示す事象であり，虚弱発生の独立した予測因子であると報告されてきた[20]．そのため，健康増進や身心機能，ADL障害予防のために生活空間の拡大が注目されている．地域在住高齢者を対象とした我々のこれまでの報告では，自宅の外に出る頻度が1週間に1回以下である者はADL障害を生じやすく，自宅の近所まで出かける頻度が1週間に1回以下である者はIADL障害を生じやすいことが明らかになった[21]．また，地域在住高齢者の1年後のIADL障害はTUGとLSAの得点の組み合わせで予測できるという結果も示した[22]．このように生活空間の範囲は，将来のADL，IADL障害と密接な関係があり，生活空間の維持，拡大を目的とした介入の重要性が挙げられる．

なお，本研究での転倒恐怖感の聴取は，転倒恐怖感の有無を指標としており，過去の報告で指摘があるように[23]，転倒恐怖感が発生する機転やどういった場面で転倒恐怖感が生じているかなどの質的な情報は把握していない．今後，IADLが自立している高齢者に転倒恐怖感が生じた機転や普段どういった活動で転倒恐怖感を持つかなどの詳細な情報を聴取し，その構造を明らかにすることで，よりよい介入方法の立案に結びつくと考えられる．また，本研究で扱った指標は，転倒恐怖感に関連する社会的支援の有無や対象者の住宅環境，住宅周囲の状態などの外的要因[24][25]を含んでおらずこれらの指標の影響については考慮できていない．

本研究では，IADLの保たれた高齢者の転倒恐怖感と生活空間の横断的な関係は明らかとなった．今後，縦断的な調査によって，この因果関係や関連の構造を明らかにし，ADL，IADL障害予防のための適切な介入方法の確立が望まれる．

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Factors associated with fear of falling among community-dwelling elderly adults without reduced performance in instrumental activities of daily living

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Abstract

Aim: The purpose of this study was to examine factors related to fear of falling (FOF) in elderly adults who showed no reduced performance regarding independent instrumental activities of daily living (IADL).

Methods: A total of 119 elderly adults participated in the study (mean age, 75.7±7.2 years, women, n=60).We investigated the prevalence of FOF, anamnesis, medications, body pain, and history of falls, the Geriatric Depression Scale, International Physical Activity Questionnaire, Life-Space Assessment (LSA). The Timed Up and Go test (TUG) and one-legged standing time were measured to evaluate physical performance. Participants were divided into elderly adults with FOF (FOF group) and those without FOF (non-FOF group). The unpaired t-test or chi-square test was used for group comparisons. Multiple logistic regression analysis was then performed to examine the factors associated with FOF.

Results: The prevalence of FOF was 51.3% overall. The FOF group had a higher prevalence of anamnesis, body pain, and history of falls than the non-FOF group. The FOF group had lower LSA scores, longer durations on the TUG, and shorter durations on the one-legged standing test than the non-FOF group. On multiple logistic regression analysis, LSA (total score, 120 points) was significantly associated with FOF (odds ratio: 0.96, 95% confidence interval=0.93-0.99).

Conclusion: Fear of falling was significantly associated with life space in community-dwelling elderly adults who showed no reduced performance regarding IADL. In future, it will be necessary to clarify any possible causal relationship by longitudinal investigations.

Key words: *Community-dwelling elderly, Fear of falling, Life space*
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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 ≥ 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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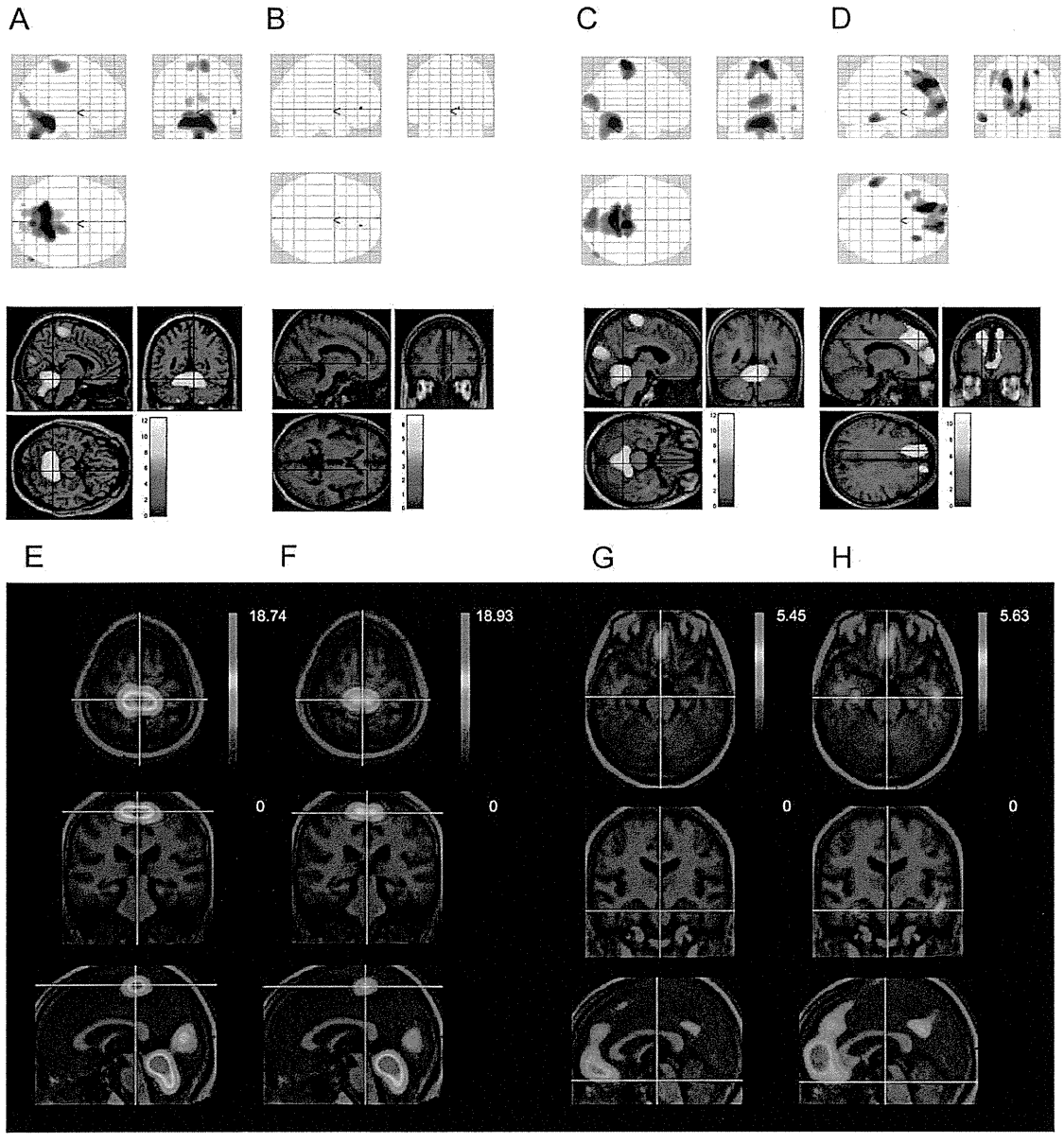

Fig. 1. FDG–PET activations and deactivations during treadmill walking in the LSV and HSV groups. During treadmill walking in the LSV group, activations (A) were prominent in the primary motor areas, visual cortical areas and anterior and posterior lobe of cerebellar. Slight deactivation (B) was found 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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Table 1
FDG activations and deactivations during treadmill walking in the low step-length variability group.

