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Physical Exercise with Music Maintains Activities of Daily Living in Patients with Dementia: Mihama-Kiho Project Part 2[1]

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Abstract.
Background: Recent studies suggest that combined non-pharmacological interventions are more beneficial than single interventions for primary and secondary prevention of dementia. We previously reported enhanced effects of physical exercise with music (ExM) on cognitive function in normal elderly people compared to exercise alone.
Objective: To identify if ExM improves cognitive function and activities of daily livings (ADLs) in dementia patients over cognitive stimulation (CS).
Methods: We enrolled 85 patients with mild to moderate dementia. Forty-three subjects performed ExM developed by the Yamaha Music Foundation, and 42 subjects performed cognitive stimulation using portable game consoles and drills involving easy calculations, mazes, and mistake-searching in pictures. Interventions were performed once a week for 40 minutes. Before and after the six-month intervention, patients were assessed using neuropsychological batteries, and ADLs were assessed by patients' caregivers using the functional independence measure (FIM). Voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) was used to assess medial temporal lobe atrophy.
Results: Twenty-three subjects dropped out during the intervention. Thirty-one patients from each group were analyzed. Post-intervention, both groups showed significantly improved visuospatial function. Significant benefits were observed in psychomotor speed or memory in the ExM or CS groups, respectively. FIM scores, reflecting ADLs, and VSRAD scores were significantly preserved in the ExM group, but significantly worsened in the CS group.
Conclusions: ExM produced greater positive effects on cognitive function and ADLs in patients with mild to moderate dementia than CS, excluding memory. Optimal interventions for dementia will likely be achieved by combining ExM and CS.

Keywords: Activities of daily living, functional independence measure, neuropsychological assessments, physical exercise with music, psychomotor speed, Voxel-based specific regional analysis system for Alzheimer's disease

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INTRODUCTION

The number of people with dementia is rising rapidly along with increased longevity. Approximately 46.8 million people worldwide are estimated to be living with dementia, and 9.9 million new cases of dementia are diagnosed every year [1]. According to Alzheimer's Disease International [2], these numbers will nearly double every 20 years to an estimated 74.7 million in 2030, and 131.5 million in 2050, with a large number coming from Asia. Currently, there are no disease-modifying therapies against most dementia-related diseases, thus multifaceted efforts, including non-pharmacological intervention, are necessary to prevent the occurrence and progression of dementia. The positive effects of aerobic physical exercise on primary [3–10] and secondary [11–15] prevention of dementia have been well established.

Several studies have reported that a combination of physical exercise with cognitive training can enhance cognitive function more than could be achieved independently, in both cognitively normal subjects [16–18] and elderly subjects with age-related declines [19–21]. In our previous paper on non-pharmacological intervention in community-dwelling normal elderly people, we reported that musical accompaniment increased the positive effects of physical exercise on cognitive function [22]. Forty subjects performed physical exercise (once a week for an hour) with musical accompaniment and 40 subjects performed the same exercise without music; 39 subjects in the control group received no intervention. Before and after the year-long intervention, each patient was assessed using neuropsychological batteries. Results showed that physical exercise combined with music produced more positive effects on cognitive function in elderly people than exercise alone, especially in visuospatial function. We attributed this improvement to the multifaceted nature of combining physical exercise with music, which can act simultaneously as both cognitive and physical training.

In the present study, we investigated the effects of physical exercise with music on cognitive function in patients with dementia. Patients with mild to moderate dementia participated in sessions of either physical exercise with music or cognitive stimulation, once a week for six months. Cognitive stimulation tasks such as drills, portable games, and calculations are often used in clinical and welfare situation for patients with dementia. Before and after the intervention period, neuropsychological assessments and interviews pertaining to their activities of daily livings (ADLs) were carried out. We compared the changes in cognitive function and ADLs between the two groups, and showed the non-inferiority of physical exercise with music to cognitive stimulation task.

METHODS

Subjects

This study was conducted in the towns of Mihama and Kiho, which are situated at the southern end of the Kii peninsula in Japan. These towns suffer from depopulation and 37% of the population is over 65 years old (mean rate in Japan is 25%). It has been suggested that these towns represent the "super-aged" community that will exist throughout Japan in 20 years, therefore the prevention of dementia is an urgent problem of great importance. This study was carried out as one of the public welfare projects in these towns. The subjects were patients with mild to moderate dementia who utilized the nursing services of these towns such as a day care or a group home. Four public nursing-care facilities which were established by each town were selected by the public health nurses of these towns based on the following three conditions: i) sufficient number of care staff, ii) availability of a room for physical exercise that could accommodate twenty people, and iii) willingness to cooperate in a non-pharmacological intervention for dementia. The inclusion criteria for subjects were as follows: (a) having been already diagnosed as untreatable dementia by neurological specialists based on the diagnosis criteria of dementia in ICD-10 [23]; (b) a score from 16 to 26 on the Mini-Mental State Examination (MMSE); (c) stable physical and psychological condition; and (d) preserved hearing, visual acuity, and physical movement sufficient to enable participation in the intervention. Subjects were excluded if they met any of the following exclusion criteria: (a) the presence of chronic debilitating disease such as malignancy and infection; (b) the presence of severe cardiac, respiratory, and/or orthopedic disabilities which would prevent subjects from participating in the intervention; (c) the presence of paresis or coordination disturbance which would prevent subjects from participating in the intervention; and (d) having been diagnosed with treatable dementia (Fig. 1). We recruited 85 subjects, and the subjects were randomly classified into two groups based on the unit of the floor or ward in which they were patients: physical exercise with music group (ExM; $n = 43$;

