impairment compare with those without cognitive impairment. In older individuals with mild cognitive impairment (MCI) in particular, consideration of a broad range of causes of falls could play a role in reducing the fall risk and providing strategies to prevent falls among the high-risk population.

Several studies have examined falling in older adults with dementia, such as Alzheimer's disease [11,12]. However, little research has focused on falling among people with MCI, even though mild declines in cognitive function have been reported to be an important factor associated with falling [13]. Liu-Ambrose et al. demonstrated that older community-dwelling people with MCI but not dementia were at greater risk of falling than those without MCI [14]. Brain structural changes represent one of the key clinical features associated with MCI, including gray matter volume loss [15] and white matter hyperintensities (WMH) [16]. A recent prospective study indicated that greater WMH burden predicts falls over 12 months in non-demented community-dwelling older adults [17].

Although prospective evidence suggests that WMH are an important risk factor for falls in community-based older populations [17,18], it remains unclear whether gray matter volume predicts falls and which regions are related to a greater risk of falls in older adults with MCI. Structural changes in the brain have been linked to motor performance deficits [19]. WMH was reported to exhibit a negative correlation with postural stability involved balance, stepping and gait [20], while reduced gray matter density is associated with impaired gait performance [21-23] and postural instability [24]. Kido et al. [24] suggested that postural instability is associated with gray matter volume loss, and is related to pathological cognitive decline, such as MCI and AD. Lower gray matter volume has been found to be related not only to cognitive decline, but also to decreased physical function. Thus, gray matter volume loss may increase the risk of falls in older adults with MCI. In particular, a smaller volume of the prefrontal area might be associated with poor physical performance [22,23], such as slower gait and poor balance, but no evidence has been reported that smaller brain volume of specific regions is related to the occurrence of subsequent falls in older adults with MCI. In the current study, we sought to examine whether physical performance and gray matter volume were related to falls during a 12-month follow-up period among community-dwelling older adults with MCI.

Methods

Participants

The sample for this longitudinal study consisted of 42 community-dwelling older adults with MCI who completed a randomized controlled trial (RCT) (trial registration: UMIN-CTR UMIN000003662) evaluating the effects of multicomponent exercise on cognitive function. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The study design and the primary results of the RCT have been described previously [25]. All participants gave written informed consent prior to taking part in the study. Briefly, participants enrolled in the RCT were: aged 65 years and over, community dwelling, and did not suffer from dementia. All participants met the Petersen criteria for MCI [26]. Participants who had a Clinical Dementia Rating (CDR) = 0, or a CDR of 1–3, a history of neurological, psychiatric, or cardiac disorders or other severe health issues, use of donepezil, impairment in basic activities of daily living (ADL), and participation in other research projects were excluded from the RCT study. A total of 100 participants took part in the RCT and completed neuropsychological assessments including language, memory, attention, and executive function tests. All subjects in this study had objective impairments at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. The participants were classified to an amnestic MCI (aMCI) group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were then randomly assigned to either a multicomponent exercise group or an education control group using a ratio of 1:1. The sample for this longitudinal study involved participants in a control group. Of the 50 participants in the control group, 42 completed fall follow-up assessments during the 12-month follow-up period.

Physical performance measures

At baseline, all participants underwent an extensive assessment of measures by licensed and well-trained physical therapists.

Knee-extension strength

Isometric knee extension strength was tested twice using a dynamometer (Model MDKKS, Molten Co Ltd, Hiroshima, Japan) from the dominant leg (self-reported side they would use to kick a ball as far as possible). 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 maximal isometric strength was determined as the peak torque (Nm) in the data analysis.

One-legged standing (OLS) test

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 50 cm 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 (0–60 s) participants were able to stand on one leg. The better of the two trials was used for statistical analysis.

Walking speed

WS was measured using a 5-m walking test. The participants' usual WS 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 3 m 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 and was used to calculate walking speed (m/min).

Falls follow-up

Fall frequency during the 12-month follow-up period was measured with two face-to-face interviews at 6 months and 12 months after baseline measurements. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [27]. In this study, 'fallers' were defined as people who had at least one fall during the 12-month follow-up period [28].

Magnetic resonance imaging (MRI) procedure

Magnetic resonance imaging (MRI) was performed using a 1.5-T system (Magnetom Avanto, Siemens, Germany). 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, 1,700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 x 256, 1.3-mm slice thickness). Tissue segmentation, regulation, registration, and normalization were conducted in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) [29] was conducted for the image analysis. The normalized images were transformed into Montreal Neurological Institute space. The gray matter images were then smoothened using a Gaussian kernel of 12-mm full-width at half-maximum.

Statistical analysis

For baseline comparisons, basic characteristics and physical performance tests including knee-extension strength, OLS, and WS were compared between fallers and non-fallers using *t*-tests. Chi-square tests for differences in proportions were used to compare differences in sex and history of falling in the past year at baseline between the faller and non-faller groups. To describe variations in different physical performance factors related to falls, multivariate logistic regression analyses were performed to reveal the physical performance factors independently related to falls during the 12-month follow-up after adjusting for age, sex, body mass index (kg/m^2), and history of falling in the past year at baseline. We calculated the odds ratios (OR) with 95% confidence intervals (CI). These statistical analyses were calculated using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL).

In the voxel-based morphometry (VBM) analysis, data preprocessing and analysis was performed with the VBM8 toolbox, which is incorporated in the SPM8 software. VBM [30] was used to examine differences in baseline gray matter volume between fallers and non-fallers. We used unpaired t-tests in SPM8 to identify the locations of smaller gray matter volume in fallers compared to non-fallers during the 12-month follow-up period using MRI data at baseline. Age and sex were included as covariates. The statistical threshold selected for these analyses was $P < .001$ (uncorrected), with an extent threshold of 100 voxels.

Results

The characteristics and physical performance tests at baseline are presented in Table 1. Over the 12-month follow-up period, 11 of the 42 participants (26.2%) experienced at least one fall. Fallers exhibited poorer one-legged standing time ($p < .01$) and slower walking speed ($p < .01$) compared with non-fallers. In addition, the faller group had a significantly higher rate of fall history at baseline compared with the non-faller group ($p < .01$). In the multivariate logistic regression, OLS time (sec) (OR [95% CI]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. There was no statistical evidence of associations between falls and knee-extension strength (Nm) (1.02 [0.96, 1.08], $p = .59$) and walking speed (m/min) (0.91 [0.81, 1.03], $p = .13$) (Table 2).

Table 1 Comparison of characteristics and physical performance tests between non-fallers and fallers at baseline

	Total (n = 42)	Non-fallers (n = 31)	Fallers (n = 11)	P-value
Age, years	75.6 ± 6.3	75.2 ± 6.5	76.8 ± 5.9	0.462
Female, n (%)	18 (42.9)	12 (38.7)	6 (54.4)	0.362
History of falling in the past year, n (%)	13 (31.0)	6 (19.4)	7 (63.6)	0.006
Knee-extension strength, Nm	60.5 ± 26.8	63.4 ± 23.3	52.3 ± 34.7	0.242
One-legged standing time, sec	32.3 ± 24.2	38.9 ± 22.3	13.8 ± 19.7	0.002
Walking speed, m/m	66.7 ± 12.6	70.0 ± 11.8	57.5 ± 10.4	0.004
Mini-mental state examination, score	26.3 ± 2.7	26.6 ± 2.0	25.5 ± 3.9	0.112

The gray matter density profiles used for examining differences between fallers and non-fallers at baseline are shown in Figure 1. VBM analysis revealed that fallers exhibited lower gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus (Table 3). These regions correspond to the premotor cortex and supplementary motor area.

