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Effects of Exercise and Amino Acid Supplementation on Body Composition and Physical Function in Community-Dwelling Elderly Japanese Sarcopenic Women: A Randomized Controlled Trial

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OBJECTIVES: To evaluate the effectiveness of exercise and amino acid supplementation in enhancing muscle mass and strength in community-dwelling elderly sarcopenic women.

DESIGN: Randomized controlled trial.

SETTING: Urban community in Tokyo, Japan.

PARTICIPANTS: One hundred fifty-five women aged 75 and older were defined as sarcopenic and randomly assigned to one of four groups: exercise and amino acid supplementation (exercise + AAS; n = 38), exercise (n = 39), amino acid supplementation (AAS; n = 39), or health education (HE; n = 39).

INTERVENTION: The exercise group attended a 60-minute comprehensive training program twice a week, and the AAS group ingested 3 g of a leucine-rich essential amino acid mixture twice a day for 3 months.

MEASUREMENTS: Body composition was determined using bioelectrical impedance analysis. Data from interviews and functional fitness parameters such as muscle strength and walking ability were collected at baseline and after the 3-month intervention.

RESULTS: A significant group × time interaction was seen in leg muscle mass ($P = .007$), usual walking speed ($P = .007$), and knee extension strength ($P = .017$). The within-group analysis showed that walking speed significantly increased in all three intervention groups, leg muscle mass in the exercise + AAS and exercise groups, and knee extension strength only in the exercise + AAS group (9.3% increase, $P = .01$). The odds ratio for leg muscle mass and knee extension strength improvement was more than four times as great in the exercise + AAS group (odds ratio = 4.89, 95% confidence interval = 1.89–11.27) as in the HE group.

CONCLUSION: The data suggest that exercise and AAS together may be effective in enhancing not only muscle strength, but also combined variables of muscle mass and walking speed and of muscle mass and strength in sarcopenic women. **J Am Geriatr Soc 60:16–23, 2012.**

Key words: sarcopenic women; exercise; amino acid supplementation; muscle mass; muscle strength

Sarcopenia, defined as age-related involuntary loss of skeletal muscle mass and strength,[1,2] has been associated with physical disability, functional decline, falls, impaired mobility, and mortality in elderly people.[3,4] Therefore, treating or reversing sarcopenia is important in the maintenance of health and life expectancy in the elderly population. Although many factors, such as chronic disease, physical inactivity, and decreased muscle protein synthesis, may contribute to loss of muscle mass,[5–7] it has been suggested that only skeletal muscle disuse and undernutrition are potentially preventable or reversible with targeted interventions.[8]

Many studies have shown a strong relationship between resistance exercise and strength improvement, through which the efficacy of resistance exercise for the prevention and treatment of sarcopenia has been confirmed.[9] The previous studies have also shown that ingestion of essential amino acids can induce muscle protein anabolism in elderly adults.[10,11] One study showed that the combination of resistance exercise and essential amino acid supplementation (AAS) augmented muscle protein

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synthesis, suggesting it as a strategy to reverse sarcopenia[12] but in a small sample size. There are few randomized controlled trials (RCTs) on the effects of exercise and AAS on body composition and functional capacity.

The purpose of this study was to investigate the effects of exercise and AAS on muscle mass, strength, and walking ability in sarcopenic women.

METHODS

Subjects

A letter outlining the comprehensive geriatric health examination survey, describing its objective and the way that the personal data would be used, was mailed to the women randomly selected from the Basic Resident Register of 5,932 people aged 75 and older residing in the Itabashi ward of metropolitan Tokyo inviting them to participate in the study. Two thousand eighteen people responded to the mailed letters of invitation to participate in the study, with 1,670 people agreeing and 348 people declining to participate. The baseline assessment was conducted at the Tokyo Metropolitan Institute of Gerontology (TMIG) from October 12 to November 3, 2008. One thousand three hundred eighty-three women aged 75 and older were screened; 287 who originally agreed to participation were absent. Written informed consent was obtained for baseline screening; six people did not sign the informed consent form and were not included in this study.

Three hundred four of 1,377 women (22.1%) were operationally defined as sarcopenic (Figure 1), with selection based on categorization into one or more of the following inclusion criteria groups: appendicular skeletal muscle mass/height^2 less than 6.42 kg/m^2 and knee extension strength less than 1.01 Nm/kg[13,14] (n = 68), appendicular skeletal muscle mass/height^2 less than 6.42 kg/m^2 and usual walking speed less than 1.22 m/s (n = 65),[14] body mass index (BMI) less than 22.0 kg/m^2[14] and knee