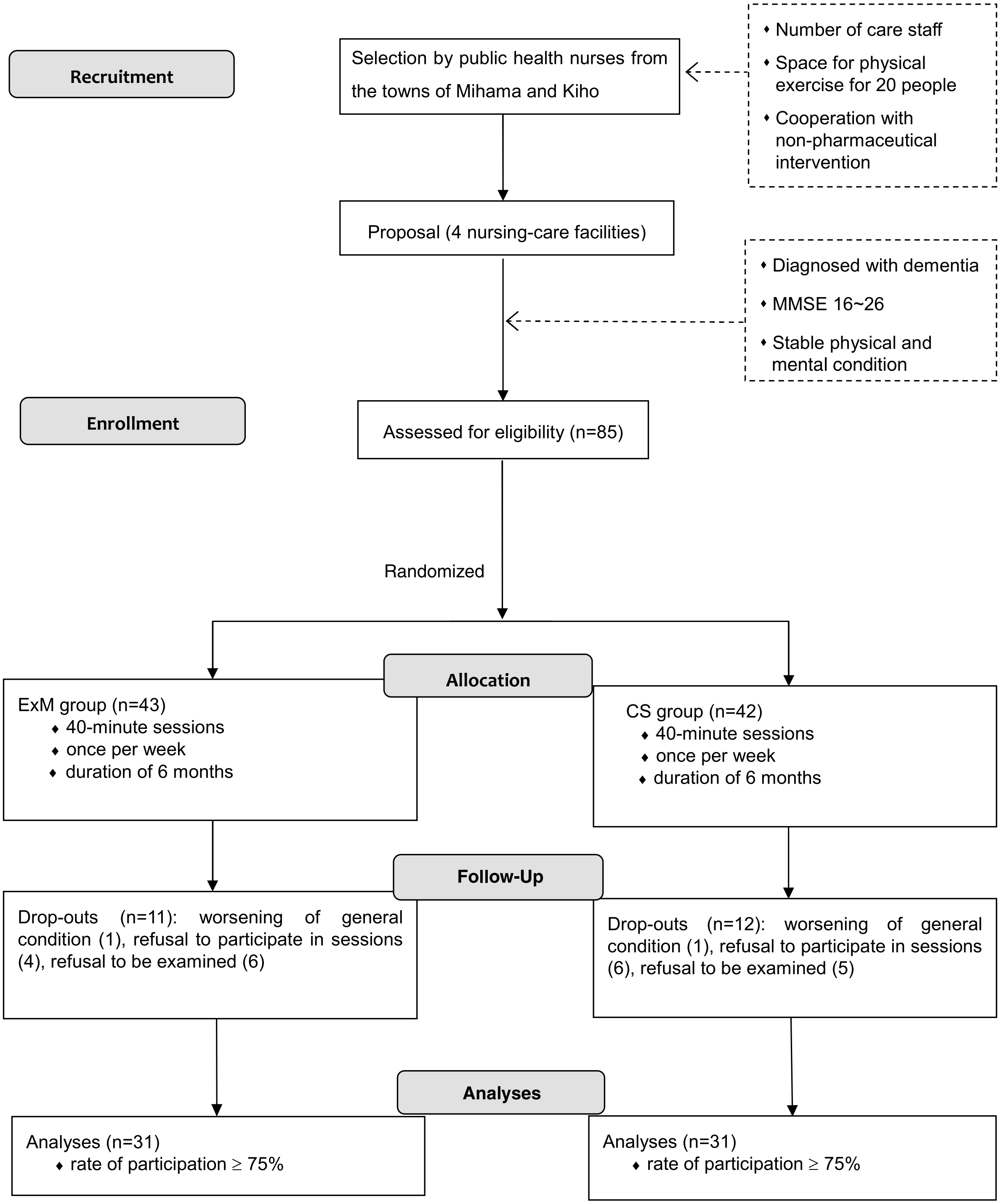

Fig. 1. Flow diagram of the ExM and CS groups.