Discussion

The present study examined whether baseline physical performance and gray matter volume are related to falls during a 12-month follow-up period in community-dwelling older adults with MCI. Our results indicated that older adults with MCI exhibiting poor balance had a greater risk of falls during the 12-month follow-up period, while adjusting for age, sex, body mass index, and history of falling at baseline. In addition, baseline lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with the occurrence of subsequent falls. To our knowledge, this is the first study to examine the association between lower gray matter density and risk of falls in older adults with MCI.

Problems with gait and balance have been reported to have the strongest association with falling [2,31]. Slower walking speed has been found to be an independent predictor of falling [32,33]. Poor balance represented by increased postural sway and gait asymmetry has been reported to approximately triple the risk of falling [2]. A previous systematic review and meta-analysis provided a summary estimate for falls due to balance impairment at a relative risk of 1.42 [34]. Therefore, an assessment of balance and gait for older adults, particularly those without a history of falling, has been recommended [35]. Moreover, cognitive impairment has been associated with the risk of falls as well as deficits of physical function [2]. A recent systematic review and meta-analysis confirmed that cognitive deficits detected in clinical assessment are associated with an increased fall risk in community and institution-dwelling older adults [36]. A number of studies have examined the risk of falls in older adults with dementia [37]. However, little research has focused on individuals with MCI. MCI is increasingly recognized as a substantial clinical problem in older populations [38], so it is important to determine risk factors for falling among older individuals with MCI, and to develop effective fall-prevention strategies. A previous study showed that older women with MCI demonstrated a greater number of risk factors for falling compared with older women without MCI [14]. The results of the present study indicate that poor balance assessed by one-legged standing time predicts falls in people with MCI prospectively over 12 months. Although fallers exhibited slower walking speed compared with non-fallers, walking speed was not associated with the occurrence of subsequent falls after adjusting for age, sex, body mass index, and history of falling at baseline. There was no difference in the extension strength between fallers and non-fallers. The results of this study indicate that poor balance is the important factor related to an increased risk of falling among people with MCI. Muscle weakness and problems with mobility had been considered to be the important contributors to the risk of falling in older people [5], and there are presumably some relationships. In study cohorts including older people with MCI and similar lower muscle strength, like the present study, poor balance may have a greater impact on increased risk of falling

Table 2 Multivariate logistic regression summary for physical performance on falls (n = 42)

Variables	Odds ratio	95% confidence intervals	*p* Value
Knee-extension strength, Nm	1.017	0.957-1.080	0.588
One-legged standing time, sec	0.891	0.809-0.981	0.019
Walking speed, m/m	0.911	0.806-1.029	0.133

Notes: Age, sex, body mass index (kg/m^2) and history of falling in the past year at baseline were included as covariates.

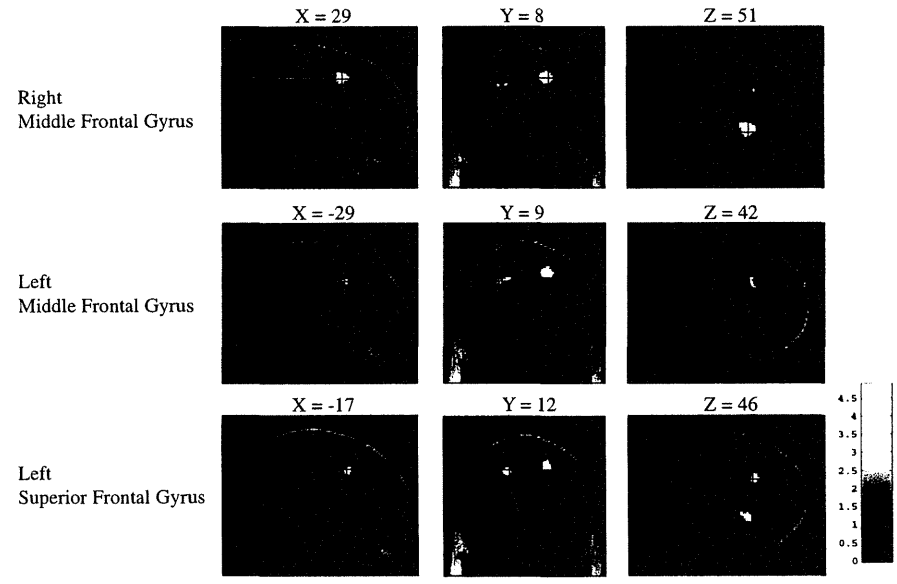

Figure 1 Gray matter density in fallers versus non-fallers. Regions of gray matter reduction in fallers compared to non-fallers ($p < 0.001$, uncorrected). Fallers exhibited a greater reduction of gray matter loss in the bilateral middle frontal gyrus and superior frontal gyrus.

than walking performance. Certainly, poor balance could be one of the predictors of walking decline among older people [39]. Balance ability may be an important dimension of physical functioning to predict the occurrence of subsequent falls among older people with MCI, as well as those with intact cognition. The present study has advantages including the examination of occurrence of subsequent falls during a 12-month follow-up period and neuroimaging assessments in older adults with MCI. However, our sample was not large, and selection bias may affect the results of the relationships between physical performance and occurrence of subsequent falls. Therefore, future studies with larger numbers of MCI subjects and a longitudinal design are needed to add evidence to the present results.

Unlike previous investigations, the current study included MRI scanning and a follow-up assessment of falls in community-dwelling older adults with MCI. The results provide the first evidence that lower gray matter volume in the middle and superior frontal gyrus is related to the occurrence of subsequent falls among older adults with MCI. Age-related changes in the brain may contribute to the subtle onset of motor disturbances in older people. Previous brain-imaging studies of older adults have reported that age-related changes in the brain, such as lower global brain volume, WMH, and microbleeds, are associated with clinical measures of poor balance and slow gait [40-43]. The association between MRI-detected lower brain volume and falls in older adults with MCI has not been examined longitudinally. In the present study, fallers exhibited decreased gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus corresponding to premotor cortex and supplementary motor area. These particular regions are likely to play an important role in predicting fall-risk because the middle frontal gyrus is involved in controlling behavior with spatial and sensory guidance.

Growing evidence suggests that brain function is associated with physical function, as confirmed by neuroimaging techniques. Structural changes of the brain in older people are reported to be related to physical performance, such as gait dysfunction [44,45], postural instability [24], and lack of cardiorespiratory fitness [46].

Table 3 VBM results including age and sex as covariates

Location	Cluster size (K)	Peak T	Z score	P (uncorrected)	MNI coordinates		
					X	Y	Z
Right middle frontal gyrus	594	4.87	4.27	< 0.001	29	8	51
Left middle frontal gyrus	165	4.35	3.90	< 0.001	−29	9	42
Left superior frontal gyrus		4.78	4.20	< 0.001	−17	12	46

Note: *VBM* voxel-based morphometry.

