EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189
Published online: August 16, 2013

1664–5464/13/0031–0223$38.00/0
www.karger.com/dee

Karger Open access

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

Hyuma Makizako[a, d] Hiroyuki Shimada[a] Takehiko Doi[a, d] Hyuntae Park[b]
Daisuke Yoshida[a] Takao Suzuki[c]

Sections for [a]Health Promotion and [b]Physical Functioning Activation, Center for Gerontology and Social Science, and [c]Research Institute, National Center for Geriatrics and Gerontology, Obu, and [d]Japan Society for the Promotion of Science, Tokyo, Japan

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.

Hyuma Makizako, PT, PhD, Section for Health Promotion
Center for Gerontology and Social Science
National Center for Geriatrics and Gerontology
35 Gengo, Morioka-machi, Obu, Aichi 474-8511 (Japan)
E-Mail makizako@ncgg.go.jp

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

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

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

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].

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

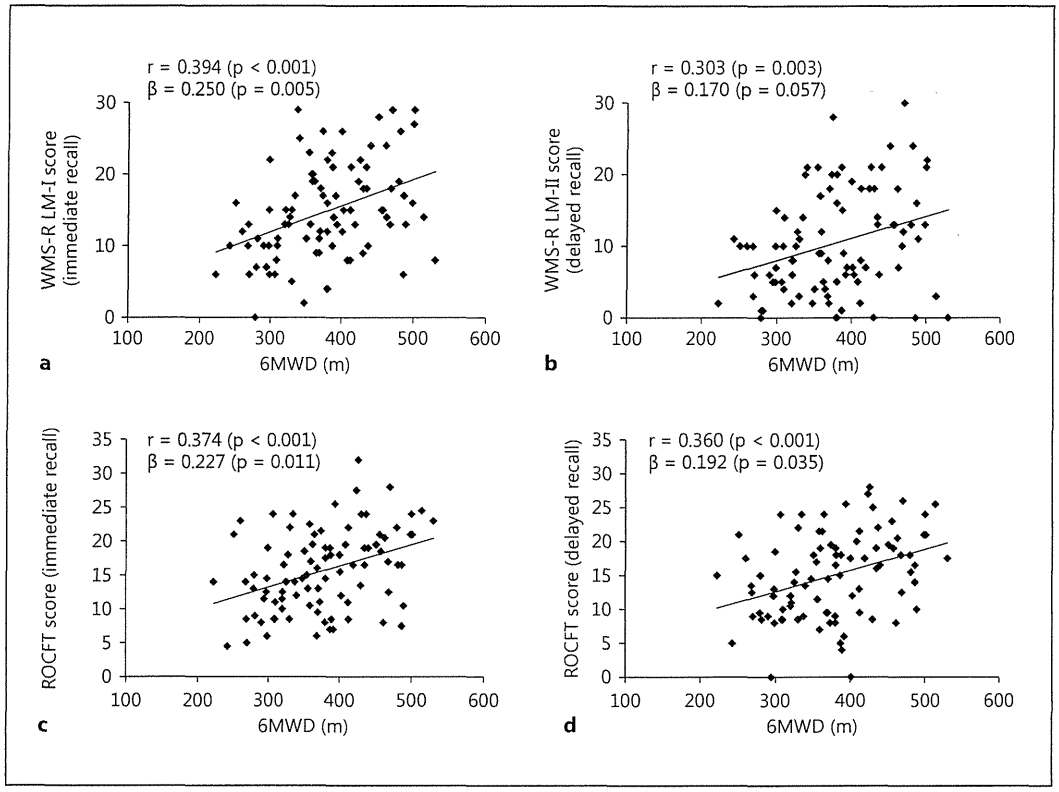

Fig. 1. Correlations between 6MWDs and memory performance tests. Pearson correlation coefficients (r) and standardized beta values (controlling for age and sex) are presented. **a** WMS-R LM-I (immediate recall). **b** WMS-R LM-II (delayed recall). **c** ROCFT (immediate recall). **d** ROCFT (delayed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

Results

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

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

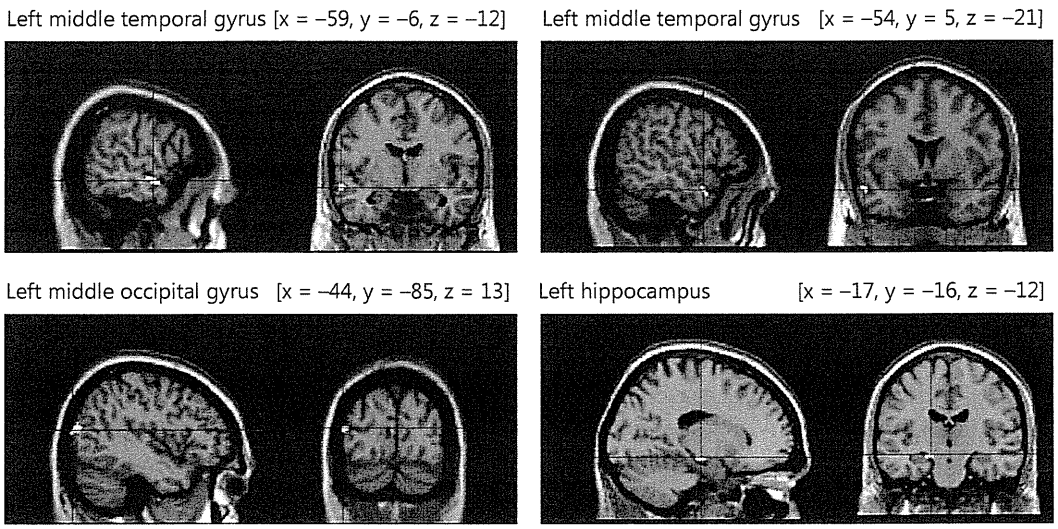

Fig. 2. Brain regions showing an association between a better performance in the 6MWT and a greater gray matter volume. After adjusting for age and sex, gray matter density in the left middle temporal gyrus, middle occipital gyrus, and hippocampus showed positive correlations with the 6MWD.