(a) FDG activation during treadmill walking in the low step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Left cerebellum, anterior lobe, culmen		5196	6.57	12.26	<0.001	−20	−52	−16
Right cerebellum, anterior lobe, culmen			6.46	11.75	<0.001	12	−46	−16
Right cerebellum, posterior lobe, inferior semi-lunar lobule			5.83	9.4	<0.001	4	−68	−38
Right cerebrum, frontal lobe, precentral gyrus		936	5.44	8.22	0.001	10	−30	66
Left cerebrum, parietal lobe, postcentral gyrus	3		4.84	6.69	0.014	−10	−32	66
Right cerebrum, occipital lobe, inferior occipital gyrus	19	39	5.17	7.48	0.004	56	−72	−2
Right cerebellum, posterior lobe		57	4.89	6.8	0.011	20	−50	−58
Left cerebrum, occipital lobe, superior occipital gyrus, cuneus	17	130	4.82	6.63	0.015	−14	−78	12
Right cerebrum, occipital lobe, cuneus	18	147	4.68	6.31	0.027	8	−84	16
Left cerebellum, posterior lobe		4	4.64	6.24	0.03	−24	−84	−46
Left cerebellum, posterior lobe		23	4.63	6.21	0.032	−20	−52	−56
Right cerebrum, occipital lobe, middle or lateral occipital gyrus	19	1	4.54	6.02	0.045	28	−86	38

(b) FDG deactivation during treadmill walking in the low step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Right cerebrum, frontal lobe, genu of the corpus callosum		5	4.82	6.64	0.015	12	40	0

(Table 3, Fig. 1H) showed relative deactivation in the middle and superior temporal gyrus white matter ($P = 0.03$) and hippocampus ($P = 0.03$) during treadmill walking compared with resting than did the LSV group (Table 3, Fig. 1G). There were no significant differences in occipital lobe, cerebellum, frontal lobe, posterior cingulate cortex, and pons between groups.

4. Discussion

This study examined changes in whole brain glucose metabolism using FDG-PET during rest and unaccustomed treadmill walking in healthy elderly females, classified as either low or high step-length variability walkers. The main findings of the study were that females with high step-length variability showed relative deactivations in the supplementary motor areas and dorsolateral prefrontal cortex compared to rest and that females with low step-length variability exhibited greater relative activations in the primary motor area during treadmill walking compared to the HSV group. The HSV group showed greater relative deactivations in the temporal lobe, especially in the hippocampus, during treadmill walking compared with the LSV group.

Hanakawa [23] proposed a hypothesis regarding the neural mechanisms that control human bipedal gait. This author postulated that multiple channels from the basal ganglia–thalamocortical system and basal ganglia–brainstem system are involved in the regulation of the central pattern generator (CPG) in the spinal cord (Fig. 2). In the present study, the most prominent relative activations during treadmill walking were found in the primary sensorimotor areas, occipital lobe, and cerebellar areas for both groups. The primary motor area projects to the spinal cord through the corticospinal tract, and it is believed that the primary motor area is involved in the precise control of limb movement during walking. The coordination of limb and trunk movements to adjust for a shift in the center of gravity associated with locomotion may be one of the primary functions of the cerebellum in gait control. Previous neuroimaging experiments have shown that the cerebellar vermis and the anteromedial part of the cerebellar hemispheres are bilaterally activated during walking in healthy individuals [9,11,12]. The cerebellum is able to make immediate alterations in ongoing movement patterns [24]. It functions as a real-time sensory processing device and modulates motor responses in a reactive or feedback manner based on sensory perturbations [25].

Our findings also suggest that the cerebellum plays an important role in gait adaptation to unfamiliar environments, such as walking on a treadmill. The occipital lobe, including the

Table 2
FDG activations and deactivations during treadmill walking in the high step-length variability group.

(a) FDG activation during treadmill walking in the high step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Right cerebellum, anterior lobe, culmen		3715	6.54	12.12	<0.001	0	−50	−18
Right cerebrum, parietal lobe, postcentral gyrus	6	1878	6.37	11.38	<0.001	8	−32	72
Left cerebrum, parietal lobe, postcentral gyrus	3		5.75	9.16	<0.001	−10	−34	72
Left cerebrum, parietal lobe, postcentral gyrus white matter			5.4	8.09	0.001	−14	−28	54
Right cerebrum, occipital lobe, cuneus		1402	5.52	8.46	0.001	2	−84	18
Left cerebrum, occipital lobe, cuneus			5.47	8.29	0.001	−6	−82	14
Right cerebrum, occipital lobe, middle or lateral occipital gyrus		60	5.06	7.2	0.005	52	−78	4
Left cerebellum, posterior lobe		40	4.74	6.45	0.017	−22	−46	−52
Right cerebellum, posterior lobe		7	4.67	6.3	0.022	36	−84	−40
Right cerebrum, occipital lobe, middle or lateral occipital gyrus	17	3	4.52	5.99	0.039	26	−100	−12

(b) FDG deactivation during treadmill walking in the high step-length variability group (vs. resting condition)

Cerebral hemispheres	BA	Cluster	Z	T	p	x	y	z
Left cerebrum, frontal lobe, superior frontal gyrus		5131	6.31	11.14	<0.001	−18	46	40
Right cerebrum, frontal lobe, superior frontal gyrus white matter			5.74	9.13	<0.001	10	60	6
Right cerebrum, frontal lobe, superior frontal gyrus	8		5.7	8.98	<0.001	12	54	40
Left cerebrum, temporal lobe, inferior temporal gyrus		397	5.62	8.74	<0.001	−52	−44	−14
Right cerebrum, frontal lobe, middle frontal gyrus	6	113	5.38	8.04	0.001	30	22	58

