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Effect of Brain Gym ® exercises on cognitive function and brain-derived neurotrophic factor plasma level in elderly: a randomized controlled trial

Donna Adriani Kusumadewi Muhammad[*], Yudhisman Imran[**], Martiem Mawi[*], Patwa Amani[*], and Ermita I.I.Ilyas[***]

ABSTRACT

BACKGROUND
Cognitive impairment and dementia are some of the major health concerns in the aging population. Many studies showed positive effects of physical exercise in delaying or preventing these conditions. Brain Gym ® exercises is a structured aerobic exercise involving head, eyes and crossing movements of the extremities in order to stimulate both brain hemispheres. This study was conducted to evaluate the effect of Brain Gym ® exercises sessions on cognitive function and plasma brain-derived neurotrophic factor (BDNF) in the elderly.

METHODS
A non-blinded randomized controlled study involving 64 healthy women aged >60 years who were randomized into Brain Gym ® exercises treatment group (n=32) and control group (n=32). Treatment group joined 60 minutes of brain gym exercises sessions twice a week for 12 weeks. The measured outcomes were cognitive function (assessed by mini-mental state examination [MMSE] questionnaire) and plasma BDNF levels. The outcomes were measured at base-line and after the intervention. An independent t-test was used to analyze the data.

RESULTS
The BDNF levels were increased in both groups after 12 weeks, and there was a significant difference between treatment group (41.26 ± 6,82 ng/mL) and control group (37.10 ± 8.11 ng/mL)(p=0.040). However, the MMSE score was not significantly different between the two groups (p=0.200).

CONCLUSION
Brain Gym ® exercises sessions significantly increase plasma BDNF level in the elderly population. In practical terms, we may suggest evaluation of the effects of Brain Gym ® exercises as a strategy in the treatment of disorders associated with central degenerative changes.

Keywords: BDNF, Brain Gym exercises, elderly population

*Department of Physiology,
Faculty of Medicine,
Trisakti University, Jakarta
**Department of Neurology,
Faculty of Medicine,
Trisakti University, Jakarta
***Magister Program in Biomedical Sciences, Faculty of Medicine,
Universitas Indonesia, Jakarta

Correspondence:
dr. Donna Adriani Kusumadewi Muhammad, M.Biomed
Departement of Physiology
Faculty of Medicine,
Trisakti University, Jakarta
Jl. Kyai Tapa No.260 Grogol
Jakarta, 11440
Phone: +628991777777
Email: donna.adriani@trisakti.ac.id

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INTRODUCTION

The increase in longevity impacts on an increase in the elderly population (60 years and above).[1] In 2010 there were 18.1 million elderly or around 7.6 % of the total population of Indonesia.[2] By the year 2025, it is estimated that the number of elderly will increase to 33.7 million, or 11.8 percent of the total population. In the year 2035, the number of elderly will increase to 48.2 million, or 15.8 percent of the total population.[2] The increase in the number of elderly requires measures for improving the quality of life of the elderly.[2]

The prevalence of age-related health problems has attracted attention as a result of the increased growth of the elderly population worldwide.[3] Cognitive disturbances such as mild cognitive disorder and dementia are some of the health problems encountered in the elderly.[3] The number of patients with dementia is estimated to increase two-fold every 20 years.[3] In 2050 the number of patients with dementia is projected to increase to 70.5%.[3] The more advanced a person's age, the higher the decrease in cognitive function.[3] Cognitive disturbances may cause a reduction in the quality of life of the elderly and become an economic burden for the family.[4] One of the strategies for preventing cognitive disturbances is the prevention of the modifiable risk factors, such as poor physical activity.[3,4]

Physical activity is associated with increased cognitive function and decreased risk of dementia in several meta-analytical studies.[5] Regular and measurable physical exercise has been demonstrated to increase the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus that is directly associated with improved plasticity of the brain synapses and cognitive function.[6] The improvement in synaptic plasticity has an important role in the learning process and memory functions. ·Physical exercise triggers increases in cellular and molecular processes, such as angiogenesis, neurogenesis, and brain synaptogenesis. In addition, there is a biological mechanism, namely increased blood flow, increased synthesis and utilization of neurotransmitters, and increased synthesis and release of BDNF. Brain-derived neurotrophic factor is a protein that increases the survival of neurons and synapses that play a role in the learning process and memory.[6]

