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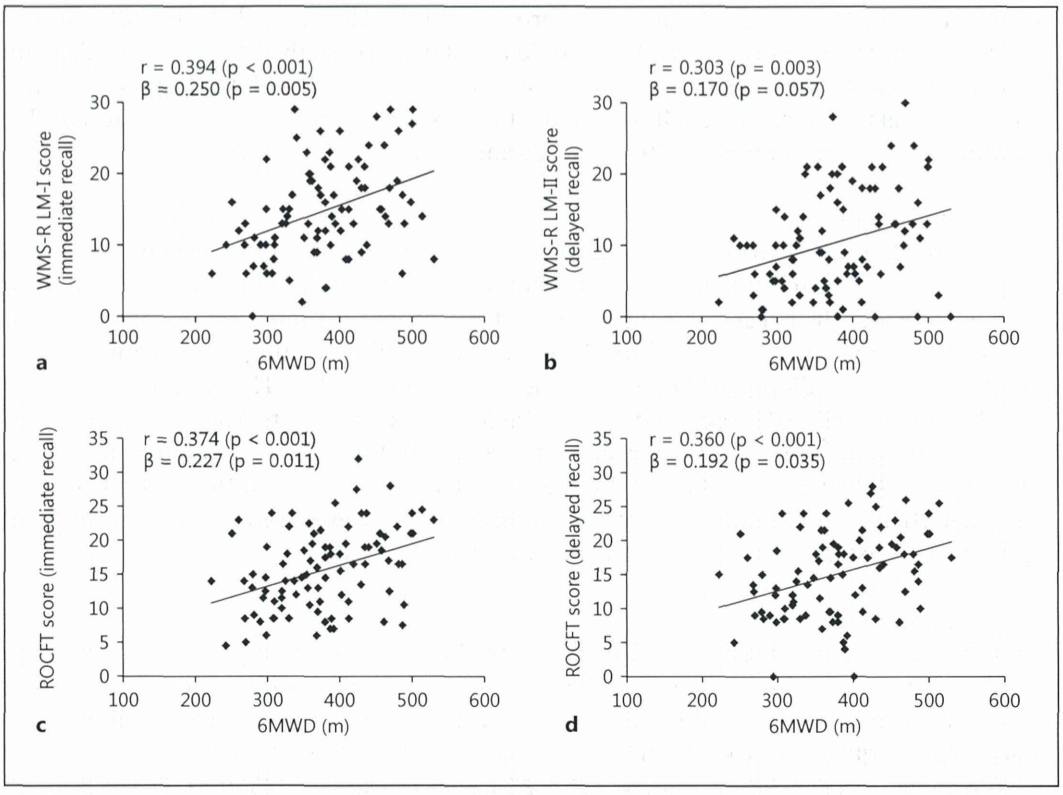

Fig. 1. Correlations between 6MWDs and memory performance tests. Pearson correlation coefficients (r) and standardized beta values (controlling for age and sex) are presented. **a** WMS-R LM-I (immediate recall). **b** WMS-R LM-II (delayed recall). **c** ROCFT (immediate recall). **d** ROCFT (delayed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

Results

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

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

EXTRA Dementia and Geriatric Cognitive Disorders

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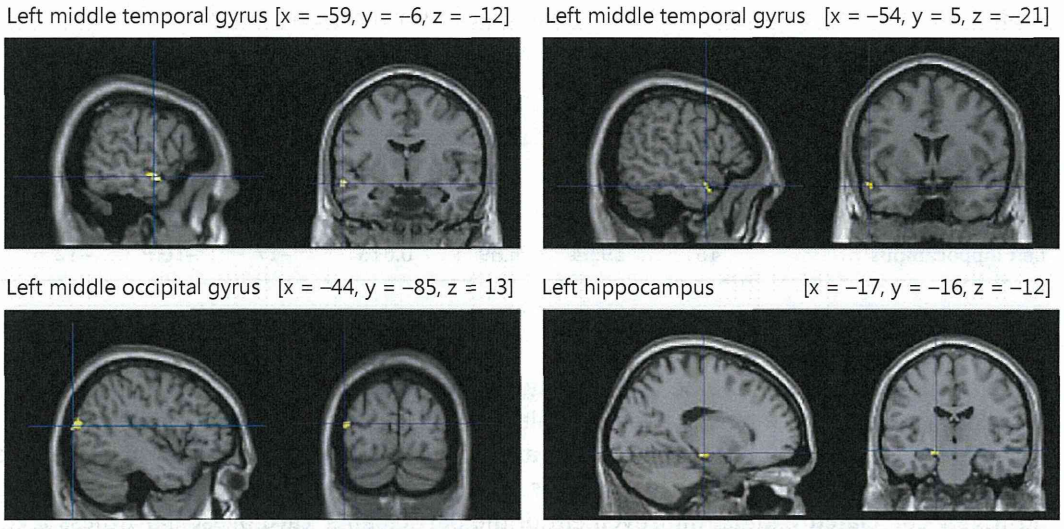

Fig. 2. Brain regions showing an association between a better performance in the 6MWT and a greater gray matter volume. After adjusting for age and sex, gray matter density in the left middle temporal gyrus, middle occipital gyrus, and hippocampus showed positive correlations with the 6MWD.

