Effect of Cognitive and Aerobic Training Intervention on Older Adults with Mild or No Cognitive Impairment: A Derivative Study of the Nakajima Project

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Key Words
Community-based study · Dementia · Cognitive rehabilitation · Aerobic exercise · Non-pharmacological therapies · Reasoning · Memory performance/appraisal

Abstract
Background: An increasing elderly population in Japan requires effective cognitive intervention programs for dementia. This study demonstrates the effectiveness of such programs for older adults. Methods: The participants were local community-dwelling non-demented older adults and adults with mild cognitive impairment who underwent executive function and group aerobic training. In addition, a non-intervention group participated in activity sessions involving handicraft, Skutt ball matches, and cooking. The four criteria for assessment were cognitive function, instrumental activities of daily living, human relationships, and physical function. Results: The participants in both intervention groups showed a significant improvement in their memory function compared with the non-intervention group. Conclusion: Early rehabilitation intervention using executive function and aerobic training programs may improve memory.

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Introduction

A rise in healthcare expenditure especially because of a de facto aging society has recently become a major cause of concern in Japan and other industrialized countries. The expenditure encompasses, among other factors, the yearly increase in care for older adults with dementia. Consequently, interventions to delay the onset and progression of dementia have attracted the attention of healthcare professionals who are attempting to develop suitable methods for their application in the treatment of the condition. Regarding prevention of onset and progression of dementia, interventions can be approached from two aspects: firstly, selective prevention, targeting persons ‘at risk’, and secondly, universal prevention, targeting persons without dementia. Older adults with mild cognitive impairment (MCI) are ten times more likely to develop dementia compared to healthy older adults [1]. Selective prevention aims at delaying the onset of dementia by means of aggressive intervention in ‘at risk’ individuals who show early signs of MCI.

There have been a few successful cognitive interventions carried out in persons with MCI: cognitive and social interventions, such as reality orientation and reminiscence, have resulted in an immediate improvement of cognitive function, and continuous improvement has been noted 9 months later [2]; improvement in the participants’ memory was achieved on termination of mnemonic training and was seen to be maintained at 6-month follow-up [3]; and the intervention of nutrition counseling, cognitive function, and physical training exhibited an immediate improvement in the participants’ cognitive function [4]. These interventions proved to be successful to a certain degree in their effect on MCI. In addition, a study on cognitive rehabilitation was carried out by Sugano et al. [5], which involved 5 participants (3 women and 2 men), 2 of whom had MCI and 3 Alzheimer’s disease (AD). The intervention administered was a 1-hour executive function and mnemonic training program once per week for 8 weeks. As a result, the participants with MCI showed an overall improvement in their cognitive function, which was maintained at 6-month follow-up. This finding may indicate that early cognitive intervention can be effective for individuals with MCI.

Universal prevention has also been implemented by regimes, such as ‘breath-of-life’, ‘purpose’, and ‘task execution’. However, there have been few studies utilizing these regimes due to the difficulty in measuring the effects because of difficulties in maintaining the consistency of the intervention and procuring long-term participants. Also, it is not productive to continue universal prevention if the set task is inappropriate to the participants’ ability. According to a meta-analysis by Colcombe et al. [6] of 18 studies carried out between 1996 and 2001, aerobic training was found to be effective for improvement of cognitive function. However, a combination of aerobic and strength training was found to be more effective than aerobic training alone, and executive function tasks were most effective.

In a double-blind trial involving 60-year-old healthy individuals, Mahncke et al. [7] implemented a 60 min/day task execution regime 5 times a week for 8–10 weeks with the use of computers. The comparison between the intervention, placebo, and non-intervention groups yielded a significant improvement in the training group not only in the targeted cognitive function, but also in memory, which was significantly maintained at 3-month follow-up. According to Mahncke et al. [7], these results suggested that AD could possibly be prevented. However, Mahncke et al. [7] also stated that, with regard to the study design, it was not possible to use a true placebo control for a behavioral training program because a single active ingredient cannot, in general, be removed from the experimental condition. Furthermore, an improvement in memory performance/appraisals was only possible when a targeted memory was trained. However, executive function training was found to be superior because improvement could not only be achieved in the trained executive functions, but also in memory performance and appraisals [8]. Mahncke et al. [7] have stated that a brain plasticity-
based training program targeting degraded sensory processing and the down-regulation of neuromodulatory control nuclei may produce stronger, more sustained and more generalized improvement in cognitive function. However, opinions on this subject remain divided due to insufficient clinical evidence.

The purpose of our study was to examine the efficacy of cognitive function and physical function programs for the elderly with and without MCI.