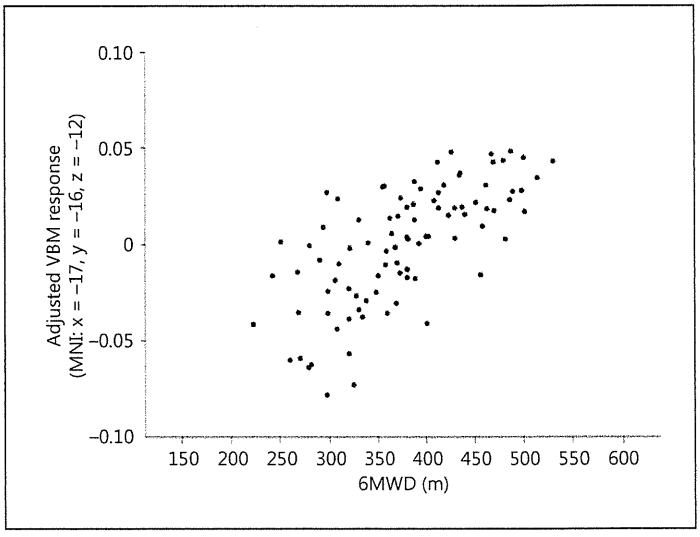

Fig. 3. Correlation between VBM response in the left hippocampus peak voxel (adjusted for effects of age and sex) and the 6MWD.

Discussion

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

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

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

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

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

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.

Acknowledgments

We would like to thank the Obu City Office for their assistance with participant recruitment. We would also like to thank the technical staff from the Department of Radiology, National Hospital for Geriatric Medicine, National Center for Geriatrics and Gerontology for MRI data acquisition. This work was supported by a grant from the Japanese Ministry of Health, Labour and Welfare (Project for optimizing long-term care; B-3) to T.S. and a grant-in-aid for JSPS Fellows (23-9862) from the Japan Society for the Promotion of Science to H.M.

Disclosure Statement

There are no conflicts of interest.

References

1 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.
2 Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142.
3 Barnes DE, Yaffe K, Satariano WA, Tager IB: A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J Am Geriatr Soc 2003;51:459–465.
4 Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W: Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73–81.
5 Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF: Exercise, brain, and cognition across the life span. J Appl Physiol 2011;111:1505–1513.
6 Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF: Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006;61:1166–1170.
7 Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF: Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 2011;108:3017–3022.
8 Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, Kramer AF: Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 2009;19:1030–1039.
9 Weinstein AM, Voss MW, Prakash RS, Chaddock L, Szabo A, White SM, Wojcicki TR, Mailey E, McAuley E, Kramer AF, Erickson KI: The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. Brain Behav Immun 2012;26:811–819.
10 Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB, Satterfield S, Rosano C, Rubin SM, Ayonayon HN, Harris TB: Predictors of maintaining cognitive function in older adults: the Health ABC study. Neurology 2009;72:2029–2035.
11 Chang M, Jonsson PV, Snaedal J, Bjornsson S, Saczynski JS, Aspelund T, Eiriksdottir G, Jonsdottir MK, Lopez OL, Harris TB, Gudnason V, Launer LJ: The effect of midlife physical activity on cognitive function among older adults: AGES-REYKJAVIK Study. J Gerontol A Biol Sci Med Sci 2010;65:1369–1374.
12 Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH: Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 2010;75:1415–1422.
13 Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S: Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010;67:71–79.
14 van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M: Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med 2008;42:344–351.
15 Cyarto EV, Lautenschlager NT, Desmond PM, Ames D, Szoeke C, Salvado O, Sharman MJ, Ellis KA, Phal PM, Masters CM, Rowe CC, Martins RN, Cox KL: Protocol for a randomized controlled trial evaluating the effect of physical activity on delaying the progression of white matter changes on MRI in older adults with memory complaints and mild cognitive impairment: the AIBL Active trial. BMC Psychiatry 2012;12:167.
16 Cataneo DC, Kobayasi S, Carvalho LR, Paccanaro RC, Cataneo AJ: Accuracy of six minute walk test, stair test and spirometry using maximal oxygen uptake as gold standard. Acta Cir Bras 2010;25:194–200.
17 Steffen TM, Hacker TA, Mollinger L: Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther 2002;82:128–137.
18 Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC: Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.
19 Prins ND, van der Flier WM, Brashear HR, Knol DL, van de Pol LA, Barkhof F, Scheltens P: Predictors of progression from mild cognitive impairment to dementia in the placebo-arm of a clinical trial population. J Alzheimers Dis 2013;36:79–85.
20 Korf ES, Wahlund LO, Visser PJ, Scheltens P: Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 2004;63:94–100.
21 Petersen RC: Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–194.
22 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
23 Yesavage JA: Geriatric depression scale. Psychopharmacol Bull 1988;24:709–711.
24 Wechsler D: Wechsler Memory Scale-Revised Manual. San Antonio, The Psychological Corporation, 1987.
25 Meyers J, Meyers K: Rey Complex Figure Test and Recognition Trial: Professional Manual. Odessa, Psychological Assessment Resources, 1995.

