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Brain Vitalization Gymnastics Improved Cognitive Function Marked by Increased BDNF, Decreased Serum Interleukin-6 and Decreased S-100β Expression among Elderly in West Denpasar Primary Health Clinic

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Keywords: Brain vitalisation gymnastics (BVG); Elderly cognitive function; BDNF; IL-6; S100β; Brain plasticity markers

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Abstract

BACKGROUND: Brain vitalisation gymnastics (BVG) is a form of physical exercise which attempts to synchronise bodily movements with cognition within the same time frame.

AIM: This study aims to prove BVG can improve cognitive function among the elderly.

METHODS: The impact of BVG was evaluated as opposed to elderly gymnastics (regarded as a control group) for a 4-week study period. Outcomes measured were improvements of cognitive function assessed by MoCA-Ina questionnaire, as well as the difference in serum levels of BDNF, IL-6, and S100β. An experimental pretest-posttest control design was applied to evaluate BDNF and IL-6 levels, while the post-test only designed to evaluate S100β levels. Parametric data were tested for normality before being proceeded into either parametric (independent student' t) or non-parametric (Mann Whitney) test.

RESULTS: BVG significantly improved cognitive function better than elderly gymnastics with MoCA-Ina score of 1.53 ± 1.58 dan 0.11 ± 2.54, respectively ($p \leq 0.047$). BVG group also had increased BDNF levels when compared with control (-6020.58 ± 7857.22 dan 0.11 ± 2.54; $p = 0.027$). Whereas BVG had lower IL-6 levels as opposed to the control group (median pre-test IL-6: 2212, median post-test IL-6: 3197.50; $p = 0.004$). Meanwhile, S100β levels were found lower among BVG when compared with the control group, although statistically insignificant ($p = 0.40$).

CONCLUSION: BVG programme for 4 weeks improved: (1) brain plasticity as shown by increased serum BDNF and S100β levels (although the latter was statistically not-significant), as well as marked decrease of IL-6 levels, (2) cognitive function as proven by an increase of MoCA-Ina score when compared with elderly gymnastics.

Introduction

Ageing causes a variety of biological changes, including the brain. In humans, brain ageing causes cognitive deterioration in many aspects that have been studied and documented. Referring to Harada et al. (2013), the brain's cognitive abilities consist of crystallised and fluid intelligence [1]. Crystallised intelligence includes the ability of individuals in the acquisition of skills and knowledge learned and repeatedly practised, while fluid intelligence is an individual's ability to solve problems and analyse new concepts and not depend on what has been learned before. Brain ageing has minimal impact on crystallised intelligence but has a major effect on the decrease of liquid intelligence. This is demonstrated by the slowing of thinking and motor responsiveness (including fluency of language), decrease of attention especially related to selective attention (i.e. the ability to focus on specific information and ignoring other information that is considered irrelevant, e.g. driving a vehicle), shared attention (e.g. the ability to perform multiple activities simultaneously, e.g. speaking on the phone while cooking), and working memory (e.g. temporary memory capacity while manipulating information,

decreased memory function, especially related to semantic memory, decreased ability to remember new things (memory acquisition) and accessing memory (memory retrieval), decreased visuospatial ability, particularly related to constructive ability (e.g. assembling 3-dimensional objects, such as assembling furniture), and decreasing executive function, e.g. the ability of individuals to engage in independent, purposive, and proportional activities [2], [3], [4], [5], [6]. The executive function is more general and encompasses various cognitive areas, such as the ability to plan, organise, monitor, argue, solve problems, and mental flexibility [1]. Studies show that concept formation, abstraction, and mental flexibility decrease with age [7].

The mechanism underlying the decline in cognitive function due to biological ageing varies. It can be assumed, however, that the impairment of cognitive function is the implication of structural and functional changes in the brain as the ageing process proceeds. For example, the volume of grey substance declines from the age of 20 and atrophy often occurs in the prefrontal cortex, as well as the moderate-scale volume reduction in the hippocampus [8], [9]. The cause of atrophy is the death of neurons that are not matched by meaningful cell replication, but to a greater degree due to the decrease in synaptic density, both in terms of number and size. The synaptic density change involves the decrease of dendritic arborisation complex, shortening of the dendrite, and decreased neuritic spines which are the main location of the excitatory synapse [10], [11]. Also, pathological conditions such as beta-amyloid protein accumulation (Aβ) are found in even healthy elderly brains, which were originally regarded as non-pathological processes, but have recently been recognised as a prognostic factor of future Alzheimer's dementia in subjects with protein accumulation Aβ [12]. Furthermore, there is a decrease in the volume of cerebral white matter which is more significant than that of grey matter, especially in the precentral gyrus, rectus and corpus callosum [13]. Decreased cerebral white matter, such as in the parahippocampal area, can lead to decreased brain communication with other structures such as the hippocampus and is assumed to cause cognitive decline with advancing age.