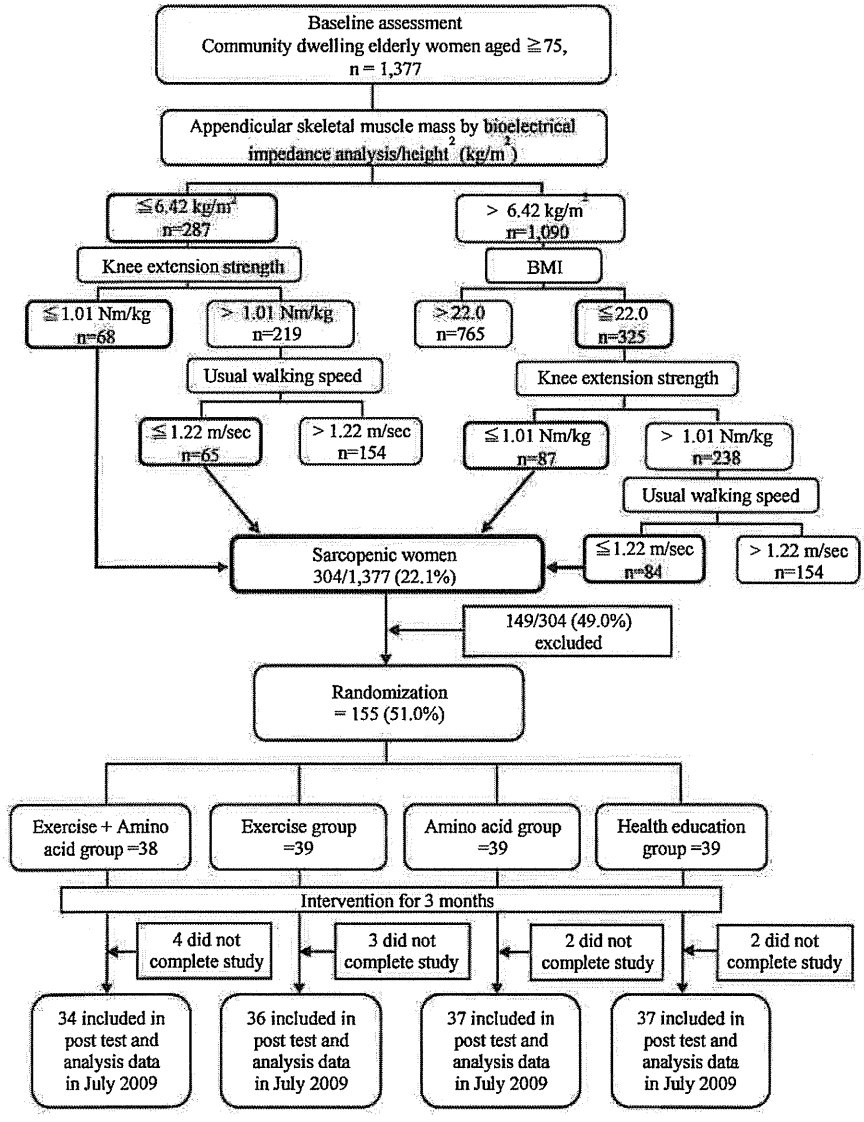

Figure 1. Algorithm for the selection of women who were operationally defined as sarcopenic and flowchart of participants in the randomized controlled trial of exercise and amino acid supplementation.

extension strength less than 1.01 Nm/kg (n = 87), and BMI less than 22.0 kg/m^2 and usual walking speed less than 1.22 m/s (n = 84). Exclusion criteria were severe knee or back pain; severely impaired mobility; impaired cognition (Mini-Mental State Examination (MMSE) score < 24);[16] missing baseline data; and unstable cardiac conditions such as ventricular dysrhythmias, pulmonary edema, or other musculoskeletal conditions. One hundred forty-nine (49.0%) of the potential sarcopenic participants were excluded because they were classified into one or more of the exclusion criteria or declined participation. The Clinical Research Ethics Committee of TMIG approved the study protocol. The intervention procedures were fully explained to all participants, and written informed consent was obtained (Figure 1).

Randomization

Randomization was performed after the baseline assessment; any variable that identified personal information was not included in the randomization process. Computer-generated random numbers were assigned to 155 participants who were then sorted and divided into four equal groups. The groups were randomly assigned to one of the four interventions groups: exercise + AAS (n = 38), exercise (n = 39), AAS (n = 39), or health education (HE; n = 39). All participants agreed to the group allocations that were mailed to them. There was no attempt to equalize the size of the groups based on their characteristics or to recruit subjects with specific characteristics. The co-investigators were blind to the randomization procedure and group allocations, separate physical therapy staff members who were also blind to the allocation of treatments collected data.

Outcome Measures

Outcome measures were evaluated according to data collected from interviews, body composition assessments using bioelectrical impedance analysis (BIA), and physical fitness tests at baseline and after the 3-month intervention.

Interview Survey

Face-to-face interviews were conducted to assess the individual's history of fractures and falls over the previous year, number of falls, cause of falls, urinary incontinence, exercise habits, smoking status, and MMSE score.

Body Composition Assessment

Measurements of height and weight were used to calculate BMI (kg/m^2). Body composition was measured using a segmental multifrequency BIA instrument that operated at frequencies of 5, 50, 250, and 550 kHz (Well-Scan 500, Elk Corp., Tokyo, Japan). Participants removed their socks, stood on two metallic electrodes on the floor scale barefoot, and held metallic grip electrodes placed in the palm of the hand with the fingers wrapped around the handrails. Using segmental body composition and muscle mass values of both legs, both arms, and the trunk, appendicular skeletal muscle mass and leg muscle mass values were obtained

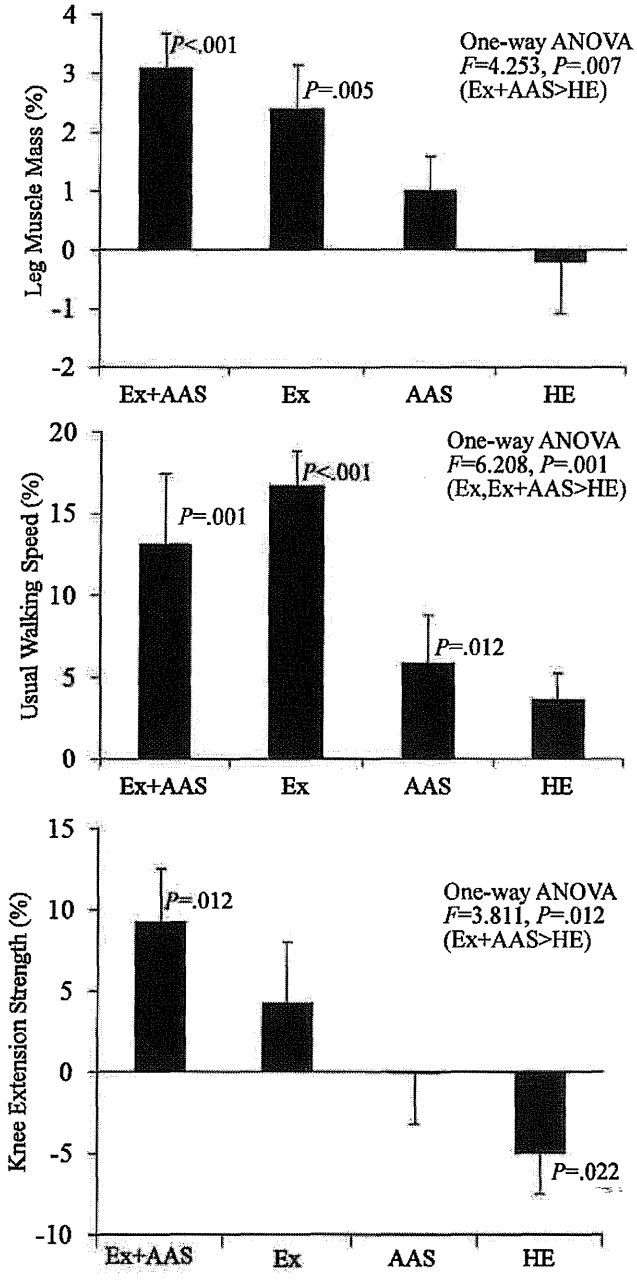

Figure 2. Mean percentage changes (standard errors) in leg muscle mass, usual walking speed, and knee extension strength after exercise (Ex), amino acid supplementation (AAS), both (Ex + AAS), or health education (HE). Bars indicate average changes from baseline to after the 3-month intervention. ANOVA = analysis of variance.

and used for analysis by summing the appropriate segmental muscle mass values.[13,17,18] Reliability of body composition measurements in all 155 participants in this study was not analyzed, although for the AAS group (n = 39), measurements were taken for a second time 1 week after baseline testing, and reliability was examined; the intraclass correlation coefficients (ICC) were: 0.98 for the right arm, 0.97 for the left arm, 0.97 for the right leg, 0.96 for the left leg, and 0.93 for the trunk.