mean ± sd 85.6 ± 7.6 years old; male 2, female 41) and cognitive stimulation group (CS; $n = 42$; mean ± sd 86.6 ± 4.2; male 2, female 40). Patients were not sequestered to a specific floor, ward, or room based on the types of diseases, severity of dementia, of presence and absence of BPSD. The baseline sub-score of Behave-AD [24] was significantly different only in the item of diurnal rhythm disturbances (ExM 0.29 ± 0.11; CS 0.00 ± 0.00, $p = 0.006$). We may say that the selection bias was not so large. The diagnoses were performed based on following criteria. The diagnoses for Alzheimer's disease were made according to the criteria established by the National Institute of Neurologic Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) [25]. The diagnoses of vascular dementia were made according to the criteria established by the National Institute of Neurologic Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [26]. Subjects in both groups participated in the intervention program for forty minutes once a week for six months. The time of forty minutes was chosen for the intervention sessions based on the following reasons: i) in the Japanese medical system, twenty minutes is regarded as one unit of intervention, and the medical expense is paid depending on the number of units a day during which the intervention was performed. In Japan, most of the rehabilitation and the intervention are performed for forty or sixty minutes a day. And ii) for patients with dementia, forty minutes was the maximum time during which they could maintain focus without fatigue. All of the subjects were medicated by anti-dementia drugs, mostly the donepezil hydrochloride, and pharmacological and non-pharmacological activities in nursing-care facilities were unchanged during the intervention period for six months. Before and after the intervention period, neuropsychological assessments, assessments of ADLs by caregivers, and brain MRI were performed. This study received approval from the Kinan Hospital Research Ethics Committee, and all patients provided written informed consent. This study was registered to UMIN-CTR (UMIN000017066) on 7 April 2015.

Physical exercise with music (ExM)

We performed physical exercise sessions for forty minutes once a week. The intervention period was six months, and the total number of exercise sessions was 24. The exercise program was developed by the Yamaha Music Foundation based on a program used in our previous study investigating the efficacy of physical exercise with music in cognitively normal elderly people [22]. Because the mean age of the subjects in the present study was more than ten years older than in the previous study of normal elderly people, and cognitive function in the subjects of the present study was impaired, the exercise program was performed in the sitting position and had a lighter physical and cognitive burden compared to the previous study [22]. The program consisted of muscle training for the upper and lower extremities, hand clapping to music, breath and voice training, and singing. The exercise trainers were professional musicians who also held private licenses as physical trainers with the Yamaha Music Foundation. These licenses are granted when referees of professional fitness examiners and sports medicine regard the applicant as being sufficiently skilled. The intensity of the exercise was gradually increased with each session.

Cognitive stimulation (CS)

Subjects interacted with the software called "Yawaraka-atama-juku (flexible thinking club)" developed by Nintendo Co., Ltd. using a portable game console (Nintendo DS LL), and drills consisting of easy calculations [27], mazes, and mistake-searching in pictures. We chose these items for the following reasons: (i) they are popular and frequently advertised in the mass media, and (ii) they are often used in clinical and welfare settings. Each session was forty minutes in length once a week, and the intervention period was six months. The total number of sessions was 24. Each session was performed by nursing-care facility staff including nurses, certified care workers, or psychiatric social workers. The difficulty of the tasks gradually increased with each session.

Neuropsychological and activities of daily living assessments

Before and after the six-month intervention period, the following neuropsychological assessments were administered. To quantify intellectual function, the MMSE and the Japanese Raven's Colored Progressive Matrices (RCPM) [28] were administered. RCPM measures not only the score but also the performance time which reflects the psychomotor speed of the subject. Memory was evaluated using logical memory I and II (LM-I/-II) of the Rivermead Behavioral Memory Test (RBMT) [29], which consists of immediate and delayed recall of a short story. The RBMT has four stories in which the difficulty and number of words and sentences are identical. A different story was used before and after the intervention period. The assessment of constructional ability was based on the method described by Strub & Black [30]. A three-dimensional cube was shown to the examinees and they were asked to draw it. The drawing was scored by assigning one of 4 possible grades (0: poor, 1: fair, 2: good, and 3: excellent). Frontal function was assessed by two types of tasks: word fluency (WF) and the Trail-Making Test A (TMT-A). TMT-B was not performed because it was too difficult for patients with moderate dementia. The WF test consisted of two domains: category and letters. For the categorical WF, subjects were asked to name as many animals as possible in one minute. For the letter WF, for each of 4 phonemes *ka, sa, ta*, and *te*, the subjects were asked to name objects which have that phoneme at the beginning of the word [31]. We used the average scores of these 4 phonemes for statistical analysis. It is generally accepted that the cognitive processing of categorical and letter WF is somewhat different, categorical WF being more reflective of memory function than letter WF. These neuropsychological assessments were administered before and after the six-month intervention period to both the ExM and CS groups.