However, the brain has a special ability to compensate for structural and functional changes, both in physiological states such as ageing as well as on pathological conditions. The brain can adapt to the changing of the internal and external environment of an organism. The corresponding adaptability refers to the regeneration of neurons and synapses, as well as changes (remodelling) of neural pathways [14]. This adaptive skill is known as brain plasticity. Plasticity of the brain in humans are known to persist through old age [15]. For example, ageing individuals are shown to use more brain areas more actively in the process of formation and memory access as a way to compensate for the decline in cognitive function due to advancing age [14]. Brain plasticity reflects the brain's ability to re-organise continuously in the maturation process and respond to changes in stimuli or injury. Various mechanisms of plasticity have been widely studied, including (but not limited to) neurogenesis, synaptogenesis, and angiogenesis [16]. Brain plasticity can be observed at the cellular level in the form of changes in neurons and supporting cells, as well as dendrites and synapses. Functionally, the plasticity of the brain can be subdivided into 3 types, namely the plasticity of neurons (related to brain adaptation at the level of synapses), brain plasticity (changes in brain tissue activity), and individual ability to improve cognitive function after training [17], [18].

Physical activity in various types and levels has been shown to slow the decline in cognitive function and reduce the incidence of dementia [19]. This concept is supported by various types of studies, ranging from observational studies in experimental animals, humans, to biomolecular research. A meta-analysis that studied the relationship between physical activity and cognitive function found that from 11 randomised intervention studies found improvements in cognitive function, particularly in the motor area and auditory attention (strong degree), as well as moderate cognitive speed and visual attention [20]. In addition to physiologic brain ageing, physical activity is also known to improve cognitive function in mild cognitive impairment patients who are the prodromal phase of Alzheimer's dementia [21], [22].

An animal study conducted by Laksmidewi, et al., (2016) proved that regular physical exercise can improve brain plasticity and cognitive function, evident from significant beta-amyloid depletion, significant increase in BDNF serum, decreased serum CRP, and a new finding that astrocytes play an important role in brain plasticity marked by increasing numbers of astrocytes that express BDNF [23]. BDNF is a neurotrophic factor that has a pleiotropic effect on synapse plasticity and plays an important role in short-term memory acquisition and access, formation, consolidation, re-consolidation, maintenance, and long-term memory removal through various molecular signalling pathways including PI3K, PLC-gamma, and ERK1/2, in addition to potassium sodium ion pump regulation, and modulation of NMDA and AMPA receptors [24].

In addition to physiological processes, cognitive function decline can also be found in pathological conditions such as Alzheimer's dementia. Various enzymatic activities in neurons and enzymatic defects within myelin-forming cells oligodendroglia and Schwann cells occur in dementia [25]. One indicator of microglial activation is the secretion of S100β which is a protein that binds to calcium under conditions of metabolic stress and is a biological marker of central nervous system (CNS) damage.

Also, microglia activation results in a state of

neuroinflammation characterised by secretion of proinflammatory cytokines, such as interleukin-6 (IL-6). Excessive secretion of IL-6 is neurotoxic in the CNS and is found in a variety of pathological conditions [26], [27], [28].

Brain Vitality Gymnastics (BVG) is an exercise with repeated stimulation that seeks to harmonise the movement of the body with thinking activity, optimising the ability of memory simultaneously. BVG is associated with cooperation between the function of motion, respiration, and cognition. The movements in BVG can stimulate cooperation between the two cerebral hemispheres [29]. Furthermore, physical exercise can improve cardiac output, increasing the body's oxygen demand, improving neurobiology as well as synthesising brain tissue, improving angiogenesis, neurogenesis, synaptogenesis, neurotransmitter synthesis, and cognitive function [30], [31]. This BVG has also been used by the Health Intelligence Center of the Ministry of Health of the Republic of Indonesia in the elderly group [32].

