 1). All of these relationships disappeared when the linear regression model was adjusted for age, except the relationship between MTA-ERC atrophy and 6MWT in the aMCI group ($\beta=-.46$, $P=.014$) (see table 2). In the stepwise multiple regression analyses, 6MWT and BMI scores were found to be significant determinants of MTA-ERC atrophy in all participants ($R^2=.28$), and in both the aMCI group ($R^2=.42$), and the non-aMCI group ($R^2=.22$) when analyzed separately (table 3). The β estimates of 6MWT for all participants, the aMCI group, and the non-aMCI group (−.42 to −.59) were higher than those for BMI scores (−.27 to −.29).

DISCUSSION

The present results demonstrated that lower exercise capacity levels measured by the 6MWT in older adults with aMCI were associated with MTA-ERC atrophy, even after controlling for age. In addition, 6MWT and BMI scores were significant determinants of MTA-ERC atrophy in not only the aMCI group, but also the non-aMCI group. There was no association between MTA-ERC atrophy and OLS and WS in the non-aMCI group, or knee extension strength in either group. Although OLS and WS in the aMCI group were simply associated with MTA-ERC atrophy, these relationships were not significant after controlling for age. In short, 6MWT scores were closely related to MTA-ERC atrophy without an effect of age. These data suggest that exercise capacity in subjects with MCI