For the assessment of ADLs, the functional independence measure (FIM) was used. The total possible FIM score was 126, and its assessment was divided into two main aspects (motor function: 91, and cognitive function: 35). The assessment of motor function included thirteen items such as the act of eating, dressing, evacuation, urination, and walking. Cognitive function was assessed by five items including understanding, expression, and memory. A higher score indicates better motor or cognitive function. We also evaluated the behavioral and psychological symptoms of dementia (BPSD) using the behavioral pathology in Alzheimer's disease (Behave-AD) [24]. A higher score on Behave-AD indicates more severe BPSD. Both the FIM and Behave-AD were evaluated by observations of the subjects' daily lives by caregivers.

Voxel-based specific regional analysis system for Alzheimer's disease (VSRAD)

The VSRAD was developed in 2003 [32]. It aims to semi-quantitatively show the degree of atrophy of the parahippocampal gyrus for the purpose of diagnosing Alzheimer's disease (AD), and is based on statistical parametric mapping (SPM, Wellcome Trust Center for Imaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Performing the VSRAD assessment was very easy and the analysis could be completed by a few clicks of a computer mouse. In general, it is considered that if a patient has a VSRAD value over 2, they might have AD, and if the value is under 1, the subject might be normal. It is important to note that the VSRAD is just one biomarker of AD, and a diagnosis of AD should be based on the overall results from neurological, neuropsychological, biological, and neuroimaging findings.

Statistical analysis

For statistical analyses, subjects who participated in more than 75% of the sessions (more than 18) were included. Statistical analyses were performed as follows: first, the difference in changes between the ExM and CS group over the six-month intervention period were analyzed. The Shapiro-Wilk test was used to test for normality. If the result was parametric, two sample-*t* test or Welch test was used according to the result of the test for homogeneity of variance (Levene test), and if non-parametric, the Mann-Whitney U test was used. Second, for intra-group analyses, the results of each test before and after the intervention were compared for each group. The Shapiro-Wilk test was used for the normality test; if the result was parametric, paired-*t* test was used, and if non-parametric, the Wilcoxon signed rank test was used. We regarded the result as significant if the p-value was under 0.05. All statistical analyses were performed using IBM SPSS Statistics 23 software.

RESULTS

Subject characteristics

During the six-month intervention period, eleven subjects in the ExM group and twelve subjects in CS group dropped out because of worsening general conditions, refusal to participate, and refusal to be examined (Fig. 1). Because the dropped-out patients were not assessed after the intervention period, we adopted the Per protocol (PP) analysis. As a result, both the ExM and CS groups included 31 subjects in the analyses [ExM: Alzheimer's disease (AD), 27 and vascular dementia (VaD), 4; CS: AD, 27 and VaD, 4). The difference in age was significant between patients that dropped out and those that completed the six-month study in the ExM and CS groups ($p = 0.017$; Table 1). The subjects used in the statistical analyses were older than the patients who had dropped out.

Table 1
Characteristics of statistically analyzed subjects and patients that dropped out

	Subjects ($n = 62$)		Dropped-out ($n = 23$)		p-value
	mean	±s.d.	mean	±s.d.	
Age	87.2	4.9	84.1	6.0	**0.017**
Education	7.7	1.8	8.1	2.1	0.45
MMSE_pre	20.5	3.5	20.5	3.0	0.98
FIM_pre	112.5	14.9	113.8	9.7	0.70
Behave-AD_pre	2.0	4.2	1.7	2.1	0.89

Behave-AD, behavioral pathology in Alzheimer's disease; FIM, functional independence measure; MMSE, Mini-Mental State Examination; n, number; s.d., standard deviation. The bold number indicates statistical significance.

Table 2
Baseline characteristics of the ExM and CS groups

	ExM ($n = 31$)		CS ($n = 31$)		p-value
	mean	±s.d.	mean	±s.d.	
Age	87.0	5.40	87.4	4.4	0.719
Education	7.2	1.9	8.3	1.5	0.134
MMSE	20.1	3.17	20.9	3.72	0.372
RCPM					
score	18.6	6.7	17.2	6.1	0.387
time	853	775	617	322	0.352
LM-I	3.9	2.3	4.0	3.1	0.907
LM-II	1.9	2.6	2.5	3.0	0.309
Cube	0.52	0.51	0.87	0.50	**0.009**
WF_animal	9.0	2.60	9.2	2.6	0.810
WF_letters	5.2	1.90	4.8	2.1	0.328
TMT-A	374	173	349	180	0.617
FIM					
total	113	13.6	112	16.3	0.805
motor	83.1	11.30	80.1	13.5	0.357
cognition	30.6	4.70	31.8	3.69	0.284
Behave-AD	1.8	2.1	0.74	1.3	0.079
VSRAD	1.65	1.22	1.45	1.11	0.56

Behave-AD, behavioral pathology in Alzheimer's disease; CS, cognitive stimulation; ExM, exercise with music; FIM, functional independence measure; LM, logical memory; MMSE, Mini-Mental State Examination; n, number; RCPM, Raven's Colored Progressive Matrices; s.d., standard deviation; TMT, Trail-Making Test; VSRAD, Voxel-based Specific Regional analysis system for Alzheimer's Disease; WF, word fluency. Bold numbers indicate statistical significance.

