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The relationship between the brain gym and the changes in interleukin 6 levels and the cognitive function in the elderly

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ABSTRACT

Background: The prevalence of cognitive impairment increased by 10% that is doubling every 20 years. Brain gym is one of the non-pharmacological cognitive stimulation therapies that effectively increases brain neuroplasticity and is easy to do. The interleukin 6 biomarker is a pro-inflammatory blood marker that is sensitive to cognitive impairment. This research aims to analyze the relationship between the brain gym and the changes in interleukin 6 levels and the cognitive function in the elderly.
Methods: This research is a quasi-experimental observational study with a pretest and post-test approach without controls. The subjects are the elderly from the Tresna Werdha Social Home, Semarang. For comparative hypothesis test between categorical and numerical scale variables, normal data distribution was conducted by Independent T-test.
Results: In this research, 33 subjects had the average age of 70.06 ± 6.43 years and the dominant sex was male. There was a significant difference between interleukin 6 levels in pre and post brain gym (p<0.001). There was also a significant difference between the MoCA-Ina values in pre and post brain gym (p<0.001).
Conclusion: Interleukin 6 levels decreased after doing brain gym compared to before while the MoCA-Ina value increased after doing brain gym compared to before. Brain gym is safe, easy to do, and effective as a non-pharmacological therapy of neuroplasticity in cognitive impairment.

INTRODUCTION

There has been a transition of the increase of life expectancy in the developing countries from 65 years to 75 years due to health care systems improvement. Increasing the elderly without control of less metabolic, cardiovascular, cerebrovascular risk factors leads to an increase in neurodegenerative diseases in the future.[1-4] 5-8% of people over 65 years of age have some form of dementia and it is doubling every five years. More than 65 years have a prevalence of moderate-severe dementia of 5%, while those over 85 years have a prevalence of 20-40%.[4,5]

The Delphi consensus published a 10% increase in the prevalence of cognitive impairment that is doubling every 20 years with an estimated number of 35.6 million people with cognitive impairment in 2010

that would increase to 65.7 million in 2030 to 115.4 million in 2050.

Cognitive is a process in which all sensory stimuli (tactile, visual, and auditory) will be changed, processed, stored, and then used for perfect interneuron relations so that individuals can do reasoning about these sensory inputs. Each cognitive domain does not run alone in carrying out its function, but as a unit, which is called the limbic system.[6,7]

The cognitive domain consists of attention (elements of attention), language (understanding speech/communication, fluency, understanding, repetition and naming), memory (sensory memory, primary memory, secondary memory), visuospatial (ability to feel and recognition of space), executive

function (way of thinking and problem solving). Cognitive changes that occur in the elderly, including reduced ability to improve intellectual function, reduced efficiency of nerve transmission in the brain (causing information processing to slow down and a lot of information is lost during transmission), reduced ability to accumulate new knowledge and retrieve information from memory, and the ability to remember past events better than remembering recent events.[8,9]

Patomechanism of cognitive impairment is the formation of Aβ plaques. Their brain parenchyma deposits increase the response of microglia that bind to Aβ fibrils via cell surface receptor complexes, secrete inflammatory cytokines, and activate ROS. Inflammation and dysfunction of neurons, phosphate

Table 1. Clinical characteristics of study participants

Variables	f	%	Mean ± SD	Median
Age			70.06 ± 6.43	70
Late Elderly	6	18.2		(57 - 86)
Seniors	27	81.8		
Gender				
Male	18	54.5		
Female	15	45.5		
Education				
Not in school	7	21.2		
Elementary	10	30.3		
Junior High	1	3.0		
Senior High	15	45.5	5.69 ± 0.84	
HbA1c				5.4
Not DM	30	90.9	89.58 ± 45.90	(4.5 - 8.4)
DM	3	9.1		
Cholesterol				
Low	33	100		73
High	0	0		(37 - 251)
Blood pressure				
Normal	5	15.2		
Pre HT	16	48.5	22.59 ± 5.69	
HT Stage 1	9	27.3		
HT Stage 2	3	9.1		
BMI				
Normal	17	51.5		
Underweight	7	21.2		21
Overweight	5	15.2		(14.6- 40)
Obesity	4	12.1		
Moca Ina				
Normal	6	18.2		
Impaired	27	81.8		
Interleukin 6				
Normal	16	48.5		
Impaired	17	51.5		

organs from Aβ destroy microtubules of tau protein, becoming NFTs that activate the intracellularly inflammatory cascade. Interleukin 6 is secreted by T cells from microglia, its role is to stimulate the immune response and also acts as an essential mediator of inflammation which is proportional to the increase in microglia which have good and bad effects on brain cells.[10]

