Preventing aging-related cognitive decline of healthy elderly people: A preliminary report on exchanging letters method

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老年期の認知機能を維持するための提案——介入訓練実験のデータから——

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要約

高齢期に伴う認知機能の低下を鈍化させるための訓練方法を開発する目的で、65 歳以上の健常者 40 名を対象に介入訓練実験を実施した。認知訓練群は 1 週間に 1 回の割合で手紙を書く課題を行った。手紙は実験者側が「子どもの頃どんな遊びをしましたか」などの回想的質問に単文を書くように求める課題と、未知の 4 名の人物写真に対して「職業、年齢、性格」を推論すること求める課題から構成されていた。運動訓練群には 1 日 15 分程度のバルーンを用いる体操、散歩などを課すものであった。8 週間の介入訓練の前後で測定した認知（注意、記憶、言語）検査と重心動揺検査結果を比較したところ、認知訓練群では認知検査及び重心動揺検査で成績の上昇が認められたが、運動訓練群では介入訓練での変化は認められなかった。これらの結果に基づいて、加齢に伴う認知機能低下に対する手紙課題の有効性を検討した。

Key words

letter writing, attention, word fluency, cerebello-thalamo-cortical circuit, cognitive aging

1. Introduction

The aim of this study was to report preliminary results of an intervening experiment on cognitive and postural function in upper middle age community dwellers. In the previous study, a certain relationship between the performances in D-CAT (digit cancellation test for assessment attention) and postural tremor on stabilometer in healthy elderly people was confirmed and offered behavioral evidence for the relationship between prefrontal cortex and cerebro-cerebeller function (Hatta, Masui, Ito, Ito, Hasegawa, & Matsuyama, 2004).

The proposal of mutual functional linkages between prefrontal cortex and cerebro-cerebellum is based on recent findings on primates showing that the cerebellum plays a significant role in cognitive functions, especially in relation to the prefrontal cortex (Ito, 1998; Desmond & Fiez, 1998; Leiner et al., 1993; 1998; Middleton & Strick, 1998; Schmahmann, 1998; Thach, 1998). This notion has been supported by the fact that cerebellar lesions result in impaired cognitive function (Levinson, Cronin-Golomb, & Schmahmann, 2000). In their study, neuropsychological abilities were evaluated with 19 children who underwent resection of cerebellar tumors, but received neither cranial irradiation nor methotrexate chemotherapy. The neuropsychological tests revealed that they had impairments in executive function, visuo-spatial function, expressive language, verbal memory and modulation of affect. A recent report by Vokaer, et al. (Vokaer, Bier, Elincx, Claes, Paquier, Goldman, Bartholome, & Pandolfo, 2002) showed bilateral anterior ponto-cerebellar lesions associated with the deficit in verbal learning, verbal fluency, and executive task performance. However, several studies claim this finding and require further examination in order to substantiate their conclusions (Beldarrain, 2002; Louis, 2002).

A neuroimaging study also supported the notion of the inter-relationship. The fMRI experiments showed that prominent activation was found in the left middle frontal gyrus and left caudate nucleus in the easy cognitive task condition, while the right cerebellar hemisphere and cerebellar vermis were activated in the difficult task condition (Desmond et al., 1998). Strick and colleagues succeeded to identify anatomical networks between the cerebellar cortex and the prefrontal cortex (Lamnani, & Miall, 2001; Middelton & Strick, 2001). A fMRI experiment by Hubrich-Ungureanu, Kaemmerer, Henn, & Braus (2002) demonstrated that a right handed subject showed an activation of the left fronto-parietal cortex and right cerebellar cortex while a left handed subject showed an activation in the right fronto-parieto-temporal cortex and the left cerebellar hemisphere in the silent verbal fluency task.