Table 3
Comparison of the differences after the six-month intervention between the ExM and CS groups

	ExM ($n = 31$)		CS ($n = 31$)		p-value
	mean	±sd	mean	±sd	
MMSE					
total	0.71	3.5	0.61	3.60	0.916
orientation	–0.13	1.7	0.10	2.1	0.638
memory	0.23	1.2	0	0.93	0.462
RCPM					
score	–0.52	5.0	0.90	4.4	0.242
A	–0.35	2.6	0.58	2.5	0.155
AB	–0.23	2.1	0.16	2.2	0.477
B	–0.42	2.7	0.03	1.6	0.424
time	–237	662	–68.8	324.0	0.360
A	–42	200	–8.2	89.3	0.965
AB	–79	181	–33	114	0.387
B	–116	346	–13.6	66.2	0.110
LM-I	0.60	2.8	1.1	2.8	0.502
LM-II	0.72	3.4	0.50	3.2	0.825
Cube					
score	1.0	0.61	0.55	0.77	**0.009**
WF					
animal	–0.55	2.6	0.35	2.3	0.239
letter	0.10	2.1	–0.06	2.4	0.778
TMT-A	–53	104.0	3.6	104.0	*0.070*
FIM					
total	0.06	1.4	–2.03	5.3	*0.066*
motor	0.03	0.95	–1.7	5.0	0.140
cognition	0.03	0.80	–0.55	1.4	0.141
Behave-AD	0.50	3.80	0.30	2.42	0.746
VSRAD	–0.18	0.056	0.24	0.077	**0.008**

Behave-AD, behavioral pathology in Alzheimer's disease; CS, cognitive stimulation; ExM, exercise with music; FIM, functional independence measure; LM, logical memory; MMSE, Mini-Mental State Examination; n, number; RCPM, Raven's Colored Progressive Matrices; s.d., standard deviation; TMT, Trail-Making Test; VSRAD, Voxel-based Specific Regional analysis system for Alzheimer's Disease; WF, word fluency. Bold or italic numbers indicate statistical significance or trend toward improvement, respectively.

Differences in other characteristics, including educational history, MMSE score, FIM, and Behave-AD, were statistically insignificant between the patient groups (Table 1).

The baseline characteristics of the ExM and CS groups are shown in Table 2. All differences except for cube copying were insignificant. The baseline results for cube copying were significantly worse in the ExM group than the CS group, suggesting that visuospatial function was worse in the ExM group.

Neuropsychological assessments

Results of the differences in neuropsychological assessments before and after the six-month intervention are shown in Table 3. Improvement in cube copying was significantly greater in the ExM than the CS group ($p = 0.009$). When compared to the CS group, the results of TMT-A and the total FIM score of the ExM group showed an improving trend (TMT-A, $p = 0.070$; FIM $p = 0.066$). These results suggest that physical exercise with music had greater effects than cognitive stimulation on visuospatial function and activities of daily living.

The intra-group analyses before and after the intervention revealed some positive effects of the interventions in both the ExM and CS groups (Table 4, Fig. 2). Because some patients could not perform several tests, several data shown in Table 4 were a little different from those in Table 2. Significant improvement in cube copying, which reflects visuospatial function, was observed in both the ExM ($p < 0.001$) and CS groups ($p = 0.001$). The performance time on the RCPM, which indicates psychomotor speed, or the LM-I score, which reflects immediate recall, were significantly improved in the ExM group ($p = 0.021$) or CS group ($p = 0.039$), respectively. It is noteworthy that, although the total FIM score significantly decreased in the CS group, the score was unchanged in the ExM group. This suggests that ADLs in the ExM group were preserved while they were worsened in the CS group. The change in VSRAD score after the six-month intervention was significantly different between the two groups ($p = 0.008$; Table 3). The ExM group score decreased, suggesting an increased volume of the medial temporal lobes. In contrast, the score of the CS group increased suggesting a progression of medial temporal lobe atrophy (Table 4).