Dement Geriatr Cogn Disord Extra 2013;3:223–232
DOI: 10.1159/000354189

26 Cooper KH: A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. JAMA 1968;203:201–204.
27 Ashburner J: A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95–113.
28 Ashburner J, Friston KJ: Unified segmentation. Neuroimage 2005;26:839–851.
29 Eickhoff SB, Heim S, Zilles K, Amunts K: Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. Neuroimage 2006;32:570–582.
30 Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, Dalmonte E: Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology 2008;70:1786–1794.
31 Sattler C, Erickson KI, Toro P, Schroder J: Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. J Alzheimers Dis 2011;26:709–718.
32 Floel A, Ruscheweyh R, Kruger K, Willemer C, Winter B, Volker K, Lohmann H, Zitzmann M, Mooren F, Breitenstein C, Knecht S: Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 2010;49:2756–2763.
33 Ruscheweyh R, Willemer C, Kruger K, Duning T, Warnecke T, Sommer J, Volker K, Ho HV, Mooren F, Knecht S, Floel A: Physical activity and memory functions: an interventional study. Neurobiol Aging 2011;32:1304–1319.
34 Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA: An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 2007;104:5638–5643.
35 Honea RA, Thomas GP, Harsha A, Anderson HS, Donnelly JE, Brooks WM, Burns JM: Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. Alzheimer Dis Assoc Disord 2009;23:188–197.
36 Chetelat G, Landeau B, Eustache F, Mezenge F, Viader F, de la Sayette V, Desgranges B, Baron JC: Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. Neuroimage 2005;27:934–946.
37 Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV: Neurostructural predictors of Alzheimer's disease: a meta-analysis of VBM studies. Neurobiol Aging 2011;32:1733–1741.
38 Apostolova LG, Morra JH, Green AE, Hwang KS, Avedissian C, Woo E, Cummings JL, Toga AW, Jack CR Jr, Weiner MW, Thompson PM: Automated 3D mapping of baseline and 12-month associations between three verbal memory measures and hippocampal atrophy in 490 ADNI subjects. Neuroimage 2010;51:488–499.
39 Phillips HS, Hains JM, Laramee GR, Rosenthal A, Winslow JW: Widespread expression of BDNF but not NT3 by target areas of basal forebrain cholinergic neurons. Science 1990;250:290–294.
40 Kang H, Schuman EM: Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 1995;267:1658–1662.
41 Griffin EW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM: Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiol Behav 2011;104:934–941.
42 Gobbo OL, O'Mara SM: Exercise, but not environmental enrichment, improves learning after kainic acid-induced hippocampal neurodegeneration in association with an increase in brain-derived neurotrophic factor. Behav Brain Res 2005;159:21–26.
43 Griffin EW, Bechara RG, Birch AM, Kelly AM: Exercise enhances hippocampal-dependent learning in the rat: evidence for a BDNF-related mechanism. Hippocampus 2009;19:973–980.
44 Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, Kramer AF: Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 2003;58:176–180.
45 Thomann PA, Roth AS, Dos Santos V, Toro P, Essig M, Schroder J: Apolipoprotein E polymorphism and brain morphology in mild cognitive impairment. Dement Geriatr Cogn Disord 2008;26:300–305.

Geriatrics Gerontology International
Medline Indexed

Geriatr Gerontol Int 2013; **13:** *860–866*

Evaluation of multidimensional neurocognitive function using a tablet personal computer: Test–retest reliability and validity in community-dwelling older adults

Hyuma Makizako,[1,4] Hiroyuki Shimada,[1] Hyuntae Park,[2] Takehiko Doi,[1] Daisuke Yoshida,[1] Kazuki Uemura,[1,4] Kota Tsutsumimoto[1] and Takao Suzuki[3]

[1]Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, [2]Section for Physical Activity and Health, Department of Functioning Activation, Center for Gerontology and Social Science, [3]National Institute of Longevity Science, National Center for Geriatrics and Gerontology, Aichi, and [4]Japan Society for the Promotion of Science, Tokyo, Japan

Aim: This study sought to confirm the test–retest reliability and validity of the National Center for Geriatrics and Gerontology functional assessment tool (NCGG-FAT), a newly developed assessment of multidimensional neurocognitive function using a tablet personal computer (PC).

Methods: This study included 20 community-dwelling older adults (9 females, aged 65–81 years). Participants were administered the NCGG-FAT twice, separated by approximately 30 days to determine test–retest reliability. To test the validity of the measure, participants underwent established neurocognitive measurements, including memory, attention, executive function, processing speed and visuospatial function within a week from the first administration of the NCGG-FAT.

Results: Test–retest reliability was in an acceptable range for each component of the NCGG-FAT, with intraclass correlation coefficients ranging from 0.764 to 0.942. Each task in the NCGG-FAT showed a moderate to high correlation with scores on widely-used conventional neurocognitive tests ($r = 0.496$ to 0.842).

Conclusion: We found that the NCGG-FAT using a tablet PC was reliable in a sample of community-dwelling older adults. The NCGG-FAT might be useful for cognitive screening in population-based samples and outcomes, enabling assessment of the effects of intervention on multidimensional cognitive function among older adults. **Geriatr Gerontol Int 2013; 13: 860–866.**

Keywords: aged-population, assessment, cognitive functioning, screening.

Introduction

Declining cognitive function is one of the most important health problems in an aging population, and older adults showing cognitive decline are at increased risk for progressing to mild cognitive impairment (MCI) and dementia. MCI is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia,[1,2] and might be the optimum stage at which to intervene with preventive therapies.[3,4]

Accepted for publication 24 October 2012.

Correspondence: Dr Hyuma Makizako PhD, Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8551, Japan. Email: makizako@ncgg.go.jp

The prevalence of MCI in older populations has been estimated in previous community-based epidemiological studies, and the reported prevalence estimations of MCI have varied widely.[5] For instance, the reported prevalence of MCI in adults aged 70 years and older ranges from 16% to 39%,[6,7] and the reported progression rates to dementia and Alzheimer's disease (AD) for individuals with MCI vary from 6% to 25% per year, depending on the criteria for MCI.[8] A reliable quantitative tool for assessing neuropsychological function is required for early and accurate screening of MCI.

Variable neurocognitive tests are used to determine cognitive decline in a clinical community-based setting. Most of these measures for assessment of multidimensional cognitive functions among older adults need to be administered by well-trained assessors, such as clinicians, clinical psychologists and speech or occupational therapists. However, it is difficult to manage

large numbers of well-trained assessors to assess multidimensional cognitive functions in clinical community-based settings with large populations. As such, developing a valid tool for assessing multidimensional neurocognitive function that does not require a specialized assessor is important in countries with large populations of older adults, because the capacity to administer specific assessments with specialized assessors is limited for large samples.

We developed the National Center for Geriatrics and Gerontology functional assessment tool (NCGG-FAT), which includes measurements for evaluating multidimensional neurocognitive function using a tablet personal computer (PC). The purpose of the present study was to confirm the test–retest reliability and validity of the NCGG-FAT among Japanese adults aged 65 years or older. If the test–retest reliability and validity of our assessment system for evaluating multidimensional neurocognitive function using a tablet PC can be confirmed, the system could be useful for cognitive screening in large populations of older adults.