Functional Fitness Test

Calf girth and functional fitness variables including usual and maximum walking speeds and knee extension strength were measured. In measures of walking speed, participants were allowed to use assistive walking devices only if they expressed strong concerns about walking without a device or if there was any danger of falling. The knee extension strength measurement was taken twice, and the higher value divided by body weight (Nm/kg) were analyzed. The procedures for the functional fitness tests have been described in detail in previous reports.[19,20]

Intervention

Exercise

A comprehensive physical fitness and muscle mass enhancement training program of moderate intensity was provided for the participants in the exercise groups. The exercise intervention consisted of 60-minute exercise sessions held at the TMIG twice per week for 3 months. Each exercise intervention group was divided into two subgroups, with participants exercising together within their assigned group in one of four exercise sessions offered per day.

Each exercise session consisted of a 5-minute warm-up, 30 minutes of strengthening exercise, 20 minutes of balance and gait training, and 5 minutes of cool down. The strengthening exercises were performed in a progressive sequence from seated to standing positions. For each type of exercise, participants were instructed to complete up to eight repetitions of the movements. When the exercises were properly executed without significant fatigue or loss of proper execution, the resistance was increased. The progressive resistance was provided through the use of resistance bands or ankle weights. Intensity was maintained at approximately 12 to 14 on the Borg Rate of Perceived Exertion scale.[21] The principal investigator, along with the exercise instructor and assistant trainers, assessed each individual's ability to increase intensity.

Chair exercise: The chair-seated exercises were used in the early stages of the program because the participants were frail older adults and it provided a secure and stable position. Repetitions of toe raises, heel raises, knee lifts, knee extensions, and others were performed while seated on a chair. Hip flexions, lateral leg raises, and repetitions of other exercises were performed standing upright behind the chair and holding the back of the chair for stability.

Ankle-weight exercise: To strengthen lower extremities, a fixed weight was placed on the ankle while participants performed strengthening exercises. Weights of 0.50, 0.75, 1.00, and 1.50 kg were prepared and used in accordance with each participant's strength level as the resistance progressively increased. The exercises performed using these ankle weights included seated knee flexion and extension and standing knee flexion and extensions.

Exercises using a resistance band: Resistance bands were used to strengthen the upper and lower body. Lower body exercises included leg extension and hip flexion. Upper body exercises included double-arm pull downs and biceps curls.

Balance and gait training: The balance training was focused on improvement of static, dynamic, and lateral balancing ability. Exercises included standing on one leg, multidirectional weight shifts, tandem stand, and tandem walk. Participants practiced proper gait mechanics that focused on the maintenance of stability during walking and increasing stride length, toe elevation of the forward limb, heel elevation of the rear limb, frequency of stepping, and heel–floor angle. Exercises included raising the toes (dorsiflexion) during the forward swing of the leg, kicking off the floor with the ball of the foot, walking with directional changes, and gait pattern variations.

Amino Acid Supplementation

Essential AAS was provided for the participants in the AAS groups every 2 weeks. Packets of powdered amino acid supplements (42.0% leucine, 14.0% lysine, 10.5% valine, 10.5% isoleucine, 10.5% threonine, 7.0% phenylalanine, and 5.5% other) were provided for the participants to be taken with water or milk, and they were instructed to take the 3-g supplement two times a day (6 g daily) every day for 3 months.[22] To monitor their amino acid intake accurately, participants were given record sheets that were collected every 2 weeks on which they recorded what time of day they took the supplement and the amount of amino acid taken every day.

Health Education

Participants in the HE group took a class once a month for 3 months, a total of three times. The classes focused on cognitive function, osteoporosis, and oral hygiene. Participants were asked to continue their regular lifestyle habits, and no specific instructions on diet or physical activity were given.

Data Analysis

Sample size calculations using univariate one-factor repeated-measures analysis of variance (ANOVA) to examine significant differences in means at baseline and after the 3-month intervention ($\alpha = 0.05$, power = 0.80) with an effect size of 0.15 required a sample size of 28 participants. Esimating a potential attrition rate of 25%, 38 subjects per group were required.[23] One-way ANOVA was used to test any differences in baseline measures and percentage changes between groups, and chi-square tests were performed on categorical variables. Percentage changes in muscle mass and functional fitness after the intervention were calculated using the following formula: % change = ((postintervention value–baseline value)/(baseline value) × 100). Two-way repeated-measures ANOVA was used to evaluate the differences in the effect of the intervention on the outcome measures between groups, and a post hoc test was done on variables showing significant differences to determine which groups were different. Multiple logistic regressions were performed to compare the effects of the four intervention groups on each outcome variable after 3 months of intervention. All analyses were performed using SPSS version 15.0 of Windows (SPSS, Inc., Tokyo, Japan).

RESULTS

The baseline demographic, fitness, and interview variables of the participants in the four groups are summarized in Table 1. All of the baseline characteristics were similar between the groups.

The mean attendance rates during the 3-month intervention were 70.3% in the exercise + AAS group, 80.5% in the exercise group, 72.2% in the AAS group, and 71.8% in the HE group. Eleven participants (exercise + AAS = 4, exercise = 3, AAS = 2, HE = 2) were unable to complete the study after randomization because of spouse care (n = 3), admission to nursing home (n = 2), lack of motivation (n = 2), severe knee or back pain (n = 1), death (n = 1), falls and hip fracture (n = 1), and hospitalization (n = 1; Figure 2).

