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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 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].

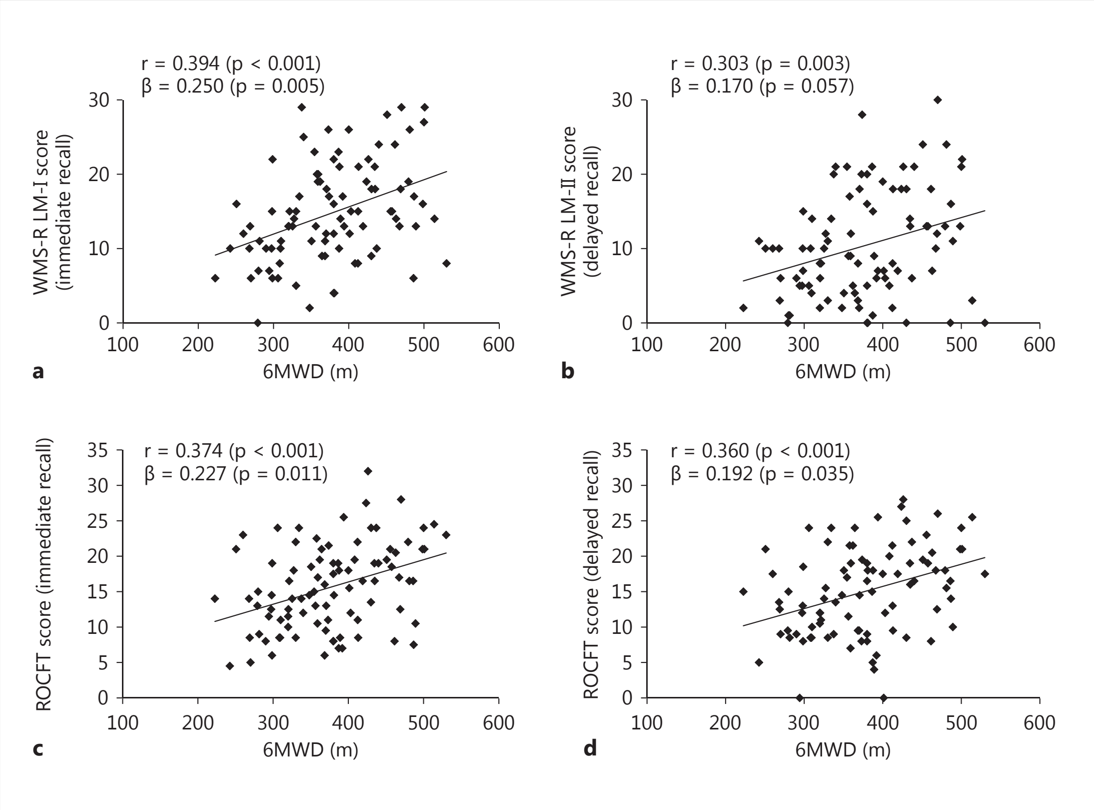

Fig. 1. Correlations between 6MWDs and memory performance tests. Pearson correlation coefficients (r) and standardized beta values (controlling for age and sex) are presented. **a** WMS-R LM-I (immediate recall). **b** WMS-R LM-II (delayed recall). **c** ROCFT (immediate recall). **d** ROCFT (delayed 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, β = 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, β = 0.250, p = 0.005; ROCFT (immediate), β = 0.227, p = 0.011; ROCFT (delay), β = 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.

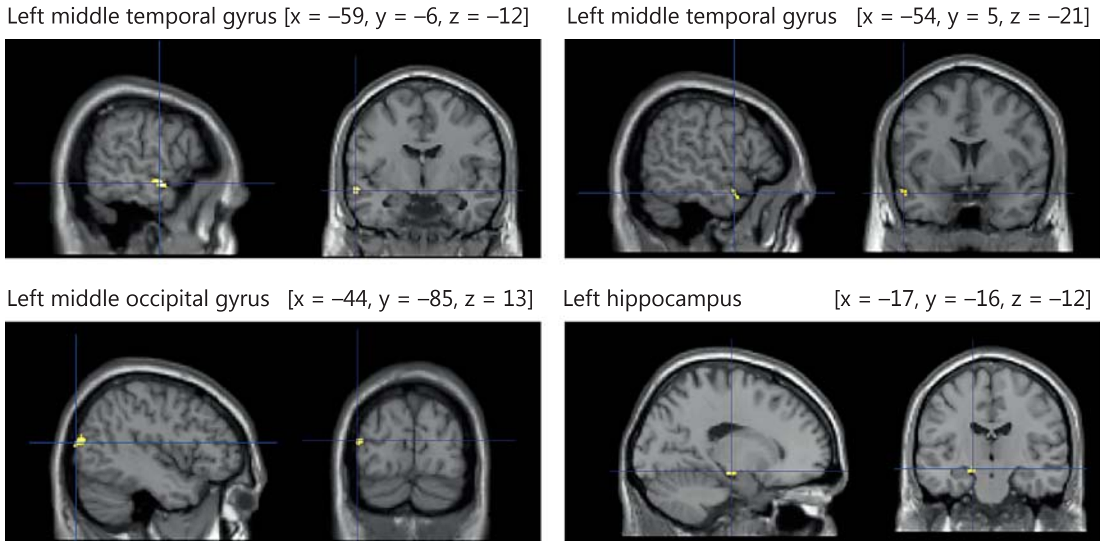
Left middle temporal gyrus [x = –59, y = –6, z = –12]
Left middle temporal gyrus [x = –54, y = 5, z = –21]
Left middle occipital gyrus [x = –44, y = –85, z = 13]
Left hippocampus [x = –17, y = –16, z = –12]

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.

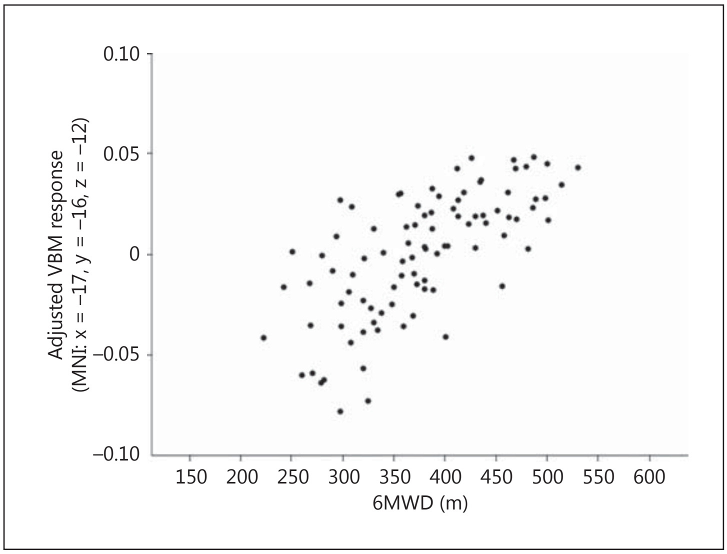

Fig. 3. Correlation between VBM response in the left hippocampus peak voxel (adjusted for effects of age and sex) and the 6MWD.

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 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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