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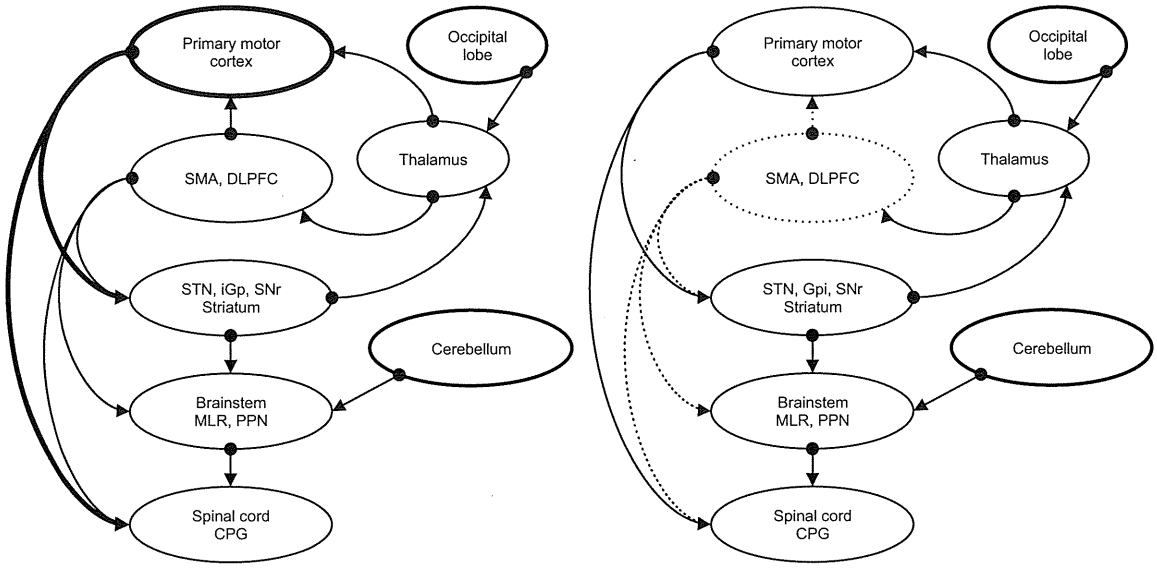

Fig. 2. Differences in neural mechanisms controlling treadmill walking in LSV compared to HSV individuals. Multiple channels from the 'basal ganglia–thalamo-cortical system' and 'basal ganglia–brainstem system' are both involved in regulating the central pattern generator (CPG) in the spinal cord. The primary motor cortex and non-primary motor areas such as supplementary motor areas constitute multiple parallel circuits with the basal ganglia counterparts. (a) Left panel displays our hypothesized neural network for the LSV group. The projections from M1 increased during walking to adapt to the unaccustomed environment (treadmill walking). (b) Right panel displays our hypothesized neural network for the HSV group. The HSV group deactivated FDG uptakes in SMA during treadmill walking and the deactivations may lead to dysfunction of 'basal ganglia–thalamo-cortical system' and 'basal ganglia–brainstem system'. *Abbreviations*: STN, subthalamic nucleus; iGP, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; MLR, midbrain locomotor region; PPN, pedunculopontine nucleus.

cuneus (BA 17) and precuneus (BA 7/31), is believed to play a role in visuomotor coordination. The areas which showed relative activation were compatible with those reported in a previous activation study using FDG–PET [10]. In addition, online visual feedback was the requisite for locomotor adaptation [26] and was thought to override internal model predictions of control during locomotion [27]. Our study further supports the hypothesis that locomotor adaptation requires neuronal activation in the region related to visuomotor coordination.

In the HSV group, relative deactivations in FDG uptake were observed over a broad area of the prefrontal cortex, including the supplementary motor area and the dorsolateral prefrontal cortex. Cortical locomotor commands originating from the premotor and supplementary motor cortices are conveyed to the brainstem locomotor centers via the basal ganglia. The structure of the dorsolateral prefrontal cortex is important for selecting and planning voluntary movements [28] or simulating motor actions [29]. The relative deactivation of the supplementary motor area and dorsolateral prefrontal cortex may be associated with the finding that the participants in the HSV group might have found it difficult to adapt to an unfamiliar environment, i.e., treadmill walking.

Detailed group comparison revealed that the LSV group had a more prominent relative activation in the primary sensorimotor area compared to the HSV group and that the HSV group exhibited relative deactivation in the hippocampus compared to the LSV group during treadmill walking. The relative activation of the primary motor area may improve projection to the basal ganglia and to the CPG in the spinal cord, thus facilitating the strengthening of the basal ganglia–thalamocortical system during walking (Fig. 2). Regarding relative deactivation in the hippocampus, Zimmerman et al. (2009) found that increased variability in step length was associated with poorer hippocampal metabolism in elderly individuals. The authors suggested

Table 3
A region of interest analysis based on the standardized uptake value as the relative difference in gait-induced glucose uptake changes between groups.

	LSV group Mean (SD)	HSV group Mean (SD)	*p* value
Walk>Rest			
Primary sensorimotor area (BA 3, 4)	13.56 (3.01)	10.93 (2.16)	0.02
Occipital lobe (BA 17, 18, 19)	11.42 (4.29)	9.25 (3.55)	0.19
Cerebellum (vermis, anterior and posterior lobe)	17.18 (4.85)	17.36 (4.07)	0.92
Rest>Walk			
Orbitofrontal cortex (BA 11)	3.85 (3.18)	3.67 (2.94)	0.89
Superior frontal gyrus (BA 10)	4.16 (2.54)	4.76 (2.83)	0.59
Dorsolateral prefrontal cortex (BA 9, 46)	3.16 (2.09)	4.45 (2.25)	0.16
Supplementary motor area (BA 6, 8)	3.79 (1.74)	4.12 (1.83)	0.65
Middle and superior temporal gyrus white matter	1.85 (1.45)	3.07 (1.15)	0.03
Posterior cingulate cortex (BA 31)	3.01 (2.16)	3.67 (3.58)	0.59
Pons	2.40 (1.89)	1.84 (0.94)	0.37
Hippocampus	1.24 (1.31)	2.44 (1.29)	0.03

LSV: high step-length variability; HSV: low step-length variability.

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that the hippocampus plays an important role in the timing or rhythmicity of locomotion, which may be compromised in elderly adults [30]. Additionally, PET study showed that imagined walking with obstacles was associated with increased prefrontal and parahippocampal activation, suggesting that higher brain centers become progressively engaged when the locomotor task demands increased cognitive and sensory information processing [31]. Beauchet et al. (2003) reported that stride-to-stride variability increased significantly in older subjects with the interfering task of counting, although there was no significant change in young subjects. The authors suggested the involvement of higher cortical regions for the motor control of gait under a dual-task in older adults [32]. Our findings therefore support and extend previous research via the identification of an association between FDG–PET activation/deactivation and gait *variability* in an unfamiliar environment in elderly adults. Walking task used a treadmill, as a stimulator to increase cognitive demand may be beneficial tool for identifying the involvement of cortical regulation in gait of the older adults.

Limitations of our study were that the sample was drawn from a larger study of community-dwelling adults over the age of 75 years, and we were not able to examine the relationships between brain activity and cognitive functions across the entire adult lifespan.

In conclusion, FDG PET revealed that the most prominent relative activations during treadmill walking were the primary sensorimotor areas, occipital lobe, and cerebellar areas. The high step-length variability group exhibited a lesser relative activation in the primary sensorimotor area and a greater relative deactivation in the white matter of the middle and superior temporal gyrus and hippocampus during treadmill walking than the low step-length variability group. These results suggested the involvement of cortical regulation in gait adaptation of the older adults. Additional studies are necessary to examine the longitudinal sequence and relationships of gait, cognitive status, and presynaptic functional changes that emerge across the spectrum from normal aging to advanced functional decline.

