not only protecting the neuronal cells but also improving the function of cholinergic system.

The reduction of PREGS has been found in AD patients' brains compared with that of age-matched non-demented controls (Weill-Engerer et al., 2002), indicating that the administration of PREGS might exert a neuroprotective effect against the Aβ-neurotoxicity. However, the significance of PREGS-neuroprotection has recently been put into question because of the failure to detect significant levels of PREGS within the brain and plasma of rats and mice (Schumacher et al., 2008). The P450scc and hydroxysteroid sulfotransferase are highly expressed in hippocampal neurons (Kimoto et al., 2001). Although available direct analytical methods have failed to detect levels of PREGS in brain tissue, it cannot exclude the local formation of biologically active PREGS within specific nervous system. In addition, numerous studies have reported that the neuromodulatory and neuropharmacological effects of PREGS on the hippocampal synaptic transmission and synaptic plasticity. The synthesis and release of PREGS have been reported to be dependent on postsynaptic Ca^{2+} influx by NMDAr (Shibuya et al., 2003). Thus, one explanation is that the local concentration of PREGS around the neurons, particularly in synaptic clefts *in vivo*, may be greater than that in brain tissues (Caldeira et al., 2004).

In summary, the α7nAChR agonists or the σ_1R agonists have been reported to attenuate the Aβ-neurotoxicity and glutamate toxicity in APP/PS1 mice, $A\beta_{1-42}$-rats and $A\beta_{25-35}$-mice, which are able to improve the Aβ-induced impairment of learning and memory. This study provides a new insight that PREGS targeting α7nAChR and σ_1R against Aβ-neurotoxicity may exert a powerful anti-amnesic effect.

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Suitability of the Montreal Cognitive Assessment versus the Mini-Mental State Examination in Detecting Vascular Cognitive Impairment

Masafumi Ihara, MD, PhD, FACP, Yoko Okamoto, MD, and Ryosuke Takahashi, MD, PhD

The Mini-Mental State Examination (MMSE) has been criticized as being an insufficient screening test for patients with vascular cognitive impairment because of its insensitivity to visuospatial and executive functional deficits. The Montreal Cognitive Assessment (MoCA) was designed to be more sensitive to such deficits, and thus may be a superior screening instrument for vascular cognitive impairment. Twelve patients with extensive leukoaraiosis detected on magnetic resonance imaging (average age, 76.0 ± 8.7 years) underwent neurologic and cognitive testing, including MMSE and the Japanese version of the MoCA (MoCA-J). Accepted cutoff scores of <27 for the MMSE and <26 for the MoCA-J were taken to indicate cognitive impairment. Z-scores were calculated to evaluate the discriminating ability of individual MMSE and MoCA-J subtest scores. Although there was a strong correlation between the total MMSE and total MoCA-J scores ($r = 0.90$; $P < .0001$), MMSE scores were skewed toward the higher end of the range (range, 18-30; median, 28), whereas MoCA-J scores were normally distributed (range, 9-28; median, 21). Of the 7 patients with an unimpaired MMSE score, 6 (86%) had an impaired MoCA-J score. Z-scores were >5 for 4 MMSE subtests (orientation, registration, naming, and language) but for only 1 MoCA-J subtest (naming). The MoCA-J better discriminated cognitive status in subjects with extensive leukoaraiosis. Our findings suggest that the MoCA-J is more sensitive than the MMSE in screening for cognitive impairment in patients with subcortical vascular cognitive impairment. **Key Words:** Leukoaraiosis—MoCA—screening—stroke—dementia.

Cognitive impairment resulting from cerebrovascular insufficiency has been termed vascular cognitive impairment (VCI).[1] VCI comprises a spectrum that includes mild cognitive impairment of vascular etiology (vascular MCI), vascular dementia, and mixed Alzheimer's disease with a vascular component.[2,3] Given that patients with vascular MCI with more severe impairment are known to be at greater risk of conversion to dementia compared with patients with less severe or no cognitive impairment,[4] early detection of cognitive deficits may facilitate intervention to prevent cognitive deterioration.

The widely used Mini-Mental State Examination (MMSE)[5] is considered inaccurate for screening VCI, because it is insensitive to MCI and complex cognitive deficits.[1,6] In comparison, the Montreal Cognitive Assessment (MoCA) was designed to be sensitive to mild deficits[7] and has been evaluated in patients with amnestic MCI[7] and Parkinson's disease.[8] Importantly, the MoCA is reported to detect more cognitive abnormalities after ischemic stroke or transient ischemic attack compared with MMSE, particularly in relation to executive

From the Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

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Address correspondence to Masafumi Ihara, MD, PhD, FACP, Department of Neurology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo, Kyoto 606-8507 Japan. E-mail: ihara@kuhp.kyoto-u.ac.jp.