These studies from various methods strongly suggest a certain inter-relationship between the function of the prefrontal and the cerebellar cortices. Though neural mechanisms still remain controversial because several other studies have failed to demonstrate positive relational findings (Globas, Bosch, Zuhlke, Daum, Dichgans, & Burk, 2003; Tanaka, Harada, Arai, & Hirata, 2003), one of the most important concerns of almost all elderly people is how to delay and prevent inevitable prefrontal and cerebellar cortices aging effects (Cavanaugh & Blanchard-Fields, 2006; Stern, 2007). To clarify the ways to delay and prevent age-related cognitive decline must be an important mission of neuroscience researchers as well as to clarify the precise neural mechanisms. The purpose of this study was to propose one of the possible ways of a practice to delay and prevent cognitive decline for elderly, though it is still preliminary. Two kinds of intervention practices, cognitive and physical, were given to the two groups of elderly people, and cognitive and postural functions were compared Before and After the intervention.

The intervention in the cognitive group consisted of exchanging letters to an assigned partner, while the intervention in the physical exercise group consisted of playing with balloons and a therapeutic rubber band, and walking.

2. Method

2.1 Participants

Forty healthy rural community dwellers, all over 65 years of age, participated in this project. They were selected on the basis of the results of a collaborative health examination project between the Yakumo town (a rural town on Hokkaido island) and Nagoya University Medical School. The participants showed no sign of physical disorders, internal disease, or dementia at the first phase of examination. For signs of internal diseases, the participants were examined by physicians in accordance with the health examination program, and for signs of mild dementia or other neurological defects were evaluated by neuropsychologists using tests such as the Clock Drawing test, D-CAT (attention), memory tests (immediate, delayed and prospective memories), Stroop test, Money road test, the QOL (quality of life) questionnaire.

The participants were randomly assigned to the cognitive or physical exercise groups. Some of them were not included in the data because of absence, visiting relatives or sickness, during the intervention experiment period. The cognitive group, therefore, consisted of 17 participants (7males and 10 females), whose mean age was 73.22 (SD = 3.79) years. The physical exercise group consisted of 18 participants (9 males and 9 females), whose mean age was 72.28 (SD = 4.22) years. There was no significant age difference between the two groups (t = 0.28). The mean period of education in the cognitive and the physical exercise groups was 8.81 and 9.31 years, respectively, and there was no statistical age difference between the two groups (t = 0.22).

The Before-intervention data of the cognitive and physical exercise examination tests were collected in the summer and those of After-intervention were collected in the winter. The same examiners collected both times of data.

2.2 Apparatus and procedures

The postural function was measured by a stabilometer (Anima, co.). The manual and the standard norm for diagnosis were developed and normalized by Tokita (1996). Two examiners, an orthopedic surgeon and an assistant, administered the postural examination to all participants. The stabilometer used can provide 7 indices. Two of the indices, the size of moving tracks for 60 seconds in the open eye condition and the Ronberg ratio were used because these reflect the cerebello-thalamo-cortical circuit functions more directly than other indices (Hatta et al., 2004). The Ronberg ratio refers to the ratio of the size of moving tracks in the closed eye condition and to that of the open eye condition. These indices have been employed as a useful tool for the diagnosis of Parkinson's disease and equilibrium disorders (Mauritz, Dichgans, & Hufschmidt, 1979; Njiokiktjien, DeRijke, van Ophem et al., 1978; Tokita, 1996).

To examine the prefrontal cortex function, attention and word retrieving tests were used. Attention was evaluated by the Digit Cancellation Test (D-CAT) (Hatta, Ito, & Yoshizaki, 2001; 2004), and word retrieving ability was assessed by the Japanese letter fluency test (LFT, by Ito & Hatta, 2001). The D-CAT evaluates the three levels; focused attention, sustained attention or concentration and selective attention, according to the hierarchical attention model by Sohlberg and Mateer (1989).

The same examiners administered both D-CAT and LFT for each participant. In D-CAT, participants were requested to search the given target digit(s) (1 or 2 digits) on the randomly arranged digit sequences sheet and mark a slash on the target digit for 60 seconds. The Total Performance score refers to the total number of digits that the participant could scan, and it assesses information processing speed, focused attention, and sustained attention (Hatta, Ito, & Yoshizaki, 2001; Hatta, Yoshizaki, & Ito, 2009).