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Conflict of interest statement

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ORIGINAL ARTICLE

Relationship between dual-task performance and neurocognitive measures in older adults with mild cognitive impairment

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Aim: The aim of this study was to examine the relationship between dual-task performance and neurocognitive measures in community-dwelling older people with mild cognitive impairment (MCI).

Methods: A total of 98 subjects (mean age 74.8 years, 52.0% female) participated in the study. We compared 36 participants with amnestic MCI (aMCI) with 62 participants with non-amnestic MCI (non-aMCI) on dual-task performance as measured by reaction time responses. The relationships between dual-task performance and multiple domains of neurocognitive functions, including general cognitive function, visual memory, working memory, executive function and processing speed, were examined.

Results: Although there were no statistically significant group differences in simple reaction times ($P = 0.734$), the aMCI group showed significantly slower dual-task reaction times than the non-aMCI group ($P = 0.012$). Using multiple regression analysis, we found that there was a significant relationship between executive function and dual-task reaction times ($\beta = 0.298$, $P = 0.006$).

Conclusion: These results showed that aMCI subjects showed a specific deficit in dual-task performance compared with non-aMCI subjects, and poor dual-task performance was associated with declines in executive function in older people with MCI. Future longitudinal and interventional studies should investigate the use of dual-task testing with varying levels of cognitive demand in older adults at risk of dementia. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: dual-task, executive functioning, mild cognitive impairment, reaction time.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, and mild cognitive impairment (MCI) is associated with an elevated risk of developing AD.[1] Along with amnesia, a decline of attentional control of executive function is one of the earliest symptoms of dementia.[2]

Dual-task performance can be measured while a person carried out two concurrent tasks, and reflects divided attention, considered an important executive function.[3,4] Several studies have reported an association between AD and impairments in dual task performance, indicating a specific deficit of dual-task functioning in the disease.[5–8] Additionally, MCI patients might also show specific deficits in dual-task performance, as impaired executive function in MCI plays a crucial role in the conversion to AD.[9,10] In contrast, a previous study reported that dual-task performance has been found to have lower sensitivity in discriminating between controls, MCI patients and AD patients, whereas dual-task performance during walking in MCI patients resembled that of AD patients but not control subjects.[11] Thus, it is currently unclear whether poor dual-task performance is related to decline in neurocognitive functions among older adults with MCI.

Sheridan *et al.* suggested that dual-task-related performance changes were correlated with executive and neuropsychological function in patients with AD.[12] In MCI patients, neuropsychological functioning of working memory was associated with impaired dual-task performance.[13] However, few studies of dual-task performance and multiple domains of neurocognitive

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functioning have focused on older adults at risk of developing dementia, especially those with MCI.[14] If dual-task performance is closely related to specific domains of neurocognitive function, it might provide an objective measure of the effectiveness of new intervention strategies in older adults with cognitive decline.

In the present study, the dual-task reaction time (RT) paradigm[15–17] was used to assess attentional demands, because we considered that measurements of RT were simple and easy to understand in older adults (including MCI patients), even in a clinical setting. It is currently unclear whether neuropsychological measures in MCI patients are correlated with dual-task performance. The current study sought to assess attention-related performance using RT in a dual-task, and to examine the relationships between dual-task performance and multiple domains of neurocognitive functions, including general cognitive function, visual memory, working memory, executive function and processing speed in community-dwelling older adults with MCI. Furthermore, we compared amnestic MCI (aMCI) and non-amnestic MCI (non-aMCI) participants, because aMCI is likely to progress to AD.[18,19]

Methods

Participants

Participants were recruited from two volunteer databases ($n = 1543$), which included elderly individuals aged 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 the Petersen criteria.[20] A total of 126 older adults that had a clinical dementia rating (CDR) of 0.5 or a memory complaint were assessed for 2 days by neuropsychological tests, physical performance tests and face-to-face interviews. Other criteria for inclusion into the present study required that the participant was aged 65 years or older, living independently in the community (i.e. 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][21] scores between 24 and 30). Exclusion criteria included a history of major psychiatric illness, other serious neurological or musculoskeletal diagnoses, and clinical depression. Finally, 98 participants with MCI (mean age 74.8 years, male/female 47/51, mean education 10.7 years) satisfied the inclusion criteria, and their data were analyzed in the present study. Participants were classified into aMCI and non-aMCI groups. Of the 98 participants, 36 were included in the aMCI group, because they showed memory impairments that were objectively established through education-adjusted scores on the Wechsler memory Scale – Revised (WMS-R) Logical Memory II.[22,23] The non-aMCI participants ($n = 62$) did not show objective memory impairment as measured by education-adjusted scores on the WMS-R Logical Memory II scale. However, they had a CDR of 0.5 or a memory complaint, and they met the threshold for an MCI diagnosis using the Petersen criteria (not normal for age, not demented, cognitive decline and essentially normal functional activities).[20] The present study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants provided written informed consent.

Dual-task performance measures

We measured RT under two conditions of cognitive demand of attentional resources: a low demand (simple-task) condition and a high demand (dual-task) condition. Simple RT was measured by pushing a handheld button as quickly as possible in response to a visual stimulus (a bright red light). In addition, each participant's RT were measured in the dual-task condition while carrying out a concurrent cognitive task. This was defined as dual-task performance. First, participants' simple RT were measured in a quiet standing position. RT were defined as the temporal interval between the presentation of a visual stimulus and the onset of a pushing response. During simple RT measurement, participants were asked to push a handheld button as quickly as possible after the presentation of a red light stimulus composed of seven small lights (each with a diameter of 5 mm). The experimenter confirmed that participants stood quietly, then issued the verbal command, "ready", as a verbal starting signal before RT measurement. The visual starting signal and verbal command preceded each trial. RT responses were measured by a time counter (PTS-010; DKH, Itabashi, Japan) and displayed in milliseconds (ms). In the dual-task condition, participants were asked to count backward to 1, starting from 100, 90, 80, 70, 60, 50, 40, 30 and 20 (selected randomly). They were asked to carry out RT responses during the dual-task with cognitive demands. RT were measured three times for each participant in both conditions. In both task conditions, participants practiced once before data collection commenced. In each task condition, the average RT over three trials was submitted to statistical analysis.

Neurocognitive assessments

Participants underwent comprehensive neurocognitive evaluation, including measures of general cognitive function, visual memory, working memory and executive function. The neurocognitive assessment had a standardized format and was administered by licensed and well-trained clinical speech therapists.