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function, attention, and delayed recall.[9,10] In addition, the Hong Kong MoCA is reportedly useful for use in Chinese patients with leukoaraiosis[11]; however, direct comparison of the MoCA with the MMSE has not been performed in patients with VCI.

The primary aim of the present study was to test the hypothesis that the MoCA is more sensitive than the MMSE in detecting cognitive impairment in patients with ischemic leukoaraiosis—specifically, subcortical VCI, which encompasses 2 clinical entities, Binswanger's disease and lacunar state. To do so, we compared the feasibility and psychometric properties of the MoCA-J (modified for the Japanese population) and the MMSE.

Methods

Subjects

Twelve patients with magnetic resonance imaging (FLAIR and T2-weighted) findings of confluent hyperintensities in the subcortical white matter (Schmidt scale score of 3)[12] and several punctate high-intensity areas in the basal ganglia were studied. The patients were enrolled between May 2008 and March 2011 after visiting our Neurology Clinic with various neurologic signs and symptoms. Patients with mild to moderate leukoaraiosis (Schmidt scale score of 1 or 2) were not enrolled, to exclude the possibility of leukoaraiosis associated with neurodegenerative disorders, such as Alzheimer's disease. Each patient received an explanation of the experimental procedure and provided written informed consent. The study design was approved by our institution's Medical Ethics Committee. None of the patients had any apparent lesions in the cerebral cortex or hippocampus, or >50% stenosis in any major intracranial and extracranial vessel detected by magnetic resonance angiography or duplex color-coded ultrasonography.

Neuropsychological Evaluation

All subjects underwent a general physical and neurologic examination and neuropsychological assessment, including the MoCA-J and MMSE. To avoid habituation and interference effects, the MMSE was performed at least 1 week after the MoCA-J assessment. Two neurologists were involved in the neuropsychological assessment; if their assessments did not correlate, then the patient was reexamined by the team, which then reached a consensus. A cutoff score of ≥27 on the MMSE was chosen to indicate normal cognitive function,[13] and the accepted cutoff of <26 on the MoCA-J was taken to indicate cognitive impairment.[14]

Z-Score Analysis

For subtests of both the MMSE and MoCA-J, z-scores were calculated by dividing the mean subtest score by its standard deviation. A lower z-score indicates greater discrimination between subjects.

Statistical Analysis

The statistical significance of intergroup differences was assessed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables of demographic data. Possible links between the variables were evaluated by Pearson's correlation analysis.

Results

Demographic Data

Clinical features and demographic data of the study patients are summarized in Table 1. All 12 patients had at least one risk factor for ischemic cerebrovascular disease, including hypertension and diabetes mellitus. Eight patients (67%) exhibited gait disturbance, the most frequent neurologic deficit. The mean modified Rankin Scale score was 1.4 (range, 1-2). Most of the patients had lacunar infarctions or microbleeds in the basal ganglia or the thalamus as a manifestation of underlying small vessel pathology. These patients' clinical histories and radiological features excluded the possibility of coexisting single-strategic infarct dementia.

Table 1. *Patient clinical features and demographic data*

Variable	Value
Age, years, mean ± SD (range)	76 ± 8.7 (55-84)
Sex, n	Males, 7; females, 5
Modified Rankin Scale score, mean ± SD (range)	1.4 ± 0.5 (1-2)
Gait disturbance, n (%)	8 (67)
Dysarthria, n (%)	4 (33)
Urinary incontinence, n (%)	3 (25)
Hypertension, n (%)	7 (58)
Diabetes mellitus, n (%)	3 (25)
Cigarette smoking, n (%)	3 (25)
Sleep apnea, n (%)	2 (17)
Previous cerebrovascular disease, n (%)	6 (50)
Use of antithrombotics, n (%)	8 (67)
Use of statins, n (%)	6 (50)
LDL cholesterol, mg/dL, mean ± SD	115 ± 44
Triglyceride, mg/dL, mean ± SD	112 ± 45
Hematocrit, %, mean ± SD	39.6 ± 3.9
Fibrinogen, mg/dL, mean ± SD	286 ± 53
Microbleeds in the basal ganglia/thalamus, mean ± SD	1.5 ± 2.0
Lacunas in the basal ganglia/thalamus, mean ± SD	2.9 ± 2.8