Activation in the frontal cortex, including the premotor cortex and the supplementary motor areas, have been reported to increase during human gait by studies using near-infrared spectroscopic imaging [47-50]. Previous studies have reported that lower brain volume in the prefrontal areas is associated with slower gait in high-functioning or cognitively normal older adults [23,40,51]. Other neuroimaging studies have indicated that gait requires complex visuo-sensorimotor coordination, and is associated with activation of the medial frontoparietal region, e.g. the primary sensory and motor areas, supplementary motor area, lateral premotor cortex, cingulate cortex, superior parietal lobule, precuneus, and the infratentorial region including the dorsal region [52-54]. The middle frontal gyrus is involved in motor output and the direct control of behavior, as well as planning, spatial guidance, and sensory guidance of movement [55]. Lower gray matter volume in the premotor cortex and supplementary motor area may be risk factors for falls in older adults. Falls often occur when older individuals attempt to avoid an obstacle in their path, requiring the control of behavior and the planning of movement under sensory guidance. The premotor cortex and supplementary motor area may play an important role in preventing falls when spatial and sensory guidance are required for movement.

Several limitations of the current study should be noted. First, fall experience during the 12-month follow-up period were confirmed with two face-to-face interviews at 6-months and 12-months after baseline, while previous studies have reported that monthly fall diaries and follow-up telephone calls provide more accurate measures of fall frequency [56,57]. Second, participants who had at least one fall during the 12-month follow-up period were categorized as fallers in this study. A previous study reported that single fallers are more similar to nonfallers than to recurrent fallers on a range of medical, physical, and psychological risk factors [58]. Other studies defined fallers as people who had at least one injurious or two non-injurious falls [17,59]. In addition, our MRI scans were performed using a 1.5-T system with relatively low resolution. We performed the VBM analysis to identify the locations of group differences in gray matter volume. Therefore, we consider that our results cannot provide evidence for whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk. Although it is unclear whether lower gray matter volume is related to poor balance in older adults with MCI, the current study revealed that poor balance and lower gray matter volume in the middle frontal gyrus and superior frontal gyrus were associated with falls. To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed.

Conclusions

The current findings indicate that poor balance predicts falls over a 12-month period, and that lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HM has made substantial contributions to conception and design, subject recruitment, analysis and interpretation of data, and writing the manuscript. HS has made substantial contributions to conception and design, subject recruitment, interpretation of data, and writing the manuscript. TD has made substantial contributions to subject recruitment, acquisition of data, interpretation of data, and manuscript preparation. HP has made substantial contributions to conception and design, interpretation of data, and writing the manuscript. DY contributed subject recruitment and manuscript preparation. KU and KT contributed subject recruitment and acquisition of data. TLA has been involved in drafting the manuscript or revising it critically for important intellectual content. TS has made substantial contributions to conception and design and writing the manuscript. All authors read and approved the final manuscript.

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Original Research Article

Six-Minute Walking Distance Correlated with Memory and Brain Volume in Older Adults with Mild Cognitive Impairment: A Voxel-Based Morphometry Study

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Key Words
Exercise capacity · Logical memory · Visual memory · Brain atrophy · Fitness · Walking · Cognitive impairment

Abstract
Background/Aims: High fitness levels play an important role in maintaining memory function and delaying the progression of structural brain changes in older people at risk of developing dementia. However, it is unclear which specific regions of the brain volume are associated with exercise capacity. We investigated whether exercise capacity, determined by a 6-min walking distance (6MWD), is associated with measures of logical and visual memory and where gray matter regions correlate with exercise capacity in older adults with mild cognitive impairment (MCI). ***Methods:*** Ninety-one community-dwelling older adults with MCI completed a 6-min walking test, structural magnetic resonance imaging scanning, and memory tests. The Wechsler Memory Scale-Revised Logical Memory and Rey-Osterrieth Complex Figure Tests were used to assess logical and visual memory, respectively. ***Results:*** The logical and visual memory tests were positively correlated with the 6MWD ($p < 0.01$). Poor performance in the 6MWD was correlated with a reduced cerebral gray matter volume in the left middle temporal gyrus, middle occipital gyrus, and hippocampus in older adults with MCI. ***Conclusions:*** These results suggest that a better 6MWD performance may be related to better memory function and the maintenance of gray matter volume in older adults with MCI.

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Introduction

Mild cognitive impairment (MCI) is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia [1]. Progression rates to dementia and Alzheimer's disease (AD) for individuals with MCI have been reported as being in the range of 6–25% per year [2]. MCI may be the optimum stage at which to intervene with preventive therapies.

Increased physical activity and higher aerobic fitness levels, defined as cardiorespiratory fitness, have been associated with the maintenance of cognitive function and a decreased risk for developing dementia [3, 4]. Recent randomized controlled trials (RCTs) of aerobic exercise for healthy older adults provided evidence that participation in exercise programs involving aerobic exercise leads to an improvement in cognitive function [5] and a greater brain volume in specific regions, e.g. in the prefrontal cortex [6] and hippocampus [7]. Previous cross-sectional studies have suggested that higher fitness levels associated with greater brain volumes in these regions were characteristic among healthy older adults [8, 9]. Some longitudinal studies have shown supportive results of the assumption that a greater physical activity predicts a stable cognitive function [10, 11] and gray matter volume [12].

Physical activity and exercise interventions can have a positive effect on cognitive function in older adults and even in those in the MCI stage [13, 14]. In addition, a recently proposed RCT will examine the effects of a moderate physical activity program on delaying the progression of structural brain changes in older adults with MCI [15]. These studies suggest that a higher exercise capacity plays an important role in maintaining cognitive function and delaying structural brain changes in MCI. However, it is unclear which specific brain regions are associated with exercise capacity performance in older adults with MCI.

We investigated whether a 6-min walking distance (6MWD), to be established as exercise capacity performance, is associated with measures of gray matter volume in older adults with MCI. The 6-min walking test (6MWT) is useful for predicting the maximal oxygen uptake related to cardiorespiratory fitness [16] and is easily administered in clinical settings [17]. The relationship between a 6MWD and memory performance was also examined in this study. A decline in memory performance represents a typical clinical sign of AD and can be observed 10 years prior to the expected symptom onset of AD [18]. In addition, poor memory performance and a lower gray matter volume in the medial temporal area, including the hippocampus, could predict progression to AD in older individuals with MCI [19, 20]. Maintaining exercise capacity may be related to a better memory performance and less brain atrophy in MCI subjects, and this positive relation may contribute to decreasing the risk of progression to AD. However, few studies have reported associations between fitness performance and memory performance in MCI subjects. We hypothesized that a better exercise capacity performance would correlate with a better memory performance and a greater brain volume among MCI subjects. A high exercise capacity may be sustained by a physically active lifestyle; this is potentially an important pathway for maintaining a healthy brain, both in terms of size and reduced damage.

Participants and Methods

Participants

Subjects in this study were recruited from our volunteer databases (n = 1,543), which included elderly individuals (≥65 years old). Participants had to be community-dwelling adults aged ≥65 years. Furthermore, all participants were required to meet the definition of MCI based on the Petersen criteria (not normal cognitive function for age, not demented, and

Table 1. Demographic and health characteristics (n = 91)

Age, years	74.2±6.3
Female gender	47 (51.6)
BMI	23.2±3.2
Diagnosis	
Hypertension	40 (44.0)
Diabetes mellitus	8 (8.8)
Medication, ≥3	33 (36.3)
Mental status	
GDS, points	3.6±3.1
MMSE, points	27.0±1.9
Physical status	
Instrumental self-maintenance[a], points	4.9±0.3
Walking speed, m/s	1.1±0.3

Values are mean ± SD or number (percentage). GDS = Geriatric Depression Scale.

