

Effect of Combination of Heart Exercise and Anagram Cognitive Training on Cognitive Function in Indonesian Elderly: A Preliminary Study

Antonius Ngadiran^{1, 2*}, Amin Husni², Dian Ratna Sawitri³, Blacius Dedi⁴, Maria Suryani⁵

¹Institut Kesehatan Immanuel, Bandung, Indonesia

²Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

³Faculty of Psychology, Universitas Diponegoro, Semarang, Indonesia

⁴Universitas Karya Husada, Semarang, Indonesia

⁵STIKES Elisabeth, Semarang, Indonesia

Abstract

Background: A person is increasingly at risk for cognitive function decline with increasing age. Brain-derived neurotrophic factor (BDNF) and dopamine levels are thought to correlate with cognitive function. A combination intervention may more effective at increasing cognitive function than single intervention. This study aims to evaluate the effect of heart exercise and anagram training combination on cognitive function, BDNF, and dopamine levels in the elderly over 12 weeks. **Methods:** We conducted a preliminary study using a quasi-experimental study. Twenty elderly participants were included in a combined intervention group (10 participant) to join heart exercise and anagram cognitive training three times a week for 12 weeks, and in a single intervention group to join anagram cognitive training (N=10). Outcomes were measured 12 months after the intervention. Outcome measures included cognitive function, brain-derived neurotrophic factor (BDNF), and dopamine levels. Cognitive function was evaluated with the Montreal Cognitive Assessment (MoCA). **Results:** Both groups demonstrated a significant cognitive improvement before and after intervention ($p < 0.05$), but the combined intervention group showed significantly greater improvement than the single intervention group ($p = 0.001$). No significant improvements in BDNF or dopamine levels were observed among the groups ($p > 0.05$). **Conclusions:** A combination of anagram cognitive training and heart exercise was found to significantly improve cognitive function levels in elderly participants, but not their BDNF or dopamine levels.

Keywords: BDNF, Cognitive, Dopamine, Elderly, Cognitive Training, Heart Exercise

1. Introduction

The elderly population around the world is growing annually[1], with Indonesia having the eighth largest elderly population[2]. Around 5.1%-41% of elderly individuals globally have cognitive impairments[1], with the mean cognitive score of elderly people in Indonesia, as measured through a telephone survey of cognitive status (TICS), being 14.7 out of a maximum score of 34[3]. As people age, their cognitive function tends to deteriorate[4], [5], with cognitive impairment being one of the most common issues among the elderly population.

Cognitive changes in the elderly are associated with alterations in brain structure and function, without necessarily leading to neural death, synapse loss or neural network dysfunction[5]. Nevertheless, not all cognitive functions deteriorate with age[5], with some elderly individuals retaining cumulative knowledge and experiential skills into their later years[5]. Cognitive changes in the elderly involve changes in brain-derived neurotrophic factors (BDNF) and

dopamine levels[6]-[13].

Brain-derived neurotrophic factor (BDNF) is a factor that regulates cognitive function both under normal and pathological conditions related to learning and memory[12]. BDNF is essential for maintaining the survival of nerve cells and plasticity synaptic connections[12]. Moreover, BDNF regulation varies greatly among individuals[12], with a decrease in BDNF levels being observed in elderly individuals with cognitive impairment[13].

Dopamine is one of the neurotransmitters in the brain that plays a role in cognitive function[14], regulating six cognitive skills vital to human language and thinking, including motor planning, working memory, cognitive flexibility, abstract reasoning, temporal analysis/sequencing, and generativity[15].