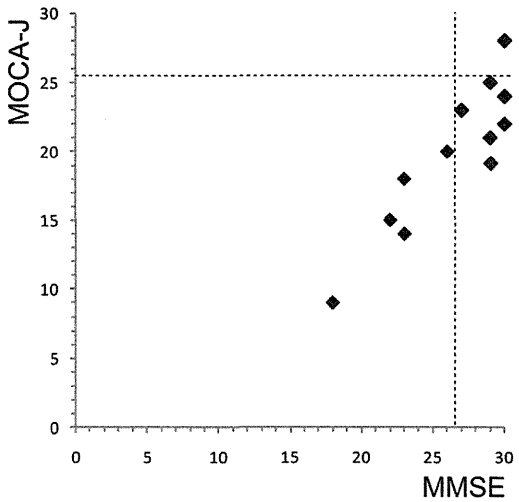

Figure 1. *Distribution of MoCA-J and MMSE scores of the patients with extensive leukoaraiosis. Cutoff scores of <27 for MMSE and <26 for MoCA-J were taken to indicate cognitive impairment (dotted line).*

Relationship Between MoCA-J and MMSE Scores

There was a significant relationship between the MoCA-J and MMSE scores ($r = 0.90$; $P < .0001$). MMSE scores were skewed toward the higher end of the range (range, 18-30; median, 28), whereas MoCA-J scores were normally distributed (range, 9-28; median, 21) (Fig 1). Of the 11 patients with an impaired MoCA-J score, only 5 (45%) had an impaired MMSE score, whereas all 11 patients with an impaired MMSE score had an impaired MoCA-J score. Of the 7 patients with an unimpaired MMSE score, 6 (86%) had an impaired MoCA-J score.

Z-Score Analysis

Results for individual subtests of the MMSE and MoCA-J are presented in Table 2 and Table 3, respectively. Z-scores were >5 for 4 MMSE subtests (orientation, registration, naming, and language) but for only 1 MoCA-J subtest (naming).

Clinical Utility of the MoCA-J

The MoCA-J was completed by all 12 of the elderly Japanese subjects with VCI enrolled in this study. The average administration time was 12 minutes.

Correlation Analysis Between MoCA-J Score and MRI-Based Cerebrovascular Lesions

The MoCA-J score was significantly correlated with the number of lacunar infarctions ($r = -0.67$; $P = .03$) but not with the number of microbleeds in the basal ganglia or the thalamus ($r = -0.39$; $P = .28$).

Discussion

The main finding of this study is that the MoCA-J is more sensitive than the MMSE in detecting subcortical VCI. Eleven of the 12 patients with an impaired MoCA-J score or impaired MMSE score were detected only by the impaired MoCA-J score, whereas none of the patients had only an impaired MMSE score. In addition, the z-score analysis suggested that the MoCA-J better discriminates cognitive status between subjects. Thus, the MoCA-J could be a useful instrument for detecting VCI at an earlier stage in patients with extensive leukoaraiosis.

Table 2. *MoCA-J subtest scores with cognitive screening test results*

	Visuoexecutive/5	Naming/3	Attention/6	Language/3	Abstraction/2	Recall/5	Orientation/6
Patient 1	1	2	4	1	1	0	5
Patient 2	1	3	3	0	0	0	2
Patient 3	3	3	6	1	2	3	6
Patient 4	2	3	3	1	2	0	4
Patient 5	3	2	6	2	1	4	5
Patient 6	4	3	5	2	2	3	6
Patient 7	3	3	6	1	1	2	6
Patient 8	4	3	5	1	1	0	6
Patient 9	2	3	6	2	2	0	6
Patient 10	5	3	6	2	2	4	6
Patient 11	3	3	5	1	0	0	5
Patient 12	2	3	6	2	2	0	4
Average	2.8	2.8	5.1	1.3	1.3	1.3	5.1
SD	1.2	0.4	1.2	0.7	0.8	1.7	1.2
Z-score	2.3	7.3	4.4	2.0	1.7	0.8	4.1

MoCA-J domain subtest/maximum score, details: visuoexecutive/5, trail B test, cube copy, clock drawing; attention/6, digit span, vigilance (tapping at the Hiragana "a" in a list of Hiragana characters), serials 7 s; recall/5, recall a list of 5 words; orientation/6, date, month, year, day, place, city; abstraction/2, similarities between two items; language/3, sentence repetition, verbal fluency; naming/3, confrontation naming (lion, rhino, camel).

Table 3. *MMSE subtest scores with cognitive screening test results*

	Orientation/10	Registration/3	Attention/calculation/5	Recall/3	Naming/2	Language/6	Drawing/1
Patient 1	9	3	4	2	2	3	0
Patient 2	5	2	4	0	1	5	1
Patient 3	10	3	5	3	2	6	1
Patient 4	10	3	1	0	2	5	1
Patient 5	10	3	4	2	2	5	1
Patient 6	10	3	5	2	2	6	1
Patient 7	10	3	5	3	2	6	1
Patient 8	10	3	4	0	2	6	1
Patient 9	10	3	4	3	2	6	1
Patient 10	10	3	5	3	2	6	1
Patient 11	10	3	1	0	2	6	1
Patient 12	9	3	5	3	2	6	1
Average	9.4	2.9	3.9	1.8	1.9	5.5	0.9
SD	1.4	0.3	1.4	1.4	0.3	0.9	0.3
Z-score	6.5	10.1	2.7	1.3	6.6	6.1	3.2

MMSE domain subtest/maximum score, details: attention/calculation/5, serial 7 s; recall/3, recall a list of 3 words; orientation/10, orientation to place and time; naming/2, confrontation naming (pen, watch); language/6, sentence repetition, comprehension, reading, writing; registration/3, repeat 3 words; praxis/1, copy intersecting pentagons.