In LFT, participants were asked to generate Japanese nouns that begin with the letters, /a/, /ka/, and /shi/, for 60 seconds for each letter. The total number of generated nouns was measured.

2.3 Intervention procedure

All participants agreed to participate in this project as volunteers at the first meeting. They were then randomly assigned to the cognitive and physical groups. After the grouping, they were given instructions for the procedures. The ethical committee of Nagoya University Medical School approved the present research plan.

The intervention practice in the cognitive group consisted of exchanging letters with an assigned student partner. Each participant was told that she/he would receive a letter every week from the partner, and was asked to return hand-written letters containing replies to the questions. This procedure was repeated for 8 weeks and each participant exchanged letters with the same partner 8 times. Each letter from the partner involved one reminiscent question relating to a memory of the "old days", which required the participant to remember events from the distant past (e.g., what was a play on New Year's Day in your childhood? What is your happiest memory of your childhood?) and to respond to questions (estimate job, age and character) regarding each of four unknown faces printed on a sheet of paper. That is, the cognitive task consisted of writing, remembering and problem solving (reasoning and speculation) of the unknown faces. From the preliminary study, it became clear that responding to photos of unknown faces was the most interesting task for the elderly rather than any other problem solving tasks. To estimate the age and the job of an unknown person was regarded as a task, which involves prefrontal cortex functioning. Recent studies have suggested an important role of the Von Economo neurons in fronto-insular and anterior cingulate cortex in rapid intuition decisions (Allman, Watsdon, Tetreault, & Hakeem, 2005).

The intervention practice in the physical group continued for 8 weeks. It consisted of balloon playing, walking and physical exercise with/without a therapeutic rubber band. Balloon playing consisted of legs extension movement, stretching arm, arm extension, and sitting on the balloon (55 cm size). To increase the physical load, a therapeutic rubber band was used in stretching movements. Physical exercise without the therapeutic rubber band consisted of jumping, standing on one leg, and leg arm stretching. Taking a walk every day was also recommended. The participants were requested to do these physical exercises for 15 minutes every day. They were given a notebook to record their performance each day.

3. Results

To examine the effect of intervention, ANOVAs were conducted for two cognitive and two postural function measurements. As our main interest was to ascertain whether the intervention had a positive effect on prefrontal and thalamo-cerebellar functions, the results of the attention test, verbal fluency test, size of moving tracks in the open eye condition (SES-Open) and Ronberg ratio of stabilometer measurement were analyzed separately.

3.1 SES-Open score

According to Tokita (1996), the index of SES-Open relates to thalamo-cerebellar functions, and high scores of the SES-Open relate to the deterioration of thalamo-cerebellar functions. Figure 1 shows SES-Open scores of Before- and After- intervention for both groups.

In order to examine the effect of intervention, a 2 (group) × 2 (Before- and After-intervention) mixed type of ANOVA was conducted. The ANOVA revealed a significant effect for all factors as well as the interaction (F (1, 33) = 9.22, $p < 0.005$; F (1, 33) = 34.44, $p < 0.0001$; and F (1, 33) = 4.32, $p < 0.045$, respectively). The interaction shows that score increment in the physical exercise group was larger than that of the cognitive group from Before-intervention to After-intervention. This