Anagram training is one of the cognitive training interventions believed to enhance cognitive functions such as attention, concentration, or memory[16]. These interventions might be applied to elderly individuals, though their efficacy remains uncertain. Cognitive intervention usually consists of cognitive training, cognitive rehabilitation, and

cognitive stimulation[17], [18], with cognitive training and stimulation interventions possibly providing better outcomes than cognitive rehabilitation with regards to cognitive function in the elderly[19]. Despite this, a systematic review and meta-analysis study found that cognitive interventions only had a minimal effect on global cognitive function among patients with mild cognitive impairment[20], with no effect on global cognition of patients with cognitive decline[21]. Memory anagram therapy, however, has been proven to improve cognitive function among the elderly[22]–[24], while interventions such as brain gym and exergame have not been shown to be effective[25]. Moreover, cognitive interventions need to be tailored to the sociodemographic of the elderly to increase their efficacy in improving cognitive function[25].

Physical exercise is widely recommended for elderly individuals[26], with some research suggesting that it can improve cognitive function, although there is still controversy regarding its effect on BDNF levels[26]. Moderate intensity aerobic and resistance exercise have been found to be more effective for improving executive cognitive function among older individuals than high intensity aerobic exercise[26], although high-intensity aerobic exercise does show more benefit for improvements in information processing speed[26]. Ultimately, the design of physical exercise must be tailored to the individual needs of the elderly.

A cross-sectional study found that a combination of high physical activity and high cognitive activity, high physical activity and low cognitive activity, or low physical activity and high cognitive activity could better improve cognitive impairment than low physical activity and low cognitive activity in the elderly[27]. However, a randomized control trial study found that a combination of aerobic exercise and computer cognitive training in 12 weeks did not improve global cognitive function[28]. This study will examine the efficacy of a combination of anagram cognitive training and series 1 heart exercise, developed by the Indonesian Healthy Heart Foundation, in improving cognitive function, BDNF, and dopamine levels within 12 weeks. It is hypothesized that this combination will be beneficial in this regard.

2. Methods

The protocol was approved by the local ethics committee of the Faculty of Medicine Universitas Diponegoro and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to participating in the study.

This quasi-experimental study recruited 20 elderly individuals residing in nursing homes located in West Java, Indonesia. They were divided into two groups (combined intervention group; N=10, single intervention group; N = 10) based on the

nursing home they lived in. Inclusion criteria included being able to perform the physical activity and being over 59 years old. Exclusion criteria included severe dementia, Alzheimer's, depression, and mental disorders.

Cognitive function analysis and blood collection for BDNF and dopamine analysis were conducted before and after the intervention on the same day. Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA), a screening tool that assesses various domains of cognition such as attention, executive function, memory, language, visuospatial skills, conceptualization, calculation, and orientation, with a total score range of 0-30. The MoCA score was measured by a researcher who was blinded to the study.

Blood samples were taken from the antecubital vein of subjects before and immediately after the intervention (12 weeks) and sent to the clinical laboratory to measure BDNF and dopamine levels. These levels were analyzed using enzyme-linked immunosorbent assays (ELISA's), with the BDNF level expressed as nanograms per milliliter and the dopamine level expressed as nanograms per milliliter.

The subjects in the single intervention group were given anagram cognitive training three times a week over a 12-week period. The combined intervention group was given a series of heart exercises developed by the Indonesian Healthy Heart Foundation, as well as anagram cognitive training. The heart exercise and anagram training combination were administered three times a week on the same day for 12 weeks in a group setting. The heart exercise was to be performed outdoors, while the anagram training was to be done indoors. The exercise was supervised by a professional heart exercise trainer and was conducted at 7 o'clock for 20 minutes, after which the subjects continued with 15 minutes of anagram training. The subjects were instructed to follow the movements of the trainer during the exercise and to perform the exercise with a regular rhythm. The exercises consisted of walking and running movements, as well as movements involving the hands, feet, head, and body. For the cognitive anagram training, the researchers gave 10 new words commonly used in daily life to the subjects every three weeks. The subjects were then tasked with rearranging the words into as many new words as they could.