In comparing the pre- and postintervention changes in body composition and functional fitness of the groups (Table 2), there was a significant group × time interaction for leg muscle mass ($F = 4.253$, $P < .007$; exercise + AAS > HE), usual and maximum walking speeds (exercise and exercise + AAS > HE), and knee extension strength ($F = 3.558$, $P = .02$; exercise + AAS > HE).

The within-group analysis showed significant changes in leg muscle mass in the exercise + AAS ($P < .001$) and exercise ($P = .005$) groups and changes in usual walking speed in the exercise + AAS ($P = .001$), exercise ($P < .001$), and AAS groups ($P = .01$). Knee extension strength improved significantly only in the exercise + AAS group ($P = .01$), no improvement was seen in exercise or AAS, and a statistically significant decrease was observed in the HE group ($P = .02$; Figure 1).

Table 3 shows the effects of the type of intervention on changes in combined variables of muscle mass and physical function. Significant increases in leg muscle mass and knee extension strength (odds ratio (OR) = 4.89, 95% confidence interval (CI) = 1.89–11.27) and leg muscle mass and usual walking speed (OR = 4.11, 95% CI = 1.33–13.68) were observed in only the exercise + AAS group.

DISCUSSION

Although many definitions of sarcopenia have been reported,[1–3,24] there has recently been a focus not only on the loss of appendicular skeletal muscle mass, but also on functional decline.[25] In this study, sarcopenic women were operationally defined based on declines in muscle strength or walking ability that accompany the loss of skeletal muscle mass or low BMI. Because defining sarcopenia was beyond the scope of this study, the focus of the discussion will be on the effects of the intervention. To evaluate the intervention effects, the changes observed in the single variables as well as the combined variables will be discussed.

Many studies have focused on exercise or nutrition as interventions to reverse sarcopenia, but the results of these studies have not always been consistent.[8,9,12,26]

This study demonstrated that appendicular muscle mass and walking speed increased with the combination of exercise and essential amino acid ingestion, as well as with the separate exercise and amino acid interventions, but muscle strength improved only with the combination of exercise and amino acid ingestion.

A recently published meta-analysis[9] and a Cochrane review article also confirmed that resistance training two to three times a week can improve physical function and functional limitations and can reduce disability and muscle weakness in older people.[27] Previous studies have demonstrated that resistance training in elderly people produces

Table 1. Selected Variable Characteristics of Participants at Baseline According to Study Group

Characteristic	Exercise + AAS (n = 38)	Exercise (n = 39)	AAS (n = 39)	Health Education (n = 39)	*F*-Value*	*P*-Value*
Age, mean ± SD	79.5 ± 2.9	79.0 ± 2.9	79.2 ± 2.8	78.7 ± 2.8	0.577	.63
Height, cm, mean ± SD	147.1 ± 6.7	147.7 ± 4.4	145.8 ± 4.5	146.5 ± 4.9	0.960	.41
Body weight, kg, mean ± SD	39.5 ± 5.5	41.1 ± 4.7	40.1 ± 3.2	40.4 ± 3.9	0.874	.46
Body mass index, kg/m^2, mean ± SD	18.3 ± 2.5	18.9 ± 2.0	18.9 ± 1.6	18.8 ± 1.7	0.745	.53
Calf girth, cm, mean ± SD	18.3 ± 2.5	18.9 ± 2.0	18.9 ± 1.6	18.8 ± 1.7	0.745	.53
Lean body mass, kg, mean ± SD	29.1 ± 3.4	30.0 ± 2.6	28.8 ± 2.0	29.3 ± 2.4	1.505	.22
Muscle mass, kg, mean ± SD	26.9 ± 3.1	27.7 ± 2.3	26.5 ± 1.8	27.0 ± 2.2	1.538	.21
Appendicular muscle mass, kg, mean ± SD	13.3 ± 1.6	13.7 ± 1.3	13.1 ± 1.0	13.3 ± 1.2	1.502	.22
Legs muscle mass, kg, mean ± SD	9.8 ± 1.2	10.1 ± 1.0	9.7 ± 0.7	9.9 ± 0.9	1.570	.20
Usual walking speed, m/s, mean ± SD	1.26 ± 0.27	1.29 ± 0.28	1.29 ± 0.20	1.18 ± 0.22	1.701	.17
Maximal walking speed, m/s, mean ± SD	1.62 ± 0.37	1.67 ± 0.31	1.67 ± 0.27	1.55 ± 0.32	1.150	.33
Knee extension strength, Nm, mean ± SD	45.9 ± 11.3	46.6 ± 11.1	46.7 ± 7.8	47.4 ± 10.5	0.139	.94
Falls, %	21.1	17.9	15.4	20.5	0.519	.91
Exercise habit, %	26.3	25.6	38.5	33.3	2.029	.57
Urinary incontinence, %	44.7	38.5	41.0	25.6	3.414	.33
Osteoporosis history, %	36.8	43.6	48.7	30.8	2.987	.39
Heart disease history, %	10.5	15.4	12.8	17.9	0.977	.81
Diabetes mellitus history, %	7.9	5.1	5.1	12.8	2.156	.54

* One-way analysis of variance for continuous variables and chi-square test for categorical variables.
AAS = amino acid supplementation; SD = standard deviation.

Table 2. Comparison of Muscle Mass and Functional Fitness Variables Between Groups After 3-Month Intervention