Although physical exercise is beneficial in delaying dementia, frequently aerobic sports or resistance training are difficult to perform by the elderly population who have a limited range of motion (ROM) and have comorbidities (hypertension, coronary heart disease (CHD), diabetes mellitus (DM)). Brain Gym ® (BG) exercises is one of the alternative forms of physical exercise that may be performed by the elderly. Studies that compared three types of exercise; 1) physical exercise, 2) virtual reality-based exercise, and 3) brain exercise, concluded that brain exercise is better in increasing cognitive ability in the elderly.[7] Computer-based brain exercise and games are also known to significantly increase cognitive function.[8,9]

Furthermore, the lowered BDNF concentrations, especially in the elderly, are associated with atrophy in the hippocampus and may contribute to memory impairment, which is possibly associated with cognitive challenges in Alzheimer's disease.[10]

The results of a Korean study on the impact of a 12-week senior brain health exercise (SBHE) program in elderly women as compared to basic active physical fitness, on cognitive function and BDNF, showed that Mini-Mental State Examination Korean version (MMSE-K) scores and BDNF concentrations, were significantly increased in the exercise group as compared with the control group.[11]

The results of a study carried out by Huang et al.[12] showed that physical exercise significantly increased BDNF concentrations. However, different results were obtained in the study conducted by Schega et al.[13] on 38 elderly, in that 30 minutes of aerobic training at the rate of three times per week for four consecutive weeks did not increase the VO2max and serum BDNF level.

These inconsistent study results need to be further investigated. Therefore the aim of the present study was to evaluate the effect of BG exercises on cognitive function and plasma BDNF concentration in the elderly.

METHODS

Research design

This non-blinded randomized controlled study was conducted at the Mampang public health center, South Jakarta. The laboratory examinations were performed in the Prodia laboratories. The study was carried out from January to May 2018.

Research subjects

Elderly males and females who met the inclusion and exclusion criteria were selected for this study. Participants were recruited from the Mampang area, South Jakarta, among those meeting the inclusion criteria, namely age 60 years and older, capable of walking unaided, and agreeing to participate in the study (by signing the informed consent form) after receiving particulars on this study. The exclusion criteria were: suffering from psychotic and/or neurologic disturbances, consuming antidepressants or antipsychotics, having malignancies, or not participating until completion of the study.

The sample size was determined from an effect size of 0.7, $\alpha=0.05$ and $\beta=0.2$, so that the optimal sample size was 26 per group, which with the addition of an anticipated drop-out rate of 20%, yielded the required total sample size of 32 per group. Therefore the 64 participants who were qualified for the study were block-randomized with a block size of four into the control group (n=32) and the Brain Gym group (n=32).

Data collection

The demographic data (age, sex, job, and educational level) of the participants were collected during an interview using a questionnaire. The interview also obtained data on regular physical exercise, history of past illness, current illness and smoking.

Measurements

Height was measured with a portable Microtoise with accuracy of 0.1 cm and weight was measured with portable Sage scales with accuracy of 0.1 kg. The body mass index was determined by dividing the weight in kilograms by the square of the height in meters. The blood pressure was measured using a pre-calibrated mercury sphygmomanometer.

The blood pressure was measured as follows: The respondents were seated or at rest for 10 minutes, the right arm was positioned on the table at heart level, the cuff was wrapped around the upper right arm at a distance of 3 cm above the cubital fossa, the "On" button was pressed so that the instrument automatically inflated the cuff, and the resulting systolic and diastolic blood pressure became visible on the screen. The results of the first blood pressure measurement was recorded, followed by a waiting period of 1-2 minutes, then a second blood pressure measurement was performed, followed by another waiting period of 1-2 minutes, then a third blood pressure measurement was done. The results of the three blood pressure measurements were added and divided by three to obtain the mean blood pressure.

In case there were differences of >10 mmHg between the three systolic or diastolic blood pressures, the blood pressure examination had to be repeated.