The results can be summarized as follows: (i) both the ExM and CS groups showed significant improvement in visuospatial function, but to a significantly greater degree in the former group; (ii) psychomotor speed was improved in the ExM group; (iii) memory was improved in the CS group; (iv) ADLs in the ExM group were preserved during the six months, but significantly worsened in the CS group; and (v) atrophy of the medial temporal lobes only progressed in the CS group.

DISCUSSION

Visuospatial function was improved in both the ExM and CS groups, but to a greater degree in the former group. The efficacy of ExM on visuospatial function had been demonstrated in our previous study which targeted normal elderly people [22]. We proposed the following mechanism for improvement due to ExM. It is well known that the parietal lobes participate in visuospatial and somatosensory function, including body image. Moreover, several activation [33–38] and case studies [39, 40] have shown that the parietal lobes likely participate in music perception in the brain. During the physical exercise regimen, the subjects monitored the movement of their bodies and perceived the position, posture, and acceleration of motion of their extremities. Therefore, stimulation of the parietal lobes by music and the somatosensory inputs from physical exercise could cause improvements in visuospatial function. In the CS group, several tasks involving figures were performed, these included mazes and mistake-searching in pictures. It has been suggested that the ability to perform calculations is also managed by the parietal lobes [41]. The improvement in visuospatial function in the CS group might be caused by the six-month cognitive training using figures and calculations. We can propose other mechanisms which possibly brought the efficacy in ExM and CS group, for example enhanced function of the prefrontal region or cerebello-thalamo-prefrontal circuit induced by exogenous stimulation such as physical exercise, music, or playing computer games. It needs further consideration about the mechanism of mental and physical processing which brought the efficacy of ExM and CS group.

The efficacy of ExM on psychomotor speed was also congruent with our previous report [22]. Subjects listened to music, perceived the rhythm and the tempo of that music, judged whether their body movements and music were synchronous or not, and controlled their movements accordingly. The important factor is that these processes were performed simultaneously and continuously. This suggests that ExM consists of dual or triple tasks, and, by doing such a complex task simultaneously, the psychomotor speed of the ExM group was improved.

The software used with the CS group in the present study consisted of various cognitive tasks such as memory, calculations, figures, and language. In the memory task, the subject was required to memorize the object and, after some retention time, he or she had to select it among three or four alternatives. The memory improvement observed in the CS group might be related to playing the portable games which included memory tasks. While the exercise and music might enhance attention and feeling of happiness/well-being, the mental work might result in mental fatigue that could cause loss of interest. The result of TMT-A which related to the attention was significantly improved only in the ExM group. This finding might reflect the difference of psychological burden during the intervention of ExM and CS.

We should pay great attention to the difference in FIM changes over the intervention period. The FIM

Table 4
Results of intragroup analyses before and after the intervention in the ExM and CS groups

	Exercise with music (ExM)							Cognitive stimulation (CS)						
	before			after			*p*-value	before			after			*p*-value
	N	mean	±sd	N	mean	±sd		N	mean	±sd	N	mean	±sd	
MMSE	31			31				31			31			
total		20.1	3.2		20.8	4.40	0.276		20.9	3.72		21.5	5.50	0.253
orientation		7.1	2.0		7.0	2.5	0.778		7.1	1.8		7.2	2.4	0.639
memory		1.2	1.2		1.5	1.2	0.342		1.5	1.1		1.5	1.2	0.922
RCPM	31			31				31			31			
score		18.6	6.7		18.1	6.9	0.573		17.2	6.10		18.1	5.94	0.260
A		7.6	2.7		7.2	2.9	0.458		6.7	2.8		7.3	2.7	0.204
AB		6.5	2.6		6.2	2.8	0.550		5.9	2.3		6.0	2.6	0.683
B		5.1	2.6		4.7	2.3	0.388		4.7	2.1		4.7	1.8	0.908
RCPM	31			31				31			31			
time		853	775		616	337	**0.021**		617	322		548	281	0.134
A		250	244		208	129	0.393		183	69.8		175	106	0.222
AB		286	215		207	138	0.386		217	120		185	105	0.171
B		342	362		226	171	0.462		197	85.1		184	86.6	0.202
LM-I	31	4.0	2.3	30	4.6	3.2	0.247	31	4.0	3.1	31	5.1	4.1	**0.039**
LM-II	31	1.8	2.6	29	2.6	3.2	0.146	31	2.5	3.0	31	3.0	4.1	0.250
Cube	31			31				31			31			
score		0.52	0.51		1.6	0.72	**<0.001**		0.87	0.50		1.4	0.85	**0.001**
WF	31			31				31			31			
animal		9.0	2.6		8.5	2.6	0.246		9.2	2.6		9.6	3.6	0.401
letter		5.2	1.9		5.3	2.6	0.951		4.8	2.1		4.7	3.0	0.874
TMT-A	27	375	180	26	322	150	**0.014**	29	312	139	22	316	162	0.987
FIM	31			31				31			31			
total		113	13.6		113	13.8	0.385		112	16.3		110	17.6	**0.048**
motor		83.1	11.3		83.1	11.5	0.595		80.1	13.5		78.4	14.6	0.071
cognition		30.6	4.70		30.7	4.64	0.942		31.8	3.69		31.2	3.92	**0.027**
Behave-AD		1.81	2.11		2.31	3.22	0.623		0.74	1.29		1.04	2.48	0.856
VSRAD		1.65	1.22		1.63	1.25	0.96		1.45	1.11		1.69	1.24	0.49