**Methods**

This study was carried out in collaboration with the Nakajima Project by the Department of Neurology and Neurobiology of Aging, Kanazawa University, Graduate School of Medical Science, Japan. The project was concerned with the early detection of dementia and the effectiveness of intervention for dementia in the town of Nakajima in the Nanao district of Ishikawa Prefecture, Japan. The participants’ flowchart for the trial is shown in figure 1.

**Participants**

From 2006 to 2007, 947 older adults underwent a mass-screening program for brain function in the Nanao district. This resulted in 806 individuals being selected as potential candidates for a trial that was to be carried out in 2007. On closer examination, candidates who showed abnormal findings, such as the presence of somatic disorders, brain disease or dementia, were eliminated from the program. The tests performed for the more detailed examination were the following: past and present medical history taking, blood testing, Mini-Mental State Examination (MMSE <25), and administration of a Revised Version of Hasega-
wa’s Dementia Scale (HDS-R <23) [9, 10]. Of the 806 individuals who were selected as possible participants, only 67 (45 women and 22 men) signed a written informed consent to participate in the trial. Their mean ± SD age was 74.1 ± 5.8 years (range 64–87) with a mean ± SD of 11.0 ± 7.5 years of education. These participants were randomly assigned to either the cognitive function program (18 women and 14 men) or physical function program (27 women and 8 men). Eleven women and 9 men out of the 806 individuals who decided not to participate in the intervention program agreed to be assessed for their cognitive and physical functions and also to participate in the non-intervention group. Their mean ± SD age was 71.8 ± 2.3 years (range 65–77) with a mean ± SD of 9.7 ± 2.5 years of education. This non-intervention group participated in activity sessions involving handicraft, Skutt ball matches (a modified form of putting golf invented in Japan), and cooking.

**Procedures**

The first four authors of this study carried out the various forms of evaluation and executed the two programs for this trial. Pre-intervention assessment was carried out within a 3-week period prior to the commencement of the program, and post-intervention assessment within 2 weeks of completion of the program. The 4 criteria for assessment were cognitive function, instrumental activities of daily living (IADL), social and human relationships, and physical function.

The participants’ cognitive function was assessed by the 5 cognitive tests (5-Cog). This is a set of tests developed by the Tokyo Metropolitan Institute of Gerontology, Japan, the criteria of which include the presence of subjective gradual cognitive decline (over a period of at least 6 months) and objective evidence of abnormal performance in any principal domain of cognition, i.e., memory and learning, attention and concentration, reasoning, verbal fluency, or visuospatial functioning [11, 12]. The 5-Cog was proposed by the International Psychogeriatric Association in 1993 and designed to meet one of the diagnostic criteria stated above for the screening of aging-associated cognitive decline (AACD) that is a precursor to dementia. Furthermore, the 5-Cog has the advantage of being easy to administer for mass examinations. The results from the 5-Cog were graded into 3 levels by means of adjusted standard deviation scores for the participants’ age, gender, and years of education. These results determined whether or not the examinee had dementia or a precursor to it. Specifically, the adjusted standard deviation scores for each task were ranked as follows: <35 as rank 1, from 35 to 40 as rank 2, and >40 as rank 3, respectively. The total rank score was calculated by the sum of the rank scores for each of the 5 cognitive domains with the exception of the one for the motor function tasks for the hands. A total rank score of 5–10 was defined as ‘probable dementia’, 11–14 as ‘probable AACD’, and 15 as ‘normal’.

The assessment tasks for the 5-Cog for the diagnosis of AACD are composed of 5 domains: memory/learning, attention, verbal fluency, visuospatial function, and reasoning. MCI in this study was defined according to Petersen et al. [1]: (1) memory complaint; (2) normal activities of daily living; (3) normal general cognitive function; (4) abnormal memory for age, and (5) not demented. Also, the criteria for assessing cognitive decline in this study were the same as those used by Petersen [13] who classified them into amnestic MCI, multiple-domain MCI and single non-memory domain MCI. Therefore, in this paper, AACD was defined by the 5-Cog as MCI. The participants’ IADL was measured using the IADL scale that corresponds to the 5-Cog. The Lubben Social Network Scale (LSNS) [14] was used to measure the participants’ social and human relationships revolving around older adults. The participants’ physical function was assessed by the use of the Physical Fitness Test for the Elderly [15] that has been extensively used for the assessment of older adults’ physical function [16]. The test battery for persons aged 65–79 years includes grip strength, sit-ups, sit and reach, one-leg balance with eyes open, a 10-meter obstacle walk, and a 6-min walk. Each item
was tested according to the implementation guidance manual, and the results were classified into 10 levels. The scores were summed for each classified item, determining the total score as a comprehensive evaluation that was ultimately used to divide the participants’ physical function into 5 categories (A, B, C, D, and E).