The participant performed the six-minute walk test, during which he or she evaluated his or her own fitness using the Borg scale, which measures dyspnea and fatigue scores from 6 (signifying no exertion at all or zero exertion) to 20 (maximal exertion). The procedure of the six-minute walk test is as follows: Before starting the test, the participant's weight, height, blood pressure, pulse rate per minute, oxygen saturation, and Borg dyspnea and fatigue score are measured. Then the participant is tested for static and dynamic balance. The subjects are instructed to walk along a path at the highest speed possible for six minutes, after which they are to come to a stop. The total distance walked from the start to the stop sign is measured in meters. The subjects are then asked to sit down and immediately afterward their blood pressure, pulse rate per minute, oxygen saturation and Borg dyspnea and fatigue score are again measured. Subsequently the predicted VO2 max is calculated using a standard formula.

Measurement of cognitive function

The Mini-Mental State Examination (MMSE) is a widely used cognitive screening test, where scores from 24 to 30 are considered to be within the normal range. Items address orientation, memory, recall, attention, naming objects, following verbal and written commands, writing a sentence, and copying a figure.[14]

Intervention

The treatment group joined BG sessions twice a week for 12 weeks. Each session lasted 60 minutes with 10 minutes warming up, 40 minutes BG, and 10 minutes cooling down. The exercise was led by a professional who made sure every participant made the correct movements. The control group did not participate in any course.

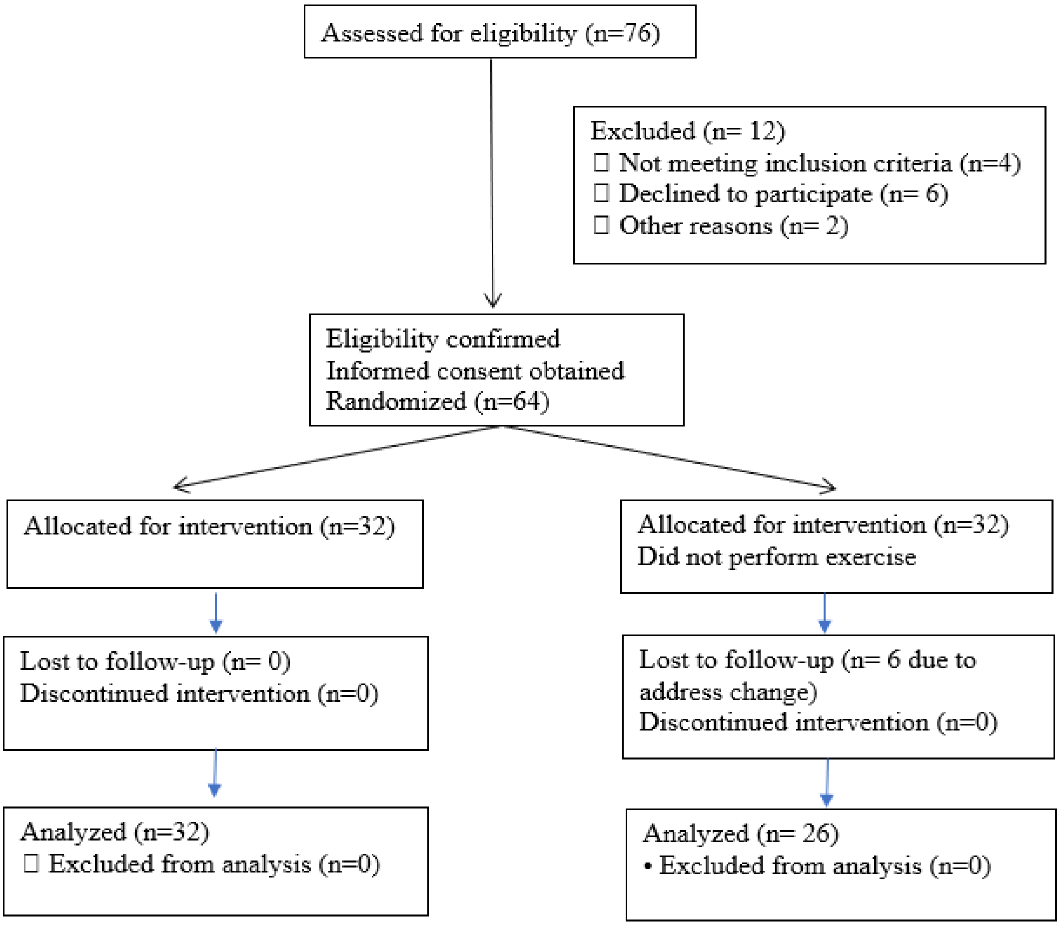

Figure 1. Flow diagram of the subjects included in this study

The BG protocol used in the present study followed the Super Body, Super Brain procedure of Michael Gonzales-Wallace.[15] The exercise was preceded by a warming-up period of 10 minutes, consisted of core movements for 40 minutes, and was followed by a cooling-down period of 10 minutes.