Variable	Group	Mean ± Standard Deviation		Analysis of Variance (Group × Time), *P*-Value	Post Hoc Analysis*
		Baseline	After 3-Month Intervention		
Muscle mass, kg	Exercise + AAS	26.76 ± 2.77	27.26 ± 3.04	$F = 1.076, .36$	
	Exercise	28.09 ± 1.90	28.51 ± 2.39		
	AAS	26.25 ± 1.81	26.53 ± 2.10		
	HE	27.48 ± 2.04	27.66 ± 2.23		
Appendicular muscle mass, kg	Exercise + AAS	13.25 ± 1.35	13.59 ± 1.53	$F = 1.354, .26$	
	Exercise	13.90 ± 1.06	14.19 ± 1.33		
	AAS	12.86 ± 0.99	13.03 ± 1.10		
	HE	13.57 ± 1.16	13.67 ± 1.05		
Legs muscle mass, kg	Exercise + AAS	9.76 ± 1.01	10.07 ± 1.13	$F = 4.253, .007$	Exercise + AAS > HE
	Exercise	10.28 ± 0.81	10.53 ± 1.05		
	AAS	9.55 ± 0.73	9.65 ± 0.83		
	HE	10.14 ± 0.87	10.11 ± 0.81		
BMI, kg/m^2	Exercise + AAS	18.30 ± 2.64	18.14 ± 2.68	$F = 0.606, .61$	
	Exercise	18.80 ± 1.30	18.50 ± 1.41		
	AAS	18.84 ± 1.43	18.56 ± 1.62		
	HE	18.83 ± 1.75	18.77 ± 1.67		
Usual walking speed, m/s	Exercise + AAS	1.27 ± 0.25	1.43 ± 0.29	$F = 4.213, .007$	Exercise and Exercise + AAS > HE
	Exercise	1.31 ± 0.24	1.50 ± 0.23		
	AAS	1.30 ± 0.18	1.36 ± 0.18		
	HE	1.19 ± 0.21	1.22 ± 0.23		
Maximum walking speed, m/s	Exercise + AAS	1.64 ± 0.34	1.92 ± 0.37	$F = 9.374, <.001$	Exercise and Exercise + AAS > HE
	Exercise	1.72 ± 0.27	2.04 ± 0.27		
	AAS	1.71 ± 0.28	1.92 ± 0.27		
	HE	1.57 ± 0.31	1.64 ± 0.31		
Knee extension strength, Nm/kg	Exercise + AAS	1.15 ± 0.27	1.23 ± 0.29	$F = 3.558, .02$	Exercise + AAS > HE
	Exercise	1.12 ± 0.30	1.14 ± 0.26		
	AAS	1.15 ± 0.25	1.14 ± 0.25		
	HE	1.14 ± 0.26	1.00 ± 0.26		

* A post hoc analysis was performed using the Scheffe method.
AAS = amino acid supplementation; HE = health education; BMI = body mass index.

Table 3. Change in Leg Muscle Mass and Functional Fitness After Intervention According to Study Group

Dependent Variable*	Adjusted Odds Ratio (95% Confidence Interval)		
	AAS	Exercise	Exercise + AAS
Change in leg muscle mass and knee extension strength	1.99 (0.72–5.65)	2.61 (0.88–8.05)	4.89 (1.89–11.27)
Change in leg muscle mass and usual walking speed	1.35 (0.45–4.08)	2.41 (0.79–7.58)	4.11 (1.33–13.68)

Reference: health education.
* 1 = improve, 0 = no change or decrease.
AAS = amino acid supplementation.

9% to 15% increases in strength and approximately 5% in thigh muscle volume.[28,29] Also, many studies have shown that resistance training in elderly people must be conducted at high intensities and volumes to see improvements.[9,27] In contrast, less-intense resistance exercise programs have produced little or no strength gains.

The data in this study show improvements of 2.4% in leg muscle mass, 2.0% in appendicular muscle mass, and 4.3% in leg strength in the exercise group. The moderate-intensity exercise provided in this trial produced strength gains that were smaller than those seen in previous studies, but the combination of moderate intensity exercise and AAS increased muscle mass 3.1% and muscle strength 9.3%, gains that are comparable with those observed in previous studies of high-intensity exercise.[28]

The results of the current study showed that total muscle mass, appendicular muscle mass, and walking speed significantly increased in the exercise group, suggesting that exercise is effective in the improvement of muscle mass and functional fitness, but increases in muscle

strength were not observed. These results indicate that exercise alone is insufficient for recovery in sarcopenic elderly women.

Previous studies have indicated that declines in muscle mass are related to declines in muscle protein synthesis rates in older adults and that leucine-enriched essential amino acid mixtures are primarily responsible for the amino acid-induced muscle protein anabolism in elderly people.[11,22] These studies investigated the effects of different amino acid dosages (from 6.7 to 20.0 g/d) on protein synthesis, and the 6.0-g/d dosage provided in this study is lower than in previous studies, but the mean weights of the subjects in such studies were from 71.0 to 81.3 kg, making the dosage of amino acid between 0.090 and 0.246 g/kg of body weight. The amino acid dosage in the current study was 0.151 g/kg, which is comparable with the amounts found in the literature.[11,22,26] The results of the current study showed that muscle mass, appendicular muscle mass, and leg muscle mass significantly increased in the AAS group, which is consistent with previous findings.

Many studies have demonstrated an increase in muscle mass from nutritional supplementation, but an increase in muscle strength does not always accompany an increase in muscle mass. A recent study concluded that essential AAS alone was not sufficient to increase muscle strength.[26] Similarly, although the results of the current study showed that AAS alone increased muscle mass, improvement in muscle strength was not observed. The results of the present study showed that muscle mass increased significantly with exercise or essential AAS, although muscle strength, measured according to knee extension strength, improved significantly only in the exercise + AAS group.

Next, the discussion will focus on the changes in the combined variables. One study that investigated the effects of resistance exercise and nutritional supplementation on muscle mass and strength in older adults concluded that high-intensity resistance exercise was beneficial in increasing muscle mass and muscle strength, but the nutritional supplementation, which contained only a small percentage of a soy-based protein within a mixture of mainly carbohydrates, did not contribute to those gains.[8] As illustrated in Figure 2, exercise alone was effective in enhancing single variables such as leg muscle mass or usual walking speed. Similarly, the AAS group improved usual walking speed, but rationally, to treat sarcopenia, improvements in single variables are not sufficient. Improvements observed in the combined variables would presumably lead to the most-efficient reversal of sarcopenia. Significant improvements in the combinations of leg muscle mass, knee extension strength, and walking speed were seen only in the exercise + AAS group. Although whether exercise + AAS was better than either intervention alone remains inconclusive, these results suggest that exercise + AAS may be necessary for benefits in muscle mass and strength.