Categorical variables were reported as frequencies and percentages, with Fisher exact tests utilized when appropriate. The Shapiro-Wilk test was employed to confirm the normal distribution of all continuous variables, expressed as mean and standard deviation (SD). The study employed within-group analysis (Paired-sample T-test and Wilcoxon test) to compare the cognitive, BDNF, and dopamine levels before and after the intervention. Intergroup analysis (Independent sample t-test and Mann-Whitney U test) was

employed to evaluate the effects of the heart exercise and anagram cognitive training combination on the cognitive function delta, BDNF delta, and dopamine delta.

3. Results

Twenty subjects participated in this study, with the combined intervention and single intervention groups being well-matched for age, gender, education level, and hypertension history (Table 1). According to the logbook, all subjects in both groups demonstrated excellent compliance with the anagram cognitive training. Observation revealed that all subjects in the combined intervention group completed the heart exercise three times a week over a 12-week period. Graphical representation in Figure 1 illustrates the mean values of the cognitive

function, BDNF, and dopamine in each group at baseline and after the intervention period. Within 12 weeks, the combination of heart exercise and anagram cognitive training produced a statistically significant increase in cognitive function, with the mean post-intervention MoCA score being 27.40 ± 2.27 , compared to 24.10 ± 2.42 at baseline ($p=0.000$). Similarly, the single intervention (anagram cognitive training) also yielded a statistically significant increase in cognitive function, with the mean post-intervention MoCA score being 26.80 ± 2.25 , compared to 25.30 ± 2.36 at baseline ($p=0.000$). The mean of BDNF decreased in the combined intervention group but increased in the single intervention group, though the changes in both groups were statistically insignificant ($p>0.05$). Lastly, the mean of dopamine in both groups improved, yet failed to reach statistical significance ($p>0.05$).

Table 1. Characteristic of the Subjects

Characteristics	Combined intervention group	Single intervention group	P
Subject	10	10	
Gender			0.325
Male	3 (37.50)	5 (62.50)	
Female	7 (58.30)	5 (41.70)	
Education			0.500
High education	1 (33.30)	2 (66.20)	
Low education	9 (52.90)	8 (47.10)	
Age (year)	71.80 ± 7.22	70.90 ± 8.57	0.803
History of Hypertension	2 (33.30)	4 (66.70)	0.314

Data are presented as mean ± standard deviation and frequency (%)

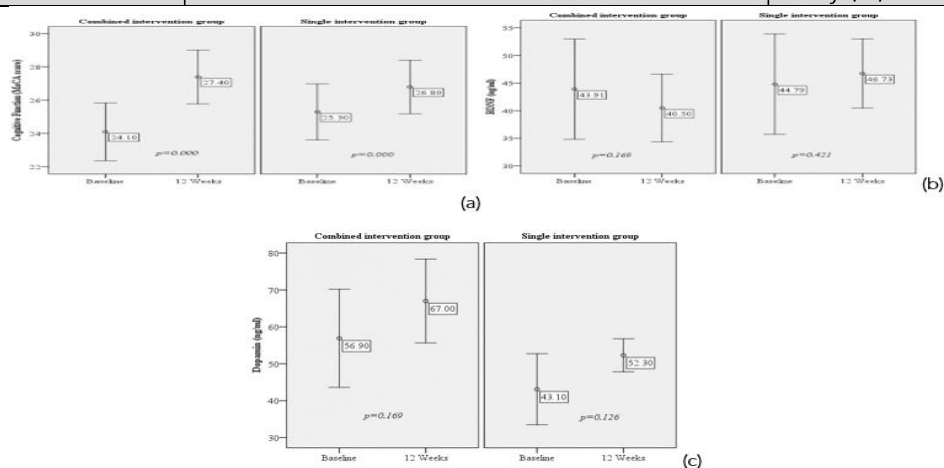


Figure 1. Comparison of cognitive function, BDNF, and dopamine between baseline and after the twelfth week's intervention program. (a) Compared with the baseline, cognitive function at the twelfth weeks of combined and single intervention groups showed significant difference ($p = 0.000$), but (b) insignificant difference in dopamine level (combined intervention $p = 0.169$, single intervention group $p = 0.126$) and (c) insignificant difference in BDNF level (combined intervention $p = 0.169$, single intervention group $p = 0.421$)