The significant correlation between the MoCA-J score and the number of lacunar infarctions further supports the clinical relevance of this screening test in the detection of VCI characterized by small vessel pathology. Administering the MoCA-J took an average of only 12 minutes even in patients with subcortical VCI.

The poorer performance of the MMSE in detecting subcortical VCI may be related to several factors. The MMSE is less sensitive in detecting impairment in visuospatial or executive function, characteristic features that are preferentially impaired in VCI.[2,15] In light of such restrictions of the MMSE, the trail-making test or digit symbol test has been recommended to supplement the MMSE to improve its sensitivity in the cognitive assessment of subjects with leukoaraiosis.[16]

Because visuoexecutive dysfunction has been found to predict poor survival after stroke,[17] the MoCA is ideal for early detection of VCI, allowing for earlier initiation of intervention and leading to improved outcomes. Vascular risk factors should be adequately controlled to reduce the risk of dementia.[18]

The MoCA-J demonstrated deficits in other cognitive domains, such as recall and language. Because the specific assessment criteria to test recall and language are less complicated in the MMSE than in the MoCA-J, a ceiling effect may prevent the MMSE from detecting intersubject differences in cognitive impairment. In support of this idea, the *z*-scores for recall and language were lower on the MoCA-J than on the MMSE, indicating greater discriminating power of the MoCA-J in assessment of cognitive impairment.

Recently, vascular risk factors have been reported to promote conversion from MCI to Alzheimer's disease.[19] Moreover, in patients with clinically diagnosed Alzheimer's disease, treatment of vascular risk factors is associated with a slower decline in MMSE score.[20] A recent animal study suggested that the effect of Alzheimer's neurodegeneration and VCI are not only additive, but also synergistic in worsening cognitive impairment.[21] Therefore, the early diagnosis of amnestic MCI with the MoCA[7,14] also may benefit patients by promoting the optimal control of all vascular risk factors, which may help prevent conversion of MCI to dementia.

The present study's main limitation is the small number of patients enrolled. Only patients with the most severe white matter changes were eligible for this study, to minimize the heterogeneity of VCI and to exclude those with white matter changes secondary to neurodegenerative changes to the utmost extent.[22] Thus, this preliminary study should be viewed as hypothesis-generating and should be followed by larger studies to confirm the results.

Nevertheless, this study provides a direct comparison of the MMSE and the MoCA-J and clearly demonstrates that the MoCA-J is more suitable for the detection of VCI. In conclusion, the MoCA-J is a promising screening tool for cognitive impairment in patients with VCI and leukoaraiosis, and may detect complex cognitive impairments, such as in executive function and visual perception, at earlier stages of VCI.

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Association of Physical Activity with the Visuospatial/Executive Functions of the Montreal Cognitive Assessment in Patients with Vascular Cognitive Impairment

Masafumi Ihara, MD, PhD, FACP,* Yoko Okamoto, MD, PhD,† Yoshiki Hase, MD, PhD,† and Ryosuke Takahashi, MD, PhD†

Background: The Montreal Cognitive Assessment (MoCA) is more suitable than the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment. In this study, we performed a correlation analysis of MoCA/MMSE scores with daily physical activity in patients with subcortical ischemic white matter changes. *Methods:* Ten patients (average 75.9 ± 9.1 years old) with extensive leukoaraiosis detected on magnetic resonance imaging underwent cognitive testing, including the MMSE and the Japanese version of the MoCA (MoCA-J). Physical activity was monitored with the Kenz Lifecorder EX device (Suzuken, Nagoya, Japan) to assess daily physical activity in terms of caloric expenditure, motor activity, number of steps, and walking distance for 6 months. Correlations of individual physical activity with total and subscale scores of MMSE/MoCA-J or 6-month interval change of MoCA-J scores were assessed. *Results:* The total or subscale scores of the MMSE did not correlate with any parameters of physical activity. However, the mean number of steps and walking distance significantly correlated with the total MoCA-J scores (r = .67 and .64, respectively) and its visuospatial/executive subscores (r = .66 and .66, respectively). The mean interval change of MoCA-J was + .6; those who improved number of steps (n = 4; 80.5 ± 3.0 years of age) had significantly preserved MoCA-J scores compared to those who did not (n = 6; 73.0 ± 11.6 years of age; +2.0 versus − .3; P = .016). *Conclusions:* These results suggest that MoCA is useful to detect a biologically determined specific relationship between physical activity and executive function. In addition, physical exercise, such as walking, may help enhance cognitive function in patients with vascular cognitive impairment of subcortical origin. **Key Words:** Leukoaraiosis—Montreal Cognitive Assessment—physical activity—stroke—vascular cognitive impairment.