This study has several limitations. First is the measurement of body composition estimated using BIA. Although magnetic resonance imaging (MRI), computed tomography, and dual-energy X-ray absorptiometry are common, accurate clinical methods of measuring muscle mass,[30,31] they are cost ineffective and are not always appropriate for field studies. BIA is simple, noninvasive, and inexpensive and has been widely used in field studies. The comparison of MRI and BIA measurements has revealed a strong correlation between the two, confirming the validity of the BIA method for muscle mass measurement in older adults.[13,17,18] Therefore, the validity of the data collected using BIA has little influence on the interpretation of the results of this study. Second, it has been reported that AAS enhances muscle protein synthesis,[11,22,32] but the mechanism of the increase in muscle mass from AAS was not explored in the current investigation. Therefore, the results of this study were interpreted based on the assumption that muscle protein synthesis had been enhanced. Third, the effects of the exercise + AAS should have been determined with the use of placebos, but placebo treatments were not provided in this study, so future research should include placebos to observe the effects of exercise and AAS on physical function and muscle strength. Fourth, the total number of dropouts in this study was 11 people, and they were not included in the data analysis. Many studies have used intention-to-treat (ITT) analyses to determine the effects of RCTs, and the use of ITT analyses are increasing, although one previous study found that only approximately 35% of 274 RCTs used ITT analyses.[33] The current study was not an ITT analysis because it confirmed that there were no significant differences between the dropouts and the participants who completed the study, and the exclusion of the 11 dropouts from the analysis did not affect the integrity of the baseline randomization. Finally, previous research has shown that milk contains essential amino acids.[34,35] Because some of the participants took the AAS with milk, the exact essential amino acid dosage in this study could not be determined, and the effect of drinking milk on the results of this study was not confirmed. Future research should avoid the intake of milk with amino acids when investigating the effects of amino acids on muscle strength and mass and physical function.

This study demonstrated that exercise and nutrition may be necessary for the basic treatment of increasing muscle mass and strength to reverse the effects of sarcopenia in community-dwelling sarcopenic women. Exercise and AAS together have significant effects on enhancing not only muscle strength, but also the combined variables of muscle mass and walking speed and of muscle mass and strength in this study population, but further follow-up studies on larger populations are required to confirm these results.

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Author Contributions: H. Kim developed the study concept and design, recruited subjects, developed the intervention program, analyzed and interpreted the data, and prepared the manuscript. S. Takao interpreted the data and reviewed the manuscript for accuracy. K. Saito assisted in AAS and supervised the interview survey. Y. Hideyo assisted in subject recruitment, supervised the

interviewers, and interpreted the data. M. Kobayashi assisted in AAS and subject recruitment and interpreted the data. H. Kato assisted in assisted AAS and body composition assessment. M. Katayama assisted in AAS and interview survey.

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words
Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract
Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. ***Methods:*** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backword (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. ***Results:*** In all subjects, MTA-ERC atrophy showed significant relationships with age ($r = 0.43$), education ($r = -0.25$), WMS-R, LM I ($r = -0.21$), DSC ($r = -0.32$), and SCWT-IL ($r = 0.32$). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age ($r = 0.34$), DSC ($r = -0.28$), and SCWT-IL ($r = 0.25$). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$) and RCF-30 min ($r = -0.74$). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age ($\beta = 0.374$) and SCWT-IL ($\beta = 0.247$) in all subjects. Age ($\beta = 0.301$), and RCF-30 min ($\beta = -0.521$) and age ($\beta = 0.460$) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. ***Conclusion:*** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between in vivo measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to interregional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnestic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men n = 48, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean ± SD)

Age, years	75.3 ± 6.8
Male, %	50
Education, years	10.6 ± 2.5
Body mass index	23.0 ± 3.1
Cognitive functions	
MMSE, points	26.5 ± 2.5
WMS-R, LM I, points	14.4 ± 7.1
WMS-R, LM II, points	10.0 ± 7.4
RCF-3 min, points	15.5 ± 6.3
RCF-30 min, points	14.9 ± 6.7
DSB, points	5.2 ± 1.6
DSC, points	46.1 ± 15.9
SCWT-IL, s	21.1 ± 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number ± SD	2.3 ± 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T_1-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, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T_1 MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) – (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