Blood sample collection

After overnight fasting, venous blood samples were collected between 8:00 and 10:00 a.m. Blood samples were taken at the very beginning and at the end of the BG program. Blood samples were drawn from a vein in the cubital fossa region to a volume of 10 ml and immediately put in the EDTA tubes. The blood samples were then centrifuged at 3000 rpm and the plasma was obtained. Plasma aliquots were made in 1 ml vacutainer tubes and were kept at -80^{0}C until required for examination.

Serum BDNF concentration was measured using an ELISA kit provided by MyBiosource, USA. The principle of the procedure was indirect competitive enzyme immunoassay, where the BDNF concentration was determined spectrophotometrically at 450 nm in a microplate ELISA reader and compared with the standard curve. The color intensity was inversely proportional to the BDNF concentration.

Blood glucose was measured spectrophotometrically using the Advia 1800 instrument and Bayer Advia 1800 74024 glucose reagent.

Statistical analysis

Normally distributed data were presented as mean ± SD. The Kolmogorov-Smirnov test ($p>0.05$) was used to check sample normality An independent t-test analysis was used to verify difference in BDNF and cognitive function (MMSE-K) between groups (exercise group and control group). Statistical significance for all tests was accepted at the level below 0.05.

Table 1. Distribution of the general characteristics of the participants at base-line

Characteristics	Brain Gym Treatment (n=32)	Control (n=32)	p value
Age (years)	65.48 ± 4.51	64.77 ± 4.31	0.530
Height (cm)	151.59 ± 5.75	150,80 ± 7.12	0.633
Body weight (kg)	56.99 ± 6.67	60.150 ± 8.16	0.100
BMI (kg/m^2)	25.75 ± 2.13	26.73 ± 2.78	0.091
SBP (mmHg)	124.65 ± 18.31	130.87 ± 25.50	0.145
DBP (mmHg)	79.84 ± 9.87	82.00 ± 13.26	0.102
Pulse rate	80.32 ± 5.19	79.55 ± 4.99	0.824
BDNF (ng/mL)	39.43 ± 10.98	33.61±14.52	0.091
MMSE	25.032 ± 2.99	23.42 ± 3.43	0.324

*BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BDNF: brain-derived neurotrophic factor; MMSE: Mini Mental State Examination

Ethical clearance

Ethical clearance for this study was issued by the Ethics Commission, Faculty of Medicine, Trisakti University, under no. 119/KER/FK/XII/2017.

RESULTS

At the beginning of the program, 64 participants met the criteria and volunteered to join the program (control group n=32 and treatment group n=32). However, 6 participants from the control group could not finish the program. A total of 58 subjects finished the program and the data were analyzed. There was no report of injury or medical concern during the BG sessions.

At base-line there were no significant differences between the treatment and control groups. This showed that the block randomization that had been performed was successful in equalizing all other variables in both groups, apart from the treatment variable (Table 1).

After 12 weeks of training there was a significant difference in plasma BDNF levels between the treatment and control groups (p=0.040). However, there was no significant difference in MMSE scores between treatment and control groups (p=0.200) (Table 2).

DISCUSSION

Our study showed that BG exercise for 12 weeks was capable of increasing serum BDNF concentrations in the elderly. These study results were in agreement with the results of the study of Szuhany et al.[5] on 1111 subjects, in which the investigators stated that BDNF concentrations had a statistically significant increase in the physical exercise group. The increase in plasma BDNF concentration in the group with regular physical exercise was higher than that in the group with a single exercise. The increase in plasma BDNF concentration was relatively associated with exercise dose.[5]

In the study conducted by Zoladz et al.[16] it was also found that aerobic physical exercise may increase BDNF concentration. Brain-derived neurotrophic factor is capable of regulating long-term potentiation (LTP) in the hippocampal area by strengthening the synaptic responses toward tetanic stimulation. Long-term potentiation as a form of synaptic plasticity that plays a role in long-term memory formation.[16]

The human brain is a structure that easily undergoes functional adaptation, so as to affect cognitive function. Brain plasticity is affected by experience, which can be stimulated by physical activity. Physical activity may make various changes in the brain.