[a] The Tokyo Metropolitan Institute of Gerontology Index of Competence subscale (0–5).

essentially normal functional activities) [21]. A total of 528 potential participants exhibiting a Clinical Dementia Rating score of 0.5 or a subjective memory complaint were enrolled in the first eligibility assessment. Of these, 135 participants underwent the second eligibility assessment, including neuropsychological tests, physical performance tests, face-to-face interviews, and magnetic resonance imaging (MRI) scans. The inclusion criteria required that the participants were ≥65 years old, lived independently in the community (i.e., had no impairment of activities of daily living), were Japanese speaking with sufficient hearing and visual acuity to participate in the examinations, and had general cognitive function (Mini-Mental State Examination [22]) scores between 24 and 30. Exclusion criteria were a history of major psychiatric illness (e.g. schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, and clinical depression (Geriatric Depression Scale [23] score ≥10). In addition, we excluded 9 participants who could not perform the physical performance tests and did not meet satisfactory requirements for the MRI scan. Finally, 91 participants complied with the inclusion criteria, and their data were analyzed in the present study. This study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology, and all participants provided written informed consent. Table 1 summarizes the characteristics of the participants.

Logical and Visual Memory

Logical and visual memory performances were in a standardized format and were administered by licensed, well-trained clinical speech therapists.

The Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM) [24] was used to assess logical memory. The WMS-R LM subtest requires the examiner to read aloud two short stories to the participant, each with 25 content units. In this study, stories from the Japanese version of the WMS-R LM test were used. After each story, the participant was asked to repeat the story immediately as close to verbatim as possible (immediate recall, Logical Memory-I). The recall was recorded verbatim and scored later according to the manual guidelines. After a 30-min delay, the examiner asked the subject to repeat each of the two stories once again for the delayed recall measure (delayed recall, Logical Memory-II).

The Rey-Osterrieth Complex Figure Test (ROCFT) [25] was used to assess visual memory. The ROCFT is a widely used instrument for assessing visual memory. The participants were

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requested to copy the ROCFT figure and reproduce it immediately and again after a 30-min delay. They were not informed that they would be asked to recall the figure. The participants were allowed as much time as they needed for both copy and recall. During the retention interval, unrelated tests (e.g. Mini-Mental State Examination) were administered. The drawings were scored based on a 36-point scoring system.

Six-Minute Walking Test

We used the 6MWT to quantitatively measure participants' exercise capacity. The 6MWT measures the maximum distance that a person can walk in 6 min. The 6MWT is a modification of the 12-min walk/run test originally developed by Cooper [26] and is commonly used as an assessment of exercise capacity. The 6MWT is useful for predicting the maximal oxygen uptake related to cardiorespiratory fitness and is easily administered in clinical settings [17]. The 6MWT was assessed by licensed, well-trained physical therapists. The participants were instructed to walk from one end of a 10-meter course to the other and back again as many times as possible in 6 min, while under the supervision of a physical therapist. After each minute, participants were informed of the time elapsed and were given standardized encouragement. The distance (meters) walked in 6 min was recorded.

MRI Procedure

MRI was performed using a 1.5-tesla system (Magnetom Avanto; Siemens, Germany). 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, 1,700 ms; echo time, 4.0 ms; flip angle, 15°; acquisition matrix, 256 × 256; slice thickness, 1.25 mm). Tissue segmentation, regulation, registration, and normalization were conducted in the voxel-based morphometry (VBM) 8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) [27] was conducted for the image analysis. The normalized images were transformed into the Montreal Neurological Institute (MNI) space. The gray matter images were then smoothened using a Gaussian kernel of 12 mm full width at half maximum.

Statistical and VBM Analyses

We calculated Pearson correlation coefficients, assessing simple relationships between memory tests and the 6MWD. We used linear regression analyses to assess independent relationships between the variables, while controlling for age and sex to minimize the confounding influence of age-related changes in exercise capacity and memory performance. Standardized beta values were calculated. These statistical analyses were performed using SPSS for Windows, version 19.0. Statistical significance was set at 0.05 for these analyses.

In the VBM analysis, data preprocessing and analysis was performed with the VBM8 toolbox, which is incorporated in the SPM8 software. VBM [28] was applied to determine regions where gray matter density showed a positive correlation with exercise capacity assessed by the 6MWT. We performed a multiple regression analysis on the smoothed gray matter images in SPM8. Age and sex were included in the model as covariates. The statistical threshold was set to $p < 0.05$, corrected for multiple comparisons across the reduced search volume using the family-wise error rate (FWE), with an extent threshold of 40 voxels. The detection of labeled regions from coordinates in the results was conducted using the SPM Anatomy Toolbox [29].

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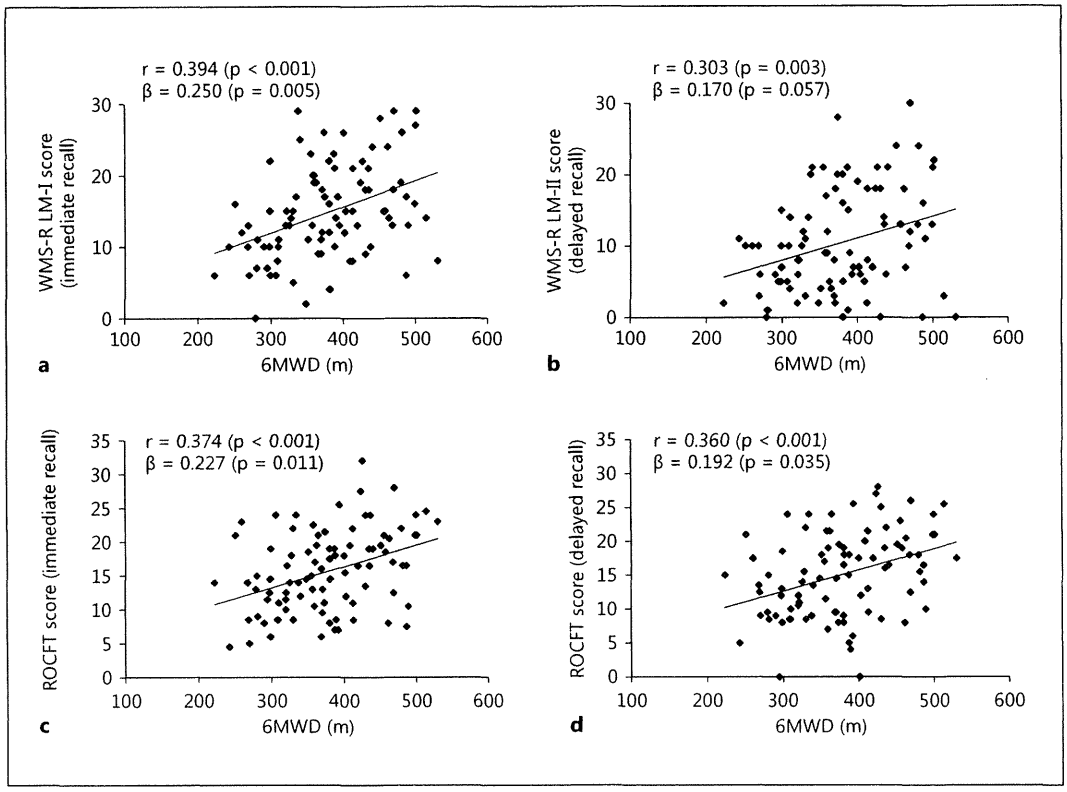

Fig. 1. Correlations between 6MWDs and memory performance tests. Pearson correlation coefficients (r) and standardized beta values (controlling for age and sex) are presented. **a** WMS-R LM-I (immediate recall). **b** WMS-R LM-II (delayed recall). **c** ROCFT (immediate recall). **d** ROCFT (delayed recall).