BVG is known to improve cognitive function in the elderly. In this study, we want to know the effect of BVG on improving cognitive function of elderly and biological markers on brain plasticity (BDNF), CNS damage (S100β), and neuroinflammation (IL-6) compared with elderly gymnastics.

Methods

Study Design and Procedure

This is experimental research with pretest-posttest control design for BDNF and IL-6 groups, and post-test only design for the S100β group. This study was conducted at the Elderly Primary Health Clinic in West Denpasar from May to June 2017.

The elderly were selected based on the inclusion and exclusion criteria, and 38 subjects were divided into two groups of 19, each treated with BVG and elderly gymnastics. All subject within the two groups will be interviewed with a MoCA-Ina assessment questionnaire, blood samples were then taken for BDNF and IL-6 (pre-exercise) levels measurement, and then the elderly were given BVG treatment in the treatment group and the elderly gymnastics for the control group. During the experiment, both BVG and elderly gymnastics were given twice a week for 4 weeks in a row with a duration of 20-30 minutes for each session. After four weeks of BVG training and elderly gymnastics, MoCA-Ina and serum levels of BDNF, IL-6, and S100β were reevaluated (post-exercise). The data obtained were analysed statistically.

Results

In Table 1, the overall age (either control or treatment group) was 67.00 ± 4.66 years. The mean age of the control group was 66.74 ± 4.51, while the treatment group was 66.00 ± 4.93 years. The number of men and women in each group (control and treatment) was relatively balanced, i.e. about 50 percent. All subjects received formal education from junior high school to university, with the highest number of universities 17 (44.7%), senior high school 13 (34.2%) and junior high school 8 (2%). Subject's occupation within the control and treatment group were mostly retired civil servants (PNS), which consists of 9 subjects (23.7%) in the control group and 13 subjects (34.2%) in the treatment group.

Table 1: Baseline Characteristics of Subjects

Parameters	Control (n = 19)	Treatment (n = 19)
Mean age (± SD)	66.74 ± 4.51	66.00 ± 4.93
Sex		
Male	9 (47.4%)	9 (47.4%)
Female	10 (52.6%)	10 (52.6%)
Educational level		
Junior high school	7(36.8%)	1 (5.3%)
Senior high school	4 (21.2%)	9 (47.4%)
Academy/Dipl./Univ.	8 (42.1%)	9 (47.4%)
Occupation		
Civil servant	9 (47.4%)	
Private employee	2 (10.5%)	4 (21.1%)
Entrepreneur	3 (15.8%)	1 (5.3%)
Others	5 (36.3%)	1 (5.3%)

SD = standard deviation.

Table 2 showed that the effect of BVG in cognitive function improvement could be assessed by comparing the mean increase of MoCA-Ina cognitive function score between the treatment group (BVG) and control group (elderly gymnastics) after 4 weeks of gymnastics training. An independent t-test was conducted to determine the significance of BVG compared with elderly gymnastics in improving the cognitive score. The result showed an average increase of MoCA-Ina score by 1.53 ± 1.58 in the BVG group and 0.11 ± 2.54 in the elderly gymnastics group. In this study, it was found that the observed increase of MoCA-Ina score among the treatment group was significantly different (higher) than the control group ($p = 0.047$).

Table 2: The average increase in MoCA-Ina scores between brain vitalisation gymnastics groups and elderly exercise groups

Groups	Average MoCA-Ina score increase	p-value
BVG	1.53 ± 1.58	0.047*
Elderly gymnastics	0.11 ± 2.54	

BVG = brain vitalization gymnastics; MoCA-Ina = Montreal Cognitive Assessment-Indonesia.

Table 3 showed that the effect of BVG on elevated serum BDNF level in elderly was assessed by comparing the mean of BDNF increase between treatment group (BVG) and control group (elderly gymnastics) after 4 weeks of gymnastics training. In the independent t-test, the average increase in BVG group was -6020.58 ± 7957.22, and the mean of the

elderly gymnastics group increased by 0.11 ± 2.54. In this study, it was found that the elevated serum levels of BDNF treatment group were significantly different from the control group (p = 0.027).