Besides giving pharmacological interventions, there are non-pharmacological interventions that also affect cognitive function improvement.[1] Brain Gym is non-pharmacological therapeutical management of cognitive impairment. It is a series of simple activities designed to stimulate the brain by coordinating the brain function and increasing brain neuroplasticity through movement skills. Brain gym is a number of simple movements that can balance
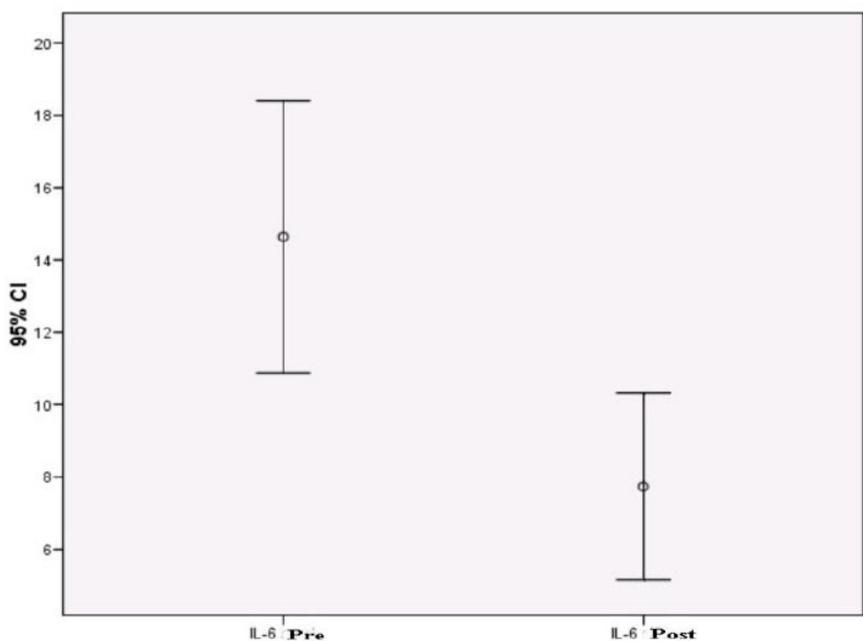
Figure 1. Error Bar for Interleukin - 6 level differences in pre and post brain gym

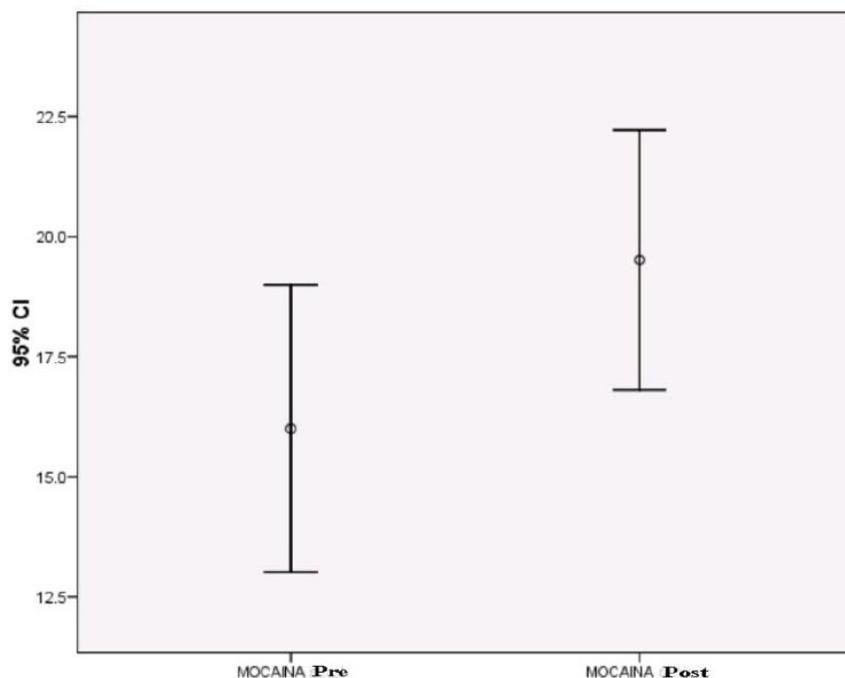**Table 2.** The differences of IL-6 level in pre and post brain gym

IL - 6	Mean ± SD (pg/dl)	Median (Min-Max)	Paired T	p
Pre	14.64 ± 10.63	11.9 (3.5–44.7)	4.878	<0.001*
Post	7.73 ± 7.28	5.4 (0.3 – 35.4)		

*Significant (p<0.05)