Results

Simple correlations were examined between the 6MWD and memory tests (fig. 1). Higher scores in all memory tests were significantly associated with a better performance on the 6MWT (WMS-R LM-I, $r = 0.394$, $p < 0.001$; WMS-R LM-II, $r = 0.303$, $p = 0.003$; ROCFT (immediate), $r = 0.374$, $p < 0.001$; ROCFT (delay), $r = 0.360$, $p < 0.001$). Although the relationship between the WMS-R LM-II and 6MWT was not statistically significant when the linear regression model was adjusted for age and sex (WMS-R LM-II, $\beta = 0.170$, $p = 0.057$), the other three memory tests were associated with the 6MWT even after controlling for age and sex [WMS-R LM-I, $\beta = 0.250$, $p = 0.005$; ROCFT (immediate), $\beta = 0.227$, $p = 0.011$; ROCFT (delay), $\beta = 0.192$, $p = 0.035$].

Using multiple regression analysis in SPM8, we examined regions where gray matter density showed a positive correlation with exercise capacity. After adjusting for age and sex, gray matter density in the left middle temporal gyrus, middle occipital gyrus, and hippocampus showed positive correlations with the 6MWD (FWE, $p < 0.05$) (fig. 2). For the MNI coordinates, cluster size, peak F values, and Z values, please refer to table 2. Figure 3 shows the highly linear relationship between 6MWD and adjusted gray matter density in the left hippocampus.

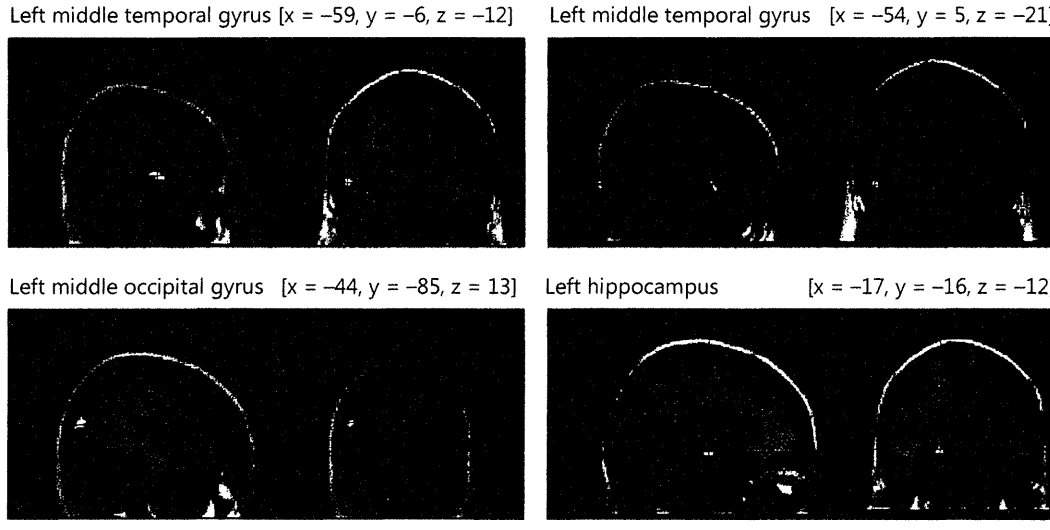

Fig. 2. Brain regions showing an association between a better performance in the 6MWT and a greater gray matter volume. After adjusting for age and sex, gray matter density in the left middle temporal gyrus, middle occipital gyrus, and hippocampus showed positive correlations with the 6MWD.

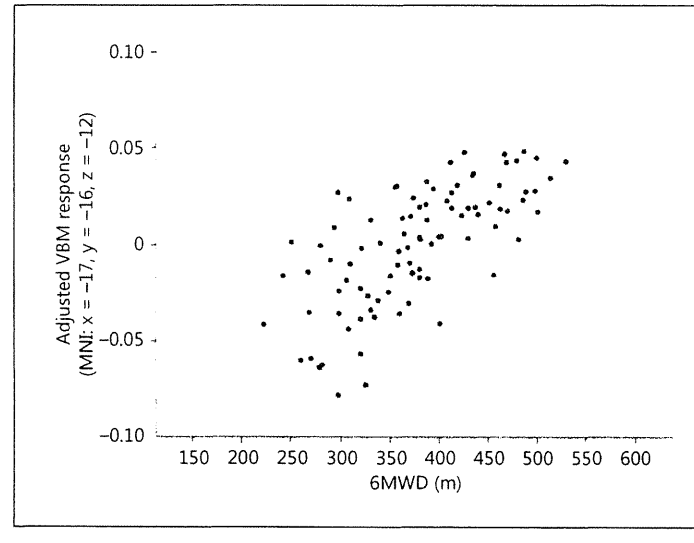

Fig. 3. Correlation between VBM response in the left hippocampus peak voxel (adjusted for effects of age and sex) and the 6MWD.

Discussion

We confirmed that memory performance was significantly positively associated with exercise capacity as assessed by a 6MWD in older adults with MCI. After adjusting for age and sex, gray matter density in the left middle temporal gyrus, middle occipital gyrus, and hippocampus showed positive correlations with exercise capacity.

Previous epidemiological studies in aging populations have suggested beneficial effects of increased physical activity on brain health and function [30, 31]. In a cross-sectional study of 75 healthy older individuals, a positive association between physical activity and memory performance was reported [32]. An interventional study among older adults indicated a

Table 2. VBM results of a 6MWD and volume regions of interest after adjusting for age and sex

Location	Cluster size, K	Peak F	Z-score	FWE, p	MNI coordinates, mm		
					x-axis	y-axis	z-axis
Left middle temporal gyrus	79	32.81	5.13	0.004	−59	−6	−12
	27	27.58	4.74	0.024	−54	5	−21
Left middle occipital gyrus	105	28.87	4.84	0.016	−44	−85	13
Left hippocampus	46	29.54	4.89	0.013	−17	−16	−12

correlation between an increase of total physical activity and improved episodic memory after low- and medium-intensity physical training [33]. Pereira et al. [34] demonstrated that verbal memory performance was improved after completion of a 3-month aerobic exercise regime among adults aged 21–45 years. This improvement in verbal memory performance positively correlated with an improvement of the participants' cardiovascular fitness level and with the cerebral blood volume in the dentate gyrus of the hippocampus. These results support the present study, indicating associations between a greater 6MWD and a better memory function among older adults with MCI.