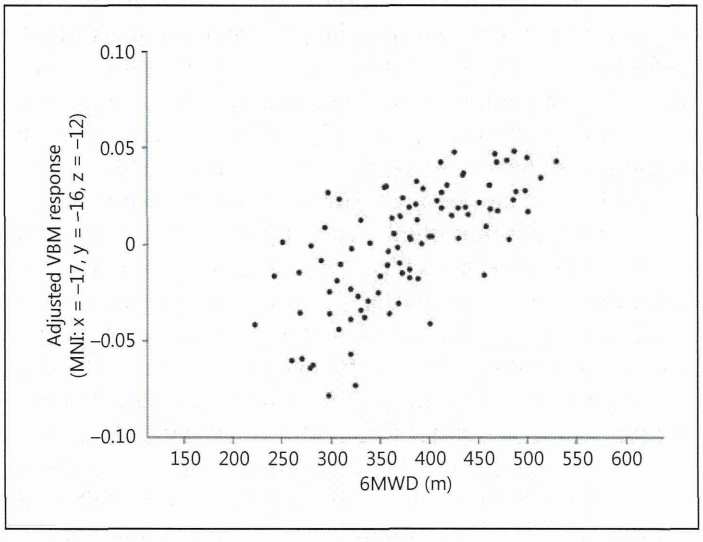

Fig. 3. Correlation between VBM response in the left hippocampus peak voxel (adjusted for effects of age and sex) and the 6MWD.

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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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

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

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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]

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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.

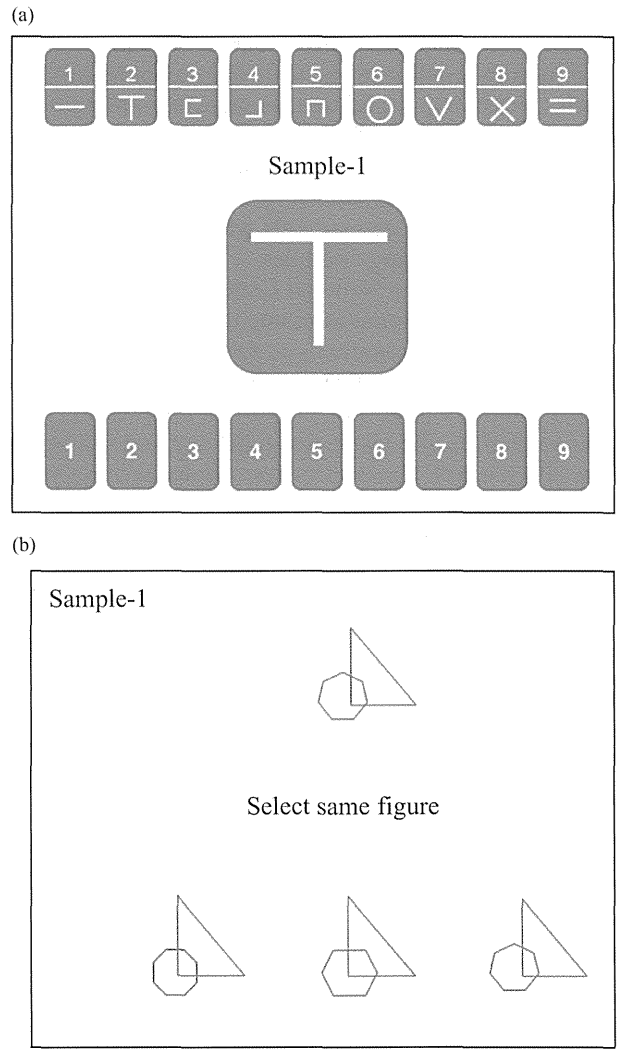

Figure 1 Samples of the representative tests on the tablet personal computer. (a) Task 7, the tablet version of the Symbol Digit Substitution Task. (b) Task 8, figure selection. The task instructions and questions in the original version of the National Center for Geriatrics and Gerontology functional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