Table 3. The differences of Moca Ina levels in pre and post brain gym

Moca - Ina	Mean ± SD	Median (Min-Max)	Paired T	p
Pre	16.00 ± 8.44	17 (2 – 28)	6.324	<0.001*
Post	19.52 ± 7.64	21 (4 – 30)		

*Significant (p<0.05)

Figure 2. Error Bar for Moca Ina value differences in pre and post brain gym

every part of the brain, where it is known that motor and cognitive circuits have an adjacent anatomical location of the brain and activating the right motor movements will have an effect in cognitive function.[11,12,13]

The referenced research of guideline Mild Cognitive Impairment (MCI) stated that MCI pharmacological treatment might have ineffective results or insufficient data, but non-pharmacological treatment (Brain Gym) for 6 months increases cognitive output.[2] Montreal Cognitive Assessment (MoCA) examines cognitive function covering all cognitive domains, with high sensitivity and specificity. The Interleukin 6 (IL-6) biomarker is a proinflammatory blood marker that is sensitive to cognitive impairment.[3] It prompted researchers to examine cognitive function, which in this case was checked with the Indonesian version of MOCA (Moca-Ina) and IL-6 levels in the elderly who were given non-pharmaceutical therapy treatment of brain gym. The researchers are interested in examining whether there is an effect of motor activity (brain exercise) with the changes in Interleukin 6 levels and cognitive function changes in the elderly?

METHOD

This research is Neurological research. The research was conducted at the Tresna Werdha Pucang Gading Social Home, Semarang from November 2019 to January 2020. This research is a quasi-experimental analytic observational study with a pre and post-test approach without control. The subjects were the elderly from the Tresna Werdha Social Home in Pucang Gading, Semarang, Indonesia. In this research, the number of research subjects was 33 subjects determined by consecutive sampling that met the inclusion criteria. The independent variable in this research is the Brain gym while the dependent variables were the value of cognitive function (Moca-Ina) and the levels of Interleukin 6 (IL-6).

Subjects were given brain gym intervention twice a week for 6 weeks then a cognitive function evaluation was carried out with the MoCA-Ina instrument while the IL-6 assessment was carried out after the brain gym intervention finished. Bivariate analysis was conducted to determine the correlation between variables. Data on a numerical scale was tested using Shapiro-Wilk normality. Hypothesis testing comparative in IL-6 levels between pre and post-intervention (numerical), normal data distribution was done by Independent T-test. The comparative hypothesis test in Moca - Ina values between pre and post-intervention (numeric), normal data distribution was carried out by the Independent T-test.[14,15]

RESULTS

Characteristics of Research Subjects
Table 1 showed that 33 elderly research subjects followed the complete brain gym intervention 12 times. Mocha-Ina examination was used to measure the research subjects' cognitive condition at the beginning of the research. Moca - Ina contains 30 values, defined as normal if the value is: ≥ 26, defined as disturbed when the value is: <26, while the levels

of IL - 6 defined as normal when <11 pg/dl, defined as disturbed when> 11 pg/dl. Clinically significant increases in IL-6 were divided into 3 levels; (low: < 1.8, moderate: 2.13 - 3.8, high: > 3.8). It is considered as clinically significant increase in Moca Ina if the value increase is >3.

Figure 1 showed that the mean of IL-6 pre-intervention group was 14.64±10.63 pg/dl, which experienced a decrease in IL-6 levels in the post-intervention group mean ± SD 7.73 ± 7.28 pg/dl after intervention with brain gym. Table 2 showed a difference from the comparative test relationship in IL-6 levels between pre and post brain gym intervention. It means that there was a significant relationship between brain gym and the changes in Interleukin-6 levels. In table 3, it showed that there was a difference from comparative test relationship in the Moca-Ina scores between pre and post brain gym intervention, there was a significant relationship between brain gym and the changes in Moca Ina Value.

Figure 2 showed that the mean of Moca Ina in the pre-intervention group was ± SD 16.00 ± 8.44 which experienced an increase in Moca-Ina values in the post-Intervention group mean ± SD 19.52 ± 7.64 after the intervention with brain gym.

DISCUSSION

This research aimed to determine the relationship between the brain gym and the changes in IL-6 levels and cognitive function in the elderly. The independent variable in this research was brain exercise associated with pro-inflammatory biomarkers and clinical output of cognitive function in the elderly as measured by comparing the changes in IL-6 levels and the changes in Moca-Ina values after brain gym interventions carried out for 6 weeks as many as 12 times.