Methods

Participants

A total of 20 older adults (nine females), aged 65–81 years, and independently in a community, participated in the present study, after giving written informed consent. None of the participants had a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, or clinical depression. All participants showed general cognitive functioning (Mini-Mental State Examination[9] scores between 24 and 30) and did not meet the definition of MCI using the Petersen criteria.[10] Although seven participants reported subjective memory complaints, none of them showed objectively determined memory impairment, as assessed by the education-adjusted score on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II.[11] Table 1 shows a summary of participant characteristics in the present study. The study protocol was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

Protocol

To examine test–retest reliability, participants were administered the computerized multidimensional neurocognitive task battery on two separate occasions, separated by approximately 30 days to determine test–retest reliability of the tablet version of the multidimensional neurocognitive task battery. To examine validity, participants underwent comprehensive neurocognitive evaluation, including measures of memory, attention, executive function, processing speed and visuospatial function within a week after the first administration of the computerized multidimensional neurocognitive task battery. The neurocognitive assessment had a standardized format, and was administered by licensed and well-trained clinical speech therapists.

Table 1 Summary of participant characteristics

Characteristics	Value
Mean age (years)	71.6 ± 4.6
Male, *n* (%)	11 (55.0)
Mean education (years)	10.8 ± 1.9
Current diseases/conditions, *n* (%)	
Heart disease	4 (20.0)
Diabetes	2 (10.0)
Cancer	3 (15.0)
Hypertension	9 (45.0)
Fractures (after age 60 years)	1 (5.0)
Cognitive status	
General cognitive function	
MMSE (score)	27.5 ± 2.0
Memory	
WMS-R Logical Memory-I, score	20.4 ± 7.4
WMS-R Logical Memory-II, score	15.9 ± 6.8
Attention/executive function	
Written TMT-A (s)	97.9 ± 19.7
Written TMT-B (s)	130.4 ± 29.7
Processing speed	
Digit Symbol-Coding subtest of the WAIS-III, score	62.1 ± 16.3
Visuospatial function	
Block Design subtest of the WAIS-III, score	34.8 ± 8.2

Values are expressed as mean ± SD. MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test-part A; TMT-B, Trail Making Test-part B; WAIS-III, Wechsler Adult Intelligence Scale III; WMS-R, Wechsler Memory Scale-Revised.

Component of the NCGG-FAT

The computerized multidimensional neurocognitive task battery was presented on an i-Pad (Apple, Cupertino, CA, USA) with a 9.7-inch touch display. The task instructions and questions were presented with a letter size of at least 1.0 × 1.0 cm^2 on the display. This battery consists of eight tasks to assess memory (task 1, -2, -3 and -4), attention and executive function (task 5 and -6), processing speed (task 7) and visuospatial function (task 8). The participants were given approximately 20–30 min to complete the battery, which consisted of following eight initial tasks. An operator supported each participant to set up the tablet PC, understand the task protocols and record their data. Participants only needed to touch the display to complete tasks using a digital pen.

Task 1: Story memory-I (immediate recognition) and task 2: story memory-II (delayed recognition)

In task 1 and task 2, the participants heard a short story (approximately 1 min in length) through an auditory system using headphones. They were instructed to remember the details of a story, then immediately select the correct answer that described the details of the story from four choices (Story memory-I), then again after 20–30 min (Story memory-II). All 10 questions in each task were shown and we calculated the total number of correct answers.

Task 3: Word list memory-I (immediate recognition) and task 4: word list memory-II (delayed recall)

Task 3 and task 4 involved immediate recognition and delayed recall of a 10-word target list. In task 3, which tested word list memory, participants were instructed to memorize 10 words that were shown on the tablet PC. In this task, each of 10-target words was shown for 2 s. A total of 30 words, including 10 target and 20 distracter words was then shown, and participants were asked to choose the 10 target words immediately (Word list memory-I). This was repeated for three trials. The average number of correct answers was calculated with a score range of 0 to 10. Additionally, participants were instructed to recall (write down) the 10 target words after approximately 20 min (Word list memory-II). We calculated the total number of recalled target words. One point was given for each correctly recalled word completed within 60 s for a maximum score of 10.

Task 5: The tablet version of the Trail Making Test-part A and task 6: the tablet version of TMT-part B

The tablet version of the Trail Making Test (TMT) consists of part A and B, as well as the original written version of TMT.[12] In the tablet version of TMT-A, participants were required to touch the target numbers shown randomly on the panel as rapidly as possible, in consecutive order (1–15). In the tablet version of TMT-B, participants must touch target numbers or letters alternately between consecutive numbers and letters (Japanese Kana characters). We recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s.

Task 7: The tablet version of the Symbol Digit Substitution Task

In the tablet version of the Symbol Digit Substitution Task (SDST), nine pairs of numbers and symbols were provided at the top of the display. A target symbol was shown at the center of the display. Participants then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible (Fig. 1). The score was the number of correct numbers chosen within 90 s. One point was given for each correctly chosen number completed within the time limit.