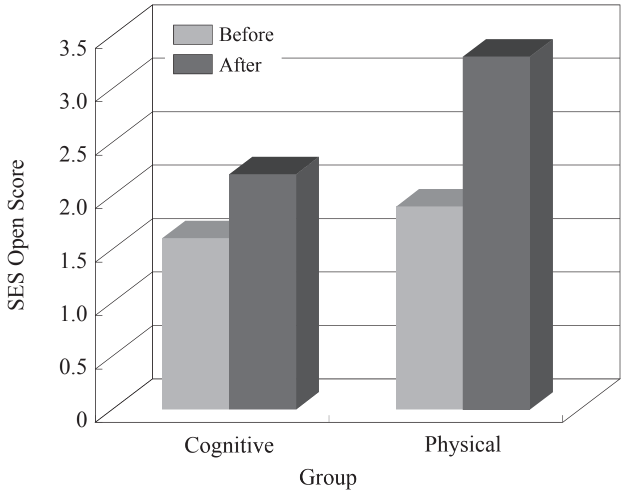

Figure 1: Results of SES-open scores Before- and After-intervention in the cognitive and physical exercise groups

result suggests that even though SES-Open Before-scores in the physical exercise and cognitive groups were almost similar (1.93 and 1.55), the intervention tended to cause deterioration in the physical group more than in the cognitive group.

3.2 Ronberg ratio

The Ronberg ratio refers to the ratio of the size of moving tracks in the closed eye condition to the size of moving tracks in the open eye condition. Generally, a low Ronberg ratio score relates to a deterioration of equilibrium in posture when using visual guidance (Tokita, 1996). It reflects the failure of using visual guidance properly to maintain posture.

To examine the effects of intervention, a 2 (group) × 2 (Before- and After-intervention) mixed type of ANOVA was conducted. The ANOVA revealed no significant effect for group, phase or interaction (F (1, 33) = 3.72, 1.67, and 0.68, respectively). The effect for group seems to suggest a difference, but

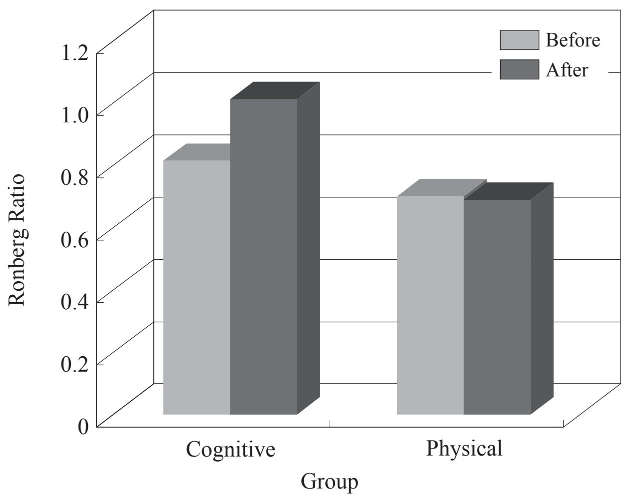

Figure 2: Results of Ronberg ratio scores Before- and After-intervention in the cognitive and physical exercise groups

it was not statistically significant ($p = 0.062$). These results suggest no effect of the intervention for both groups.

3.3 Attention score

3.3.1 Total performance score (TP-1: single digit cancellation trial)

This index of D-CAT reflects information processing speed (Ito & Hatta, 2001; Hatta, Ito, & Yoshizaki, 2001). An ANOVA of a 2 (group) × 2 (Before- and After-intervention) mixed type did not show any significant effect or interaction. Figure 3 shows the results.

3.3.2 Total performance score (TP-2: two digits cancellation trial)

This index of D-CAT reflects abilities of executive control and information processing speed (Ito & Hatta, 2001; Hatta, Ito, & Yoshizaki, 2001). It is considered that the cognitive load is larger than that of the TP-1 trial. To examine the effect of intervention, a 2 (group) × 2 (Before- and After-intervention) mixed type of ANOVA was conducted. The interaction between the two factors was significant (F (1, 30) = 3.96, $p < 0.046$) and the factor of intervention showed a non-significant but slight tendency (F (1, 30) = 3.01, $p < 0.083$). The results shown in Figure 4 indicate the different effects of the intervention.