General cognitive function was examined using the Japanese version of MMSE.[24] The Rey-Osterrieth Complex Figure Test (ROCF)[25] and the verbal digit span test[26] were used to assess visual and working memory, respectively. The ROCF is a widely-used instrument for assessing visual memory. The participant was requested to copy the ROCF figure and reproduce it after a 30-min delay. We assessed working memory using the verbal digit span test.[26] The digit span test includes both forwards and backwards conditions, in which a participant is given a number sequence and is asked either to repeat it as it was given or to repeat it in the reverse order. The test includes two sequences of each length and testing ceases when the participant fails to recollect any two with the same length. The score recorded, ranging from 0 to 14, is the number of successful sequences. The difference between the verbal digits forward test score and the verbal digits backward test score was used as an index of the central executive component of working memory. Smaller difference scores indicate better working memory.

We used the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III (WAIS-III)[26] and Trail Making Test (TMT)[27] to assess processing speed and executive function. In the Digit Symbol-Coding test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score is the number of correct symbols drawn within 120 s, and a maximum score of 133. Higher scores indicate better processing speed. The TMT consists of two parts, A and B. Part A requires the participant to draw a line as rapidly as possible joining consecutive numbers (1–25). In Part B, the participant must draw a line alternately between consecutive numbers and letters (1-A-2-B-12-L). In the Japanese version of the TMT-B, letters from the Roman alphabet are exchanged for Kana characters. We recorded the amount of time (in seconds) it took to complete each task. We calculated the difference between Part B and Part A completion time (delta TMT). Smaller difference scores indicate better executive function.

Statistical analyses

Student's *t*-tests or χ^2-tests were used to compare the demographic, reaction time responses, and neurocognitive functions between the aMCI and non-aMCI groups. Pearson's correlation coefficients were used to quantify the bivariate associations between RT during single-task and dual-task conditions, and neurocognitive measures. While controlling for the possible confounding influences of age-related changes and length of education in reaction times during simple-task and dual-task conditions, standardized β-values were calculated using linear regression analysis to assess the relationships between the variables. Multiple linear regression models were constructed to determine the independent association of neurocognitive measures using simple RT and dual-task RT. We calculated the R^2- and standardized β-values for each regression model. The statistical analyses were carried out using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). The level of statistical significance was set at 0.05 for all analyses.

Results

Table 1 summarizes the characteristics of the participants in the aMCI and non-aMCI groups. There were no statistically significant between-group differences in age, sex, hypertension, diabetes mellitus, medication and clinical depression status. The participants in the aMCI group had significantly lower ROCF scores compared with the non-aMCI group ($P = 0.008$). There were no statistically significant between-group differences in other neurocognitive measurements. Although there were no statistically significant group differences in simple RT ($P = 0.734$), the participants in the aMCI group had significantly longer dual-task RT than the participants in the non-aMCI group ($P = 0.012$).

Table 2 shows the correlation coefficients of the relationships between RT during the single-task and dual-task conditions and neurocognitive measures, and shows the standardized β-values derived from the linear regression analyses after controlling for age and education. Simple RT were significantly correlated with Digit Symbol-Coding test scores ($r = -0.282$, $P = 0.027$) in the participants in the non-aMCI group, but this was not statistically significant after controlling for age and education ($\beta = -0.111$, $P = 0.476$). Dual-task RT were significantly correlated with Digit Symbol-Coding scores in the participants in both groups (non-aMCI $r = -0.386$, $P < 0.001$; aMCI $r = -0.402$, $P = 0.015$). These relationships were no longer significant in the participants in the aMCI group after controlling for age and education ($\beta = -0.163$, $P = 0.374$), but remained significant in the participants in the non-aMCI group ($\beta = -0.363$, $P = 0.021$). Additionally, dual-task RT were associated with ROCF scores ($r = -0.317$, $P = 0.012$) and delta TMT (times of TMT-B minus TMT-A; $r = -0.429$, $P = 0.001$) in the participants in the non-aMCI group, and these relationships were still significant after controlling for age and education (ROCF $\beta = -0.275$, $P = 0.035$, delta TMT $\beta = 0.380$, $P = 0.003$).

Table 3 shows the results of the multiple regression models that were used to independently determine the associations between neurocognitive functions and simple RT and dual-task RT. The group (aMCI), age, education, MMSE, ROCF, delta TMT, scores of the Digit Span Forward–Backward and Digit Symbol-Coding score parameters accounted for 13.0% of the variance in simple RT. Using multiple regression

Table 1 Characteristics, reaction times, and neurocognitive functions in the participants in the non-amnestic mild cognitive impairment and amnestic mild cognitive impairment groups

Characteristics	non-aMCI ($n = 62$)	aMCI ($n = 36$)	P-value
Age (years)	74.0 (6.1)	76.2 (7.2)	0.119
Sex, *n* (%)			
Male	26 (41.6)	21 (58.3)	0.117
Female	36 (58.1)	15 (41.7)	
Diagnosis, *n* (%)			
Hypertension†	31 (50.8)	13 (36.1)	0.160
Diabetes mellitus	6 (9.7)	5 (13.9)	0.524
Medication† (three or more)	22 (36.1)	17 (50.0)	0.186
GDS (score)	3.0 (2.3)	2.9 (2.4)	0.857
Reaction time/dual-task performance			
Simple reaction time (ms)	257.6 (45.9)	260.8 (41.7)	0.734
Dual-task reaction time (ms)	398.5 (117.2)	473.5 (171.2)	0.012
General cognitive function			
MMSE (score)	27.0 (2.0)	27.1 (1.8)	0.858
Visual memory			
ROCF‡ (score)	16.4 (5.7)	12.8 (6.5)	0.008
Working memory			
Digit Span Forward–Backward (score)	2.5 (2.3)	2.8 (1.9)	0.458
Executive function			
Trail Making Test Part B–Part A‡ (s)	52.8 (86.4)	73.6 (75.5)	0.245
Processing speed			
Digit Symbol-Coding (score)	47.6 (15.7)	47.3 (15.2)	0.934

The data are expressed as the mean (SD) score unless otherwise indicated. Significance was arbitrated at $P < 0.05$ using the unpaired Student's *t*-test or χ^2-test (for sex and diagnosis). †One participant in the non-amnestic mild cognitive impairment (aMCI) group did not report whether he or she had hypertension. One participant in the non-aMCI group and two participants in the aMCI group could not describe their current medication. ‡One participant in the aMCI group did not complete the Rey-Osterrieth Complex Figure Test (ROCF). Two participants in the aMCI group and two participants in the non-aMCI group did not complete the Trail Making Tests. GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

analysis to examine dual-task RT, we found a R^2-value of 30.5% and a standardized β-value of 0.298 for executive function assessed by the delta TMT ($P = 0.006$).

Discussion

The present results examined the relationships between neurocognitive measures and dual-task performance (measured by RT to visual stimuli) in older adults with MCI. The aMCI participants showed specific deficits in dual-task performance compared with the non-aMCI participants, and low dual-task performance was associated with declines in executive function in older adults with MCI.