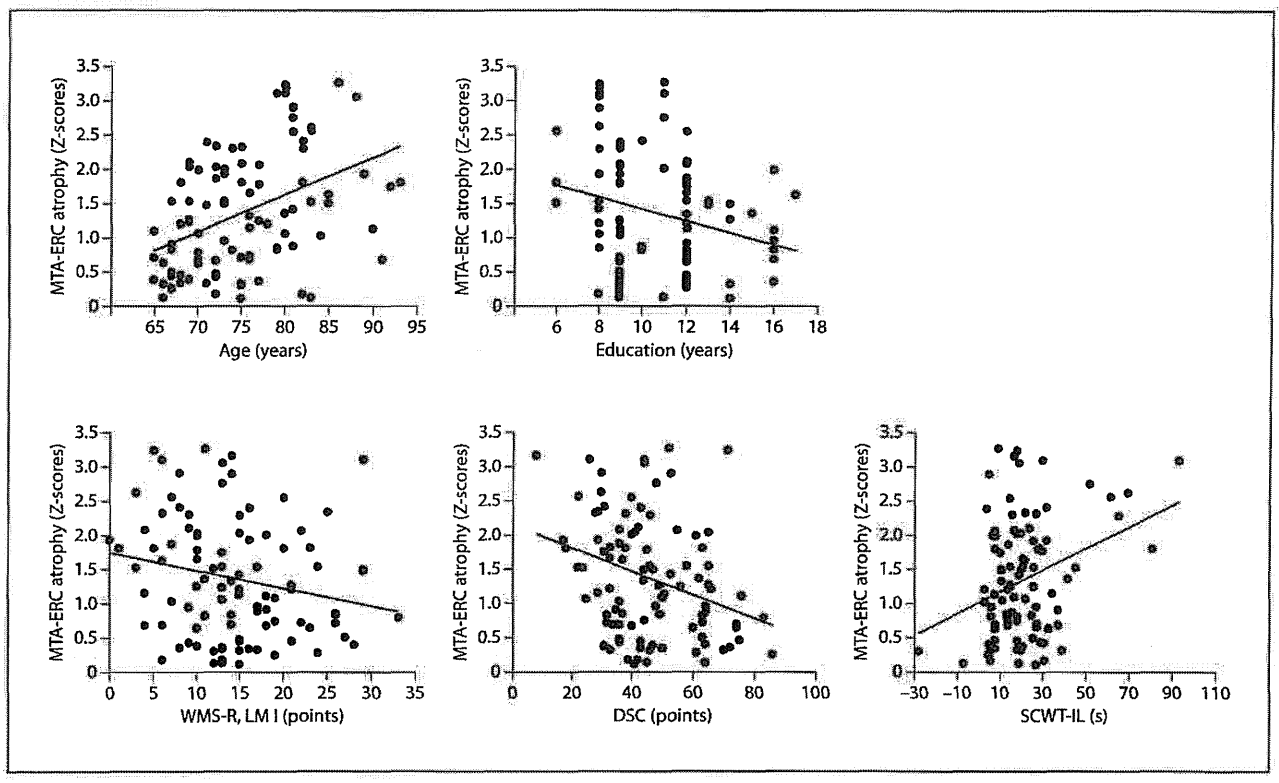

Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	**<0.001**	0.34	**0.003**	0.71	**<0.001**
Education	−0.25	**0.012**	0.01	0.921	−0.26	0.224
WMS-R, LM I	−0.21	**0.040**	−0.17	0.155	−0.06	0.774
WMS-R, LM II	−0.09	0.370	0.03	0.812	−0.22	0.308
RCF-3 min	−0.16	0.119	−0.10	0.396	−0.70	**<0.001**
RCF-30 min	−0.13	0.201	−0.11	0.386	−0.74	**<0.001**
DSB	−0.15	0.134	−0.12	0.298	−0.14	0.511
DSC	−0.32	**0.002**	−0.28	**0.016**	−0.05	0.825
SCWT-IL	0.32	**0.002**	0.25	**0.031**	0.18	0.404

For abbreviations, see table 1.

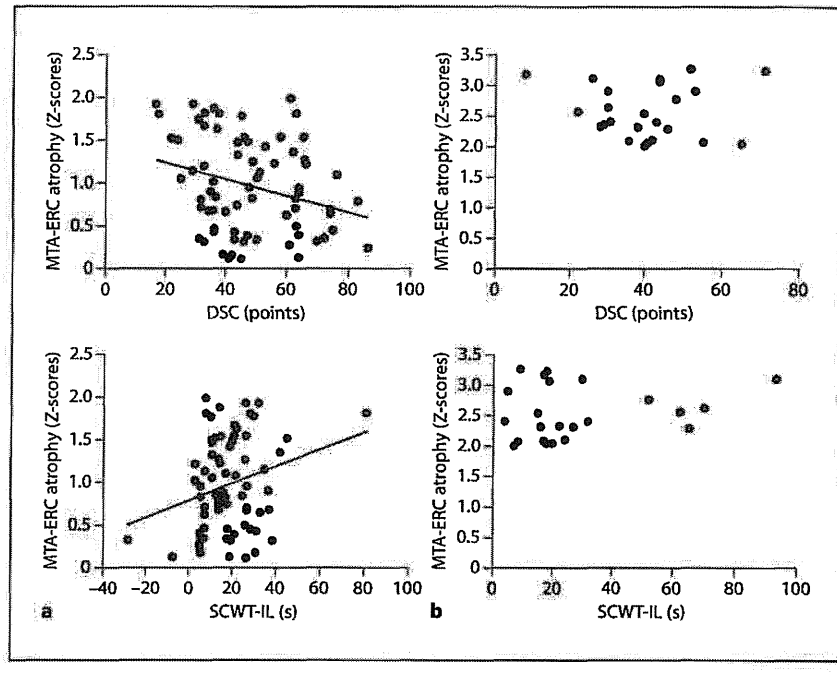

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	−0.521	−3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta = 0.374$, $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-

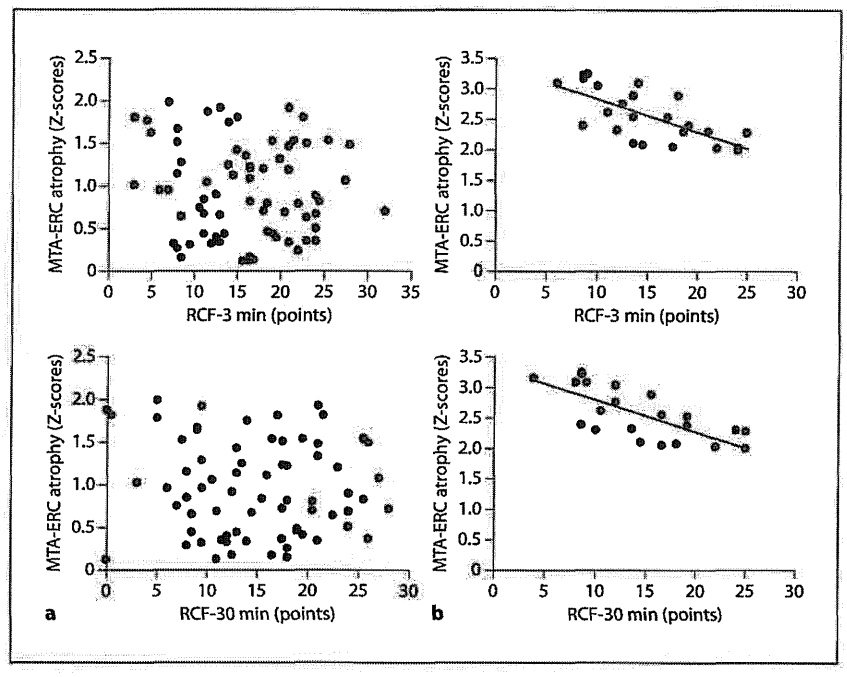

Fig. 3. Relationship between the Z-score of MTA-ERC and Rey complex figure retention test in mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and RCF-3 min and the lower panel shows scatter plots between MTA-ERC atrophy and RCF-30 min. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group.

dence that these brain regions are substantially affected by disease in the early stages of AD [34, 35], in accord with the finding that memory impairment is the earliest symptom of disease in most AD patients. The ERC is part of a critical pathway in the neural system underlying memory. Zola-Morgan et al. [36] reported that this area receives afferents from widespread association and limbic areas, projects to the dentate gyrus of the hippocampal formation, receives afferents from the hippocampus, and sends afferents back to association neocortex. An epidemiological study reported that ERC atrophy was greater than hippocampal atrophy in patients suffering from MCI [35]. However, the two measures were found not to differ in AD, suggesting that the ERC atrophies before the hippocampus in incipient AD [37]. An autopsy study of early AD patients reported neurofibrillary tangles in the ERC before evidence of hippocampal involvement [35]. Thus, volumetric MRI analysis of the MTA included ERC may be a sensitive predictor to identify AD conversion and decline of neuropsychological performances in MCI elderly adults.