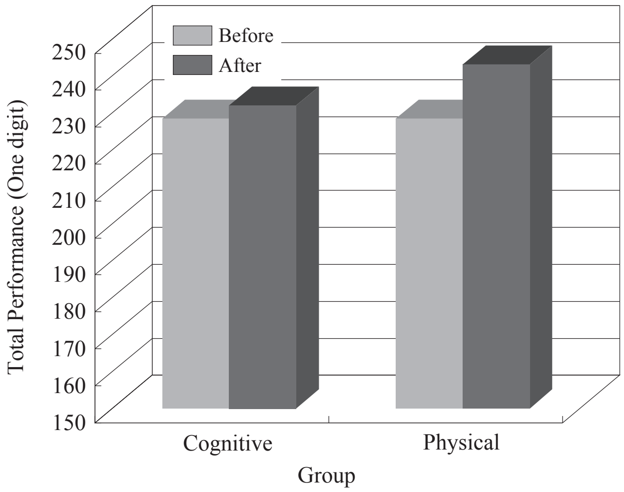

Figure 3: Total performance scores (single digit condition) Before- and After-intervention in the cognitive and physical exercise groups

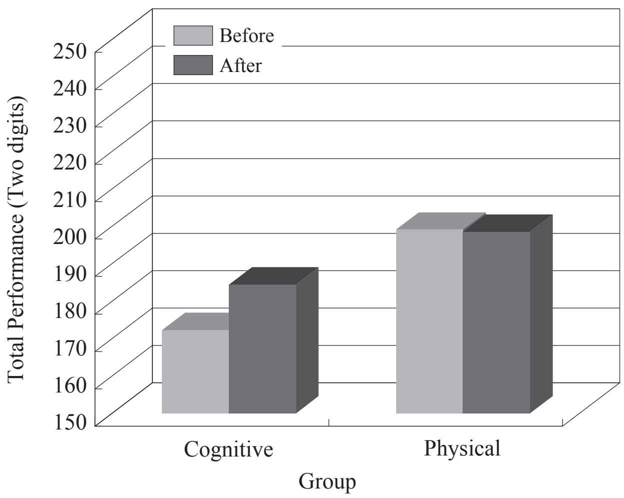

Figure 4: Total performance scores (two digits condition) Before- and After-intervention in the cognitive and physical exercise groups

3.4 Verbal fluency score

Figure 5 shows the results of a letter fluency test of both groups. To examine the effect of intervention, a 2 (group) × 2 (Before- and After-intervention) mixed type of ANOVA was conducted. The results revealed a slight, though not significant, interaction (F (1, 28) = 3.54, $p < 0.07$). As seen from Figure 5, the interaction reflected the fact that the cognitive group showed an improvement from After-intervention to Before-intervention, while the physical exercise group did not show such a tendency of improvement.

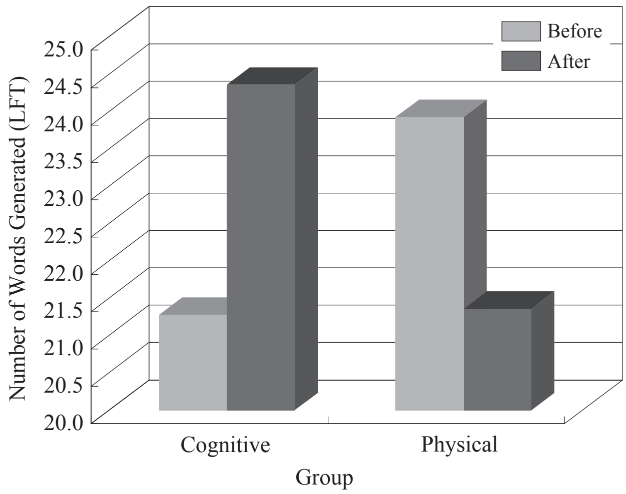

Figure 5: The results of the letter fluency test scores Before- and After-intervention in the cognitive and physical exercise groups

4. Discussion

In this study, the effects of two intervening tasks on the cognitive and postural functions in daily life situations were examined. This project is based upon the previous findings in the Yakumo cohort project, namely that prefrontal function measured by the D-CAT (attention test) and verbal fluency related strongly to thalamo-cerebeller function evaluated by stabilometrical indices (Hatta et al., 2004).