A large number of previous studies reported a relationship between dual-task performance and cognitive function, particularly attentional capacity[28] and executive function.[29–32] Executive function plays an important role in older adults' ability to effectively adapt to complex environments and to adequately allocate the attentional resources necessary for successfully completing a given task.[28,29,33,34] Additionally, executive function is an important mediator of memory function in older adults suffering from age-related functional decline,[35] and MCI.[36] In the present study, we found that increased attentional costs under dual-task conditions were related to reduced executive function in older people with MCI. These findings are in accord with the results of previous studies showing a relationship between dual-task costs and neurocognitive functions. However, the relationship between the Digit Symbol-Coding scores, the delta TMT and dual-task RT in the aMCI group did not remain after controlling for age and education. Our data could not provide a definite association between dual-task performance and neurocognitive functions in the aMCI participants.

Dual-task performance reflects divided attention and is considered an important executive function.[3,4] Therefore, it would be expected that participants with non-aMCI showed lower dual-task performance based on

Table 2 Bivariate correlations between reaction times and neurocognitive functions

Outcome measure	Non-aMCI (n = 62)				aMCI (n = 36)			
	Simple-task RT		Dual-task RT		Simple-task RT		Dual-task RT	
	Simple-Correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)	Simple-correlation (r)	Age and education-controlled (β)
MMSE	−0.089	0.006	−0.102	−0.035	−0.221	−0.177	−0.231	−0.083
ROCF	−0.084	0.004	−0.317*	−0.275*	−0.081	−0.038	−0.180	0.027
Digit Span Forward–Backward	−0.175	−0.215	−1.000	−0.130	−0.218	−0.191	−0.066	0.105
Trail Making Test Part B–Part A	0.251	0.171	0.429**	0.380**	0.025	0.043	0.370*	0.229
Digit Symbol-Coding	−0.282*	−0.111	−0.386**	−0.363*	−0.135	−0.042	−0.402*	−0.163

*P < 0.05, **P < 0.01. aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth Complex Figure Test; RT, reaction time.

criteria for classification of groups. Contrary to expectations, the aMCI group showed significantly lower dual-task performance than the non-aMCI group in the present study. The aMCI group included not only participants with amnestic single domain MCI subtype (showing a memory deficit), but also those with amnestic multiple domain MCI subtype (showing deficits of memory in addition to other domains). The results of the present study showed that there were no statistically significant between-group differences in other domains, such as executive function and processing speed. The present findings might suggest that older adults showing deficits of multiple domains including memory deficits exhibit decline of dual-task performance compared with those without memory deficits. Unfortunately, it was difficult to analyze using detailed subtype categories of MCI, because the sample size was small. Clarifying these problems by future research with a large sample size would be required.

The present findings indirectly corroborate a number of other studies, showing that patients with MCI experienced high dual-task costs.[11,37,38] Previous studies reported that dual-task-related changes in performance were greater in patients with MCI compared with cognitively normal age-matched controls,[37,38] and that dual-task performance during walking was significantly impaired in MCI patients.[11] However, the current findings conflict with the results of some previous studies. One study reported that there were no differences in dual-task performance between aMCI patients and controls.[14] Additionally, in a study using the Talking While Walking assessment as a dual-task test, no differences in dual-task performance were reported between MCI and healthy participants, although participants with AD showed greater performance changes between single task and dual-task conditions compared with healthy participants.[39] Previous results regarding the relationships between cognitive status and dual-task decrements among older adults at risk of dementia have not been consistent, particularly for MCI patients.[6,7,40] Studies investigating the relationship between dual-task performance and cognitive status have tended to focus on patients with AD, who generally show impaired dual-task performance. AD patients also show difficulties in dual-task performance requiring the completion of a cognitive task while walking.[7,40] These results suggest that the ability to divide attention, in combination with a cognitive task, is reduced among patients with AD. Thus, decreased dual-task performance might be considered an early symptom of AD. Although the present study included only MCI patients, our findings provide indirect evidence that poor dual-task performance with cognitive demand might be related to impaired executive functioning in older adults with MCI.

Executive functions are higher order cognitive processes that control, integrate, organize and maintain

Table 3 Multiple linear regression model summary for simple reaction time and dual-task reaction time experiments

Independent Variable	Simple reaction time (ms)			Dual-task reaction time (ms)		
	R^2	Standardized β	*P*-value	R^2	Standardized β	*P*-value
Model	0.130			0.305		
Group (aMCI)		0.028	0.797		0.184	0.061
Age		0.153	0.233		0.211	0.067
Education		−0.155	0.175		−0.073	0.470
MMSE		−0.059	0.213		0.052	0.622
ROCF		0.051	0.661		−0.107	0.302
Digit Span Forward–Backward		−0.216	0.038		−0.071	0.433
Trail Making Test Part B–Part A		0.137	0.246		0.298	0.006
Digit Symbol-Coding		0.030	0.829		−0.063	0.616

Dependent variable: simple reaction time (ms) and dual-task reaction time (ms). aMCI, amnestic mild cognitive impairment; MMSE, Mini Mental State Examination; ROCF, Rey-Osterrieth Complex Figure Test.

other cognitive abilities.[41] Associations between physical performance and executive function were shown in community-dwelling older adults.[42] Similarly, these associations were confirmed in older adults with MCI.[43] The beneficial effects of physical exercise have been shown in older adults with MCI.[44,45] It might be clinically important to improve executive function among older adults with MCI, because deficits in executive function strongly predict conversion to AD.[46] The results of the present study support the hypothesis that interventions that include the dual-task paradigm might be effective for increasing executive function among older adults with MCI.

Several limitations of the current study should be considered. First, we used cross-sectional data, meaning causal relationships could not be assessed. For lack of longitudinal cognitive changes, the results of the present study fail to indicate that measurements of dual-task performance might be useful as a prognostic measure of cognitive decline. Second, the absence of a large sample size limits the conclusions that can be drawn. The sample size of aMCI participants was markedly smaller than the non-aMCI participants, limiting the interpretation of the results. Third, we could not assess whether the participants correctly and rapidly participated in the concurrent task (counting backwards) that relied on increasing demands of the dual-task. In the present study, it was important for the participants to divide their attention during the dual-task conditions. Although participants in both groups showed significantly longer RT under the dual-task conditions compared with the simple-task conditions, some participants would divide the minimum attention required to complete the concurrent tasks. Finally, our study cohort did not contain healthy subjects or AD patients, meaning that we could not examine the association between dual-task performance and the risk of cognitive decline in AD-related processes. In addition, analysis of neuroimaging data was not included in the present study. MCI represents a complex heterogenous condition, including degenerative and vascular brain pathologies. Brain conditions potentially affect cognitive decline including dual-task performance.[47]

In conclusion, we found that aMCI patients showed deficits in dual-task performance compared with non-aMCI participants, and poor dual-task performance was associated with declines in executive function in older people with MCI. Future longitudinal and interventional studies should investigate the use of dual-task testing with varying levels of cognitive demand in subjects at risk of dementia, and analyses of imaging data, because these studies might elucidate the factors that lead to the conversion to AD from MCI.