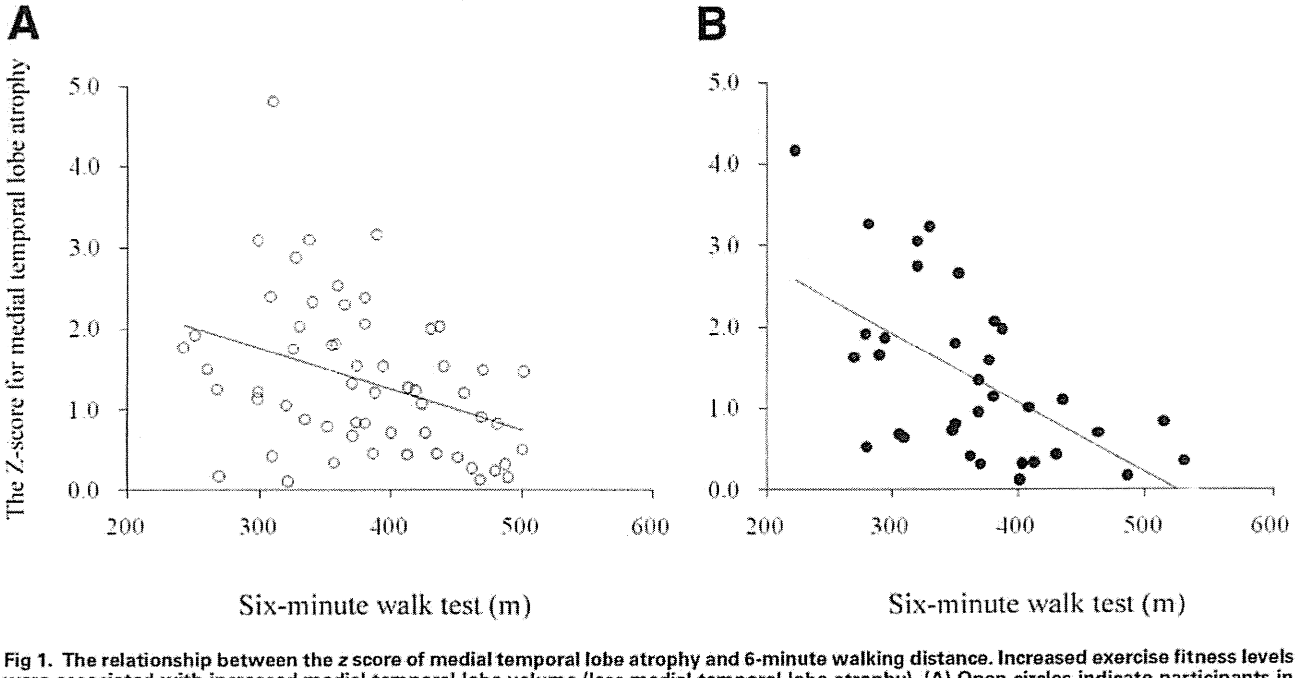

Fig 1. The relationship between the *z* score of medial temporal lobe atrophy and 6-minute walking distance. Increased exercise fitness levels were associated with increased medial temporal lobe volume (less medial temporal lobe atrophy). (A) Open circles indicate participants in the non-aMCI group ($r=-.37$, $P=.004$). (B) Filled circles indicate participants in the aMCI group ($r=-.58$, $P<.001$).

Table 3: Determinants of the Atrophy of Medial Temporal Areas in All Participants, and the aMCI and Non-aMCI Groups Analyzed Separately

Determinants of Atrophy	βEstimates (95% CI)
Atrophy of the medial temporal areas	
All participants, R^2=.28	
6MWT	−.48 (−.01 to −.00)*
BMI	−.27 (−.14 to −.03)*
aMCI group, R^2=.42	
6MWT	−.59 (−.01 to −.01)*
BMI	−.29 (−.20 to −.00)†
Non-aMCI group, R^2=.22	
6MWT	−.42 (−.01 to −.00)*
BMI	−.29 (−.16 to −.01)†

NOTE. Independent variables were age, BMI, knee extension strength, OLS, WS, and 6MWT.
Abbreviation: CI, confidence interval.
*P<.01; †P<.05.

might be closely associated with a reduction in MTA-ERC atrophy compared with other physical functioning. A possible reason for these results is that the maintenance of exercise capacity might have a positive effect on neuropathologic substrates in older adults with MCI.

Our finding that 6MWT scores were closely related to MTA-ERC atrophy was consistent with previous studies[10,34] showing that exercise and cardiorespiratory fitness, as defined by peak oxygen consumption, were positively associated with whole-brain, whole white matter, and medial temporal lobe (including hippocampus) volumes in subjects with AD or early AD. Previous studies using animal models have demonstrated that a higher level of fitness through increased physical activity is associated with enhanced neuronal survival to brain insults,[35,36] increased vascularization,[37] and elevated levels of growth factors in brain areas important for memory.[38,39] Other studies with nonhuman animals reported that increased physical activity in a transgenic mouse model of AD was associated with decreased neuropathologic burden in both cortical and hippocampal regions, suggesting that exercise may mediate the amyloid cascade in favor of reduced production of β-amyloid protein.[40] In addition, recent studies on early AD have indicated that increased cardiorespiratory fitness is closely related to increased brain volume (eg, decreased whole-brain atrophy,[10] less medial temporal lobe atrophy[34]), and that relationship may be affected by neuronal proliferation as indicated in nonhuman studies. The present findings also suggest a relationship between exercise capacity (as defined by a physical performance test using the maximum distance walked in 6min) and MTA-ERC atrophy, consistent with a fitness-related increased capacity for neuronal proliferation in older adults with MCI.

On the other hand, our results revealed no significant correlations between MTA-ERC atrophy and knee extension strength, WS, or OLS after controlling for age. Previous studies[4,7-9,27,28] indicated that muscle weakness, gait dysfunction, and reduced postural stability were related to brain function and cognitive abnormalities in older people. However, other studies[27,41,42] reported that these relationships were not necessarily significant between older adults with and without MCI. Eggermont et al[27] examined differences in lower extremity function in older people by using 3 different measurements: WS, functional mobility, and lower body strength. The results suggested that there were differences between cognitively healthy control subjects and MCI and AD groups in WS, differences between controls and patients with AD in functional mobility, but no between-group differences in lower body strength. Another study by Kido et al[9] demonstrated an association between static postural instability, and brain abnormalities and cognitive decline. They found that reduced postural stability was an independent marker of brain atrophy and cognitive decline in older adults. However, these studies did not analyze multidimensional physical functioning, including muscle strength, mobility, fitness, and balance. To our knowledge, this is the first study to demonstrate a relationship between brain atrophy and multidimensional physical functioning in older adults with MCI, and to examine these relationships between aMCI and non-aMCI groups. The results of the present examination of muscle strength, balance, WS, and exercise capacity suggest that higher exercise capacity may be the most important physical factor related to brain volume in the medial temporal lobe in older adults with MCI, especially aMCI. Moreover, we speculate that higher levels of fitness are closely related to higher levels of physical activity, and that higher levels of physical activity have a strong influence on cognitive function.[43-45] Previous evidence suggests that physical exercise confers biological benefits related to increased oxygen delivery[46] and reduced cell loss in sensitive areas such as the hippocampus[47] in older adults. Therefore, exercise capacity may be more closely related to medial temporal lobe atrophy compared with the other physical performance tests included in this study.