In the current study, 25% of elderly adults with MCI exhibited severe atrophy in the MTA-ERC. The VSRAD analysis revealed that Z-scores indicating probable AD and amnestic MCI patients averaged 1.94 ± 1.24 (ranging from 0 to 4.69) [22]. Subjects exhibiting MTA-ERC atrophy as well as probable AD were included in the present MCI study. Numerous imaging studies have reported a correlation between increasing age and decreasing brain volume [38–42]. This decline in brain volume may be due to a non-linear acceleration in rates of atrophy after 70 years of age [43]. In the current study, 72 subjects (75%) were 70 years and over. Thus, the brain volume of our sample may have been affected by advancing age. In fact, we found significant relationships between age and MTA-ERC atrophy in MCI elderly adults. Similar findings were revealed in the relationship between MTA-ERC atrophy and educational level. Educational level was also a potential confounding factor of the prevalence and risk of dementia [44–46]. Educational level is thought to construct cognitive reserve, which modifies the relationship between brain atrophy and cognitive decline [47].

In the cognitive tests, WMS-R, LM I, DSC, and SCWT-IL showed significant correlations with MTA-ERC atrophy in univariate regression analysis. However, a multivariate regression model that included age and educational level revealed that MTA-ERC atrophy, i.e. high Z-score of VSRAD, was related only to SCWT-IL score in all subjects. Functional neuroimaging studies during executive tasks suggest that dorsolateral prefrontal cortex is responsible for maintenance of task demands and preparatory deployment of attention, and anterior cingulate

cortex is responsible for monitoring performance in order to detect cognitive and behavioral conditions with potential negative outcomes, and triggering dorsolateral prefrontal cortex to increase attention or change behavior [48–52]. A volumetric MRI study showed that there was an association between left hemisphere dorsolateral prefrontal cortex and anterior cingulate cortex atrophy and poorer attentional control accuracy. In the right hemisphere, atrophy of the temporal-parietal junction and ventrolateral and dorsolateral prefrontal cortices were associated with slower response times during attentional control on accurate trials [53]. This evidence from neuroimaging studies suggests that an executive deficit was caused by brain disorders in widespread regions that included prefrontal cortex, parietal lobe, and cingulate cortex. Neuropathological studies have shown that axonal pathology is strongly associated with cognitive impairment [54], and MCI patients may have increased white matter diffusivity in frontal and temporal regions [55]. The disruption of neural networks between the anterior and posterior cerebral areas, known as disconnection syndrome, during the initial stage of AD and MCI causes executive dysfunction, including changes in inhibition control [56–58]. Atrophy of the MTA is correlated with the degree of dementia and also with the extent of temporoparietal hypometabolism; both results are assumed to reflect changes in cerebral connectivity, especially between the MTA and the neocortex [59–61]. AD patients, as well as older adults with MCI, have shown selective disruption of default network intrinsic connectivity, most prominently in connectivity between the precuneus/posterior cingulate and medial temporal lobe regions [58, 61–64]. In diffusion tensor imaging study, the cingulum fibers, which connect the posterior cingulate gyrus and the hippocampus, may be compromised in the early stage of AD [65]. In recent years, Grambaite et al. [66] reported that frontal and temporal white matter diffusivity changes in the posterior cingulate region as well as the anterior cingulate region in MCI patients who had attention and executive dysfunctions. Reciprocal connections between the dorsolateral frontal cortex and anterior cingulate cortex [67–70] are part of a frontolimbic network [71, 72]. In the present study, MCI subjects showed a relationship between Z-score of the VSRAD and cognitive tests, especially tests of executive function. This relationship may be affected by not only MTA-ERC atrophy but also disconnectivity among MTA, temporoparietal, anterior cingulate, and prefrontal regions.

In a sub-analysis dividing subjects into two groups, the mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and DSC and SCWT-IL. The multivariate analysis on the mild to moderate atrophy group did not sustain the statement that DSC and SCWT-IL performances may be a reliable indicator of MTA-ERC atrophy in MCI patients. Increasing age is related closely with decreasing brain volume [38–42]. In fact, age remains the only significant variable indicating that its relative weight is too high and deletes the association between Z-scores and DSC and SCWT-IL observed in univariate models. In contrast, MTA-ERC atrophy was related closely to RCF-3 min and RCF-30 min in the severe atrophy group. In the multivariate regression model, MTA-ERC was associated independently with visual memory adjusted for age, educational level, and other cognitive functions. For the right temporal lobe there is some evidence that damage specifically in temporomesial structures may be the cause of impairments in nonverbal memory functions. Patients with hippocampal damage showed preoperatively [73] and postoperatively [74] impaired visual memory performance, whereas patients without hippocampal damage exhibited no deficiencies in visual memory. In line with previous operative studies, our results from MCI elderly adults with severe atrophy suggest a special involvement of MTA in visual memory performance. However, the VSRAD system was developed to measure the total atrophy in the bilateral parahippocampal gyrus and ERC. Thus, the association between visual memory and right hippocampal volume reduction should be investigated in the future.

It should be noted that this study may have been limited by a restricted sample. In addition, we did not include an analysis of genetic factors. Because genetic and physical factors such as apolipoprotein E genotype [75] and head size [76] may impact on neurodegenerative disorders and brain volume, analyzing genetic factors may extend the current results. Fitness level may have also acted as a confounding factor. Many studies have reported that physical activity can reduce the likelihood of the development of cognitive decline over time [77, 78]. Higher levels of fitness related to increased physical activity have been associated with enhanced neuronal survival in response to brain insult [79, 80], increased vascularization [81], and elevation of growth factors in areas important for memory [82]. More detailed analysis adjusting for these confounding variables will be required to further elucidate the relationship between MTA-ERC atrophy and memory function.

Overall, the present findings revealed that MTA-ERC atrophy was associated with age, educational level, and executive function, whereas no significant relationship

was found between MTA-ERC atrophy and memory tests in elderly subjects with MCI. This included the adults who had mild to moderate atrophy in MTA-ERC. In contrast, there was a significant relationship between MTA-ERC atrophy and visual memory test scores in elderly adults with severe MTA-ERC atrophy. These results suggest that executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy. A decline of visual memory function suggested severe MTA-ERC atrophy in elderly adults with MCI. Future research needs to determine the relationships between cognitive functions and brain atrophy except MTA-ERC in elderly adults with MCI.

Take Home Message

(1) MTA-ERC atrophy was significantly related to age, educational level, and executive function in elderly subjects with MCI.

(2) The subjects with severe MTA-ERC atrophy showed significant relationships between MTA-ERC atrophy and a decline in visual memory score.

(3) Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and decline in the RCF test suggests severe MTA-ERC atrophy in elderly adults with MCI.

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