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Disclosure statement

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The relationship between atrophy of the medial temporal area and daily activities in older adults with mild cognitive impairment

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ABSTRACT. ***Background and aims:*** *Many studies have suggested that social network, leisure activity, and physical activity can have protective effects against dementia and Alzheimer's disease. However, previous studies have not examined the relationship between daily activities and brain atrophy in older adults. This study aimed to explore what kind of daily activities were associated with atrophy of the medial temporal area including the entorhinal cortex (MTA-ERC) in older adults.* ***Methods:*** *In total, 122 older adults (aged 65 and over) with subjective memory complaints or a Clinical Dementia Rating of 0.5 underwent magnetic resonance imaging, and MTA-ERC atrophy was assessed by the voxel-based morphometry method. Based on magnetic resonance imaging data, the subjects were divided into atrophy and non-atrophy groups. Daily activities were assessed using a 20-item questionnaire (e.g., instrumental activities of daily living, social activities), and we compared activity participation between the groups.* ***Results:*** *The atrophy group (n=37) showed significantly lower participation in 4 out of 20 activity items (cleaning, intellectual activity, culture lessons, and using a personal computer) than the non-atrophy group (n=85). Summed scores of these 4 items (range from 0 to 4) were significantly associated with MTA-ERC atrophy even after adjustment for age, sex, education status, and Mini-Mental State Examination score.* ***Conclusions:*** *In conclusion, MTA-ERC atrophy was associated with cognitive activities or household-related activities requiring planning.*

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INTRODUCTION

Memory impairment is the earliest symptom of Alzheimer's disease (AD) in most patients (1), and brain atrophy of the medial temporal region is observed in those patients (2). The medial temporal lobe has long been known to play a critical role in memory (3). In a recent review, the most reliable and well-documented finding was an association between impaired verbal memory and medial temporal lobe atrophy that is particularly robust for the hippocampal and entorhinal regions (3). Moreover, hippocampal and entorhinal cortex atrophy have been shown to predict conversion to AD (1, 4, 5). It is important to assess atrophy of the medial temporal areas (MTA), especially the hippocampus and entorhinal cortex for understanding AD pathology.

Many studies have suggested that social network, leisure activity, and physical activity have protective effects against dementia and AD (6-13). For example, a popu-

Key words: Alzheimer's disease, magnetic resonance imaging, brain atrophy, activities of daily living.

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lation-based longitudinal study, with a mean follow-up of 6.2 years, confirmed a reduced incidence rate of dementia for people who exercised 3 or more times a week (13.0 per 1000 person-years), compared with those who exercised fewer than 3 times per week (19.7 per 1000 person-years). People who exercised 3 or more times a week had a relative hazard of 0.68 (CI 0.48-0.96) for developing dementia compared with those who exercised fewer than 3 times per week (12). Moreover, Scarmeas et al. (7) demonstrated that engagement in leisure activities may reduce the risk of incident dementia. These findings support the hypothesis that physical and leisure activities reduce the likelihood for cognitive decline in community-dwelling older adults.

Some studies have failed to observe the benefits of physical activity (or exercise) in preserving cognitive function (14-18), suggesting that the effects of physical activity on cognitive functions might change according to the type of activity; but most of the studies examined the effects of composite physical activity (17), and the effect of individual activities is not well known. Furthermore, these previous studies did not examine brain atrophy; the relationship between these activities and brain atrophy (especially the MTA) was not clear.

To address these issues, we recruited community-dwelling older adults who had memory problems and conducted magnetic resonance imaging (MRI). The purpose of this study was to determine what kind of daily activity was associated with MTA atrophy as assessed by the voxel-based morphometry method.

METHODS

Subjects

The subjects were recruited from two volunteer databases (n=1543) that included elderly (aged 65 and over), who were selected by random sampling or who attended a health check in Obu, Japan. In the first eligibility assessment of this study, 528 potential subjects who had a Clinical Dementia Rating of 0.5 or memory complaints were enrolled. One hundred sixty-five subjects responded to the second eligibility assessment, and 125 out of 165 subjects completed all assessments. People who needed assistance for basic activities of daily living or who had neurological or psychiatric illness, cardiovascular disease, head trauma, drug abuse issues, alcoholism, severe pain, and contraindication of MRI were excluded. Finally, 122 subjects remained and met the definition of MCI using Petersen criteria (19).

All subjects received an MRI, a questionnaire on daily activity, and neuropsychological tests; Mini-mental State Examination (20) and Wechsler Memory Scale-Revised (WMS-R) Logical Memory (21) were assessed by speech therapists. Depressive symptoms were assessed by the Geriatric Depression Scale (22). The details of the study were explained to all subjects in advance, and written consent was obtained from each subject. In addition, this study was conducted in accordance with the Helsinki Declaration, and was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

MRI procedure and voxel-based MRI analysis

We determined the atrophy of MTA including the entorhinal cortex (MTA-ERC) using the voxel-based specific regional analysis for Alzheimer's disease (VSRAD) (23-25), 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 (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, 1700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 × 256, 1.3-mm slice thickness). According to the VSRAD procedure proposed by Matsuda and Hirata et al. (23, 25), the acquired MRI images were reformatted to gapless 2-mm thin-slice transaxial images.

In the voxel-based MRI analyses, the first anatomical 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 non-uniformity correction. The segmented gray matter images were then subjected to an affine and non-linear anatomical standardization using an *a priori* gray matter template. The anatomically standardized gray matter images were smoothed with an isotropic Gaussian kernel 12 mm 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 the smoothing kernel. Each gray matter image of the patients was compared with the mean and SD of gray matter images of the healthy volunteers using voxel-by-voxel Z-score analysis after voxel normalization to global mean intensities: Z-score = (control mean-individual value) / (control SD). The Z score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z scores indicate clearer MTA-ERC atrophy.

Daily activities assessment

Daily activities were assessed using a questionnaire of 20 items that originated from brainstorming. The members who participated in brainstorming were 4 male physical therapists (the years of experience as a physical

therapist were 18 years, 9 years, 4 years, and 1 year, respectively) and 2 female office workers (a married woman and a single woman). They discussed and chose the questionnaire items based on what was necessary for older adults to live independently in the community. In the present study, we used the 20 activity items (e.g., instrumental activities of daily living, social activities) that remained after discussion. We excluded items for basic activities of daily living (such as taking a bath, going to the toilet, and changing clothes) from the present questionnaire because all of our subjects were living independently in a community. The details of the questionnaire can be found in the *Appendix*. The subjects were asked whether they did each activity during the past one month, and they answered "yes (did)" or "no (did not)".

Statistical analysis

Subjects were divided into two groups: older adults without or with slight atrophy (Z score <2; non-atrophy group) and those with moderate or severe atrophy (Z score ≥2; atrophy group) in the MTA-ERC based on the results of the VSRAD. At first, we conducted an unpaired t-test or chi-square test to compare the characteristics of the subjects and the proportions of each daily activity in the two groups. If there were significant differences in the proportions of daily activity, we assigned 0 (did not) or 1 point (did) to these items in accordance with subject's response. Then, we summed the number of points by each subject. Second, multiple logistic regression analysis was performed to examine the independent associations between MTA-ERC atrophy and daily activity adjusted for demographic variables. We used moderate or severe MTA-ERC atrophy (Z score ≥2) as the dependent variable. The independent variables included age, sex, education status, MMSE score, state of achievement of each daily activity, and the summed score of daily activities (0 to 4). Statistical analysis was done using SPSS 12.0 for Windows, and all statistics were processed at a significance level of $p<0.05$.