Our multiple regression analyses revealed that BMI was also a significant determinant of MTA-ERC atrophy, although β estimates of BMI were no higher than those for 6MWT. Previous research on the relationship between BMI and dementia has yielded inconsistent results, with some studies reporting that participants with higher BMI were at greater risk of dementia,[48] others reporting a reduced risk,[49-51] and some reporting no significant association between BMI and dementia.[52] Other studies[50,53] have reported that low BMI and declining BMI are associated with a greater risk of dementia. Our finding that low BMI was a significant determinant of MTA-ERC atrophy is in accord with some previous reports. In general, obesity is less prevalent among Japanese compared with Westerners.[54,55] The mean BMI in our sample (23.4kg/m^2) was relatively low, and lower BMI was likely to be related to poor nutritional status, potentially impacting on cognitive decline and brain atrophy.[56] Although low BMI was a significant determinant of MTA-ERC atrophy, the relationship between BMI and risk of dementia with brain atrophy was not consistent in previous studies, as previously described. Thus, longitudinal studies with large samples are needed to fully elucidate the relationship between BMI and brain atrophy in Japanese older adults with MCI.

Figure 2 shows z-score maps from 2 typical cases of aMCI participants. Both participants exhibited preserved general cognitive function (MMSE scores: participant A, 27; participant B, 29) and intact activities of daily living (the subscales of the Tokyo Metropolitan Institute of Gerontology Index of Competence,[57] both exhibiting high scores on each scale). However, both participants met aMCI criteria using education-adjusted scores on the WMS-R Logical Memory II. In addition, even though they were of a similar age and BMI, the z score of VSRAD in participant A was greater than 2.0 (z score, 2.66), indicating significant atrophy, but participant B did not show atrophy (z score, .70). Interestingly, we found physical performance differences between the 2 cases; participant B exhibited little or no atrophy of the MTA-ERC (z score, <1.0), and walked more than 100m further in the 6MWT than participant A, who exhibited moderate atrophy of the MTA-ERC. These