Table 3: Mean elevation of serum BDNF levels between BVG group and elderly exercise group

Groups	Mean BDNF increment	
BVG	-6020.58 ± 7957.22	0.027
Elderly gymnastics	-12028.32 ± 8062.32	

BVG = brain vitalization gymnastics; BDNF= brain derived neurotrophic factor.

Table 4 showed that the effect of BVG on decreasing levels of IL-6 in the elderly was assessed after four weeks of gymnastics training. The median pre-test IL-6 levels were 2212.00, while the median post-test IL-6 levels were 3197.50. There were 12 people with higher IL-6 levels after gymnastics than before gymnastics, and 26 people showed lower levels of IL-6 than before exercise. In the Wilcoxon test, it was found that the difference in serum IL-6 decrease was significantly (p = 0.004).

Table 4: The decrease in serum IL-6 levels between the BVG and the elderly exercise group

	IL-6 levels (pg/mL)			
Parameters	Median	Minimum	Maximum	p-value
Pre-test IL-6 levels	2212.00	566	5741	0.004
Post-test IL-6 levels	3197.50	1013	7669	

IL-6 = interleukine 6.

Table 5 showed that BVG decreased subjects' S100β levels (pg / mL) in the elderly, which was assessed after four weeks of gymnastics training. Mann Whitney test was conducted to compare the S100β's rate of decrease among BVG-treated and elderly gymnastics group. It was found that the decrease of S100β treatment group did not differ significantly with the control group (p = 0.404).

Table 5: The difference between serum S100β levels of BVG group and the elderly exercise group

	S100β levels (pg/mL)			
Parameters	Median	Minimum	Maximum	p-value
BVG	19.63	19.48	21.17	0.404
Elderly gymnastics	19.98	19.48	22.60	

BVG = brain vitalization gymnastics.

Discussion

The concept of brain plasticity is the reorganisation of neural interconnection through a sustained new experience. It is an intrinsic development of adult brain tissue, where ineffective synapses will undergo shrinkage [33], [34], [35]. Animal studies have shown that regular exercise improves brain plasticity as evidenced by significant beta-amyloid depletion, a significant increase in serum BDNF, decreased serum CRP and that astrocytes play an important role in brain plasticity characterised by an increase in the number of astrocytes expressing BDNF [23].

In this study, 38 subjects met the eligibility criteria, which were divided into 19 subjects in the treatment group and 19 subjects were the control group. All subjects were recruited in the area of West Denpasar Puskesmas Bali. In this study, the overall age (either the control group or the treatment group) was 67.00 ± 4.66 years. The mean age of the control group was 66.74 ± 4.51, while the treatment group was 66.00 ± 4.93 years. All subjects of this study run formal education ranging from junior high school to college, with the highest number of academy/diploma/ colleges that is 17 subjects (89.5%). This indicates that the study subjects in both groups had a high educational background, thus contributing to better synapse density and cognitive reserve than subjects with low education [36]. Also, to assess cognitive function using the MoCA-Ina test requires a good level of attention (attention) and has a minimum level of formal education completed primary school. The provision of BVG to increase the cognitive function of MoCA-Ina in elderly was assessed by comparing the mean improvement of cognitive function score between the treatment group (BVG) and control group (elderly gymnastics) after 4 weeks of gymnastics training. The average score improvement of MoCA-Ina in the BVG group was 1.53 ± 1.58 and the MoCA-Ina's mean score improvement in elderly gymnast group was 0.11 ± 2.54. The Montreal Cognitive Assessment (MoCA) is a questionnaire to assess global cognitive functioning including executive and memory functions. Efficient MoCA examination for various causes of cross-age cognitive dysfunction and more sensitive level of education compared with MMSE, particularly significant with frontal lobe abnormalities [37], [38]. In this study, it was found that the effectiveness of MoCA-Ina improvement score between treatment groups increased by 1.53 ± 1.58 which was significantly different compared to the control group of 0.11 ± 2.54 (p = 0.047). It can be concluded that the application of BVG resulted in significantly improved cognitive function compared to the elderly gymnastics group for 4 weeks with regular training.