One advantage of the present results is the indication of the association between exercise capacity performance and gray matter volumes using MRI data among MCI subjects. In a large cross-sectional study of elderly subjects without dementia, physical fitness was highly and significantly associated with hippocampal volumes [8]. Another cross-sectional study also indicated that increased cardiorespiratory fitness was associated with a better preservation of gray matter volumes, particularly in the medial temporal lobes, including the hippocampus and parahippocampal gyrus [35]. Moreover, recent RCTs of aerobic exercise for older adults provided evidence for positive associations between aerobic exercise and greater brain volumes in specific regions. An RCT in a large cohort of older adults documented significantly larger hippocampal volumes after 1 year of aerobic exercise compared with the control intervention of simple stretching and toning [7]. The results of this study also confirmed that an increased exercise capacity performance was associated with greater brain volumes in specific regions, including the left middle temporal gyrus, middle occipital gyrus, and hippocampus even after adjusting for age and sex among MCI subjects.

A previous study using VBM analysis revealed that there was a significantly greater gray matter loss in converters from MCI to probable AD relative to nonconverters in the hippocampal area, inferior and middle temporal gyrus, posterior cingulate, and precuneus [36]. In a longitudinal study where individuals in late adulthood were followed up for 9 years, a greater physical activity predicted greater volumes of the frontal, occipital, entorhinal, and hippocampal regions [12]. Gray matter volumes in the medial temporal lobe, including the entorhinal, parahippocampal, and hippocampal regions, may contribute to the prediction of subsequent cognitive decline and conversion from MCI to AD [37], and may be important for maintaining memory function [38]. We demonstrated linear relationships between VBM response in the left hippocampus peak voxel and the 6MWD in figure 3. This association may indicate protective effects of exercise capacity on cognitive decline in older adults with MCI.

Recent interventional studies suggested that physical activity and aerobic exercise have beneficial effects on memory function. These effects are possibly mediated by gray matter volume and neurotrophic factors, especially brain-derived neurotrophic factor (BDNF) [7, 33], which is highly concentrated in the hippocampus [39] and is important for synaptic plasticity [40]. In a previous study including young adult males, both acute and chronic exercise improved medial temporal lobe function concomitant with increased concentrations of BDNF

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in the serum. This suggests a possible functional role for this neurotrophic factor in exercise-induced cognitive enhancement [41]. Exercise has consistently been shown to enhance learning and persistently upregulate expression of BDNF in the hippocampus of rodent models [42, 43]. These previous results may support the present findings that exercise capacity is related to brain volume including the medial temporal lobe. However, this study did not provide evidence of mechanisms for protective effects of aerobic fitness on brain volume through neurotrophic factors. Future studies are needed to provide insight into how mechanisms that increase fitness may enhance cognition, especially memory, and prevent age-related structural brain changes.

Several possible limitations should be considered when interpreting our findings. We are conscious of the limitations of our cross-sectional design. Longitudinal and interventional studies should be designed to clarify the relationship between exercise capacity and cognitive function among MCI subjects. In addition, we recognize that there is important information regarding the effect of exercise capacity on the conversion rate from MCI to AD. Our results indicate that a higher exercise capacity may be related to a better memory function and a greater gray matter volume in several brain regions. This has been found in other studies including healthy older adults [44] or AD patients [35]. However, in the present and previous studies, different methods of assessment were used to identify fitness levels. Previous studies that examined the relationships between aerobic fitness and brain volume used the measurement of peak oxygen consumption [35, 44]. We assessed participants' exercise capacity with the 6MWT. This measure is widely used in clinical settings to identify exercise capacity and is associated with peak oxygen consumption in older adults. We did not include data from healthy older persons and patients with AD in the present study. Additional neurological analyses that include data from healthy older adults and AD patients are needed to determine the relationships between exercise capacity and brain changes in AD-related processes. Although a previous neuroimaging study suggested that the apolipoprotein Eε 4 genotype in MCI might be associated with structural changes typically found in the early stages of AD [45], our data did not consider the effects of genetic factors, such as the presence of the apolipoprotein E risk allele.

In conclusion, a higher exercise capacity measured by the 6MWT is associated with a better memory function and a greater gray matter density, including the left middle temporal gyrus, middle occipital gyrus, and hippocampus in older adults with MCI. To strengthen our findings, future studies are required to examine the effects of intervention on exercise capacity and the related change in brain volume in the specific regions and memory function among MCI subjects.

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Disclosure Statement

There are no conflicts of interest.

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Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females

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ABSTRACT

This study evaluated brain activity during unaccustomed treadmill walking using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose. Twenty-four healthy elderly females (75–82 years) participated in this study. Two PET scans were performed after 25 min of rest and after walking for 25 min at 2.0 km/h on a treadmill. Participants were divided into low and high step-length variability groups according to the median coefficient of variation in step length during treadmill walking. We compared the regional changes in brain glucose metabolism between the two groups. The most prominent relative activations during treadmill walking compared to rest in both groups were found in the primary sensorimotor areas, occipital lobe, and anterior and posterior lobe of the cerebellum. The high step-length variability group showed significant relative deactivations in the frontal lobe and the inferior temporal gyrus during treadmill walking. There was a significant relative activation of the primary sensorimotor area in the low step-length variability group compared to the high step-length variability group ($P = 0.022$). Compared to the low step-length variability group, the high step-length variability group exhibited a greater relative deactivation in the white matter of the middle and superior temporal gyrus ($P = 0.032$) and hippocampus ($P = 0.034$) during treadmill walking compared to resting. These results suggest that activation of the primary sensorimotor area, prefrontal area, and temporal lobe, especially the hippocampus, is associated with gait adaptability during unaccustomed treadmill walking.

1. Introduction

Increased gait instability and inconsistency from one step to the next are common in many elderly adults [1,2]. Gait variability, such as the coefficient of variation (CV) in step length [1,2], is a quantifiable feature of walking that is altered in clinical situations, such as falling, frailty, and gait disorders in neurodegenerative diseases [3–5]. The increase in gait instability observed in elderly adults without apparent neurological disease is multifactorial. Age-associated changes may contribute to gait instability, including reduced range of motion, decreased aerobic capacity and muscle function, and impaired balance [6,7]. However, the relationship between gait instability and brain function has not been studied in detail.

Gait is a complex sensorimotor action that is based on automated and reflexive spinal programs that are under the control of several distinct supraspinal centers located in the brainstem, basal ganglia, cerebellum, and cerebral cortex. Several imaging techniques have been developed to identify activation patterns during walking. These include the measurement of glucose metabolism during actual walking using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) [8–10] and single-photon emission tomography (SPECT) with technetium-99m hexamethylpropylene amine oxime or ^{99m}Tc-ethyl cysteinate dimer to measure fixed regional cerebral blood flow [11–13].

Previous PET and SPECT studies revealed that gait disturbance in Parkinson's disease may be associated with underactivity in the medial motor area and cerebellar hemispheres and overactivity in the cerebellar vermis [8,10–12] Recently, it was reported that elderly adults with gait disturbance, secondary to age-related white matter changes, exhibited underactivation

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of the supplementary motor area, thalamus, and basal ganglia compared to elderly adults without gait disturbance [13].

Treadmills are commonly used for gait analysis in clinical and research settings [14]. Treadmill walking, in theory, is mechanically equivalent to overground walking [15,16]. In reality, however, walking on a treadmill can initially be an unfamiliar experience [16,17]. Unimpaired younger adults required 4–6 min to familiarize themselves with the treadmill [14,17]. However, complete familiarization with treadmill in a 15-min single session was not attained in elderly adults [18]. Therefore, a treadmill walking task may be used to investigate the process of adaptation to an unfamiliar environment during walking.