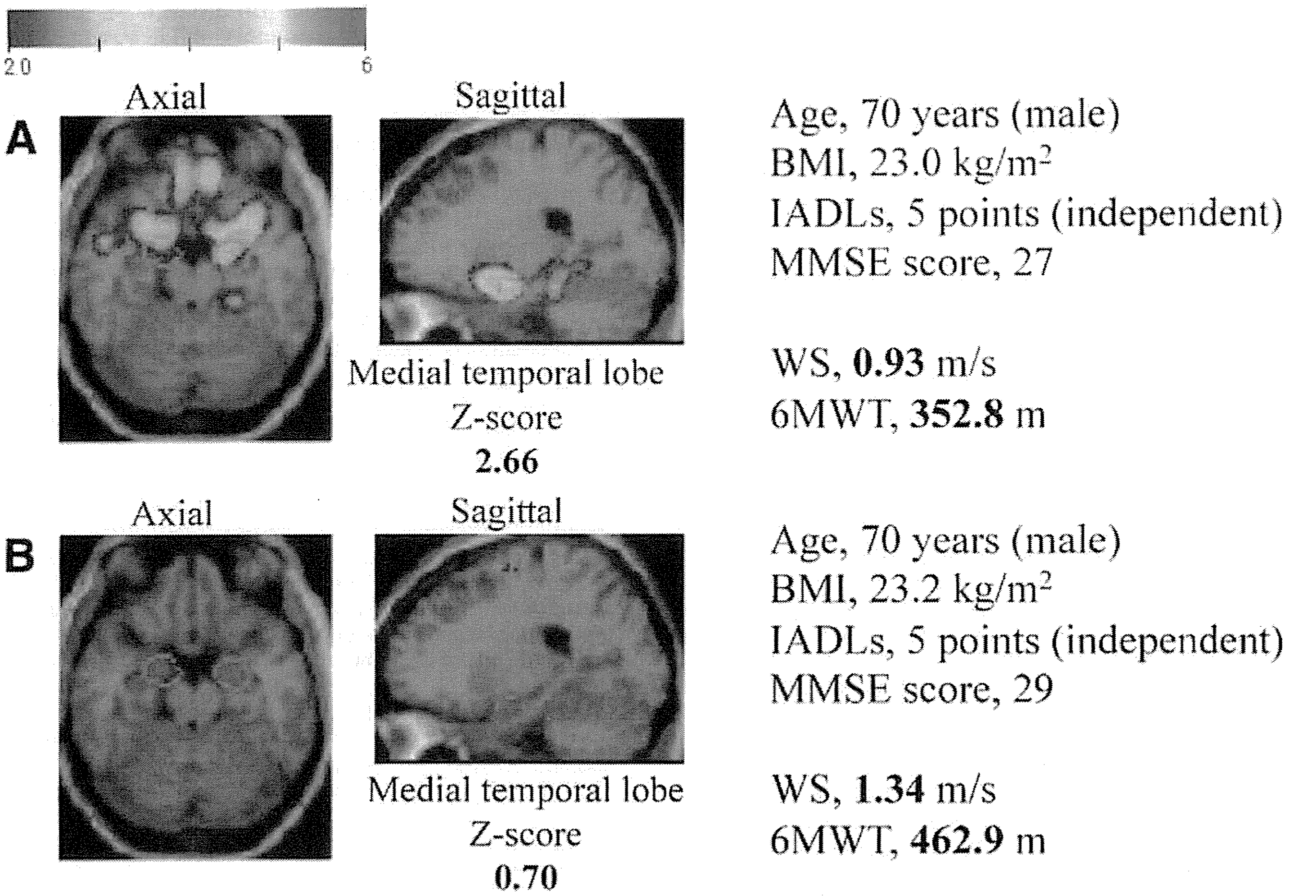

Fig 2. The *z* score of VSRAD maps in 2 typical cases of the aMCI group in this study. Purple lines indicate the bilateral medial temporal areas including entorhinal cortices. Colored areas on the MRI are those with a *z* score greater than 2.0 (significant atrophy). The color-scaled *z*-score maps ranging from 2.0 to 6.0 were displayed by overlaying on orthogonal sections of the anatomically standardized MRI of the participants. The color scale for *z* score is shown in the upper left of the figure. The instrumental activities of daily living (IADLs) score was determined using the subscales (0–5 points) of the Tokyo Metropolitan Institute of Gerontology Index of Competence.[52]

typical cases in the aMCI group indicate that physical function, particularly exercise capacity, may be the most important factor related to preserved medial temporal lobe volume loss in older adults with memory impairments. Recent meta-analyses[58,59] have demonstrated that exercise interventions can improve cognitive function in people with AD and MCI. Our results suggest that increased exercise capacity, rather than muscle strength, mobility, or balance, may be the most effective physical function in preventing structural changes of the brain associated with cognitive decline in subjects with MCI. Further investigation of the effects of aerobic exercise on preventing brain atrophy and developing AD in older adults with MCI is required to assess this possibility in more detail.