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophic factor about Nerve Growth Factor as a marker of brain plasticity. The brain in adulthood has the ability to keep producing new nerve cells known as neurogenesis processes. BDNF is one of the most active markers of plasticity and plays an important role in neural development [39], [40], [41]. As it is known that cognitive function and memory were arranged in the cerebral cortex, hippocampus, and the frontal part of the brain, it is known that BDNF is important for long-term memory associated with Nerve Growth Factor [41], [42]. Four weeks of BVG administration affected elevated serum BDNF levels in the elderly. In this study, the average increase of BVG group was-6020.58 ± 7957.22 and average of elderly gymnastics

group was 0.11 ± 2.54. In this study, it was concluded that elevated serum BDNF levels among the treatment group were significantly different with the control group (p = 0.027). This indicates that BVG not only improves functional cognitive functioning as evaluated by MoCA-Ina but also plays an important role in improving neuroplasticity. As is known, BDNF plays an important role in short and long-term memory regulation, through the mechanism of long-formation reinforcement, consolidation, re-consolidation, care and elimination involving various molecular signaling pathways, including PI3K, PLC-gamma, and ERK1/2, in addition to potassium sodium ion pump regulation, and NMDA and AMPA receptor modulation [24]. Thus, the increase in BDNF levels due to BVG, as found in this study, is expected to have a positive impact on improving cognitive function, both in healthy elderly and people with dementia. This is also supported by experimental animal studies conducted by Laksmidewi, et al., (2016), where BDNF increased after the 7th, 14th, 28th day of training when exercise is regular and not excessive. BDNF levels reportedly rose much higher after 14 days of regular training compared to the seventh-day post-exercise [23]. BDNF increment is evidence that BDNF is a key protein in the regulation of the successful balance of neuronal growth and also shows the association of physical exercises with brain plasticity.

Interleukin-6 (IL-6) is a proinflammatory cytokine secreted mainly by astrocytes in the CNS. Although IL-6 has a beneficial effect because it is neurotropic, its excessive expression is generally neurotoxic [43]. Changes in cognitive function after acute systemic inflammation are thought to be the result of cellular and molecular interactions, especially in the hippocampus. Acetylcholine inhibits the release of IL-6 pro-inflammatory cytokines to control inflammation in the brain [44], [45]. BVG in this study proved to lower IL-6 levels in the elderly as assessed after four weeks of gymnastics. The median pre-test and post-test IL-6 levels were each 2212.00 and 3197.50 pg/mL. There were 12 people with higher IL-6 levels after than before gymnastics, and 26 people showed IL-6 levels to be lower than before exercise. In this study, BVG training for 4 weeks regularly was proven to lower IL-6 levels when compared with elderly gymnastics group.

Furthermore, in this study, S100β was found decreased among the treatment group (BVG) but did not differ significantly with the control group (elderly gymnastics) with p = 0.404. S100β is a protein attached to calcium, secreted by glial cells, Schwann cells, and astrocytes under the influence of metabolic stress conditions. The synaptic transmission of S100β affects the excitability of nerve cells and cerebral blood flow, thereby increasing neurobehavioral and cognitive symptoms [44]. The release of S100β by astrocytes is associated with oxidative stress mechanisms, but also has a beneficial effect on the maintenance of nerve cells, neurogenesis, and cognitive function described through brain repair processes especially in the hippocampus region [46], [47], [48]. Increased secretion of S100β by activated astrocytes suggests a neurodegenerative process, found in Alzheimer's dementia, stroke, schizophrenia, and traumatic brain injury [49], [50].

In this study, the BVG administration for 4 weeks did not demonstrate a significant difference between treatment and control group with regards to S100β levels decrement. Referring to the dualism nature of S100β secretion related to oxidative stress and neurogenesis (along with cognitive function), the physical exercise should be conducted longer and more regularly as well as evaluated both on pre- and post-test. The insignificant result of S100β levels among the treatment and control group was assumed due to the post-test evaluation only.

In conclusion, BVG performed regularly in the elderly at intervals of 2 times a week with a duration of 20-30 minutes per session for 4 weeks has been shown to improve cognitive function and brain plasticity, as well as decrease the neuroinflammation process is shown by increasing MoCA-Ina score and BDNF levels, IL-6 levels, respectively, were statistically significant compared to elderly exercise. Meanwhile, BVG did not show any significant effect on S100β compared to elderly gymnastics.

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