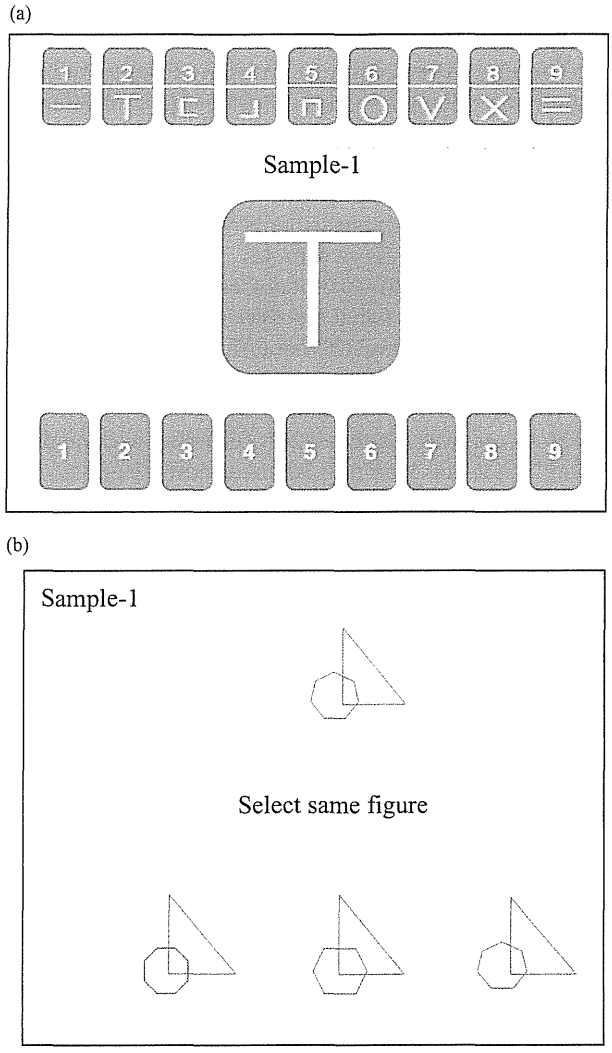

Figure 1 Samples of the representative tests on the tablet personal computer. (a) Task 7, the tablet version of the Symbol Digit Substitution Task. (b) Task 8, figure selection. The task instructions and questions in the original version of the National Center for Geriatrics and Gerontology functional assessment tool were presented in Japanese.

Task 8: Figure selection

In the figure selection task, participants were required to select the same figure from three choices shown at the bottom of the display. This task consists of nine questions and one point is given for each correctly selected figure (Fig. 1). The time limit for each question was within 15 s. We calculated the total number of correct answers (0–9).

Assessment instruments for validity

The conventional neurocognitive tests included the WMS-R Logical Memory, the Word Recognition subtest of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the TMT, the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale (WAIS) III and the Block Design subtest of the WAIS-III to examine the validity of the NSGG-FAT. These neurocognitive tests were administered by licensed and well-trained clinical speech therapists.

WMS-R Logical Memory

WMS-R Logical Memory was used to assess the validity of story memory tasks (task 1 and 2) in the tablet PC version of multidimensional neurocognitive tests. In the WMS-R Logical Memory, two short stories (story A and B) were read aloud to the participant, who was instructed to recall details of the stories immediately (Logical Memory I) and after 30 min (Logical Memory II).[11] We calculated the total score (i.e. sum score of story A and B) of WMS-R in the Logical Memory I and II tasks.

Word recognition subtest of ADAS-cog

ADAS-cog consists of 11 tasks including the assessment of memory, comprehension, orientation in time and place, praxis, and attention.[13] We used the Word Recognition subtest of ADAS-cog as assessment measures for validity of word list memory tasks (task 3 and 4) in the tablet PC version of multidimensional neurocognitive tests. In the Word Recognition subtest of ADAS-cog, participants read out 12 words. They were then asked to identify 12 target words that were mixed with 12 distracter words. This process was repeated for three trials, with new distracters for each trial. The average error score was calculated with an error score range of 0–12. In addition, participants were instructed to recall the 12 target words after 30 min. We calculated the total number of recalled target words. One point was given for each correctly recalled word completed within 90 s for a maximum score of 12.

TMT

We used the TMT[12] to assess attention and executive function. 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 was required to 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. These tests evaluated the validity of the tablet version of TMT-A and -B (task 5 and 6).

Digit Symbol-Coding subtest of the WAIS-III

Participants were measured processing speed by the Digit Symbol-Coding subtest of the WAIS-III.[14] In the Digit Symbol-Coding subtest, 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, which has been found to decline with old age,[15] is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133. Higher scores indicate better processing speed. This test evaluated the validity of the tablet version of the SDST (task 7).

Block Design subtest of the WAIS-III

The Block Design subtest of the WAIS-III[16] was used to assess visuospatial function and examine the validity of the figure selection test using a tablet PC (task 8). In the Block Design task, participants were presented with increasingly difficult patterns consisting of blocks with red, white, and red and white sides, then asked to arrange the same pattern using blocks that had all white sides, all red sides, and red and white sides. The number of correctly arranged blocks was used as a performance variable. The maximum score for this subtest was 68. A previous study in Sweden showed the reliability of impaired glucose metabolism and a cognitive measure of visuospatial function in predicting progression from MCI to AD.[17]

Data analysis

Means, standard deviations and proportions were calculated to describe the samples, and provide summary information of the measures used. A P-value of <0.05 was considered to show statistical significance. All data entry and analysis were carried out using SPSS Windows 19.0 (SPSS, Chicago, IL, USA). The test–retest reliability of each component of the NCGG-FAT was assessed by intraclass correlation coefficient (ICC) with a 95% confidence interval (CI). For the validity of each neurocognitive task of the NCGG-FAT, we used Pearson's correlation coefficients to test relationships between each score of the NCGG-FAT items and each score of the conventional neurocognitive tests.

Results

The score of each component of the NCGG-FAT for the entire sample are presented in Table 2. Table 3

Table 2 Each content score for the entire sample ($n = 20$)

Contents	First administration				Second administration		
	Scale range	Mean	SD	Observed range	Mean	SD	Observed range
Memory							
Story memory-I (immediately) score	0–10	7.50	1.47	5–10	7.95	1.36	5–10
Story memory-II (delay) score	0–10	7.35	1.63	4–10	7.85	1.50	4–10
Word recognition (immediately) score	0–10	7.72	1.01	5.7–9.0	8.22	0.97	6.3–9.7
Word recall (delay) score	0–10	3.85	1.60	1–6	4.70	1.81	1–7
Attention/Executive function							
Tablet version of TMT-A (s)	0–90	19.80	5.48	13–32	19.25	3.96	12–27
Tablet version of TMT-B (s)	0–90	40.40	16.30	19–81	37.50	15.08	17–80
Processing speed							
Tablet version of SDST score	0–90	40.60	9.23	23–55	43.45	8.11	27–57
Visuospatial function							
Figure selection score	0–9	6.35	1.35	4–9	5.90	1.21	4–9

SDST, Symbol Digit Substitution Task; TMT, Trail Making Test.