From the *Department of Regenerative Medicine Research, Kobe Institute of Biomedical Research and Innovation, Kobe; and †Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

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Address correspondence to Masafumi Ihara, MD, PhD, Department of Regenerative Medicine and Research, Kobe Institute of Biomedical Research and Innovation, 2-2 Minatojima Minamimachi Chuo-ku, Kobe 650-0047, Japan. E-mail: ihara@fbri.org.

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The widely used Mini-Mental State Examination (MMSE)[1] is inaccurate in screening vascular cognitive impairment (VCI) because it is insensitive to mild cognitive impairment (MCI) and complex cognitive deficits specifically.[2,3] By comparison, the Montreal Cognitive Assessment (MoCA) has been designed to be sensitive to mild deficits[4] and has been evaluated in amnestic MCI[4] and Parkinson disease.[5] Importantly, the MoCA has been reported to detect more cognitive abnormalities after ischemic stroke or transient ischemic attack compared to the MMSE, particularly in relation to frontal executive function.[6-9]

Executive function is positively associated with physical activity participation in a community-dwelling cohort

of older adults,[10] suggesting that the relationship between physical activity and executive function may be specifically biologically determined. This specific relationship may be explained by the increasing lines of evidence that physical exercise that targets cardiovascular fitness prevents ischemic changes in the frontal lobe, the primary target of the vascular cognitive impairment. However, such a relationship may not be determined with the MMSE, which lacks scope for screening visuospatial/executive performance.

The primary aim of the present study was to test the hypothesis that the MoCA is more sensitive than the MMSE in detecting the relationship between cognitive function and physical activity in patients with ischemic leukoaraiosis, namely subcortical VCI. Because no studies have investigated such relationships using cognitive screening tools, such as the MMSE and MoCA, this study may provide additional evidence that the assessment of physical activity with a continuous monitoring device may provide a practical predictor of domain-specific cognitive decline of ischemic origin, which may be detected with the MoCA in patients with VCI.

Methods

Subjects

Ten patients, whose fluid-attenuated inversion recovery– and T2-weighted magnetic resonance imaging scans revealed confluent hyperintensities in the subcortical white matter (Schmidt scale score of 3)[11] and several punctate high-intensity areas in the basal ganglia, were studied. Patients matching the criteria were enrolled in the study after admission to the Kyoto University Neurology Clinic between May 2008 and March 2011 with various neurologic signs and symptoms. Patients with mild to moderate leukoaraiosis (Schmidt scale score of 1 or 2) were not enrolled in this study in order to exclude the possibility of leukoaraiosis associated with neurodegenerative disorders, such as Alzheimer disease. Patients presenting with severe gait disturbances were also withdrawn, because their inclusion would prevent the assessment of spontaneous physical activity. Each subject was fully instructed on the experimental procedures, and all patients taking part in the study gave written, informed consent, as approved by the Committee of Medical Ethics within our faculty. None of the patients had apparent lesions in the cerebral cortex or hippocampus. Magnetic resonance angiography and duplex color-coded sonography did not reveal >50% stenosis in the major intracranial and extracranial vessels.

Assessment of Physical Activity

Physical activity intensity was monitored with the Kenz Lifecorder EX device (Suzuken, Nagoya, Japan)[12] to assess day-to-day physical activity in terms of caloric expenditure (kcal), motor activity (kcal), number of steps (no.), and walking distance (km) for 6 months. The data were retrieved with physical activity analysis software (Suzuken) in the outpatient clinic every 2 months to ensure adherence to the device and inform the patients of the results of the monitoring. To minimize individual gait variability, the above parameters were averaged over the observational period of 6 months and used for subsequent analysis. In addition, to avoid seasonal gait variability and to cover both warm and cool climates, 6 patients underwent gait assessment from winter to summer and 4 patients from summer to winter. Verbal instructions were given to the patients and their caregivers to encourage physical activity at the outpatient clinic. Those who walked more steps during the last 2 months, compared to the initial 2 months, were retrospectively labeled "improvers," while those who did not were labeled "non-improvers."

Neuropsychological Evaluation

All subjects underwent a general physical and neurologic examination and neuropsychological assessment, including the MMSE and the Japanese version of the MoCA (MoCA-J).[13] The diagnosis of VCI was made according to the diagnostic criteria proposed by Gorelick et al.[14] To avoid habituation and interference effects, the MMSE was carried out at least 1 week after MoCA-J assessment. Two neurologists were involved in the neuropsychological assessment; if their assessments did not correlate, patients were reexamined for a final evaluation. Changes in MoCA-J over 6 months (ΔMoCA-J) were calculated and compared between the improvers and the nonimprovers.