The purpose of the study was, first, to compare the relative brain activation and/or deactivation during treadmill walking compared to resting condition and, second, to determine whether gait adaptability measured as gait variability could be explained through differences of brain activation and/or deactivation in response to an unaccustomed treadmill walk in the elderly adults.

2. Materials and methods

Two hundred and seventy-four females were selected from our database of elderly volunteers ($n = 1289$). Inclusion criteria were: age $\geq$ 75 years, no history of neurological or psychiatric disorders, cardiovascular disease, hypertension, heart failure, diabetes mellitus, head trauma, drug or alcohol abuse, or severe pain. Of the initial 274 females, 106 completed cognitive and physical performance tests including preferred walking speed. Sixty-nine females were excluded because of low cognitive function (Mini Mental State Examination score < 27 points), multiple medications, drug allergy, and gait disturbance (gait freezing, wide-based gait, or remarkable body sway during gait). Magnetic resonance imaging (MRI) with T1-weighted contrast was performed in 37 females using a 1.5-T Sigma Horizon scanner (GE, Milwaukee, WI, USA). Thirteen females were excluded based on MRI exclusion criteria (cerebrovascular lesions or high cortical atrophy). The remaining 24 females participated in the study (mean age, 78.0 ± 2.3 years; range, 75–82 years).

Participants were fully informed of the purpose and potential risks of the experiments, including radiation dose, and provided written, informed consent. The Ethics Committee of the Tokyo Metropolitan Institute of Gerontology approved the study protocol.

Brain glucose uptake in the rest and treadmill walking conditions was assessed on separate days (within two weeks, at least two days apart). Each condition consisted of three phases: preparation, rest or treadmill walking, and a PET scan. Total time of the FDG–PET measurement was about 85 min in each condition. The preparation period was 40 min in duration, after which the participants either rested for 35 min or walked for 25 min on a treadmill. A 6 min FDG–PET scan was performed subsequently.

During the preparation period, a catheter for injection of FDG was inserted into a vein of the left forearm. FDG (180 MBq) was injected intravenously at the onset of rest and treadmill walking. For the resting condition, participants lay supine with their eyes closed for 35 min. For the treadmill walking condition, participants walked on a treadmill (PW-21; Hitachi, Tokyo, Japan) for 25 min at 2.0 km/h while holding the handrails, to avoid falling during walking and to provide a uniform visual environment. The participants then rested on a bed with their eyes closed for 10 min.

A step counter with an infrared ray device (m-Stride ST-1100; S & ME, Tokyo, Japan) recorded walking speed, cadence, and step length during the treadmill walking period to evaluate temporal changes in gait characteristics. The step counter was placed on side-rail of a treadmill to measure belt speed (cm/s) of the treadmill and step time (s) during treadmill walking using infrared ray. The step length (cm) and cadence (steps/min) were calculated as follows.

$$\text{Step length} = \text{Belt speed} \times \text{Step time}, \quad (1)$$

$$\text{Cadence} = 60/\text{Step time}, \quad (2)$$

Step length was measured for 1 min at 0, 5, 10, 15, 20, and the 24th–25th min. We used 200 steps for the analysis of step length and cadence, 50 steps from each 1 min period starting at the 10th–11th min, 15th–16th min, 20th–21st min, 24th–25th min of treadmill walking. Five minutes following the rest or walking periods, PET scans were performed using a Headtome-V (SET 2400W, Shimadzu, Kyoto, Japan) in the three-dimensional (3D) mode. This 6 min emission scan therefore occurred 40 min after the intravenous injection of FDG. The scan produced images that had the following parameters: matrix size, 96 × 96 × 50; and voxel size, 2 mm × 2 mm × 3.125 mm. The attenuation was corrected via a transmission scan using a $^{68}Ga/^{68}Ge$ source.

The images were reconstructed using a filtered back projection algorithm with a second-order low-pass filter with a cutoff frequency of 1.25 cycles/cm. Corrections were applied for dead time and detector non-uniformity. Image processing and data analysis were performed using statistical parametric mapping (SPM8 software, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK) implemented on MATLAB (MathWorks, Natick, MA, USA). The tasks performed using SPM8 were MRI/PET coregistration, spatial normalization, spatial smoothing, MRI segmentation, normalization, and SPM analysis. Anatomical brain MR images were spatially normalized into the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) standard template using an affine transformation (12 parameters for rigid transformations) [19]. The parameters were applied to the coregistered FDG–PET images. Therefore, all stereotactic coordinates given in this paper refer to the MNI coordinate system. Subsequently, the spatially normalized images were blurred with a Gaussian filter (FWHM 12 mm) to increase signal-to-noise ratio. All scans were analyzed after normalization to the white matter. The normalization prior to voxel-based statistics was performed using an anatomical mask in MNI space. This normalization was used for all participants to remove the effects of differences in the overall counts. The pixel values were normalized by scaling the activity in each pixel in proportion to the global activity. This ensured that the variance related to the substantially different global activity between high- and low-dose images was stabilized. In this process, the mean global activity of each scan was adjusted to 50. Planned comparisons between the rest and exercise conditions were performed using t statistics for each voxel. These analyses generated statistical parametric maps of the t statistic (SPM {t}), which were subsequently converted to unit normal distribution (SPM {Z}). The estimated final spatial resolution was 19 mm × 21 mm × 18 mm.

The standard deviation for the CV, the ratio of the standard deviation to the mean, in step length during the treadmill walk was large in our sample (mean 7.2 ± 6.0%). However, there was a bimodal distribution around the median value for the CV for step length and it was therefore appropriate to use the median step length for CV as the cut-point dividing the females into low step-length variability (LSV) and high step-length variability (HSV) groups. Student's t test was used to compare age and gait variables between the LSV and HSV groups during treadmill walking. The significance threshold was set at $P < 0.05$. SPSS version 19 (Chicago, IL, USA) was used for statistical analyses.

The locations of relatively activated and deactivated brain areas were identified and listed according to stereotaxic coordinates and visual inspection of the structural MRI provided by SPM8. Significant relative increase (walk > rest) and decrease (rest > walk) in cerebral glucose uptake during the gait condition compared with the rest condition were explored for each group separately. Both relative increases and decreases in glucose metabolism were calculated and considered significant at $P < 0.05$, and were corrected for multiple comparisons using a familywise error (FWE) method [20].

A region of interest (ROI) analysis was used to assess activated and deactivated brain areas during treadmill walking between the HSV and LSV groups, which were interpreted as the relative difference in gait-induced glucose uptake changes between groups. The ROIs were determined on visually apparent regions of relative activation (walk > rest) and deactivation (rest > walk) images for all participants. Glucose metabolism in the ROIs was measured based on the standardized uptake value (SUV), which was defined as follows.

$$\text{SUV} = C/D/w, \quad (3)$$

where C represents the radioactive concentration in the tissue (Bq/mL), D represents the injected dose (Bq), and w represents body mass (g) [21]. FDG dose was adjusted to body weight. Student's t test was used to compare the SUV between the LSV and HSV groups. The significance threshold was set at $P < 0.05$ during between-group comparisons in specific regions. The ROI analysis was performed using the Dr. View software (AJS, Tokyo, Japan). The anatomical designations used to the Talairach Client and MRI atlas of human white matter [22].