Table 3 Pearson's correlation coefficients between each component and assessment instruments for validity and intraclass correlation coefficients of each measurement

Contents	Validity		Test-retest reliability		
	r	*P* value	ICC	95%IC	*P* value
Memory					
Story memory-I (immediately)	0.583	0.007	0.764	0.415, 0.906	0.001
Story memory-II (delay)	0.496	0.026	0.809	0.526, 0.924	<0.001
Word recognition (immediately)	0.550	0.012	0.793	0.486, 0.917	<0.001
Word recall (delay)	0.565	0.009	0.788	0.475, 0.916	0.001
Attention/executive function					
Tablet version of TMT-A	0.611	0.004	0.837	0.596, 0.935	<0.001
Tablet version of TMT-B	0.550	0.012	0.850	0.628, 0.940	<0.001
Processing speed					
Tablet version of SDST	0.842	<0.001	0.942	0.857, 0.977	<0.001
Visuospatial function					
Figure selection	0.723	<0.001	0.815	0.540, 0.926	<0.001

The following assessment instruments were used to test validity: the Wechsler Memory Scale-Revised (WMS-R) Logical Memory-I for the tablet version of story memory-I (immediately), the WMS–R Logical Memory-II for the tablet version of story memory-II (delay), the subtest of ADAS-cog (immediately recognition) for the tablet version of word recognition (immediately), the subtest of Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog; delay recall, modified) for the tablet version of Word recall (delay), the written Trail Making Test-part A (TMT-A) for the tablet version of TMT-A, the written Trail Making Test-part B (TMT-B) for the tablet version of TMT-B, the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence (WAIS)-III for the tablet version of SDST, and the Block Design subtest of the WAIS-III for the tablet version of Figure selection.

shows the test–retest reliability and validity of each component of the NCGG-FAT. For the test–retest reliability, all of the ICC for each task component were higher than 0.750, and those of eight task components (story memory-I, story memory-II, word recognition, word recall, tablet version of TMT-A, TMT-B, SDST, and figure selection) were 0.764, 0.809, 0.793, 0.788, 0.837, 0.850, 0.942 and 0.815, respectively. Thus, the test–retest reliability of each component of the developed multidimensional neurocognitive task battery were in an acceptable range.[18] Pearson's correlation coefficients were calculated to examine the validity of each component of the NCGG-FAT. In the validity assessment, we examined the WMS-R Logical Memory-I and -II, the Word Recognition subtest of the ADAS-cog, the TMT-A and -B, and the Digit Symbol-Coding subtest and the Block Design sub-test of the WAIS-III, which are used widely in clinical settings internationally.

Pearson's correlation coefficients between those widely used clinical neurocognitive tests and each task component of the NCGG-FAT ranged from 0.496 to 0.842, and the following relationships were statistically significant: story memory-I and the WMS-R Logical Memory-I ($r = 0.583$, $P = 0.007$), story memory-II and the WMS-R Logical Memory-II ($r = 0.496$, $P = 0.026$), word recognition and the Word Recognition subtest of the ADAS-cog ($r = 0.550$, $P = 0.012$), and word recall and the recall version of the Word Recognition subtest of the ADAS-cog ($r = 0.565$, $P = 0.009$), the tablet version of TMT-A and the original version of TMT-A ($r = 0.611$, $P = 0.004$), the tablet version of TMT-B and the original version of TMT-B ($r = 0.550$, $P = 0.012$), the tablet version of SDST and the Digit Symbol-Coding subtest ($r = 0.842$, $P < 0.001$), and figure selection and the Block Design subtest ($r = 0.723$, $P < 0.001$).

Discussion

The current study investigated the test–retest reliability and validity of our newly multidimensional neurocognitive task battery using a tablet PC. High test–retest reliability was found for each task component of the NCGG-FAT (the ICC ranged from 0.764 to 0.942). The results showed moderate and high validity values for all task components of the NCGG-FAT.

Older adults with memory impairment are at an increased risk for progression to dementia. Previous community-based longitudinal studies have shown that amnestic MCI is likely to convert to AD.[19,20] In contrast, non-amnestic MCI patients without memory impairment but with cognitive decline in other domains are expected to represent the early stages of non-AD dementia.[21] Therefore, measures for multidimensional neurocognitive function were required to examine the risk of developing dementia earlier among older populations. The NCGG-FAT consists of multiple tasks including memory, attention, executive function, processing speed and visuospatial function. We evaluated the validity of each task component using measurements that are commonly used in clinical settings. In the results of the present study, moderate to high correlations were shown between the NCGG-FAT items and conventional neurocognitive measures ($r = 0.496$ to 0.842), and the results support the external validity of the NCGG-FAT.

The Japanese public long-term care insurance system was launched in April 2000 in response to the growing elderly population.[22] The rapid aging of the population has also increased the demand for formal long-term care services in Japan, and it is important to prevent conditions related to age-related physical and cognitive decline, such as frailty and MCI. The current results confirmed that the NCGG-FAT, which includes multidimensional cognitive domains, showed good test–retest reliability (ICC = 0.764 to 0.942), and moderate to high external validity ($r = 0.496$ to 0.842). The NCGG-FAT has several advantages over conventional neurocognitive assessments. First, the NCGG-FAT is easily administered using a tablet PC with instructions shown on the display. Therefore, it is not necessary for assessors to have a thorough knowledge of neurocognitive measures, and the particular assessor des not strongly affect the results. The simplicity and portability of the application permits assessment in the community and non-clinical settings by non-specialized persons. Participants were able to complete the NCGG-FAT battery in approximately 20–30 min. Administering an equivalent range of traditional psychiatric tests, including measures of memory, attention and executive function, processing speed, and visuospatial function using the original version would require twice this amount of time. The NCGG-FAT might be useful for cognitive screening in a population-based sample to assess the risk of cognitive decline on multidimensional functions. In addition, data collected from a large population using tablet PCs can be aggregated quickly, as the data is digital rather than paper-based.

A number of limitations were identified in the present study. Although the tablet version of the neurocognitive task battery was found to show good test–retest reliability and validity, it was not found to show predictive validity. This suggests that an operator might be required to support older participants in using a tablet PC, especially those showing cognitive decline. Importantly, our sample included community-dwelling older adults without cognitive impairment and did not include participants meeting the criteria for dementia and MCI. In addition, although story memory scores in the NCGG-FAT were significantly correlated with WMS-R Logical Memory scores, these two tasks differ in the terms of retrieval. The story memory scale in the NCGG-FAT is a recognition task, whereas WMS-R Logical Memory is a recall task. Therefore, studies using the NCGG-FAT require experimental design and cautious interpreting of results. Despite these limitations and the need for further research, our tool for assessing multidimensional neurocognitive function using a tablet PC appears to be helpful in evaluating cognitive decline among older adults in clinical settings.