Two kinds of intervening tasks, which are believed to improve or sustain cognitive and postural functions of elderly community dwellers, were prepared. One was cognitive directed intervention and the other was physical directed intervention. In accordance with the cognitive intervention, participants were requested to exchange letters, and in the physical intervention, the participants were asked to do physical exercise with/without a balloon and therapeutic rubber band. The content of both tasks was selected on the basis of a preliminary study. There were criteria for the selection of cognitive and physical exercise tasks. One was that participants who have a wide range of intellectual and socio-economical backgrounds must be interested in the task, and another was that it could be carried out without being a financial burden. In other words, the task should involve elements to maintain a high level of motivation for the elderly community dwellers. Further, the task could be performed in the subjects own home without the need to go out. Both the cognitive and physical intervention tasks fitted these requirements. In fact, in interviews following the intervention project, most participants said that writing letters to a new young partner was a pleasure, and the exercise tasks were all described as fun.

Although the period between Before- and After-intervention in the present preliminary study was short and no control group was prepared for an ethical reason (i.e., noting given control group can not expect cognitive and physical improvement), the comparison of findings between the cognitive and the physical exercise groups were suggestive enough.

The most suggestive finding was the interaction between group (cognitive and physical) and phase (Before- and After-) was significant or nearly significant. There was a significant interaction both for TP 2 and SES-open indices. TP2 refers to the task in which participants were asked to cancel two target digits simultaneously. In this task, not only focused attention but also the working memory component is involved more than in TP1 (cancel only one target digit as fast as possible). The significant interaction reflects that both groups showed similar levels of performance at Before-intervention, but the cognitive group showed better performance than the physical exercise group at After-intervention. The TP1 did not show significant interaction, that is, effects of intervention were small even in the cognitive group.

There is ample evidence that suggests a strong relationship between the prefrontal cortex and attention (especially focused attention and sustained attention or working memory). Functional brain-imaging studies of intact adults have shown that the prefrontal cortex is activated during the performance of sustained attention or working memory (e.g., Awh et al., 1996; Fiez et al., 1996; Paulesu et al., 1993; Jonides et al., 1993; Smith et al., 1995). A fMRI study by Mead, Mayer, Bobholz, Woodley, Cunninghum, Hammeke and Rao (2002) also indicated that the component of selective attention invites the activation of the frontal cortex, especially around the area of BA44.

Although no group difference was found in the Ronberg ratio, the SES-open showed a significant interaction between group and phase, where both groups showed similar levels at Before-intervention, whereas the cognitive group showed a better score than the physical exercise group at After-intervention. The postural function was measured by means of a stabilometer, and employed two indices (SES-open and Ronberg ratio) which are considered to reflect cerebello-thalamo-cortical functions (Mauritz, Dichgans, & Hufschmidt, 1979; Nijiokiktijen, Rijke, van Ophem et al., 1978; Tokita, 1996).

Many studies have suggested that a stabilometer can diagnose cerebello-thalamo-cortical circuit functional diseases (e.g., Kapteyn, et al. 1983; Japanese Society of Neuroequilibrium Medicine, 1983; Tokita, 1996). According to Tokita (1996), equilibrium diseases resulting from various causes such as vestibular ataxia, a reflex disorder controlled by the spinal cord and visual system, or cerebello-thalamo-cortical circuit system dysfunction can be diagnosed by using indices of a stabilometer. One of the most common disorders of the cerebello-thalamo-cortical circuit function is Parkinson's disease. Disorders of movement function related to posture, balance, and gait are common occurrences among many Parkinson's disease sufferers (Bronte-Stewart et al., 2002; Rogers, 1996).