Study Limitations

Several limitations of the current study must be considered. First, we did not collect the full range of data potentially affecting the relationship between exercise capacity and atrophy of the medial temporal areas. For instance, we did not examine whether the relationship between exercise fitness and brain volume was modified by the presence of the apolipoprotein E∊4 (apoE4) risk allele.[34] In addition, no measure of physical activity, such as a self-report inventory or recording pedometer, was included. Second, we did not include data from healthy older persons and patients with AD in the present study. Further studies considering the effects of genetic factors (eg, apoE4,[60] brain-derived neurotrophic factor,[38] and insulin-like growth factor[35]) on neurologic brain changes using data including patients with AD are needed to determine the relationships between physical function and MTA-ERC atrophy in AD-related processes. Furthermore, our data were collected using a cross-sectional design, and the sample size of aMCI participants was markedly smaller than non-aMCI participants, limiting the interpretation of the results. Further experiments with longitudinal and interventional designs are required for more accurately defining the role of physical functions, especially exercise capacity, in modifying the processes of brain aging with risk of developing AD.

CONCLUSIONS

A decline in exercise capacity was found to be more closely associated with atrophy of the MTA-ERC compared with the other aspects of physical functioning in older adults with MCI, especially those with the amnestic type. Future studies should investigate the effects of aerobic activity on improving brain volume and cognitive function in older adults with MCI.

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Suppliers

a. Model MDKKS; Molten Co Ltd, Hiroshima, Japan.
b. Eisai, Tokyo, Japan.
c. Magnetom Avanto; Siemens, Germany.
d. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

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The Relationship between the Subjective Risk Rating of Specific Tasks and Falls in Frail Elderly People

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Abstract. [Purpose] The purpose of this study was to determine whether a subjective risk rating for falls is more valuable than other screening tools in relating falls in frail elderly people. [Subjects] The study included 232 elderly subjects (48 men, 184 women, mean age 82.8 ± 6.3 years) who had been using day care services. [Methods] Data included history of falls during the previous year, the subjective risk rating of specific tasks (SRRST), which is composed of seven questions, and potential confounding factors including demographic variables, primary diseases or general health status, physical performance, and behavioral variables. To determine the independent factors related to falls, a multiple logistic regression analysis was used to measure odds ratios adjusted for all measurement variables. [Results] Eighty-one subjects (34.9%) had fallen during the previous year. In the multiple logistic regression analysis, a significant relationship was found only with the SRRST score (odds ratio; 1.22). [Conclusion] The SRRST is related independently with falls, and may be useful for determining interventions for preventing falls, such as the supervision approach in the frail elderly people.
Key words: Falls, Aged, Day care service

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INTRODUCTION

Frail elderly adults have a higher risk of falls and fall-related injuries than healthy elderly people[1]. In our previous study of 8,335 frail elderly adults utilizing day-care services, the rates of falls and fall-related fractures during a 1-year period were 25.3% and 9.7%, respectively[2]. That national survey revealed that frail elderly people utilizing long-term care insurance had a higher rate of fall-related fractures than healthy elderly people[3]. Fall-related fractures, especially hip fractures, cause disability in activities of daily living (ADL) in this population[1,4]; thus, health care providers must take care to prevent falls in their clients.

For prevention of falls in the elderly adults, numerous studies have identified risk factors associated with falling in the frail elderly adults. Moreland et al. studied falls in institutionalized elderly adults and reported the following critical risk factors: low cognitive functions, depression, urinary incontinence, hypotension, dizziness, hearing and visual impairment, balance and gait disturbances, lower extremity impairments, ADL disability, use of a walking aid, low physical activity, use of psychotropics and analgesics, and mechanical restraint[5]. The frail elderly have multiple risks for falls and some risks cannot be improved by intervention[6]. Thus, a multifactorial evaluation and intervention is required to determine how to prevent falls in the frail elderly adults[7]. However, we have found that about half of frail elderly subjects cannot complete physical performance tests such as the functional reach test and tandem walk test[8].

Some subjective assessments by care staff have been developed for identifying the fall risks in frail elderly adults[9–11]. Care staff members possess knowledge of their residents' potential fall risk, and this encompasses both predisposing and precipitating factors. Therefore, their global assessment of fall risks could have the highest predictive value[11]. In this study we aimed to clarify