In conclusion, the current results showed that the NCGG-FAT assessment for multidimensional neurocognitive function using a tablet PC was reliable and valid for a sample of community-dwelling older adults. The NCGG-FAT might be useful for cognitive screening in population-based samples and outcomes to assess intervention effects on multidimensional cognitive function among older adults.

Acknowledgments

This work was supported in part by a grant from the Japanese Ministry of Health, Labour and Welfare and a Grant-in-Aid for JSPS Fellows from the Japan Society for the Promotion of Science. We thank the speech therapists of the Ukai rehabilitation hospital for their assistance with data collection.

Disclosure statement

There are no financial and personal relationships with other people or organizations that may lead to a conflict of interest.

References

1 Petersen RC, Doody R, Kurz A *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; **58**: 1985–1992.
2 Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; **256**: 240–246.
3 Chertkow H. Mild cognitive impairment. *Curr Opin Neurol* 2002; **15**: 401–407.
4 Yesavage JA, O'Hara R, Kraemer H *et al.* Modeling the prevalence and incidence of Alzheimer's disease and mild cognitive impairment. *J Psychiatr Res* 2002; **36**: 281–286.
5 Kochan NA, Slavin MJ, Brodaty H *et al.* Effect of different impairment criteria on prevalence of "objective" mild cognitive impairment in a community sample. *Am J Geriatr Psychiatry* 2010; **18**: 711–722.
6 Petersen RC, Roberts RO, Knopman DS *et al.* Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology* 2010; **75**: 889–897.
7 Sachdev PS, Lipnicki DM, Crawford J *et al.* Risk profiles of subtypes of mild cognitive impairment: the sydney memory and ageing study. *J Am Geriatr Soc* 2012; **60**: 24–33.
8 Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56**: 1133–1142.
9 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
10 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; **256**: 183–194.
11 Wechsler D. *Wechsler Memory Scale-revised Manual.* San Antonio, TX: The Psychological Corporation, 1987.
12 Lezak M. *Neuropsychological Assessment*, 4th edn. New York: Oxford University Press, 2004.
13 Graham DP, Cully JA, Snow AL, Massman P, Doody R. The Alzheimer's disease assessment scale-cognitive subscale: normative data for older adult controls. *Alzheimer Dis Assoc Disord* 2004; **18**: 236–240.
14 Wechsler D. *Wechsler Adult Intelligence Scale-revised.* New York: Psychological Corporation, 1981.
15 Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III digit symbol – coding subtest across the adult lifespan. *Arch Clin Neuropsychol* 2004; **19**: 759–767.
16 Wechsler D. *Wechsler Adult Intelligence Scale-III.* San Antonio, TX: The Psychological Corporation, 1997.
17 Arnaiz E, Jelic V, Almkvist O *et al.* Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuroreport* 2001; **12**: 851–855.
18 Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials* 1986; 7: 267–275.
19 Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Subclassifications for mild cognitive impairment: prevalence and predictive validity. *Psychol Med* 2003; **33**: 1029–1038.
20 Fischer P, Jungwirth S, Zehetmayer S *et al.* Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* 2007; **68**: 288–291.
21 Hughes TF, Snitz BE, Ganguli M. Should mild cognitive impairment be subtyped? *Curr Opin Psychiatry* 2011; **24**: 237–242.
22 Matsuda S, Yamamoto M. Long-term care insurance and integrated care for the aged in Japan. *Int J Integr Care* 2001; **1**: e28.

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2013;3:398–406
DOI: 10.1159/000355553
Published online: October 26, 2013

1664–5464/13/0031–0398$38.00/0
www.karger.com/dee

Original Research Article

Cognitive Activities and Instrumental Activity of Daily Living in Older Adults with Mild Cognitive Impairment

Takehiko Doi[a, c, d] Hiroyuki Shimada[a] Hyuma Makizako[a, c, d]
Sangyoon Lee[b] Hyuntae Park[b] Kota Tsutsumimoto[a] Kazuki Uemura[a, d]
Daisuke Yoshida[a] Yuya Anan[a] Takao Suzuki[c]

[a]Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly and [b]Section for Physical Functioning Activation, Department of Functioning Activation, Center for Gerontology and Social Science, and [c]Research Institute, National Center for Geriatrics and Gerontology, Obu, and [d]Japan Society for the Promotion of Science, Tokyo, Japan

Key Words
Cognitive impairment · Dementia · Alzheimer's disease · Cognitive reserve

Abstract
Aims: This study aimed to identify differences in the implementation of cognitive activities and instrumental activities of daily living (IADLs) between healthy individuals and subjects with mild cognitive impairment (MCI). ***Methods:*** The study included 2,498 cognitively healthy subjects (mean age, 71.2 ± 5.1 years) and 809 MCI subjects (mean age, 71.8 ± 5.4 years). The subjects were interviewed regarding their participation in cognitive activities and the implementation of IADLs. ***Results:*** We found a significant association between participation in any cognitive activities ($p < 0.001$), using a bus or a train ($p < 0.001$), and MCI. After adjusting for covariates, cognitive activity of any type remained significantly associated with MCI ($p < 0.005$) but not with the implementation of IADLs. ***Conclusions:*** Our study revealed that greater participation in cognitive activity was associated with lower odds of MCI. Participation in cognitive activities may reflect differences between healthy and MCI subjects. To clarify the causal relationship between cognitive activities and MCI, further studies are required.

Takehiko Doi, PhD, PT, Section for Health Promotion
Department for Research and Development to Support Independent Life of Elderly
Center for Gerontology and Social Science, NCGG
35 Gengo, Morioka, Obu, Aichi 474-8511 (Japan)
E-Mail take-d@ncgg.go.jp

Dement Geriatr Cogn Disord Extra 2013;3:398–406
DOI: 10.1159/000355553

Introduction

Alzheimer's disease (AD) is the most common cause of dementia. An estimated 33.9 million individuals worldwide have AD, and the prevalence is predicted to triple over the next 40 years [1, 2]. There is a lack of available treatments; therefore, research has focused on establishing strategies to prevent AD [1]. Mild cognitive impairment (MCI) is an early indication of cognitive disease and a crucial target for the prevention of AD [3, 4]. Focused modifiable risk factors for dementia and an active lifestyle, e.g., greater participation in a leisure activity involving physical and cognitive activity, play a potentially protective role against the progression from MCI to AD [1, 5].