Behave-AD, behavioral pathology in Alzheimer's disease; FIM, functional independence measure; LM, logical memory; MMSE, Mini-Mental State Examination; N, number; RCPM, Raven's Colored Progressive Matrices; s.d., standard deviation; TMT, Trail-Making Test; VSRAD, Voxel-based specific regional analysis system for Alzheimer's disease; WF, word fluency. Bold numbers indicate statistical significance. Bold numbers with underlines indicate that the results had significantly worsened.

score in the CS group significantly decreased during the six-month period. This implies that, regardless of the improvement in some neuropsychological test items, performance in the subjects' daily lives may still decline. However, in the ExM group, the FIM scores were almost unchanged before and after the intervention period. This might indicate that ExM not only influences the results of neuropsychological tests but may also be appreciated by caregivers in the patients' daily lives. Thus, we can reasonably conclude that ExM has greater and more reliable beneficial effects on patients with dementia.

It must be noted that changes in the VSRAD score were significantly different between the ExM and CS groups. Atrophy of the medial temporal lobes was improved in the ExM group, whereas it worsened in the CS group. This result is congruent with a previous report which showed the positive effects of physical exercise on the volume of the medial temporal lobes as described below [9]. In a randomized controlled trial of community-dwelling older adults, aerobic exercise training for 6 months increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1 to 2 years [9]. In contrast, hippocampal volume declined in the control group which only performed stretching exercise, although the volumetric change in the caudate nucleus and thalamus was insignificant between the aerobic exercise and control stretching groups. These studies demonstrate that aerobic physical activity can have protective and regenerative effects against the progression of medial temporal lobe atrophy.

This current study has several limitations that should be noted. First, the number of subjects was limited, and the intervention period was only six months. However, many published studies on non-pharmacological interventions included similar or fewer numbers of subjects [9, 42, 43] and shorter intervention periods [10, 44, 45]. Further study with a larger number of participants and a longer