Table 2 demonstrates that, in comparison to the single intervention group, the combined intervention group experienced a statistically significant increase in cognitive function, but not in

dopamine and BDNF levels. The mean of the cognitive function in the combined intervention group increased up to 13.30 ± 1.15 , in contrast to the single intervention group's 1.50 ± 0.52 .

Table 2. Results for delta of cognitive function, BDNF, and dopamine

Delta (12-0 weeks)	Combined Intervention Group	Single Intervention Group	P
Cognitive function	3.30 ± 1.15	1.50 ± 0.52	0.010*
BDNF (ng/ml)	-3.41 ± 7.22	1.94 ± 7.28	0.116
Dopamine (ng/ml)	10.10 ± 21.34	9.20 ± 15.71	0.916

Data are presented as mean ± standard deviation. * Significant. BDNF, Brain-derived neurotrophic factor.

4. Discussion

To the best of our knowledge, this is the first study to explore the effects of a heart exercise and anagram cognitive training combination on cognitive function, BDNF, and dopamine levels. The study was conducted on elderly with an average age of over 70 years residing in a nursing home. The participants were assessed in the cognitive domain, such as memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation, using the MoCA instrument[29]. The results revealed that the mean MoCA score of cognitive function of the elderly in both groups prior to the intervention was below 26, with no difference in cognitive function level between groups. The mean MoCA score of the elderly indicated mild cognitive decline.

The cognitive function decline in the elderly can be attributed to the deterioration in brain structure and function[5]. It has also been demonstrated that cognitive decline in the elderly involves decreases in serum levels of BDNF and dopamine[6]–[13]. The study found that, prior to the intervention, there were no differences in BDNF and dopamine levels between groups.

The study also showed that cognitive interventions in the form of anagram training can significantly improve cognitive function as measured by MoCA, with a mean improvement of 1.5 points. This is in agreement with the results of a systematic review and meta-analysis study, which concluded that cognitive interventions can improve global cognitive function[20]. In this study, the cognitive intervention was conducted in the form of anagram cognitive training. The participants were trained to think, remember, and make decisions by arranging as many words as they could using a language they were familiar with. The cognitive intervention was tailored to the sociodemographic of the elderly to maximise its effectiveness on cognitive function[25]. Prasetyo and Sukrillah's study also found that anagram therapy can improve cognitive function[24].

The study demonstrated that the combination of anagram cognitive training and heart exercise could increase the mean MoCA score by 3.3 points, and this combination was found to be more effective at improving cognitive function than anagram cognitive intervention alone. The mean delta difference in cognitive function scores between the groups was 1.8 points, which was attributed to the synergistic effect of exercise and cognitive training[20].

The results indicated insignificant changes in dopamine and BDNF levels before and after the intervention in both groups. This is in contrast to the findings of the Miyamoto et al study, which suggested that the combination of physical and cognitive exercise can significantly increase BDNF in the elderly[30]. BDNF has been linked to learning

and memory processes, while dopamine is a major factor in aspects of language and thinking, such as motor planning, working memory, cognitive flexibility, abstract reasoning, temporal analysis/sequencing, and generativity[12], [15]. The results showed that anagram cognitive training could increase BDNF by 1.94 ng/ml and dopamine by 9.20 ng/ml, while the combination of exercise and anagram cognitive training could decrease BDNF by 3.41 ng/ml but increase dopamine by 10.10 ng/ml. Although BDNF decreased in the group that performed the combination of exercise and cognitive anagram training, their cognitive function was better than the group that performed anagram cognitive intervention. This could be attributed to the higher increase in dopamine in the combined intervention group, which was found to be.