A growing body of evidence suggests that participation in cognitive activities leads to a slower cognitive decline [6, 7] and reduces the risk of incident AD [6, 8] and dementia [9]. Engagement in cognitive activity, even in mid-life adults, is associated with a reduced risk of AD [10, 11]. Cognitive activity is generally regarded as a leisure activity [9] and contributes to an enhanced cognitive reserve, restricting cognitive decline and progression to dementia [12]. The cognitive reserve is thought to withstand the burden of the neuropathologic condition of AD and to maintain cognitive function [12]. In fact, a low degree of participation in cognitive activities is associated with the risk of amnestic MCI [13], while more frequent participation in leisure activities, especially intellectual ones, accelerates cognitive decline in patients with AD [14]. The role of these activities against the progression of AD may be varied and dependent on the disease course. Although cognitive activities have the potential to be related to MCI, few population-based studies with small samples have investigated the association between cognitive activities and MCI [13, 15]. As a result, our current understanding of the association between cognitive activity and MCI is insufficient.

Elderly activities range from activity in daily living (ADL) in order to live independently to complex activity such as instrumental activity of daily living (IADL). IADL is associated with the development of dementia [16, 17] as well as cognitive inactivity. Furthermore, deficits in IADL are characteristic of older adults with MCI [18–21]. However, the results are dependent on the measurement of IADL and therefore vary between different studies. Based on the Lawton and Brody IADL scales [22], MCI subjects were similar to subjects without MCI in the implementation of conventional IADL [18, 23]. However, the deficits in the other IADLs were more likely in subjects with MCI [19–21]. There is insufficient evidence regarding the specific activities associated with MCI.

The purpose of this study was to examine whether the implementation of cognitive activity and/or IADL was different between healthy and MCI subjects. We hypothesized that participation in cognitive activities and IADLs is lower in MCI subjects as compared to healthy older adults. To confirm this hypothesis, we conducted a cross-sectional study to examine differential associations of MCI with specific cognitive activities and IADL tasks.

Methods

Participants

Subjects eligible for this study were participants of a population-based cohort study (Obu Study of Health Promotion for the Elderly; OSHPE) that was conducted from August 2011 to February 2012. Participants aged ≥65 years at the time of examination and who lived in Obu were eligible for the OSHPE (n = 15,974). Prior to recruitment, 1,661 subjects were excluded because (a) they had participated in another study; (b) they were hospitalized or in residential care, or (c) they were certified as grade 3–5 cases and required support or care by the Japanese public long-term care insurance system. Recruitment was conducted via a mail sent

to 14,313 individuals, and 5,104 of these individuals underwent a health check. In addition, to be included in our study, participants had to be independent with basic ADL, could not be certified as any grade needing support or care by the Japanese public long-term care insurance system and had to be cognitively healthy (i.e., without subjective and objective cognitive impairment) or have MCI. In total, 3,307 participants (cognitively healthy: n = 2,498, MCI: n = 809) were eligible for inclusion and participated in all assessments.

MCI was classified according to Petersen's criteria [3]. The criteria involve the following: (a) subjective memory complaint; (b) objective cognitive decline; (c) general cognitive health (Mini-Mental State Examination score >23 [24]); (d) independence in ADL, and (e) absence of clinical criteria for dementia. Objective cognitive decline was defined as a cognitive function 1.5 standard deviations below the reference threshold of any of the tests. Cognitive function was comprehensively assessed using the National Center for Geriatrics and Gerontology functional assessment tool (NCGG-FAT). NCGG-FAT contains cognitive tests, and measurement has been described in detail in a previous study [25]. The test consists of tasks to assess memory (story memory, word recognition, and word recall), attention, processing speed (symbol digit substitution task), and visuospatial cognition (figure selection). Cognitively healthy participants were defined as not having both subjective memory complaints and objective cognitive impairment. Informed consent was obtained from all participants before their inclusion in the study. The Ethics Committee of the NCGG approved the study protocol.

Cognitive Activities and IADL

Subjects were interviewed regarding participation in cognitive activities such as reading books or newspapers, using a personal computer, going to an unknown location with a map, and operating a video or DVD player. IADL was assessed using the following items: using a bus or a train, grocery shopping, management of finances, housekeeping, and telephone use. The items of cognitive activities were selected according to previous studies [6, 9, 26], and the domains of IADL were based on the Lawton and Brody IADL scales [22]. Subjects were asked whether they had performed each activity during the past month; responses were 'yes (did)' or 'no (did not)'. In addition, we totaled the number of activities for which each participant answered 'yes' for both cognitive activities and IADL.

Other Measures

Participants completed a questionnaire on medical conditions, current medications, and lifestyle habits. The medical questionnaire captured information on various diseases (hypertension, stroke, heart disease, diabetes mellitus, respiratory disease, and others) and medication use. Weight and height were measured, and BMI was calculated. The questionnaire also inquired about age, gender, educational history, smoking status, and alcohol consumption, and the Geriatric Depression Scale (GDS) score was measured [27]. Walking speed was measured as an indicator of physical performance. Participants were asked to walk on a straight, flat walkway 6.6 m in length 5 times faster than their usual walking speed. Walking time was measured over a 2.4-meter distance between marks at 2.1 and 4.5 m from the start of the walkway, and the mean walking speed (m/s) was calculated. The total amount of time spent walking in a day was assessed using a subscale of the International Physical Activity Questionnaire [28, 29].

Statistical Analysis

Medical history, lifestyle habits, and cognitive function measures were compared between healthy controls and MCI subjects using t tests and χ^2 tests where appropriate. Multiple logistic regression analysis was performed to explore independent associations between participation in cognitive activity or IADL ability and MCI, while controlling for potential