RESULTS

The characteristics of the atrophy group (Z score ≥2; n=37) and the non-atrophy group (Z score <2; n=85) are listed in Table 1. There were significant differences in age (74.3±6.9 *vs* 79.5±6.2, $p<0.01$), sex (men/women=35/50 *vs* 26/11, $p<0.01$), education (10.9±2.7 *vs* 9.5±2.0, $p<0.01$), and MMSE score (26.7±2.2 *vs* 25.4±3.1, $p<0.05$) between the two groups. However, there were no significant differences in other characteristics.

In regard to 4 activity items (cleaning, intellectual activity, culture lesson, using a personal computer), the atrophy group had a significantly lower proportion of the people who had answered "yes (did)" than the non-atrophy group ($p<0.05$). Other items did not show significant differences between groups (Table 2). Therefore, the summed score included the number of those activity items where group differences were found and ranged from 0 to 4. The mean values of the summed score of the atrophy and non-atrophy groups were 1.5±1.1 and 2.4±1.0, respectively.

In multiple logistic regression analysis, no association was observed between MTA-ERC atrophy and the proportions of each daily activity, whereas the summed score showed a significant relationship with MTA-ERC atrophy even after adjustment for age, sex, education, and MMSE (odds ratio 0.576, 95% CI 0.358-0.924, $p=0.022$; Table 3).

DISCUSSION

Atrophy of the medial temporal lobe, especially the hippocampus and entorhinal cortex, is an MRI-based measure validated to predict conversion and understand progression to AD (1, 4, 5). In recent studies, the VSRAD was used to automatically and quantitatively assess MTA-

Table 1 - *Characteristics of the subjects.*

Variables		Z score <2 (n=85)	Z score ≥2 (n=37)	p-value
Age	year	74.3±6.9	79.5±6.2	<0.001**
Men	n (%)	35 (58.8)	26 (29.7)	0.003**
Education	year	10.9±2.7	9.5±2.0	0.003**
MMSE	score	26.7±2.2	25.4±3.1	0.028*
GDS	score	3.6±3.2	4.1±2.9	0.477
Atrophy of MTA-ERC	z-score	0.9±0.5	2.7±0.7	<0.001**
Diagnosis				
CVD	n (%)	3 (3.5)	3 (8.1)	0.258
Hypertension	n (%)	28 (32.9)	17 (45.9)	0.171
Diabetes mellitus	n (%)	10 (11.8)	1 (2.7)	0.088

Values are mean±SD or n (%). **p<0.01; *p<0.05. MMSE: Mini-mental State Examination; GDS: Geriatric Depression Scale; MTA-ERC: Medial temporal area including the entorhinal cortex; CVD: Cerebrovascular disease.

Table 2 - *The relationship between atrophy of the medial temporal area and individual daily activities in atrophy and non-atrophy groups.*

No	Item		Z score <2 (n=85)		Z score ≥2 (n=37)		p-value
1	Reading	n (%)	83	(97.6)	36	(97.3)	0.665
2	Going to a neighborhood	n (%)	84	(98.8)	37	(100.0)	0.697
3	Cleaning	n (%)	83	(97.6)	29	(78.4)	0.001**
4	Talking by telephone	n (%)	82	(96.5)	33	(89.2)	0.124
5	Taking out garbage	n (%)	74	(87.1)	31	(83.8)	0.631
6	Talking with somebody	n (%)	80	(94.1)	35	(94.6)	0.641
7	Caring for a grandchild	n (%)	59	(69.4)	22	(59.5)	0.285
8	Gardening	n (%)	70	(82.4)	28	(75.7)	0.394
9	Going out by bus or train	n (%)	73	(85.9)	30	(81.1)	0.501
10	Sports or hobbies	n (%)	61	(71.8)	20	(54.1)	0.057
11	Intellectual activities	n (%)	54	(63.5)	15	(40.5)	0.019*
12	Attending a meeting	n (%)	44	(51.8)	22	(59.5)	0.433
13	Working as a coordinator	n (%)	28	(32.9)	7	(18.9)	0.115
14	Culture lessons	n (%)	45	(52.9)	9	(24.3)	0.003**
15	Going to unknown place	n (%)	46	(54.1)	16	(43.2)	0.269
16	Carrying a heavy load	n (%)	62	(72.9)	26	(70.3)	0.762
17	Managing money	n (%)	85	(100.0)	35	(94.6)	0.090
18	Visiting friends	n (%)	69	(81.2)	28	(75.7)	0.489
19	Operating a video	n (%)	33	(38.8)	9	(24.3)	0.111
20	Using a personal computer	n (%)	23	(27.1)	4	(10.8)	0.047*

Values are the number (%) answered "yes (did)". **p<0.01; *p<0.05.

ERC atrophy and has been introduced for the diagnosis of Alzheimer-type dementia with MRI. Hirata et al. (23) found a high accuracy (87.8%) for discriminating patients with very early AD at the mild cognitive impairment (MCI) stage from control subjects by VSRAD. It is assumed that VSRAD data are effective for assessing initial brain atrophy in an AD progression process. To determine the relationship between MTA-ERC atrophy and daily activities, we conducted MRI scanning and an interview on detailed daily activities in older adults who had memory problems, but not dementia.

In the group comparison, there were significant differences in age. A previous study found a correlation between increasing age and decreasing brain volume (26), and found that brain atrophy may accelerate with increasing age (27). Our results are consistent with previous studies, and suggest that MTA-ERC atrophy was affected by advancing age. On the other hand, there were no significant differences in vascular risk factors, such as hypertension, diabetes mellitus, and cerebrovascular disease. White-matter changes appear to be more frequent in individuals with vascular risk factor, and apathy is a prominent syndrome related to cerebral white-matter changes (28). We consider that this result reflects the equivalence of subcortical vascular damage in both groups.

Older adults who carried out cleaning activity, intellectual activity, a culture lesson, and personal computer

Table 3 - *Relationship between atrophy of the medial temporal area and daily activities.*

Variables		OR	95% CI	p-value
Cleaning	(yes/no)	0.143	(0.020-1.013)	0.052
Intellectual activities	(yes/no)	0.510	(0.204-1.279)	0.151
Culture lessons	(yes/no)	0.484	(0.174-1.343)	0.163
Using a personal computer	(yes/no)	0.407	(0.103-1.608)	0.200
Summed scores of activities	(0-4)	0.576	(0.358-0.924)	0.022*

Dependent variable, the presence of medial temporal area atrophy (Z score ≥2). *p<0.05 (adjustment for age, sex, education, MMSE score). OR: odds ratio; CI: confidence interval; MMSE: Mini-Mental State Examination.