Statistical Analysis

The statistical significance of intergroup differences was assessed with the Fisher exact test for categorical variables, and continuous variables of demographic data were assessed with the Mann–Whitney *U* test. Correlations of individual physical activity with total and subtest scores of MMSE/MoCA-J or ΔMoCA-J were assessed using Pearson correlation analysis.

Results

Patient Demographic Data

Patient clinical features and demographics are summarized in the Table 1. All patients had at least 1 risk factor for ischemic cerebrovascular disease, including hypertension and diabetes mellitus. All participants were right-handed and ambulant, though 7 patients (70%) had at least some slight postural instability. Most of the patients had lacunar infarctions or microbleeds in the basal ganglia or the thalamus as a manifestation of underlying small vessel pathology.

Table 1. *Patient clinical features and demographics*

Variable	
Mean age, y (range)	76.0 ± 9.1 (55-84)
Gender (M:F)	6:4
Dysarthria, no. (%)	3 (30)
Urinary incontinence, no. (%)	3 (30)
Hypertension, no. (%)	6 (60)
Diabetes mellitus, no. (%)	1 (10)
Cigarette smoking, no. (%)	2 (20)
Sleep apnea, no. (%)	1 (10)
Previous CVD, no. (%)	4 (40)
Use of antithrombotics, no. (%)	6 (60)
Use of statins, no. (%)	4 (40)
LDL cholesterol, mg/dL (±SD)	119 ± 40
Triglyceride, mg/dL (±SD)	118 ± 47
Hematocrit, % (±SD)	40.3 ± 2.8
Fibrinogen, mg/dL (±SD)	272 ± 46
No. of MBs in the BG/thalamus (±SD)	1.4 ± 2.0
No. of lacunas in the BG/thalamus (±SD)	2.6 ± 3.0

Abbreviations: BG, basal ganglia; CVD, cerebrovascular disease; F, female; LDL, low-density lipoprotein; M, male; MBs, microbleeds; SD, standard deviation.

Monitoring of Physical Activity

The monitoring of physical activity was successful at least in 60% of the observation period of 6 months in the 10 patients enrolled. The comparison in number of steps between the initial and the last 2 months found 4 "improvers" (mean age 80.5 ± 3.0 years; 1 man and 3 women) and 6 "nonimprovers" (mean age 73.0 ± 11.6 years; 5 men and 1 woman). Women tended to increase their steps in response to the instructions given in the outpatient clinic (Table 2). There were no significant correlations of age or educational years with the number of steps, walking distance, and motor activity. However, there was a significant inverse correlation of age with the total energy expenditure (r = − .743; P = .01).

Relationship Between Physical Activity and MMSE Scores

The total or subscale scores of the MMSE did not significantly correlate with any parameters assessed with the exercise-measuring device in terms of caloric expenditure, motor activity, number of steps, and walking distance (Fig 2).

Relationship Between Physical Activity and MoCA-J Scores

The total MoCA-J scores significantly correlated with mean number of steps per day (r = .67; P = .032; Fig 3A) and mean walking distance per day (r = .64; P = .045; Fig 3B). Among the subscores of the MoCA-J, only the visuospatial/executive subscores significantly correlated with mean number of footsteps per day (r = .66; P = .034; Fig 3C) and mean walking distance per day (r = .66; P = .037; Fig 3D).

Difference in ΔMoCA-J Between Physical Activity Improvers and Nonimprovers

The mean ΔMoCA-J over the 6 months of the 10 patients enrolled in this study was + .6. The mean ΔMoCA-J of the 4 improvers was +2.0, while that of 6 nonimprovers was − .3. There were significant differences in ΔMoCA-J between the 2 groups (P = .016). However, there were no statistical differences in ΔMoCA-J between the "physically active" group (n = 4, with >5000 steps per day; 79.0 ± 7.3 years of age) and "physically sedentary" group (n = 6, with <5000 steps per day; 74.0 ± 11.0 years of age; P = .38).