There was a limitation of the study. While there was a high homogeneity characteristic between the groups and there was no drop out of the subjects of the study, the sample size of the study was very small. We believe that our findings will encourage future investigation with larger samples.

5. Conclusion

The study represents that combination of heart exercise and anagram cognitive training can significantly improve cognitive function, but not in BDNF and dopamine levels. Combination of aerobic exercise and anagram cognitive training can improve cognitive function better than anagram cognitive training.

6. Acknowledgements

The authors thank to all the participants of the study and Prodia laboratory that had helped to analyze the blood samples. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

All authors have disclosed no conflicts of interest. None

Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request

References

- [1] R. Pais, L. Ruano, O. P. Carvalho, and H. Barros, "Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults—A Systematic Review," *Geriatrics*, vol. 5, no. 4, p. 84, 2020.
- [2] S. Setiati et al., "Frailty state among Indonesian elderly: prevalence, associated factors, and frailty state transition," *BMC Geriatr.*, vol. 19, no. 1, pp. 1–10, 2019.
- [3] S. Pengpid, K. Peltzer, and I. H. Susilowati,

"Cognitive functioning and associated factors in older adults: results from the Indonesian family life survey-5 (IFLS-5) in 2014–2015," *Curr. Gerontol. Geriatr. Res.*, vol. 2019, 2019.

[4] I.-M. Dohrn, G. Papenberg, E. Winkler, and A.-K. Welmer, "Impact of dopamine-related genetic variants on physical activity in old age—a cohort study," *Int. J. Behav. Nutr. Phys. Act.*, vol. 17, pp. 1–8, 2020.

[5] D. L. Murman, "The impact of age on cognition," in *Seminars in hearing*, 2015, vol. 36, no. 03, pp. 111–121.

[6] C. Baeuchl, H.-Y. Chen, Y.-S. Su, D. Hämmerer, M. A. Klados, and S.-C. Li, "Interactive effects of dopamine transporter genotype and aging on resting-state functional networks," *PLoS One*, vol. 14, no. 5, p. e0215849, 2019.

[7] A. S. Berry et al., "Aging affects dopaminergic neural mechanisms of cognitive flexibility," *J. Neurosci.*, vol. 36, no. 50, pp. 12559–12569, 2016.

[8] J. M. Collins et al., "Association Between Components of Cognitive Reserve and Serum BDNF in Healthy Older Adults," *Front. Aging Neurosci.*, p. 489, 2021.

[9] K. M. Costa, "The effects of aging on substantia nigra dopamine neurons," *J. Neurosci.*, vol. 34, no. 46, pp. 15133–15134, 2014.

[10] K. I. Erickson et al., "Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume," *J. Neurosci.*, vol. 30, no. 15, pp. 5368–5375, 2010.

[11] T. M. Karrer, A. K. Josef, R. Mata, E. D. Morris, and G. R. Samanez-Larkin, "Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis," *Neurobiol. Aging*, vol. 57, pp. 36–46, 2017.

[12] M. Miranda, J. F. Morici, M. B. Zanoni, and P. Bekinschtein, "Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain," *Front. Cell. Neurosci.*, vol. 13, p. 363, 2019.

[13] Y. Mizoguchi, H. Yao, Y. Imamura, M. Hashimoto, and A. Monji, "Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the Sefuri study," *Sci. Rep.*, vol. 10, no. 1, pp. 1–9, 2020.

[14] A. Nieoullon, "Dopamine and the regulation of cognition and attention," *Prog. Neurobiol.*, vol. 67, no. 1, pp. 53–83, 2002.

[15] F. H. Previc, "Dopamine and the origins of human intelligence," *Brain Cogn.*, vol. 41, no. 3, pp. 299–350, 1999.