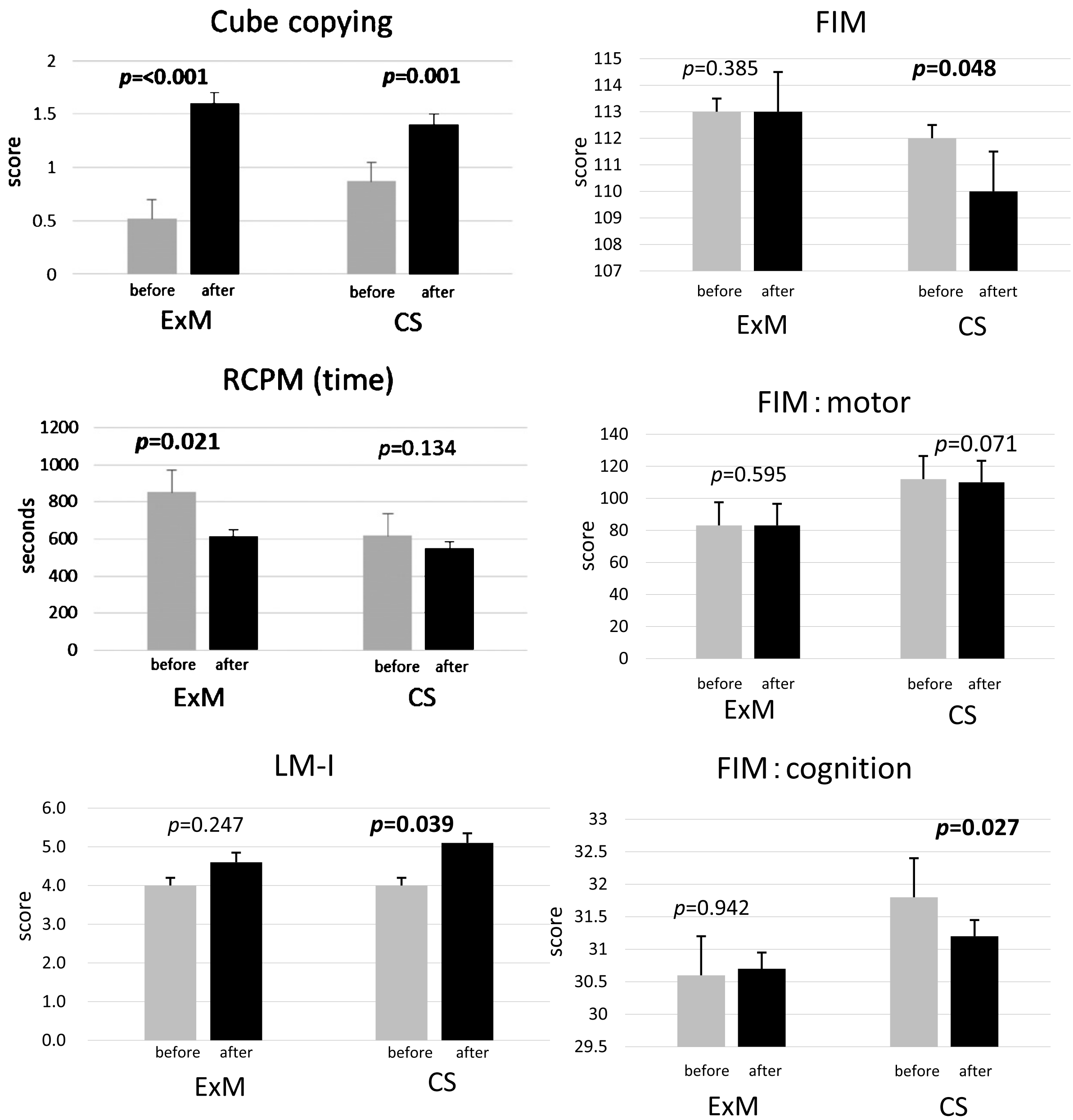

Fig. 2. Main findings of the intra-group analyses of the ExM and CS groups. Grey and black boxes show the results before and after the six-month intervention period, respectively. Bold letters indicate that the results were significant. In both groups, cube copying, which reflects visuospatial function, was significantly improved. The time to complete the RCPM was significantly improved only in the ExM group. The CS group showed significant improvement in LM-I. It is noteworthy that the total FIM score significantly decreased in the CS group, whereas the score was unchanged in the ExM group. This indicates that the activities of daily living in the CS group worsened, while they were preserved in the ExM group. CS, cognitive stimulation; ExM, exercise with music; FIM, functional independence measure; LM, logical memory; RCPM, Raven's Colored Progressive Matrices.

intervention period might show other significant positive effects. Second, there might be selection bias in the subjects, because the participating nursing-care facilities were selected based on their capability and willingness to cooperate with the intervention. It remains to be determined if the same results can be achieved using the same intervention at other institutes with different backgrounds. Third, we cannot completely eliminate the influence of learning effects on the results of the neuropsychological assessments.

However, in the LM test, we used different stories with the exact same number of words, sentences, and level of difficulty before and after the intervention. In the field of neuropsychology, there is general agreement that the learning effect disappears after an interval of six months, even in cognitively normal subjects. The present study involved patients with dementia, and the results showed a significant difference between the ExM and CS groups which were assessed during the same interval. Thus, it is not likely that learning effects would affect the conclusions of the study. Fourth, we cannot strictly discriminate the effect of ExM group was caused by physical exercise or the music accompaniment. Our previous study revealed that physical exercise with music accompaniment had produced more positive effect on cognitive function in normal elderly people, compared with that without music. This result suggested that the effectiveness of ExM group in the present study might be also brought by the combination of physical exercise and music, though, in order to prove that, the third group of physical exercise without music was necessary. Lastly, we may say that not only the intervention but also the change of daily activities on non-intervention days might related to the improvement. Other physical and mental activities during the intervention period were unchanged. It is possible that the virtuous cycle induced by ExM also related to the effectiveness of the ExM group. But, in CS group, the memory was improved though the FIM score was significantly decreased. We cannot completely discriminate the effect brought by the intervention itself or the change of daily activities. It seems reasonable to suppose that the intervention might influence the physical and mental activities of daily livings of the subjects. It is clear that further studies are needed to clarify the effects and mechanisms of action of combining multiple intervention strategies for the improvement of cognitive function in patients with severe dementia.

Summary

We performed two kinds of interventions, physical exercise with music and cognitive stimulation, in patients with mild to moderate dementia. The intervention was performed once a week for six months; before and after the intervention period, changes in cognitive function and ADLs were analyzed. In the ExM and CS groups, visuospatial function was significantly improved. The ExM and CS groups showed significant improvement in psychomotor speed and memory, respectively. While ADLs significantly worsened in the CS group, those of the ExM group were preserved. We hypothesize that ExM could help prevent age-related declines in elderly patients with dementia, and this effect might be enhanced by the combination of two different strategies which act simultaneously on both cognitive and physical exercise training.

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