Table 3. BDNF and MMSE levels after 12 weeks of BG exercises

	Brain Gym (n=32)	Control (n=26)	p value
BDNF (ng/mL)	41.26 ± 6.82	37.10 ± 8.11	0.040
MMSE	25.93 ± 2.78	24.50 ± 3.36	0.200

BDNF: brain-derived neurotrophic factor; MMSE: Mini Mental State Examination

The physical exercise that is capable of affecting cognitive function is aerobic physical exercise, since it can provide the best environment for cortical activity, hemodynamics, and metabolism.(17)

Aerobic physical exercise is an activity that is planned, structured, and performed repeatedly, to improve physical fitness.(18) Physical exercise can increase neuroplasticity. In humans, the indicator that plays a role in changing to brain structure is the brain-derived neurotrophic factor that is correlated with increased cognitive function. The biological mechanism that causes this is aerobic physical exercise that increase blood flow to the brain, increases oxygen in the cerebral tissues, and increases neuroplasticity.(19)

This increase in cognitive function is caused by BDNF activity. Brain-derived neurotrophic factor is a protein found at high concentrations in the central nervous system, particularly in the hippocampus, cerebral cortex, hypothalamus, and cerebellum. BDNF is capable of penetrating the blood-brain barrier so that its concentrations can be detected in the blood.(5)

In the study of Rasmussen et al.(20) it was found increased plasma BDNF concentrations during aerobic physical exercise. BDNF plays an important role in neuronal growth and endurance. Brain-derived neurotrophic factor also affects learning and memory. Synthesis of BDNF is mediated and influenced by physical activity. Physical exercise increases the transcription of BDNF in the brain. Physical exercise increases circulatory BDNF concentrations.

Physical exercise increases the concentrations of BDNF, which is a trophic factor associated with increases in cognitive function. In a study on the effect of exercise on BDNF expression in the laboratory mouse *(Mus musculus)*, it was found that exercise resulted in the release of an endogenous molecule, namely β-hydroxybutyrate, which increases the activity of BDNF promoters and leads to an increase in neurotransmitter release that is dependent on the Trkb receptor. This explains the endogenous mechanism of increased BDNF by physical exercise.(21)

The results of our study showed that after performing BG exercise for 12 weeks, there were no significant differences in cognitive function between the treatment and control groups. Differing results were obtained in a study involving 24 women the age range of 65-79 years, who underwent a SBHE program for 12 weeks. It turned out that cognitive function was underwent a statistically significant increase in the experimental group when compared with the control group.(11)

A different study found that a physical exercise and cognitive program for 12 weeks could increase the efficiency of brain activation during cognitive tasks in elderly aged more than 60 years. The group performing aerobic physical exercise had significantly increased memory and executive functions as compared with the control group.(22)

According to a number of systematic reviews, aerobic-type training in the elderly has mild but heterogeneous effects on cognition and memory capacities.(23,24) This may have been the result of the necessity for minimal duration, frequency and intensity in a program of short duration, to induce changes in global cognition.

Brain-derived neurotrophic factor is the main regulator of neurogenesis that is associated with synaptic transmission and long-term potentiation. Aerobic physical exercise performed for 4 weeks may increase memory function in individual who previously were in the habit of performing aerobic physical exercise.(25) The aging process is associated with a gradual decrease in cognitive function and increased risk of cognitive disturbances.(26) The aerobic physical exercise and cognitive program (Brain Gym) for 12 weeks is expected to be capable of preventing decreased cognitive function in the elderly.(20)

Our study has several limitations. We cannot exclude that participants performed additional unrecorded physical exercise outside the program, constituting an additional confounding factor affecting the results. Other limitations include unknown group differences in the presence of genetics factors, such as BDNF gene polymorphism, which could influence BDNF synthesis.

In addition, further research is also needed to determine whether peripheral plasma BDNF reflects central BDNF in the elderly.

CONCLUSIONS

Based on the results of this study it can be concluded that BG exercise performed regularly twice weekly for 12 weeks by healthy elderly women can significantly increase plasma BDNF concentrations.

CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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CONTRIBUTORS

DAKM, YI, MM, PA, EIII contributed to the concept and design of the study, data acquisition, data analysis, and/or interpretation. DAKM and YI drafted and revised the manuscript critically for important intellectual content. All authors had read and approved the final manuscript.

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