The cognitive function and physical function programs were implemented as a means of intervention in order to assess their effectiveness on dementia. The purpose of these programs was explained to all participants at the first session.

In the cognitive function program, emphasis was placed on improving executive function, although other cognitive functions, such as episodic memory and alternating attention, are also likely to deteriorate in individuals with a precursor to dementia. After the first session, the participants in the cognitive function program were divided into groups of 5–6 and, from the 2nd to 6th sessions, they drew up a travel plan. At the 7th session, they conducted a coach tour according to their travel plan and, at the 8th session, they revised this travel plan for the coach tour.

With regard to the physical function program, group aerobic training was implemented because this has been demonstrated to be effective for improving cognitive function in a number of previous studies. The following items were also implemented from the second to final (8th) session: (1) measurement of blood pressure and confirmation of the participants’ subjective feeling concerning their physical condition during the current and previous session(s); (2) warm-up exercises lasting 10–20 min, which included one muscle strengthening exercise for the lower limbs and one exercise selected from the following three: making a pose using the whole body, exercises using a ball, or selected rhythmic movements, all of which were taken from the Television Program *Exercise for Everyone* run by the Japan Broadcasting Corporation; (3) 10-min walking synchronized with music at the initial session, increasing to 15 min from the 7th to final sessions depending on the participants’ physical capability for daily activities, and (4) calisthenics accompanied with slow breathing and stretching of all limbs and the trunk for the purpose of cool down. All exercises were performed within the participants’ aerobic capacity, and each session lasted 25–45 min. These exercises were considered ‘moderate’ in view of absolute exercise intensity for the elderly [17], which is equivalent to 3.5 METs for the warm-up, 3.0– 3.3 METs for walking, and 3.0 METs for calisthenics according to the Research Committee on Exercise and Physical Activity Guidelines by the Ministry of Health, Labour and Welfare of Japan, 2006 [18].

Both the cognitive function and physical function programs were carried out once per week, and the participants spent approximately 1 h at each session. The period of implementation for the trial was approximately 2 months or 8 sessions.

**Statistics**

The pre- and post-trial scores were compared using the Student t test for the 5-Cog testing and Physical Fitness Test for the Elderly, and the Wilcoxon test for IADL and LSNS. The statistical outcome for cognitive function was further tested by a multiple comparison of Bonferroni. An α level of 0.05 was selected for statistical significance in this study. The computer software used for the trial was the Statistical Package for Social Sciences version 16.0J (SPSS Japan Inc.).

**Ethics**

The medical ethics review board of Kanazawa University approved this study.
Results

Rate of Participation and Characteristics of the Participants

Of the 67 participants who had decided to participate in the intervention programs, 21 did not attend any session, which led to their elimination from the analysis. The number of those who actually participated in the trial was 46, with an attendance rate of 79% for the cognitive function program and 66% for the physical function program.

The final assessment was carried out in only 31 participants who had attended the intervention programs more than once and who had undergone both the initial and final assessments (table 1). Among the 3 groups in the trial, there was no statistically significant difference in the age and years of education of the participants.

The Scores for the Cognitive Function, Physical Function, and Non-Intervention Programs

Figure 2 presents the comparison of the pre-/post-trial total rank scores for the 31 participants (19 women and 12 men) in the two intervention groups and the 13 participants (7 women and 6 men) in the non-intervention group. Among the participants of the cognitive function program, 23% (3/13) of ‘normal’ participants deteriorated to ‘probable Aacd’ on
Among the participants of the physical function program, all ‘normal’ participants maintained the same status, 29% (2/7) of ‘probable AACD’ participants improved to ‘normal’, and 100% (1/1) of ‘probable dementia’ participants improved to ‘probable AACD’. Among the participants in the non-intervention group, 17% (1/6) of ‘normal’ participants deteriorated to ‘probable AACD’, and 17% (1/6) of ‘probable AACD’ participants deteriorated to ‘probable dementia’. However, 50% (3/6) of ‘probable AACD’ participants improved to ‘normal’, and 100% (1/1) of ‘probable dementia’ participants improved to ‘probable AACD’.