The significant difference of the changes in IL-6 levels between pre and post-intervention brain gyms in the elderly was shown in the comparative hypothesis test Independent T-test (p<0.001), the mean of IL - 6 level pre-intervention was 14.64 (SD 10.63) pg/dl. The lowest value was 3.5 pg/dl while the highest value was 44.7 pg/dl. The mean IL-6 level post-intervention was 7.73 (SD 7.28) pg/dl with the lowest value was 0.3 pg/dl and the highest value

is 35.4 pg/dl. In this research, 30 subjects experienced a decreased levels of IL-6, which means there was an improvement in proinflammatory biomarkers of cognitive function. 3 subjects had an increased level of IL-6, which means there was a deterioration of the pro-inflammatory biomarkers of cognitive function. From the data showing the discrepancy, additional data were obtained from the three subjects. 1 subject had a history of schizophrenia, 1 subject had an asthma attack in the last week of the research, 1 subject had an allergy attack from food in the last week of the study, that was not an exclusion criteria in the study, and the patients were able to complete the whole brain gym intervention without difficulty. These results were consistent with the study by Fraga et al.[16] who assessed the cognitive function using MMSE and IL-6 levels in 27 subjects, showing a significant increase in IL-6 at 51.8% (p=0.012; RR = 3.095 IC 95% = 1.087- 8.812) affected by genetic, age, and varied Apo E4 levels because it depends on neurological conditions, blood vessel function, and psychiatric status.[16]

These results were also in accordance with Gómez-Rubio et al.[17] study which examined the changes in IL-6 levels in patients with cognitive impairments and schizophrenia, which showed that the cognitive function improvements were significant with the changes in IL -6 levels. The improvement in clinical symptoms of schizophrenia was not significant, some experienced an improvement and some did not experience an improvement. It was influenced by the immune status and chronic increase levels of IL-6 due to impaired immune function in the pathophysiology of schizophrenia.[17] These results could also be explained in Lee et al.[18] which explained that allergic contact dermatitis is an autoimmune response process causing inflammation, increasing IL-6. Asthma is a chronic inflammation of the airways with various cells and cellular elements involved. Chronic inflammation is associated with airway hyperresponsiveness resulting in repeated wheezing episodes, chest tightness, shortness of breath, and coughing, especially at night or early morning. Asthma symptoms are varied,

multifactorial, and potentially associated with bronchial inflammation.[18]

The significant difference between the changes in the pre and post Moca - Ina value of the brain gym intervention in the elderly was shown in the comparative independent T-test (p=0.001), the mean value of Moca - Ina pre-intervention was 16.00 (SD 8.44) with the lowest score was 2 and the highest score was 28. The mean score of Moca - Ina post-intervention was 19.52 (SD 7.64)with the lowest score was 4 and the highest score was 30. In this research, it was found that 31 subjects experienced an increase in Moca-Ina scores, which means an improvement in the clinical symptoms of cognitive function. It was obtained that 2 research subjects had consistent Moca-Ina scores with a pre-Moca-Ina score of 28 and still had 28 in the post result of the initial Moca - Ina score, where the normal Moca - Ina score was 26 - 30. This is in accordance with the research of Yaguez et al.[19] who examined the effect of brain gym on 70.5 + 8 elderly, it was found that the cognitive function changes in the elderly who were assessed using CANTAB after brain gym intervention twice a week for 6 weeks compared to the controls who did not perform intervention (p<0.01).[19] The increase in the clinical cognitive function (MMSE/MOCA) is considered to have a clinically significant increase when it increases > 3, the clinical decline in IL-6 is divided into 3 levels (low: <1.8, moderate: 2.13 - 3.8, height: >3.8).[20]

This research's limitation is that this research used a pre and post-test design without control, so that the risk factors cannot be tested with a control group that intervenes with brain gym. This research did not assess the subjects' diseases during the examination that could affect the results. The exercise was carried out only twice a week for 6 weeks so that the changes in IL-6 and Moca Ina had not shown optimal clinical changes as recommended by Peterson et al.[2] on the Mild Cognitive Impairment (MCI) guideline which stated that non-pharmacological therapy (Brain Gym) for 6 months increases cognitive output clinically.[2,21]

CONCLUSION

Brain gym program is safe, easy to do, and effective as a non-pharmacological therapy of neuroplasticity in cognitive impairment. It can be used as a reference for cognitive impairment subjects in general, especially the elderly.

ETHICAL APPROVAL

The ethical approval for this research was issued by the Health Research Ethics Committee of Faculty of Medicine Universitas Diponegoro with ethical clearance references number No. 452/EC/KEPK/UNDIP/10/2019

CONFLICTS OF INTEREST

There is no conflict of interest.

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AUTHOR CONTRIBUTIONS

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