It was assumed that word retrieving activity, LFT, is one of the representative tests for evaluation of prefrontal function. Functional brain-imaging studies have demonstrated an activation of the prefrontal cortex and temporal regions during performance of the verbal fluency test (e.g., semantic category fluency, phonemic fluency) with techniques (Cuenod et al., 1995; Friston, Frith, Liddle, & Frackowiak, 1991; Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; Klein, Milner, Zatorre, Meyer, & Evans, 1995; Stuss et al., 1998), and behavioral studies by brain damaged (Troyer, Saint-Cyr, & Lang, 1990; Troster et al., 1998) as well as by healthy adults (Troyer, Moscovitch & Winocur, 1997; Troyer, 2000) have also demonstrated that a verbal fluency test reflects prefrontal cortex functions.

The results of the LFT showed an interaction between groups and between Before- and After-intervention but it remained at 7 % level (if the sample size is increased, it may be possible to find significance). This discrepancy may be explained by the following reasons. Two different components are involved in LFT and this weakens sensitivity as an index. Troyer, Moscovitch and Winocur (1997) suggested that clustering, ability to generate words within clusters or subcategories, relates mainly to the temporal lobe function while switching, the ability to shift between clusters, reflects mainly the frontal lobe function. Recently, York et al. (2003) also reported a verbal fluency study with patients using pallidomy for the treatment of Parkinson's disease and found that a more precise analysis of phonemic fluency test, such as clustering and switching, could differentiate locus of frontal cortex function. The low sensitivity of word fluency performance (generated number of words) might be due to the fact that word fluency performance (number of words generated) relates to the temporal rather than the frontal lobe.

This result seems to suggest that LFT is not so sensitive in detecting prefrontal cortex function in comparison to TP2. This was confirmed recently by the new brain imaging technique, NIRS (Near-Infrared Spectroscopy), in which prefrontal cortex showed stronger activation in TP2 than in the verbal fluency task (Hatta, Kanari et al. 2009).

To conclude, the present findings suggest that the intervention was effective in indices, which sensitively reflects prefrontal cortex function. Particularly, the findings showed firstly that cognitive intervention was more effective than physical intervention not only in cognitive performances but also in postural indices, and secondly that physical exercise does not improve postural function in elderly people. In the physical exercise group, effects of intervention were small even in other indices not mentioned here (e.g., difference was shown in length of footstep, 10 m walking speed, etc.).

One may notice and claim that the score did not increase between Before- and After-intervention in the cognitive group. In fact, no difference was found in the cognitive group. The fact that the cognitive score decreased between Before- and After-intervention in the physical group invites a significant interaction. This may be explained by the difference in the examination situation and the fact that the participants were all elderly people. The Before-intervention was performed in summer when most of the participants could take a rest for waiting of the examination because the target participants of this study was mixed among many community dwellers, whereas After-intervention took place in winter (Yakumo town is located on the northern island of Japan and cold in winter) and only the target participants were convened, which means that the participants had little opportunity to rest. Therefore, it might be reasonable to consider that when there is no deterioration between Before- and After-intervention, it should be regarded as an improvement.

The findings that the cognitive group showed an improvement in cognitive functions as a result of the letter exchange method but no improvement was shown in the physical group seem to suggest an important issue that physical exercise alone, such as walking, may not be enough to sustain cognitive function in old age. Rather, to continue engaging in cognitive tasks, especially ones which involve prefrontal cortex function, is necessary to sustain not only cognitive but also physical or motor kinetic function in old age. These results, together with previous studies, support Hatta's proposal that to keep on continuing cognitive tasks acquired at a later stage in life, such as keeping a diary, writing letters or poetry, is crucially important (Hatta, 2004; Hatta, Ito, Masui, Ito, Nagahara, Watanabe, Kawaguchi, Matsuyama, & Hasegawa, 2004).

Considering the small size of the recent sample, the results should be taken only as preliminary. However, the results definitely suggest a new way to look for a method to prevent deterioration in cognitive function in elderly community dwellers.

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