[16] G. J. McDougall Jr, "Cognitive interventions among older adults," *Annu. Rev. Nurs. Res.*, vol. 17, no. 1, pp. 219–240, 1999.

[17] N. Tulliani, M. Bissett, R. Bye, K. Chaudhary, P. Fahey, and K. P. Y. Liu, "The efficacy of cognitive interventions on the performance of instrumental activities of daily living in individuals

with mild cognitive impairment or mild dementia: protocol for a systematic review and meta-analysis," *Syst. Rev.*, vol. 8, no. 1, pp. 1–9, 2019.

[18] A. Bahar-Fuchs, L. Clare, and B. Woods, "Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia," *Cochrane database Syst. Rev.*, no. 6, 2013.

[19] M. E. Kelly, D. Loughrey, B. A. Lawlor, I. H. Robertson, C. Walsh, and S. Brennan, "The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: a systematic review and meta-analysis," *Ageing Res. Rev.*, vol. 15, pp. 28–43, 2014.

[20] Z. Xu, W. Sun, D. Zhang, V. C.-H. Chung, R. W.-S. Sit, and S. Y.-S. Wong, "Comparative effectiveness of interventions for global cognition in patients with mild cognitive impairment: a systematic review and network meta-analysis of randomized controlled trials," *Front. Aging Neurosci.*, vol. 13, 2021.

[21] R. Bhome, A. J. Berry, J. D. Huntley, and R. J. Howard, "Interventions for subjective cognitive decline: systematic review and meta-analysis," *BMJ Open*, vol. 8, no. 7, p. e021610, 2018.

[22] D. Adriani, Y. Imran, M. Mawi, P. Amani, E. I. I. Ilyas, and others, "Effect of Brain Gym@exercises on cognitive function and brain-derived neurotrophic factor plasma level in elderly: a randomized controlled trial," *Universa Med.*, vol. 39, no. 1, pp. 34–41, 2020.

[23] M. M. Cavalcante et al., "Exergame training-induced neuroplasticity and cognitive improvement in institutionalized older adults: A preliminary investigation," *Physiol. Behav.*, vol. 241, p. 113589, 2021.

[24] H. Prasetyo, P. N. DS, and U. A. Sukrillah, "The Effect of Memory Training: Anagram Towards Improving Cognitive Memory Training Anagram for Improving Kognitif Function of Eldery," *J. Ris. Kesehatan. Vol*, vol. 4, no. 3, 2015.

[25] M. Sanjuán, E. Navarro, and M. D. Calero, "Effectiveness of Cognitive Interventions in Older Adults: A Review," *Eur. J. Investig. Heal. Psychol. Educ.*, vol. 10, no. 3, pp. 876–898, 2020.

[26] C. Coetsee and E. Terblanche, "The effect of three different exercise training modalities on cognitive and physical function in a healthy older population," *Eur. Rev. Aging Phys. Act.*, vol. 14, no. 1, pp. 1–10, 2017.

[27] S. Kurita et al., "Association of physical and/or cognitive activity with cognitive impairment in older adults," *Geriatr. Gerontol. Int.*, vol. 20, no. 1, pp. 31–35, 2020.

[28] F. Roig-Coll et al., "Effects of aerobic exercise, cognitive and combined training on cognition in physically inactive healthy late-middle-aged adults: The projecte moviment randomized controlled trial," *Front. Aging Neurosci.*, vol. 12, pp. 1–11, 2020.

[29] P. Julayanont and Z. S. Nasreddine, "Montreal Cognitive Assessment (MoCA): concept

and clinical review," in *Cognitive screening instruments*, Springer, 2017, pp. 139–195.

[30] T. Miyamoto et al., "Response of brain-derived neurotrophic factor to combining cognitive and physical exercise," *Eur. J. Sport Sci.*, vol. 18, no. 8, pp. 1119–1127, 2018.

Appendix

BDNF, Brain-derived neurotrophic factor, MoCA, Montreal Cognitive Assessment