3. Results

There was no difference in age between the LSV and the HSV groups (77.4 ± 2.3 versus 78.7 ± 2.2 years; $P = 0.19$) or the following treadmill variables: walking speed (34.7 ± 0.4 versus 34.4 ± 0.5 m/min; $P = 0.26$), cadence (101.4 ± 15.1 versus 96.0 ± 15.7 steps/min; $P = 0.39$), and step length (34.9 ± 5.2 versus 37.4 ± 6.4 cm; $P = 0.31$). The HSV group had a higher step length CV compared to the LSV group (2.7 ± 0.8 versus 11.8 ± 5.5; $P < 0.001$).

The most prominent relative activations during treadmill walking in the LSV group were found in the primary sensorimotor areas (Broadman area (BA) 3 and 4), occipital lobe (BA 17, 18, and 19), and anterior and posterior lobe of the cerebellum compared with the resting condition (Table 1, Fig. 1A). The LSV group did not

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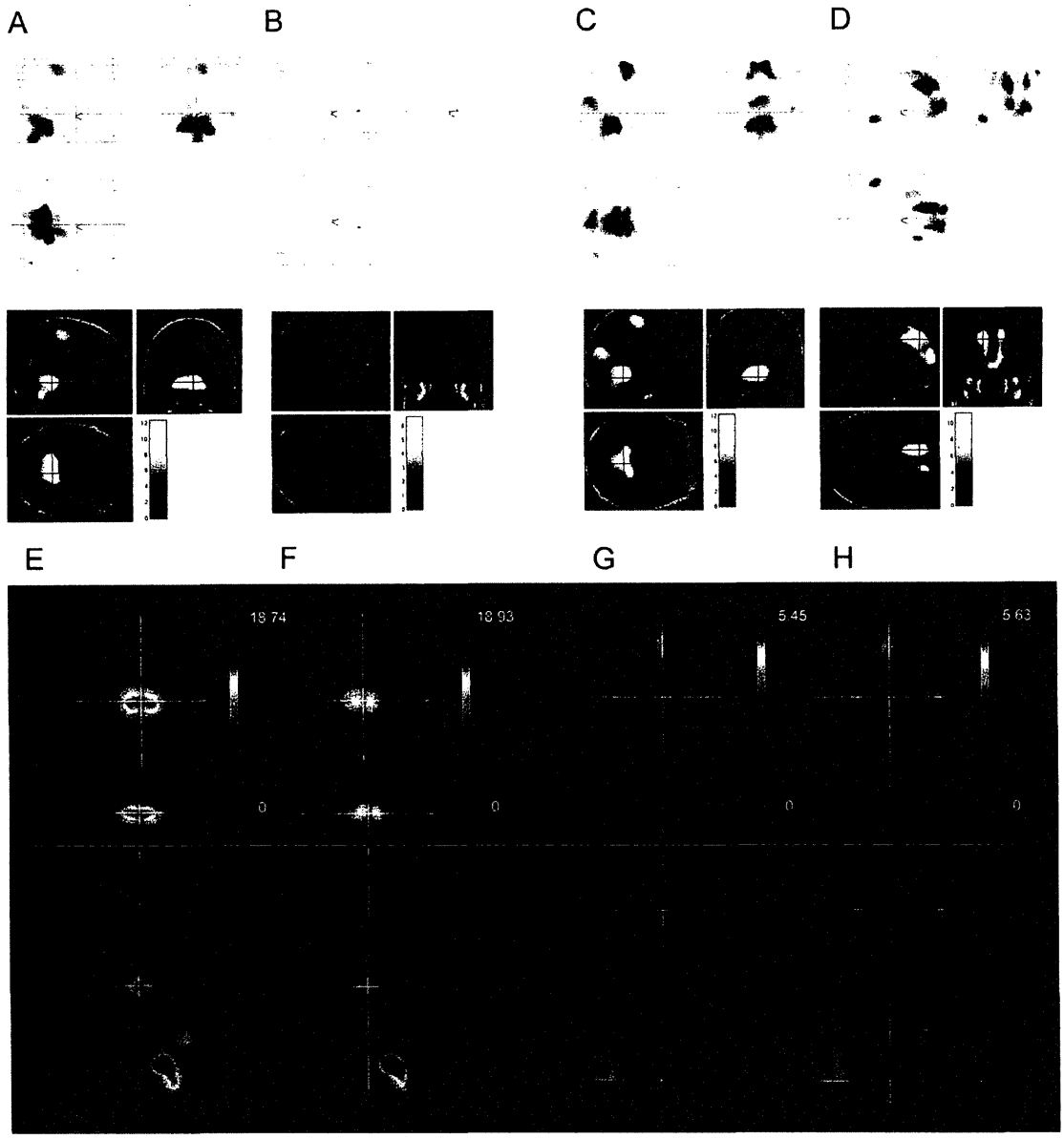

Fig. 1. FDG–PET activations and deactivations during treadmill walking in the LSV and HSV groups. During treadmill walking in the LSV group, activations (A) were prominent in the primary motor areas, visual cortical areas and anterior and posterior lobe of cerebellar. Slight deactivation (B) was found in the right sub-gyral. In the HSV group, activations (C) were prominent in the primary motor areas, visual cortical areas and anterior and posterior lobe of cerebellar. Deactivations (D) were found in the supplementary motor areas (superior and medial frontal cortex, dorsolateral prefrontal cortex). The primary sensorimotor cortex was activated more during treadmill walking versus the resting condition, in the LSV group (E) compared to the HSV group (F). Hippocampus and temporal lobe were deactivated more for treadmill walking versus the resting condition, in the HSV (H) group compared to the LSV group (G).

exhibit prominent relative deactivation during treadmill walking compared with the resting condition (Table 1, Fig. 1B)

The HSV group exhibited marked relative activation in the primary sensorimotor areas (BA 3 and 4), occipital lobe (BA 17, 18, and 19), and anterior and posterior lobe of the cerebellum during treadmill walking compared with the resting condition (Table 2, Fig. 1C). However, the HSV group showed relative deactivation in some regions during treadmill walking. The most prominent relative deactivations during treadmill walking were found in the frontal lobe, including the dorsolateral prefrontal cortex (BA 9 and 46), supplementary motor area (BA 6 and 8), and inferior temporal gyrus (Table 2, Fig. 1D).

Lower panels of Fig. 1 show FDG images of relative activations and deactivations during treadmill walking compared with the resting condition in the participants of the LSV and HSV groups. The SUV uptakes of the relatively activated and deactivated regions are shown in Table 3. The primary sensorimotor areas (BA 3 and 4), occipital lobe (BA 17, 18, and 19), and cerebellum (especially the vermis) were activated during treadmill walking. Relative deactivation of FDG was observed in the orbitofrontal cortex (BA 11), superior frontal gyrus (BA 10), dorsolateral prefrontal cortex (BA 9 and 46), supplementary motor area (BA 6 and 8), middle and superior temporal gyrus white matter, posterior cingulate cortex (BA 31), pons, and hippocampus in all participants. A detailed comparison of the relative activations and deactivations using ROI analysis revealed a more prominent activation of the primary sensorimotor area in the LSV group (Table 3, Fig. 1E) compared with the HSV group (Table 3, Fig. 1F) ($P = 0.02$). The HSV group

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