Table 2 presents the pre-/post-trial raw scores for the 5-Cog tasks in the two intervention groups and the non-intervention group. For the participants in the cognitive function program, the scores for the cued recall (memory) tasks significantly increased from 13.4 to 17.1. Furthermore, in the physical function program, the scores for the cued recall (memory) tasks significantly increased from 12.4 to 15.6. However, no significant change was noted in the raw scores for any of the 5-Cog tasks in the non-intervention group.

### Comparison of Post-Trial Changes in the Scores for the IADL, LSNS, and Physical Function

There was no significant pre/post-trial change in the scores for IADL and LSNS. As for the participants’ physical function scores, the total score decreased significantly after the trial (from 31.6 ± 8.5 to 28.8 ± 8.8; p < 0.05), suggesting that there was no specific trend. The total score did not yield a significant difference, demonstrating that there was no item that showed statistical significance. Also, there was no significant difference in the post-trial scores among the tasks for the non-intervention group.

### Discussion

**Efficacy of Cognitive Rehabilitation**

This study compared the efficacy of cognitive rehabilitation in local community-dwelling older adults with and without MCI with a non-intervention group. There have been a number of studies that have focused on improvement in cognitive function of healthy older adults and older adults with MCI and early-onset AD [19–23]. Many of these studies have demonstrated that the memory performance and appraisals of healthy older adults and old-
er adults with MCI improved significantly following the intervention, which is in agreement with the results of this study. Talassi et al. [24] verified the efficacy of systematic cognitive function training, together with a physical training group as a control. Their study incorporated persons with MCI and mild dementia. The training consisted of a cognitive intervention by the use of a computer-based program so as to focus on specific cognitive areas. Both groups received occupational therapy with emphasis on ADL as well as behavioral therapy. Any changes in cognitive function, behavior, ADL, IADL, and physical function were measured for the efficacy of the intervention. The results yielded an improvement in memory performance and appraisals and a significant reduction in symptoms for depression and anxiety in the persons with MCI. For those with mild dementia, there was a significant improvement in their global cognitive status and also a significant reduction in symptoms for depression and anxiety. However, the study by Talassi et al. [24] consisted of participants who were attending a day hospital. Contrary to Talassi et al.’s study, this study was aimed at healthy community-dwelling older adults and older adults with MCI, none of which were on any medication for alleviating dementia. Therefore, any improvement in the participants’ cognitive function achieved in this study could not be attributed to the effect of medication, but was due to the effect of the intervention.

How long can efficacy of cognitive rehabilitation be maintained? In general, some positive effects have been demonstrated, lasting from 6 months to 5 years; they are as follows: (1) not only improvement in memory was noted, which was the principal focus of the training, but also improvement in ADL was seen, with a positive change in mood lasting up to 1 month [25]; (2) improvement in memory performance and appraisals lasting 6 months was observed, even though these were not the principal foci of the training [19]; (3) increased use of mnemonic skills was noted, using training tasks such as cueing, categorization, chunking and method of loci, consequently improving the targeted memory performance and appraisals lasting 6 months [3]; (4) no improvement in overall cognitive function and ADL or apparent reduction in nursing care was observed, but the skills to use the memory support system improved, lasting 6 months [23]; (5) a series of 10 group training sessions over a 5- to 6-week period with a follow-up 11 months later of 4 booster training sessions over a 2- to 3-week period resulted in a lasting effect of 2 years [26], and (6) the targeted cognitive outcomes for participants were maintained at a 5-year follow-up of an interventional study for memory, reasoning, and speed-of-processing training [21]. Although only the immediate resultant effect of this study has been presented in this paper, it would be of scientific interest to carry out a follow-up evaluation so as to investigate its long-term effect on the participants living in the town of Nakajima.

What class of participants was the cognitive rehabilitation effective for? It was found that a comparison between the two intervention groups and the non-intervention group did not yield much change in the participants who were classified as ‘normal’ in terms of cognitive function. However, the negative changes that occurred in the participants classified as ‘probable AACD’ tended to be small for the two intervention groups. Therefore, the intervention may be effective for improving the cognitive function of individuals with MCI. Among previous studies, Kurz et al. [25] have demonstrated that cognitive rehabilitation has not produced any significant effect on individuals with mild AD, but has been effective for those with MCI. In addition, Unverzagt et al. [22] have demonstrated that cognitive interventions have been effective for improving memory performance/appraisals, reasoning, and speed of processing in individuals with normal memory. However, among the three aforementioned tasks in memory-impaired individuals, only memory performance/appraisals did not yield any improvement. Thus, cognitive techniques have been shown to be effective for persons with MCI.
Cognitive Rehabilitation Program vis-à-vis Executive Function

This study consisted of a cognitive function and physical function program. After conducting the programs, the outcomes were compared. The cognitive function program was designed by monitoring executive function of the participants. It was observed whether or not they could plan and execute an event with an emphasis on their ability to modify it. As for the physical function program, it was constructed with an emphasis on aerobic training, so that it would especially influence the executive domain of the participants’ cognitive function. As a result, both programs were effective not only for the targeted executive functions, but also for improving targeted memory performance/appraisals that were the principal foci of this study. Thus, this study demonstrated that training of executive function used as the target of the cognitive rehabilitation programs could lead to possible improvement in memory function.