Discussion

The main finding of this study is that, in patients with VCI, physical activity (measured by number of steps and walking distance) significantly correlated with the total MoCA-J scores and the MoCA-J visuospatial/executive subscores. In addition, those who increased their physical activity after placement of the device had

Table 2. *Parameters obtained from the activity-monitoring device and the cognitive performance of the subjects included in this study*

Age and sex	83 F	83 F	79 M	77 F	82 M	68 M	67 M	82 F	55 M	84 M
Mean steps, no.	6959	5257	2364	2016	7179	6604	3802	3700	2468	676
% Increase of steps	29.0	52.4	33.6	14.2	−6.6	−33.1	−32.1	−52.8	−13.2	−51.7
Mean walking distance, km	4.36	3.12	1.53	1.44	4.54	4.56	2.48	2.48	1.64	.50
Mean calorie expenditure, kcal	1405	1377	1614	1279	1328	1848	1792	1434	1835	1655
Mean motor activity, kcal	116.7	104.8	65.5	30.6	134.2	177.6	103.0	77.0	61.2	19.9
Educational history, y	14	11	6	9	12	12	12	9	16	11
MMSE score	29	27	22	26	30	23	29	30	30	18
MoCA-J score	25	23	15	20	28	18	21	24	22	9
ΔMoCA-J score	1	1	2	4	−2	0	0	0	−1	1

Abbreviations: F, female; M, male; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ΔMoCA-J, 6-month interval change of MoCA-J.

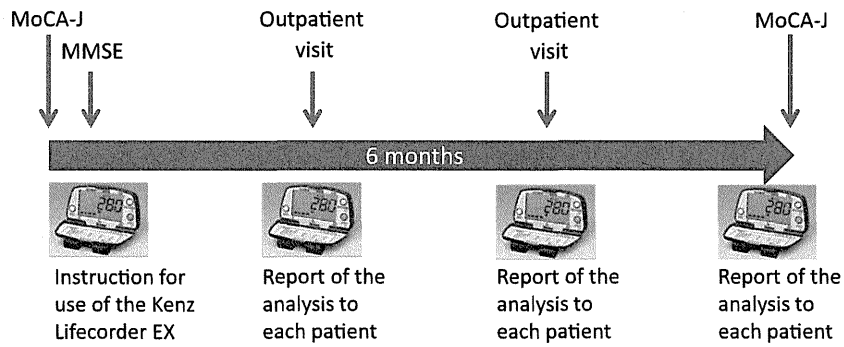

Figure 1. *Observational study protocol. Physical activity intensity was monitored with the Kenz Lifecorder EX device (Suzuken, Nagoya, Japan) to assess day-to-day physical activity in terms of caloric expenditure (kcal), motor activity (kcal), number of steps (no.), and walking distance (km) for 6 months. In the outpatient clinic, the data were retrieved every 2 months to ensure adherence to the device and to inform the patients of the results of the monitoring. All subjects underwent the Japanese version of the Montreal Cognitive Assessment (MoCA-J) and the Mini-Mental State Examination (MMSE) at the beginning of the study and the MoCA-J at the end of the study. To avoid habituation and interference effects, the MMSE was carried out at least 1 week after the MoCA-J assessment.*

significant preservation of the MoCA-J scores. However, the parameters of physical activity did not correlate with MMSE total scores or any subscores. The MoCA is reported to be more suitable in the detection of frontal executive function after ischemic stroke or transient ischemic attack when compared to the MMSE.[6-9] These results suggest that the MoCA is more appropriate in the detection of the biologically determined specific relationship between physical activity and executive function in patients with VCI, and that increased physical activity contributes to cognitive enhancement in such patients.

The Kenz Lifecorder EX physical activity measuring device (Suzuken) used in this study (Fig 1) is a community- and home-based monitoring system with a maximum of 200 days' memory for analyzing patient lifestyle.[15] Data from the device can be downloaded to a computer in an outpatient clinic and analyzed using physical activity analysis software. This allows continuous in-home monitoring, giving a more accurate assessment than, for example, a single gait test given at an annual physical examination, because walking speed taken at a single time point may overestimate walking abilities in the elderly, especially in a hospital setting. Because daily physical activity is thought to affect brain health, such a device could be valuable in monitoring sedentary behavior as a predictor of executive dysfunction in patients with VCI.

In this study, physical activity was monitored for 6 months, and the MoCA-J was assessed at the start and end of the study. Intriguingly, the mean MoCA-J scores increased by .6 points after the observation period of 6 months, while verbal instructions were given to patients to increase physical activity every 2 months. In addition, the patients were informed of the aim of this study at the beginning, which may have served as a motivating factor for physical activity and contributed to subsequent cognitive preservation in the patients, especially in the physical activity "improvers." Consistent with this notion, aerobic-based exercise may be of specific benefit in delaying the progression of cognitive decline among elderly individuals with VCI.[16] In addition, physical exercise appears to have a preventative effect on VCI in a group of elderly female patients.[17] Further study involving a longer observational period is required to clarify whether such exercise-monitoring devices are helpful in motivating VCI patients to continue exercise and thus potentially halt the progression of the cognitive impairment.

The main limitation of this study is the small number of patients enrolled, because only those with most severe white matter changes were eligible in order to minimize the heterogeneity of VCI and to maximally exclude those with white matter changes secondary to neurodegenerative changes.[18] To explore our findings, future studies should be performed in larger cohorts by recruiting not only patients with subcortical VCI but also those with

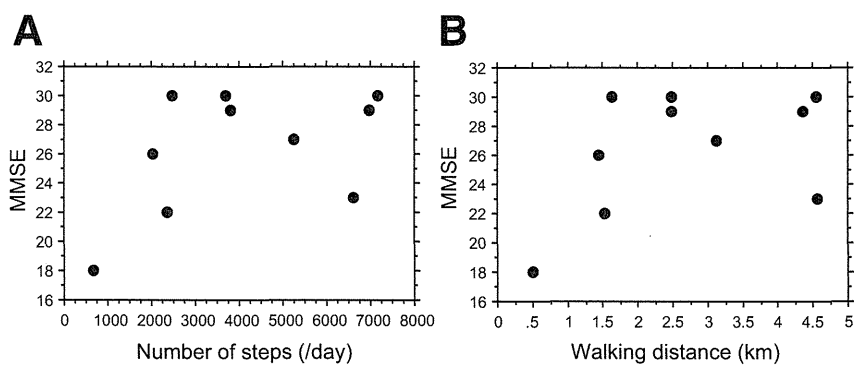

Figure 2. *There was no correlation of the Mini-Mental State Examination (MMSE) scores with physical activity. The total scores of the MMSE did not significantly correlate with the number of footsteps or walking distance assessed with the Kenz Lifecorder EX device (Suzuken, Nagoya, Japan).*

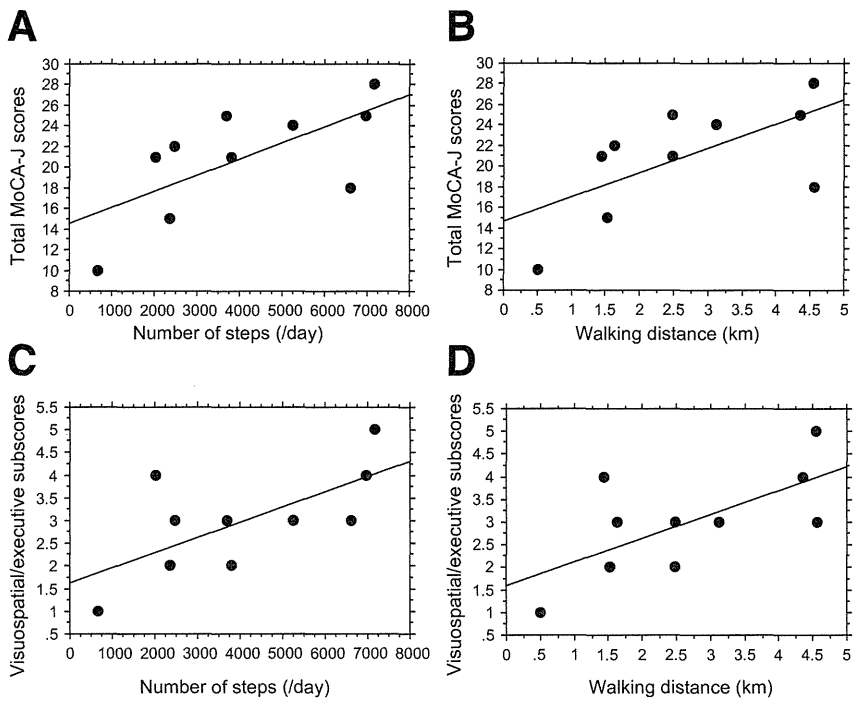

Figure 3. *There was significant correlation with the Japanese version of the Montreal Cognitive Assessment (MoCA-J) scores and physical activity. The total MoCA-J scores significantly correlated with the mean number of steps per day (r = .67; P = .032; A) and the mean walking distance per day (r = .64; P = .045; B). Among the subscores of the MoCA-J, only the visuospatial/executive subscores of the MoCA-J significantly correlated with the mean number of steps per day (r = .664; P = .034; C) and the mean walking distance per day (r = .658; P = .037; D).*

other VCI subtypes. Another limitation is that although the MoCA-J score was significantly preserved in the patients with improved physical activity, the 6-month follow-up period may be too short to influence the underlying mechanisms of VCI. Because of the above limitations, this preliminary study should be viewed as hypothesis-generating and should be followed by larger studies to confirm the results and to explore the lifestyle determinants of dementia. Nevertheless, our study has suggested that the assessment of physical activity with a continuous monitoring device may provide a practical predictor of domain-specific cognitive decline of ischemic origin and a rationale for intervention in patients with VCI.

In conclusion, the positive correlation of the executive and visuospatial performance of the MoCA-J with daily physical activity suggests potential benefits of exercise against domain-specific cognitive decline of subcortical ischemic origin.

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