It is a well-known fact that the principal characteristic symptom in persons with MCI and early AD is a decrease in memory function. The present common interventions for treatment of such persons are mnemonic training as stated by Brooks III et al. [27] and Hampstead et al. [28], a combination of memory and relaxation skills as stated by Rapp et al. [4], or combined interventions including mnemonic training, physical exercises, and creative activities as stated by Kurz et al. [25]. Memory performance and appraisals have been used both as a content and measure of mnemonic training, and many investigators have demonstrated improvement in memory following these interventions. However, it is difficult to exclude the learning effect during evaluation. Furthermore, impact on other cognitive aspects has rarely been addressed because these aspects are seldom employed for evaluation. Ball et al. [26] have compared mnemonic training and the type of training in which other cognitive aspects have been utilized. The following is an example of the principal focus they used for training of cognitive function: (1) memory (verbal episodic memory); (2) reasoning (ability to solve problems that follow a serial pattern), and (3) speed of processing (visual search and identification). The measures they employed were pre-/post-training changes in the principal/non-principal foci and their application to ADL. The results showed that if the targeted function was memory, then memory improved, and if it was reasoning, then reasoning improved. However, Ball et al. [26] have demonstrated that if the targeted function was memory, then reasoning, speed of processing, and ADL did not improve, although improvement in targeted function was maintained at 2-year follow-up.

A study that conducted a comprehensive program for cognitive rehabilitation that included mnemonic training, physical exercises, and creative activities resulted in the improvement of many aspects of cognitive function, such as memory, ADL, and emotion, in individuals with MCI, but this improvement was not apparent in the non-participants with MCI [25]. These results suggest that the efficacy of cognitive rehabilitation may extend to other aspects of cognitive functions. Therefore, in order to improve non-targeted cognitive function by means of cognitive intervention, a combined program is desirable, so that executive function programs may be the most applicable to achieve this goal.

Participation in the executive function and physical function programs demonstrated improvement in the participants’ memory performance/appraisals. This statement can be explained as follows: the transitional process to early dementia from MCI is a process in which a slow deterioration of the neural network takes place. By means of incorporating an intervention into a cognitive rehabilitation program for individuals with MCI, a stage at which mental deterioration is at a minimum, it may be possible to slow down or prevent deterioration [29].

In a program with emphasis on executive function, a person requires a complex cognitive function, i.e., not only being capable of accomplishing a single task such as memorization of a subject, but also memorizing the process of a task, such as depicting a map in one’s mind.
and calculating the required time for its execution. This leads one to take advantage of the neural network already in existence, while at the same time establishing a new one. This may bring about improvement not only in the targeted function of the training, but also in additional functions, such as memory performance and appraisals. As for the aerobic training program, if rats were subjected to low intensity exercise at below-lactic-acid threshold, this brought about activation of the hippocampal neurons and an increase in the local blood flow of the brain with consequent improvement in memory [30].

Although the period of intervention was only 2 months, some degree of improvement, such as that in memory, was achieved. In this way, we demonstrated a certain measure of success in a short period of time, despite a dearth of studies concerning intervention periods for cognitive rehabilitation.

The relevance of preservation and improvement of cognitive function for the incidence of dementia has not been examined extensively. With regard to AACD, Ball et al. [26] have stated that a 2-year maintenance of memory and reasoning abilities is comparable with the expected decline over a 7- to 14-year interval in elderly persons without dementia, so an intervention could be effective for maintaining cognitive function, consequently delaying the onset of dementia. Many investigators of previous studies have concentrated only on the relationship between the intervention and maintenance/improvement of cognitive function. They have, however, not directly examined the relationship between maintenance/improvement of cognitive function and its relevance to the incidence of dementia. This study, too, has described nothing besides the immediate effect of intervention without further investigating the incidence of dementia. It is therefore important to further investigate the incidence of dementia in a community of non-demented individuals with and without any intervention. By observing a decrease in the incidence of dementia in such a community, the implementation of such an intervention would demonstrate its long-term efficacy.

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